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Editorial

Expected treatment for endometrial polyp

Intrauterine pathologies are common in women, regardless whether those are stated in pre-menopausal or post-menopausal status [1,2]. However, degrees of severity of intrauterine diseases varied greatly from asymptomatic benign situations (asymptomatic endometrial polyps or atrophic endometrium) to life-threatening diseases, such as uterine adenocarcinoma [1–5]. Therefore, clinical evaluation following with subsequent appropriate treatment is of the critical importance, since either under- or over-treatment may be associated with bad results. Over-treatment may increase the unnecessary anxiety, harm to the body and increased expense of medical care. By contrast, under-treatment may result in the delayed diagnosis and impaired immediate and adequate management and all may be associated with poor prognosis. Recently, two articles addressing the above dilemma have been published in the 2023 *Taiwanese Journal of Obstetrics and Gynecology* (*TJOG*) [6,7]. Besides careful history taking and comprehensive evaluation of clinical manifestation of patients, transvaginal ultrasound (TVUS) may be one of the most cost-effective tools assisting the detection of the underlying intrauterine pathologies [8]. However, the consensus about the threshold of intrauterine findings, such as endometrium thickness and subsequent front-line tools for making an accurate and precise intrauterine pathologies is not in agreement yet, resulting in a biggest challenge in the management of women with suspicious intrauterine pathologies [8,9]. An article in the 2023 July issue of the *TJOG* by Drs. Mak and Wang was conducted to evaluate the clinical outcomes of women with endometrial polyps undergoing conservative management [7].

The authors enrolled 1006 women with asymptomatic uterine polyps diagnosed by both positive ultrasound findings and confirmation of outpatient hysteroscopy to evaluate the outcomes of these women who underwent conservative treatment (either by expectancy or by medication) [7]. Among these 1006 women, 448 were treated with hormonal drugs and the remaining 558 were managed in expectancy [7]. During the mean 14-month follow-up period (range 1~162 months), 337 women (33.5 %) had a regression of endometrial polyp [7]. In patients treated with hormonal medication therapy, 55.1 % (247/448) had a regression compared to 16.1 % (90/558) in patients without treatment, and the difference was statistically significant [7]. Additionally, younger age was associated with a higher risk of persistent endometrial polyp [7]. Furthermore, a trend of shortening regression time was apparent in women treated with hormonal medication compared to that in women without treatment (9 months vs. 12 months), although the difference did not reach the statistical significance [7]. Moreover, except at the end of 3-month follow-up (23.3 % vs. 24.3 %), the cumulative percentage of regression at 6, 9 and 12 months seemed to be higher in women treated with hormonal therapy than women without (57.1 % vs. 52.2 %; 75.3 % vs. 65.6 %; 83.4 % vs. 71.1 %, respectively) [7]. Finally, the authors found that oral contraceptives (OCs) may be a better choice if hormonal medication is applied to women with endometrial polyp, since 61.7 % women taking OCs had a success to regress the endometrial polyp compared to 35.5 % women treated with progestin alone did, suggesting that OCs are more effective than other types of hormonal medication in treating women with endometrial polyp [7].

However, the risk of recurrent endometrial polyp after regression seemed to be higher in women treated with hormonal therapy. Except younger age as increased risk of persistent presence of endometrial polyp and recurrence after regression, both hormonal medication and a longer-period follow-up were associated with an increased risk of recurrence after regression [7]. It is not clear to explain why the hormonal therapy is associated with an increased risk of recurrence, but it is easy understanding that a longer follow-up is associated with an increased risk of recurrence.

Endometrial polyp may be a benign condition, and the majority of them are not accompanied with more severe intrauterine pathologies, and this concept is supported by authors. Among their enrolled 1006 subjects, none was complicated with malignant endometrial cancer during the follow-up period [7]. In fact, 56 women had a pathological confirmation, because finally, these women were treated with hysteroscopic transection and removal of these endometrial polyp [7]. Based on the excellent results and lowest risk of intrauterine malignancies, the authors offered the rational and adequate support to show their expectant therapy is a good choice for women with diagnosed endometrial polyp. Although the results of the current study are clear, some uncertainties are worthy of further discussion.

The authors found that hormonal therapy with estrogen and progestin (E + P) combo (either OCs or E + P) is the most effective regimen because this regimen is associated with a higher regression rate of the endometrial poly. But, it is interesting to find that this combo treatment is unexpectedly associated with an increased risk of recurrence. The authors proposed the possible mechanism of E + P regimen for this relatively conflicted findings, and one is beneficial for treating endometrial polyp (regression) in the shorted period but the other is harmful for protective effect in the long term period (high risk of recurrence after regression). Hormonal medication inducing cyclic change of endometrium (withdrawal bleeding or slough of endometrium) can shed the covering structure of endometrial polyp resulting in regression of endometrial polyp but cannot totally interrupt the “regrowth” of the covering structure of the endometrial polyp from the residual stalk of endometrial polyp since this E + P regimen cannot amputate this “stalk” of endometrial polyp, which can be considered as

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"bud" corresponding to the regrowth of endometrial polyp [7]. In fact, to date, the available evidence did not establish the correlation between hormonal therapy and endometrial polyp [10]. One against to the role of hormone is a higher prevalence of endometrial polyp occurred in women using hormonal therapy but the other favoring the role of hormone is a protective role of progesterone, since administration of progesterone is associated with lower risk of developing endometrial polyp, and this positive protection is apparent while levonorgestrel-releasing intrauterine devices has been applied [10,11].

There is no doubt of the coincidence of endometrial cancer and endometrial [10]. The prevalence of premalignant and malignant lesions in patients with endometrial polyps is estimated between 3.4 % and 4.9 % in postmenopausal women and 1.1 % in premenopausal women, respectively [10]. Besides menopausal status, the following parameters are also associated with an increased risk of intrauterine malignancy, including presence of symptom (symptomatic) with odd ratio (OR) of 1.47, age >60 years with OR of 2.41, diabetes mellitus with OR of 1.76, hypertension with OR of 1.50, obesity of OR 1.40 and tamoxifen use of OR of 1.53 [10].

In agreement with the aforementioned finding, the age >50 years of subjects in Dr. Mak's study was only 10.7 %, suggesting that majority of their enrolled subjects were premenopausal, and this age factor contributes to the lower risk of the development of endometrial cancers [7]. Additionally, obesity of subjects was also rare with 17.2 %, which supposed that the enrolled subjects were at low risk for the development of endometrial cancer. Of most importance, all enrolled subjects were asymptomatic, further confirming the lower risk of endometrial cancer in the current study [7]. If the authors could provide additional other factors, such as diabetes, hypertension, tamoxifen use and age >60 years, which are associated with an increased risk of endometrial malignancy in endometrial polyp, the rationale of using expectant therapy for endometrial polyp might be much more stronger. However, the aforementioned critiques do not argue the recommendation by authors, since evidence is enough to propose that the enrolled subjects as shown by the authors are really a good candidate for the expectant management with close follow-up.

Furthermore, the underlying infertility status was also absent in Dr. Mak's study [7]. Although evidence linking hysteroscopic polypectomy to in vitro fertilization (IVF) and embryo transfer (ET) success rates is unclear, a cost-analysis showed hysteroscopic polypectomy is one of the best considerations not only associated with clinical significance but also with cost-effectiveness when performed before intrauterine insemination or IVF over a range of plausible pregnancy rates and procedural costs [10], suggesting that the choice of expectant management should be used in concern for women with needing the assisted reproductive technology (ART) even though they are asymptomatic. Of course, hysteroscopic surgery is not free of the risk, and perforation, postoperative infection, intrauterine adhesion cannot be totally avoided [12,13]. However, with a new technology and adequate postoperative care [14,15], hysteroscopic polypectomy is a safe surgery and nearly all of them can be performed uneventfully.

Taken together, endometrial polyp is a common clinical disease and many of them are diagnosed by accident via routine TVUS examination. Expectant therapy is one of the alternatives, particularly for those women are premenopausal and asymptomatic and also do not need ART for infertility evaluation. Hormonal therapy can be considered, although the recommended regimen is discrepancy between the current study and literature review. We hope more studies would provide a better treatment of choice for those women with asymptomatic endometrial polyp based on the clear criteria to enroll the lowest risk of concomitant endometrial cancer.

Conflicts of interest

All authors declare no conflict of interest.

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Editorial

Chronic pelvic pain and Chinese medicine body constitution deviation

Chronic pelvic pain (CPP), with pain lasting for more 6 months is a complex and possible overlapping disease [1–3]. CPP is common in women with reporting to affect 15–27 % of female population, regardless of age, and result in functional disability and the need for medical care [3]. CPP is considered a major burden in person and socio-economy, partly because of its biggest challenge to medical service with unnecessary but dramatical increased risks of gynecological surgeries and consuming much medication, which are estimated to have at least three-to four-fold increases compared to healthy patients, and partly because of its struggling to accurately diagnose the cause of CPP by physicians [3]. CPP is often accompanied with chronic overlapping pain conditions (COPCs) or secondary to the underlying pathological and/or functional disorders, such as irritable bowel syndrome, major depressive disorders, pelvic inflammatory disease (PID), pelvic venous disorders (also called as nutcracker syndrome, pelvic congestion syndrome and May-Thurner syndrome), interstitial cystitis, painful urinary bladder syndrome, endometriosis, adenomyosis, pelvic adhesion, pelvic floor dysfunction, fibromyalgia, neuropathic pain, chronic lower back pain and others [1–7]. Besides the aforementioned COPCs or underlying pathological disorders, it is frequent to fail to identify any specific etiology for CPP even though extensive systematic review and a series of examinations are performed. As a result, the frustration, ineffective treatment and prolonged pain and suffering for patients occurs, of which condition is referred to as chronic regional pain syndrome or functional somatic pain syndrome due to absence of identified organic and functional causes related to CPP [8]. Due to lack of recognition of CPP and ineffective treatment by modern medicine, traditional Chinese medicine (TCM) is a hope and considered an alternative to restore the body constitution to a balanced state and subsequently interrupt the vicious cycles of CPP and improve quality of life (QoL) [8]. In the September issue of the *Taiwanese Journal of Obstetrics and Gynecology* (*TJOG*), Dr. Chen and colleagues conducted a study to assess the TCM body constitution profiles, demographic characteristics and lifestyle of CPP women to address the risk factors for CPP [8].

Dr. Chen and colleagues enrolled 378 reproductive-aged women with (223 for tolerable pain and 47 for incapacitating pain) or without (n = 108) complaining of CPP to assess the difference of TCM body constitution profiles among three groups [9]. The authors used the following tools, such as the Short Form 36 Health Survey Questionnaire (SF-36), the TCM Body Constitution Deviation (BCQ-44) Questionnaire and the Behavior Rating Scale (BRS) to test their hypothesis [8]. As predicted, QoL evaluated by SF-36 showed those patients with either incapacitating CPP or tolerable pain had a significant impairment of QoL and this observation was found in all evaluated terms, such as physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and metal health [8]. The CPP patients had a significantly higher percentage of late sleeper (after midnight), and sour taste preference [8]. For considering the TCM body constitution, the subjects belonging to the higher Yang-Xu scores (lack of energy) group had preference of sour taste, alcohol drinking, and smoking habit, but did not have habit of regular exercise compared to the subjects with lower Yang-Xu scores [8]. Similarly, the subjects belonging to the higher Yin-Xu (lack of material) had preference of late sleeper, sour taste preference, iced food consumption, fried food consumption, and smoking habits significantly and these subjects also had less frequency of regular exercise [8]. Moreover, in agreement of the observation between higher Yang-Xu or higher Yin-Xu states and the "worse" life-styles, the subjects belonging to the higher phlegm stasis scores (accumulation of pathological products) had a significant increase of favoring sour taste, iced food consumption, and smoking, but those subjects were also unlikely to do regular exercises [8]. All suggest that lifestyles, such as sour taste preference and smoking habit and less frequency of regular exercise were frequently noted among the subjects with higher Yang-Xu scores, higher Yin-Xu, or higher phlegm stasis scores who had positively been correlated with presence of CPP or the severity of CPP. To support the aforementioned positive correlation between the TCM body constitution and CPP, the subjects with organic lesion-associated CPP, such as COPCs, including endometriosis, adenomyosis, uterine fibroids, and PID had statistically or in trend higher Yang-Xu scores, higher Yin-Xu, and higher phlegm stasis scores than the subjects without organic lesion-associated CPP [8]. The current article is particularly interesting and worthy of further discussion.

As shown before [9,10], the authors wanted to present of worse global health of patients with CPP, since they not only found patients with CPP had a statistically significant higher TCM constitution, including higher Yang-Xu scores, Yin-Xu scores, and phlegm stasis scores than healthy controls without CPP, but also found this deteriorated global health in patients with CPP was apparent compared to those patients with pelvic diseases (uterine fibroids, adenomyosis, chocolate cysts, and PID) but without presentation of CPP [9]. Based on this part and agreement with the authors' previous publication [9], CPP patients had really a worse TCM body constitution, regardless of accompanied with and without pelvic diseases. We totally agree that CPP may be an underestimated disorder although CPP had a profound impact on physical health, emotional well-being, and ability to function across family, social and professional roles, notoriously challenging to manage, frustrating patients and physicians alike [10,11]. The difficulty to both physicians and patients with CPP is mainly due to presence

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of COPCs in these CPP patients [10,11]. Therefore, in the current report, the authors further provided evidence to support their hypothesis that the CPP patients had worse TCM body constitutions, regardless whether organic lesion is present or not [8,9], which we concerned the uncertainty why women with CPP had worse TCM body constitutions compared to women with pelvic diseases, such as uterine fibroids, adenomyosis, endometriosis (chocolate cyst) and PID before [10].

The authors found that heavy menstrual bleeding (HMB) was associated with presence of CPP or positively correlated with severity of CPP [8], and this indirect data supported their previous publication about the using levonorgestrel intrauterine devices (LNG-IUD) in the successful management of women with HMB to improve TCM body constitution deviations and also QoL [9]. In fact, the current data indirectly gave an answer that HMB is associated with CPP. HMB patients may have higher Yang-Xu scores, Yin-Xu scores, and phlegm stasis scores, although the difference did not reach the statistical significance in the current study [8].

For CPP subjects, it is not only difficult to make an accurate diagnosis, but also to manage patients with CPP [10]. To obtain the adequate and positive therapeutic effects, physicians should consider the multimodal and multidisciplinary approaches. Multimodal and interdisciplinary therapy includes pharmacotherapy based on disorder-specific Food-Drug Administration (FDA)-approved and non-FDA-approved drugs, nonpharmacological or interventional therapeutic agents and tools, physical therapies, psychological therapies and self-care [12]. Among the above, biopsychological evaluation of factors contributing to pain and modification of life-style are both critical. The latter is always considered one of the best and most cost-effective strategies in the management of CPP patients, and in fact, this strategy is also important for various kinds of chronic illnesses and even life-threatening diseases (cancers, cardiovascular accidents or others) [13–16]. Additionally, faithful and thorough communication with patients and sharing decision-making with patients may be the best step to offer the better therapeutic benefit to patients [10].

Finally, the value of the current study is that the authors establish the relationship between TCM body constitutions and CPP. We congratulated Dr. Chen's success of using TCM body constitutions in the prediction of severity of subjects with CPP and also emphasizing the critical role of altered bad life-styles to healthy life-styles in improvement of global health of CPP women.

Conflicts of interest

All authors declare no conflict of interest.

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Editorial

Subclinical hypothyroidism and outcomes of IVF

Female infertility is an important issue now, since the birth rate has been dramatically dropped in the recent years, particularly in Taiwan [1]. Endocrine disorders exert a substantial impact on the prevalence of female infertility, with thyroid dysfunction emerging as the predominant endocrine disorder in women during the reproductive age [2]. Thyroid disorders affect nearly 14 % of adult women with prevalence rates ranging from 5 % to 7 % for subclinical hypothyroidism, 0.2 %–4.5 % for overt hypothyroidism, 0.3 %–1 % for hyperthyroidism, and 5 %–10 % for thyroid autoimmunity (TAI, presence of thyroid autoantibodies [A-Abs], including anti-thyroid peroxidase and/or anti-thyroglobulin Abs), respectively [2,3]. Besides infertility, thyroid dysfunction has also been linked to other reproductive dysfunction and often associated with ovulatory dysfunction, menstrual disturbance, poor pregnancy outcomes, and gynecological conditions [2,3]. The relationship between thyroid function and female reproductive function may be mediated by direct or indirect ways, since thyroid hormone impacts on various levels of the female reproductive function by a pleiotropic fashion of hypothalamic–pituitary axis [3]. With continuously advanced and improved assisted reproductive techniques (ARTs), infertile couples will be beneficial from the above-mentioned ARTs, particularly widely using *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) technique with following embryo transfer (ET) procedure [4,5]. However, for women who will undergo ARTs, the high estradiol levels induced by controlled ovarian stimulation (COS) may alter thyroid function by increasing the concentration of thyroid-stimulating hormone (TSH), with hypothyroid women being most affected [6–9]. All suggest the thyroid disorders in women may be influence the reproductive outcomes; although several questions remain unclear. New research on this topic continues to emerge [10–12]. Recently, one article piqued our interest and it has been published in the September issue of the *Taiwanese Journal of Obstetrics and Gynecology* (*TJOG*) in 2023, which aimed to investigate the impact of thyroid A-Abs and serum TSH levels on clinical IVF outcomes [11].

The authors conducted a retrospective study to enroll 215 Korean women who underwent the first IVF/ET procedure between 2013 and 2017 [11]. The authors found that both stimulation outcomes (number of total oocyte retrieval, number of mature oocyte, number of fertilized oocyte, number of ET, and number of good-quality ET) and pregnancy outcomes (clinical pregnancy rate, ongoing pregnancy rate and miscarriage rate) between women with presence (n = 29) and absence (n = 186) of thyroid A-Abs were similar [11]. Additionally, the women who were diagnosed with subclinical hypothyroidism (serum TSH $\geq$ 4.2uIU/mL) also had the similar outcomes of stimulation and pregnancy compared to those without, except ongoing pregnancy rate was statistically significantly lower compared to the women without subclinical hypothyroidism [11], suggesting that even subclinical hypothyroidism with euthyroid status may show the negative impact on the reproductive outcomes, particularly for ongoing pregnancy outcomes. However, it is interesting to find that mild form of subclinical hypothyroidism (called as pre-subclinical hypothyroidism), which is defined as TSH $\geq$ 3.4uIU/mL was dramatically correlated with worse pregnancy with a trend to decrease clinical pregnancy rate (39.1 % versus 54.4 %) and a statistically significantly decreased ongoing pregnancy rate (23.9 % versus 46.7 %) and increased miscarriage rate (38.9 % versus 14.1 %) [11], which may be more important for us to consider the need to give consultation and intervention for those women with above upper limit of TSH serum level. If their observation can be further validated, all women who are planned to undergo the IVF/ET protocol may need normalization of their serum TSH levels.

In the current study [11], presence of thyroid A-Abs did not seem to show the negative impact on IVF/ICSI outcomes. In fact, a systematic review and meta-analysis enrolling 14 studies revealed that there was no significant difference in clinical pregnancy rate overall (odd ratio [OR] 0.86; 95 % confidence interval [CI] 0.70–1.05; 11 studies), or in euthyroid women (OR 0.88; 95%CI 0.69,~1.12 10 studies); in clinical miscarriage rate overall (OR 1.04; 95%CI 0.52,~2.07; 8 studies), or in euthyroid women (OR 1.18; 95%CI 0.52,~2.64; 7 studies); in biochemical pregnancy loss (OR 1.14; 95%CI 0.48–2.72; 4 studies), live birth rate per cycle (OR 0.84; 95%CI 0.67–1.06), live birth rate per clinical pregnancy (OR 0.67; 95%CI 0.28–1.60), both overall and in euthyroid women as all studies included consisted of euthyroid women only, compared with women who did not have thyroid A-Abs [13], suggesting that presence of thyroid A-Abs has no effect on stimulation outcome and pregnancy outcomes in euthyroid women alone, or in euthyroid women and women with subclinical hypothyroidism [13].

However, for considering the impact of serum TSH levels to define subclinical hypothyroidism, there is no consensus among endocrinologist and gynecologists regarding the cut-off TSH concentrations for women pursuing pregnancy, where <2.5uIU/mL or <4.0/4.5uIU/mL [14]. Although the above-mentioned uncertainty is found, the use of low-dose or extra-low dose of LT4 seems to be supported by many experts. Dr. Tsai's group used the extra-low dose of levothyroxine (LT4: 25mcg/day) to treat women with subclinical hypothyroidism, which was defined as serum TSH $\geq$ 4.0uIU/mL, who underwent the first IVF/ET procedure and found that these women with subclinical hypothyroidism after extra-low dose of LT4 treatment had the similar stimulation outcomes and pregnancy outcomes compared to those euthyroid

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women (25 % versus 20 % for miscarriage rate and 75 % versus 80 % for live birth rates, respectively) [12], suggesting that extra-low dose of LT4 may be beneficial to women with subclinical hypothyroidism who plan to receive ART procedures.

Evidence suggests that subclinical hypothyroidism may be associated with adverse pregnancy outcomes as shown above, and the relationship between presence of thyroid A-Abs and adverse pregnancy outcomes is not inclusive, although the trend also supports its negative impact of presence of thyroid A-Abs on pregnancy outcome [15]. However, the LT4 supplementation is recommended in infertile women with subclinical hypothyroidism and/or presence of thyroid A-Abs to improve pregnancy when they underwent IVF or ICSI procedure [15]. Based on four published randomized clinical trials (787 infertile women), the authors found women treated with LT4 supplementation had a significantly decreased miscarriage rate relative to those treated with a placebo or no treatment (risk ratio [RR] 0.51, 95%CI 0.32–0.82), although no significant associations of LT4 treatment with the clinical pregnancy rate (RR 1.46, 95%CI 0.86–2.48), live birth rate (RR 2.05, 95%CI 0.96–4.36), or preterm birth rate (RR 1.13, 95%CI 0.65–1.96) [15].

Taken together, women with thyroid disorders are frequently noted in the infertility clinics. Evaluation of serum levels of TSH in subfertile women is recommended because they belong to a high risk of thyroid illness, including asymptomatic infertile ones. The role of LT4 supplementation is worthy of further testing.

Conflicts of interest

All authors declare no conflict of interest.

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Editorial

Conservative treatment for retained gestational tissue following miscarriage or abortion

An estimated over 30 % of women experience abortion and/or miscarriage history [1]. Although it is very common for clinical practice in obstetrics and gynecology clinics, miscarriage and/or abortion is still a biggest health and economic issue in the world, partly because abortion itself and abortion-related procedure not only damage the global health of affected women but also result in heavy psychological and social burden [1]. Additionally, it is the fourth leading cause of maternal mortality in the world [1]. Many causes are associated with miscarriage and abortion, including maternal factors, embryo factors, and socio-psychological factors [1–4]. No people will be in doubt that an unwanted pregnancy still plays a major role for requesting abortion procedure [1–4]. To provide the access for safe pregnancy services, particularly for those women with miscarriage and/or abortion, the awareness about safe pregnancy (abortion) services and post-abortion care is of the critical importance. We welcome the publication in the 2023 *Taiwanese Journal of Obstetrics and Gynecology* (*TJOG*), which addressed the important issue and discussed the management strategy for women with vascular retained products of conception (RPOC) following miscarriage and/or abortion [5].

The authors enrolled 35 women with RPOC, and 30 had presented with vaginal bleeding and 6 (one sixth) were complicated with heavy bleeding needing inpatient management [5]. The authors used the EPT (estrogen + progestin therapy) regimen, including conjugated estrogen (0.625 mg tablet twice a day) and norethisterone (5 mg tablet once a day) in the management of women with symptomatic RPOC [5]. The treatment duration was ranged from 10 days to 30 days, which was considered as one cycle dependent on the findings of follow-up ultrasound and this regimen will induce the withdrawal bleeding [5]. Some of women needed an additional cycle to expel the remaining RPOC [5]. The first course of EPT could stop 90 % (27/30) of women with RPOC complicated with vaginal spotting successfully, and result in two thirds (23/35) of women who had been cured, of whom were diagnosed with a thin and linear endometrium by follow-up ultrasound [5]. The remaining women (34 %, n = 12) were also cured by the additional course of EPT [5]. Based on the aforementioned promising results, the authors concluded that the retained tissues of women with RPOC can be successfully managed by oral administration of EPT, since this strategy not only provided a high response rate to stop vaginal bleeding but also induced spontaneous expulsion of the retained tissue of women with RPOC [5]. The current study is interesting and worthy of further discussion.

First of all, it is not easy to make an accurate diagnosis of RPOC, since the sensitivity and specificity of the ultrasound examination range from 44–85 % and 88–92 %, respectively [6,7]. In the Yamaguchi's study, we do not know how many women with RPOC really had a residual trophoblastic tissue (main components of RPOC) [5], although traditionally, the diagnosis of RPOC can be made based on clinical signs and ultrasound examination (echogenic focus and distension of the uterine cavity and flow parameters) [7], as shown by Dr. Yamaguchi [5]. Additionally, serum hCG (human chorionic gonadotropin) was very low in their enrolled patients and the data ranged from <0.5 mIU/mL to 427 mIU/mL, further supporting that there were some women did not have any residual trophoblastic tissue within the uterine cavity in their study. Moreover, serum progesterone levels were also low and the value ranged from <0.1 ng/mL to 13.3 ng/mL, also revealing that little or extremely scarce of residual gestational trophoblast tissue was found in certain percentage of women in the current study, and all may be the reason why the authors could use EPT strategy in the successful treatment for women with "supposed" RPOC. We suggest that 100 % of the success rate in the current study using EPT regimen for treating women with RPOC, although promising, needs further validation.

Following the above-mentioned issue, the current study recommended EPT may be an effective protocol in the management of women with RPOC [5]; however, this treatment is not frequently applied in the current clinical practice. Traditionally, the administration of uterotonics for women with RPOC is more frequently used in our daily routine work. One randomized clinical trial was conducted to compare the effectiveness and safety of repeat misoprostol versus expectant management in women with first-trimester incomplete miscarriage (similar to RPOC status) and the results showed the women treated with misoprostol (prostaglandin E1) had a higher successful expulsion rate then women without (69 % versus 16.7 %) one week later after randomization [8], suggesting that uterotonics may be a better choice compared to expectant management. Although so far, there is absence of any clinical trial to compare the effectiveness and safety of using uterotonics or EPT in the management of women with RPOC, we believe uterotonics are winner. In fact, EPT is frequently applied in women with acute and heavy vaginal bleeding, either secondary to dysfunctional uterine bleeding (menstruation-related heavy bleeding) or secondary to post-abortion (post-uterine operation) bleeding due to the consideration of defective endometrium based on the better understanding of pathophysiology for cyclic change of endometrium (defect or impaired synchronism of cyclic change of endometrium), since recent publications had extensively reviewed or reported the

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aforementioned clinical situations [9–12]. Moreover, the management of first trimester abortion via medical methods can offer more evidence about this debated issue. A recent meta-analysis summarized the effectiveness and effects of different medical methods for first trimester abortion, and data showed combined regimens (prostaglandin combined with mifepristone, letrozole, estradiol valerate, tamoxifen, or methotrexate) may be more effective than single agents (prostaglandin alone or mifepristone alone) [13], suggesting that uterotonics (prostaglandin) may be a critical component for the purpose to succeed to induce abortion via medical treatment. The result from this meta-analysis further confirmed the critical role of uterotonics in the management of women with an early conception, regardless whether it is successful or defective. Since the RPOC is complicated by retaining residual gestational trophoblast tissue after miscarriage and/or abortion, and even postpartum from the delivery, it is rationale to suppose that the standard medical treatment for RPOC is still a regimen which should include uterotonic agents.

The aforementioned evidence seemed not to support the EPT as a treatment alternative in the management of women with RPOC, we do not argue the potential effectiveness of EPT regimen for treating women with RPOC as shown by authors. Similar to previous publication addressing the intrauterine pathologies [14], EPT inducing cyclic change of endometrium can pave the defective endometrium attaching to RPOC to stop the vaginal bleeding (similar to breakthrough bleeding or breakdown of defective endometrium) and then make the adhesive structure of RPOC into the endometrium slough away from the uterine cavity (similar to withdrawal bleeding after complete estrogen and progesterone cyclic stimulation) to clean out the RPOC.

Taken together, RPOC is a rare clinical disease and many of them are diagnosed by clinical diagnosis without pathological confirmation. Expectant therapy and/or conservative medical treatment should be always taken into consideration, because surgical intervention may be correlated with a significant increase of operation-related adverse events and side effects, such as intrauterine synechia, uterine perforation and others [14,15]. Although EPT is suggested by authors, we believe that the recommended regimen should contain uterotonic agents. We hope more studies would provide a better choice of treatment for those women with symptomatic RPOC based on the clear criteria and solid data. These further studies may have adequate evidence to respond to this uncertain issue.

Conflicts of interest

All authors declare no conflict of interest.

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Review Article

Front-line chemoimmunotherapy for treating epithelial ovarian cancer: Part II promising results of phase 2 study of paclitaxel-carboplatin-oregovomab regimen

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ABSTRACT

In the Part I, we have discussed the background of CA125 and the development of anti-CA125 monoclonal antibody (MAb) to highlight the potential role of CA125 and anti-CA125 MAb in the management of women with advanced stage epithelial ovarian cancer (EOC). Glycosylation change either by *N*-link or by *O*-link of CA125 is supposed to play a role in the modification of immunity. Anti-CA125 MAb, which can be classified as OC 125-like Abs, M11-like Abs, and OV197-like Abs, is often used for diagnosing, screening, monitoring and detecting the mesothelin-related diseases of the abdominal cavity, particular for those women with EOC. Additionally, anti-CA125 MAb also plays a therapeutic role, named as OvaRex MAb-B43.13 (oregovomab), which has also been extensively reviewed in the Part I review article. The main mechanisms include (a) forming CA125 immune complexes to activate the antigen-presenting cells; (b) triggering induction of CA125-specific immune responses, including anti-CA125 Abs against various epitopes and CA125-specific B and T cell responses; and (c) triggering CD4 and CD8 T-cell responses specific for B43.13 to produce specific and non-specific immune response. With success *in vitro*, *in vivo* and in primitive studies, phase II study was conducted to test the effectiveness of chemoimmunotherapy (CIT) for the management of EOC patients. In the 97 EOC patients after optimal debulking surgery (residual tumor <1 cm or no gross residual tumor), patients treated with CIT had a dramatical and statistically significant improvement of both progression-free survival (PFS) and overall survival (OS) compared to those treated with chemotherapy alone with a median PFS of 41.8 months versus 12.2 months (hazard ratio [HR] 0.46, 95 % confidence interval [CI] 0.28–0.7) and OS not yet been reached (NE) versus 42.3 months (HR 0.35, 95 % CI 0.16–0.74), respectively. The current review as Part II will explore the possibility of using CIT as front-line therapy in the management of advanced-stage EOC patients after maximal cytoreductive surgery based on the evidence by many phase 2 studies.

Introduction

Although cancer treatment has been far-advanced recently, particularly after an introduction of immunotherapy (IT) and/or targeted therapy into the clinical practice for treating various kinds of cancers [1–9], epithelial ovarian cancer (EOC) is still the most lethal of the gynecologic cancers, partly because the advance-

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related success and/or promising therapeutic effect (IT and targeted therapy), unlikely to other cancers, such as gastric cancer, endometrial cancer, cervical cancer, and breast cancer etc., is not successfully or totally reproducible to the EOC patients [10–15]. So far, the cornerstone of primary treatment for EOC is still based on the successful and complete cytoreduction of tumors and following adjuvant platinum-based chemotherapy (carboplatin plus paclitaxel regimen, paclitaxel-carboplatin regimen-PC regimen) with or without an angiogenesis inhibitor, such as bevacizumab [14,15]. To achieve the optimal therapeutic effectiveness, maximal cytoreduction surgery and following front-line chemotherapy by PC regimen should be completed (at least six cycles) [15]. After completing primary therapy (maximal cytoreductive surgery plus postoperative adjuvant PC regimen therapy), more than 75 % of patients can reach a clinical complete remission [15]. However, the clinical complete remission is short. The majority of patients will recur within the three years after completing primary therapy [16]. A median progression-free survival (PFS) and/or disease-free survival (DFS) is ranged from 12 to 18 months [16], contributing to the worse outcomes, even though an intensive and aggressive treatment, such as the second-line therapy has been applied. More than half of patients will die within 5 years after primary treatment, resulting in 40.7 months of a median overall survival (OS) [16].

Although some advanced therapeutic agents are available in clinical practice, the standard-of-care front-line therapy for EOC remains unchanged in the past three decades [15]. In fact, many efforts attempted to search for the better front-line therapies for EOC patients, such as the use of triple chemotherapeutic agents (triplet therapy, such as carboplatin + paclitaxel + gemcitabine), the use of intraperitoneal route to administer chemotherapy, the use of dose-dense chemotherapy by a shorten therapeutic period and an increased dosage of chemotherapy, and intraperitoneal hyperthermia treatment [15,17–21], but the therapeutic effect is not consistent. Additionally, the costs and risks are significantly increased when the EOC patients have been treated with the forementioned modifications. The unacceptable benefit/risk ratio results in no change of the standard front-line therapy for treating EOC patients in the past three decades [15].

Recently, an advanced and better understanding of pathophysiology of cancers as well as continuous improvement of biochemical technology has resulted in a new development of molecules, bioagents, and biochemical agents to target the specific cancer-specific antigens, attack the underlying repair system of cancer cells, inhibit the angiogenesis, change the interaction between surrounding cells and cancer cells, modify behaviors of cancer cells, enhance immune clearance ability, augment the therapeutic effect of the original chemotherapy with complex engineered molecules that consist of monoclonal antibody (MAb) directed toward or targeted tumor-associated antigens, conjugated via a stable linker to a potent cytotoxic agent (antibody drug conjugates [ADCs]) in the cancer research [15,22–46]. Various kinds of cancer can be well controlled and moreover, many of cancers can be cured, even though previous conventional therapy has a limited therapeutic effect. However, except a big success obtained from poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) and/or antiangiogenic agent, bevacizumab in the certain-type subgroup of advanced-stage EOC patients [15,22,45], the therapeutic effects are not successful and some of them eventually are out of markets. Additionally, these magnetic agents (PARPi or bevacizumab) are considered as maintenance therapy and cannot be classified as the front-line therapy. Therefore, the optimal front-line therapy for EOC is still unavailable yet. Among these, IT, although the previous clinical trials didnot satisfy the clinical use based on IT alone yielding little effect on solid tumor, regardless of using it as adjuvant therapy or maintenance therapy. Additionally, primary and acquired resistance of IT (particularly for those immune checkpoint inhibitors [ICIs]) has been found, resulting in the therapeutic failure, particular for those EOC patients [46]. Based on the disappointing results of IT for EOC patients, another choice, such as combination of chemotherapy and immunotherapy (chemoimmunotherapy [CIT]) has been attempted to evaluate the therapeutic effects of this combination. Fortunately, CIT seemed to work well because IT has shown the potentiated therapeutic effects combined with chemotherapy. However, the above-mentioned vision needs further validation and approval, contributing to no change of the front-line therapy of EOC yet. In fact, conventional chemotherapy has been the cornerstone of cancer treatment for more than 70 years.

The current review as Part II, particularly focusing on real world clinical data will explore the rationale and new advance about using CIT as front-line therapy to treat patients with advanced-stage EOC.

The background of chemoimmunotherapy (CIT)

chemoimmunotherapy (CIT), combining traditional chemotherapy with IT is an emerging treatment option for cancer [46]. Many excellent reviews either by Dr. Sordo-Bahamonde or by Dr. Liu provide the rational of this combination, including (a) chemotherapy may potential the efficacy of IT mediated by easy elimination by immune cells because of decreased burden of tumor mass, decreased number of tumor cells, reduced immunosuppressed factors produced by tumor cells and enhancing the antigenicity of tumor cells; (b) chemotherapy may boost antitumor immunity via modulating immune systems, such as trafficking and infiltration of immune effector cells, activating T cell response, activating natural killer cells which cause immunogenic cell death through the exposure and release of danger-associated molecular patterns and stimulate antigen presentation through dendritic cells and T cells, depleting immunosuppressive cells (mostly T regulatory cells and myeloid-derived suppressor cells) and dampening the immunosuppressive tumor microenvironment [46,47]. At the same time, IT may injury the substantial barriers that hinder the penetration of chemotherapeutic agents, overcome immune resistance to chemotherapeutic agents and off-target immunosuppressive side effects of chemotherapeutic agents [47]. Combination of ICIs and traditional chemotherapy may be one of the most well-known and popular regimens in clinical cancer treatment, particularly in some difficult-to-treat cancers [46,47]. The main advantage of this combination (CIT) is no or few additional overlapping toxicities (adverse events: AEs) between each drugs [46,47].

The first and foremost success of CIT (combination of chemotherapy and ICI) has been achieved in lung cancer treatment [41,48–50]. A recent systematic review and meta-analysis enrolling 53 trials (seven randomized, 29 prospective nonrandomized, and 17 retrospective studies) showed that non-small cell lung cancer (NSCLC) patients treated with neoadjuvant CIT had a statistically significantly higher rate of major pathological response rate (MPR, the pooled MPR rate of 53.8 %, 95 % confidence interval [CI] 47.0 % ~59.6 %) than those treated with neoadjuvant chemotherapy (NACT) with odd ratio (OR) of 6.19 (95 % CI 4.39–8.74), contributing to better PFS and OS in NSCLC patients treated with CIT (hazard ratio [HR] 0.28, 95 % CI 0.10–0.79; HR 0.80, 95 % CI 0.72–0.88, respectively) [48]. In fact, neoadjuvant CIT applied to patients with NSCLC not only seem to achieve population-wide treating coverage irrespective of program death ligand 1 (PD-L1) expression but also enable achieving a pathological complete response (pCR), resulting in using neoadjuvant CIT as mainstream in the treatment of NSCLC [48,49]. CIT takes significant advantages of MPR, pCR, PFS (DFS) and OS in NSCLC patients compared to chemotherapy alone [48,49], and these benefits are also reproducible and apparent in extensive stage

small cell lung cancer (ES-SCLC) patients [50]. A meta-analysis enrolling eight studies and including 3952 ES-SCLC participants showed that ES-SCLC patients treated with CIT had better PFS and OS than those treated with chemotherapy alone (5.15 months versus 4.5 months with HR 0.75, 95 % CI 0.70–0.80 for PFS; 9.1–15.4 months versus 8.5–12.8 months with HR 0.79, 95 % CI 0.73–0.85 for OS, respectively) [49]. Additionally, the aforementioned advancements in survival and efficacy come without significant impairment in quality of life (QoL) or increases in treatment-related AEs, suggesting that CIT to SCLC treatment may continue to improve survival and alleviate symptom burden in ES-SCLE patients [50].

Besides the success of CIT in the management of SCLC and NSCLC patients, there are many other cancers which are beneficial to CIT treatment, including triple negative breast cancer (pembrolizumab or atezolizumab), head and neck squamous cell carcinoma (SCC), digestive malignancies (esophageal adenocarcinoma, esophageal SCC, gastroesophageal junction adenocarcinoma, gastric adenocarcinoma, and biliary tract cancer by pembrolizumab or nivolumab), and cervical cancer (pembrolizumab), compared to conventional chemotherapy alone [46]. However, all above-mentioned CITs can be considered as ICI-based chemotherapy, because CITs consist of two main essential components. One is traditional chemotherapy and the other one is ICIs. Compared with other above-mentioned cancers, the outcomes of EOC patients treated with ICIs-based chemotherapy seemed to yield inconsistent benefits [46]. Additionally, optimal conditions for CIT for EOC are unknown and remain inclusive. Moreover, no consensus has yet been achieved regarding the optimal dose, appropriate timing, and sequence of CIT combinations (simultaneously, delayed and precedingly) that may maximize the clinical benefits [46]. Therefore, there is still a long way to go for the use of CIT in the management of EOC patients.

In the Part I, we have introduced the recent development of oregovomab (MAb B43.13) and potentially acting actively for patients with advanced-stage EOC accompanied with elevated CA125 (carbohydrate antigen 125 or cancer antigen 125) levels [15]. The following review is conducted continuously to show the clinical advance about the oregovomab in combination of chemotherapy in the management of EOC patients.

The pre-clinical trials and clinical observation about the use of oregovomab with or without combination of chemotherapy for treating EOC patients

We have previously reviewed the development of oregovomab extensively [15]. The key and active component of oregovomab is murine MAb-B43.13, an IgG1k subclass immunoglobulin (OvaRex MAb-B43.13; named as Ab1, Unither Pharmaceuticals, Wellesley Hills, MA), binding the glycosylated region of MUC16 with high affinity (1.16×10^{10}/M), and induces indirect immune responses via an anti-idiotype antibody induction cascade [51–57]. In 1993, Dr. Baum first attempted to use oregovomab in the management of far-advanced or recurrent EOC patients [54]. A series of their studies showed the presence and particularly accompanied with higher titers of anti-oregovomab Ab (human anti-mouse Ab [HAMA], named as anti-MAb B43.13 Abs and called Ab2 which is responsible to direct immunity and which in turn anti-anti-MAb B43.13 Abs [anti-anti-idiotype Abs], named as Ab3, which recognized the original MUC16 antigen, resulting in immune cell-mediated killing of MUC16-expressing tumor cells) reaction was associated with tumor regression and both presence and higher titers are associated with the therapeutic effectiveness [54–57]. The work of oregovomab on EOC patients not only induces CA 125-specific cellular and humoral response of patients but also activates the interferon gamma (IFN-γ) production and subsequently upregulates the expression of major histocompatibility complex (MHC) I, MHC II (also called as HLA I and II, human leucocyte antigen I and II), and intercellular adhesion molecule (ICAM) I of ovarian cancer cells [57–66]. All enhance the cytotoxicity of host immune system to the ovarian cancer cells. Dr. Gordon further found that the use of oregovomab with or without concomitant chemotherapy to EOC patients may prolong the survival of these patients and of the most importance, this combination therapy does not add additional AEs. All suggest well tolerability of EOC patients when they were treated with oregovomab, regardless of whether chemotherapy is added or not [63].

Besides the effects of IT by pure form of MAb B43.13 [54–66], the modification of MAb B43.13 has further expanded its potentiality in clinical practice or management of EOC. For example, MAb B43.13 carries radio-isotopes have unique localization and therapeutic potential [67]. The ^{188}Re (rhenium)-MAb-B43.13 product retains its biochemical purity, its immunoreactivity and presented with a typical stability and biodistribution profile, suggesting the possible clinical setting in using immunoradiotherapy for EOC patients [67]. Additionally, MAb B43.13 is also capable of facile radiolabelling with 99 Tcm and has been shown to localize in the tumors of EOC patients successfully [68]. A pharmacokinetic analysis indicated a shorter residence time and higher clearance of (99m)Tc-MAb-B43.13 that was ascribed in part to the circulating CA125 antigen in this group of ovarian cancer patients [69]. MAb B43.13 is attempted to be encapsulated in poly (DL-lactic-co-glycolic acid) microspheres resulting in enhanced humoral and cellular immune responses compared with MAb B43.13 alone or MAb B43.13 mixed with microspheres [70]. Moreover, MAb B43.13 is also modified as bispecific Abs with specificity for tumor antigen CA 125 and CD3 (cytotoxic T lymphocytes [CTL]) to destroy ovarian cancer cells [71]. Taken together, all suggest that specificity and sensitivity of using MAb B43.13 for diagnosing and treating EOC patients. Fig. 1 showed the development of MAb B43.13 in the treating advanced-stage EOC patients.

The phase 2 clinical trials about the use of oregovomab with or without combination of chemotherapy for treating recurrent EOC patients

An open-label, prospective, single arm phase II study designed to evaluate the humoral and cellular immune responses induced by oregovomab treatment in 20 women with advanced recurrent EOC who had previously responded to platinum-based chemotherapy and the results showed the median disease progression interval was 11 weeks, ranging from 2.6 weeks to 114.6 weeks, and a median OS was 70.4 weeks, ranging from 4.6 weeks to 141.6 weeks [63]. If patients who mounted a T-cell response to CA125 and/or autologous tumor showed significantly improved survival (median not reached versus 51.9 weeks, compared to patients who did not [63].

Another pilot phase 2 study conducted by Dr. Ehlen enrolling 13 heavily pre-treated women with recurrent EOC showed a median time to disease progression was 8.4 weeks (range from 2 to 61 weeks, 95 % CI 4.3–12.3 weeks), and OS ranged from 11 to 110 weeks with a median of 37 weeks (95 % CI 28.7–70.4 weeks) [72]. In this study, the authors found the safety profile of oregovomab did not overlap with toxicities common to cytotoxic chemotherapies, and suggest that oregovomab would be well tolerated when administered serially or concurrently with chemotherapy for treatment of recurrent EOC patients and that serial dosing to extend the chemotherapy-free interval would not negatively impact eh ability to later deliver salvage chemotherapy [72].

Berek and coworkers conducted a phase 2 clinical trial to evaluate the using oregovomab as maintenance therapy in the management of 145 advanced stage EOC patients with complete clinical

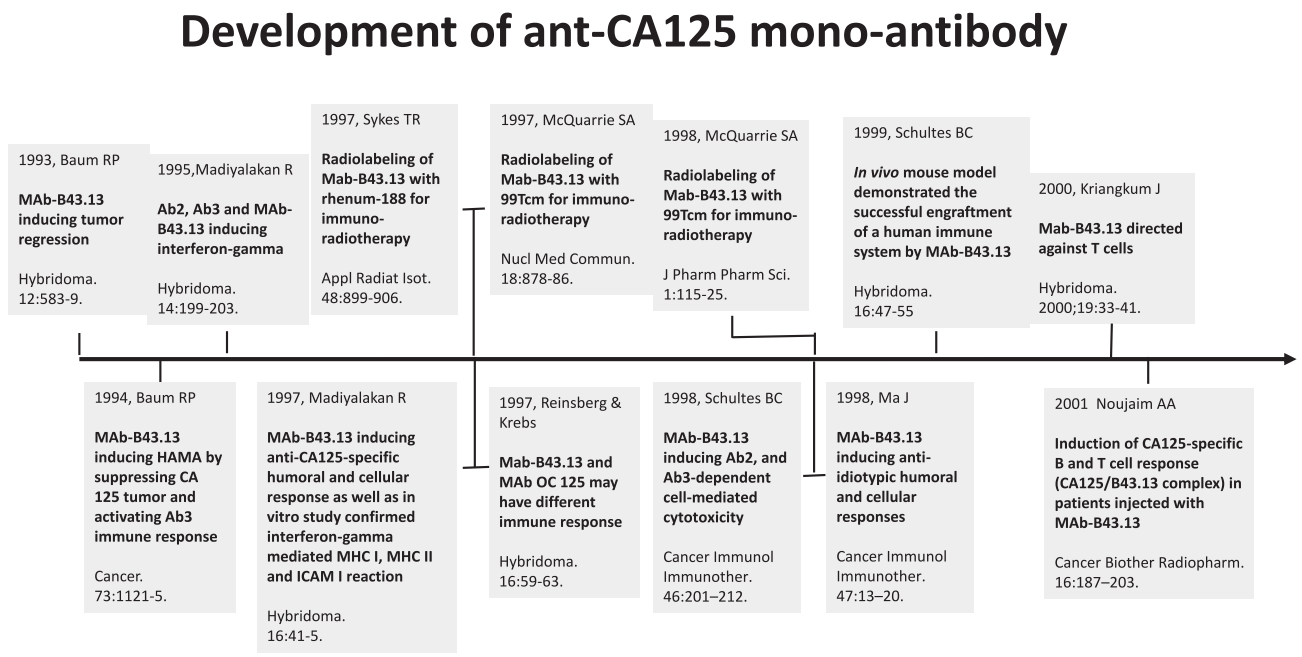

Fig. 1. Development of anti-CA125 mono-antibody (Oregovoma) for the treatment of epithelial ovarian cancer (EOC) patients. MAb: monoclonal antibody; HAMA: human anti-mouse antibody; Ab: antibody; CA125: carbohydrate antigen 125 or cancer antigen 125; OC: ovarian cancer; MHC: major histocompatibility complex; ICAM: intercellular adhesion molecule.

response to primary treatment, who were randomly assigned to oregovomab or placebo administered at weeks 0, 4, and 8, and every 12 weeks up to 2 years or until recurrence [73]. A median PFS was similar between two groups (13.3 months for oregovomab versus 10.3 months for placebo), suggesting that oregovomab maintenance mono-IT does not improve outcomes in advanced stage EOC patients in this phase 2 study [73]. However, the authors identified the favorable prognostic indicators for the successful front-line therapy (SELT) population, including a better performance status, CA125 before third cycle, and baseline CA125 (24 months in the oregovomab group compared with 10.8 months for placebo [unadjusted HR of 0.54, 95 % CI 0.29–1.03]), contributing to the establishment of a following phase 3 study, which will introduce in the next section. Although the results of the phase 3 study using oregovomab maintenance mono-IT are relatively disappointing [74], the modification of strategy (combination of mono-IT and chemotherapy) in using anti-CA125 MAb for the EOC patients has dramatically changed based on findings of the following phase 2 study [75].

Braly and co-workers in their phase 2 study (n = 40) found that front-line chemotherapy with carboplatin-paclitaxel has immune adjuvant properties when combined with oregovomab IT (as CIT) and additionally, schedule of CIT is very important and simultaneous infusion of oregovomab at the chemotherapy day is preferred, not only association with better cellular and humoral immune responses but also associated with a better outcome [75]. With the aforementioned concept (simultaneous administration of oregovomab and chemotherapy as CIT front-line therapy), Brewer and co-workers conducted a QPT-ORE-002 multi-site phase 2 randomized study (n = 97) to test the hypothesis that schedule dependent CIT with oregovomab improves PFS and OS in optimally resected advanced stage EOC, and the results, as expected showed unexpected large therapeutic effects of CIT front-line therapy (paclitaxel-carboplatin-oregovomab) in terms of PFS and OS than those of front-line chemotherapy alone, with median PFS of 41.8 months (95 % CI 21.8 ~ not reached) for CIT and 12.2 months (95 % CI 10.4–18.6) for chemotherapy (HR 0.46, 95 % CI 0.28–0.70) and the median OS of not reached (95 % CI 45.2~not reached) for CIT and 43.2 months (95 % CI 31.8~NE) for chemotherapy alone (HR 0.35, 95 % CI 0.16–0.74) [45].

Battaglia and colleagues added an Italian cohort to explain the aforementioned dramatical therapeutic effects of front-line CIT for optimally resected advanced stage EOC patients and demonstrated that adding oregovomab to chemotherapy resulted in increased patient numbers with amplified CA125-specific $CD8^{+}$T lymphocytes/ml peripheral blood counts, which might explain the improved therapeutic effect of CIT over chemotherapy alone [76]. The authors further provided a predictive model for oregovomab efficacy, as a less suppressive immune environment at baseline as indicated by low numbers of circulating myeloid-derived suppressor cells, subset type 4, and a low neutrophil-and-monocyte to lymphocyte ratio [76]. All advances about using CIT by paclitaxel-carboplatin-oregovomab regimen in the management of EOC patients have shown as Fig. 2.

Disappointing results of early phase 3 study (maintenance therapy) and expecting impressive results of the new phase 3 study (CIT as front-line therapy)

In the early phase 3 study conducted by Berek, the results were relatively disappointing, since data showed oregovomab maintenance mono-IT does (2 mg of oregovomab or placebo infused over 20 min at weeks 0, 4, and 8 and then 12 weeks after primary treatment) not improve outcomes in a highly selected advanced stage EOC (SELT) population (n = 373) with 10.3 months (95 % CI 9.7–13.0 months) for oregovomab and 12.9 months (95 % CI 10.1–17.4 months) for placebo [74]. Although this phase 3 study showed the strategy of mono-IT is not effective as maintenance therapy after front-line therapy, the authors think that this tumor-antigen specific immunotherapy should seek ways to further augment induced immunity [74].

By contrast, in the previous section, we demonstrated that the phase 2 study (NCT01616393) is very much impressive and amazing and the results of this phase 2 study demonstrated the strong evidence supporting using front-line CIT as a better choice

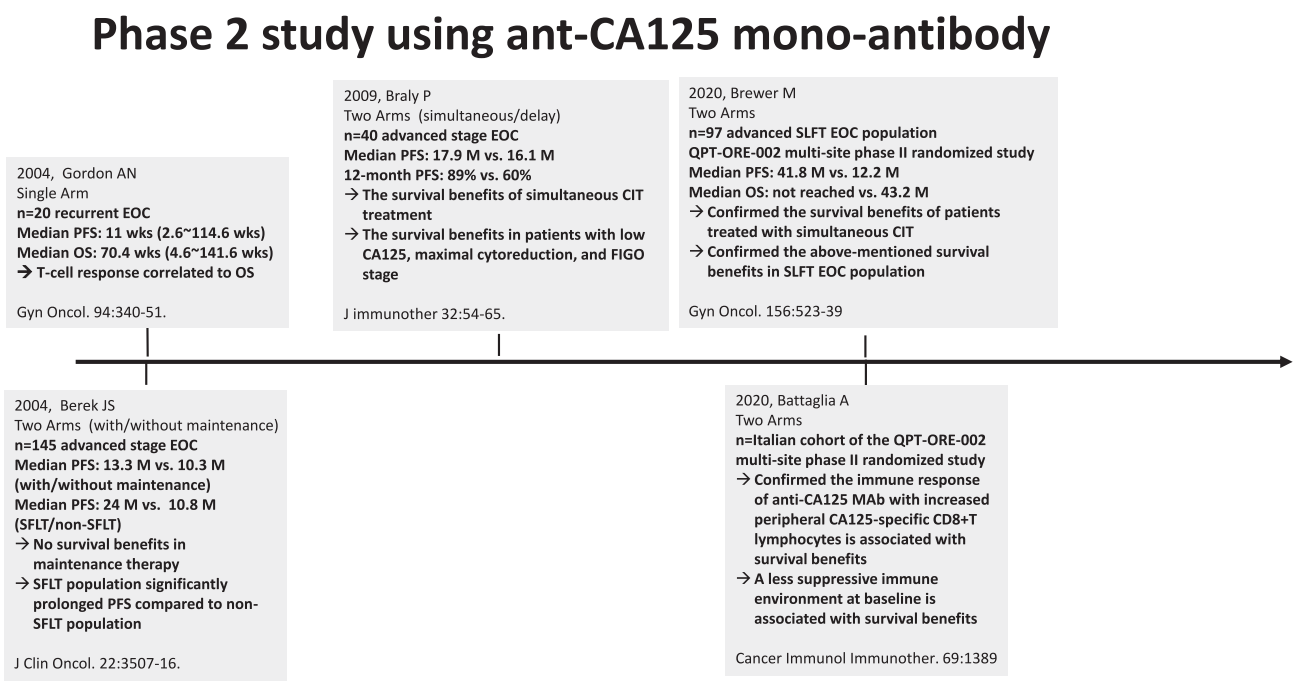

Fig. 2. Phase 2 study of using oregovomab for the treatment of epithelial ovarian cancer (EOC) patients. n: number of the subjects; PFS: progression-free survival; wks: weeks; OS: overall survival; M: months; SFLT: successful front-line therapy, including optimal debulking surgery (microscopic residual or absence of residual tumors after maximal cytoreductive surgery), favorable response to chemotherapy as assessed by serum CA125 $\leq$ 65 U/mL before third cycle, and normalized but measurable CA125 at study entry (CA125 > 5 and $\leq$ 35 U/mL); FIGO: the International Federation of Gynecology and Obstetrics; CIT: chemoimmunotherapy; MAb: monoclonal antibody.

compared to using front line chemotherapy for optimally resected advanced stage EOC patients, the FLORA-5 (NCT 04498117), the definitive confirmatory global registration trial (phase 3 study), recruited patients in the front-line setting, including oregovomab/placebo is administered simultaneously at cycles 1, 3, and 5 of chemotherapy with a single maintenance dose at 12 weeks following cycle 5 in Cohort 1 and neoadjuvant patients (Cohort 2) is administered oregovomab/placebo post interval debulking surgery at cycles 4 and 6 with maintenance doses at 6- and 18-weeks following cycle 6 [77]. In this year, Gregory and coworkers further clearly demonstrate FLORA-5 entitled "oregovomab plus chemo in newly diagnosed patients with advanced EOC following optimal debulking surgery in more detail and attempted to confirm the safety and efficacy of oregovomab in combination with systemic chemotherapy [78]. The authors proposed the pre-specified PFS benefit of 11 months for the front-line therapy (n = 372, randomised in 1:1) and 9.3 months for NACT plus optimal interval cytoreductive surgery plus adjuvant therapy (n = 230, randomized in 1:1) should be achieved to change the standard of care for advanced stage EOC [78]. We are looking forward to seeing these data to change the 30-year standard front-line therapy for advanced stage EOC patients.

Conclusion

The oral treatments as PARPi have recently been approved in the EOC first line maintenance therapy for patients with BRCA mutation after primary treatment; however, more than three-quarters of patients do not have BRCA mutation, who may not be beneficial for PARPi therapy. Additionally, the standard of care front line therapy is still not altered. Based on the easy management for the toxicity profile while adding oregovomab into conventional chemotherapy as CIT, CIT (paclitaxel-carboplatin-oregovomab regimen) is an ideal candidate to become the standard-of-care front-line therapy for further management of advanced stage EOC patients after maximal cytoreductive surgery.

Declaration of competing interest

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Review Article

Chromosomal abnormalities associated with fetal megacystis

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ABSTRACT

Fetal megacystis has been reported to be associated with chromosomal abnormalities, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), obstructive uropathy, prune belly syndrome, cloacal anomalies, limb-body wall complex, amniotic band syndrome, anorectal malformations, VACTERL association (vertebral anomalies, anal atresia, cardiac malformations, tracheo-esophageal fistula, renal anomalies and limb abnormalities) and fetal overgrowth syndrome such as Bechwith-Wiedemann syndrome and Sotos syndrome. This review provides an overview of chromosomal abnormalities associated with fetal megacystis which is useful for genetic counseling and fetal therapy at prenatal diagnosis of fetal megacystis.

Introduction

Fetal megacystis has been reported to be associated with chromosomal abnormalities, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), obstructive uropathy, prune belly syndrome, cloacal anomalies, limb-body wall complex, amniotic band syndrome, anorectal malformations, VACTERL association (vertebral anomalies, anal atresia, cardiac malformations, tracheo-esophageal fistula, renal anomalies and limb abnormalities) and fetal overgrowth syndrome such as Bechwith-Wiedemann syndrome and Sotos syndrome [1–12].

In a systemic review of fetal megacystis, Taghavi et al. [8] reported an estimated first-trimester prevalence of fetal megacystis of 1/330–1/1670 with a male/female ratio of 8/1. Taghavi et al. [8] additionally reported the common underlying diagnosis including urethral valves (57 %), urethral atresia/stenosis (7 %), prune belly syndrome (4 %), MMIHS (1 %), cloacal anomalies (0.7 %) and chromosomal anomalies (15 %) such as trisomy 18, trisomy 13 and trisomy 21. Therefore, genetic diagnosis of genetic abnormalities associated with fetal megacystis is helpful in elucidating genotype–phenotype correlations in cases with fetal megacystis detected by prenatal ultrasound.

Chromosomal abnormalities

The incidence of chromosomal abnormalities in association with fetal megacystis or low urinary tract obstruction has been reported to be 7%–20 % [8,10,13,14]. Fetal megacystis has been well described to be in association with chromosomal abnormalities. Chen et al. [3] reported isochromosome 18q in a fetus with congenital megacystis, intrauterine growth retardation (IUGR) and cloacal dysgenesis sequence, which provides evidence for the disturbance of the caudal developmental field and the chromosomal abnormality with monosomy 18p and trisomy 18q. Sebire et al. [15] found fetal megacystis in 15 of 24,492 (1/1633) pregnancies of which chromosomal abnormalities occurred in 3/15 (20 %) cases including trisomy 18 (n = 1), trisomy 13 (n = 1) and unbalanced 14/20 translocation (n = 1). Favre et al. [16] found chromosomal abnormalities in 4/15 (26.7 %) cases of fetal megacystis at 11–15 weeks of gestation including trisomy 13 (n = 2), trisomy 18 (n = 1) and trisomy 21 (n = 1). Papageorghiou et al. [17] found fetal megacystis in 21/181 (11.6 %) cases of fetal trisomy 13 in the first trimester. Boissier et al. [18] found chromosomal abnormalities in 3/12 cases (25 %) of fetal megacystis in the first trimester including trisomy 18 (n = 2) and trisomy 21 (n = 1). Sánchez-Prieto et al. [12] found chromosomal abnormalities in 3/16 cases (19 %) of fetal megacystis including trisomy 18 (n = 2) and trisomy 21 (n = 1).

In a study of chromosomal abnormalities and outcome according to bladder length in 145 cases of fetal megacystis at 10–14

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weeks of gestation, Liao et al. [13] found chromosomal abnormalities such as trisomy 13 (n = 17), trisomy 18 (n = 7), trisomy 21 (n = 2), triploidy (n = 1), trisomy 4 (n = 1), mosaic trisomy 15 (n = 1) and unbalanced 14/20 translocation (n = 1) in 30 cases with an incidence of chromosomal abnormalities associated with fetal megacystis as 20.7 % (30/145). In their study, in the group with longitudinal bladder diameter of 7–15 mm, the incidence of chromosomal abnormalities was 23.6 % (26/110), whereas, in those with longitudinal bladder diameter of >15 mm, the incidence of chromosomal abnormalities was 11.4 % (4/35).

In a systemic review of fetal megacystis, Taghavi et al. [8] found 15 % of the cases with fetal megacystis had chromosomal abnormalities. In a review of 616 cases with fetal megacystis and karyotyping, Taghavi et al. [8] found 15 % (92/616) had abnormal karyotypes including trisomy 18 (5.7 %, 35/616), trisomy 13 (4.9 %, 31/616), trisomy 21 (2.6 %, 16/616) and others (1.6 %, 10/616) such as triploidy (n = 1), trisomy 4 (n = 1), mosaic trisomy 15 (n = 1), trisomy 16 (n = 1), Turner syndrome (n = 1), 47,XXY (n = 1), complex chromosomal abnormality (n = 1) and unbalanced 14/20 translocation (n = 2).

In a review of 1088 fetuses with fetal megacystis, Chen et al. [14] found the overall incidence of chromosomal abnormalities was 10 % (95 % CI: 6%–14 %) with the most common aneuploidy being trisomy 13, trisomy 18 and trisomy 21.

In a study of 541 fetuses with fetal megacystis, Fontanella et al. [10] reported that 40 cases (40/841 = 7.4 %) had typical chromosomal abnormalities including trisomy 18 (n = 24), trisomy 21 (n = 5), Turner syndrome (n = 5), trisomy 13 (n = 3) and 22q11 deletion (n = 3). In additional to 40 cases with typical chromosomal abnormalities, Fontanella et al. [10] reported other variants including one case with 1.9-Mb 19q13.33 duplication, one case with 22q11.2 microduplication and 14q31 duplication, one case with 5q35.2 deletion, one case with 46,X, der(X)t (X; Y) (p22.33; p11.31) and one case with t (14; 16) (q24.3; q24.1)pat.

In conclusion, prenatal diagnosis of fetal megacystis should include genetic analysis to exclude chromosomal abnormalities by non-invasive prenatal testing (NIPT) or invasive methods of chorionic villus sampling (CVS), amniocentesis and vesicocentesis. Rapid exclusion of the possible underlying etiology of common aneuploidy such as trisomy 18, trisomy 13 and trisomy 21 is significant when fetal therapy such as serial vesicocentesis and/or vesicoamniotic shunting are planned.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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Review Article

Syndromic and single gene disorders associated with fetal megacystis (I): Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)

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ABSTRACT

Fetal megacystis has been reported to be associated with chromosomal abnormalities, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), obstructive uropathy, prune belly syndrome, cloacal anomalies, limb-body wall complex, amniotic band syndrome, anorectal malformations, VACTERL association (vertebral anomalies, anal atresia, cardiac malformations, tracheo-esophageal fistula, renal anomalies and limb abnormalities) and fetal overgrowth syndrome such as Bechwith-Wiedemann syndrome and Sotos syndrome. This review provides an overview of syndromic and single gene disorders associated with fetal megacystis which is useful for genetic counseling at prenatal diagnosis of fetal megacystis.

Introduction

Fetal megacystis has been reported to be associated with chromosomal abnormalities, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), obstructive uropathy, prune belly syndrome, cloacal anomalies, limb-body wall complex, amniotic band syndrome, anorectal malformations, VACTERL association (vertebral anomalies, anal atresia, cardiac malformations, tracheo-esophageal fistula, renal anomalies and limb abnormalities) and fetal overgrowth syndrome such as Bechwith-Wiedemann syndrome and Sotos syndrome [1–12].

In a systemic review of fetal megacystis, Taghavi et al. [8] reported an estimated first-trimester prevalence of fetal megacystis of 1/330–1/1670 with a male/female ratio of 8/1. Taghavi et al. [8] additionally reported the common underlying diagnosis including urethral valves (57 %), urethral atresia/stenosis (7 %), prune belly syndrome (4 %), MMIHS (1 %), cloacal anomalies (0.7 %) and chromosomal anomalies (15 %) such as trisomy 18, trisomy 13 and trisomy 21. Therefore, genetic diagnosis of genetic abnormalities associated with fetal megacystis is helpful in elucidating genotype-phenotype correlations in cases with fetal megacystis detected by prenatal ultrasound.

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)

In a review of 541 pregnancies with fetal megacystis, Fontanella et al. [10] reported that five cases (1 %) was diagnosed to be MMIHS, and only one case was diagnosed prenatally. Brar et al. [11] used gene sequencing and identified seven cases with pathogenic variants including *MYOCD* (n = 2), *ACTG2* (n = 2), *MYH11* (n = 1), *KMT2D* (n = 1) and *BBS10* (n = 1). Prathapan et al. [13] identified eight cases among 25 patients with MMIHS having mutations in *ACTG2* (n = 5), *MYH11* (n = 2) and *MYL9* (n = 1). MMIHS is characterized by megacystis caused by bladder distention in the absence of mechanical obstruction, microcolon and intestinal hypoperistalsis caused by dysmotility [9]. Reported prenatal ultrasound findings of MMIHS include megacystis with or without hydronephrosis, normal or increased amniotic fluid volume in the first trimester in association with less common findings of gastric distension in the second trimester and dilated bowel loops in the third trimester [10,14–16]. In a review of

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prenatal ultrasound findings of 50 cases of MMIHS, Tuzovic et al. [14] reported that 88 % manifested fetal megacystis with or without hydroureteronephrosis, 10 % had isolated bilateral hydronephrosis, 2 % had isolated dilated stomach, 69 % had normal amniotic fluid, 27 % had polyhydramnios and 24 % had gastrointestinal abnormalities. The genetic causes of MMIHS include autosomal dominant (AD) disorders of mutations in *ACTG2* (44.1 %), rare occurrence (0.9 %) of autosomal recessive (AR) disorders of mutations in *LMOD1*, *MYH11*, *MYL9* or *MYLK* and unknown cases in 55 % [9].

MMIHS1 (OMIM 249210) is caused by homozygous mutation in the *MYLK* gene (OMIM 600922) on chromosome 3q21.1 and is an AR disorder.

MMIHS2 (OMIM 619351) is caused by homozygous or compound heterozygous mutation in the *MYH11* gene (OMIM 160745) on chromosome 16p13.11 and is an AR disorder.

MMIHS3 (OMIM 619362) is caused by mutation in the *LMOD1* gene (OMIM 602715) on chromosome 1q32.1 and is an AR disorder.

MMIHS4 (OMIM 619365) is caused by compound heterozygous mutation in the *MYL9* gene (OMIM 609905) on chromosome 20q11.23 and is an AR disorder.

MMIHS5 (OMIM 619431) is caused by heterozygous mutation in the *ACTG2* gene (OMIM 102545) on chromosome 2p13.1 and is an AD disorder.

The most common genetic disorder associated with MMIHS is the AD disorder of MMIHS5 caused by *ACTG2* mutations. *ACTG2* is human smooth muscle (enteric) γ-actin gene. Heterozygous mutation in the *ACTG2* gene will cause the AD disorders of MMIHS5 and visceral myopathy 1 (VSCM1) (OMIM 155310) which is characterized by myopathic pseudo-obstruction, impaired function of enteric smooth muscle cells and abnormal intestinal mobility [17–23]. Assia Batzir et al. [23] ascertained 53 families with visceral myopathy based on megacystis, functional bladder/gastrointestinal obstruction or microcolon with a targeted *ACTG2* sequencing and exome sequencing and reported a molecular diagnostic rate of 64 % (34/53), of which 97 % (33/34) was attributed to *ACTG2*. They also found that *ACTG2*-negative group has a more favorable clinical outcome, and within the *ACTG2*-positive group, arginine missense group has poor outcomes.

MYLK encodes myosin light chain kinase which is a key enzyme in muscle contraction. Mutations in *MYLK* will cause the AD disorder of familial thoracic aortic aneurysm 7 (OMIM 613780) and the AR disorder of MMIHS1. Halim et al. [24] identified homozygosity for mutations in the *MYLK* gene in two unrelated consanguineous families of which five children died because of MMIHS1, and the unaffected parents in each family were heterozygous for the mutation. They suggested that loss-of-function variants in *MYLK* cause the AR disorder of MMIHS1.

MYH11 is a smooth muscle myosin heavy-chain gene. Mutations in the *MYH11* cause the AD disorders of familial thoracic aortic aneurysm 4 (OMIM 132900) and visceral myopathy 2 (OMIM 619350) characterized by gastrointestinal smooth muscle dysfunction, and the AR disorder of MMIHS2. Gauthier et al. [25] identified homozygosity for a missense mutation in the *MYH11* gene in an infant with MMIHS, and heterozygosity for the mutation in his unaffected consanguineous parents. Yetman and Starr [26] identified compound heterozygosity for the frameshift mutations in the *MYH11* gene in an infant with MMIHS and heterozygosity for the mutation in his parents. Wang et al. [27] identified compound heterozygosity for a missense mutation and a deletion/insertion mutation in the *MYH11* gene in the second fetus on umbilical cord and in the third fetus by chorionic villus sampling (CVS) in a family with three consecutive fetuses affected with MMIHS. The unaffected parents had the heterozygous mutation of the *MYH11* gene. Kloth et al. [28] reported a missense mutation in *MYH11* and a heterozygous 1.3-Mb deletion in 16p13.11 encompassing *MYH11* in a girl with MMIHS. This case demonstrates a very rare occurrence of both *MYH11* sequence alteration and copy number imbalance in different alleles in the patient with MMIHS. Maddirevula et al. [29] identified homozygosity for splicing mutations in the *MYH11* gene in a fetus in the fifth pregnancy of a mother who had one abortion, one intrauterine fetal death (IUFD), one fetus with megacystis and one fetus with Potter syndrome.

LMOD1 encodes leiomodin 1, which is an actin-binding protein that has the function as a strong filament nucleator in muscle cells. Mutations in *LMOD1* cause the AR disorder of MMIHS3. In an infant with MMIHS, Halim et al. [30] identified homozygosity for nonsense mutations in the *LMOD1* gene for which her unaffected consanguineous parents were heterozygous. Halim et al. [30] suggested that loss of *LMOD1* impairs smooth muscle cytocontractility and causes MMIHS in humans and mice. In an infant with typical symptoms of pediatric intestinal pseudo-obstruction (PIPO) but without MMIHS, Liu et al. [31] identified two compound heterozygous missense variants and suggested that loss-of-function variants within *LMOD1* actin-binding site 2 cause pediatric intestinal pseudo-obstruction by impairing protein stability and actin nucleation.

MYL9 encodes myosin light chain regulatory 9, and compound heterozygous mutations in *MYL9* and homozygous deletion in *MYL9* have been presorted to be associated with the AR disorder of MMIHS4 [21,32,33]. Moreno et al. [21,32] reported detection of homozygous deletion in *MYL9* in patients with MMIHS in a consanguineous family, and the unaffected parents were heterozygous for the deletion. Kandler et al. [33] identified compound heterozygosity for two mutations in the *MYL9* gene in a child with MMIHS, and the unaffected parents were each heterozygous for one of the mutations.

PDCL3 (OMIM 611678) encodes a protein involved in the folding of actin, which is a key step in thin filament formation [Billon et al., 2020]. Billon et al. [34] identified compound heterozygous mutations in the *PDCL3* gene in an affected patient with MMIHS with a complete absence of PDLC3 expression and suggested that *PDCL3* is an excellent candidate gene for the AR forms of MMIHS.

In summary, genetic molecular diagnosis of single gene disorders associated with MMIHS detected by fetal megacystis on prenatal ultrasound is useful in elucidating genotype-phenotype correction, especially in cases of recurrent fetal megacystis and under the circumstance of consanguineous marriage in the parents.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Review Article

Immunotherapy that leverages HPV-specific immune responses for precancer lesions of cervical cancer

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ABSTRACT

Cervical cancer and its precursor lesion, cervical intraepithelial neoplasia (CIN), are caused by high-risk human papillomavirus (HPV) viral infection and are highly susceptible to host immunity targeting of HPV viral proteins, which include both foreign antigens and cancer antigens expressed by tumors. Immunotherapy that induces Th1 immunoreactivity against viral proteins is expected to take advantage of this immunological regression mechanism. However, although cancer immunotherapies for cervical cancer and CIN have been developed over the past several decades, none have been commercialized. Most of these immunotherapies target the viral cancer proteins E6 and E7, which are generally the same. The reasons for the underdevelopment of HPV-targeted immunotherapy differ depending on whether the target is invasive cancer or CIN. We here summarize the developmental history of cancer immunotherapy for CIN and discuss strategies for solving the problems that led to this underdevelopment. We note that CIN is a mucosal lesion and propose that inducing mucosal immunity may be the key.

HPV-infected cells and host immunity: immune evasion in the cervix

The immune system controls most human papillomavirus (HPV) infections using multi-steps: 1) The detection of damage by the innate immunity by local antigen-presenting cells (APCs), 2) The secretion of pro-inflammatory cytokines and chemokines supports the migration to regional lymph nodes. 3) Activated APCs stimulate various viral-antigen-specific CD4+ and CD8+ T cells or help B cells to produce antibodies. 4) The local activation of the innate immune response results in the attraction of natural killer (NK) cells, the secretion of interferons for activation of adaptive immunity. 5) This inflammatory responses induce the effector CD8+ T cells targeting HPV-infected and neoplastic cells and are critical to clearance of the virus infection. 6) Neutralizing Abs target viral particles for prevention additional HPV infections.

Responses of infected keratinocytes and their suppression by HPV gene products

When infected with HPV, keratinocytes respond to viral infection through PRRs such as TLRs and activate innate immunity through the expression of pro-inflammatory cytokines. However, HPV suppresses immune responses by inhibiting TLR9 expression in infected cells [1]. Other high-risk HPV-derived oncogenes, E6 and E7, suppress NFκB activity and inflammatory cytokine expression [2]. In addition, HPV-derived E5 downregulates major histocompatibility complex (MHC) class I expression, which is required for antigen presentation, and suppresses the ability of host cells to present HPV antigens [3,4]. Furthermore, E6 and E7 suppress the activity of the interferon (IFN) viral response pathway by inhibiting the activity of STAT1, which is the first step of the IFN response in the viral infection response pathway. E6 inhibits the production of

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IFN-β by inhibiting the activation of interferon regulatory factor (IRF)-3 [5], and E7 inhibits the expression of IFN-stimulated gene (*ISG*) by suppressing the transcriptional activity of both IRF1 and IRF9 through their interaction [6]. Thus, HPV has many functions that attenuate the antiviral immune response of infected cells.

Activation of antigen-presenting cells and their suppression by HPV gene products

HPV-infected cells are recognized by antigen-presenting cells such as tissue dendritic cells (Langerhans cells [LC] in the epithelium) and tissue macrophages, and cytotoxic T cells are activated via these antigen-presenting cells. However, high-risk HPV-derived E6 inhibits the differentiation of monocytes into dendritic cells [7], and high-risk HPV-infected keratinocytes reduce the expression of macrophage inflammatory protein (MIP)-3α and inhibit LC migration (Fig. 1) [8]. Because of these effects, it has been reported that E6 and E7 expression and LC distribution are inversely correlated in CIN and cervical cancer [9,10]. In other words, HPV suppresses the activation of acquired immunity by inhibiting the function of antigen-presenting cells through inhibition of LC differentiation and migration. In addition to innate and acquired immunity, natural killer T (NKT) cells play an intermediate role in immune activity. HPV-derived E5 also suppresses the CD1d presentation of HPV-infected cells and avoids recognition by NKT cells (Fig. 1) [11].

In HPV-infected cells, viral proteins (E5, E6, and E7) regulate the cell-surface expression of molecules involved in immune mechanisms, thereby suppressing the immune response against infected cells.

Function of T cells in HPV infection

Antigen-presenting cells that recognize HPV-infected cells induce anti-HPV CTLs. However, after the establishment of persistent HPV infection, CTLs against HPV-infected cells may not be efficiently induced because of the mechanism described above. Therefore, we speculate that to induce anti-HPV CTLs, induction of anti-HPV TH1 immunity in other immune-guided tissues would be more efficient than induction of anti-HPV TH1 cellular immunity in the local cervix. On the basis of this logic, therapeutic vaccines targeting HPV have been considered. For patients who are unable to induce anti-HPVTH1 cellular immunity in the cervix, anti-HPV cellular immunity can be induced by administering HPV vaccine antigens via a different route.

In addition to CTLs, other T cells involved in the elimination of HPV infection include CD4 T cells, the number of which correlates with the persistence of HPV infection in HIV patients, suggesting that CD4 T cells, along with CTLs, are important in the elimination of HPV infection [12]. As described above, multiple types of T cells are closely involved in the elimination of HPV infection.

Immunosuppressive pathways and biomarkers of CIN progression and regression

Thus far, we have described the innate and acquired immune responses in HPV-infected lesions and the mechanisms of immune evasion by HPV gene products. However, there are subsets of immune cells in the tumor microenvironment that "suppress" tumor immunity. In HPV-infected lesions, Treg infiltration is also observed in CIN3 HPV-infected lesions, and it has been reported that Treg infiltration is more common in CIN3 lesions. Treg infiltration has also been reported to be a biomarker of poor regression [13,14]. In addition to Treg, tumor-associated macrophages (TAMs), which are "suppressor" immune cells in the microenvironment, have recently been reported to be correlated with the prognosis of HPV-related tumors [15,16].

History and future of development of immunotherapy for CIN

Development of therapeutic agents for CIN, an unmet medical need

The only treatment for CIN2/3 is surgical treatment, and most surgical treatments performed in Japan are conization, LEEP, or laser vaporization. In Japan, approximately 15,000 women undergo this surgery annually, and the peak age at which women undergo this surgery is the early 30s. With the trend towards later marriages

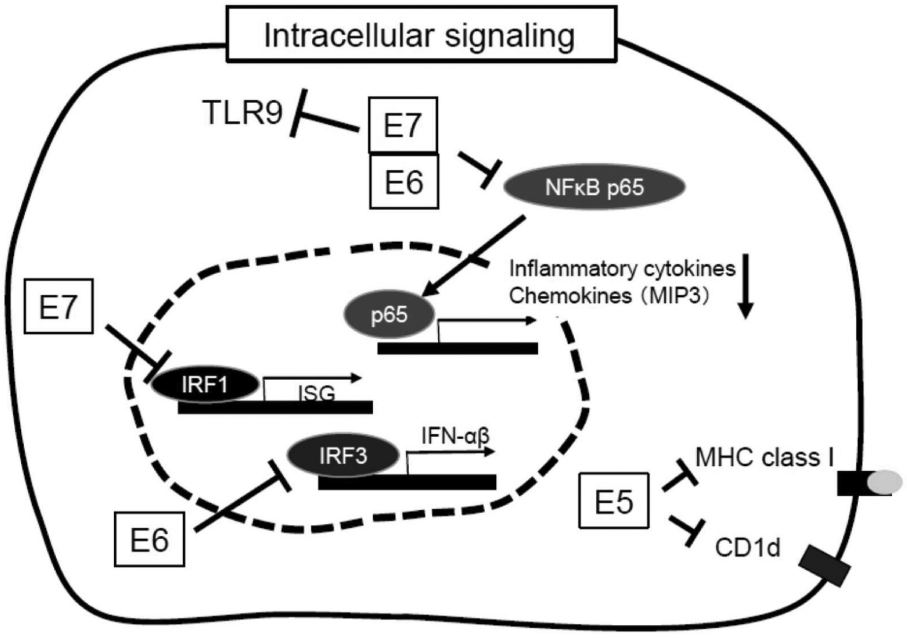

Fig. 1. Molecular mechanisms of immune evasion by HPV.

Table 1
Summary of clinical trials for therapeutics targeting CIN2/3.

Code	TA-HPV	GLBL101c-1	tipapkinogen sovacivec (TS) vaccine	pNGVL4a-CRT/E7(detox)	VGX-3100-1	E6 peptides + Candin®	GLBL101c-2	BLS-ILB-E710c-1
Phase	Phase1	Phase 1/2a	Phase2b	Phase1	Phase2	Phase 1	Phase 2b	phase 1/2a
Agent	pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccine + imiquimod	GLBL101c	tipapkinogen sovacivec (TS)vaccine(RO5217790)	pNGVL4a-CRT/E7(detox)	VGX-3100	Pepcan(E6 peptides) +Candin®	GLBL101c	BLS_ILS_E710c
No. ClinicalTrials.gov	NCT00788164	UMIN000001686	NCT01022346	NCT00988559	NCT01304524	NCT01653249	UMIN000012229	NCT02195089
Country	USA	Japan	USA	USA	USA	USA	Japan	Korea
Main facility	Johns Hopkins	University of Tokyo	University of Missouri	Johns Hopkins	Inovio Pharmaceuticals	University of Arkansas	University of Tokyo	BioLeaders Corporation
Disease	CIN3	CIN3	CIN2/3	CIN2/3	CIN2/3	CIN2/3	CIN2	CIN3
Trial period	2008.11 ~ 2023.7	2009.2–2013.11	2009.8 ~ 2013.9	2009.11 ~ 2013.9	2011.4–2015.4	2012.8–2015.7	2014.3–2017.9	2014.3–2016.4
No. of Enrolled Patients	75	17	192	27	167	34	40	18
Endpoint	41w	9w	24w	15w	36w	21w	16w	16w
Bind	No	No	double-blind	No	double-blind	No	double-blind	No
Placebo	No	No	placebo-controlled	No	placebo-controlled	No	placebo-controlled	No
Endpoint Bind Placebo	No	No	randomized	No	randomized	No	randomized	No
No. of dose	days 1, 29, 57	weeks 1, 2, 4, 8	days 1, 8, 15	weeks 0, 4 ,8	weeks 0 , 4 , 12	weeks 0, 3 , 6, 9	weeks 1, 2, 4, 8	weeks 1, 2, 4, 8
Route (S.C., subcutaneous injection; I.M., intramuscular injection; P.O., oral administration)	i.m.	p.o.	s.c.	i.m.	i.m.	s.c.	p.o.	p.o.
Publicaion No.	Ref. [43]	Ref. [39]	Ref. [44]	Ref. [45]	Ref. [28]	Refs. [31,46]	Ref. [40]	Ref. [47]

and childbirth, many women who have undergone conization become pregnant later in life, and the risk of preterm birth and low birth weight increases approximately threefold in pregnancies after this surgery, affecting infants born to women with CIN2/3 [17]. The rise in preterm birth rates and low birth weight babies will put pressure on perinatal services. The development of non-invasive therapeutic agents for CIN2/3 is therefore urgently needed, but there are still no therapeutic agents available worldwide. CIN2/3-targeting therapeutic agents are an unmet need and a social demand in a society with later marriages and fewer children.

Cancer immunotherapy for cervical cancer targeting HPV

In cervical cancer, high-risk HPVs are essential for carcinogenesis and the maintenance of cancerous behavior, and thus HPV-targeted therapies have been expected. However, no effective inhibitor has yet been developed for the former. However, many studies on the latter have been conducted worldwide since the 1990s. A cancer vaccine targeting HPV is a cancer immunotherapy "specific" to cervical cancer. Many clinical trials (phases I–III) have been conducted overseas in cervical or vulvar lesions [18–30]. Most of them target the E7 oncoprotein of HPV. The target disease of these clinical trials is mostly CIN2-3, all of which are caused by HPV16 (Table 1). In the past, there were a few scattered clinical trials of HPV E7-targeted cancer immunotherapy for advanced or recurrent cervical cancer, but all of them did not show efficacy and seemed to be abortive at times.

Immunotherapy for precancerous lesions

Many clinical trials have been conducted for CIN2/3 as cancer immunotherapy for cervical cancer. In these trials, vaccine antigens were administered by either intramuscular or subcutaneous injection. Although it has been confirmed that an anti-E7 cell-mediated Th1 immune response is induced in peripheral blood, it does not necessarily correlate with clinical efficacy, and no drug has been applied clinically. As shown in Table 1, various vaccine carriers have been used to induce a systemic (peripheral blood) anti-E7 Th1 immune response, but this therapeutic strategy has only shown anti-tumor effects in animal models. There is no tumor-bearing model of tumor formation from cervical mucosa in mice or other animals, and subcutaneous tumors have been used instead. No anti-tumor effect was obtained against tumors in the cervix, which has a completely different immune environment from that of subcutaneous or intravaginal tumors.

Among the clinical trials of HPV-targeted immunotherapeutic agents against CIN2/3, the most advanced is in VGX-3100, a DNA vaccine developed by Inovio in the U.S. that consists of a three-dose intramuscular injection of E6-/E7-expressing DNA (vector) of HPV16 and HPV18 into humans. In a phase IIb study, CIN2/3 of HPV16 was compared with a placebo group [28]. They found that the regression rate was 48 % with the vaccine and 30 % with placebo ($p = 0.034$). However, inflammation at the site of muscle injection was observed in 80 % of patients, and adverse events were significantly higher in the placebo group ($p = 0.007$). However, the results of the phase III study of VGX-3100 published by Inovio showed that in the intention-to-treat (ITT) population ($n = 201$), the efficacy of the vaccine was 22 % and that of the placebo group was 11 %, which was not significantly different ($p = 0.029$; 11.4 % difference in percentage, 95%CI: −0.4, 21.2). Moreover, the efficacy rate of the vaccine was much lower than the rate shown in the phase II study [29]. In addition, DNA vaccines may be incorporated into cells in the tissue of the vaccination site, and there is a risk of future carcinogenesis by activating oncogenes through genetic recombination. The long-term safety of DNA vaccines is unknown.

Nakagawa et al. conducted a phase I dose-escalation clinical trial of PepCan, which consists of four peptides covering HPV16 E6 oncoprotein and a *Candida* skin test reagent [30,31]. PepCan was administered intradermally four times every 3 weeks in limbs. The highest regression rate of 50 % (7/14) was observed at the lowest dose level of 50 μg. In this clinical trial, no dose-dependency was demonstrated.

Because CIN is a mucosal disease, we consider that mucosal immunity should be induced to promote cellular immunity, and thus the use of mucosal immunity could be a breakthrough in cancer immunotherapy for cervical cancer [19].

Development of cancer immunotherapy using mucosal immunity

Strategies for immunotherapy via the mucosal immune system in the cervix

On the mucosal surface, these immune responses can be completed on the mucosal surface and in the lymph nodes to which it belongs. This is the mucosal immune system. Lymphoid tissue in the submucosa is called mucosal-associated lymphoid tissue (MALT). The nasal mucosa has nasal-associated tissue (NALT), the bronchial mucosa has bronchial-associated tissue (BALT), the intestinal mucosa has gut-associated tissue (GALT), and the tear duct mucosa has tear-duct associated tissue (TLT). The mucosal epithelium is invaded by a variety of bacteria. Innate immunity and antigen-presenting cells detect foreign substances that invade the mucosal epithelium, causing priming of MALTs such as Peyer's

GX-188E-1	GX-I7	GX-188E-2	BLS-ILB-E710c-2	VGX-3100-2	VGX-3100-3	VB10.16	E6 peptides/ Candin®2	MILACLE study
Phase2	Phase1	Phase2	Phase2b	Phase3 (REVEAL 1)	Phase3 (REVEAL 2)	Phase2a	Phase 2	Phase 1/2
GX-188E	GX-I7	GX-188E + imiquimode	BLS_ILS_E710c	VGX-3100	VGX-3100	VB10.16/ Atezolizumab	Pepcan(E6 peptides) + Candin®	IGMKK16E7
NCT02139267	NCT03144934	NCT03206138	NCT03274206	NCT03185013	NCT03721978	NCT04405349	NCT02481414	UMIN000034253
Korea	Korea	Korea	Korea	USA	USA	EU	USA	Japan
Genexine, Inc.	Genexine, Inc.	Genexine, Inc.	BioLeaders Corporation	Inovio Pharmaceuticals	Inovio Pharmaceuticals	Nykode	University of Arkansas	Nihon University
CIN3	HPV infection	CIN3	CIN2/3	CIN2/3	CIN2/3	Cervical cancer	CIN2/3	CIN2/3
2014.7–2016.3	2017.2–2018.3	2017.5–2018.10	2017.8–2020.8	2017.6–2021.4	2019.4–2022.9	2020.7–2024.3	2015.11–2025	2019.6–2022.7
72	32	50	126	201	203	50	125	164
20w	4w	36w	16w	36w	36w	52w	48w	24w
No	double-blind	No	double-blind	double-bilnd	double-blind	No	double-blind	double-blind
No	placebo-controlled	No	placebo-controlled	placebo-controlled	placebo-controlled	No	placebo-controlled	placebo-controlled
randomized	randomized	randomized	randomized	randomized	randomized	No	randomized	randomized
weeks 0, 4, 12	weeks 0, 4	NA	weeks 1, 2, 4, 8	weeks 0, 4, 12	weeks 0, 4, 12	every 6wks for wks for Atezolizumab VB10.16/every 3	weeks 0, 3, 6, 9	weeks 1, 2, 4, 8
i.m.	local	i.m.+local	p.o.	i.m.	i.m.	i.m. for VB10.16/i.v. for Atezolizumab	S.C.	p.o.
Ref. [48]	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)

patches, as well as the lymph nodes associated with each mucosa (mesenteric lymph nodes in the case of the intestine), which are then memorized and stand ready for a second attack [32]. In the case of mucosal adaptive immunity, MALTs deployed throughout the body and the lymph nodes associated with each mucosal surface play a central role. These MALTs can form a network and share immune responses. Mucosal T cells express integrin α4β7 and CCR9, a surface antigen molecule, in GALT [33]. Mucosal T cells are expressed in GALT by surface antigen molecules, integrin α4β7, and CCR9, and infiltrate mucosal tissues by binding to ligands expressed on endothelial cells in submucosal tissues, Peyer's patches, and mesenteric lymph nodes throughout the peripheral circulation (homing) (Fig. 2).

In the inductive site of GALT, mucosal lymphocytes are educated by stimulation from antigen-presenting cells and through imprinting by dendritic cells. These lymphocytes acquire surface antigen markers, integrin and CCR9, and use them to home to the effector sites, the mucosa of the whole body, via the peripheral circulation.

Memory T cells homing to the systemic mucosa express integrin αEβ7 (CD103) and CD69 instead of integrin α4β7 at the mucosa. The ligand for integrin αEβ7 is E-cadherin, which is highly expressed on mucosal epithelial cells. This binding allows integrin αEβ7 T cells to infiltrate and accumulate in the mucosal epithelium and efficiently attack CIN lesions.

Focusing on the mucosa of the reproductive tract, the inductive site, which is responsible for acquired immunity, does not have its own organ, but is substituted by the Peyer's patches and mesenteric lymph nodes of the gut. Sacral lymph nodes have also been reported to be involved in the induction of mucosal immunity in the reproductive tract [34]. The authors have reported the presence of integrin αEβ7 lymphocytes in the mucosa of the human cervix [35]. This indicates that mucosal T cells imprinted in the intestine home to the cervical mucosa (Fig. 3).

In the cervical epithelium, as mucosal T cells home to the submucosa, the surface antigen marker is converted from integrin α4β7 to αEβ7 by TGF-β from dendritic cells. Integrin αEβ7 is retained in the cervical epithelium where E-cadherin is expressed.

Interestingly, the authors and Trimble's group in the U.S. have reported a correlation between high integrin αEβ7 lymphocyte populations and regression of CIN [36]. HPV E6 and E7 oncoproteins are the cancer antigens that maintain the carcinogenesis of HPV-associated cancers, and especially HPV E7 is well-known to be highly immunogenic in humans. Approximately 50%–60 % of CIN2 and 70 % of CIN1 spontaneously regress [37], which is due to the host immune response against HPV molecules. If this immune response can be induced by a "therapeutic vaccine," a clinical therapeutic effect can be expected.

We consider that HPV-specific cellular immunity via mucosal immunity should be induced to control and treat the lesions, and we have developed the world's first mucosal cancer immunotherapy that incorporates this concept in cancer vaccines. We developed an HPV16E7-expressing *Lactobacillus*-based vaccine by expressing modified E7 protein of HPV16 on the surface of *Lactobacillus casei* strain (*L. casei*). *L. casei* is not only a vaccine carrier that conveys vaccine antigens, but also a vaccine adjuvant that predominantly activates the Th1 immune response. Moreover, the HPV16 E7 protein is expressed within the bacteria and is displayed on the surface of the bacterium using an original display system.

In animal experiments using mice, oral administration of E7-expressing *Lactobacillus* induced an E7-specific Th1 immune response in the intestinal mucosa, while intramuscular and subcutaneous injections of HPV16 E7 protein did not show the ability to induce E7-specific immunity in the intestinal mucosa [38].

Clinical trials of our mucosal immunotherapy for CIN

A phase I/IIa proof of concept (POC) study of E7-expressing *L. casei* (code name: GLBL101c) in cervical precancerous lesions (CIN3) was conducted from 2009 to 2013 (Table 1). The study design was a 17-cohort dose-escalation study with a once-daily GLBL101c dosing schedule for 5 days for four cycles (1, 2, 4, and 8 weeks) [39]. Of the 10 CIN3 patients in the GLBL101c group who took four caplets (1 g)/day, eight (80 %) regressed to CIN2 at 9 weeks after the start of the first dose. Among these eight patients, three (30 %) had normalized in the subsequent follow-up. Finally, the clinical efficacy of GLBL101c in the 1.0–1.5 g/day group was 61.5 % regression to CIN2 (PR) at 9 weeks after the start of treatment, and 38.4 % regression to CIN1/normal (CR) at 12 months after the start of the first dose. Because the probability of spontaneous regression of CIN3 in general is approximately 10 % in 1 year, the regression rate in this trial was clearly higher than that of spontaneous regression.

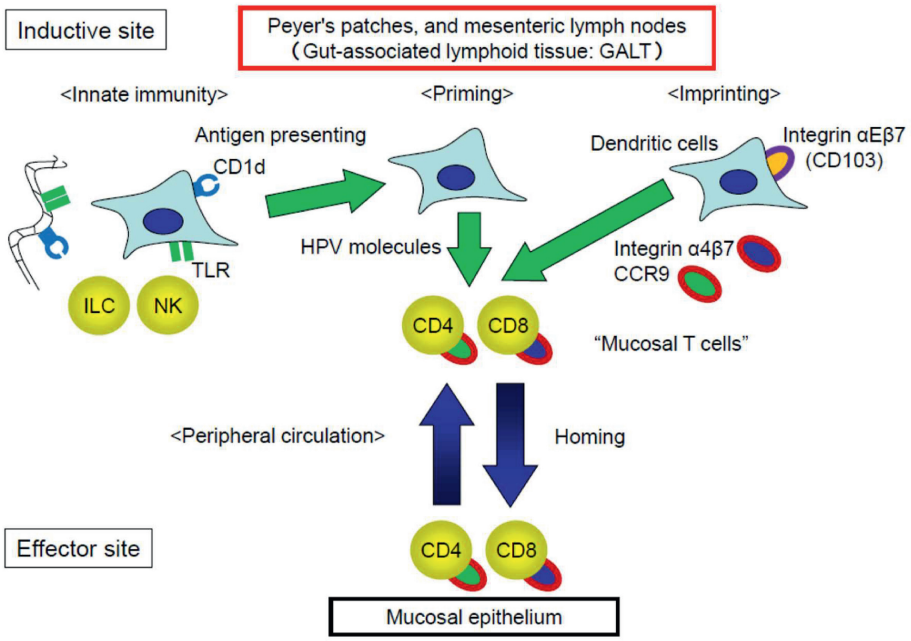

Fig. 2. Mucosal immune system and mucosal T cell behavior.

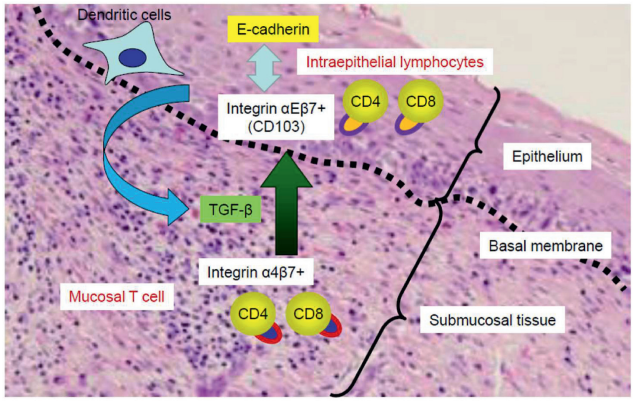

Fig. 3. Mechanism of homing of mucosal T cells to the cervical mucosa.

Our immunological evaluation demonstrated that oral administration of GLBL101c induced E7-specific Th1 cellular immunity on the intestinal mucosal surface and homed to the cervical mucosa via the peripheral circulation (Fig. 4). Interestingly, cases with higher numbers of E7-specific IFNγ-producing lymphocytes by ELIspot assay showed pathological regression, and there was a strong correlation between the E7-specific Th1 immune response in the cervical lesions and pathological efficacy. For all 17 patients, there were no adverse events of grade 2 or higher, and no grade 1 adverse events were causally related [39].

When E7-expressing *Lactobacillus*-based vaccines are administered orally, E7-specific mucosal CD4 and CD8 T cells are educated in the GALT. After homing to the cervical epithelium, recognition of HPV16 E7 expressed in CIN2/3 leads to Th1 immune responses, including IFN-γ production, and immunological clearance of the lesion.

A randomized, double-blind, placebo-controlled, phase IIb clinical trial of a *Lactobacillus*-based vaccine was conducted between 2014 and 2017 with limited efficacy for CIN2, and the results suggested higher efficacy for CIN3 [40]. Compared with the placebo group, there was no difference in adverse events and its safety was confirmed.

Because these results were insufficient for the therapeutic effects in CIN2/3, we developed a new HPV16 E7-expressing *Lactobacillus*-based vaccine to further enhance the E7-specific Th1 immune response. In this study, we prepared a purified protein with an anchor molecule attached to the HPV16 E7 protein and covalently combined it to the surface of *L. casei*. In flow cytometry analysis to detect E7-positive bacteria, it was confirmed that the content of E7 protein bound to the surface of the bacteria reached saturation at 0.3 μg E7/10^8 cells of bacteria, and it was demonstrated in mouse immunization experiments that E7-expressing *Lactobacillus* with 0.3 μg E7 induced the highest E7-specific Th1 immune response [41]. This improved E7-expressing *Lactobacillus*-based vaccine was named IGMKK16E7 and was patented in January 2019. Approximately fourfold higher E7-specific Th1 immune responses were induced by oral administration of IGMKK16E7 in mouse immunization experiments.

A phase I/II investigator-initiated clinical trial of IGMKK16E7 in HPV16-positive CIN2/3, the MILACLE study, was commenced in June 2019 and consisted of a parallel-group randomized controlled trial of four groups (1:1:1:1): placebo, low-dose, medium-dose, and high-dose. This was a multi-center study conducted at Nihon University Itabashi Hospital and other institutions, with a target enrollment of 164 patients (124 for CIN3 and 40 for CIN2). The primary endpoint was pathologic remission (CR = normal, PR=CIN1, SD=CIN2/3, PD = invasive cancer), and the protocol was designed to determine efficacy at 16 weeks after the start of treatment [42].

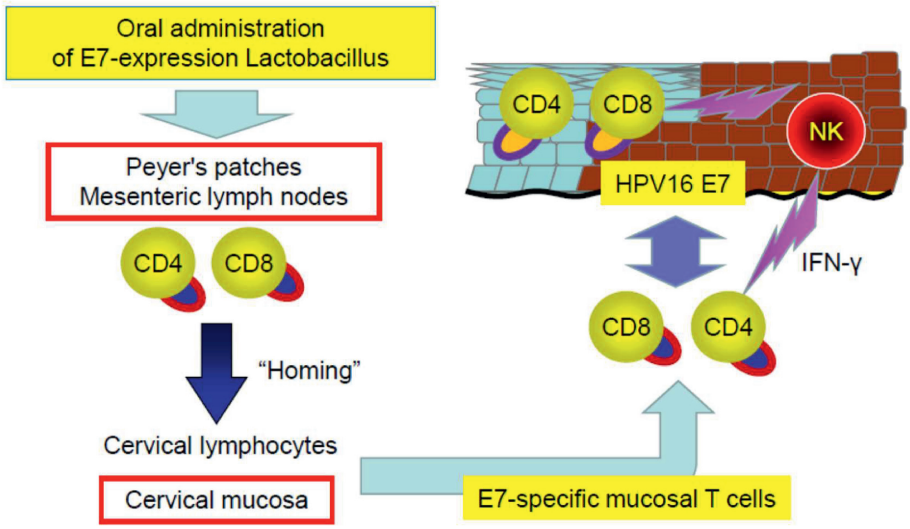

Fig. 4. Pharmacological effects of E7-expressing *Lactobacillus*-based therapeutic vaccine.

Future prospects

In this review, we described the development of cancer immunotherapy targeting HPV16 E7 according to the natural history of cervical cancer. Recently, HPV-related cancers, not only cervical cancer but also ortho-pharyngeal and anal cancers, have become a problem, especially in men. When commercialized as therapeutic agents for CIN2/3, immunotherapies may be widely applied to mucosal lesions in the ortho-pharynx, anus, and vagina. The use of these agents to induce mucosal immunity to HPV16 E7 in HPV16-infected patients, with or without precancer lesions, may lead to the prevention of HPV-related cancer development rather than the prevention of HPV infection. In such an indication, the agent to be administered can be selected according to HPV infection type, and oral administration will be useful.

When attempting pharmacotherapy for CIN2/3, it should be performed by a physician skilled in the diagnosis and management of CIN2/3. This is because colposcopic findings that are suspicious for invasive carcinoma require histologic diagnosis by conization, and the ability to make that diagnosis is a guarantee of safety. In addition, because this is an immunotherapy, the possibility of immune-related adverse events (irAE) cannot be ruled out, and it is recommended that physicians experienced in immunotherapy use this therapy."

In addition, these therapeutic agents are molecular-targeted therapies, and by using the expression level of HPV16 E7 as a molecular diagnostic tool, personalized treatment of patients with CIN2/3 will be possible.

Statement of ethics

This study has not to be done on human or animal subjects.

Author contributions

Conceptualization, K.K. and Y.I.; writing-review and editing, O.K. and K.K; All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

GLOVACC Inc. gifted GLBL101c, IGMKK16E7, and placebo, and partially supported this clinical trial.

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Review Article

The role of probiotics in women's health: An update narrative review

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ABSTRACT

Probiotics, live microorganisms that confer health benefits to the host when administered in adequate amounts, have gained considerable attention for their potential role in maintaining women's health. This overview summarizes key clinical findings on the beneficial effects of probiotics in various aspects of women's health. Probiotics, particularly *Lactobacillus* species, contribute to vaginal health by promoting a balanced vaginal microbiome to prevent infections and maintain an acidic environment. In gynecologic conditions, probiotics show potential in preventing and managing bacterial vaginosis, vulvovaginal candidiasis, and sexually transmitted infections. Probiotic supplementation has also been associated with improvements in metabolic parameters and menstrual irregularities in polycystic ovary syndrome patients. During pregnancy, probiotics may be helpful in reducing the risk of gestational diabetes, maternal group B streptococcal colonization, obstetric anemia, and postpartum mastitis. In recent years, the potential role of probiotics in the prevention and management of gynecologic cancer has gained attention. Further research is needed to better understand the specific mechanisms and determine the optimal *Lactobacillus* strains and dosages regimens for gynecologic cancer prevention and therapy. In conclusion, probiotics offer a non-invasive and cost-effective approach to support women's health and prevent obstetric and gynecologic complications.

Introduction

Human body is a natural host for a variety of microbiomes, which are communities of microorganisms that inhabit different regions of the body. It has been estimated to have trillions of microorganisms, including bacteria, viruses, fungi, and other microbes, living in and on the human body. These microbiomes are found in various parts of bodies, including the gut, skin, oral cavity, respiratory tract, urogenital tract, and other sites. The composition and diversity of these microbiomes are known to be important for human health, and a disruption in their balance has been associated with various diseases and conditions. Probiotics are live microorganisms, usually bacteria, that are beneficial for human health when consumed in adequate amounts. These microorganisms are naturally found in certain foods, such as yogurt, kefir, sauerkraut, kimchi, and kombucha, or in dietary supplements. Probiotics function through the restoration of equilibrium within the gut microbiota, the establishment of beneficial bacterial colonies, and interactions with immune cells within the gut-associated lymphoid tissue. These actions collectively enhance processes such as digestion, skin health, immune system function, and can also influence mental health via modulation of the gut-brain axis [1–4].

The vaginal microbiome is largely composed of bacteria, and the most common bacterial species found in the vagina are from the genus *Lactobacillus*. In healthy women of reproductive age, *Lactobacilli* species typically make up the majority of the vaginal microbiota, ranging from 70 to 90 % [5] and *Lactobacillus (L.) crispatus, gasseri, iners, jensenii, reuteri, rhamnosus,* and *fermentum* appear to be the most beneficial for vaginal health. These bacteria produce lactic acid in an estrogen-rich vaginal epithelial cells through the process of glycolysis, which helps to maintain a slightly acidic pH (3.5–4.5) in the vagina, creating an environment hostile to harmful bacteria and other microorganisms. Additionally, *Lactobacilli* produce hydrogen peroxide (H_2O_2), bacteriocins, and biosurfactants that have antimicrobial activity against other bacterial species (Fig. 1). However, factors such as antibiotics, hormonal changes, and sexual activity can disrupt this delicate balance, leading to an overgrowth of harmful bacteria and the development of conditions such as bacterial vaginosis (BV) and fungal infections.

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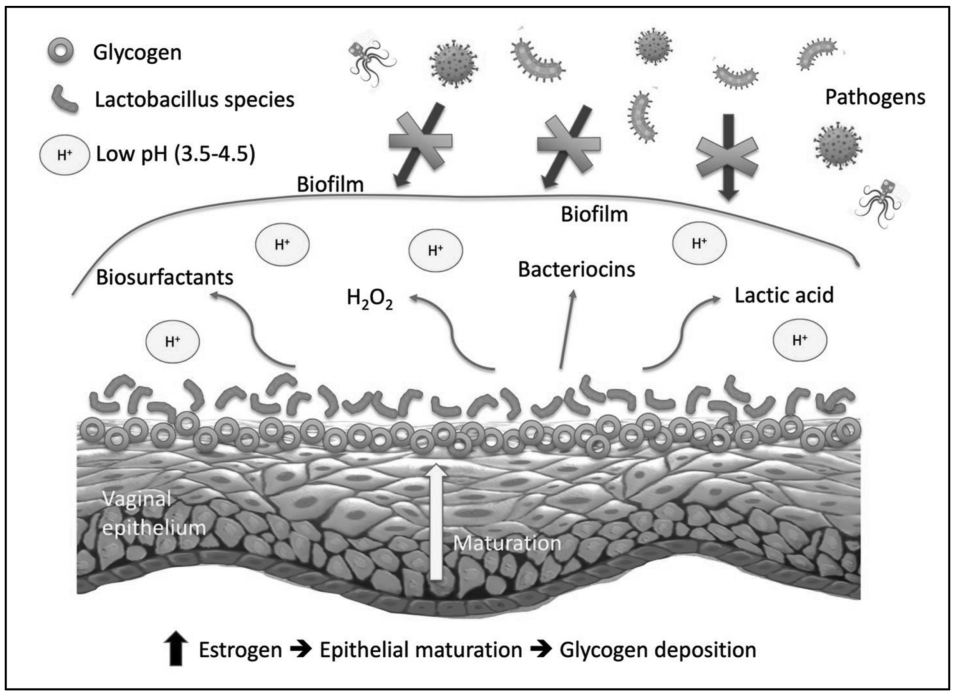

Fig. 1. *Lactobacillus* species play a crucial role in maintaining vaginal health through various mechanisms including 1) a metabolization of glycogen in the vaginal epithelial cells to convert it into lactic acid, leading to the maintenance of an acidic pH (around 3.5–4.5) in the vagina and an inhospitable environment for the growth of pathogenic bacteria, 2) an adherence of *Lactobacilli* to the vaginal epithelial cells to produce antimicrobial substances such as hydrogen peroxide, bacteriocins, and biosurfactants, which inhibit the growth of pathogens, 3) strengthening of the vaginal epithelial barrier by *Lactobacilli* to promote the production of mucus and the formation of a healthy biofilm, which acts as a physical barrier against pathogens and prevents their colonization and invasion.

The first report to demonstrate that probiotics can be applied directly to the vagina was published in 1992 by Reid et al. [6]. In this study, the researchers tested the efficacy of a vaginal suppository containing *L. acidophilus* in the treatment of BV. They found that the suppository was effective in restoring the normal vaginal microflora and reducing the recurrence of BV. Since then, several other studies have confirmed the effectiveness of oral probiotics in colonizing the vaginal environment, possibly by migration of some *Lactobacillus* strains from the rectal mucosa and perianal area directly to the vagina [7,8]. These beneficial probiotics establish themselves and compete with harmful microorganisms for space and resources and help maintain a balanced and health vaginal microbiome. In this review, we attempt to summarize the key clinical findings on the beneficial effects of probiotics in various aspects of women's health.

Clinical role of probiotics in gynecologic conditions

Bacterial vaginosis and vaginal candidiasis

Bacterial vaginosis is a common vaginal infection with a prevalence of around 10–20 % in most of the Asia countries [9]. It is caused by an imbalance in the vaginal microbiota and associated with important adverse health outcomes such as increased risk of sexually transmitted infections (STIs), infertility, pelvic inflammatory disease, and pregnancy complications [10]. The current treatment approach for BV typically involves antibiotic therapy. However, probiotics containing *L. crispatus, L. jensenii,* and *L. gasseri* have been found to be effective in treating BV [11]. A recent meta-analysis examined 17 randomized controlled trials (RCTs) involving a total of 3176 participants. The analysis revealed that probiotics alone were significantly more effective than placebo (relative risk 15.20, 95 % CI 3.87–59.63). Additionally, probiotics used in combination with antibiotic therapy were more effective than antibiotics alone (relative risk 1.23, 95 % CI 1.05–1.43) in the treatment of BV. The meta-analysis did not find any significant differences in efficacy between different types of probiotics or different formulations (oral vs. vaginal) [12].

Vaginal candidiasis is a common fungal infection involving vagina. It affects about 75 % of women at least once in life and is characterized by leukorrhea, intense pruritus, vulvar hyperemia, dysuria, and dyspareunia [13]. The current treatment approach typically involves antifungal therapy. *L. gasseri* and *L. crispatus* have been found to be effective in inhibiting the growth of *Candida albicans* [14]. In a recent meta-analysis reviewed 23 RCTs with a total of 2212 participants found that probiotics were effective in preventing recurrent vaginal candidiasis at 6 months, with a pooled relative risk of 0.36 (95 % CI 0.21 to 0.63), indicating that women who used probiotics were 64 % less likely to experience a recurrence of vaginal candidiasis compared to those without probiotics. Also, the efficacy between different types of probiotics or different formulations were the same [15].

Overall, these meta-analyses provide strong evidence that probiotics can be effective in reducing the recurrence and improving the recovery rates of BV and vaginal candidiasis.

Genitourinary syndrome of menopause (GSM)

Genitourinary syndrome of menopause mostly occurs when the urogenital tissues become thin, dry, and inflamed due to decreased levels of estrogen, typically in menopausal women. Symptoms such as vaginal dryness, burning, itching, pain during intercourse, and urinary problems can lead to discomfort, embarrassment, and decreased sexual function. These symptoms can also impact women's psychological well-being and lead to anxiety, depression, and a decreased sense of well-being. The treatment approach

typically involves hormonal therapy or lifestyle modifications. Several clinical studies have shown that certain strains of probiotics (*L. acidophilus*) taken together with ultra-low-dose (0.03 mg) vaginal estriol (E3) can improve GSM symptoms. Such improvement may be achieved through restoring the thickness and elasticity of the vaginal tissues and the natural acidity of the vagina, which can help to prevent the overgrowth of harmful bacteria and yeast [16–18] (Fig. 2). The dose of E3 in the above combination therapy is substantially lower than that of conventional preparations of 0.5 mg and has a beneficial efficacy-safety profile with a similar efficacy and the lack of endometrial proliferation or thromboembolic events, even for a long-term use [19]. The conventional treatment of vaginal atrophy is an initial therapy of 12 days with single daily application followed by a maintenance regimen with two to three doses per week.

Chlamydia and gonorrhea

Chlamydia infection is caused by the bacterium *Chlamydia trachomatis* while Gonorrhea is caused by the bacterium *Neisseria gonorrhoeae* and both pathogens can infect men and women. These diseases are common STIs worldwide and often asymptomatic. The estimated global prevalence in women is approximately 3.8 % for chlamydia and 0.9 % for gonorrhea [20]. Without an appropriate treatment, both can lead to serious health complications, such as pelvic inflammatory disease, chronic pelvic pain, infertility, and an increased risk of human immunodeficiency virus transmission. These infections are typically treated with antibiotics while probiotics may have some potential benefits in reducing the risk of these infections. Several preclinical studies investigated the role of *Lactobacillus* against these STIs. Foschi et al. found that *L. crispatus* can produce biosurfactant which exhibited a strong binding ability to *Chlamydia trachomatis* elementary bodies (EBs) to inhibit their infectivity. The biosurfactant disrupted the membrane of EBs, causing them to become non-infectious. The changes in the EBs' surface morphology also make them more susceptible to host immune defenses [21]. The same research group also found that probiotics were able to inhibit the growth and viability of *N. gonorrhoeae* through several mechanisms including the production of acidic environment with pH < 4.0, hydrogen peroxide, and biosurfactants [22]. In another preclinical study, the researchers developed a vaginal gel containing *L. crispatus* for the purpose of prevention of gonorrhea. They found that the gel was able to significantly reduce the growth of gonorrhea bacteria in culture [23]. Overall, these studies suggest that *Lactobacillus* bacteria play an important role in protecting against chlamydia and gonorrhea infections.

While these findings being promising, it should be emphasized that these studies were preclinical and further clinical research is needed to confirm these results.

Human papillomavirus (HPV) infection

According to a Finnish female population study, HPV is the most common viral infection of the female reproductive tract, with an estimated 79 % of sexually active women will contract at least one HPV infection at some point in their lives [24]. However, not all women with HPV will develop symptoms or health problems related to the infection. Most HPV infections are transient and clear up spontaneously within 1–2 years without causing any clinical symptoms or complications. However, some infections can persist and progress to precancerous lesions and eventually to invasive cervical cancer over a period of several years to decades [25]. Preclinical studies have demonstrated that specific probiotic strains can inhibit HPV growth in cell cultures by decreasing the expression of E6 and E7 oncogenes [26]. Additionally, in cell and mouse models, these probiotics can reduce HPV infectivity by upregulating E-cadherin [27]. Although promising, these data were experimental

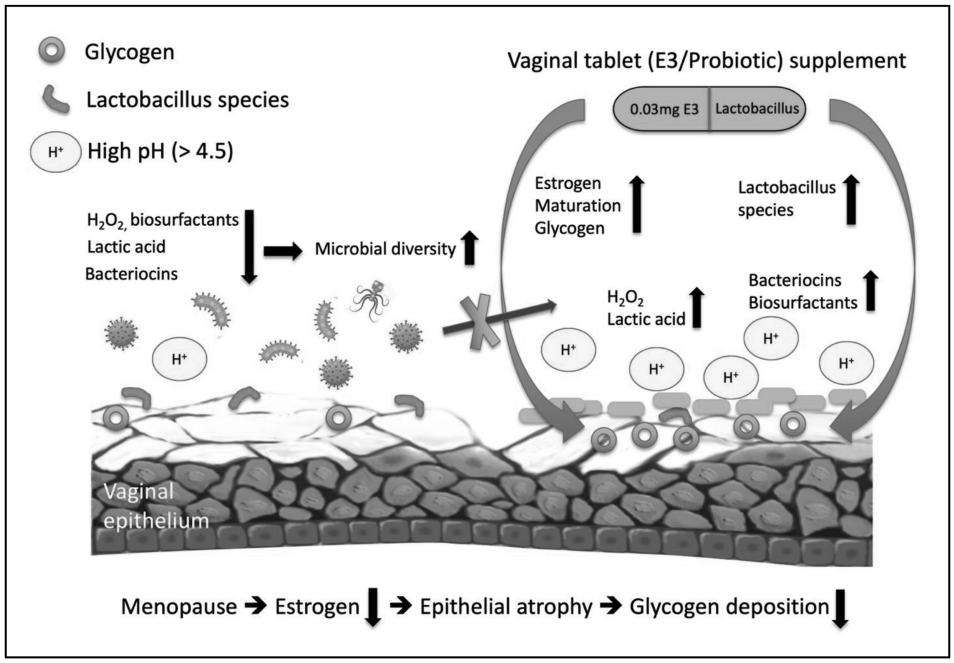

Fig. 2. During menopause, along with the decline of estrogen levels, the production of glycogen in the vaginal epithelial cells decreases. This reduction in glycogen availability can negatively impact the growth and activity of *Lactobacilli*, which rely on glycogen as a nutrient source. As a result, the vaginal pH may increase while hydrogen peroxide, bacteriocins, and biosurfactants may decrease, and the vaginal microbiome may shift towards a less favorable composition (left). A combination of Estriol (E3) with *Lactobacillus* species may contribute to restore and maintain the vaginal environment by stimulating the production of glycogen as a nutrient source for *Lactobacilli*. This, in turn, promotes the growth of *Lactobacilli* and the production of lactic acid, leading to a more acidic and healthier vaginal environment (right).

which may not replicate real-world scenarios. There is some evidence suggesting that there may be an association between BV and HPV infection since the infection rate of high-risk HPV types of women with BV were almost two folds of those of women without BV [28]. Given the facts that probiotics can be effective in improving the recovery rate of BV and the anti-HPV evidence from bench, it is reasonable to hypothesize that probiotics have a role in HPV clearance. A study in 2018 was the first to investigate the role of vaginal application of probiotics in HPV clearance. It included 117 women with abnormal cervical cytology and persistent high-risk HPV infection who were randomized to receive either 3 months or 6 months vaginal probiotic containing *L. rhamnosus*. The results showed that the longer probiotic group had a higher clearance rate of high-risk HPV infection compared to the shorter group (35.3 % vs. 12.7 %) at 9 months [29]. Another single arm trial investigating 35 HPV infected women using oral *L. crispatus*, the researchers measured the clearance rate of HPV infection at 3 months and results revealed that 25 out of 35 women (71.4 %) had cleared the virus [30]. However, both studies did not include placebo arm and the follow-up period was not long. Our group in 2019 conducted a randomized, double-blind, placebo-controlled trial including 121 women to evaluate the effect of oral probiotics (*L. rhamnosus/reuteri*) on the clearance of high-risk HPV. Unfortunately, results found no significant difference in HPV clearance rates between the probiotic and placebo groups (58.1 % vs. 54.2 %) at 15 months [31].

At present, the evidence regarding the effectiveness of probiotics in HPV clearance is still limited and inconclusive. More high-quality RCTs are needed to confirm these findings and determine the possible predictors of viral persistence.

Cervical intraepithelial neoplasm (CIN)

The cause of CIN is chronic infection of the cervix with HPV, not all cases of CIN progress to cervical cancer. In fact, many cases of CIN may regress spontaneously, especially in younger women or those with low-grade lesions [32]. The thought of probiotics for CIN treatment comes from the evidence that certain *Lactobacillus* strains were able to suppress the HPV gene expression and induce the apoptosis of cervical cancer cells in preclinical studies [26,27]. Verhoeven et al., in 2013 first conducted a prospective controlled pilot study to investigate the effects of probiotics on the clearance of HPV-related cervical lesions. That study included 54 women with HPV-positive low-grade CIN diagnosed in their Pap smear, who were randomized to receive either a probiotic containing *L. rhamnosus/reuteri* or a placebo for 6 months. The results showed that women who received the probiotic had a higher rate (60 %) of disappearance of the cervical lesions on Pap smear compared to those who received the placebo (31 %) at 6 months [33]. However, it is crucial to acknowledge that Pap smear may have limitations in detecting cervical dysplasia accurately, especially in cases of low-grade CIN. As a result, the clinical value of this study may be limited.

Endometriosis

Endometriosis is a chronic inflammatory condition that can cause painful menstruation and infertility, that affect about 10 % of women during their reproductive age. The pathogenesis of endometriosis is still not fully defined and is considered as a multifactorial process. Retrograde menstruation and coelomic metaplasia are currently the most recognized pathogenetic hypotheses [34]. There is currently no known cure for endometriosis and treatment usually involves medication (progestins) or surgery aimed at controlling symptoms. Studies have shown that the gut and vaginal microbiome may participate during the development and progression of endometriosis, and thus probiotics may be helpful to modulate the gut/vaginal microbiome to reduce inflammation and improve symptoms [35]. Preclinically, researchers reported that *L. gasseri* may be a potential therapeutic agent for the treatment of endometriosis in a murine model, and the underlying mechanism may involve the activation of NK cells [36]. To evaluate the effectiveness of *L. gasseri* in reducing menstrual pain in endometriosis patients a randomized, double-blind, placebo-controlled trial was then initiated and included 66 women with endometriosis who were randomly assigned to receive either probiotic or a placebo for 12 weeks. The results showed that the group receiving probiotics had a significant reduction in menstrual pain and an improvement in life quality compared to the placebo group [37]. A more recent pilot study included 37 women with pathologically proved endometriosis who were randomly assigned to receive either a probiotic containing *L. acidophilus/plantarum/fermentum/gasseri* or a placebo for 8 weeks. The results showed that the probiotic group had a significant reduction in menstrual pain and dysmenorrhea compared to the placebo group [38].

There are several notable limitations for these two studies such as small sample sizes, lack of standardization of probiotics, and variability in endometriosis severity when interpreting the results. Larger and well-designed clinical trials are needed to further investigate the potential role of probiotics in the management of endometriosis.

Table 1 shows the summarized results of clinical studies for probiotics in gynecologic conditions.

Clinical role of probiotics in reproductive endocrinology and infertility

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome is characterized by an excess production of androgens by the ovaries, leading to a wide range of symptoms including chronic anovulation, cysts within the ovaries, acne, hirsutism, insulin resistance, and weight gain. It is also a common cause of infertility in women. The pathogenesis of PCOS is not known because it is a complex multi-genetic disorder. Globally, the estimated mean prevalence of PCOS is around 21 % [39]. Currently, there is no cure for PCOS, with therapies focused on the management of symptoms, and/or assisted fertility. There is some evidence suggesting that probiotics may have a role in PCOS. A recent meta-analysis summarized 17 RCTs with a total of 1049 participants found that probiotic supplementation significantly reduced fasting blood glucose, insulin levels, and insulin resistance in women with PCOS. Probiotic supplementation was also associated with a significant decrease in total cholesterol, LDL cholesterol, and triglycerides levels. However, there were no significant changes observed in HDL cholesterol levels. In terms of hormonal profiles, the meta-analysis showed that probiotic supplementation significantly decreased levels of luteinizing hormone (LH) and testosterone in women with PCOS while no significant changes were observed in follicle-stimulating hormone (FSH) levels [40]. Overall, this meta-analysis suggested that probiotic supplementation may be safe and effective in improving metabolic parameters and hormonal profiles in women with PCOS.

Infertility

Infertility is a widespread global health concern that impacts millions of individuals in their reproductive years. Current data indicates that approximately one out of every six individuals worldwide will encounter infertility during their lifetime [41]. Various factors have been identified as potential causes of infertility, with age standing out as one of the most significant

Table 1
Clinical studies of probiotics in gynecologic conditions.

Gynecologic conditions	Common *Lactobacillus (L)* strains	Clinical studies	Main results and findings	Level of evidence	Reference
Bacterial vaginosis	*L. crispatus* *L. jensenii* *L. gasseri*	17 RCTs	Probiotics vs. placebo More effective, RR 15.2 (95 % CI 3.87–59.65) Probiotics + antibiotics vs. antibiotics alone More effective, RR 1.23 (95 % CI 1.05–1.43)	Strong	12
Vaginal candidiasis	*L. gasseri* *L. crispatus*	23 RCTs	Probiotics vs. placebo Less recurrence, RR 0.36 (95 % CI 0.21–0.63)	Strong	15
Genitourinary syndrome of menopause	*L. acidophilus*	3 RCTs	Probiotics + E3 vs. E3 alone More effective in improvement of clinical symptoms/signs	Strong	16–18
HPV infection	*L. rhamnosus* *L. crispatus* *L. reuteri*	2 RCTs 1 single arm	Probiotics vs. placebo Clear rate at 15 months, 58.1 % vs. 54.2 % Probiotics 6 months vs. 3 months Clear rate at 9 months, 35.3 % vs. 12.7 % Single arm, clear rate at 3 months, 71.4 %	Weak	29–31
CIN I	*L. rhamnosus* *L. reuteri*	1 controlled pilot study	Probiotics vs. placebo Clear rate at 6 months, 60 % vs. 31 %	Weak	33
Endometriosis	*L. gasseri* *L. acidophilus* *L. plantarum* *L. fermentum*	2 RCTs	Probiotics vs. placebo Significantly decrease menstrual pain Improve quality of life	Moderate	37, 38

CI: confidence interval; CIN, cervical intraepithelial neoplasm; E3, estriol; HPV, human papilloma virus; LDL, low density lipoprotein; RCTs, randomized controlled trials; RR, relative risk.

determinants of fertility decline while dysbiosis of vaginal microbiota is reported associated with female infertility [42]. Research has demonstrated that a high-*Lactobacillus* vaginal microbiota is correlated with a reduced risk of female infertility [43]. Given the ability of probiotics to promote a high-*Lactobacillus* vaginal microbiota, it is reasonable to hypothesize that probiotics could have a beneficial effect on women experiencing infertility. Furthermore, a prior RCT provided evidence that oral probiotics can restrict the proliferation of vaginal *Ureaplasma parvum* in unexplained infertile women [44]. This microorganism is known to be associated with infertility, stillbirth, chorioamnionitis, and neonatal morbidity. However, the study did not examine the subsequent fertility and pregnancy outcomes. A recent systematic review, comprising two studies investigating probiotic treatment in women undergoing assisted reproductive technology (ART) for infertility, unfortunately did not show an increase in the clinical pregnancy rate [45]. In the context of male infertility, clinical studies suggested that oral probiotics may enhance both sperm quantity (concentration) and quality (motility), although the study's sample size was limited [46–48]. Hence, there is a necessity for well-designed, high-quality RCTs to determine whether probiotics should be recommended for couples undergoing ART.

Table 2 shows the summarized results of clinical studies for probiotics in reproductive endocrinology and infertility.

Clinical role of probiotics in pregnancy

Preterm labor

Preterm labor, also known as premature labor, defined as the onset of regular uterine contractions and cervical changes before the 37th week of pregnancy. Most of preterm labors are associated with maternal infection. Other causes include cervical incompetence, multiple gestation, maternal stress, and certain medical conditions such as diabetes and hypertension. However, the real cause for many cases of preterm labor is still undetermined. Preterm birth causes 60 %–80 % of neonatal deaths while survivors can experience life-long complications [49]. Due to the anti-inflammatory properties exhibited by probiotics in the genital tract, numerous studies have explored their potential role in preventing preterm labor. However, the evidence is limited and inconclusive. Some studies have shown promising results, while others did not demonstrate a significant effect. A recent meta-analysis, including 21 RCTs with a total of 4098 women, evaluated and summarized the effectiveness of probiotics in reducing the risk of preterm birth in women with a singleton pregnancy. The probiotic interventions in the studies included various strains and formulations of probiotics. The results showed that the use of probiotics did not affect the risk of preterm birth <34 weeks

Table 2
Summarized results of clinical studies for probiotics in reproductive endocrinology and infertility.

Reproductive endocrinology & infertility	Common *Lactobacillus (L)* strains	Clinical studies	Main results and findings	Level of evidence	Reference
Polycystic ovary syndrome	*L. rhamnosus* *L. reuteri* *L. acidophilus* *L. casei*	17 RCTs	Probiotics vs. placebo Decrease fasting sugar, insulin, insulin resistant, total cholesterol, LDL cholesterol, luteinizing hormone, testosterone	Strong	40
Female infertility	*L. acidophilus* *L. casei*	2 controlled pilot studies	Probiotics vs. placebo No difference in clinical pregnancy rate	Weak	45
Male infertility	*L. paracasei* *L. rhamnosus*	3 controlled pilot studies	Probiotics vs. placebo Increase sperm concentration and motility	Weak	46–48

LDL, low-density lipoprotein; RCTs, randomized controlled trials.

(relative risk: 1.03, 95 % CI: 0.29–3.64) and the risk of preterm birth <37 weeks (relative risk: 1.08, 95 % CI: 0.71–1.63) [50]. Although some strains of probiotics have been found to have anti-inflammatory properties and can reduce the risk of preterm labor by decreasing inflammation in the maternal-fetal interface, available clinical data did not show evidence to support its utility in preterm labor prevention.

Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus (GDM) is a type of diabetes that develops during the second or third trimester of pregnancy and typically subsides after delivery. Genetics and lifestyle factors such as obesity, physical inactivity, and unhealthy diet can increase the risk of developing GDM. Several studies have investigated the potential application of probiotics in gestational diabetes, but the results were conflicting. Some studies suggested that probiotics may have a beneficial effect on glucose metabolism and insulin resistance in pregnant women with GDM, while others have found no significant effect [51]. However, a recent meta-analysis summarized 11 RCTs to look at the effects of probiotics on GDM prevention and maternal and neonatal outcomes and results showed that probiotics may have a positive effect on glycemic control and lipid metabolism [52]. They concluded that the use of specific probiotic supplementation may be a promising prevention and therapeutic strategy for GDM. However, further studies are warranted to address the limitations rising from the heterogeneity among existing evidence and to fully understand the potential role of probiotics in this condition.

Obstetric anemia

There are several reasons for the possible occurrence of anemia during pregnancy. One of the most common causes is an increase in blood volume during pregnancy, which can lead to a dilutional effect and a decrease in to decrease the concentration of red blood cells. Additionally, if the mother's iron stores are insufficient for fulfill the increased demand for iron during pregnancy to support fetal growth and development, anemia may occur. Although evidence on the role of probiotics in obstetric anemia is limited, there is some recently emerging research suggesting that certain probiotic strains may improve iron absorption and utilization, and then potentially improving anemia in pregnant women. A randomized, double-blind, placebo-controlled trial recruited 326 healthy pregnant women who were randomly assigned to receive either a daily dose of *L. plantarum* 299v and a low dose of iron or a placebo and a low dose of iron from gestation week 10 until the end of pregnancy. The results showed that the combination of *L. plantarum* 299v and a low dose of iron significantly attenuated the decrease in serum ferritin from baseline to week 28 and week 35 and resulted in reduced prevalence of iron deficiency (59 % vs 78 %, $p = 0.017$) and iron deficiency anemia (7.4 % vs 21 %, $p = 0.023$) at week 35 [53]. They concluded that intake of probiotics from early pregnancy was safe, attenuated the loss of iron stores and improved iron status in healthy pregnant women. However, more RCTs with larger sample sizes are needed to confirm these findings.

Maternal group B streptococcus (GBS) colonization

Maternal GBS colonization refers to the presence of *Streptococcus agalactiae* in the mother's body during pregnancy. It is estimated that 10–30 % of pregnant women carry GBS in their vaginal or rectal area at any given time. In most cases, GBS does not cause any symptoms or harm to the mother, but it can be passed to the newborn during delivery and cause serious infections. A preclinical study found that probiotic was able to inhibit the growth of GBS in vitro, suggesting a potential role in preventing GBS colonization [54]. Therefore, several clinical studies attempted to evaluate the role of probiotics in the prevention of maternal GBS colonization. A recent systemic review analyzed 5 RCTs including a total of 583 pregnant women to find that probiotic supplementation started after 30 weeks of gestation significantly reduced the risk of GBS colonization compared to that with placebo or no intervention, with a pooled odds ratio of 0.41 (95 % CI 0.21–0.78). The secondary outcome analysis also suggested that the probiotics administration was associated with a safe perinatal profile [55]. The authors concluded that probiotic supplementation may be an effective strategy for reducing the risk of GBS colonization for pregnant women.

Habitual abortion

Habitual abortion, also known as recurrent pregnancy loss, is defined as the occurrence of three or more consecutive pregnancy losses before the 20th week of gestation. There were various causes been identified, including genetics, anatomical, endocrine, immunological, and placental anomalies. However, in many cases, the exact cause remains unknown. One of the causes of habitual abortion is the alteration of spermatozoa antigenicity such as human leukocyte antigen (HLA) [56]. Studies have shown that sperm HLA expression is reduced in males whose partners have a history of recurrent miscarriage [57], and such reduced HLA expression has been associated with a decreased risk of developing anti-paternal cytotoxic antibodies in their female partners [58]. The reduced HLA expression on spermatozoa may make paternal antigens less visible to the maternal immune system and potentially increase the likelihood of an immune response against them or embryo, leading to recurrent miscarriage. The precise mechanisms behind decreased sperm HLA expression are not fully understood and may be due to the inappropriate composition of microbiota in habitual abortion couples (semen and vagina). A recent in vitro study has shown that a treatment with *L. rhamnosus* may enhance the expression of HLA class I & II on spermatozoa from the habitual abortion couples. The treated spermatozoa were then co-cultured with the wife's peripheral blood mononuclear cells for 12 days. The results showed an increase in both IgG and anti-paternal cytotoxic antibodies in the co-cultured supernatant [59]. The authors concluded that probiotics supplement may be beneficial for couples suffering from habitual abortion with an immunologic cause. Till now, only one pilot clinical trial investigating the potential role of probiotics in habitual abortion with 20 women who had experienced $\geq$3 miscarriages within the first 12 weeks of pregnancy. *Lactobacillus salivarius* was administrated daily to these recruited women for a maximum of 6 months. At the end of study, 15 of them had subsequent full-term pregnancies while only one had an abortion [60]. This promising result encourages investigators to conduct a larger, more thorough study such as RCT to confirm the findings.

Lactational mastitis

Lactational mastitis usually occurs in breastfeeding women. This condition typically starts in the first few months after giving birth, but also possible at any time during lactation. It can lead to decreased breastfeeding rates, which then may lead to several consequences such as increased risk of infant morbidity, negative impact on maternal health, and increased healthcare cost. There is some evidence that probiotics may participate in preventing and treating mastitis in breastfeeding women. A review of clinical studies published in 2022 included 6 RCTs indicated that probiotic supplementation during pregnancy may reduce the risk of mastitis

Table 3
Clinical studies of probiotics in obstetric conditions.

Obstetric conditions	Common *Lactobacillus (L)* Strains	Clinical studies	Main results and findings	Level of evidence	Reference
Preterm labor	*L. rhamnosus* *L. reuteri* *L. acidophilus*	21 RCTs	Probiotics vs. placebo <34 weeks birth, RR 1.03 (95 % CI 0.29–3.64) <37 weeks birth, RR 1.08 (95 % CI 0.71–1.63)	None	50
Gestational diabetes	*L. gasseri* *L. crispatus*	11 RCTs	Probiotics vs. placebo Improvement in fasting glucose, insulin, insulin resistant, total cholesterol	Strong	52
Obstetric anemia	*L. plantarum*	1 RCT	Probiotics + iron vs. iron alone IDA at 35 weeks gestational age, 7.4 % vs. 21 %	Moderate	53
Group B streptococcus colonization	*L. rhamnosus* *L. crispatus* *L. reuteri* *L. jensenii*	5 RCTs	Probiotics vs. placebo Colonization risk, RR 0.41 (95 % CI 0.21–0.78)	Strong	55
Habitual abortion	*L. rhamnosus* *L. salivarius*	1 single arm cohort	Probiotics 6 months 15/20 subsequent term pregnancy	Weak	60
Lactational mastitis	*L. salivarius* *L. gasseri* *L. fermentum*	6 RCTs	Probiotics vs. placebo Mastitis risk, RR 0.49 (95 % CI 0.35–0.69) Decrease bacteria count in milk	Strong	61

CI: confidence interval; IDA, iron deficiency anemia; RCTs, randomized controlled trials; RR, relative risk.

(OR: 0.49, 95 % CI 0.35–0.69) and significantly reduced the bacteria counts in the milk of mastitis patients [61]. Although promising, high-quality multicenter clinical trials are still required to support this result, especially focusing on the issues of probiotic strains selection, intervention doses, and efficacy evaluation criteria.

Table 3 shows the summarized results of clinical studies of probiotics in obstetric conditions.

Future directions in gynecologic cancer research

The advances in microbiomics and metagenomics have enabled investigators to start identifying microbial communities and/or particular bacterial species that might promote pathological states in the female reproductive tract and consequently contribute to certain types of gynecologic cancer. For example, a cross-sectional study included 31 women showed that simultaneous presence of *Atopobium* and *Porphyromonas* in lower and upper genital tract combined with abnormal vaginal pH (>4.5) was strongly associated with endometrial cancer [62]. Another study investigated the microbiome in ovarian tissue and adjacent normal tissue samples from 25 patients with ovarian carcinoma and results showed that there was a significant decrease in the abundance of *Lactobacilli* and an increase in the abundance of anaerobic bacteria in the ovarian carcinoma tissue samples, as compared to adjacent normal tissue samples [63]. Another robust case-control study investigated 360 women with 176 ovarian cancers and 184 controls to reveal that the cervicovaginal microbiome of women with ovarian cancer had lower abundance of *Lactobacilli* (<50 %) [64]. All the above studies suggested that there may be a potential link between alterations in the genital microbiome and the development of gynecologic cancer. Recognizing this association holds several significant clinical implications, including its potential for early detection and risk assessment, preventive strategies, treatment enhancement, improved prognostication, and patient education. However, a causal relationship has not been clearly established and the exact mechanisms linking vaginal microbial composition and the development and progression of gynecologic cancer are still not fully elucidated. Understanding the causal link and mechanism has the potential to decrease gynecologic cancer incidence and enhance treatment outcomes. This part should be the main subject of ongoing research.

Conclusion

In conclusion, the application of probiotics is a safe, effective, and natural way to support women's health. Incorporating probiotics into a woman's daily routine, either through supplementation or dietary sources, may offer numerous benefits for gynecologic and obstetric health, including preventing STIs and treating vaginal infections, improving metabolic and hormonal profiles in PCOS women, reducing the risk of obstetrics complications such as GDM, maternal GBS colonization, obstetric anemia, and postpartum mastitis, alleviating menstrual pain and endometriosis-related symptoms, and potentially even reducing the risk of certain gynecologic cancers. These benefits are likely due to the ability of probiotics to restore and maintain a healthy vaginal microbiome, as well as to modulate the immune system. Further research is required to fully understand the action mechanisms of probiotic, although current evidence strongly supports their use in promoting women's health.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Review Article

Circulating Galectin-3 levels in women with polycystic ovary syndrome: A meta-analysis

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine disorder characterized by multifactorial and intricate pathogenesis. The discovery of novel markers has been a significant step toward understanding the mechanisms of PCOS. Galectin-3 has emerged as a novel factor in metabolic disorders. This meta-analysis examines the association between circulating Galectin-3 and PCOS. A systematic review and meta-analysis were performed to identify relevant articles in the electronic databases PubMed, Web of Science, Scopus, Cochrane, EMBASE, and Google Scholar. The search covered the period from January 2000 to March 2023 and followed a predefined search strategy. Eight articles were included in the analysis with a total of 594 participants (322 patients with PCOS and 272 controls). Pooled standardized mean difference (SMD) and 95 % confidence interval [CI] were used to evaluate the association between Galectin-3 levels and PCOS. The results indicated a significant association between PCOS and galectin-3 levels (SMD = 0.58; 95 % CI: 0.15−1.01; p = 0.007). In addition, subgroup analysis showed a significant difference in serum Galectin-3 levels in women with PCOS and a higher homeostatic model assessment for insulin resistance ratio (SMD = 0.89; 95 % CI: 0.45−1.33; p < 0.001). The researchers also performed meta-regression and subgroup analyses to specify sources of heterogeneity. The results of our meta-analysis suggest an association between increased levels of galectin-3 and PCOS. Galectin-3 plays a significant role in the progression of PCOS and could be used as a novel diagnostic biomarker. Nevertheless, it is essential to perform further studies to confirm and support our conclusions.

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that affects women during their reproductive years. It is characterized by a combination of hormonal imbalances, metabolic disturbances, and reproductive abnormalities. PCOS gets its name from the presence of multiple small cysts on the ovaries, but it involves more than just cysts. It is estimated that PCOS affects approximately 5−10 % of women worldwide, making it one of the most common endocrine disorders in women of reproductive age [1].

Symptoms of PCOS can vary among women but usually include irregular menstrual cycles and the presence of polycystic ovaries. Women with PCOS may also experience other signs and symptoms, such as hirsutism (excessive hair growth), acne, weight gain, insulin resistance, and elevated insulin levels, which are believed to play a significant role in the development of PCOS. In addition, hormonal imbalances characterized by increased androgen production and decreased production of female hormones such as estrogen and progesterone contribute to the manifestation of PCOS symptoms. It is essential to know that not all women with PCOS have the same symptoms, and the severity of symptoms may also vary [2]. Early diagnosis and appropriate management are crucial to prevent long-term complications associated with PCOS, such as type 2 diabetes, cardiovascular disease, infertility, and psychological distress [3,4]. PCOS is a multifaceted condition that requires a comprehensive and individualized approach to management. Lifestyle modifications,

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including regular exercise, a balanced diet, and weight management, form the foundation of PCOS management. Medications may be prescribed to regulate menstrual cycles, control androgen levels, and improve insulin sensitivity [5,6].

Galectin-3 is a protein that has garnered significant attention in the field of biomedical research due to its diverse functions and potential implications in various diseases. Galectin-3 belongs to a family of proteins known as galectins, which are characterized by their ability to bind to β-galactoside molecules. Galectin-3 is a multifunctional protein involved in a wide range of biological processes, including cell growth, differentiation, inflammation, autophagy, and immune responses. It is found in various tissues throughout the body, including the immune system, skin, gastrointestinal tract, and cardiovascular system [7].

Galectin-3 plays a pivotal role in modulating cell-to-cell interactions and signaling pathways. One of its key functions is its involvement in inflammation and immune responses. Galectin-3 can regulate the activation and recruitment of immune cells, such as macrophages and neutrophils, to sites of inflammation. It also influences the production of inflammatory molecules, cytokines, and chemokines, which are important mediators of the immune response [8,9]. Furthermore, Galectin-3 has been associated with fibrosis, a pathological process characterized by excessive deposition of extracellular matrix components. It can promote the activation of fibroblasts, leading to increased production of collagen and other components of the extracellular matrix. This suggests a role for Galectin-3 in fibrotic diseases affecting various organs, such as the liver, lung, and heart [10,11].

The dysregulation of galectin-3 expression and function has been found in numerous diseases, highlighting its clinical importance. Elevated levels of galectin-3 have been observed in various cancers, such as breast, colon, and lung cancer, where it promotes tumor progression, angiogenesis, and metastasis. In addition, galectin-3 has been linked to cardiovascular diseases such as heart failure and atherosclerosis by contributing to inflammation, fibrosis, and tissue remodeling [12–14].

In addition to cancer and cardiovascular diseases, Galectin-3 has been implicated in other pathological conditions, including inflammatory disorders, autoimmune diseases, and neurodegenerative disorders. Its involvement in these diseases suggests its potential as a therapeutic target or a diagnostic marker for disease progression and prognosis [7,15]. The therapeutic potential of targeting Galectin-3 in various diseases, aiming to develop novel treatment strategies. Additionally, efforts are being made to develop Galectin-3 inhibitors or modulators that can selectively interfere with its functions and provide therapeutic benefits.

Galectin-3 plays a multifaceted role in regulating ovarian function. It is involved in follicular development, steroidogenesis, and the process of ovulation. The altered expression and function of Galectin-3 can disrupt these ovarian processes, leading to the formation of ovarian cysts, a defining feature of PCOS [16,17]. Galectin-3 has emerged as a captivating player in the intricate puzzle of PCOS. Its involvement in insulin resistance, chronic inflammation, and ovarian dysfunction highlights its significance in the pathogenesis of the disorder. Continued research into Galectin-3 will contribute to a deeper understanding of PCOS and potentially offer new avenues for diagnosis and treatment, bringing hope to individuals affected by this common endocrine disorder.

Materials and methods

Protocol and registration

A comprehensive systematic review and meta-analysis were conducted to ensure transparency and accuracy throughout the review process following PRISMA-recommended guidelines. In addition, our systematic review was also appropriately registered in PROSPERO, a recognized international database for prospectively registered systematic reviews [18,19]. (CRD42023438578).

Eligibility criteria

Our comprehensive analysis included a diverse range of observational studies published between January 2000 to March 2023. The main objective of these studies was to investigate galectin-3 levels in individuals with and without PCOS based on the Rotterdam criteria.

It is important to highlight that some studies were excluded from our analysis for various reasons: (I) studies with inappropriate comparison subjects, inadequate study designs, or missing controls were not included. (II) Publications such as reviews, letters, editorials, animal studies, intervention studies, and conference proceedings were also excluded. (III) Studies without extractable data were not considered.

Literature search

A comprehensive literature search was conducted in various databases, including PubMed, Web of Science, Scopus, Cochrane, EMBASE, and Google Scholar, covering the period from January 2000 to March 2023. The search strategy included a combination of relevant keywords, including “Galectin-3,” Galectin,” “Gal-3,” “LGALS3 (gene symbol for Galectin-3)," “galactoside-binding lectin 3,” “Beta-galactoside-binding lectin L-29,” “Mac-2 antigen” “GALBP,” “Galaptin,” “LGALS3A” (alternative gene symbol for Galectin-3) lectin L-29,” “polycystic ovary syndrome,” “PCOS,” and “polycystic ovary,” effectively using the coordinating conjunctions “AND” and “OR”." In addition, references to relevant articles were manually searched, and extensive efforts were made to identify relevant literature beyond commonly used sources, referred to as gray literature. All retrieved records were carefully organized using EndNote 9 software to ensure systematic management, and a thorough screening process was applied to exclude duplicate studies.

Study selection

Two independent authors searched databases and assessed the studies' eligibility before sharing their findings. In cases where different perspectives arose, a consensus was achieved through the involvement of a third observer and joint discussions to resolve any discrepancies. The evaluation process strictly adhered to a predefined extraction checklist.

Data extraction

Data extraction was performed using a developed checklist that included critical ingredients. These features included comprehensive information on the origin of the study (including the name of the first author, the year of publication, and the region of study), the study design (cross-sectional, cohort, or case–control), the characteristics of the participants (such as age, number of participants, and body mass index), the measurements performed, the diagnostic criteria, and the outcomes reported (Table 1).

Risk of bias assessment in the included studies

The Grading, Development, and Evaluation of Recommendations guideline (GRADE) assessed the quality of the studies included in this meta-analysis. The assessment found that the

Table 1
Characteristics of the studies included in the systematic review and meta-analysis.

Author, yr (Ref)	Country	Study designs	Number of participants	BMI (kg/m^2) (PCOS vs. controls)	Age (yr) (PCOS vs. controls)	Sample (unit)	GRADE Assessment
Yilmaz *et al.*, 2014 [20]	Turkey	Case-control	PCOS:56 Control:41	25.0 ± 4.7; 23.1 ± 4.1	22.7 ± 5.4; 22.3 ± 5.7	Serum (ng/dl)	⊕⊕⊕○
Anikilhan *et al.*, 2018 [21]	Turkey	Cross-sectional	PCOS:25 Control:65	27.93 ± 2.88; 27.16 ± 3.68	26.48 ± 5.46; 26.64 ± 4.48	Serum (ng/ml)	⊕⊕○○
Wu *et al.*, 2018 [22]	China	Case control	PCOS:66 Control:21	27.3 ± 4.90; 24.5 ± 4.96	31.0 ± 3.68; 35.3 ± 3.10	Serum, FF (ng/ml)	⊕⊕○○
Martinez-Garcia *et al.*, 2019 [23]	Spain	Case control	PCOS:17 Control:17	23.4 ± 2.1; 24.4 ± 2.3	26.3 ± 3.25; 24.7 ± 4.8	Serum (ng/ml)	⊕⊕⊕⊕
Yavuz *et al.*, 2019	Turkey	Case control	PCOS:30 Control:30	28.75 ± 2.84; 23.55 ± 2.82	23.17 ± 4.44; 21.50 ± 2.96	Serum (pg/ml)	⊕⊕⊕○
Alves *et al.*, 2020 [24]	Brazil	Case-control	PCOS:44 Control:25	27.80 ± 4.36; 26.93 ± 4.61	32.33 ± 6.28; 33.17 ± 6.67	Serum (ng/ml)	⊕⊕⊕○
Niu *et al.*, 2020 [25]	China	Case control	PCOS:67 Control:53	34.37 ± 3.42; 28.11 ± 3.79	25.75 ± 4.92; 25.46 ± 4.14	Serum (ng/ml)	⊕⊕○○
Salehi *et al.*, 2023 [26]	Canada	Case-control	PCOS:17 Control:20	21.86 ± 0.73; 22.20 ± 0.73	25.1 ± 1.9; 28.2 ± 3.1	Serum, FF (pg/ml)	⊕⊕⊕○

BMI: Body mass index, PCOS: Polycystic ovary syndrome, GRADE: Grading of recommendations assessment, development, and evaluation, FF: follicular fluid. The rating of GRADE is as follows: ⊕⊕⊕○ Moderate quality: We are moderately confident about the effect estimate; ⊕⊕○○ Low quality: Our confidence in the effect estimate is limited, ⊕○○○ Very low quality: We have very low confidence in the effect estimate.

studies had varying levels of quality. This variability is primarily due to factors such as the potential risk of bias, conflicting effect estimates, and imprecision due to limited sample size, resulting in a substantial degree of uncertainty. In conclusion, although the meta-analysis demonstrated a positive correlation between Galectin-3 levels and PCOS, caution should be exercised in interpreting the results (Table 1). In addition, the quality of the included studies was evaluated using the Newcastle-Ottawa scale, which was developed specifically for assessing nonrandomized studies in meta-analyses [27]. This scale assigns scores from 0 to 9. Studies with a score of $\leq$4 were considered low quality, whereas studies with a score of $\geq$5 were considered high quality (Table 2).

Statistical analysis

Circulating Galectin-3 levels in individuals with polycystic ovary syndrome (PCOS) were evaluated compared to the control group using standardized mean difference (SMD) and a 95 % confidence interval (CI). Heterogeneity between studies was assessed using the I^2 and Cochran's Q test, with statistical significance determined by $p < 0.05$ or $I^2 > 50$ %. Also, A random-effects model was employed for analysis. Egger and Begg's tests were used to examine publication bias, with a significance point at a p-value of 0.05. Subgroup analyses and meta-regressions were performed to identify sources of heterogeneity. In addition, sensitivity analysis was carried out to evaluate the impact of each individual study by excluding it from the analysis. Statistical analysis was performed using Comprehensive Meta-Analysis (CMA) v3.7z software.

Results

Characteristics of the included studies

The search strategy resulted in 252 articles in the database. Prior to the screening process, 80 duplicate records were removed. Subsequently, 117 articles were eliminated based on the evaluation of their titles and abstracts. After this initial screening, 55 articles that showed potential relevance underwent a comprehensive full-text assessment. Of these articles, 33 studies were excluded for various reasons. Finally, a total of eight studies effectively met the pre-established selection criteria, with a combined participation of 594 individuals. More detailed information can be found in Fig. 1.

Association and comparison details

A comprehensive investigation was conducted across eight studies with a total sample size of 594 participants to examine Galectin-3 levels in participants with polycystic ovary syndrome (PCOS) compared with a control group. In addition, subgroup and meta-regression analyses were performed to identify underlying sources of heterogeneity, including body mass index (BMI), age, HOMA-IR, geographic region, and year of study. This

Table 2
Quality assessment based on the Newcastle-Ottawa Scale of studies included in this meta-analysis.

Author, yr (Ref)	Selection				Comparability	Exposure			Score
	An adequate definition of case	Representativeness of the case	Selection of controls	Definition of controls	cases and controls matched and/or adjusted by factors	Assessment of exposure	The same method of ascertainment for cases and controls	the same response rate for both groups	
Salehi et al., 2023	★	★	–	★	★	★	★	★	7
Niu et al., 2020	★	★	–	★	★	★	★	–	6
Alves et al., 2020	★	★	★	★	★	★	★	★	8
Martinez-Garcia et al., 2019	★	★	★	★	★★	★	★	–	8
Yavuz et al., 2019	★	–	★	★	★	★	★	★	7
Wu et al., 2018	★	★	–	★	★	★	★	★	7
Anikilhan et al., 2018	★	★	★	★	★	–	★	–	6
Yilmaz et al., 2014	★	★	–	★	★★	–	★	★	7

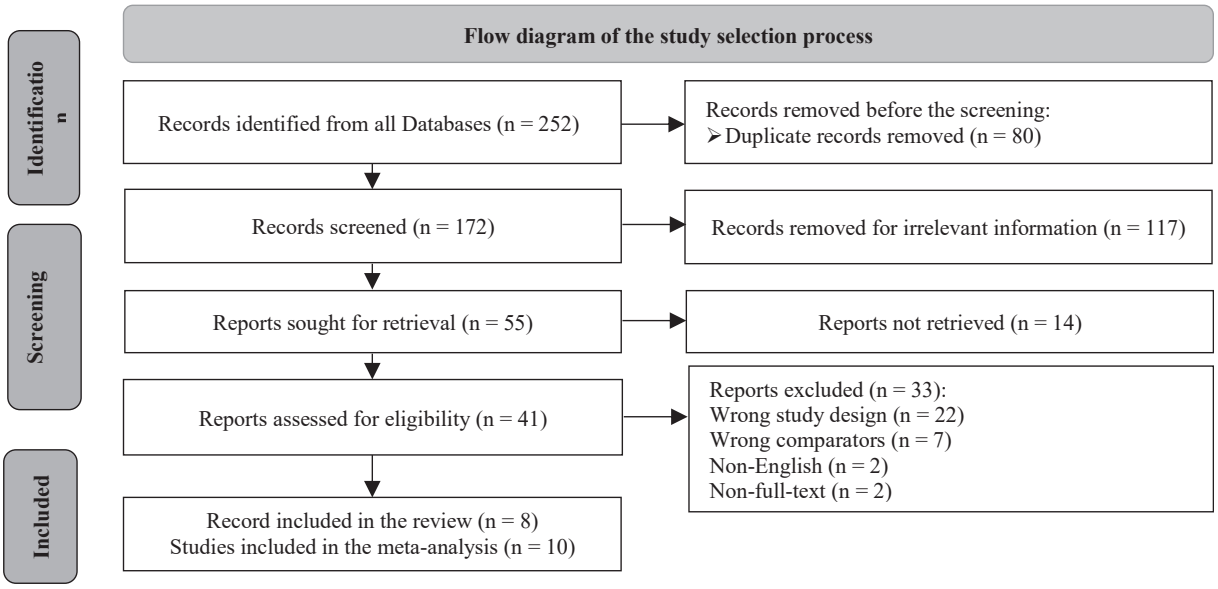


Fig. 1. Flow diagram of study selection adjusted by prisma.

comprehensive investigation has significantly enhanced our comprehension of the association between Galectin-3 levels and PCOS while providing valuable insight into the potential factors contributing to the observed heterogeneity.

Relationship between serum Galectin-3 levels and PCOS

Meta-analysis

The result of the meta-analysis revealed a significant increase in Galectin-3 level in the PCOS group compared with the control group (Standardized Mean Difference [SMD] = 0.58; 95 % Confidence Interval [CI]: 0.15–1.01; p = 0.007). In addition, significant heterogeneity was found between studies (I^2 = 93.75 %; p < 0.001), as shown in Fig. 2.

Prediction interval

Our estimation suggests a prediction interval of −0.92 to 2.09 for the true effect size, assuming a normal distribution. This range is expected to cover the effect size in 95 % of comparable populations. However, it is important to note that the true effect size may vary within this interval due to factors such as sample size and study design. Therefore, it is imperative that caution be exercised when interpreting results within this prediction interval (Fig. 3).

Subgroup analysis

A significant contrast was observed between women aged 25 years and older and those below 25 years. Subgroup analysis was conducted on studies that included participants with an average age of 25 years or above (SMD = 0.82; 95 % CI: 0.20–1.46; p = 0.009), as

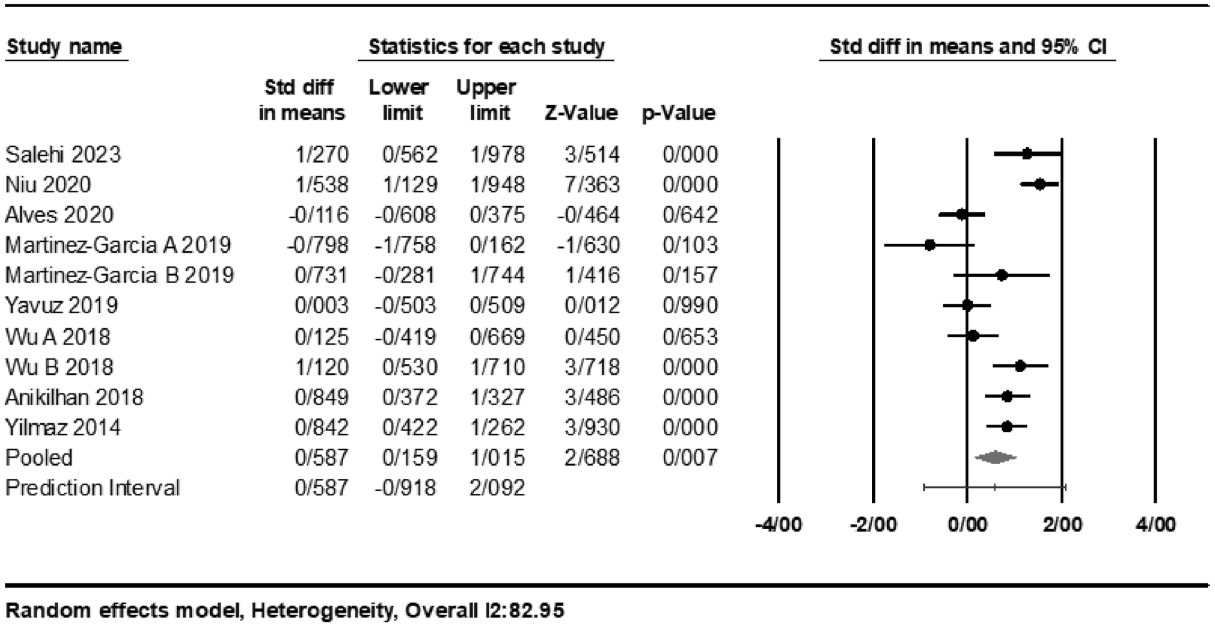


Fig. 2. The forest plots comparing serum Galectin-3 levels between PCOS and control groups.

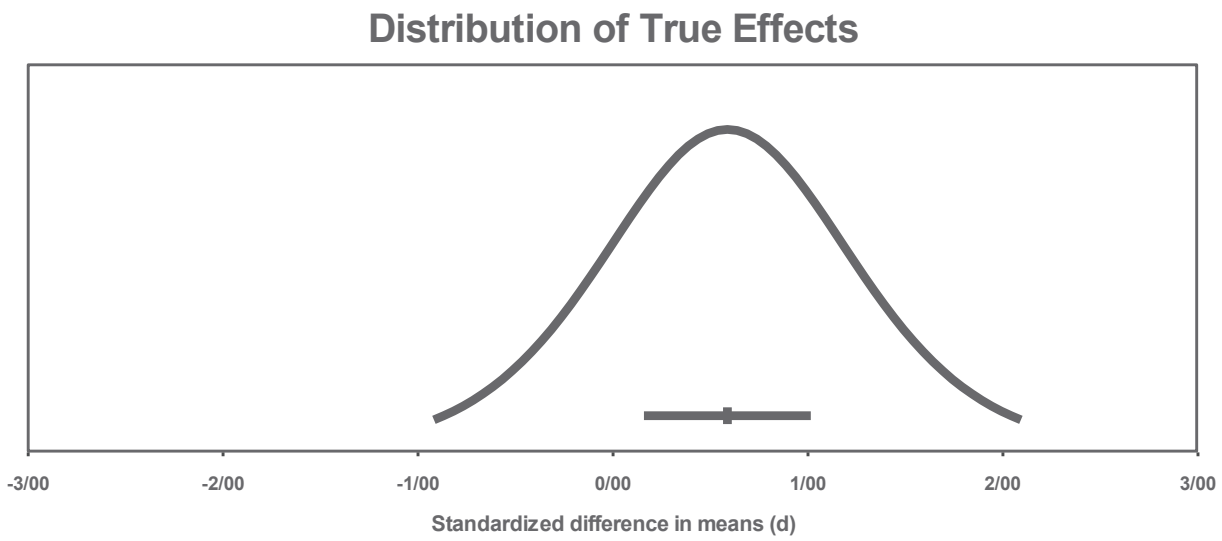


Fig. 3. The prediction interval SMD of Galectin-3 levels between PCOS and control groups.

well as those under 25 years (SMD = 0.33; 95 % CI: −0.23 to −0.91; p = 0.0) (Fig. 4). Moreover, Subgroup analyses were performed for each study based on BMI, age, and HOMA-IR. In the subgroup analysis of studies with a mean BMI ≥25 kg/m^2 or ≤25 kg/m^2, it was observed that women with a BMI >25 kg/m^2 had higher Galectin-3 levels than women with a BMI <25 kg/m^2 (SMD = 0.83; 95 % CI: 0.34–1.32; p < 0.001) (Fig. 5). In addition, subgroup analysis based on studies with a mean HOMA-IR ≥ 3 (indicating insulin resistance) or ≤3 (indicating no insulin resistance) showed that women with HOMA-IR > 2.9 had significantly higher serum Galectin-3 levels (SMD = 0.89; 95 % CI: 0.45–1.33; p < 0.001) than women with HOMA-IR < 2.9 (SMD = −0.08; 95 % CI: (−0.50)-0.34; p < 0.001) (Fig. 6). In conclusion, Table 3 presents a concise and comprehensive summary of the results of our subgroup analysis.

Meta-regression analysis

A meta-regression analysis was performed with a series of meta-analysis studies to examine the influence of sample size, HOMA-IR ratio, study year, and geographic region on the observed effect sizes. The analysis yielded the following results (Fig. 7).

Geographic region (meta-regression coefficient: −0.577; 95 % CI: −2.03 to 0.87; p = 0.43), sample size (meta-regression coefficient: 0.011; 95 % CI: −0.001 to 0.02; p = 0.08), and Year of studies (meta-regression coefficient: 0.023; 95 % CI: −0.18 to 0.23; p = 0.82) were not statistically significant. However, there was a significant positive relationship between the HOMA-IR ratio and effect sizes (meta-regression coefficient: 0.410; 95 % CI: 0.09 to 0.72; p = 0.01). This suggests that studies conducted with higher insulin resistance tended to have larger effect sizes compared with other studies.

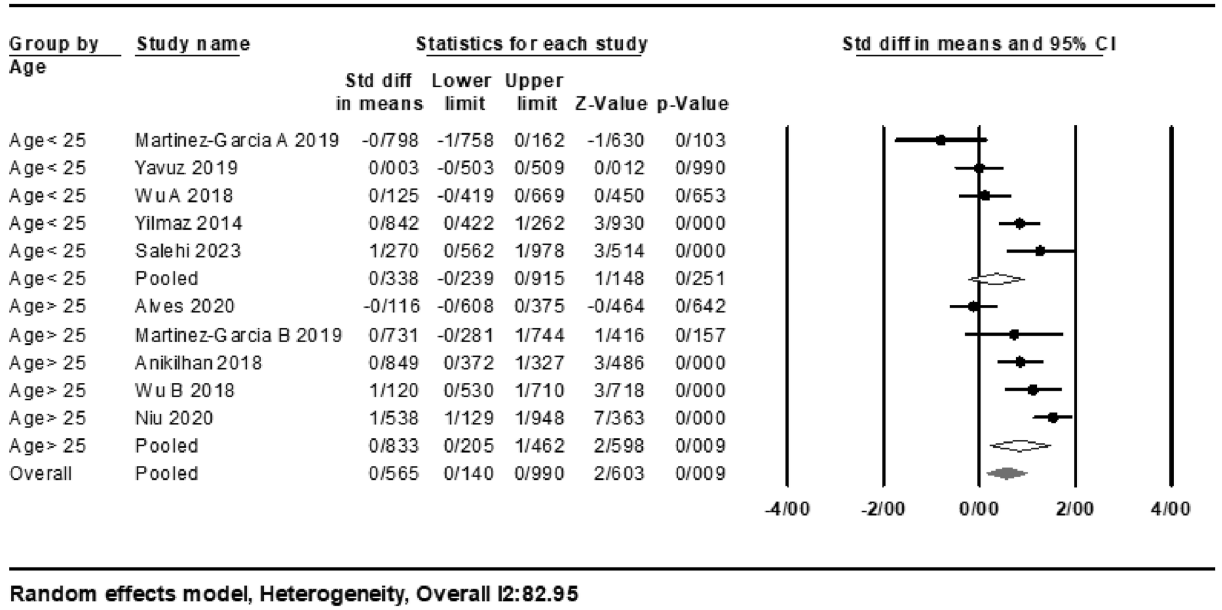


Fig. 4. Forest plot of age ≥25 years and age ≤25 years in subgroup analysis.

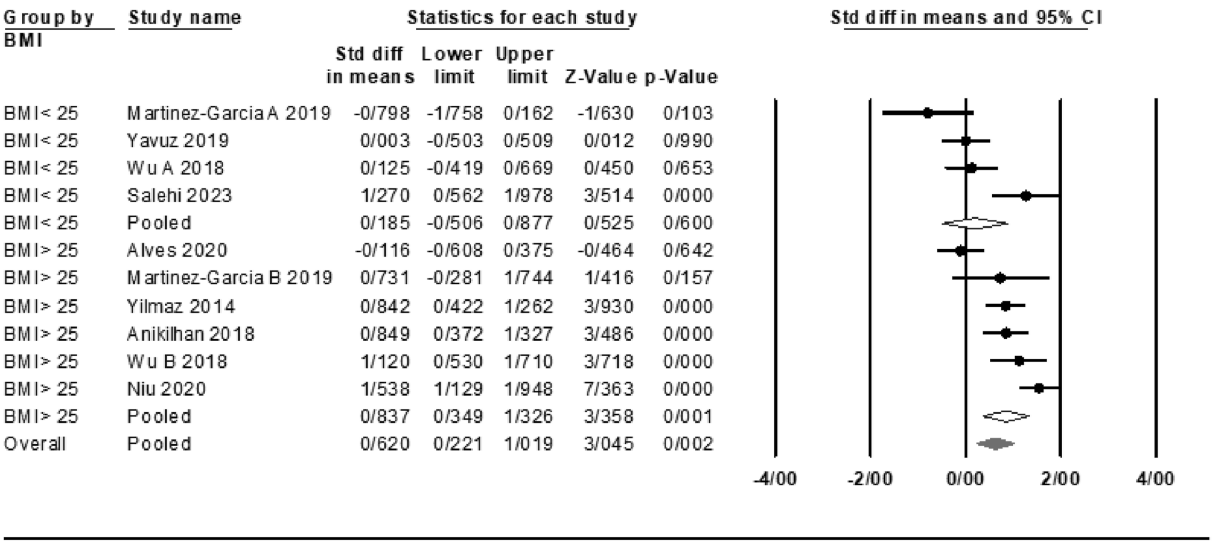


Fig. 5. Forest plot of body mass index ≥25 kg/m^2 and body mass index ≤25 kg/m^2 in subgroup analysis.

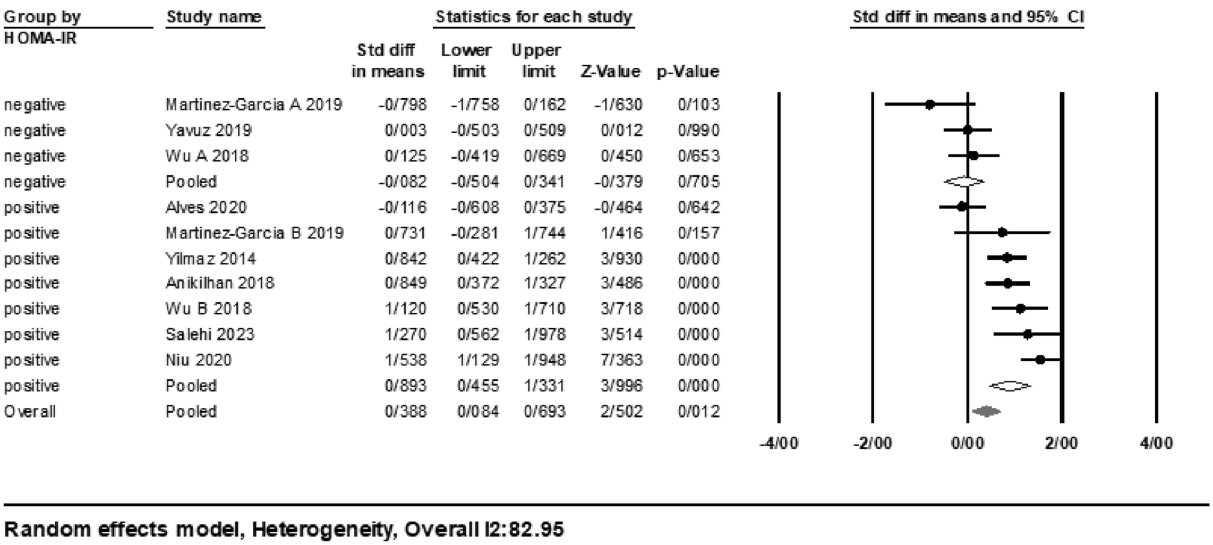


Fig. 6. Forest plot of positive/negative HOMA-IR in subgroup analysis.

Table 3
Subgroup meta-analysis of the included studies.

Subgroup analysis	Number of studies	SMD (95 % CI)	I^2	P_{value} for Heterogeneity
BMI				
<25	4	0.18 (−0.50, 0.87)	77.89	0.004
≥25	6	0.83 (0.34, 1.32)	81.13	<001
Mean Age				
<25	5	0.33 (−0.23, 0.91)	79.30	0.002
≥25	5	0.82 (0.20, 1.46)	84.88	<001
HOMA-IR ratio negative (below 2.9)	3	−0.08 (−0.50, 0.34)	27.86	0.25
positive (above 2.9)	7	0.89 (0.45, 1.33)	78.24	<001

These findings emphasize the potential influence of the ratio HOMA-IR and indicate that geographic region, sample size, and year of study did not significantly influence the results of the meta-analysis studies.

Sensitivity analysis and publication bias

Sensitivity analysis and assessments for publication bias provided additional evidence to support the credibility of the pooled

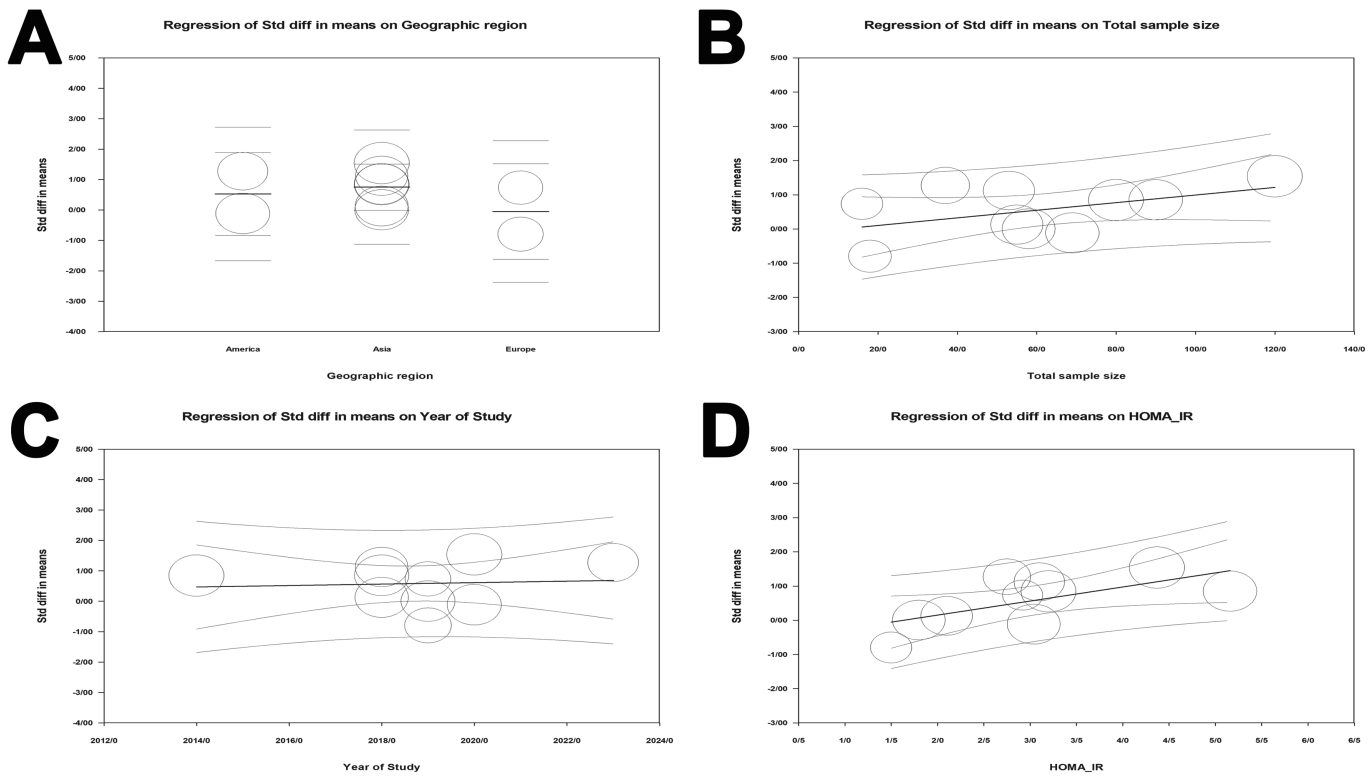


Fig. 7. Meta-regression of serum Galectin-3 levels in women with PCOS based on: A) Geographic region, B) Total sample size, C) Year of studies, D) HOMA-IR ratio.

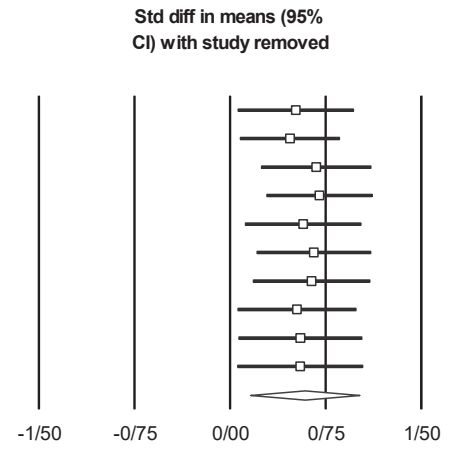
results. In order to ensure the accuracy of the study, a thorough sensitivity analysis was performed by excluding individual studies one by one. This method ensured that each study was consistent with the research objectives. The analysis revealed a standardized mean difference (SMD) range from 0.159 to 1.015 when comparing Galectin-3 values between the case and control groups. The 95 % confidence interval (CI) was calculated to range from 0.057 to 0.287 for the lower limit and from 0.861 to 1.117 for the upper limit (Fig. 8). In addition, the values of I2 retained their distinct clarity. The sensitivity analysis showed stable results throughout, with no significant changes observed.

The funnel plot method was used to detect any publication bias, and Egger's test was used to quantify the publication bias (Fig. 9). Egger's test shows no evidence of publication bias regarding the included studies (coefficient: −2.827; Standard Error: 1.963; 95 % CI: −9.660 to 4.005, P = 0.367).

Discussion

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder that affects women of reproductive age. It is characterized by hormonal imbalances, ovarian dysfunction, and metabolic

Study name	Statistics with study removed					
	Point	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Salehi 2023	0/515	0/232	0/061	0/970	2/221	0/026
Niu 2020	0/470	0/200	0/079	0/861	2/354	0/019
Alves 2020	0/675	0/220	0/244	1/107	3/066	0/002
Martinez-Garcia A 2019	0/702	0/212	0/287	1/117	3/312	0/001
Martinez-Garcia B 2019	0/574	0/232	0/118	1/029	2/469	0/014
Yavuz 2019	0/657	0/229	0/209	1/106	2/874	0/004
Wu A 2018	0/640	0/235	0/180	1/100	2/726	0/006
Wu B 2018	0/525	0/237	0/060	0/990	2/213	0/027
Anikilhan 2018	0/551	0/247	0/067	1/036	2/229	0/026
Yilmaz 2014	0/551	0/252	0/057	1/044	2/188	0/029
Pooled	0/587	0/218	0/159	1/015	2/688	0/007



Random effect model, Heterogeneity: overall I2:82.95, (pvalue):0.00

Fig. 8. Sensitivity analysis was performed by excluding each study from the eligible studies.

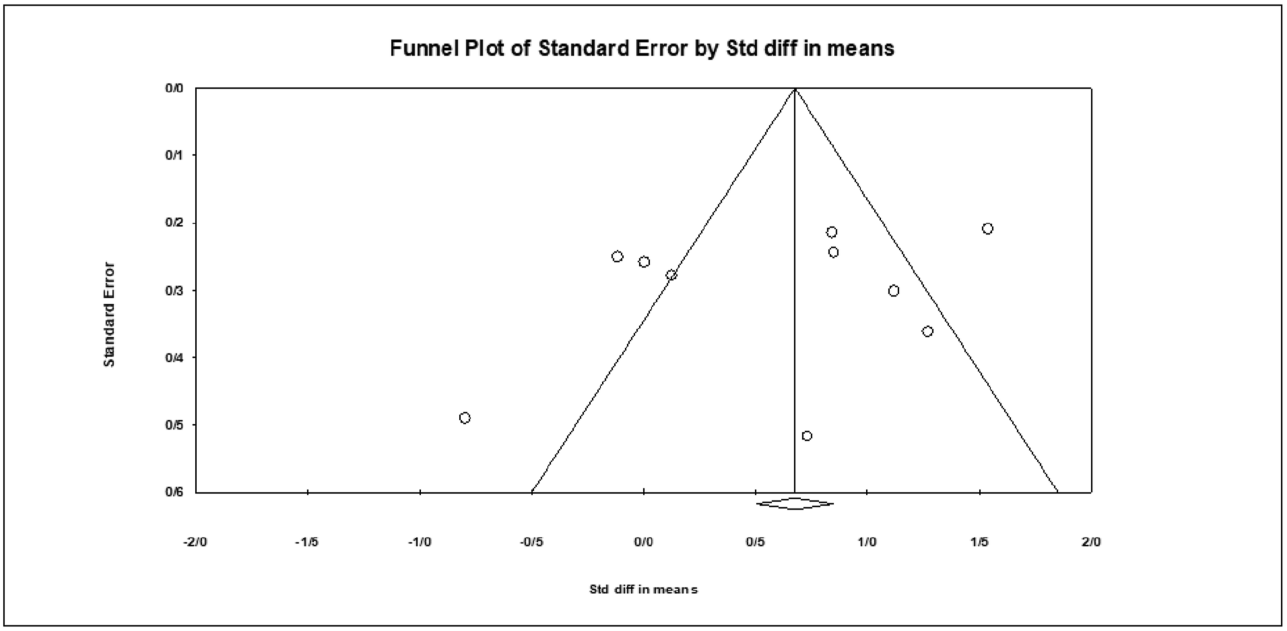


Fig. 9. Funnel plot of standard error by standard differences in the means of serum Galectin-3 level.

Disorders [28]. This condition is characterized by its association with insulin resistance, obesity, abnormal lipid levels, type 2 diabetes, cardiovascular disease, and infertility [29,30]. Recent research has focused on understanding the underlying mechanisms involved in PCOS pathogenesis, and one particular protein of interest is Galectin-3. This meta-analysis aims to explore the correlation of Galectin-3 in PCOS and shed light on its potential implications and relevance to the disease. Several studies suggest that the overall increase in galectin-3 levels in PCOS may contribute to several key aspects of the disease [26,25,22,21,31]. In contrast, other studies have found no significant changes or decreases in galectin-3 levels when comparing PCOS and non-PCOS individuals [23,16,24].

Overall, this meta-analysis shows an increase in circulating galectin-3 levels in women with PCOS compared with controls (Standardized Mean Difference [SMD] = 0.58; 95 % Confidence Interval [CI]: 0.15–1.01; p = 0.007). This meta-analysis finds a significant level of heterogeneity across studies. Multiple subgroup analyses and meta-regressions were performed to examine whether heterogeneity was caused by characteristics such as sample size, HOMA-IR ratio, study year, and geographic region.

The results of the subgroup meta-analysis indicate that PCOS patients over 25 years have higher galectin-3 levels than those under 25. In PCOS females over 25 years of age, increased galectin-3 levels may be caused by inflammation and obesity [32,33]. In addition, galectin-3 has been found to induce fibrosis in various tissues. Meanwhile, several studies have linked PCOS to ovarian fibrosis. Consequently, galectin-3 may indirectly contribute to PCOS pathogenesis [8]. Besides its well-defined role in inflammation and autoimmune disease, Women are more likely to exhibit this condition [34–36]. Several studies have shown that galectin3 levels are elevated in obese and type 2 diabetic people, and this increase is directly related to BMI and insulin resistance [37,38]. Another subgroup meta-analysis in this study demonstrated the significantly increased level of galectin-3 in PCOS patients over 25 BMI. This result could be interpreted in this way, PCOS patients encounter hormonal abnormalities that result in obesity, and a subsequent increase in Galectin-3 levels is observed; in other words, patients with PCOS who have a BMI greater than 25 kg/m^2 compared to patients with a BMI less than 25 kg/m^2 have higher levels of galectin-3 compared to the control group.

High values of HOMA-IR indicate greater insulin resistance, and this measurement is based on fasting insulin and glucose levels. A correlation has been found between galectin-3 concentrations and HOMA-IR values in populations, including those with obesity and type 2 diabetes [20,31]. HOMA-IR level above 2.9 indicates significant insulin resistance [39,40]. Among the subgroups investigated in this study, women with HOMA-IR > 2.9 had significantly higher serum galectin-3 levels than women with HOMA-IR < 2.9.

A meta-regression analysis was conducted to investigate the potential factors contributing to heterogeneity and examine the influence of sample size, HOMA-IR ratio, study year, and geographic region on the observed effect sizes. There is only one significant positive relationship between the HOMA-IR ratio and effect sizes (meta-regression coefficient: 0.410; 95 % CI: 0.09 to 0.72; p = 0.01). This suggests that studies conducted with higher insulin resistance tended to have larger effect sizes than other studies.

The correlation between Galectin-3 and PCOS holds potential clinical implications. Galectin-3 could serve as a biomarker for PCOS diagnosis and disease severity. In addition, targeting Galectin-3 signaling pathways could provide new therapeutic strategies for the treatment of PCOS. Researchers can investigate the therapeutic potential of targeting galectin-3 to alleviate symptoms and improve outcomes in individuals with PCOS by understanding its role in the development of the disease. Galectin-3 involvement in ovarian dysfunction, chronic inflammation, and insulin resistance suggests a potential role in the development and progression of PCOS. It is important to note that the present study had certain limitations. Specifically, non-English articles and academic theses were not included in the study. The research was carried out exclusively using the English language. However, further research is required to clarify the precise mechanisms through which Galectin-3 influences the pathophysiology of PCOS. Nevertheless, the findings from this study provide valuable insights into the complex nature of PCOS. These findings could potentially lead to the development of innovative diagnostic approaches to pave the way for future

advancements in diagnosing and treating this widespread endocrine disorder.

Conclusion

This meta-analysis revealed higher levels of circulating Galectin-3 in women diagnosed with PCOS, suggesting that Galectin-3 may contribute to the development of the disease. Nevertheless, it is crucial to highlight the considerable variability observed in the studies included in this analysis. In order to attain more precise and reliable results, future research should prioritize well-conducted studies with larger samples and appropriate control of confounding factors.

Declaration of competing interest

The authors affirm that no conflict of interest is associated with the publication of the article " Circulating Galectin-3 levels in Women with Polycystic Ovary Syndrome: a meta-analysis." No financial, personal, or professional relationships exist that could influence the research findings or the content presented in the manuscript. The authors have not received any financial support, grants, or funding that could have impacted the study's design, execution, or reporting. The research is solely based on scientific knowledge and unbiased evaluation of available literature and data. The authors uphold their work's highest standards of professionalism, integrity, and transparency. Any potential conflicts will be promptly disclosed to ensure ongoing objectivity and credibility.

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Original Article

LINC01234 promoted malignant behaviors of breast cancer cells via hsa-miR-30c-2-3p/CCT4/mTOR signaling pathway

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ABSTRACT

Objective: Despite continuous progress in treatment, recurrence and metastasis limit further improvement in the prognosis of breast cancer (BC) patients. Our aim was to search for a crucial prognostic biomarker of BC.

Materials and methods: Patient data were selected from The Cancer Genome Atlas (TCGA) and GTEx databases. Several online public databases, including Gene Expression Profiling Interactive Analysis (GEPIA), miRWalk, miRDB, and LncBase Predicted v.2, were used to identify potential upstream miRNAs and lncRNAs. These findings were validated through in vitro experiments.

Results: A total of 1, 097 invasive BC samples and 572 normal breast tissues (including 113 samples from TCGA and 459 samples from GTEx) were collected for the study. CCT4 was not only significantly overexpressed in BC compared with normal breast tissues but also had important prognostic significance ($P < 0.001$). By intersecting miRWalk and miRDB and conducting correlation analysis, hsa-miR-30c-2-3p was identified as the most probable upstream miRNA of CCT4. Following an extensive assessment that included survival analysis, correlation analysis, and common binding-site prediction, LINC01234 was chosen as the most likely upstream lncRNA. In vitro experiments showed that LINC01234-siRNA inhibited the proliferation, invasion, and migration abilities of BC cells. Western blot analysis further confirmed that LINC01234 promoted malignant behaviors of BC cells via the CCT4/mTOR signaling pathway.

Conclusion: The LINC01234/hsa-miR-30c-2-3p/CCT4/mTOR axis was identified as a potential ceRNA regulatory mechanism in BC. These findings established the foundation for systematically unveiling the pathological mechanisms of BC and provided new insights for targeted therapy of BC patients.

Introduction

Breast cancer (BC) is the most common malignancy among women worldwide [1]. In 2015, there were 234,190 new cases of BC and 40,730 BC-related deaths in the United States [2]. Europe saw an estimated 350,000 new cases of BC annually [3]. Histologically, BC can be classified as non-invasive BC (in situ) and invasive BC. Invasive BC accounts for the vast majority of all BC cases and can be further categorized as invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) based on cellular origins [4,5]. BC can also

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be classified into different types based on the expression status of estrogen receptor (ER), progesterone receptor (PR), Ki67, and human epidermal growth factor receptor 2 (HER2). These types include luminal-A (ER+/PR+/HER2−/Ki67 low), luminal-B (ER+/PR+/HER2-/Ki67 high, ER+/PR low/HER2-/Ki67 any, ER+/PR+/HER2+/Ki67 any), HER2-enriched (ER-/PR-/HER2+), and basal-like (ER-/PR-/HER2-). Luminal-A type patients generally exhibit the best prognosis and those with basal-like type often have the worst clinical outcomes [6]. Treatment approaches for BC include surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, and immunotherapy techniques [7–10]. Despite advancements in treatment, recurrence and metastasis hinder further improvement in the prognosis of BC patients [11]. Therefore, it is crucial to identify an ideal biomarker for monitoring BC development and investigate its underlying molecular mechanisms.

Studies have increasingly suggested that the competitive endogenous RNA (ceRNA) mechanism plays a crucial role in tumor initiation and progression [12]. The ceRNA regulation network was first proposed by Salmena et al. [13], suggesting that different classes of RNA competitively bind to microRNAs (miRNAs), regulating their target mRNAs. One common mechanism in this regulatory network is the long non-coding RNA (lncRNA)-miRNA-mRNA ceRNA interaction. In this network, lncRNA acts as a molecular sponge, binding to miRNA through complementary binding sites. As the binding is competitive, increased binding between lncRNA and miRNA reduces the ability of miRNA to bind to its target mRNA gene. This decreased binding results in upregulated expression levels of the target gene, leading to alterations in cellular phenotypes such as cell growth and invasion. Accumulating evidences suggest that the ceRNA regulatory network plays a crucial role in various pathophysiological processes of BC, including differentiation, proliferation, apoptosis, invasion, and migration [14–16]. For instance, LINC00511 regulated the expression of transcription factor E2F1 by competitively binding to miR-185-3p, thereby impacting BC tumorigenesis [17]. Using invasive BC data from The Cancer Genome Atlas (TCGA), Fan et al. [18] developed a lncRNA-miRNA-mRNA ceRNA network, consisting of 8 miRNAs, 48 lncRNAs, and 10 mRNAs, which showed potential prognostic value. However, they did not identify the most influential molecular pathway for survival. We hypothesized that there was a ceRNA regulatory network with a significant impact on BC prognosis. To test our hypothesis, we conducted bioinformatics analysis and in vitro experiments.

Patients and methods

Data and bioinformatics

Gene expression data and clinical data of BC patients and normal breast tissues were downloaded from the TCGA database (http://tcga-data.nci.nih.gov) and GETx database (https://commonfund.nih.gov/GTEx/), including mRNA, miRNA, lncRNA, age, gender, stage, ER status, PR status, HER2 status, and follow-up information. The inclusion criteria were as follows: (1) over 18 years of age; (2) available survival data; (3) available gene data. Exclusion criteria included: (1) non-invasive BC and (2) lack of histological diagnosis. The R package "Limma" was utilized to investigate the differential expression of genes. The selection criteria for differentially expressed genes (DEGs) were set to $P < 0.01$ and $\log|FC| > 1$ (P-value adjusted using Benjamini–Hochberg method). The results were presented using a volcano plot, and the complete list of DEGs was provided in Supplementary Tables. To further validate the relationship between protein levels and survival time, the Kaplan–Meier plotter (https://kmplot.com/analysis/) was applied. The optimal cutoff value for protein levels was selected automatically.

Gene expression and prognostic analysis of pan-cancer were conducted using the Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/). This interactive web server provides comprehensive information about each gene including Ensembl ID, alias, gene expression profiling, survival analysis, and principal component analysis. For the analysis, a |Log2FC| cutoff of 0.6 and a P-value cutoff of 0.05 were applied. The median method was selected as the group cutoff with cutoff-high values (50%) and cutoff-low values (50%).

The mRNA-miRNA network visualization was created using Cytoscape software (Version 3.7.2). To investigate the potential functions of candidate miRNAs, miEAA (https://ccb-compute2.cs.uni-saarland.de/mieaa2/) was utilized. The conditions were set as follows: Select type of enrichment analysis: Over-representation (ORA); Species: *Homo sapiens*; P-value adjustment method: FDR (Benjamini–Hochberg) adjustment. Gene expression correlation analysis was performed using Pearson correlation analysis. Genes were excluded if they had zero expression values in more than 30% of the samples. Based on the median expression levels of genes, BC patients were divided into high-expression and low-expression groups. Batch survival analysis was performed using the R packages "survminer" and "survival". Hazard ratio (HR), 95% confidence interval (95% CI), and log-rank P-value were calculated.

To increase the prediction accuracy of upstream miRNAs and lncRNAs, several public databases were used in combination, including miRWalk (http://mirwalk.umm.uni-heidelberg.de/), miRDB (http://mirdb.org/miRDB/), and LncBase Predicted v.2 (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=lncbasev2%2Findex-predicted). Entering the name of target gene to get the predicted upstream genes. The intersection of the miRWalk and miRDB results was recognized as effective candidate upstream miRNAs of CCT4.

The data set of immuno-correlation analysis was obtained from Tumor Immune Estimation Resource (TIMER) database version 2.0 (https://cistrome.shinyapps.io/timer/). TIMER 2.0 is a publicly available online database used for analyzing tumor-infiltrating immune cells in different types of cancer. It estimates immune cell infiltration levels using the Spearman correlation coefficient. By selecting the target gene (CCT4) and the type of immune infiltrating cell, the database automatically calculates the correlation between gene expression and immune cell infiltration levels across all cancer types. The abbreviations used for cancer types are consistent with those in the TCGA database. LinkedOmics (http://linkedomics.org/login.php) was used to explore genes most correlated to CCT4. The detailed steps were as follows: (1) SELECT CANCER COHORT: TCGA_BRCA; (2) SELECT SEARCH DATASET: HiSeq RNA; (3) SELECT SEARCH DATASET ATTRIBUTE: CCT4; (4) SELECT TARGET DATASET: HiSeq RNA; (5) SELECT STATISTICAL METHOD: Pearson Correlation test.

Clinical verification

Seventy-two paired BC tissues and adjacent breast tissues were collected from Xuzhou Central Hospital. All patients provided written informed permission, and ethics was approved by the Ethics Committee of Xuzhou Central Hospital. Gene expression of LINC01234 was measured by real time-PCR. Human BC cell line BT-20 (Procell Life Science&Technology Co., Ltd., Cat No. CL-0324) was used to carry out transient transfection of siRNA. Sequence information of LINC01234-Homo-919: sense strand: GCCUGGAACUAUUCUGAAATT; antisense strand: UUUCAGAAUAGUUCCAGGCTT. Sequence information of LINC01234-Homo-990: sense strand: GAGCCUGCCUGAUAAUAAATT; antisense strand: UUUAUUAUCAGGCAGGCUCTT. Sequence information of LINC01234-Homo-1611: sense strand: GCUUGCGUGAACAGAUAAUTT; antisense strand:

AUUAUCUGUUCACGCAAGCTT. Lipofectamine-based transfection reagent Lipo-3000 (Invitrogen, L3000008) was used to transfect the above siRNA fragments. SiRNA fragment with the highest transfection efficiency (LINC01234-Homo-990) was selected to perform the following experiments.

Proliferation, invasion, and migration assay

A Cell Counting Kit-8 (CCK8) assay kit was purchased from Boster Biotechnology Co. Ltd (Wuhan, China) and utilized to evaluate cell proliferation ability. A total of 5×10^3 cells were seeded in 96-well plates and cultured for 1, 2, 4, and 6 days, respectively. The absorbance was measured at 450 nm. Cell invasion and migration abilities were assessed using Transwell cell assays. For the invasion assay, the Transwell membrane was coated with Matrigel. Then, 1×10^5 cells suspended in serum-free DMEM medium were added to each Transwell well, while fresh DMEM containing 10% fetal bovine serum (FBS) was added to the lower chamber. After 48 h of culture, non-migrated/invaded cells were removed. The remaining Transwell procedures were carried out as previously described [19].

Dual-luciferase reporter assay

The wild-type and mutant LINC01234 and CCT4 with possible hsa-miR-30c-2-3p binding sites were constructed using pmirGlO Dual-luciferase Vectors (Promega, Madison, WI, USA). A total of 2×10^5 cells were co-transfected with the aforementioned vectors, hsa-miR-30c-2-3p mimics, and a miRNA control in a 24-well plate, and cultured for 48 h. The luciferase intensity was measured using the Dual-Luciferase Reporter Assay Kit (Promega, Madison, WI, USA).

Western blot

Western blot analysis was performed according to previous literature [20]. Briefly, total protein was extracted, adjusted to a suitable concentration, and subjected to SDS-PAGE gel electrophoresis. The gel was then transferred onto a polyvinylidene fluoride (PVDF) membrane using the sandwich method. After blocking, the primary and secondary antibodies were sequentially incubated, whose detailed information was provided below. Rabbit anti-CCT4 antibody (catalog number A6548, diluted at 1:1500), rabbit anti-S6K1 antibody (catalog number A16658, diluted at 1:2000), rabbit anti-p-S6K1-T389 antibody (catalog number AP0564, diluted at 1:2000), rabbit anti-4EBP1 antibody (catalog number A1248, diluted at 1:1000), and rabbit anti-p-4EBP1 antibody (catalog number AP0030, 1:1000) were purchased from Abclonal, China. Rabbit anti-PI3K p85 (alpha) antibody (catalog number AF6241, diluted at 1:2000), rabbit anti-PI3K p85 (Tyr458/p55Try199) antibody (catalog number AF3242, diluted at 1:1000), and mouse anti-GAPDH (T0004, diluted at 1:5000) were purchased from Affinity, USA. Rabbit anti-AKT (catalog number ab21027, diluted at 1:1000) and rabbit anti-p-AKT (S473) (catalog number 9271, diluted at 1:1000) were purchased from CST, USA. Finally, exposure, development, and photography were performed.

Statistical analysis

Analytical statistics, graphing, and plotting were performed using R software (R version 3.3.0). Two sample *t* tests were utilized to compare the gene expression differences between groups. Log-rank tests were performed to evaluate the survival differences between groups. It should be noted that two-stage procedure was utilized when HR functions crossed and P-value of the two-stage test (TSPV) was provided (R package "TSHRC" 0.1.6). Pearson or Spearman correlation analysis were utilized to test correlation. *P < 0.05 indicates statistical significance, **P < 0.01 indicates highly statistical significance, and **P < 0.001 indicates very highly statistical significance.

Results

A total of 1097 BC samples and 572 normal breast tissues were collected for the study, including 113 samples from TCGA and 459 samples from GTEx (Table 1). The age of the participants ranged from 26 to 90, with a median age of 58. The majority of participants were female (98.9%). There were 132, 445, 175, and 15 cases in stage I, II, III, and IV, respectively (33.1% missing). 599 were ER-positive and 179 were ER-negative (29.1% missing). 521 were PR-positive and 254 were PR-negative (29.4% missing). 114 were HER2-positive and 650 were HER2-negative (30.4% missing). It's important to note that approximately one-third of the cases had missing data for the stage, ER status, PR status, and HER2 status variables. However, this missing data does not affect the subsequent analysis and results.

The differential gene expression analysis identified 4546 DEGs, with 3171 genes up-regulated and 1375 genes down-regulated (Fig. 1A, Supplementary Table 1). A batch survival analysis revealed that 503 mRNA genes were associated with overall survival (OS) (Supplementary Table 2). From the top 10 genes with the most significant survival differences, including MCTS1, PDP1, QPRT, PGK1, RTN4IP1, CCT4, CISD1, FAM155B, SLC35A2, we assessed whether their corresponding proteins also had prognostic significance. The Kaplan–Meier plotter showed that three out of ten genes (both genes and proteins: MCTS1, PGK1, and CCT4) were significantly associated with OS (Fig. 1B and C, Supplementary Fig. 1A and 1B). Given the importance of MCTS1 and PGK1-associated ceRNA regulation networks in BC as shown in previous studies [21–23], we further analyzed CCT4, which has an unreported ceRNA network. CCT4 was found to be significantly associated with survival in 8 out of 33 TCGA cancer types, including BC, adrenocortical carcinoma (ACC), head and neck squamous cell

Table 1
Clinical features of entire cohort.

Clinical features	TCGA	Single-center cohort
Total	1097	72
Age		
Median (range)	58 (26–90)	62 (46–71)
Gender		
Female	1085	72
Male	12	0
Stage[a]		
I	132	23
II	445	31
III	175	17
IV	15	1
ER status[b]		
Positive	599	53
Negative	179	19
PR status[c]		
Positive	521	47
Negative	254	25
HER-2 status[d]		
Positive	114	28
Negative	650	44
Vital status		
Dead	151	0
Alive	946	72

[a] 330 missing in TCGA.
[b] 319 missing in TCGA.
[c] 322 missing in TCGA.
[d] 333 missing in TCGA.

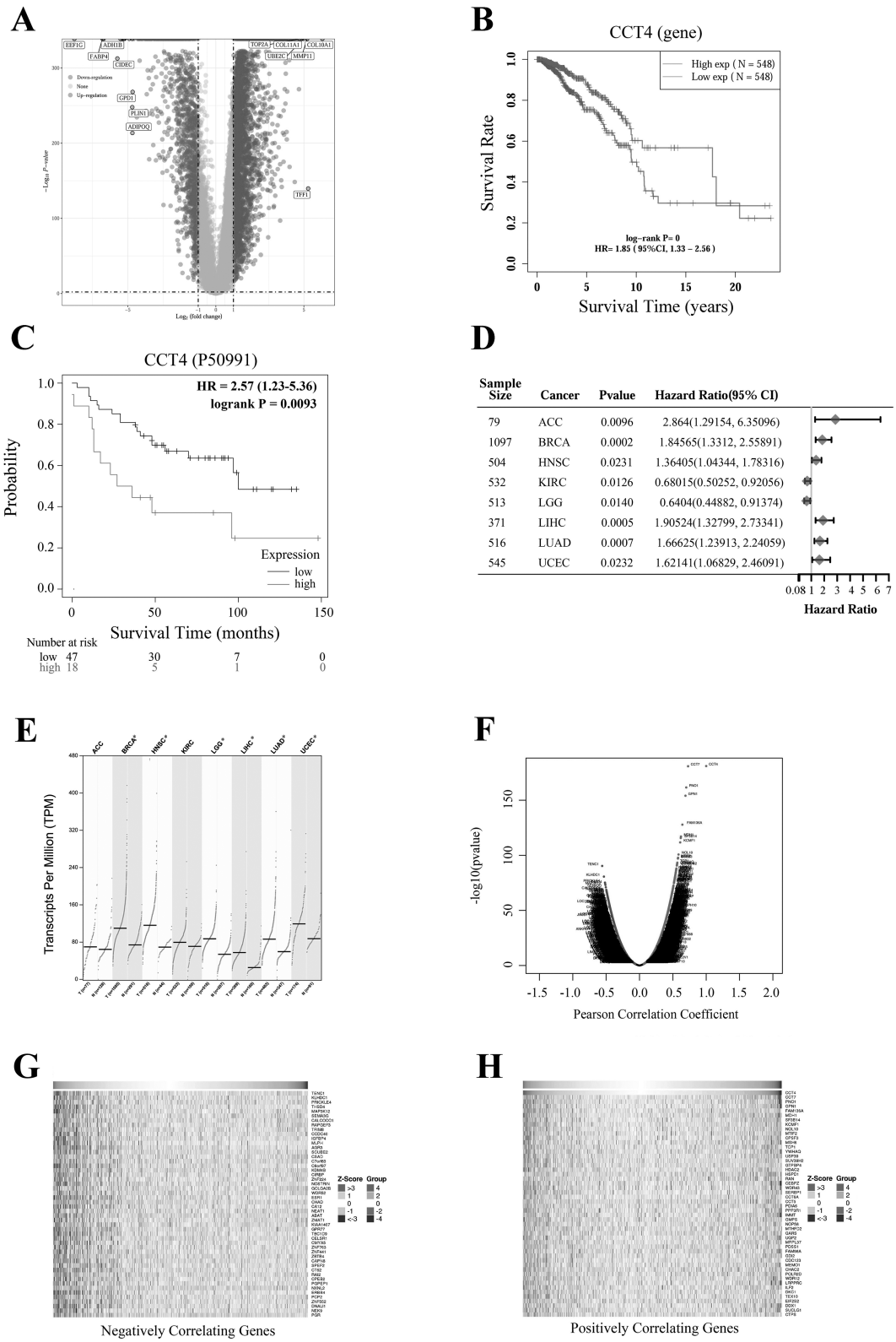

Fig. 1. CCT4 was identified as a crucial prognostic biomarker in breast cancer. (A) DEGs represented as a volcano map. (B) Survival analysis of CCT4 gene expression in BC. (C) Survival analysis of CCT4 protein in BC. (D) Pan-cancer survival analysis of CCT4 (significant results). (E) Pan-cancer analysis of CCT4 expression differences between cancerous and corresponding normal tissues (results with prognostic significance were shown only). (F) Genes most correlated to CCT4. (G) Heat map demonstrating the top 50 negatively correlating genes. (H) Heat map demonstrating the top 50 positively correlating genes.

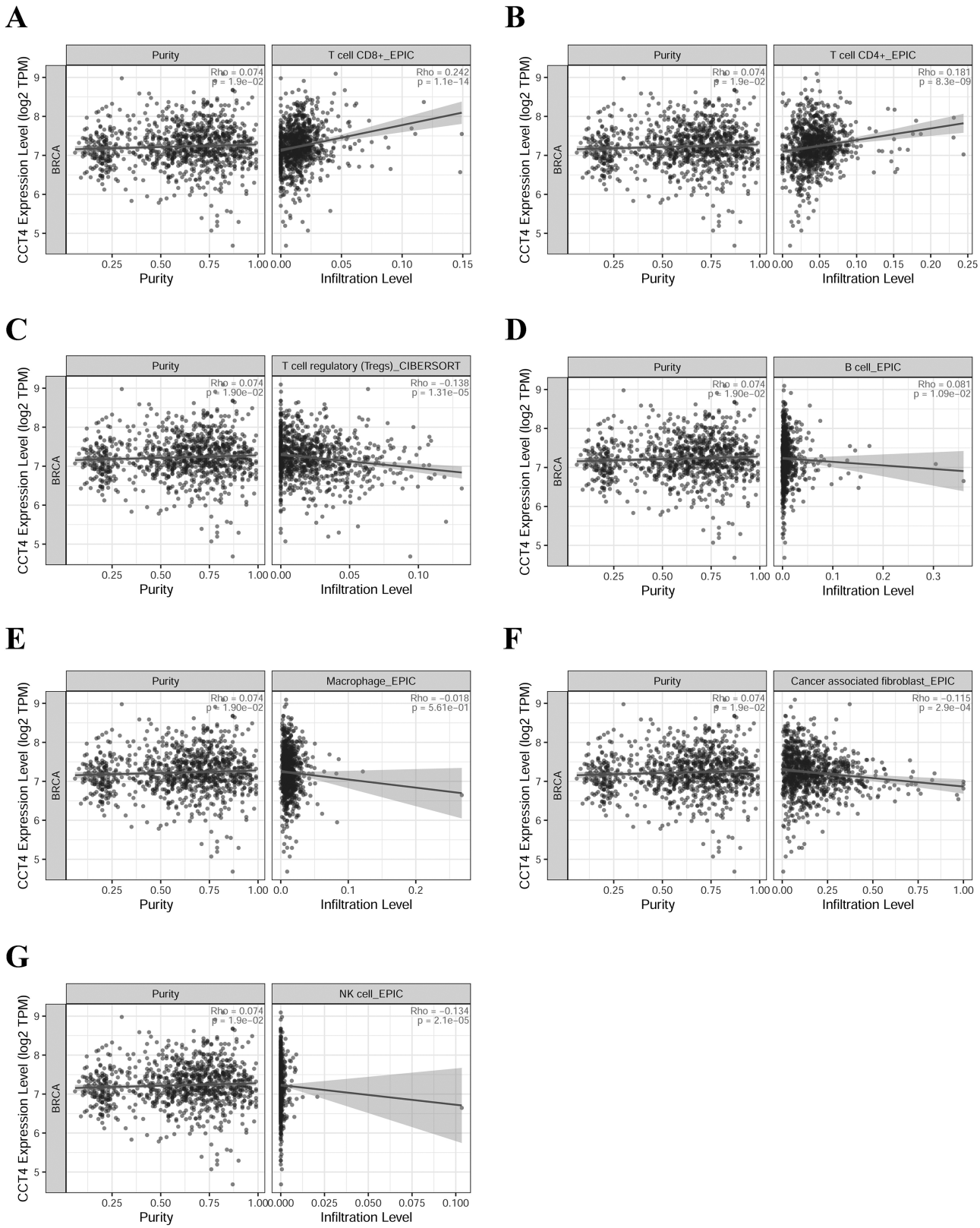

Fig. 2. Immuno-correlation analysis of CCT4. (A) Correlation analysis between CCT4 and T cell CD8+. (B) Correlation analysis between CCT4 and T cell CD4+. (C) Correlation analysis between CCT4 and Tregs. (D) Correlation analysis between CCT4 and B cell. (E) Correlation analysis between CCT4 and macrophage. (F) Correlation analysis between CCT4 and cancer-associated fibroblast. (G) Correlation analysis between CCT4 and NK cell.

carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), and uterine corpus endometrial carcinoma (UCEC) (Fig. 1D, $P < 0.05$, Supplementary Table 3). CCT4 acted as a protective factor in two cancer types and as a risk factor in the other six, suggesting distinct roles for CCT4 in different tumor types. Significant differences in CCT4 expression between cancerous and normal tissues were observed in most of these cancer types, except for ACC and KIRC (Fig. 1E). This discrepancy might be attributed to the relatively small sample size and the significant heterogeneity of the tumors. Furthermore, Pearson correlation analysis of CCT4 was performed using LinkedOmics (Fig. 1F). The top 50 negatively correlating genes, including TENC1, KLHDC1, PRICKLE4, THSD4, MAP3K12, and SEMA3G, are shown in Fig. 1G. Notably, SEMA3G is an immune-related gene with prognostic significance in various cancers [24–26]. Additionally, the top 50 positively correlating genes, including CCT7, PNO1, GPN1, GPN1, FAM136A, and MDH1, were shown in Fig. 1H.

Immuno-correlation analysis of CCT4 was conducted using TIMER 2.0. The analysis revealed significant positive associations between CCT4 expression and T cell CD8+ (Rho = 0.242), T cell CD4+ (Rho = 0.181), and B cell (Rho = 0.081) (Fig. 2A, B, and D, $P < 0.05$). Furthermore, the expression of CCT4 showed a significant negative correlation with Tregs (Rho = −0.138), cancer-associated fibroblasts (Rho = −0.115), and NK cells (Rho = −0.134) (Fig. 2C, F, and G, $P < 0.001$). However, no significant correlation was observed between CCT4 and macrophages (Fig. 2E, Rho = −0.018, $P > 0.05$). These findings indicated a strong correlation between CCT4 and most immune cells, suggesting the involvement of CCT4 in immune-related pathways.

To identify potential upstream miRNAs that could target CCT4, two miRNA target prediction databases, miRWalk and miRDB, were utilized. The candidate miRNAs predicted by both databases were selected for constructing a regulatory network. As depicted in Fig. 3A, the candidate miRNAs included hsa-miR-30c-2-3p, hsa-miR-141-5p, hsa-miR-30c-1-3p, hsa-miR-298, hsa-miR-887-5p, hsa-miR-4425, hsa-miR-4646-5p, hsa-miR-4695-5p, hsa-miR-4742-5p, hsa-miR-4781-3p, hsa-miR-5001-3p, hsa-miR-6508-3p, hsa-miR-6512-5p, hsa-miR-6512-3p, hsa-miR-6720-5p, hsa-miR-6788-5p, hsa-miR-6847-5p, hsa-miR-6878-5p, hsa-miR-7856-5p, hsa-miR-12132, and hsa-miR-8086. By performing miEAA enrichment analysis, the top three most enriched Gene Ontology (GO) terms were identified as the establishment of organelle localization (GO0051656), positive regulation of osteoclast development (GO2001206), and DNA-N1-methyladenine dioxygenase activity (GO0043734) (Fig. 3B). These GO terms played crucial roles in tumorigenesis and tumor development. For instance, abnormal organelle localization was often observed in BC cells [27]. Abnormal DNA-N1-methyladenine dioxygenase activity may lead to genome instability, DNA damage, and subsequent tumorigenesis. Moreover, three miRNAs (hsa-miR-30c-2-3p, hsa-miR-30c-1-3p, and hsa-miR-6788-5p) were found to be involved in over 95% of the top 100 GO terms (Supplementary Fig. 2), indicating their potentially significant functions. Correlation analysis of gene co-expression revealed that hsa-miR-887-5p (R coefficient = −0.08, $P < 0.05$) and hsa-miR-30c-2-3p (R coefficient = −0.15, $P < 0.001$) exhibited significant negative correlations with CCT4 (Fig. 3C). On the other hand, hsa-miR-30c-1-3p, hsa-miR-141-5p, and hsa-miR-5001-3p showed significant positive correlations with CCT4 (Fig. 3C, $P < 0.05$). Considering that miRNAs usually inhibit target gene expression by binding to specific sites, suggesting a negative relationship, hsa-miR-887-5p and hsa-miR-30c-2-3p were selected for further investigation. The expression levels of hsa-miR-887-5p and hsa-miR-30c-2-3p were then compared between cancerous and normal tissues, respectively. There was no significant difference in the expression level of hsa-miR-887-5p (Fig. 3D, $P > 0.05$). However, the expression level of hsa-miR-30c-2-3p was much lower in cancerous tissues than that in normal tissues (Fig. 3E, $P < 0.001$), which was verified by clinical samples from Xuzhou Central Hospital (Supplementary Fig. 1C). Following rigorous analysis and

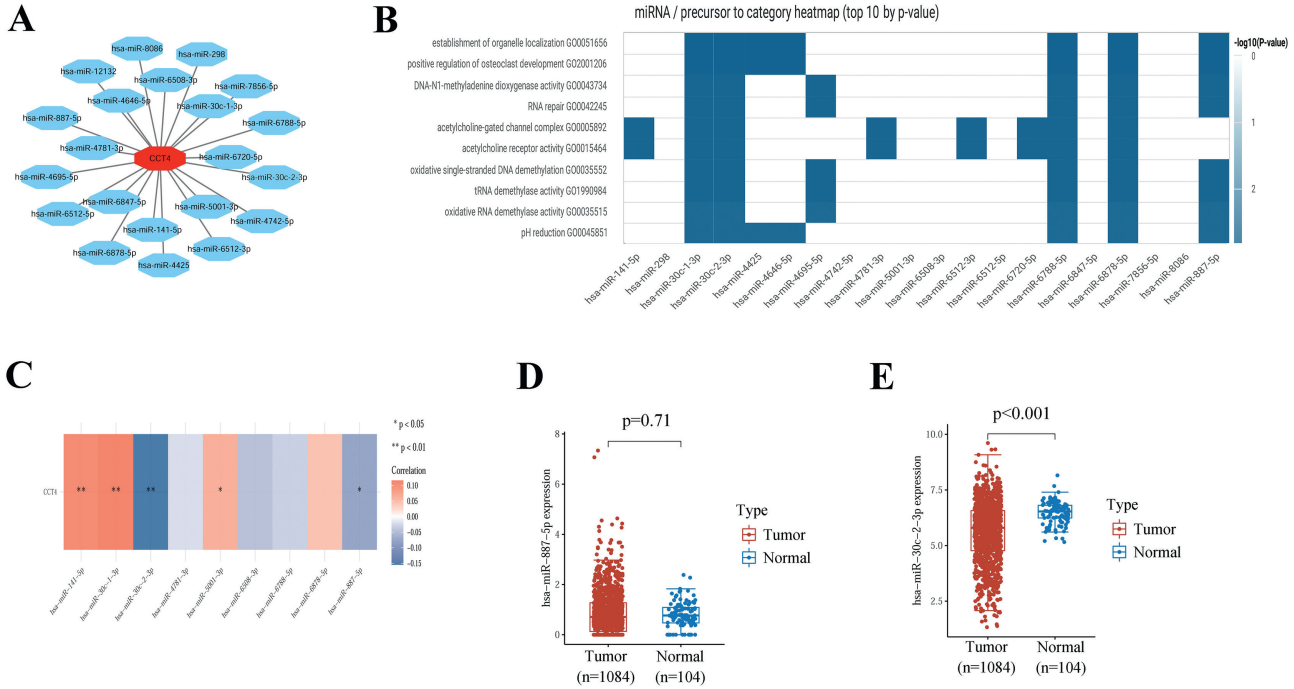

Fig. 3. hsa-miR-30c-2-3p was identified as the most probable upstream miRNA. (A) mRNA-miRNA network visualization. (B) GO enrichment analysis of candidate miRNAs. (C) Correlation analysis between CCT4 and candidate miRNAs. (D) Comparison of hsa-miR-887-5p expression between BC and normal breast tissues. (E) Comparison of hsa-miR-30c-2-3p expression between BC and normal breast tissues.

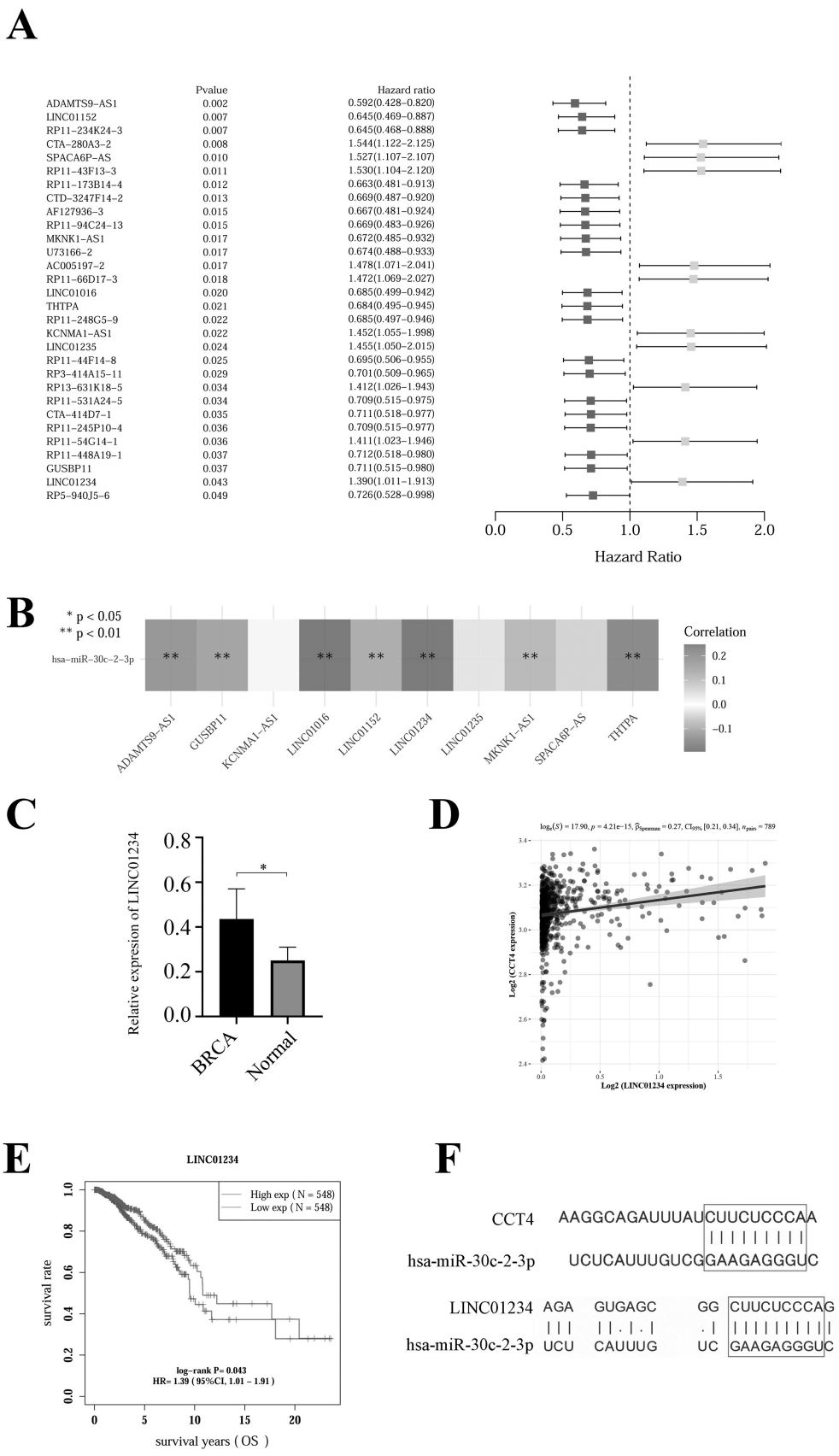

Fig. 4. LINC01234 was selected as the most probable upstream lncRNA. (A) 30 lncRNAs significantly associated with overall survival in BC. (B) Correlation analysis between hsa-miR-30c-2-3p and candidate lncRNAs. (C) LINC01234 expression levels based on clinical validation patient data. (D) Correlation between CCT4 and LINC01234. (E) Survival analysis of LINC01234 expression in BC. (F) The common binding-site predicted.

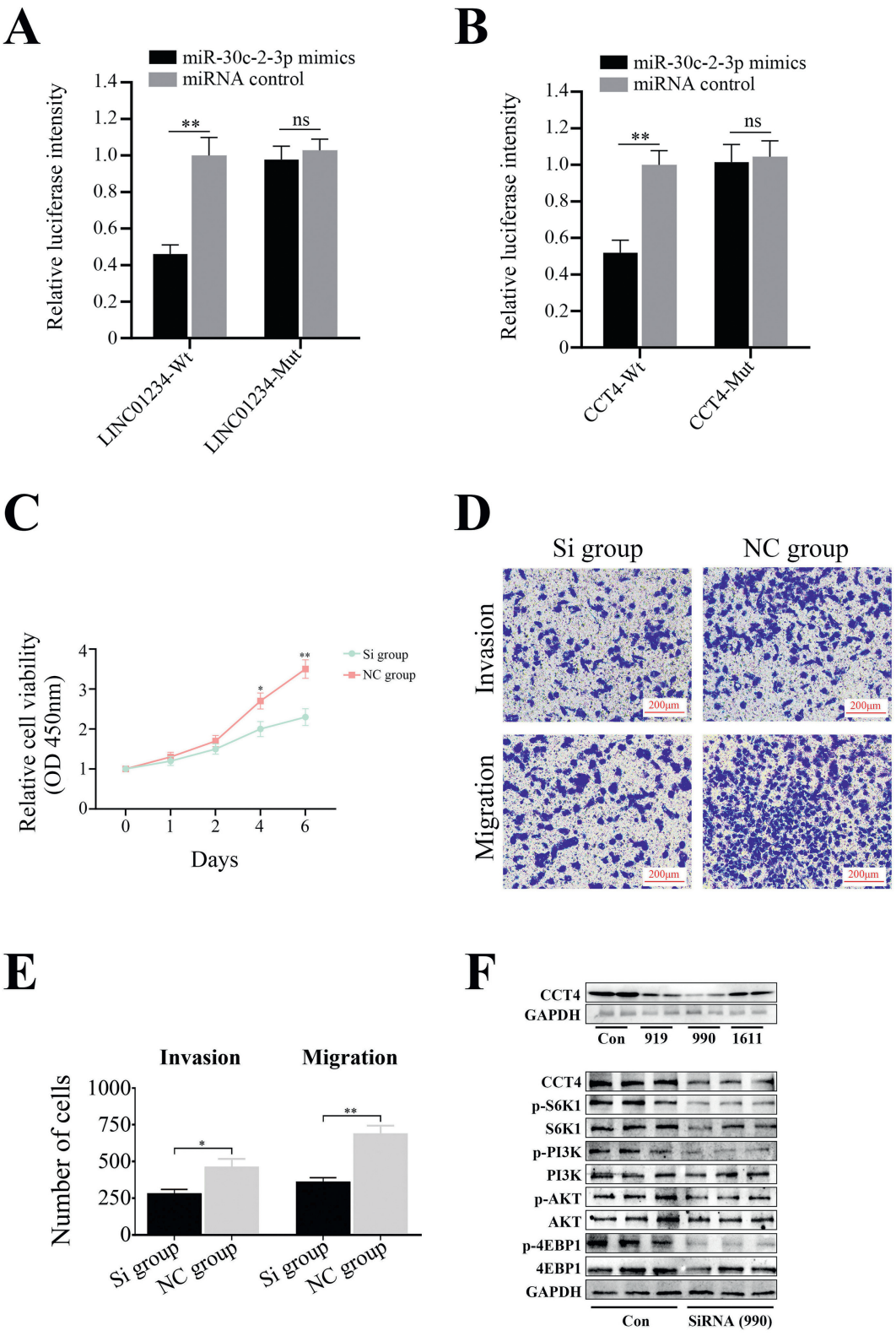

Fig. 5. Experimental verification. (A) LINC01234 binding to hsa-miR-30c-2-3p verified by dual-luciferase reporter assay. In this assay, 2×10^5 BT-20 cells were used in a 24-well plate. (B) CCT4 was a direct target of hsa-miR-30c-2-3p verified by dual-luciferase reporter assay. In this assay, 2×10^5 BT-20 cells were used in a 24-well plate. (C) CCK8 assay was performed with 5×10^3 BT-20 cells in a 96-well plate. (D) Transwell invasion and migration assays were performed with 5×10^3 BT-20 cells in a 96-well plate. (E) Statistical graph of Transwell invasion and migration assays. (F) The activity of the mTOR signaling pathway was decreased following LINC01234-siRNA interference. In the Western blot assay, BT-20 cells were used to extract total protein.

reasonable selection, hsa-miR-30c-2-3p was identified as the upstream miRNA of CCT4.

LncBase Predicted v.2 was utilized to identify potential lncRNAs that interact with hsa-miR-30c-2-3p, resulting in the prediction of a total of 1064 lncRNAs (Supplementary Table 4). Batch survival analysis revealed that 30 lncRNAs were significantly associated with overall survival (OS) (Fig. 4A). Among them, only LINC01234 exhibited a negative correlation with hsa-miR-30c-2-3p in the correlation study (Fig. 4B, $P < 0.01$). Real-time PCR analysis demonstrated that LINC01234 expression was significantly higher in BC compared to adjacent breast tissues (Fig. 4C, $P < 0.05$). Correlation analysis indicated a positive relationship between LINC01234 and CCT4 (Fig. 4D). Survival analysis further revealed that patients with high expression of LINC01234 had worse survival outcomes than those with low expression (Fig. 4E, $P < 0.05$). Binding-site prediction further indicated that LINC01234 and CCT4 shared a common binding site for hsa-miR-30c-2-3p (sequence: GAAGAGGGU, Fig. 4F). Moreover, this binding site between hsa-miR30c-2-3p and CCT4 belonged to the 8mer site type, suggesting a higher specificity. Based on these findings, we proposed a mechanism in which LINC01234 promoted upregulation of CCT4 by competitively binding to hsa-miR-887-5p, thus influencing the malignant phenotype of BC.

To further validate our findings, in vitro experiments were conducted. The dual-luciferase reporter assay demonstrated a significant reduction in luciferase activity in the LINC01234-Wt group, while there was no influence in the LINC01234-Mut group (Fig. 5A). These indicated that LINC01234 bound to hsa-miR30c-2-3p directly. In the co-transfection of hsa-miR30c-2-3p and CCT4, the luciferase activity was also significantly reduced in the CCT4-Wt group, whereas it remained unaffected in the CCT4-Mut group (Fig. 5B). Overall, these findings confirmed that LINC01234, hsa-miR-30c-2-3p, and CCT4 were indeed a ceRNA network with direct action.

After transfection with LINC01234-siRNA (Supplementary Fig. 1D), the proliferation, invasion, and migration abilities of BC cells were significantly reduced (Fig. 5C–E). Previous literature has indicated that CCT4 plays a role in tumor growth through the mTOR signaling pathway in glioblastoma [28]. Based on this knowledge, we hypothesized that LINC01234 might also promote malignant behaviors of BC cells via the CCT4/mTOR signaling pathway. Western blot analysis confirmed that several marker genes associated with the mTOR signaling pathway, including p-S6K1, p-PI3K, p-AKT, and p-4EBP1, were significantly down-regulated following LINC01234-siRNA interference (Fig. 5F). Interestingly, there were no significant changes in the protein levels of S6K1, PI3K, AKT, and 4EBP1.

Discussion

BC is a complex disease involving multiple genes and steps. Utilizing the public TCGA database, we identified thousands of genes with significant expression variations. Among these genes, CCT4 (chaperonin containing t-complex 4), the focus of our research, is a subunit of the CCT protein family. The CCT protein family primarily plays a role in maintaining cell viability and assisting in protein folding [29]. We observed that CCT4 exhibited prognostic significance across various cancers, suggesting its importance as a pathophysiological molecule in tumor initiation and progression. This finding aligned with a study by Xu et al. [30] which demonstrated that the majority of the CCT protein family members, including CCT4, were risk factors for BC. Additionally, Li et al. [31] illustrated that CCT4 interacts with CDC20 to regulate the growth of hepatocellular cancer cells. In head and neck squamous cell carcinoma (HNSC), it has been reported that the CCT protein family may influence patient outcomes through the PI3K-Akt signaling pathways [32]. However, these studies mainly focused on the downstream signaling mechanisms of CCT4 in cancer. Currently, the upstream molecular mechanisms of CCT4 remain poorly understood. To our knowledge, this is the first report elucidating the upstream ceRNA regulatory network of CCT4 in BC. Furthermore, CCT4 exhibited significant correlations with immune infiltration levels in BC, indicating its profound impact on the tumor microenvironment and consequently affecting clinical outcomes.

After thorough screening, we identified hsa-miR-30c-2-3p as the most likely upstream miRNA. Not only did hsa-miR-30c-2-3p exhibit a significant negative correlation with CCT4, but it was also found to be overexpressed in normal breast tissues compared to BC. Further analysis of the NeoALTTO study demonstrated that hsa-miR-30c-2-3p had a significant impact on the pathological complete response (pCR) of HER2-positive BC patients [33], underscoring its clinical relevance. In terms of underlying mechanisms, Shukla et al. [34] reported that hsa-miR-30c-2-3p regulated the NF-κB signaling pathway by inhibiting TRADD and CCNE1 in BC cells. Additionally, studies have shown that another member of the CCT protein family, TCP1, influenced the transcriptional regulation activities of NF-κB [35]. These findings provided valuable insights, suggesting that hsa-miR-30c-2-3p may act on CCT4 and subsequently activate the NF-κB signaling pathway in BC.

After conducting survival analysis and correlation analysis, LINC01234 emerged as the most likely upstream lncRNA. The presence of a common binding site further supported the plausibility of the LINC01234/hsa-miR-30c-2-3p/CCT4 axis in BC. LINC01234 has been utilized in the construction of several prognostic risk score models for BC [36–38], underscoring its significant clinical value. Furthermore, Bi et al. [39] discovered that LINC01234 influenced SYNJ1 by acting as a complete binding partner of miR-

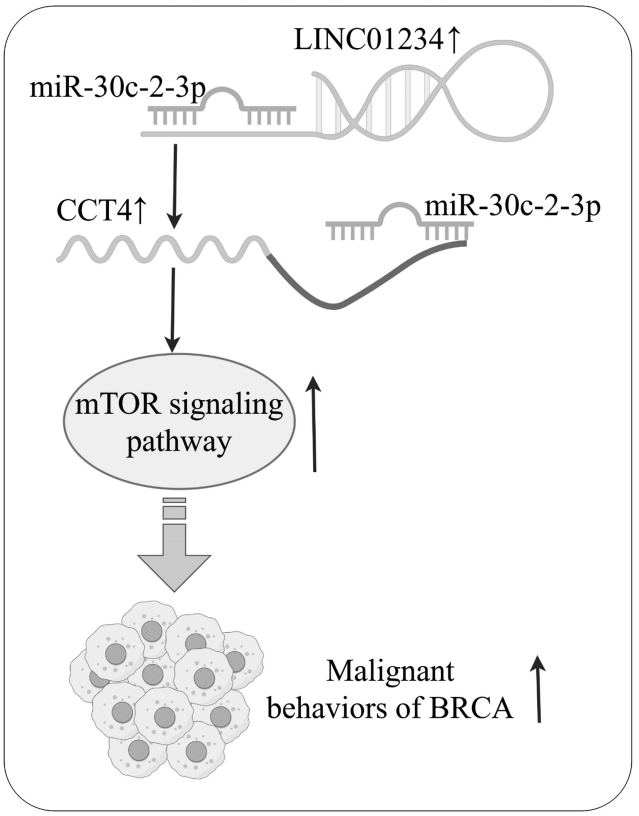

Fig. 6. Schematic overview of LINC01234/hsa-miR-30c-2-3p/CCT4/mTOR mechanism.

429 in the progression of triple-negative BC, indicating its regulatory role through the ceRNA mechanism. Additional research has revealed that LINC01234 promoted the proliferation and invasion of triple-negative BC via the miR-525-5p/MEIS2 axis, thereby impacting the Wnt/β-catenin signaling pathway [40]. In our current study, we identified a novel LINC01234/hsa-miR-30c-2-3p/CCT4/mTOR axis (Fig. 6), highlighting the significance of LINC01234 in the initiation and progression of BC.

There were a few limitations in this study. Firstly, all the data obtained from TCGA were retrospective, which inherently carried certain shortcomings such as selection bias. Secondly, the patients with BC were not further subdivided according to histological type. As a result, specific recommendations for individualized treatment cannot be provided.

Conclusion

In summary, a potential ceRNA regulatory mechanism in BC has been identified. These findings laid the foundation for systematically uncovering pathological mechanisms of BC and provided new insights for targeted therapy in BC patients.

Ethics approval and consent to participate

This study was approved by the institutional review board of Xuzhou Central Hospital. The TCGA database is a publicly available database with anonymized data.

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Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2023.09.019.

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Original Article

Pretreatment with long-acting gonadotropin-releasing hormone agonists improved pregnancy outcomes after hysteroscopic multiple polypectomies: A retrospective study of 660 frozen–thawed embryo transfer cycles

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ABSTRACT

Objective: To compare the reproductive pregnancy outcomes of pretreatment with long-acting gonadotropin-releasing hormone agonist (GnRH-a) plus hormone replacement therapy (HRT) with HRT-only cycles, and investigate differences between single polypectomy and multiple polypectomies, and between one or two doses of GnRH-a.
Materials and methods: This was a retrospective cohort study on patients undergoing polypectomy who underwent frozen–thawed embryo transfer (FET) from March 2018 to May 2019. They were divided into GnRH-a pretreatment and HRT-only groups. Each group was divided into single polypectomy or multiple polypectomies (in a single hysteroscopic session) subgroups. Clinical pregnancy rate and live birth rate (LBR) were the main outcomes. The effect of GnRH-a dosage was further analysed.
Results: There were 212 GnRH-a pretreatment cases (45 single and 167 multiple polyps) and 448 HRT-only cases (228 single and 220 multiple polyps). The LBR of the GnRH-a pretreatment group (53.3%) was significantly higher than the HRT group (43.3%; $P = 0.016$). Logistic regression analysis showed that GnRH-a pretreatment significantly affected the LBR (odds ratio, OR 1.470, 95% confidence interval, CI 1.046–2.065; $P = 0.026$). In the multiple polypectomy subgroup, the LBR with GnRH-a pretreatment was higher than with HRT-only (54.5% vs 43.6%; $P = 0.034$). However, the LBR was not different between the respective single polypectomy subgroups (48.9% vs 43.0%; $P = 0.466$). For patients with multiple polyps, two GnRH-a pretreatments produced a higher LBR than a single GnRH-a pretreatment (62.7% vs 47.8%), but without significant difference ($P = 0.055$).
Conclusion: GnRH-a pretreatment improved the LBR for FET cycles after hysteroscopic multiple polypectomies, independent of dose.

Introduction

Endometrial polyps are common in infertile women, especially in those undergoing in vitro fertilisation (IVF), with a frequency of approximately 1.4% [1]. For asymptomatic women, the reported prevalence of polyps diagnosed by hysteroscopy was between 6% and 8% [2,3]. Most studies have reported that endometrial polyps can impair reproductive outcomes [4–6]. Moreover, the outcomes of assisted reproductive technology (ART) are improved after polypectomy [7–9].

Frozen embryo transplantation (FET) is an important part of current ART. It can help avoid the effects of ovarian hyperstimulation syndrome, and high oestrogen and progesterone levels on pregnancy outcomes using fresh embryo transfer. FET enables

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better synchrony between the embryo and endometrium for implantation [10]. Protocols in FET cycles include natural cycles (NC), ovulation induction (OI), hormone replacement treatment (HRT), and pretreatment cycles with gonadotropin-releasing hormone agonist (GnRH-a). GnRH-a cycles were first used for FET in patients receiving donor oocytes to inhibit ovarian function and induce embryo–endometrium synchrony [11]. A systematic review and meta-analysis including four randomised controlled studies (RCTs) and one retrospective cohort study showed no difference in the clinical pregnancy rate (CPR) or live birth rate (LBR) between HRT with or without GnRH-a pretreatment for all patients after FET [12]. A retrospective study showed that the recurrence rate of endometrial polyps in short-acting GnRH-a plus HRT cycles was significantly lower than that of other protocols and the reproductive outcomes were similar between the four protocols [13]. At present, this is the first study on whether such pretreatment with long-acting GnRH-a has benefits for patients after polypectomy, compared with HRT alone, based on 660 FET cycles. This is also the first such study comparing patients with single polypectomy and multiple polypectomies, and evaluating the effects of the number of GnRH-a pretreatments.

Materials and methods

Subjects

This was a retrospective cohort study, including patients undergoing hysteroscopic polypectomy who underwent GnRH-a pretreatment followed by HRT or HRT alone in the IVF unit of the Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou, P. R. China, from March 2018 to May 2019. All patients had been subjected to hysteroscopic mechanical resection with gripping forceps and were diagnosed by subsequent pathology of the polyps removed. Before the transplantation cycle, ultrasound examination in the follicular phase determined whether the endometrial polyp had recurred. Transvaginal ultrasonography (TVU) is the first choice for evaluating endometrial morphology and thickness. If there was a possibility of polyp recurrence, the transplantation was cancelled and hysteroscopic surgery was performed again. Patients with the following seven conditions were excluded from the study: (1) endometriosis (diagnosed by laparoscopy or ultrasound; including adenomyosis); (2) uterine fibroids and a history of fibroid surgery; (3) repeated implantation failure (defined as at least two implantation failures each with the use of at least one good-quality embryo) [14]; (4) any history of endometrial hyperplasia, or diseases such as endometrial tuberculosis; (5) a history of surgery for intrauterine adhesions; (6) endometrial thickness <7.5 mm on the day of starting luteal support or abnormal intimal morphology; (7) uterine malformations (e.g., duplex or septate uterus); or (8) hydrosalpinx. The enrolled patients were divided into GnRH-a and HRT groups. Each group was divided into single or multiple polypectomy subgroups. Hereafter, 'multiple polypectomies' indicates resection of multiple polyps in a single hysteroscopic procedure. For GnRH-a pretreatment in the single polypectomy subgroup, only five patients received two injections, and the LBR was 20 percent. Therefore, the effect of GnRH-a doses in the GnRH-a pretreatment multiple polypectomy subgroup was analysed. The GnRH-a multiple polypectomy subgroup was divided into single- and double-dose subgroups (Fig. 1).

GnRH-a and HRT protocols

In the patients who underwent the GnRH-a plus HRT protocol, 3.75 mg leuprorelin (Leuprorelin Acetate Microspheres for Injection; the Livzon Pharmaceutical Group, Shanghai, P. R. China) was injected subcutaneously on Day 2 of the first menstrual cycle after polypectomy. A second 3.75 mg of leuprorelin was injected 28 days later and patients returned to the hospital 28 days after the last injection. Ultrasonography and hormone level measurements were used to ensure that the patient had reached pituitary down-regulation status. The endocrine and ultrasonography standards used for judging this were: oestradiol (E2) < 50 pg/mL, progesterone (P) level <1.5 ng/mL, and an intimal double thickness of <5 mm. The HRT was then started using an oral steroid preparation (Progynova, oestradiol valerate tablets; Bayer China Co., Ltd., Guangzhou, P. R. China; or Femoston, oestradiol plus dydrogesterone tablets, Abbott Healthcare Products B.V. Netherlands) 4–8 mg every day. For the HRT-only protocol, HRT was started on Day 3 of the first menstrual cycle after polypectomy. The duration from polypectomy to transplantation ranged from 1 to 3 months. In the GnRH-a group, 94.8% of patients were treated with Progynova and 5.2% were treated with Femoston, while in the HRT group, 95.3% were treated with Progynova and 4.7% were treated with Progynova. There was no significant difference between the two groups ($P = 0.780$). A transvaginal ultrasound was performed after 11–19 days of oral oestrogen treatment. The intima needed to reach at least 7.5 mm double layer thickness without abnormal morphology, then FET was scheduled.

Luteal phase support and FET

Luteal phase support consisted of intramuscular P in oil (Xianju Pharmaceutical Factory, Taizhou, P. R. China) at 60 mg/day for at least 2 weeks, along with oral administrations of P and E2 as above. The freeze-thawing process was performed by vitrification [15]. Thawing was performed on the day of transfer. Cleavage-stage frozen–thawed embryos were transferred 3 days after luteal support commenced, while blastocysts were transferred at 5 days. Cleavage-stage embryos with 6–8 cells on the third day and <20% fragmentation were considered 'good quality' [16] and blastocysts were evaluated according to a published scoring system [17].

Follow-up after FET

Patients provided blood samples 12 days after cleavage-stage FET and 10 days after blastocyst FET. A human chorionic gonadotropin level of ≥50 IU/L was considered to indicate a biochemical pregnancy. A routine ultrasound examination was arranged 5 weeks after FET to verify clinical or ectopic pregnancy. Live birth was defined as 28 weeks of gestation or greater. Preterm birth was defined as prior to 37 weeks of gestation. Abortion included early abortion (<12 weeks of gestation) and middle and late abortion (≥12 weeks of gestation and <26 weeks of gestation). The CPR and LBR were used as the main outcomes, while the biochemical pregnancy, miscarriage, ectopic pregnancy and premature birth rates were used as secondary outcomes.

Statistical analysis

IBM SPSS Statistics software (v. 25.0; IBM Corp., Armonk, NY, USA) was used for all statistical analysis. Categorical variables were presented as numbers (percentages) and analysed by Pearson's Chi-squared test and likelihood ratio detection. Continuous variables do not conform to normal distribution and were analysed by nonparametric tests. The influencing factors for reproductive outcomes were evaluated using odds ratio (OR) and its 95% confidence interval (CI) with logistic regression. All P values presented are two-tailed and $P < 0.05$ was considered significant.

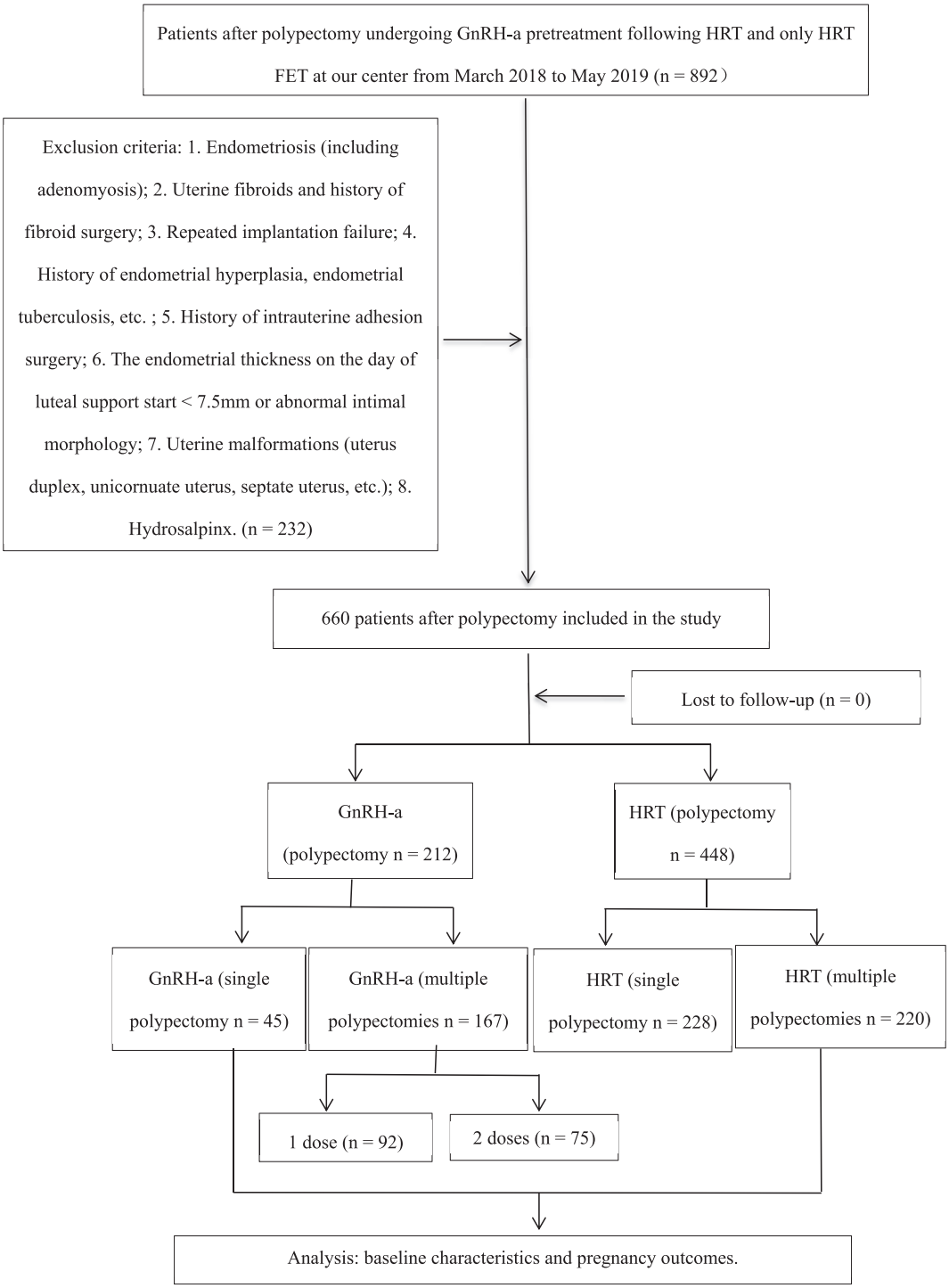

Fig. 1. Data collection and analysis. Key: GnRH-a, gonadotropin-releasing hormone agonist; HRT, hormone replacement therapy; FET, frozen–thawed embryo transplantation.

Results

There were 892 eligible patients enrolled at our centre from March 2018 to May 2019 and 232 met the exclusion criteria. None was lost to follow-up. Finally, there were 212 GnRH-a pretreatment cases (45 with single and 167 with multiple polyps) and 448 HRT cases (228 with single and 220 with multiple polyps). Of these, 92 patients received one dose of GnRH-a and 75 received two monthly doses after multiple polypectomies (Fig. 1).

GnRH-a pretreatment versus HRT alone in patients after polypectomy

There were no significant differences between the GnRH-a pretreatment and HRT-alone group either in general groups or subgroups in baseline characteristics (Table 1). The CPR of the GnRH-a group (59.9%) was significantly higher than that of the HRT group (48.7%; $P = 0.0069$), similar to the LBR (53.3% vs 43.3%; $P = 0.016$), whereas the biochemical pregnancy, abortion, ectopic

Table 1
Characteristics of FET cycles between GnRH-a-pretreatment and HRT-alone groups.

Parameter	Total		*P* value	Single		*P* value	Multiple		*P* value
	GnRH-a n = 212	HRT n = 448		GnRH-a n = 45	HRT n = 228		GnRH-a n = 167	HRT n = 220	
Age (years)	32.80 ± 4.33	33.39 ± 4.62	*0.169*	33.18 ± 4.84	33.66 ± 4.62	*0.572*	32.70 ± 4.19	33.10 ± 4.62	*0.516*
Infertility duration (years)	3.77 ± 2.87	3.63 ± 2.99	*0.236*	3.44 ± 2.62	3.67 ± 3.03	*0.931*	3.86 ± 2.94	3.58 ± 2.95	*0.218*
Infertility:									
Primary infertility	117 (55.2%)	243 (54.2%)		19 (42.2%)	119 (52.2%)		98 (58.7%)	124 (56.4%)	
Secondary infertility	95 (44.8%)	205 (45.8%)	*0.819*	26 (57.8%)	109 (47.8%)	*0.221*	69 (41.3%)	96 (43.6%)	*0.648*
Diagnostic category:									
Tubal	132 (62.3%)	271 (60.5%)		29 (64.4%)	141 (61.8%)		103 (61.7%)	130 (59.1%)	
Male	40 (18.9%)	74 (16.5%)		8 (17.8%)	32 (14.0%)		32 (19.2%)	42 (19.1%)	
Ovulation disorder	8 (3.8%)	20 (4.5%)		1 (2.2%)	10 (4.4%)		7 (4.2%)	10 (4.5%)	
Hypoovarianism	11 (5.2%)	25 (5.6%)		1 (2.2%)	17 (7.5%)		10 (6.0%)	8 (3.6%)	
PGT-SR	2 (0.9%)	6 (1.3%)		1 (2.2%)	3 (1.3%)		1 (0.6%)	3 (1.4%)	
Unknown	19 (9.0%)	52 (11.6%)	*0.864*	5 (11.1%)	25 (11.0%)	*0.687*	14 (8.4%)	27 (12.3%)	*0.283*
Number of embryo transferred:	1.79 ± 0.41	1.81 ± 0.42	*0.736*	1.76 ± 0.44	1.79 ± 0.43	*0.693*	1.80 ± 0.40	1.83 ± 0.81	*0.570*
1	44 (20.8%)	91 (20.3%)		11 (24.4%)	51 (22.4%)		33 (19.8%)	40 (18.2%)	
2	168 (79.2%)	353 (78.8%)		34 (75.6%)	175 (76.8%)		134 (80.2%)	178 (80.9%)	
3	0	4 (0.9%)	*0.210*	0	2 (0.9%)	*0.671*	0	2 (0.9%)	*0.303*
Number of good quality embryo	1.12 ± 0.78	1.10 ± 0.80	*0.740*	0.80 ± 0.76	1.04 ± 0.79	*0.058*	1.21 ± 0.77	1.15 ± 0.81	*0.562*
Stage of embryo at transfer:									
Day 3	182 (85.8%)	379 (84.6%)		37 (82.2%)	195 (85.5%)		145 (86.8%)	184 (83.6%)	
Day 5	30 (14.2%)	69 (15.4%)	*0.674*	8 (17.8%)	33 (14.5%)	*0.571*	22 (13.2%)	36 (16.4%)	*0.384*

Key: FET, frozen–thawed embryo transfer; GnRH-a, gonadotropin-releasing hormone agonist; HRT, hormone replacement therapy; PGT–SR, preimplantation genetic testing for chromosomal structural rearrangements.

pregnancy and premature birth rates had no significant differences. In the multiple polypectomy subgroup, the LBR of the GnRH-a pretreatment group was significantly higher than that of the HRT-alone group (54.5% vs 43.6%; $P = 0.034$), as was the CPR (62.3% vs 49.1%; $P = 0.0098$) and the implantation rate (43.5% vs 36.3%; $P = 0.0091$). However, there were no significant differences in the LBR of the single polypectomy subgroup with or without GnRH-a pretreatment (48.9% vs 43.0%; $P = 0.466$). The other reproductive outcomes were also no different (Table 2). There was a difference in the diagnostic category ($P = 0.017$). The LBR of the single-dose GnRH-a group (47.8%) was lower than that of the double-dose GnRH-a group (62.7%), but with no significant difference ($P = 0.055$) (Table S1).

Logistic regression analysis for all patients after polypectomy

To further evaluate the factors affecting the reproductive outcomes after polypectomy, logistic regression analysis was performed using the CPR and LBR as dependent variables, and we selected age, infertility duration, GnRH-a or HRT, single or multiple polypectomy, number of embryo transferred, number of good-quality embryos, stage of embryo at transfer (days 3 or 5), infertility (primary or secondary) and diagnostic category as independent variables. In all patients after polypectomy, this analysis selected the following variables in decreasing order of importance for affecting the CPR: age (OR 0.929; 95% CI 0.895–0.964; $P < 0.001$), number of embryo transferred (OR 1.839; 95% CI 1.252–2.700; $P = 0.0019$), infertility (primary or secondary) (OR 0.700; 95% CI 0.506–0.967; $P = 0.030$) and GnRH-a or HRT (OR 1.443; 95% CI 1.026–2.039; $P = 0.035$) (Table 3). For the LBR the following variables were identified: age (OR 0.916; 95% CI 0.882–0.951; $P < 0.001$), number of embryos transferred (OR 1.937; 95% CI 1.300–2.886; $P = 0.0012$), GnRH-a pretreatment or HRT alone (OR 1.470; 95% CI 1.046–2.065; $P = 0.026$), and infertility (primary or secondary) (OR 0.711; 95% CI 0.513–0.985; $P = 0.040$) (Table 4).

Discussion

To our knowledge, this is the first study on the effect of long-acting GnRH-a pretreatment before HRT compared with HRT alone on the reproductive outcomes of FET in patients after single or multiple polypectomy. Endometrial polyps involve local hyperplasia of the intima, and consist of glands, stroma, and blood vessels. They lead to low pregnancy rates by mechanical interference with sperm transport or embryo implantation, causing intrauterine inflammation, or reduced endometrial receptivity [18]. Markers of endometrial receptivity, such as the homeobox proteins HOXA-10 and HOXA-11, decrease in women with endometrial polyps compared with those with normal uterine cavities [19]. The levels of another marker, glycodelin (also known as human placental protein-14), increase significantly in the follicular and peri-ovulatory periods of women with polyps compared with controls,

Table 2
Reproductive outcomes of FET cycles between the GnRH-a pretreatment and HRT-alone groups.

Parameter	Total		*P* value	Single		*P* value	Multiple		*P* value
	GnRH-a n = 212	HRT n = 448		GnRH-a n = 45	HRT n = 228		GnRH-a n = 167	HRT n = 220	
Biochemical pregnancy rate	132 (62.3%)	244 (54.5%)	*0.059*	26 (57.8%)	125 (54.8%)	*0.716*	106 (63.5%)	119 (54.1%)	*0.064*
Clinical pregnancy rate	127 (59.9%)	218 (48.7%)	*0.0069*[a]	23 (51.1%)	110 (48.2%)	*0.725*	104 (62.3%)	108 (49.1%)	*0.0098*[a]
Implantation rate	159 (41.8%)	296 (37.6%)	*0.620*	28 (35.4%)	150 (38.9%)	*0.646*	131 (43.5%)	146 (36.3%)	*0.0091*[a]
Abortion rate	13 (10.2%)	32 (14.2%)	*0.289*	1 (4.3%)	21 (19.1%)	*0.051*	12 (11.5%)	11 (10.2%)	*0.368*
Live birth rate	113 (53.3%)	194 (43.3%)	*0.016*[a]	22 (48.9%)	98 (43.0%)	*0.466*	91 (54.5%)	96 (43.6%)	*0.034*[a]
Preterm birth rate	12 (5.7%)	38 (8.5%)	*0.201*	4 (8.9%)	20 (8.8%)	*0.980*	8 (4.8%)	18 (8.2%)	*0.187*
Ectopic pregnancy rate	1 (0.5%)	2 (0.4%)	*0.964*	0	1 (0.4%)	*0.548*	1 (0.6%)	1 (0.5%)	*0.845*

Key: GnRH-a, gonadotropin-releasing hormone agonist; HRT, hormone replacement therapy.
[a] Pearson Chi–Square test.

Table 3
Stepwise logistic regression analysis of the risk factors for CPR in all patients after polypectomy.

Factors	Clinical pregnancy rate	
	OR (95% Cl)	*P* value
Age (years)	0.929 (0.895–0.964)	*<0.001*
Number of embryo transferred	1.839 (1.252–2.700)	*0.0019*
Infertility (Primary or Secondary)	0.700 (0.506–0.967)	*0.030*
GnRH-a or HRT	1.443 (1.026–2.039)	*0.035*

Key: GnRH-a, gonadotropin-releasing hormone agonist; HRT, hormone replacement therapy.

Table 4
Stepwise logistic regression analysis of risk factors for LBR in all patients after polypectomy.

Factors	Live birth rate	
	OR (95% Cl)	*P* value
Age (years)	0.916 (0.882–0.951)	*<0.001*
Number of embryo transferred	1.937 (1.300–2.886)	*0.0012*
GnRH-a or HRT	1.470 (1.046–2.065)	*0.026*
Infertility (Primary or Secondary)	0.711 (0.513–0.985)	*0.040*

Key: GnRH-a, gonadotropin-releasing hormone agonist; HRT, hormone replacement therapy.

and this is known to interfere with embryo implantation [20,21]. In addition, chronic endometritis was reported in 22.6%–27.4% of infertile patients, which was significantly higher than in normally fertile women, and endometrial polyps are associated with endometritis [22,23].

In a well-designed RCT of 215 infertile women undergoing intrauterine insemination, the total pregnancy rate increased significantly in those subjected to hysteroscopic polypectomy (63%) compared with simple biopsy (28%), with a relative risk of 2.1 [24]. A meta-analysis of five studies and a separate prospective study both showed that hysteroscopic polypectomy improved the pregnancy rate in IVF cycles [8,25]. *Elbehery* et al. [26] found that glycodelin levels decreased in the mid-secretory period, while its levels normalised following polypectomy.

The risk of polyp recurrence following polypectomy is approximately 3% [27]. Clinically, repeated hysteroscopic surgery after recurrence of polyps can increase the incidence of intrauterine adhesions. The recurrence rate of polyps was significantly lower with a GnRH-a plus HRT protocol (2.13%) than in three other protocols: 6.15%, 6.7%, and 4% in HRT, NC, and OI cycles, respectively ($P = 0.038$) [13]. HRT is a standard protocol used for FET cycles in ART clinics. Early studies reported that HRT-assisted cycles had a low cancellation rate compared with NC-based cycles [28,29]. For GnRH-a pretreatment protocols, a meta-analysis of three studies showed no significant difference in cancellation rates between the HRT-alone and GnRH-a plus HRT groups [30]. Three other RCTs found no significant differences in assisted reproductive outcomes between GnRH-a pretreatment and HRT-alone groups for all patients after FET [31–33].

It was reported that glycodelin levels were reduced significantly in the peritoneal fluid of women with endometriosis in a GnRH-a treatment group compared with those without GnRH-a treatment, along with some inflammatory mediators [34]. GnRH-a treatment can also reduce the activity of proinflammatory cytokines [35]. Therefore GnRH-a pretreatment is a suitable FET protocol for patients with polypectomy. At present, there are very few studies on the effect of GnRH-a plus HRT protocols for patients after polypectomy. A retrospective study of 902 cycles in patients after polypectomy showed that the CPR and LBR were similar in GnRH-a/HRT, HRT, NC, and OI protocols [13]. The first report of the GnRH-a/HRT protocol for patients with polypectomy [13] was limited by a sample size of only 92 (the sum of the GnRH-a and HRT groups), and relevant confounding factors were not excluded. In the GnRH-a group, the rate of patients exhibiting endometriosis was 20.65%, which was significantly higher than the HRT, NC, and OI protocols studied. Here, patients with problems such as endometriosis and a history of intrauterine adhesion surgery were excluded from the study. Our study compared the GnRH-a/HRT and HRT-only cycles and found that the LBR of the GnRH-a pretreatment group (53.3%) was significantly higher than that of HRT alone (43.3%, $P = 0.016$) (Table 2). Logistic regression analysis also showed that the use of GnRH-a significantly affected the CPR and LBR (Tables 3 and 4). Therefore, GnRH-a pretreatment significantly increased pregnancy outcomes in patients after polypectomy before FET.

Next, we examined if there were differences between single polyp resection and multiple polyp resections. A previous prospective observational cohort study showed that the recurrence risk following multiple polypectomies with six or more polyps was 4.08 (95% Cl 1.89–8.81), four times higher than following single polypectomy [36]. *Guo* et al. [37] reported that multiple polypectomies (six or more polyps) was significantly associated with chronic endometritis (diagnosed using CD138 levels; 58.7% for multiple polypectomies, 28% for single polypectomy, 29.1% for no polyps) in logistic regression models. Further analysis on patients with single and multiple polypectomy were first performed in our present study. This showed that the LBR was similar between GnRH-a/HRT and HRT-alone cycles in the single polypectomy subgroup (48.9% vs 43.0%: $P = 0.466$). However, in the multiple polypectomy subgroup, the LBR in the GnRH-a pretreatment group was significantly higher than in the HRT-alone group (54.5% vs 43.6%, $P = 0.034$; Table 2). Thus, we predict that the endometrial environment had not been completely improved after polypectomy. GnRH-a pretreatment seems to have had a therapeutic effect on the endometrial environment, especially for women undergoing multiple polypectomies. Analysis of the effect of GnRH-a doses in the GnRH-a pretreatment multiple polypectomy subgroup showed no significant difference in LBR between the single-dose and two-dose GnRH-a groups (47.8% vs 62.7%, $P = 0.055$; Supplementary Table S1). Therefore, GnRH-a pretreatment would not be required before FET for patients with single polypectomy. For patients with multiple polypectomies, a single injection of GnRH-a would be recommended before FET. Further randomized controlled studies are needed to determine whether a second injection of GnRH-a is needed.

The strength of this study is that we set a number of exclusion criteria to reduce confounding factors, such as endometriosis, repeated implantation failure, history of endometrial hyperplasia, and intrauterine adhesion surgery. Also, endometrial polyps were further classified according to pathological diagnosis. However, our study had several limitations. First, it was a single-centre retrospective study, so it is possible that recall bias existed; to be further investigated in prospectively planned studies. Further multi-centre studies are needed. Second, since May 2019, our centre began two-step transplantation, which was widely used, so the sample size was moderate and subgroup analysis according to one vs two doses of agonist and single vs multiple polypectomy made the sample size ever smaller. Third, although ultrasound was used to confirm whether polyps had recurred before the transplantation cycle, the pathological diagnosis of hysteroscopy remains the gold standard. There may have been some bias caused by ultrasound diagnosis. Fourth, the duration of post-polypectomy ranged from 1 to 3 months. We started HRT using an oral steroid preparation (Progynova or Femoston; at least two different protocols). Because this was a retrospective study, the hormone replacement protocols were not uniform. Therefore, the hormone replacement protocols

(at least two different protocols) were possible impacting factors in the current study.

In conclusion, pretreatment with GnRH-a before HRT for patients after endometrial polypectomy effectively improved the CPR and LBR compared with the HRT-alone cycles. For patients subjected to single polypectomy, pretreatment with GnRH-a seemed to provide no improvement. However, for patients with multiple polypectomies, pretreatment with GnRH-a improved the reproductive outcomes, but two injections of GnRH-a demonstrated no significant improvement compared with a single injection.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2023.09.020.

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Original Article

Relations between maternal height, shoe size, and the success of vaginal delivery in birth weight over 4000 g

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ABSTRACT

Objective: Macrosomia is associated with increased risk of fetal and maternal complications such as trauma during birth, cesarean delivery, postpartum hemorrhage, and shoulder dystocia. Sonographic estimation of fetal weight is imprecise particularly in excessively large fetuses, prompting the need for additional measures to assess the feasibility of vaginal delivery of a macrosomic newborn and thus improve prenatal consultation.

Materials and methods: This retrospective case–control study included women who delivered a singleton macrosomic newborn (birth weight>4,000 g), either vaginally (N = 762) or by urgent cesarean delivery during labor (N = 109). Using multivariable analysis, we examined correlations of maternal height≥170 cm and shoe size≥40 with successful vaginal delivery.

Results: Women who delivered vaginally had lower mean intrapartum BMI ($p < 0.001$) and lower rate of gestational diabetes ($p = 0.003$). Women with a shoe size≥40 were 2.2 times more likely to give birth vaginally. Cesarean section rate was 5.9 % among women with height≥170 cm and shoe size≥40; and 16.5 % among women with height<170 cm and shoe size<40. Multivariable analysis, adjusted for gestational diabetes, parity, and BMI, revealed that shoe size≥40 and maternal height≥170 cm correlated with success in vaginal delivery, OR = 3.1 (95%CI 1.3–7.3, $p = 0.009$).

Conclusion: Shoe size and maternal height may help predict success of vaginal birth of the macrosomic newborns.

Introduction

Macrosomia implies growth beyond an absolute birth weight, but a universally accepted definition for macrosomia has not been established. It is variably defined as a birth weight over 4000 g, over 4500 g, or above the 90th centile of weight for gestation [1,2]. In high income countries, the most commonly used threshold is birth weight above 4500 g, as defined by the American College of Obstetrics and Gynecology [2], but weight above 4000 g is also commonly used [3,4]. Fetal macrosomia is associated with an increased risk of several fetal and maternal complications, such as trauma during birth, protracted labor, operative vaginal and cesarean delivery, postpartum hemorrhage, and shoulder dystocia, leading to neonatal birth trauma [3]. In pregnancies with macrosomia, the risk of emergency cesarean section during labor was reported as doubled [4]. Therefore, the presence of macrosomia is an important factor to consider during delivery. Risk factors for macrosomia include constitutional factors, maternal diabetes and obesity, gestational weight gain, multiparity, and specific heritable genetic variants [5].

Two-dimensional ultrasound examination is the standard modality used for diagnosis of fetal macrosomia; however, the sonographic estimation of fetal weight is not precise at any gestational age and particularly not in excessively large fetuses [6]. Available formulas for fetal weight estimation perform better for fetuses that are at appropriate size for gestational age than for macrosomic ones; no formula has been shown as clearly superior [6,7]. Some investigators have combined ultrasonography with pregnancy-specific data (e.g., parity, ethnicity, body mass index, and maternal height, weight, and weight gain) to create nomograms for detecting fetal macrosomia, but these methods have not demonstrated consistently adequate performance [8,9]. Fetal macrosomia is an important risk factor for poor birth outcomes, particularly maternal and infant traumatic injury. Thus, macrosomia is key to decision-making during delivery [10–12]. The limited ability of

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sonographic formulas and **physical examinations** [13–15] in predicting fetal macrosomia prompts the need for additional measures that may help assess the feasibility of vaginal delivery of a macrosomic newborn, and thus improve prenatal consultation. When evaluated separately, most human linear anthropometric dimensions were shown not to depart significantly from isometric expectations [16]. However, the evidence is controversial regarding the predictive value of maternal pelvis size, international shoe size, parity, body mass index (BMI) and weight gain during pregnancy for cephalopelvic disproportion [17–19]. A prospective comparative study of 208 primigravidas at term found a positive correlation between maternal height and vaginal delivery, but no correlation with maternal shoe size [17]. We aimed to investigate the potential of maternal height and standardized shoe size as indicators for predicting successful vaginal delivery of macrosomic fetuses. We hypothesized that the two measurements would be associated with successful vaginal delivery in this context.

Materials and methods

This retrospective case–control study included women who gave birth to a singleton macrosomic newborn (birth weight over 4000 g) at term, via vaginal birth or urgent cesarean section during labor, between January 2017 and June 2021. Inclusion criteria were a singleton pregnancy at term and a vaginal delivery or emergency cesarean section during labor of a macrocosmic newborn. Exclusion criteria were multiple pregnancy, elective cesarean section and fetal malformations. In accordance with the guidelines of the American Society for Maternal-Fetal Medicine [2], our protocol allows a trial of labor when the fetal estimated weight is under 4500, or under 4250 in women with gestational or pre-gestational diabetes. When macrosomia is suspected, the mother is informed about related birth complications such as increased risks for shoulder dystocia, cesarean section, and postpartum hemorrhage. We do not have a standard protocol for managing fetuses that weigh between 3500 and 4000 g and that are not considered macrosomic.

The IRB of our medical center approved this study. Informed consent forms were unnecessary due to the retrospective nature of the study.

During January to March 2021, we called each of the women included in the study and asked her for her shoe size before pregnancy. We compared maternal anthropological parameters (height [≥170 cm or <170 cm], pre-pregnancy weight, weight gain during the pregnancy, BMI, maternal shoe size, parity, gestational diabetes status, and estimated birth weight, according to mode of delivery. The ultrasound measurements were used to estimate individual fetal parameters such as head circumference, biparietal diameter, abdominal circumflex, and femur length. Estimated fetal weight was based on Hadlock et al.'s formula 3 [15]. A composite maternal and neonatal outcome of vaginal delivery complications was established as the occurrence of one or more of the following: difficulty in fetal extraction, anal sphincter injuries, shoulder dystocia, and postpartum hemorrhage. This composite outcome was compared between women according to their height and shoe size.

Statistical analyses

The statistical analysis was conducted using SPSS software (IBM SPSS Statistics version 25.0). Continuous variables are presented as mean ± standard deviation or as median and range. Qualitative variables are presented as frequencies and percentages. Continuous variables were compared between groups using an independent sample t-test or a Mann–Whitney test (according to the sample size of the groups and the distribution shapes of the variables). Categorical variables were analyzed using a Pearson's chi-square test or Fisher's exact test (if expectancy <5). A two tailed p value < 0.05 was considered statistically significant. The sample size was calculated using IBM Sample Power software, version 3.0. A difference of 10 % in cesarean section rate between women with maternal height ≥1.7 and shoe size ≥40 and women with maternal height <1.7 and shoe size <40 was considered a significant difference [4]. Based on an independent sample t-test (two-sided hypothesis and 5 % significance), comparing 150 women who underwent emergency cesarean section to 500 who delivered vaginally would yield power of 82 %. In a multivariable analysis, adjusted for gestational diabetes, parity, and BMI, we examined correlations of maternal height ≥170 cm and shoe size ≥40 with success in vaginal delivery.

Results

The total number of women who delivered macrosomic newborns during the study period was 1177. Of them, 263 (22.3 %) underwent elective cesarean sections, 41 (3.7 %) were excluded from the analysis due to twin pregnancies and 2 (0.2 %) were excluded due to fetal malformations.

The 871 women who delivered macrosomic newborns were included in the study. Of them, 762 (87.5 %) underwent vaginal delivery and 109 (12.5 %) underwent emergent cesarean sections. Indications for the latter included dysfunctional labor (80 %) and suspected fetal distress (19 %). Maternal age, gestational week at delivery, and newborn's actual birth weight did not differ between the women who delivered vaginally and those who underwent emergent cesarean section during labor (Table 1). Pre-labor fetal weight estimation was higher for women who underwent emergent cesarean section than for those who delivered vaginally. Overall, 24.3 % of the women were 170 cm or taller. The mean maternal height was significantly higher in women who gave birth vaginally. Of the women who were 170 cm or taller, 92.4 % had a successful vaginal delivery. Women of height ≥170 cm were 2.01 times more likely to give birth vaginally than were shorter women (95 % CI 1.16–3.51 p = 0.013). The rate of cesarean section was 7.6 % among women whose height was ≥170 cm and 14.2 % among

Table 1
Maternal demographic characteristics by mode of delivery.

	Vaginal delivery (n = 762)	C. section during labor (n = 109)	P-value
Maternal age (mean)	30.1 ± 5.2	29.4 ± 4.7	0.77
Pre-pregnancy weight (mean)	69.0 ± 13.7	71.3 ± 14.8	0.13
Gestational week at delivery (mean)	40.18 ± 0.88	40.09 ± 0.97	0.40
Fetal estimated weight (g) (mean)	3698.09 ± 228	3750.17 ± 230	0.026
Newborn's weight (g) (median)	4140 (4005–5130)	4164 (4004–4794)	0.49
Maternal height (cm) (mean)	165.5 ± 5.8	163.8 ± 5.5	0.004
Shoe size (mean)	39.0 ± 1.3	38.6 ± 1.3	0.025
Intrapartum BMI (kg/m^2) (mean)	30.57 ± 4.8	32.94 ± 5.39	<0.001
Weight gain during pregnancy (kg) (mean)	14.92 ± 6.6	16.89 ± 7.77	0.009
Nulliparous, n (%)	142 (18.6)	54 (49.5)	<0.001
GDMA1, n (%)	35 (4.6)	9 (8.3)	0.156
GDMA2, n (%)	10 (1.3)	6 (5.5)	0.009
Pre-gestational diabetes, n (%)	7 (0.9)	2 (1.8)	0.314

BMI - body mass index, GDMA1 - gestational diabetes controlled by diet and exercise; GDMA2 - gestational diabetes requiring hypoglycemic agents.

women of height <170 cm (p = 0.012). For 660 women, we had data on their shoe size. The cesarean section rate was 5.9 % among the women whose height was ≥170 cm and shoe size ≥40; and 16.5 % among the women whose height was <170 cm and shoe size <40 (Fig. 1). Women with a shoe size of ≥40 were 2.2 times more likely to give birth vaginally, odds ratio (OR) = 2.20 (1.24–3.89 p = 0.007) (Fig. 2).

Compared to women who underwent vaginal delivery, among women who underwent cesarean sections, the proportions were higher of nulliparous women and women with gestational diabetes requiring hypoglycemic agents, and the mean weight gained during pregnancy was higher (Table 1).

In a multivariable analysis, the OR for a successful vaginal delivery among women of height ≥170 cm and shoe size ≥40 was 3.152 (1.35–7.38, p = 0.008) (Fig. 2). The correlations of maternal height ≥170 cm and shoe size ≥40 with success in vaginal delivery were found to be independent (p = 0.03), ie. not related to parity, intrapartum BMI, gestational diabetes, fetal weight estimation, or the actual birth weight of the newborns. Maternal height ≥170 cm, shoe size ≥40, and parity were found to be independently related to successful vaginal delivery; while high intrapartum BMI (p = 0.001) and gestational diabetes requiring hypoglycemic agents (p = 0.001) were found to be independent risk factors for cesarean section (Table 2). The composite maternal and neonatal outcome of vaginal delivery complications was found in 15 (13.5 %) women with height ≥170 cm and shoe size ≥40, and in 30 (9.2 %) women with height <170 cm and shoe size <40 (p = 0.169).

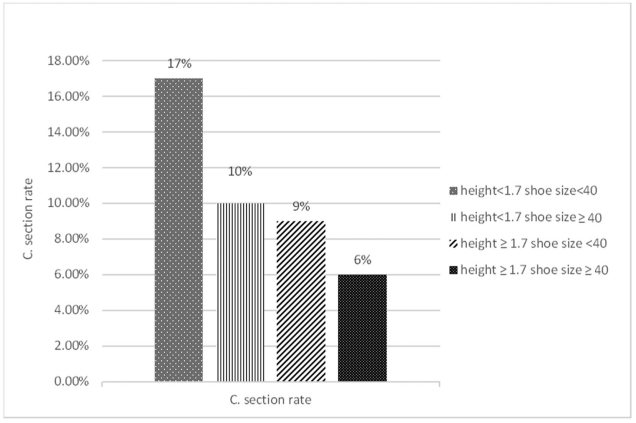

Fig. 1. Emergency cesarean section rate in macrosomia by maternal height and shoe size.

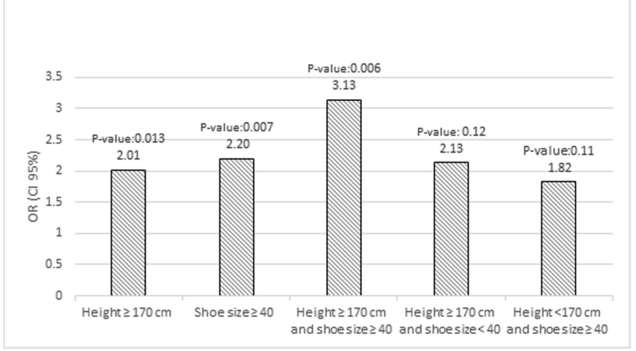

Fig. 2. The additive odds of maternal height and shoe size on succeeding in vaginal delivery.

Table 2
Multivariable analysis of the odds to succeed in vaginal delivery.

	P value	Odds ratio	
Height ≥170 cm and shoe size ≥40	0.008	3.152	1.35–7.38
Height ≥170 cm and shoe size <40	0.127	2.337	0.786–6.948
Height <170 cm and shoe size ≥40	0.03	2.52	1.096–5.81
Intrapartum BMI	0.001	0.913	0.868–0.961
multiparity	<0.001	3.606	2.157–6.028
GDMA1	0.329	0.620	0.237–1.618
GDMA2	0.001	0.123	0.036–0.421
Fetal estimated weight	0.097	0.049	0.219–1.135
Newborn actual weight	0.737	1	0.998–1.001

GDMA1 - gestational diabetes controlled by diet and exercise; GDMA2 - gestational diabetes requiring hypoglycemic agents.

Discussion

Our findings confirmed our hypothesis, namely that maternal height and standardized shoe size would be associated with successful vaginal delivery of the macrosomic fetus. In this study of 871 women who delivered macrosomic newborns, women with a shoe size ≥40 were 2.2 times more likely to give birth vaginally, compared to those with a smaller shoe size. Of the women with height ≥170 cm and shoe size ≥40, 94.1 % succeeded in vaginal delivery of newborns with birth weight over 4000 g.

Scarce data exist regarding the relation of maternal shoe size with birth weight over 4000 g. Among 208 women in England, height greater than 162.5 cm was found to be associated with successed in vaginal delivery; no correlation was found between maternal shoe size and successful vaginal delivery [17]. Maternal and paternal shoe-size were not found to be risk predictors for cesarean section performed for cephalopelvic disproportion [18]. Another study found no correlation between maternal shoe size and infant birth weight [19].

In contrast to previous studies, we found that both maternal height ≥170 cm and maternal shoe size ≥40 independently correlated with successful vaginal delivery of a macrosomic baby (OR 2.013 and OR 2.200, respectively) with additive odds when the two parameters were combined (OR 3.312).

Although univariable analyses showed associations of gestational diabetes, parity, maternal BMI, and fetal weight estimation with successful vaginal delivery, a multivariable analysis showed independent predictive value of maternal height and shoe size for successful vaginal delivery. We report no correlations of maternal height and shoe size with a composite outcome of vaginal delivery complications related to the macrosomic newborn. This may be due to the sample size that was small for assessing these outcomes. Previous studies found macrosomia to be associated with serious maternal adverse outcomes including emergency cesarean sections, postpartum hemorrhage, and anal sphincter injuries (OR = 1.98, 2.05, and 1.95, respectively); and adverse neonatal outcomes such as shoulder dystocia and birth fractures (OR of 9.54 and 6.43, respectively) [20,21]. Among 14,359 vaginal deliveries, fetal macrosomia and short maternal stature were found to be correlated with the likelihood of injury during vaginal birth [22]. Our results showed underestimation of fetal weight in the prenatal sonographic assessment. Thus, it could be appropriate to recommend that a woman with a fetal weight estimation over 3800 g should undergo a personal obstetrical evaluation, and that labor induction according to gestational week and obstetrical history would be considered.

This study has some limitations, including its retrospective design and the lack of data on paternal demographic factors. In addition, a bias could not be ruled out due to our considering sonographic rather than clinical weight assessment; and that could

have affected our assessment of clinical decisions. The strength of this study includes its large sample size for the primary outcome and its being conducted in a single medical center with uniform guidelines for managing macrosomic birth. As our hospital serves a heterogenous population of various cultural and socioeconomic sectors, of rural and urban areas, we believe the findings are applicable to other countries.

In conclusion, collecting maternal height and shoe size data can assist in decision-making concerning the mode of delivery of the macrosomic fetus, and with patient counseling.

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Conflict of interest

The authors have no conflicts of interest relevant to this article.

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Original Article

The changes in bladder function and symptoms after robot-assisted sacrocolpopexy and transvaginal mesh surgery for pelvic organ prolapse

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ABSTRACT

Objective: This study is aimed to compare the impact on bladder function and symptoms between robotic sacrocolpopexy (RSC) and transvaginal mesh surgery (TVM) in women with pelvic organ prolapse.
Materials and methods: This prospective controlled study enrolled patients who received RSC or TVM at our hospital between March 2020 and June 2022. We compared preoperative and postoperative bladder function between two groups by using a questionnaire of lower urinary tract symptom (LUTs) for subjective assessment and urodynamic study for objective assessment.
Results: A total of 60 patients were enrolled, of whom 30 received RSC and 30 received TVM. In LUTs analysis, the RSC group had a higher risk of de novo stress urinary incontinence than the TVM group (33.3% vs. 3.3%, $p = .007$). Urodynamic studies showed that both groups had a deterioration in maximal urethral closure pressure postoperatively (RSC: 56.9 ± 17.1 vs. 44.2 ± 15.5 cmH_2O; and TVM: 61.2 ± 29.4 vs. 47.6 ± 19.7 cmH_2O, $p < .01$ and $p = .03$, respectively). The incidence of urodynamic stress incontinence was also significantly increased after RSC (33.3% vs. 76.7%, $p = .01$). The de novo urodynamic stress incontinence rate was 46.7% after RSC, which was not significantly different to the TVM group (26.7%, $p = .16$). In the TVM group, the incidence of voiding difficulty decreased after surgery (43.3% vs. 10.0%, $p < .01$), and urodynamic measurements revealed that the prevalence of urine retention decreased (43.3% vs. 16.7%, $p < .01$). In the RSC group, the incidence of incomplete emptying sensation decreased (36.7% vs. 13.3%, $p = .04$), and urodynamic measurements showed that none of the patients had bladder outlet obstruction, underactive detrusor, or urine retention after surgery.
Conclusion: RSC and TVM are both beneficial to improve voiding function in women with pelvic organ prolapse. However, a deterioration in urethral function was observed and the de novo SUI rate was higher in the RSC group than in the TVM group.

Introduction

Pelvic organ prolapse (POP) is common, occurring in about 50% of parous women, and the prevalence increases with age [1]. About 11% of women will need at least one surgery for pelvic reconstruction in their lifetime [2]. Various procedures have been developed to treat POP depending on factors such as severity, medical comorbidities, reproductive and sexual status.

Mesh-augmented surgical procedures for prolapse can be via a vaginal or abdominal approach, such as transvaginal mesh surgery (TVM) or robotic-assisted sacrocolpopexy (RSC). RSC is regarded to be the optimal treatment for apical prolapse with a high success rate and low recurrence rate, however it requires a longer operative time and higher cost [3,4]. TVM is considered to be minimally invasive surgery with a shorter operative time; however, mesh exposure and de novo lower urinary tract symptoms (LUTs) are major complications.

LUTs are common in women with POP, and include stress urinary incontinence (SUI), voiding difficulty, straining to void, and incomplete bladder emptying [5]. POP surgery may resolve some

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LUTs such as straining to void and incomplete bladder emptying [6], but prompt other LUTs such as de novo SUI. Transvaginal reconstruction surgery has been associated with a 22% increased risk of de novo urodynamic stress incontinence (USI) [7]. Due to concerns over the safety of vaginal mesh, TVM is being performed less frequently. Consequently, research comparing RSC and TVM is also limited. Therefore, this study aimed to compare the impacts on bladder function and symptoms of RSC and TVM in women with pelvic organ prolapse.

Materials and methods

Patient selection

We included all women from March 2020 to June 2022 who had at least symptomatic stage II POP according to the POP-Q system [8] and underwent RSC or TVM at our hospital. The choice between two procedures depended on the patient's preference after understanding the pros and cons of both procedures. Women were excluded if they had concomitant incontinence surgery, a major medical or neurological disease, incomplete urodynamic studies before and after surgery, or did not complete three months of postoperative follow-up. We collected demographic data including age, parity, menopausal status, hormone therapy, body mass index, medical history, and previous pelvic surgery. The POP-Q stage, urodynamic studies and LUTs were evaluated pre- and postoperatively. The patients were followed up at one month, three months, and six months postoperatively. The study was approved by the Institutional Research Board of Mackay Memorial Hospital (No. 22MMHIS361e), and it was conducted in accordance with the Declaration of Helsinki.

Surgical technique

For the RSC group, the women who had not previously undergone a hysterectomy received supracervical hysterectomy. The vesicovaginal and rectovaginal spaces were then opened and dissected down to Delancey's level III of pelvic support [9]. A macroporous polypropylene double mesh (PELVI-STOP®, APIS Technologies Sarl, Aubonne, Switzerland) was then fixed to the vagina by multiple interrupted sutures with non-barbed absorbable sutures. After making a peritoneal tunnel, the mesh was fixed to the promontory with two to three nonabsorbable sutures.

For the TVM group, after vaginal hysterectomy had been completed, the vesicovaginal space was dissected from the level of the bladder neck to near the vaginal cuff. The anterior compartment was repaired by plication of the fibromuscularis, and we also applied a macroporous polypropylene transvaginal mesh with proximal two arms affixed to the sacrospinous ligament and distal two arms through obturator foramen (Surelift®, Neomedic International, Barcelona, Spain). The rectovaginal space was then dissected from the introitus to near the cuff. Posterior colporrhaphy was performed by plication of the fibromuscularis.

Lower urinary tract symptoms and urodynamic measurements

All woman filled out a questionnaire before and three months after the surgery to evaluate LUTs. The questionnaire was modified from that of Sun et al. [10], and asked about 9 symptoms which were further divided into storage- and voiding-related symptoms. The storage-related symptoms included SUI, frequency, urgency, urge urinary incontinence, and nocturia. The voiding-related symptoms included a feeling of voiding difficulty, straining to void, incomplete bladder emptying, and slow urine stream.

Urodynamic studies (UD 2000, Medical Measurement System, Enschede, Netherlands) included spontaneous uroflowmetry, filling and voiding cystometry, and urethral pressure profile, and they were performed before and three months after the surgery. All urodynamic assessments were performed using standard procedures, and the results were interpreted by a single observer to avoid bias. The terminology and urodynamic diagnoses were based on the International Continence Society (ICS)/International Urogynecological Association (IUGA) joint report [11].

Statistical analysis

For patient characteristics, chi-squared and Fisher's exact tests were used to compare categorical variables, while the independent t test was used for continuous variables. Urodynamic study values and LUTs were compared before and three months after surgery using the paired-sample t test and McNemar test. All analyses were conducted using SPSS version 26.0 for Windows (SPSS, Chicago, IL, USA). A p value less than .05 was considered to be statistically significant.

Results

A total of 60 patients met the study criteria and were enrolled. There were 30 patients in each group, and all of the patients were followed up for at least three months postoperatively.

The mean ages in the RSC and TVM groups were 62.6 and 66.7 years ($p = .04$), respectively, and the POP-Q stage was more advanced in the TVM group ($p = .02$). This may have been due to our surgical criteria for the use of transvaginal mesh, which was only used in patients with stage III or IV cystocele. There were no significant differences in the other characteristics between the two groups (Table 1).

Subjective lower urinary tract symptoms

In the RSC group, there was no significant difference in the prevalence of SUI before and after surgery (43.3% vs. 60.0%, $p = .32$). However, incomplete bladder emptying was significantly reduced postoperatively (36.7% vs.13.3%, $p = .04$), and straining to void, although not significant, also showed a trend of reduction after surgery (23.3% vs. 3.3%, $p = .07$). In the TVM group, urgency incontinence (63.3% vs. 36.7%, $p = .04$) and voiding difficulty (43.3%

Table 1
Patients' demographics.

	RSC[a] N = 30	TVM[b] N = 30	p value
Age (year)	62.6 ± 8.6	66.7 ± 6.6	.04*
Parity	2.6 ± .9	2.9 ± 1.0	.23
Menopause	26 (86.7%)	29 (96.7%)	.35
Hormone therapy	0 (0%)	0 (0%)	
BMI[c] (kg/m^2)	23.5 ± 2.8	24.2 ± 2.9	.35
Chronic disease			
Hypertension	13 (43.3%)	18 (60%)	.30
Diabetes	5 (16.7%)	11 (36.7%)	.143
Hyperlipidemia	6 (20%)	4 (13.3%)	.73
Previous prolapse surgery	5 (16.7%)	0 (0%)	.052
POP-Q[d] stage			.02*
Stage II	9 (30%)	0 (0%)	
Stage III	14 (46.7%)	19 (63.3%)	
Stage IV	7 (23.3%)	11 (36.7%)	

Data are presented as mean ± standard deviation or as number (%) of patients.
*Indicates significant p value.
[a] RSC = robotic-assisted sacrocolpopexy.
[b] TVM = transvaginal mesh surgery.
[c] BMI = body mass index.
[d] POP-Q = Pelvic Organ Prolapse Quantification.

Table 2
Lower urinary tract symptoms.

	RSC[a] N = 30			TVM[b] N = 30		
	Pre-op	Post-op	p value	Pre-op	Post-op	p value
Storage symptoms						
Stress urinary incontinence	13 (43.3%)	18 (60.0%)	.32	17 (56.7%)	11 (36.7%)	.07
Frequency	12 (40.0%)	10 (33.3%)	.75	17 (56.7%)	11 (36.7%)	.11
Urgency	12 (40.0%)	8 (26.7%)	.34	12 (40.0%)	9 (30.0%)	.61
Urgency incontinence	12 (40.0%)	15 (50.0%)	.58	19 (63.3%)	11 (36.7%)	.04*
Nocturia	18 (60.0%)	21 (70.0%)	.38	23 (76.7%)	26 (86.7%)	.55
Empty symptoms						
Voiding difficulty	5 (16.7%)	1 (3.3%)	.22	13 (43.3%)	3 (10.0%)	<.01*
Straining to void	7 (23.3%)	1 (3.3%)	.07	8 (26.7%)	6 (20.0%)	.72
Incomplete emptying	11 (36.7%)	4 (13.3%)	.04*	17 (56.7%)	9 (30.0%)	.06
Poor urinary stream	6 (20.0%)	4 (13.3%)	.69	11 (36.7%)	6 (20%)	.27

Data are presented as number (%) of patients.
*Indicates significant p value.
[a] RSC = robotic-assisted sacrocolpopexy.
[b] TVM = transvaginal mesh surgery.

vs. 10.0%, p < .01) were significantly reduced after surgery. SUI (56.7% vs. 36.7%, p = .07) and incomplete emptying (56.7% vs. 30.0%, p = .06) had a trend of reduction after surgery (Table 2).

In the RSC group, 10 (33.3%) patients had de novo SUI compared to only one (3.3%) patient in the TVM group; consequently the RSC group had a significantly higher incidence of de novo SUI (p = .007). The TVM group had a higher prevalence of de novo nocturia than the RSC group (23.3% vs. 13.3%, p = .01). There were no significant differences in other de novo LUTs between the two groups (Table 3).

Objective urodynamic outcomes

In the RSC group, the prevalence of USI significantly increased postoperatively (33.3% vs. 76.7%, p = .01). In addition, maximum urethral closure pressure (MUCP) was significantly decreased (56.9 ± 17.1 vs. 44.2 ± 15.5 cmH_2O, p < .01) and one-hour pad test increased after surgery (1.7 ± 4.1 vs. 24.9 ± 36.8 ml, p < .01). None of the patients had underactive detrusor or urine retention after surgery. Post-voiding residual urine volume decreased significantly (74.0 ± 78.5 vs. 16.3 ± 21.0 ml, p < .01) and maximal urine flow rate also had a trend of increase (15.2 ± 7.9 vs. 18.5 ± 8.05 ml/s, p = .09) (Table 4).

In the TVM group, the prevalence of urine retention decreased (43.3% vs. 16.7%, p < .01) after surgery. MUCP also significantly decreased in the TVM group (61.2 ± 29.4 vs. 47.6 ± 19.7 cmH_2O, p = .03) after surgery. Compared with the RSC group, the degree of decrease in MUCP between the two groups was not significantly different (p = .73) (Table 4).

Table 3
De novo lower urinary tract symptoms.

	RSC[a] N = 30	TVM[b] N = 30	p value
Storage symptoms			
Stress urinary incontinence	10/17 (33.3%)	1/13 (3.3%)	.007*
Frequency	4/18 (13.3%)	2/13 (6.7%)	1.00
Urgency	3/18 (10.0%)	6/18 (20.0%)	.44
Urgency incontinence	8/18 (26.7%)	2/11 (6.7%)	.23
Nocturia	4/12 (13.3%)	7/7 (23.3%)	.01*
Empty symptoms			
Voiding difficulty	1/25 (3.3%)	1/17 (3.3%)	1.00
Straining to void	1/25 (3.3%)	3/22 (10.0%)	.35
Incomplete emptying	1/19 (3.3%)	3/13 (10.0%)	.28
Poor urinary stream	2/24 (6.7%)	4/19 (13.3%)	.38

Data are presented as number of patients with de novo symptoms/negative symptoms before the procedure (% of all patients).
*Indicates significant p value.
[a] RSC = robotic-assisted sacrocolpopexy.
[b] TVM = transvaginal mesh surgery.

De novo urodynamic stress incontinence

The incidence rates of de novo USI in the RSC and TVM groups were 46.7% (n = 14) and 26.7% (n = 8), respectively, and the difference between the two groups was not significant. For the patients who had USI before surgery, 30.0% (n = 9) of the patients in the RSC group had persistent USI and 3.3% (n = 1) were cured postoperatively, compared to 30.0% (n = 9) and 13.3% (n = 4) in the TVM group, respectively, and the difference between the two groups was not significant (Table 5).

Discussion

Our results showed that both RSC and TVM effectively improved voiding function postoperatively. However, a deterioration in urethral closure pressure was also observed in both groups. In addition, the RSC group had a significantly higher de novo SUI rate than the TVM group (33.3% vs. 3.3%, p = .007). Urodynamic measurements also revealed a higher de novo USI rate in the RSC group than in the TVM group, although the difference was not statistically significant (46.7% vs. 26.7%, p = .16). These findings suggest that de novo SUI should be considered as a postoperative complication after RSC.

Only a few studies have reported the de novo SUI rate after RSC, and most did not include data of urodynamic measurements. Awad et al. reported a de novo SUI rate after RSC of 7.5%, however 30% of the enrolled patients had concomitant mid-urethral sling surgery [12]. Illiano et al. reported a de novo SUI rate of 4.1% 1 year after RSC [13]. In contrast to our results, another study comparing RSC and TVM reported that patients undergoing RSC had a lower incidence of de novo SUI within three months after surgery (23.1% vs. 5.4%, p < .05) [4]. However, other studies have reported a higher de novo SUI rate after laparoscopic sacrocolpopexy (LSC). Sato et al. reported a de novo SUI rate of 32% after LSC [14], and LeClaire reported a de novo SUI rate of 15% after LSC and RSC, and 45% after abdominal sacrocolpopexy [15]. Taken together, these findings indicate that de novo SUI should always be a concern when correcting apical and anterior prolapse.

De novo SUI may be due to the correction of urethral kinking unmasking underlying incontinence. In addition, eliminating the

Table 4
Urodynamic study parameters.

n =	RSC[a] N = 30			TVM[b] N = 30			Intergroup comparison
	Pre-op	Post-op	p value	Pre-op	Post-op	p value	p value
USI[c]	10 (33.3%)	23 (76.7%)	.01*	13 (43.3%)	17 (56.7%)	.39	
Detrusor overactivity	9 (30.0%)	7 (23.3%)	.69	10 (33.3%)	9 (30.0%)	1.00	
BOO[d]	9 (30.0%)	0 (.0%)	NA[e]	8 (26.7%)	4 (13.3%)	.34	
Underactive detrusor	2 (6.7%)	0 (.0%)	NA	4 (13.3%)	6 (20.0%)	.63	
Urine retention	8 (26.7%)	0 (.0%)	NA	13 (43.3%)	5 (16.7%)	<.01*	
Storage function							
First desire to void (ml)	190.0 ± 70.1	188.2 ± 59.86	.30	250.6 ± 87.6	245.6 ± 81.1	.78	.78
Maximal cystometric bladder capacity (ml)	559.0 ± 178.2	490.4 ± 126.1	.03*	599.7 ± 120.7	538.9 ± 103.8	<.01*	.82
Voiding function							
Maximal urine flow rate (ml/s)	15.2 ± 7.9	18.5 ± 8.05	.09	16.1 ± 9.1	15.4 ± 6.9	.66	.11
Average urine flow rate (ml/s)	9.7 ± 15.9	9.3 ± 3.8	.90	7.4 ± 4.2	6.7 ± 3.9	.37	.91
Voiding time (sec)	38.6 ± 16.0	37.3 ± 16.2	.65	46.6 ± 22.6	45.7 ± 22.6	.86	.95
Post-voiding residual urine volume (ml)	74.0 ± 78.5	16.3 ± 21.0	<.01*	117.8 ± 110.8	74.8 ± 94.2	.078	.60
Pdet@Qmax (cmH_2O)	28.8 ± 19.1	23.3 ± 13.4	.15	23.9 ± 13.0	23.0 ± 12.5	.69	.29
MUCP[f] (cmH_2O)	56.9 ± 17.1	44.2 ± 15.5	<.01*	61.2 ± 29.4	47.6 ± 19.7	.03*	.73
1-h pad test (ml)	1.7 ± 4.1	24.9 ± 36.8	<.01*	25.9 ± 54.3	28.9 ± 46.2	.81	.16

Data are presented as mean ± standard deviation or as number (%) of patients.
*Indicates significant p value.
[a] RSC = robotic-assisted sacrocolpopexy.
[b] TVM = transvaginal mesh surgery.
[c] USI = urodynamic stress incontinence.
[d] BOO = bladder outlet obstruction.
[e] NA = not applicable.
[f] MUCP = maximum urethral closure pressure.

Table 5
De novo and persistent urodynamic stress incontinence.

	RSC[a] N = 30	TVM[b] N = 30	p value
Pre-operative no USI[c]	20	17	.16
De novo USI	14 (46.7%)	8 (26.7%)	
Pre-operative USI	10	13	.34
Persistent USI	9 (30.0%)	9 (30.0%)	
Cured USI	1 (3.3%)	4 (13.3%)	

Data are presented as number (%) of patients.
[a] RSC = robotic-assisted sacrocolpopexy.
[b] TVM = transvaginal mesh surgery.
[c] USI = urodynamic stress incontinence.

mechanism of dynamic obstruction of the urethra [16], and peri-urethral denervation due to vesicovaginal space dissection may also be causes. We found a significantly decreased MUCP in both study groups, which showed the consequences of periurethral denervation. In addition, the effects of surgery on the decrease in MUCP were comparable between groups. Some studies have reported that excess tensioning of the anterior vaginal wall after mesh fixation was a risk factor for de novo SUI [15,16]. Excess tensioning may flatten the urethrovesical angle, which is normally between 90 and 100° but wider in SUI patients [17]. Kasturi et al. compared patients without de novo SUI and found a trend of lower postoperative point Ba values, meaning higher support, in the de novo SUI patients after transvaginal mesh procedures [16]. LeClaire et al. reported that the risk of de novo SUI increased with a greater reduction in point Aa values after sacrocolpopexy [15]. In our patients, the mean post-operative point Aa value was −2.9 ± .54, and the total vaginal length (TVL) was 9 ± .98 cm in the RSC group, which is relatively higher than in other studies. Illiano et al. reported a postoperative TVL of 8.2 (7.1–12.4) cm [13], and Wei et al. reported a TVL of 8.81 ± .748 cm [18]. Hence, a higher postoperative TVL may be associated with higher tension in the anterior vaginal wall, consequently leading to de novo SUI postoperatively. Another possible reason is that the TVM used was transobturator 4-arm mesh, which could effectively correct cystocele and SUI concomitantly [19]. In the present study, voiding function improved subjectively and objectively after surgery in both groups. Similar results were reported in previous studies [6,20] and were considered to be due to resolution of bladder outlet obstruction after correcting urethral kinking. In our study, the RSC group in particular had a promising outcome with regards to voiding function, as none of the patients had underactive detrusor, bladder outlet obstruction, or urine retention postoperatively. Post-voiding residual urine volume was significantly decreased after RSC, and the maximal urine flow rate also showed a trend of increasing. Despite improving voiding function, urine retention after pelvic floor reconstructive surgery may occur. Son et al. reported that the incidence of post-operative urine retention was as high as 24% after vaginal mesh procedures, where retention was defined as residual urine volume more than 30% total bladder capacity [21]. Another study reported that TVM had a 3.26 odds ratio of urine retention compared to RSC [22]. Consistent with these results, none of the patients in our RSC group had urine retention compared to 16% in the TVM group, indicating that RSC had a less negative impact on postoperative voiding function.

This is the first study to compare both subjective and objective bladder function outcomes between RSC and TVM. The limitations of this study were the relatively small sample size, and that we did not use validated questionnaires to assess the patient's quality of life. In addition, the patients varied in age, history of previous prolapse surgery and prolapse severity, which may have led to bias. However, the strengths of this study include that all surgeries were performed by the same experienced surgeon, thereby minimizing bias caused by differences in surgical techniques. De novo LUTs usually occur with three months after surgery. To collect accurate data on changes in de novo symptoms and bladder function, the patients were followed up and the data were compared within the same timeframe, preoperatively and at one month and three months postoperatively. In addition, all of the patients underwent only prolapse surgery without concomitant anti-incontinence surgery, which helped to focus on the impact of RSC or TVM on bladder function.

Conclusion

RSC and TVM both effectively improve voiding dysfunction in women with pelvic organ prolapse. However, a deterioration in urethral function was observed in both groups, and the de novo SUI rate was higher in the RSC group than in the TVM group. Surgeons should be aware of these potential outcomes and provide comprehensive counseling for the patient regarding the treatment options.

Ethical approval

The study was approved by the Institutional Research Board of Mackay Memorial Hospital (No. 22MMHIS361e).

Data availability

The data used in this study are available from the author on reasonable request.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Short Communication

Short tandem repeats genotyping of gestational choriocarcinoma – our experiences

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ABSTRACT

Objective: This short communication demonstrates how short tandem repeat genotyping can identify the origin of gestational choriocarcinoma.
Materials and methods: The origin of gestational choriocarcinoma in our three cases was determined using the short tandem repeats genotyping technique, which involved quantitative fluorescent PCR and fragmentation analysis.
Results: In Case 1 despite no medical history of molar pregnancy, DNA analysis indicated that the choriocarcinoma originated from a homozygous complete hydatidiform mole. We conclude, that the patient's complete abortion 10 years prior to the choriocarcinoma diagnosis was an undiagnosed complete hydatidiform mole. In Case 2 and Case 3 the clinically presumed origin of choriocarcinoma was confirmed.
Conclusion: Determining the origin of choriocarcinoma is essential for clinical application, as it affects the FIGO scoring system for gestational trophoblastic neoplasia, which determines the patient's prognosis and treatment approach.

Introduction

Gestational choriocarcinoma is a rare, aggressive malignancy with high metastatic potential. Its origin is linked to previous pregnancies: approximately 50 % of cases originate from molar pregnancies, 25 % from abortion or ectopic pregnancy, and 25 % from births [1–3]. While the antecedent pregnancy was traditionally assumed to be the origin of gestational choriocarcinoma, molecular genetic studies have shown that this is not always true [4,5]. Determining the origin of the malignancy is essential for clinical application, as it affects the FIGO scoring system for gestational trophoblastic neoplasia, which determines the patient's prognosis and treatment approach (Supplemental Table). Patients with lower scores (6 or less) are considered low-risk and treated with monochemotherapy, while those with higher scores (more than 6) are considered high-risk and require polychemotherapy. A patient who had an abortion 2 years ago and a birth 3 months ago and develops gestational choriocarcinoma will receive a score of 5 or 2 based on the “Antecedent pregnancy” and “Interval months from end of index pregnancy to treatment” criteria, depending on the causative pregnancy of the tumor [6]. Molecular diagnostics can also distinguish between metastases of gestational choriocarcinoma and non-gestational choriocarcinoma, a germ cell tumor that has similar characteristics but is less responsive to chemotherapy and requires distinct management [4]. In this report, we present three cases of choriocarcinoma to emphasize the importance of determining the origin of the malignancy in determining the patient's prognostic score and subsequent treatment. Overall, the mortality rate for

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choriocarcinoma is currently low because of its high chemosensitivity [1].

Materials and methods

The origin of gestational choriocarcinoma in our three cases was determined using the Short Tandem Repeats (STR) genotyping technique, which involved Quantitative Fluorescent PCR (QF-PCR) and fragmentation analysis. Blood, saliva, and tissues from paraffin blocks were used for DNA isolation with QIAGEN kits. QF-PCR was performed using the GenePrint 10 System (Promega) and Devyser Extend v2 (Devyser) commercial kits. Capillary electrophoresis was performed on ABI Prism 3130XL and ABI Prism 310 Genetic Analyzer. The recommended DNA concentration in reaction of samples isolated from formalin-fixed paraffin-embedded tissue were adjusted (increased) because of poor quality of DNA and fragmentation. The GeneMapper™ Software v4.1 was used to analyze the data.

To interpret the obtained data, two main tasks need to be performed. First, the genome composition needs to be determined by comparing the STR allelic profiles of the choriocarcinoma and the patient, which allows the identification of the type of pregnancy that gave rise to the cancer. Abnormal genome compositions are characteristic of molar pregnancies, with complete hydatidiform moles typically having two sets of paternal chromosomes (Fig. 1a and c) and partial hydatidiform moles having two sets of paternal and one set of maternal chromosomes. However, biparental complete hydatidiform mole can have a physiological genome composition, which is a potential pitfall. Non-gestational choriocarcinoma lacks identifiable paternal allelic sets (Table 1).

Matching the choriocarcinoma with a specific pregnancy based on genetic analysis is important for determining both the type of pregnancy that gave rise to the tumor and the time interval between the end of the index pregnancy and treatment (as illustrated in Fig. 1b and c).

Results

DNA analysis of presented gestational choriocarcinoma was performed in the years 2021 and 2022 in the Centre for Gestational

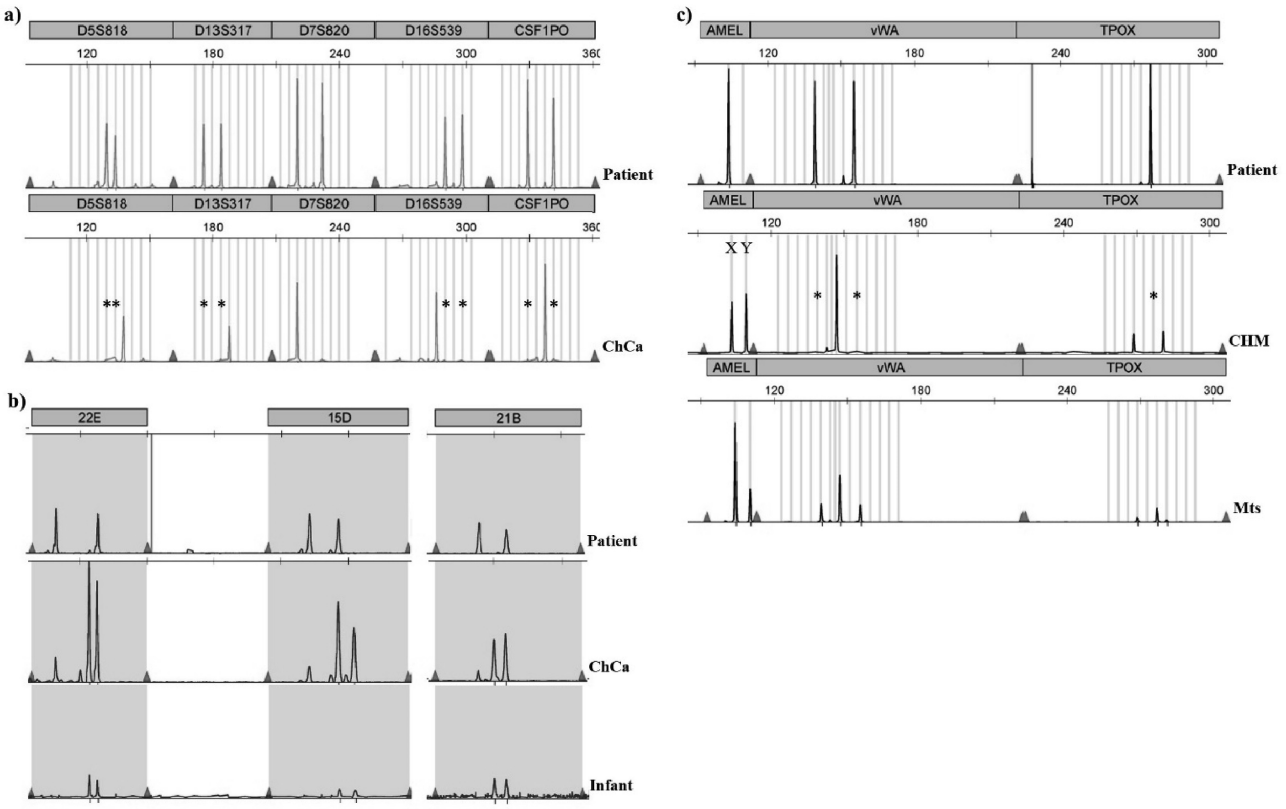

Fig. 1. Identification of the origin of gestational choriocarcinoma using short tandem repeat genotyping.
In this context - because gestational choriocarcinoma originates from a product of conception - alleles not present in the patient (mother) are evaluated as paternal (nonmaternal).
a) Gestational choriocarcinoma originating from monospermic (homozygous) androgenetic complete hydatidiform mole: Electrophoretograms of the patient (DNA isolated from unfixed fresh frozen myometrium) and the choriocarcinoma (ChCa – DNA isolated from unfixed fresh frozen tumor). Asterisks indicate alleles of loci proving the absence of maternal chromosomes in the nuclear genome of the tumor. All loci of the choriocarcinoma contain only one STR allele what suggest monospermic complete mole.
b) Gestational choriocarcinoma originating from a pregnancy ended up with birth: Electrophoretograms of the patient (DNA isolated from peripheral blood), the choriocarcinoma (ChCa – DNA isolated from paraffine block) and the infant (DNA isolated from saliva). STR allelic profiles of the choriocarcinoma and the infant are identical proving the origin of the tumor. In the tumor tissue, characteristic vascular space invasion and necrosis can lead to a certain amount of contamination with maternal blood what can be seen on electrophoretograms as minor maternal spikes. Taken together with the DNA fragmentation caused by formalin fixation, allelic imbalances may occur.
c) Gestational choriocarcinoma originating from dispermic (heterozygous) androgenetic complete hydatidiform mole: Electrophoretograms of the patient (DNA isolated from peripheral blood), the complete hydatidiform mole (CHM – DNA isolated from microdissection of formalin-fixed paraffin-embedded chorionic villi) and the vaginal excision with the metastasis of gestational choriocarcinoma (Mts – isolated from formalin-fixed paraffin-embedded tissue). Asterisks indicate alleles of loci proving the absence of maternal chromosomes in the nuclear genome of the mole. Loci of the mole contain two different paternal allelic sets suggesting dispermic complete mole. In the mole, the 1:1 ratio of the X and Y alleles of the Amelogenin (AMEL) locus points out, that the gonosomal complement is most probably XY, but XXYY cannot be excluded. In the vWA locus of the mole (CHM), the same allele was in both copies inherited from the father. This can be the result of either the homozygosity of the father for this concrete allele or the same allele was inherited from both sperms. The metastasis (Mts) specimen represents a mixture of tumor cells and the healthy cells of the patient, because tumor cells invaded the surrounding tissues extensively.

Table 1
Determining the type of the causative pregnancy of gestational choriocarcinoma based on genome composition (source: Tidy et al., 2021).

Type of the causative pregnancy	Genome composition	QF-PCR results – allelic ratios
Androgenetic complete mole	Diandric agynic diploid	**Only** paternal
Partial mole	Diandric monogynic triploid	**2** paternal: **1** maternal
Biparental complete mole	Monogynic monoandric diploid	**1** paternal: **1** maternal
Abortion, Ectopic pregnancy, Birth	Monogynic monoandric diploid, eventually aneuploid or digynic monoandric triploid	**1** paternal: **1** maternal (eventually other changes on locuses)
Non-gestational choriocarcinoma	–	Alleles identical with the patient

Trophoblastic Disease of Slovak Republic. Clinical characteristics of the patients are as follows.

Case 1

A 56-year-old patient - G3/P1 with a history of an incomplete abortion 27 years ago, a live birth 18 years ago, and a complete miscarriage 10 years ago, presented with heavy bleeding after 4 months of amenorrhea. A choriocarcinoma was detected from a curettage specimen, and further investigation revealed a 7 cm tumor in the myometrium, suggesting choriocarcinoma. The patient underwent a hysterectomy with bilateral salpingo-oophorectomy, and DNA was isolated from the unfixed tissue of the myometrium and the tumor. DNA analysis showed that the tumor - choriocarcinoma had an androgenetic composition of the genome, was homozygous in all examined loci, and had a gonosome complement XX, indicating that it originated from a homozygous (monospermic) complete hydatidiform mole. The patient's complete abortion 10 years prior to the choriocarcinoma diagnosis was found to be an undiagnosed complete hydatidiform mole with a long interval to malignant transformation (Fig. 1a). However, histopathological examination was not performed for the third pregnancy, and serum human chorionic gonadotropin levels were not monitored.

Case 2

A 29-year-old patient - G1/P1 presented with bleeding two months after giving birth to a live born boy. Curettage was performed, and gestational choriocarcinoma was detected based on ultrasound suspicion and histopathology. DNA was extracted from the patient's peripheral blood, microdissected formalin-fixed paraffin-embedded tumor tissue, and the infant's saliva. DNA analysis revealed a biparental genome composition of the tumor, and identical STR allelic profiles in the tumor and infant, confirming the origin of gestational choriocarcinoma in the pregnancy ended up with birth of a live born boy (Fig. 1b).

Case 3

A 21-year-old patient - G2/P1 developed a bleeding vaginal metastasis from gestational choriocarcinoma two weeks after the evacuation of a complete hydatidiform mole. DNA was extracted from the patient's peripheral blood, formalin-fixed paraffin-embedded chorionic villi of the complete hydatidiform mole, and formalin-fixed paraffin-embedded vaginal excision with metastatic choriocarcinoma (confirmed by histology). According to DNA analysis, the complete hydatidiform mole was proved to be dispermic with gonosomal complement XY. In the vaginal excision with the metastasis of choriocarcinoma mixed STR alleles of the mole and the patient were detected proving the origin of gestational choriocarcinoma in the above-mentioned mole (Fig. 1c).

Discussion

STR genotyping can provide clinically significant information for gestational choriocarcinoma cases.

Genetic analysis revealed misdiagnosed complete hydatidiform mole in Case 1. The patient got 1 point less in the FIGO scoring system (Supplemental Table) what did not change the stratification of the patient in this particular case, she stayed in the high-risk group.

In Case 2, the gestational choriocarcinoma originated from a term birth, and genetic analysis was crucial in excluding any unrecognized pregnancies. In Case 3, a metastatic gestational choriocarcinoma developed just two weeks after the evacuation because of the malignant transformation of a dispermic complete hydatidiform mole, highlighting the highly aggressive nature of these lesions.

According to a study recently published by Jung et al., copy-neutral loss-of-heterozygosity (CN-LOH) and copy number alterations (CNAs) are key molecular characteristics in gestational choriocarcinomas arising from complete hydatidiform moles [5]. CN-LOH occurs in homozygous (monospermic) complete hydatidiform moles on a whole genome level because of the duplication of a haploid set of chromosomes in one sperm, like in our Case 1. The CN-LOH pattern seen in heterozygous (dispermic) complete hydatidiform moles is typically segmental, what is attributable to two independent meiotic events of the two sperms fertilizing the ovum, like in our Case 3. According to the above mentioned study, malignant transformation of complete moles into choriocarcinoma may happen by the accumulation of CNAs [5].

Using STR genotyping is possible to differentiate between monospermic (homozygous) and dispermic (heterozygous) complete moles. Finding out whether the complete mole is heterozygous or homozygous in clinical practice only points to a higher risk of malignancy in the case of a heterozygous complete mole but does not predict malignancy. The close follow-up of the hCG tumor marker and the patient's clinical condition remains crucial [7].

According to the FIGO scoring system, the source of choriocarcinoma is the antecedent (last) pregnancy. DNA analysis can reveal that this was not the case, and that the choriocarcinoma did not come from the last pregnancy, but from the previous one. This can change the scoring system - the number of points not only for the pregnancy preceding choriocarcinoma, but also for the interval from the antecedent pregnancy. Ultimately, this can change the patient stratification from low risk to high risk or vice versa, which also changes the chemotherapeutic approach (monochemotherapy/polychemotherapy).

In summary, STR genotyping is an efficient and accurate method for identifying the origin of both gestational and non-gestational choriocarcinoma. Fresh frozen tissue is the preferred sample type, but formalin-fixed paraffin-embedded samples are also acceptable. The genotypes of the patient, tumor, and previous pregnancies are compared to determine the type and time interval from the end of the index pregnancy, both of which are important for prognosis and treatment. It's worth noting that the last pregnancy may not always be the source of gestational choriocarcinoma, and occult, non-diagnosed molar/nonmolar pregnancies can also contribute to this malignancy. According to our experiences, the described molecular diagnostic method is economically manageable (costs

approximately as other standard laboratory diagnostic methods in Slovakia). In clinical practice, identifying the origin of choriocarcinoma can change the FIGO score and optimize the chemotherapy regimen.

Ethics approval statement

We confirm that all published data has been anonymized in accordance with ethical standards. Prior to conducting genetic analysis and publishing the results, informed consent was obtained from the patients.

Declaration of competing interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2023.10.004.

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Case Report

Prenatal diagnosis and perinatal findings of 17q12 microdeletion encompassing *HNF1B* in a fetus with bilateral hyperechogenic kidneys on fetal ultrasound and mild renal abnormality after birth, and a review of the literature of prenatal diagnosis of 17q12 microdeletion

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ABSTRACT

Objective: We present prenatal diagnosis and perinatal findings of 17q12 microdeletion encompassing *HNF1B* in a fetus with bilateral hyperechogenic kidneys on fetal ultrasound and mild renal abnormality after birth, and a review of the literature.

Case report: A 36-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes showed a *de novo* 1.38-Mb 17q12 microdeletion encompassing *LHX1* and *HNF1B*. The parents did not have such a microdeletion. Prenatal ultrasound showed bilateral hyperechogenic kidneys with normal corticomedullary (CM) differentiation. The parents elected to continue the pregnancy, and a grossly normal 3180-g male baby was delivered at 39 weeks of gestation. aCGH analysis on the cord blood DNA revealed arr [GRCh37 (hg19)] 17q12 (34,856,055–36,248,918) × 1.0 with a 1.393-Mb microdeletion encompassing the genes of *MYO19*, *PIGW*, *GGNBP2*, *DHRS11*, *MRM1*, *LHX1*, *AATF*, *ACACA*, *TADA2A*, *DUSP14*, *SYNRG*, *DDX52* and *HNF1B*. When follow-up at age 2 years and 4 months, the renal ultrasound revealed bilateral increased renal echogenicity with normal CM differentiation and small left renal cysts. The blood test revealed BUN = 28 mg/dL (normal: 5–18 mg/dL) and creatinine = 0.5 mg/dL (normal: 0.2–0.4 mg/dL).

Conclusion: 17q12 microdeletion encompassing *LHX1* and *HNF1B* at prenatal diagnosis may present variable clinical spectrum with bilateral hyperechogenic kidneys on fetal ultrasound and mild renal abnormality after birth. Prenatal diagnosis of fetal hyperechogenic kidneys should raise a suspicion of 17q12 microdeletion syndrome.

Introduction

We previously reported detection of recurrent transmission of 17q12 microdeletion by array comparative genomic hybridization (aCGH) in a fetus with prenatally diagnosed hydronephrosis, hydroureter, and multicystic kidney, and variable clinical spectrum in the family [1]. Here, we present an additional case with bilateral hyperechogenic kidneys on fetal ultrasound and mild renal abnormality after birth, and we review the literature of prenatal diagnosis of 17q12 microdeletion.

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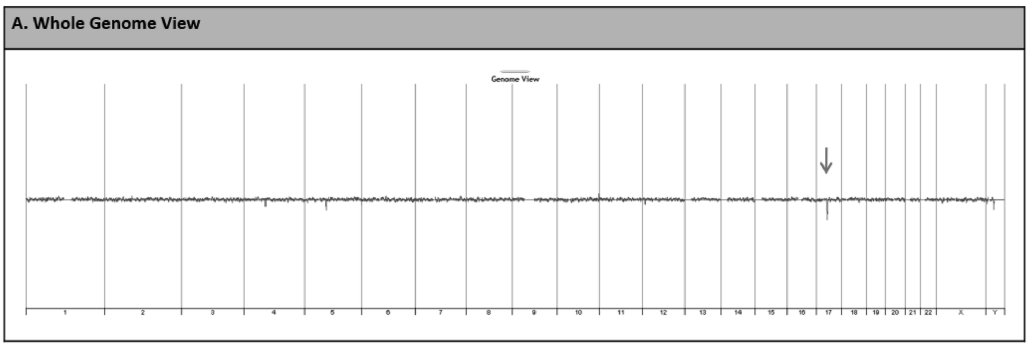
(A)



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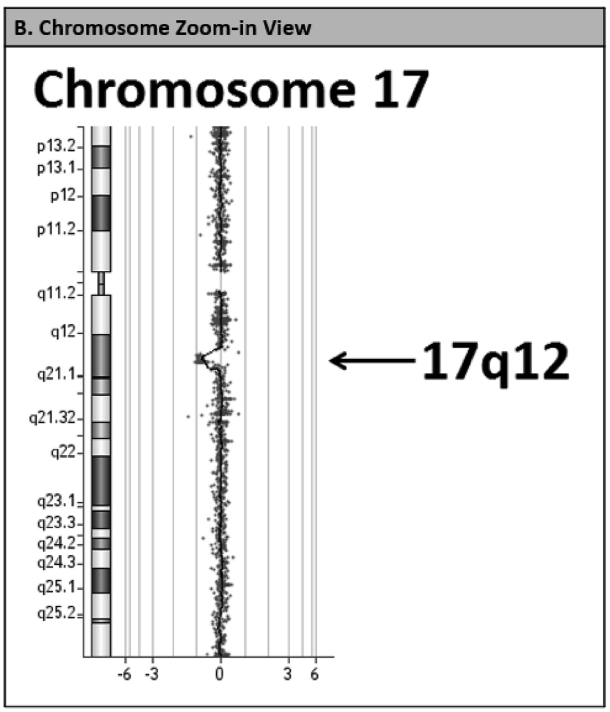

(C)

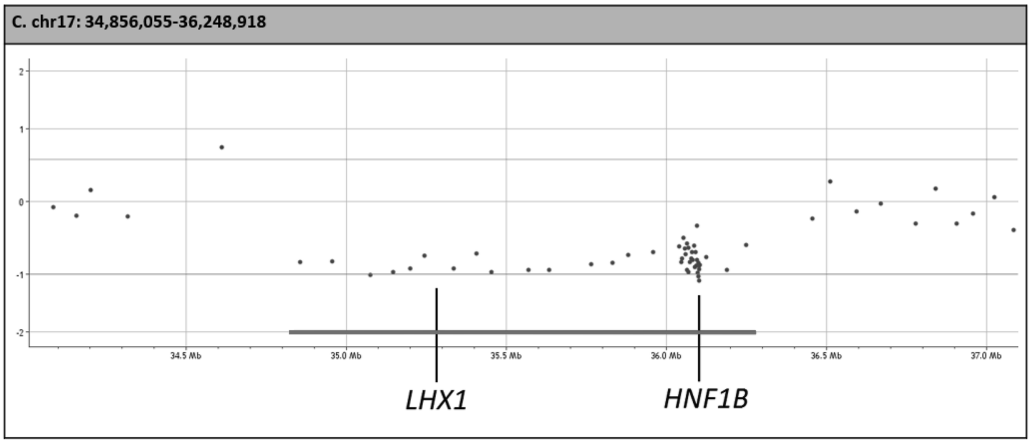

Fig. 1. (A), (B) and (C) Array comparative genomic hybridization analysis on the DNA extracted from cord blood shows a 1.393-Mb microdeletion at 17q12, or arr [GRCh37 (hg19)] 17q12 (34,856,055–36,248,918) × 1.0.

Case report

A 36-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Simultaneous aCGH analysis on the DNA extracted from uncultured amniocytes showed a *de novo* 1.38-Mb 17q12 microdeletion encompassing *LHX1* and *HNF1B*. The parents did not have such a microdeletion. Prenatal ultrasound showed bilateral hyperechogenic kidneys with normal corticomedullary (CM) differentiation. The parents elected to continue the pregnancy, and a grossly normal 3180-g male baby was delivered at 39 weeks of gestation. aCGH analysis on the cord blood DNA revealed arr [GRCh37 (hg19)] 17q12 (34,856,055–36,248,918) × 1.0 with a 1.393-Mb microdeletion encompassing the genes of *MYO19*, *PIGW*, *GGNBP2*, *DHRS11*, *MRM1*, *LHX1*, *AATF*, *ACACA*, *TADA2A*, *DUSP14*, *SYNRG*, *DDX52* and *HNF1B* (Fig. 1). When follow-up at age 2 years and 4 months, the renal ultrasound revealed bilateral increased renal echogenicity with normal CM differentiation and small left renal cysts. The blood test revealed BUN = 28 mg/dL (normal: 5–18 mg/dL) and creatinine = 0.5 mg/dL (normal: 0.2–0.4 mg/dL).

Discussion

Chromosome 17q12 deletion syndrome (OMIM 614527) is a contiguous gene syndrome caused by 17q12 deletion with clinical phenotypic features including renal cysts and diabetes syndrome or maturity-onset diabetes of the young type 5 (MODY5) (OMIM 137920), müllerian dysgenesis, autism spectrum disorder, schizophrenia, speech delay, learning difficulty, transient neonatal hypercalcemia and neonatal cholestasis [2–9].

The present case had a 1.393-Mb 17q12 microdeletion encompassing the genes of *HNF1B* and *LHX1*. *HNF1B* (OMIM 189907) encodes transcription factor-2, which is a transcription factor that belongs to the homeodomain-containing suprafamily of transcription factors. Heterozygous mutations in *HNF1B* will cause autosomal dominant renal cysts and diabetes syndrome (OMIM 137920) and autosomal dominant type 2 diabetes mellitus (OMIM 125853). *LHX1* (OMIM 601999) is essential for head-organizer function, renal, central nervous system and female reproductive duct development.

Prenatal diagnosis of 17q12 microdeletion has been well described. Hendrix et al. [10] first reported prenatal diagnosis of 17q12 microdeletion in a fetus with congenital diaphragmatic hernia, echogenic kidneys and cystic left lung on fetal ultrasound. Chen et al. [1] detected a 1.75-Mb 17q12 microdeletion in a fetus with hydronephrosis, hydroureter and multicystic kidney on fetal ultrasound at 20 weeks of gestation. Li et al. [11] detected a 1.93-Mb 17q12 microdeletion encompassing *HNF1B* and *LHX1* in a fetus with bilateral hyperechogenic kidneys and multicystic renal dysplasia on fetal ultrasound at 32 weeks of gestation. Yap et al. [12] reported prenatal diagnosis of 17q12 microdeletion syndrome in two fetuses with increased renal echogenicity and congenital diaphragmatic hernia. In a review of the prenatal finding of four fetuses in two families with 17q12 microdeletion syndrome, Jones et al. [13] suggested that prenatal testing should be offered to all cases of hyperechogenic kidneys with unknown cause. Xi et al. [14] detected two 17q12 deletions in four fetuses with isolated multicystic dysplastic kidney on fetal ultrasound. Gilboa et al. [15] detected 17q12 deletion by aCGH in five of seven fetuses with hyperechogenic renal parenchyma, and four of five cases with prenatally detected 17q12 deletion and carrying to term had neurodevelopmental disorders and autism spectrum disorder on long-term follow-up. Chen et al. [16] detected 17q12 microdeletion by aCGH in one of 72 fetuses with multicystic dysplastic kidney. Jiang et al. [17] detected 17q12 microdeletion syndrome in three fetuses, of which one case had multiple renal cysts, and two cases had bilateral hyperechogenic kidneys. Sagi-Dain et al. [18] detected 17q12 deletion by aCGH in 10 of 5750 (10/5750 = 0.17 %) cases with prenatal ultrasound abnormality, of which eight cases had genitourinary anomaly, and two cases had polyhydramnios, compared with 2 of 15,215 (2/15,215 = 0.01 %) in control population. Their report indicates an OR (90 % CI) of 13.3 (2.9–60.5) of 17q12 deletion in the fetuses with abnormal ultrasound comparing with the fetuses with normal ultrasound. Jing et al. [19] reported 17q12 deletion syndrome detected by aCGH in 11 fetuses of which 10 fetuses had *de novo* occurrence, and one fetus had familial inheritance. In their report, variable kidney abnormalities were found in all of the 11 cases and the abnormality of bilateral or unilateral hyperechogenic kidneys was the most common findings on fetal ultrasound. Wan et al. [20] detected 17q12 microdeletion by aCGH in 4 % (5/126 cases) of the fetuses with abnormal renal ultrasound findings. Hu et al. [21] detected 17q12 deletion by aCGH in 2.5 % (8/317 cases) of the fetuses with urinary anomalies on prenatal ultrasound, and the 17q12 deletion syndrome accounted for 40 % of pathogenic copy number variations.

In summary, we present prenatal diagnosis and perinatal findings of 17q12 microdeletion encompassing *HNF1B* in a fetus with bilateral hyperechogenic kidneys on fetal ultrasound and mild renal abnormality after birth, and a review of the literature. 17q12 microdeletion encompassing *LHX1* and *HNF1B* at prenatal diagnosis may present variable clinical spectrum with bilateral hyperechogenic kidneys on fetal ultrasound and mild renal abnormality after birth. Prenatal diagnosis of fetal hyperechogenic kidneys should raise a suspicion of 17q12 microdeletion syndrome.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Case Report

Use of the MS-MLPA assay in prenatal diagnosis of Prader–Willi syndrome with mosaic trisomy 15

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ABSTRACT

Objective: We present a prenatal diagnosis strategy of using Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) for the detection of maternal uniparental disomy 15/trisomy 15 (UPD(15) mat/T15) mosaicism.
Case report: A 43-year-old woman underwent amniocentesis at 19 weeks of gestation due to a high risk of trisomy 15 (T15) as indicated by non-invasive prenatal testing (NIPT). Cytogenetic analysis revealed a karyotype of 46, XX of cultured amniocytes. Further analysis using copy number variation sequencing (CNV-seq) analysis showed 55 % T15 mosaicism. The second amniocentesis was performed and showed a karyotype of 46, XX and 26 % T15 mosaicism by interphase fluorescence in situ hybridization (FISH). MS-MLPA analysis of uncultured amniocytes showed that the copy number ratio of 15q11-13 ranged from 1.3 to 1.5, and the percentage of methylation was between 70 % and 100 %. MS-MLPA assay of cultured amniocytes showed a copy number ratio of 1 and a methylation percentage of 100 %. Therefore, this fetus was identified to be an UPD(15) mat/T15 mosaicism. The parents decided to terminate the pregnancy.
Conclusion: MS-MLPA can be used in combination with karyotype and CNV-seq for prenatal diagnosis of NIPT high-risk T15 to avoid missed diagnosis of UPD(15) mat/T15 mosaicism.

Introduction

Prader–Willi syndrome (PWS) is characterized by obesity, hyperphagia, developmental delay, hypotonia, feeding problems, and hypogonadism [1]. And a number of clinical features of the fetus have been identified as indicators for PWS, including the abnormal position of feet and toes, polyhydramnios, cerebral anomalies, decreased fetal activity and hypoplasia of external genitalia [2]. Approximately 25–30 % of PWS patients have maternal uniparental disomy of chromosome 15 (UPD(15) mat) [3], This typically results from maternal meiotic non-disjunction followed by "trisomic rescue", where a trisomic conception loses the paternal chromosome 15 during mitosis after fertilization. If "trisomic rescue" happens only in partial cells of the embryo, the fetus may be UPD(15) with trisomy 15 (T15) mosaicism. However, mosaic uniparental disomy is rare in patients with Prader–Willi syndromeand only four cases of prenatally diagnosed with UPD(15) mat/T15 mosaicism have been described in the literature [4–7] (Table 1).

Detection of mosaic UPD is quite challenging, due to the contribution of genetically different cell lines. Several methods are available for clinical testing of UPD mosaicism, including short tandem repeat (STR), methylation specific multiplex ligation probe amplification (MS-MLPA) and trio single nucleotide polymorphisms (SNP) based array or whole exome sequencing (WES). However, these methods provide only semi-quantitative assessment. Among the four reported cases with UPD(15) mat/T15 mosaicism, three cases were detected by STR, and one case was analyzed by trio SNP array (Table 1). These two techniques are based on genetic polymorphisms (STR or SNP) and the segregation analysis of polymorphic alleles in the fetus and their parents. Therefore, the final proof of UPD can only be obtained by the comparative analysis of the genotype of the fetus with those of their parents. MS-MLPA is a molecular biology technique used to detect DNA methylation changes in specific genomic regions. It combines the principles of MLPA and bisulfite treatment of DNA, allowing for the quantification

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Table 1
Reported cases of UPD(15) mat/T15 mosaicism detected by prenatal diagnosis.

Study	Surh et al., 1994 [4]	Christian et al., 1996 [5]	Roberts et al., 1997 [6]	Silva et al., 2015 [7]	Present case
Maternal age (years)	38	37	39	38	43
Indication	AMA	AMA, previous child with Down syndrome	AMA, previous child with Down syndrome	AMA,NT: 5.0 mm	AMA; high-risk of T15 by NIPT
Karyotype of CVS Unculture amniocytes	MosT15(7/27)	–	MosT15(25/70)	MosT15(16/22)	–
%Abnormal cells (method)	–	–	–	–	55 %(CNV-seq)
UPD (method)	–	–	–	–	15mat/T15(MS-MLPA)
Culture amniocytes					
Karyotype	normal	MosT15(12/27)	normal	MosT15(14/50)	normal
UPD (method)	15mat(STR)	15mat/T15(STR)	15mat(STR)	15mat/T15(Trio SNP array)	15mat(MS-MLPA)
Phenotype	–	a two-vessel cord, malrotation of the bowel (autopsy)	–	VSD, nuchal pre-nasal edema, hypoplastic nasal bone (<5th centile) and clinodactily of the left hand.	–
Confirmation	Fetal heart, lung tissue: 15mat(STR)	fetal skin fibroblast: 15mat/T15(STR)	Placental tissue: MosT15(39/80); fetal muscle tissue, skin, brain, lung, liver: 15mat(STR)	–	–

AMA = advanced maternal age; CVS = chorionic villus sampling; mat = maternal; Mos = mosaic; NT = nuchal translucency; VSD = ventricular septal defect; 15mat = UPD15mat; - = not available.

of the methylation status of multiple loci simultaneously [8]. MS-MLPA has been used in a variety of research applications, including the identification of methylation changes in cancer, neurological disorders, and developmental disorders. In this study, MS-MLPA technique was applied to diagnose or exclude mosaic UPD(15) for a fetus at high risk for T15 by non-invasive prenatal testing (NIPT). This study aimed to use MS-MLPA as an alternative method for prenatal diagnosis of mosaic UPD.

Case presentation

A 43-year-old Chinese woman (gravida 4, para 2) underwent amniocentesis at 19 weeks of gestation because of an increased risk of T15 by NIPT. The amniocentesis revealed a karyotype of 46, XX in twenty cells at metaphases (Fig. 1a). Simultaneously Copy number variation sequencing (CNV-seq) analysis on the DNA extracted from uncultured amniocytes showed 55 % mosaicism for T15 (copy

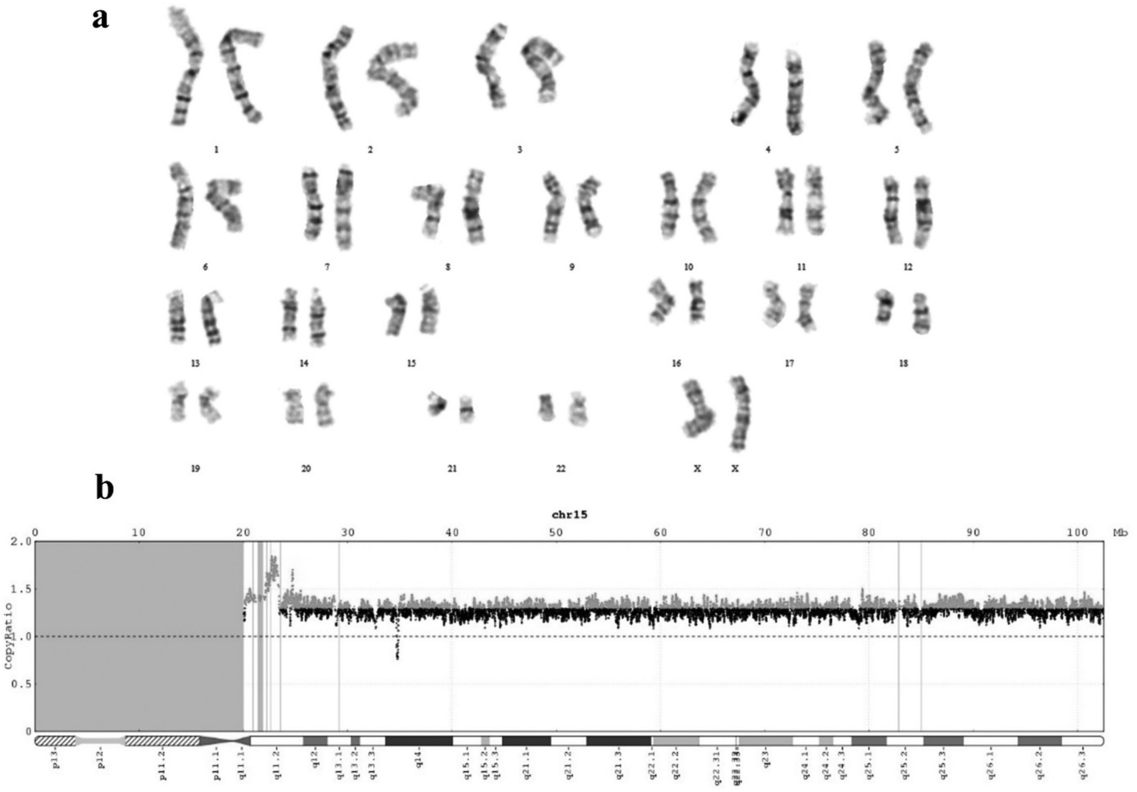

Fig. 1. Amniocentesis at 19 weeks of gestation is detected by karyotype analysis from cultured amniocytes (a) and CNV-seq from uncultured amniocytes (b).

number ratio 1.279) (Fig. 1b). The patient accepted a second amniocentesis at 23 weeks of gestation and interphase fluorescence in situ hybridization (FISH), MS-MLPA assay and conventional cytogenetic analysis were performed to uncultured and cultured amniocytes. The result revealed a karyotype of 46, XX in cultured amniocytes, and 26 % (26/100 cells) mosaicism for T15 by FISH in uncultured amniocytes (Fig. 2a and b). MS-MLPA analysis of uncultured amniocytes showed that copy number ratio value in 15q11-13 ranged from 1.3 to 1.5, suggesting a mixture of trisomic and disomic cells (Fig. 3a), and the percentage of methylation in SNRPN gene region was between 70 % and 100 %, suggesting that the diploid cells were probably the maternal UPD(15) (Fig. 3b). Furthermore, the MS-MLPA assay of cultured amniocytes showed that the copy number ratio was 1 and the percentage of methylation in SNRPN loci was 100 %, confirming that cultured amniocytes were UPD(15) mat (Fig. 4a and b). Thus, the fetus was diagnosed as UPD(15) mat/T15 mosaicism. After receiving comprehensive genetic counseling, the parents decided to terminate the pregnancy.

Discussion

The NIPT technique is commonly used for prenatal screening for common fetal aneuploidies (trisomy 21, 18, and 13), but some rare autosomal trisomies, such as trisomy 15, can also be found. Twelve published studies of high-risk T15 detected by NIPT found that UPD(15) was detected in four of 12 cases, and true T15 mosaicism was confirmed in four cases [9–11]. Our study reported the first case at high risk of T15 by NIPT identified as UPD(15) mat/T15 mosaicism by MS-MLPA. Although four cases of prenatal diagnosis of UPD(15) mat/T15 mosaicism were previously reported, their indications were

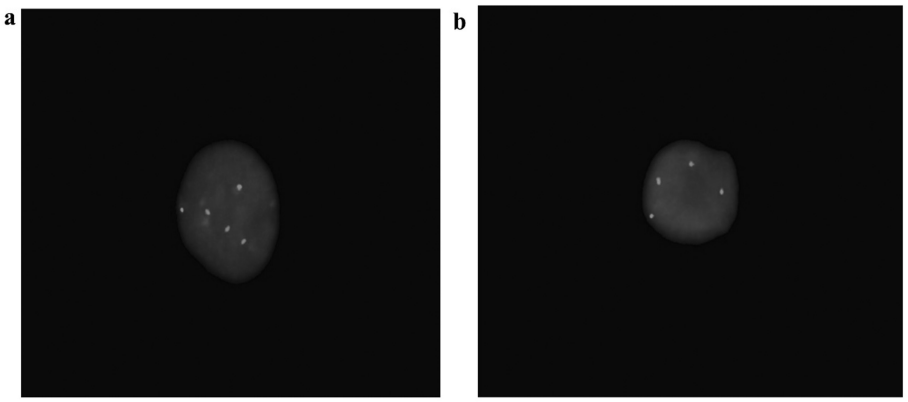

Fig. 2. Interphase FISH analysis on uncultured amniocytes using the probes of D15Z1(red) and D16Z1 (green) shows (a) a T15 cell with three red signals and two green signals, and (b) a disomy 15 cell with two red signals and two green signals.

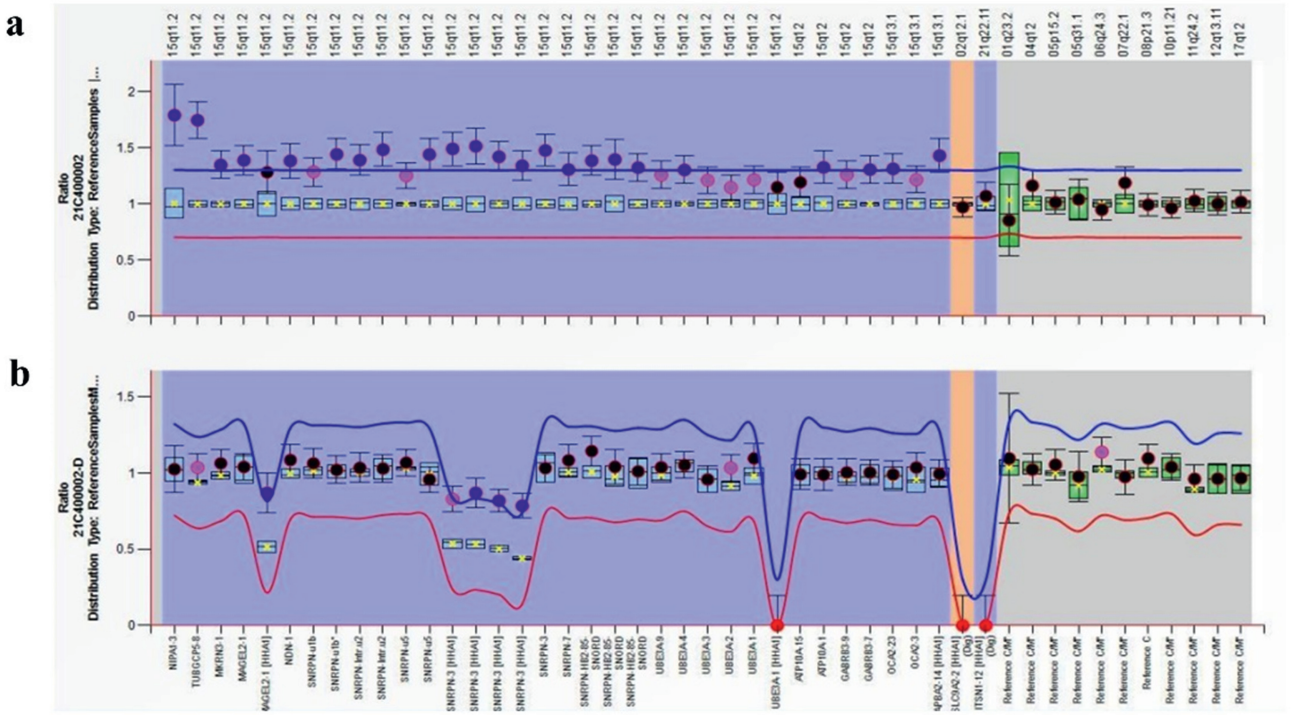

Fig. 3. MS-MLPA tests on the DNA extracted from uncultured amniocytes at 23 weeks of gestation shows the ratio value of copy number in 15q11-13 (a) and the percentage of methylation loci (b).

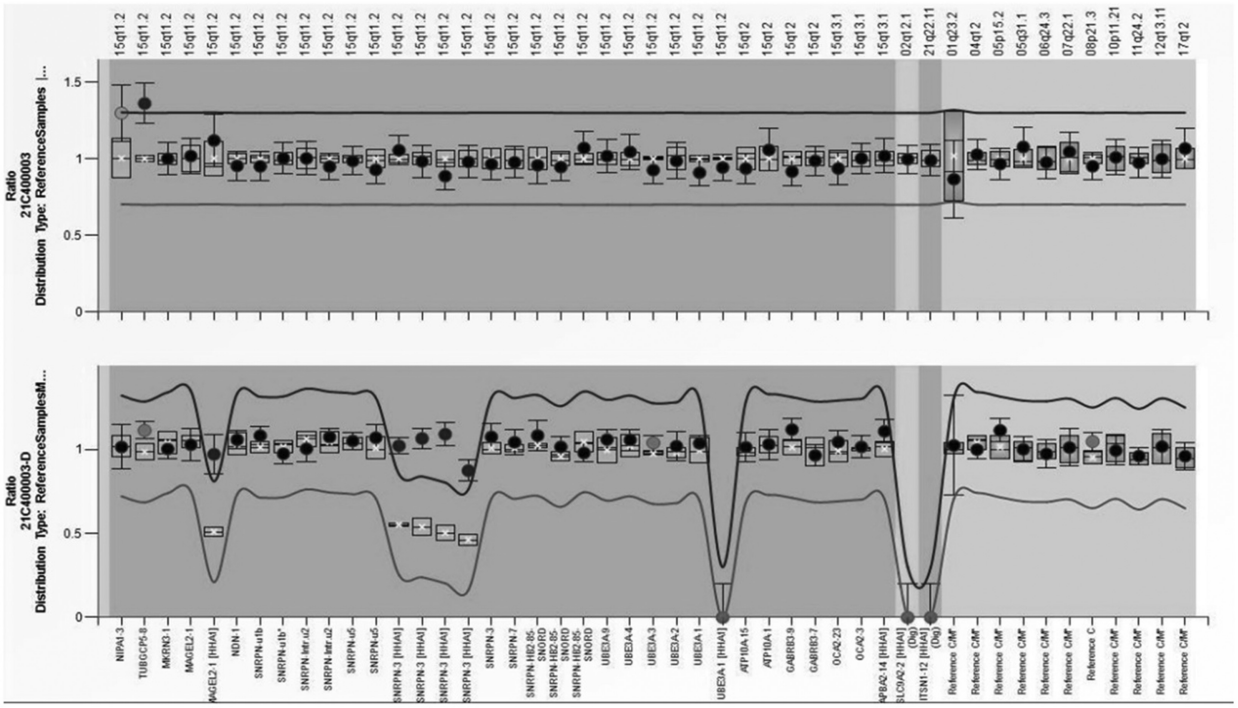

Fig. 4. MS-MLPA tests on the DNA extracted from cultured amniocytes at 23 weeks of gestation shows the ratio value of copy number in 15q11-13 (a) and the percentage of methylation loci (b).

due to advanced age of pregnant women, previous child with Down syndrome and increased fetal nuchal translucency (5.0 mm) [4–7] (Table 1). The clinical phenotypes of UPD(15) mat/T15 mosaicism are non-specific, such as a two-vessel cord, malrotation of the bowel, ventricular septal defect (VSD), nuchal pre-nasal edema and so on. And cases with a normal karyotype and no reported clinical phenotype were confirmed as UPD(15) mat by molecular testing of different fetal tissues after termination of pregnancy (Table 1). We suggest that detection of UPD(15) is necessary to diagnose or rule out PWS for fetuses at high-risk of T15 detected with NIPT. Moreover, we also recommend MS-MLPA analysis can be used for prenatal diagnosis of UPD(15) mat/T15 mosaicism.

Declaration of competing interest

The author has no conflicts of interest relevant to this article.

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None.

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Case Report

Inguinal nodal metastatic squamous cell carcinoma of unknown primary (CUP) detected 7 years before the diagnosis of vulvar squamous cell carcinoma: A case report

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ABSTRACT

Objective: Metastatic squamous cell carcinoma (SCC) of inguinal lymph node region with unknown origin is a rare condition. A patient was diagnosed to have vulvar SCC 7 years after the initial diagnosis of inguinal nodal metastatic SCC of unknown primary.

Case report: A 59-year-old woman with metastatic SCC of unknown origin in the right inguinal lymph node underwent tumor resection and no evidence of residual disease or possible tumor origin was detected after the surgery and a comprehensive work-up. Seven years later, she was diagnosed to have invasive right vulvar SCC with right pelvic lymph node metastasis. We performed a series of tests to evaluate the relationship between these two events.

Conclusion: According to our investigation, the possible relationship between the two events could not be ruled out. This case emphasizes the possibility of late recurrence and the importance of long-term follow up for patients with isolated nodal CUP.

Introduction

Cancer of unknown primary site (CUP) accounts for about 5 % of all cancers.1 [1,2]. It is defined as a histologically confirmed metastatic tumor, of which the primary site remains unknown despite a detailed clinical evaluation and work-up. The majority of CUP are characterized by aggressive behavior and poor prognosis. The mainstay of treatment for this group of patients is empirical chemotherapy. However, some subsets of CUP with distinct clinical or pathological features, such as single metastatic lesion or isolated nodal CUP, have a favorable prognosis and may be treated by excisional or radiation therapy only [3–5].

Vulvar cancer is an uncommon gynecologic malignancy and the most frequent (>90 %) histology type is squamous cell carcinoma (SCC). More than half of patients present with early-staged disease, but about 30 % of patients have nodal or distant metastasis at the time of diagnosis [6]. Most cases with vulvar cancer present with palpable or visible skin lesions with irritation, pain, burning or bleeding. Surgery remains the treatment of choice for early-stage vulvar cancer, while chemoradiation plays a role in locally advanced or metastatic disease.

Here we report a case with metastatic squamous cell carcinoma on the inguinal lymph node of unknown origin who was diagnosed to have invasive vulvar SCC 7 years after the initial diagnosis of CUP.

Case report

A 59-year-old, gravida 3, para 3, female presented to our department of general surgery for a gradually enlarging mass about 4 cm in size on the right inguinal area, of which she had been aware for 3 months. The mass was not movable and non-tender upon physical examination. She had no previous medical history, surgical history and there was no family history of malignancy. She reported no other accompanied symptoms, such as weight loss, cough, chest

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pain, skin lesion, abdominal or pelvic pain, or vaginal bleeding. An excisional biopsy of the mass was performed and it showed multiple groups of metastatic squamous cell carcinoma in the lymph node. The tumor cells are positive for CK5/6, P63, P40, P16 and CK(AE1/AE3) but negative for vimentin. Considering the histological evidence, the patient was referred to our department for gynecological evaluation.

At the time of the initially gynecological clinic visit, her general condition appeared to be good. In physical examination, the enlargement of lymph nodes in other areas such as the cervical, supraclavicular, or axillary regions was not observed. In abdominal and pelvic examination, an enlarged, non-tender, and movable lower abdominal mass extended above umbilicus was noted. The cervix appeared normal grossly but was slightly indurated. Vulvar and vagina were atrophied without discoloration or mass. Vaginal and rectal examination revealed soft and free parametrium. There was no detectable abnormality of the head and neck, chest, all extremities, the perineum, and the perianal area. Report of cervical

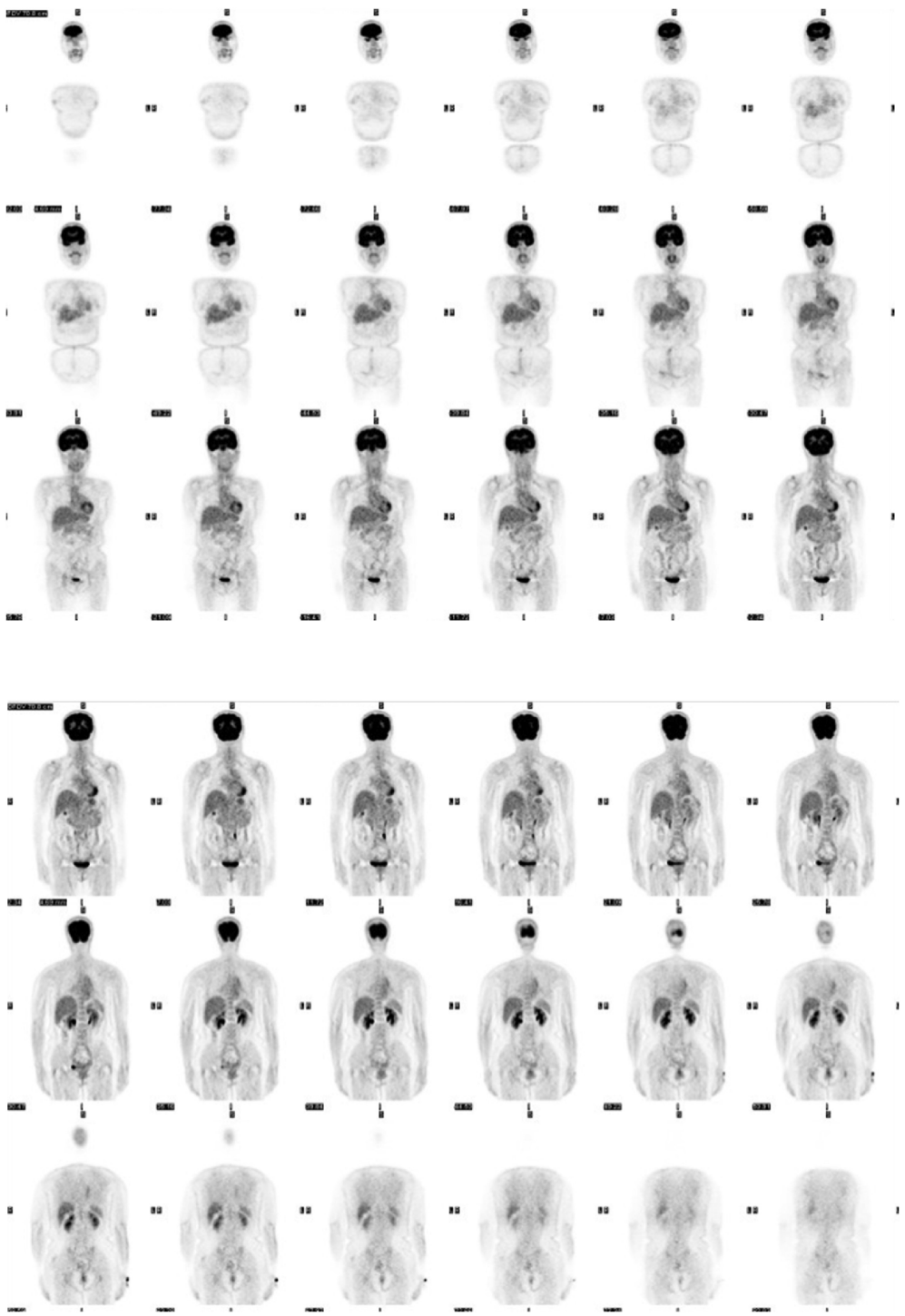

Fig. 1. FDG-PET scan after excision of the inguinal lymph node showed no other hypermetabolic abnormality suggesting malignancy.

cytology showed negative for intraepithelial lesion or malignancy. Her serum squamous cell carcinoma antigen (SCC Ag) level was normal (0.48 ng/mL). Computerized tomography (CT) scan of abdomen revealed a large heterogeneous pelvic mass with indistinct margin from uterus and bilateral adnexa. Other image studies including CT scan of chest and magnetic resonance imaging (MRI) of head and neck both revealed no suspicious lesion. She underwent a hysterectomy and bilateral salpingo-oophorectomy in October 2015 and pathological analysis revealed uterine leiomyomas in size of 18.5x11.2x9 cm. No evidence of malignancy was detected in the surgical specimens of uterine body, uterine cervix, fallopian tubes and ovaries. Since the primary site was not evident despite initial test and surgical procedure, positron emission tomography (PET) with F-18-fluorodeoxyglucose (FDG)/CT (PET/CT) scan was arranged and showed no abnormal uptake (Fig. 1). Inguinal nodal metastatic SCC of unknown primary site was diagnosed. She received no adjuvant therapy and was regularly followed at our clinic with pelvic examination and CT scan annually till September 2020. No evidence of malignancy had been detected.

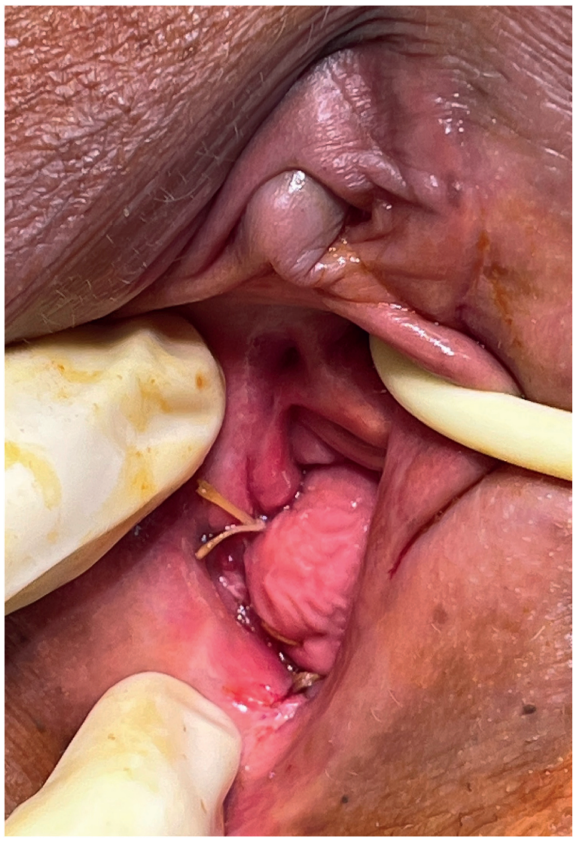

Fig. 2. Right vulvar painful mass developed 7 years after nodal CUP was biopsied and proved to be vulvar SCC.

In November 2022, the patient presented to our clinic with chief complaint of a right vulvar painful mass for 3 months. In pelvic examination, one indurated mass over inner aspect of right labia majora was noted (Fig. 2). Excisional biopsy of the mass was performed, and it showed invasive squamous cell carcinoma. SCC Ag level was normal (1.52 ng/mL). CT scan of abdomen showed an enlarged right iliac lymph node and no suspicious inguinal lymphadenopathy. PET/CT scan revealed a small focus of increased uptake in the region of lower vagina [standardized uptake value (SUV) = 8] and a small lymph node with increased uptake in the right pelvic sidewall (SUVmax = 4), suggestive of lymphadenopathy. She underwent radical vulvectomy and the final pathology report revealed stage IV invasive vulvar SCC. Chemoradiation will be arranged as further treatment.

For the histological finding was the same to the previous CUP, it raises the question of whether the prior groin LN lesion could be related to current vulvar SCC. To further investigate this question, we performed a series of tests to evaluate the relationship between these two events. Histology and immunohistochemical staining revealed similar results. Expression of p16 immunostaining, a marker for HPV infection, of the two specimens were both positive (Fig. 3). HPV DNA testing was undertaken using PCR and DNA of

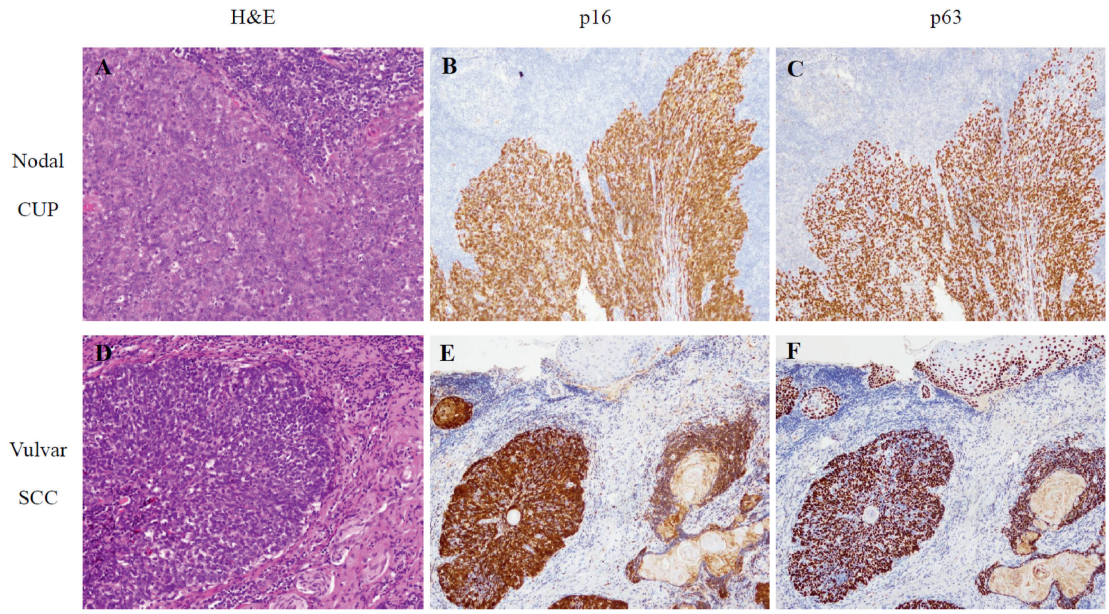

Fig. 3. Pathological features with histological and immunohistochemical staining for p16 and p63. (A, B, C) Nodal CUP lesion; (D, E, F) Vulvar SCC lesion; (A, D) H&E stain: infiltrating tumor nests in nodal CUP and vulvar SCC lesions (Magnification: 200x); (B, E) The tumor cells of nodal CUP and vulvar SCC lesions are both positive for p16; (C, F) Both lesions are positive for p63. (Magnification: 100x) H&E, hematoxylin and eosin.

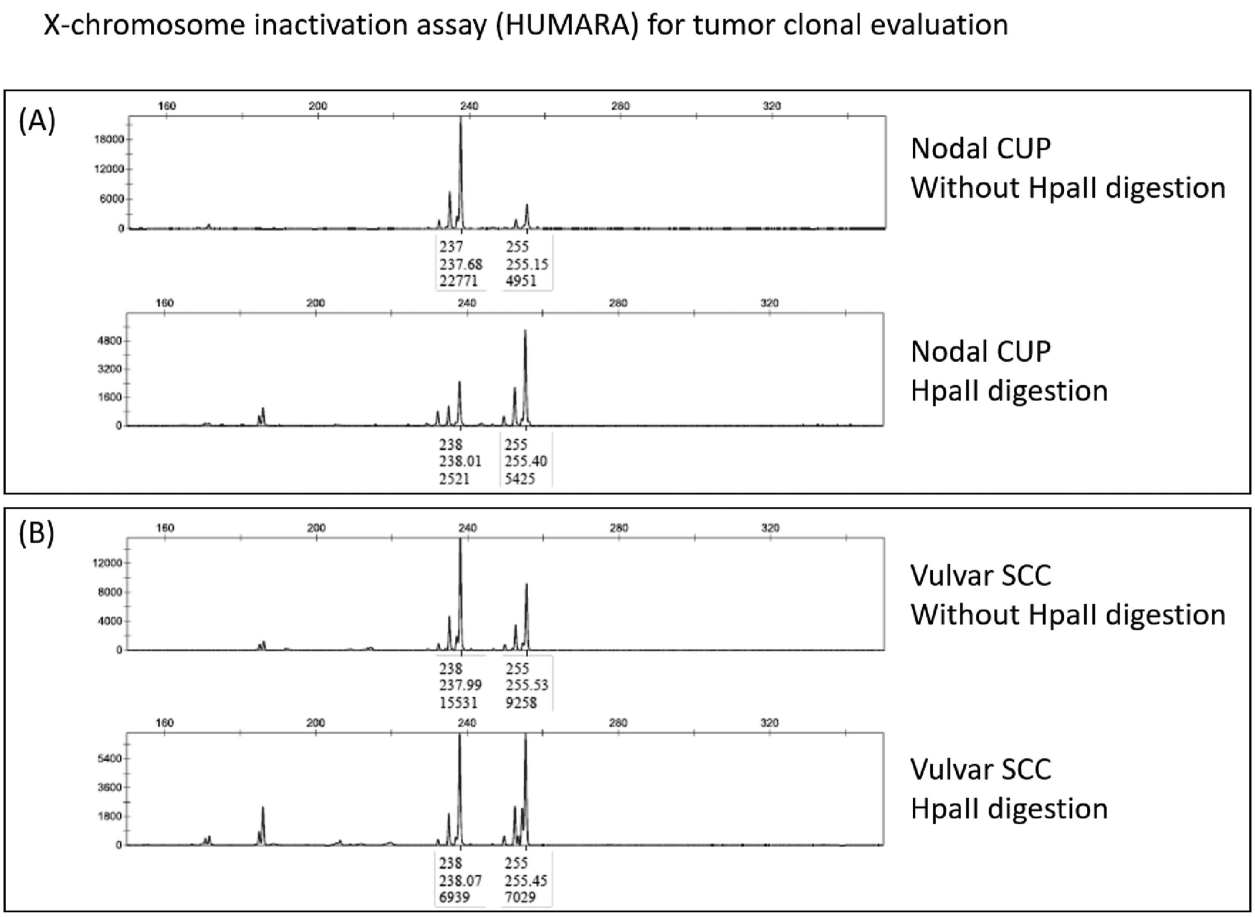

Fig. 4. Tumor clonality analysis. (A) X-chromosome inactivation assay of nodal CUP lesion showed only one allelic peak remained after HpaII digestion, indicating monoclonal nature of the specimen; (B) Upon digestion, the Vulvar SCC displayed two remained peaks, indicating a polyclonal origin. The allele with high molecular weight androgen receptors DNA became higher after HpaII digestion.

HPV 16 was detected in both specimens. The HPV genomic DNA was detected in genomic DNA extracted from formalin-fixed paraffin-embedded tissues of both specimens using nested PCR of HPV L1 region. The MY09/MY11 primer set (1) was applied for outer PCR and the GP51/GP61 primer set (2) for nest PCR. The DNA sequence of PCR products was determined by Sanger method with GP61 primer. Further alignment of the getting sequences with NCBI database using Basic Local Alignment Search Tool (BLSAT) was performed for determining of HPV genotypes. To further assess the clonal relationship between the two specimens, PCR-based HUMARA assay was performed. The result of the clonality assay for the two specimens are shown on Fig. 4. Upon HpaII digestion, the nodal CUP lesion showed a monoclonal result with only one retained peak of high molecular weight androgen receptors DNA band. The specimen of vulvar SCC revealed discrete peaks after HpaII digestion, which indicated a polyclonal nature of the specimen. Of note, the high molecular weight androgen receptors DNA band of vulvar SCC also became higher after HpaII digestion, similar to the presentation of nodal CUP lesion.

Discussion

CUP in the inguinal lymph node of squamous cell origin is a condition rarely encountered. Inguinal nodal metastatic cancer of unknown origin accounts for about 10 % of CUP in lymph node. Among these patients, adenocarcinoma was the most common histology type and only 13.7–21.4 % are of squamous cell origin [7,8]. The lymphatic drainage of the inguinal lymph nodes originates from the lower limbs, gluteal region, lower anterior abdominal wall, vulva, distal parts of vagina and anal canal. The groin nodes also receive some afferents vessels from lower pelvis and uterine horns via round ligament [9]. Careful examinations of these area might be helpful to rule out a primary site. The most appropriate management strategy for these patients remains unclear given the paucity of data, but favorable outcomes after treatment had been reported. In a case series of 9 patients with CUP of the inguinal region of squamous cell origin treated with chemoradiation, no local or distant recurrence occurred during the follow-up period with a median duration of 56 months (range, 10–76 months) [10]. For single metastatic lesion or isolated nodal CUP, a tailored treatment with local regional therapy such as surgery or radiation therapy is currently the mainstay of care due to a more favorable outcome comparing to CUP with disseminated disease at presentation [3–5].

Our case also demonstrated prolonged progression free period since no evidence of disease had been detected for 7 years after initial excision of the lesion. However, vulvar SCC presented in advanced stage developed years later. According to our investigation, there are several reasons that suggest the possible relationship of these two events. Firstly, the histopathological features including p16 staining of the two specimens were similar. Secondly, both specimens revealed positive for HPV 16 DNA. Finally, the clonality analysis of the two specimens revealed a similar pattern of change that the allelic peak with high molecular weight androgen

receptors DNA became higher after HpaII digestion. Although discrete allelic peaks were displayed after HpaII digestion of the vulvar SCC lesions, indicating a polyclonal origin, it could be a result of mixture of tumor cells and normal cells. The similar pattern of peak switch after digestion suggests that it is likely the vulvar SCC cells exhibit the same X-chromosome inactivation pattern as to the nodal CUP lesion. However, this could not be confirmed based on the non-informative result.

Almost all of the lymphatic fluid of vulvar area drains through inguinal nodes, and the most frequent site of nodal metastasis of vulvar cancer is inguinofemoral node [11,12]. To survey the possible origin of the patient's prior nodal CUP, a comprehensive work-up was performed but no lesion was detected in the external genitalia, genital or pelvic organs. The possible explanation was that the nodal CUP lesion might represent the lymphatic metastases from a very early occult primary cancer which was not clinical detectable that time. Another hypothesis regarding the pathogenesis of CUP was neoplasm arising from stem cell without primary site [4].

In conclusion, we present a rare case of inguinal nodal CUP of SCC origin who also diagnosed to have vulvar SCC 7 years later. According to our investigation, the possible relationship between the two events could not be ruled out. This case emphasizes the possibility of late recurrence and the importance of long-term follow up for patients with isolated nodal CUP.

Declaration of competing interest

There is no conflict of interest.

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Case Report

Ovarian clear cell carcinoma with uterine intramural recurrence: Case report of ovarian clear cell carcinoma with fertility sparing treatment

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ABSTRACT

Objective: Ovarian clear cell carcinoma has a poor prognosis in comparison with other pathological types of epithelial ovarian carcinoma. It also has relative resistance to first-line platinum-based chemotherapy with a great risk of recurrence.

Case report: We report a case of recurrent ovarian clear cell carcinoma status after left salpingo-oophorectomy (fertility-sparing debulking operation) and six courses of adjuvant chemotherapy (paclitaxel (175 mg/m^2)/carboplatin (AUC 6)). However, two years after diagnosis, elevated CA-125 accompanied by an intrapelvic mass was noted. Uterine intramural recurrence was found during the second laparotomy. She was treated with right salpingo-oophorectomy and abdominal hysterectomy combined with systemic chemotherapy administration (paclitaxel (175 mg/m^2)/carboplatin (AUC 6)) and maintenance therapy (bevacizumab (7.5 mg/kg)). There was no other recurrence until one and a half years postoperatively, and the patient was tumor free with regular follow-up.

Conclusion: In young patients with stage I ovarian clear cell carcinoma, fertility-sparing surgery was considered. Most patients will suffer from tumor recurrence, and also intrauterine recurrence rarely happen.

Introduction

Ovarian cancer is a heterogeneous group of tumors, each associated with unique clinicopathological and epidemiological characteristics. Ovarian clear cell carcinoma (OCCC) is a histologic subtype of ovarian epithelial ovarian carcinoma. Differences in the prevalence of OCCC were noted between different geographic locations. The prevalence is much higher in Asian populations than in Western countries [1]. In a nationwide database analysis through the Taiwan cancer registry system, the percentage of clear cell type ovarian cancer gradually increased in recent years [2]. The clear cell type is the second most common histology of ovarian cancer in Taiwan after the serous type. Young age and early stage are noted in the population of clear cell ovarian cancer patients. In a large cohort of young patients with stage I ovarian clear cell carcinoma, fertility-sparing surgery was not associated with worse survival [3]. However, OCCC has a great risk of recurrence and poor prognosis in comparison with other pathological types of epithelial ovarian carcinoma because of a relative resistance to first-line platinum-based chemotherapy. Most patients will suffer from tumor recurrence, and the recurrence site includes the pelvis, peritoneum or lymph nodes [4]. This case is a clear cell carcinoma with stage IA post status of fertility-sparing debulking surgery and suffered from a special single recurrent site two years after diagnosis. Herein, we report a special case of recurrent ovarian clear cell carcinoma with elevated CA-125 accompanied by a visible intrauterine mass that

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was successfully treated with abdominal hysterectomy combined with systemic chemotherapy administration.

Case

This 30-year-old Taiwanese nulliparous female, who was previously diagnosed with ovarian clear cell carcinoma FIGO stage IA, had regular follow-up at our hospital for over two years. She had an average BMI. In addition to ovarian cancer, there was no other remarkable medical history.

Tracing back to the history, she first reported intermittent lower abdominal pain and had a left side ovarian cyst approximately 3 cm in size. Slightly elevated serum levels of CA-125 were also detected (51.9 U/mL) (Fig. 1). A 6 cm cystic tumor containing solid parts with papillary projection of approximately 3 cm was detected in her left adnexal region at the first visit (Fig. 2a). Computed tomography of the pelvis and abdomen revealed no obvious focal lesion in the abdomen and no significantly enlarged lymph nodes in the retroperitoneum (Fig. 2b). Laparotomic left salpingo-oophorectomy was performed, and the specimen was sent for frozen sectioning, which revealed adenocarcinoma. The mass was removed smoothly without rupture (Fig. 3). Due to young age and early stage status, fertility-sparing debulking surgery was performed, including pelvic/para-aortic lymphadenectomies, infra-colic omentectomy, appendectomy, and peritoneal biopsy, on April 16, 2019. After the surgery, the final pathology was clear cell carcinoma, with FIGO stage IA (PT1a, N0, M0) (Fig. 3). Six courses of paclitaxel (175 mg/m^2)/carboplatin (AUC 6) in combination with adjuvant chemotherapy were administered smoothly. Regular monitoring of clinical presentation was performed every three months after completion of chemotherapy. The tumor markers were all within the normal range (Fig. 1).

However, two years after the diagnosis, elevated serum levels of CA-125 were detected (81.0 U/mL) (Fig. 1). A cystic mass of approximately 5 cm with low echogenic content inside was found in the left lateral pelvic region (Fig. 4). Computed tomography of the pelvis and abdomen was performed again, which revealed no other focal lesion in the abdomen and no enlarged lymph nodes, excluding the left pelvic mass (Fig. 4d). Local recurrence was highly suspected, and secondary debulking surgery was indicated. However, under laparotomy exploration, there was no visible mass or nodule inside the pelvis, including the surface of the uterus, bowel, omentum and peritoneum (Fig. 5). Intraoperative ultrasonography was performed on the vagina for tumor identification. Thus, we finally found a 5 cm cystic mass with papillary growth inside the left uterine muscular wall (intramural type) and a thin

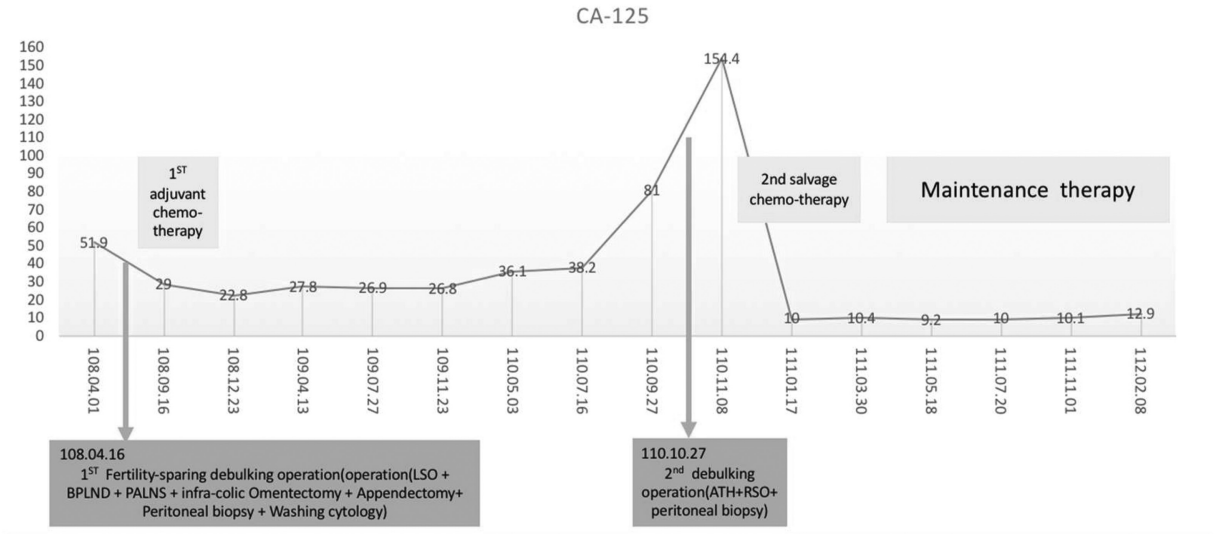

Fig. 1. The level of CA-125 during the whole treatment course.

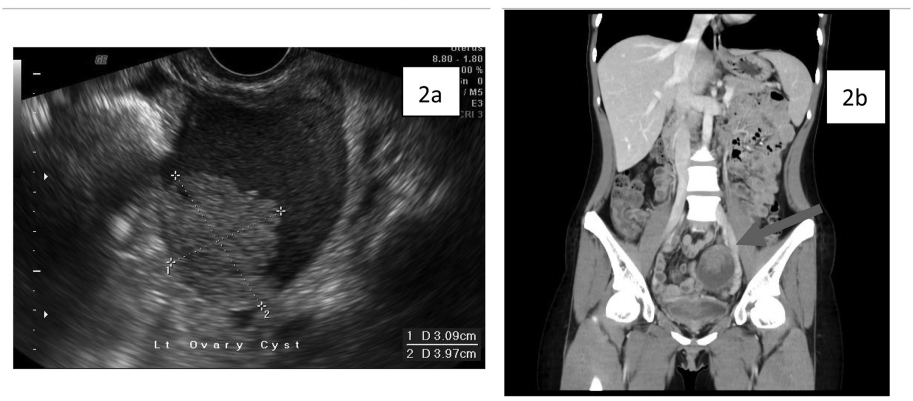

Fig. 2. Image studies before first fertility sparing debulking operation. (a)transvaginal ultrasonography: a papillary projection inside the left adnexal cyst; (b) coronal view of computed tomography of pelvis and abdomen (arrow) revealed the origin tumor location.

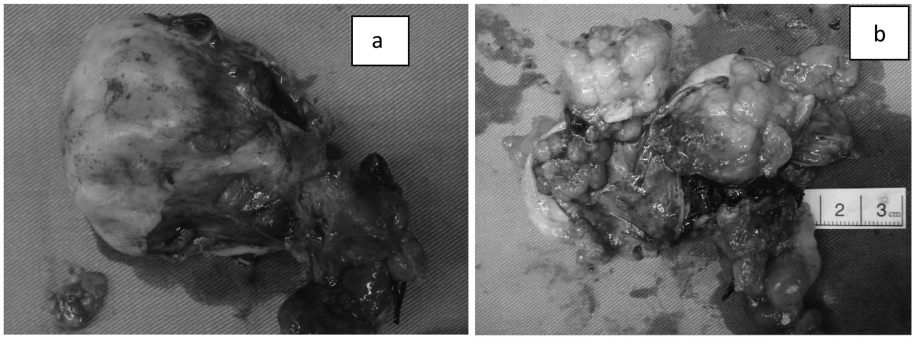

Fig. 3. Grossly picture of the primary ovary tumor under LSO. (a) Surface intact of left adnexal tumor; (b) cross section of left adnexal tumor with multiple papillary growth.

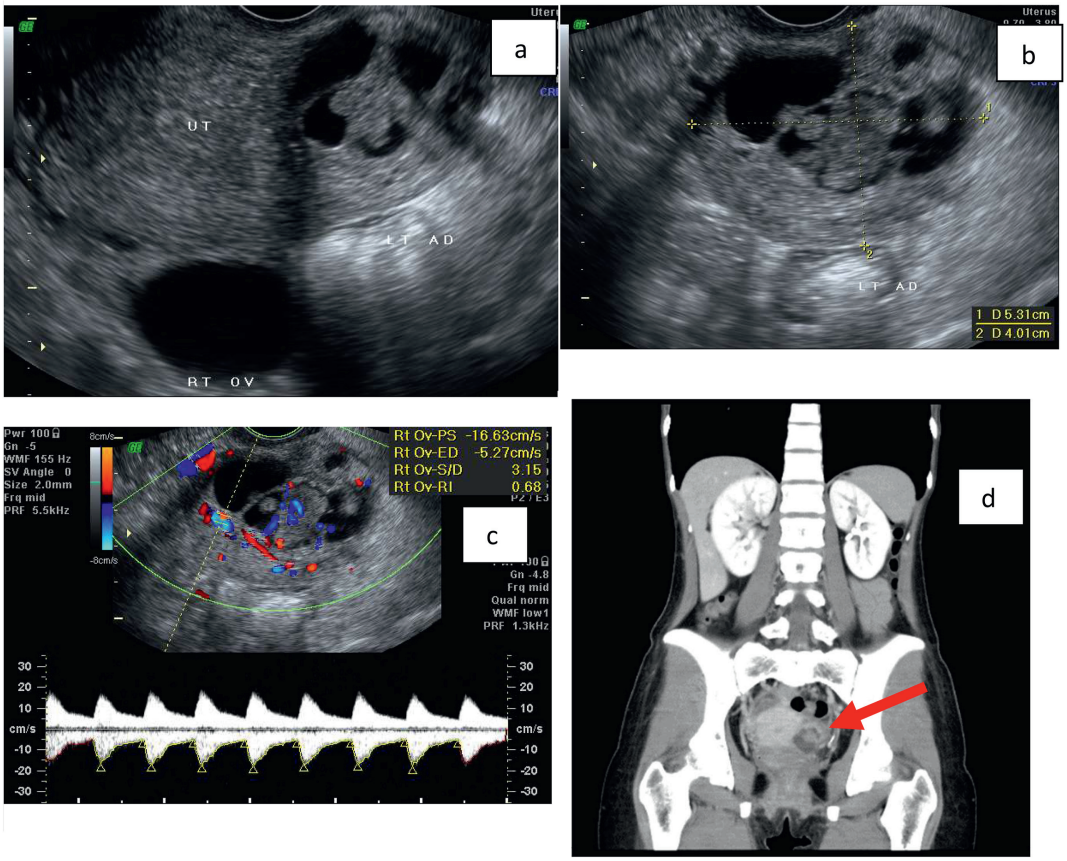

Fig. 4. Recurrent mass was suspected during follow up under image studies. (a)transvaginal ultrasonography revealed the left pelvic mass close to uterus with thick wall; (b) low-echogenic content inside the left pelvic mass; (c)resistive index was 0.68 of the solid component inside the left pelvic mass; (d)coronal view of computed tomography of pelvis and abdomen of the left pelvic mass (red arrow).

endometrium, which was compatible with preoperative radiology (Fig. 6). Excision of the uterine tumor was performed, and a frozen section of the uterine tumor was adenocarcinoma. Total abdominal hysterectomy (TAH), right salpingo-oophorectomy (RSO) and peritoneal biopsy of the left pelvic sidewall were performed on October 27, 2021. The final pathology of the intramural uterine tumor was clear cell carcinoma involving the myometrium, which was of Müllerian origin. There were no other pathology findings inside the uterus. Another six-course combination of paclitaxel (175 mg/m^2)/carboplatin (AUC 6) chemotherapy was administered, followed by bevacizumab (7.5 mg/kg) maintenance. There was no other recurrence until one and a half years postoperatively, and the patient was tumor free with regular follow-up.

Discussion

Clear cell adenocarcinoma can present in the ovary, uterus or cervix [5]. Simultaneous clear cell adenocarcinoma of the uterine corpus and ovary was reported in approximately 6 cases, 5 of which died within 4 years after diagnosis, most of which were located in the endometrium [6,7]. Clear cell carcinoma is less often simultaneous involving the endometrium and ovary [8]. Ovarian malignancy with uterine recurrence is rare. One case of ovarian sex-cord tumor with uterine tumor recurrence was once reported [9]. However, ovarian clear cell adenocarcinoma with uterine recurrence has not yet been reported in the literature. Because the mass was inside the myometrium, not inside the endometrium, we don't

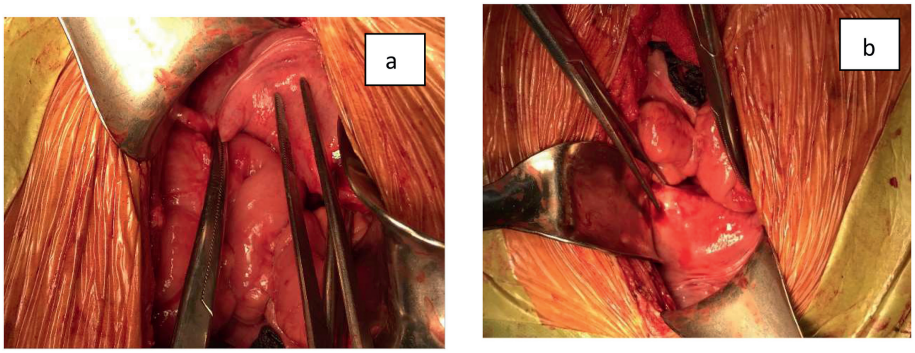

Fig. 5. No obvious mass lesion noted under secondary laparotomy. (a) (b) Second operation showed normal pelvis and unremarkable left pelvic sidewall.

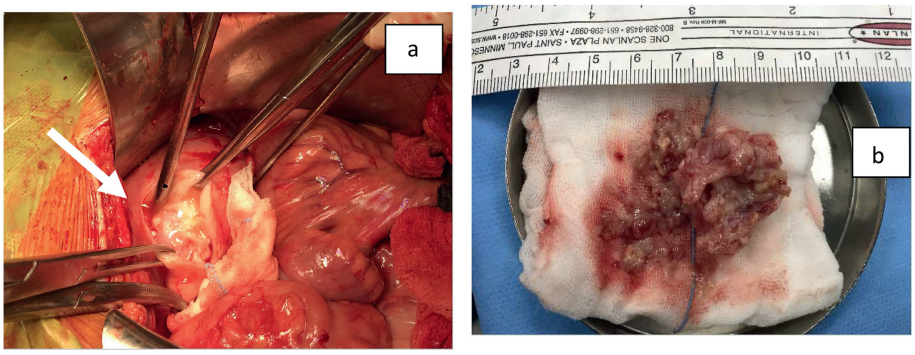

Fig. 6. After intraoperative sonography, the mass was identified inside the uterine muscular region. (a)intramural uterine tumor (white arrow) at left side; (b)excision of uterine mass showed papillary growth pattern.

consider this case to be synchronous clear cell carcinoma. However, the possibility of synchronous clear cell carcinoma is still present in the literature.

Approximately 7–8% of all stage I ovarian cancer cases affect women aged under 35 years old [10], and fertility-sparing surgery with preservation of the contralateral ovary and uterus for women with fertility desire has been indicated for stage I epithelial ovarian cancer patients. Adjuvant chemotherapy with regular follow-up is very important. Ovarian cancer is a silent killer, and most recurrences occur without specific symptoms. Monitoring tumor markers and imaging studies help in the early detection of recurrence. A double level of the tumor marker or persistent elevation of the tumor maker may imply recurrence. Sonography may be a suitable tool for primary surveys for local recurrence. Computed tomography of the pelvis and abdomen or positron emission tomography may also confirm other metastasis sites. Regarding the recurrence tumor distribution of clear cell ovarian cancer, the most common site was the pelvis (47.5 %), followed by lymph node metastases and intra-abdominal lesions [4].

Although the possibility is rare, learning from our case, uterine recurrence through hematogenous spreading may be taken into consideration. In addition, ultrasound examination under anesthesia during exploratory laparotomy is a critical method to identify tumors. Initially, we did not find obvious lesions when we entered the abdominal cavity. Then, under ultrasound guidance, a recurrent mass located at the uterine wall was clearly identified. For fertility-sparing cases, we should be aware of the possibility of uterine site recurrence. However, the good news is that patients with focal recurrence had a favorable prognosis after complete resection at secondary debulking operation [10]. We were able to achieve optimal debulking status after hysterectomy.

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There is no funding or support for this study.

Conflicts of interest

All authors have no conflicts of interest relevant to this article.

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Case Report

Successful pregnancy with in vitro fertilization after vaginal radical trachelectomy and pelvic lymphadenectomy in stage IB1 cervical cancer

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ABSTRACT

Objective: To present a case of successful pregnancy after undergoing vaginal radical trachelectomy (VRT) and pelvic lymph node dissection (PLND) for early-stage cervical cancer.
Case report: A 37-year-old female patient has been diagnosed with stage IB1 cervical cancer and underwent VRT and PLND. Two years after the surgery, the patient successfully conceived and delivered a healthy baby through a cesarean section.
Conclusion: This case report demonstrates that pregnancy after VRT and PLND for stage IB1 cervical cancer is possible and can result in a successful outcome. This report provides valuable information for patients and physicians who are considering these surgical options.

Introduction

Cervical cancer is prevalent among women globally, and treatment options include surgery, radiation therapy, and chemotherapy. The impact of these treatments on future fertility and the possibility of successful pregnancy after treatment is an important concern for many women. Radical trachelectomy is a standard treatment for selected patients with early-stage cervical cancer and can be performed via vaginal, abdominal, laparoscopic, and robotic methods. Although oncologic outcomes are not significantly different among the surgical approaches, pregnancy rates and obstetric outcomes of the vaginal approach appear to be superior to the abdominal approach [1]. In vitro fertilization (IVF) is a well-established treatment for infertility and has been used successfully in women who have undergone treatment for cervical cancer. However, limited research has been conducted on the use of IVF after vaginal radical trachelectomy and pelvic lymphadenectomy in stage IB1 cervical cancer. In this case report, we presented a 37-year-old nulligravid woman with stage IB1 cervical cancer who underwent a vaginal radical trachelectomy and subsequently became pregnant after assisted reproductive therapy.

Case report

A 37-year-old woman, who was nulligravida and married, was admitted to the gynecological oncology department with a complaint of post-coital bleeding. Upon examination, the patient has been diagnosed with stage IB1 cervical cancer. The results of the cervical biopsy revealed a moderately-differentiated squamous cell carcinoma of the ectocervix.

A magnetic resonance imaging (MRI) scan showed a cervical mass of 2 cm × 2 cm located on the posterior wall of the ectocervix, with a cranial extent of 11.5 mm. The tumor was found to be 21 mm lower than the internal cervical os and there were no signs of metastases in the parametrium, pelvic lymph nodes, para-aortic lymph nodes, upper abdomen, or thorax.

Given her desire to preserve her fertility, she underwent vaginal radical trachelectomy (VRT), which included a pelvic lymphadenectomy. After general anesthesia, bilateral double J catchers were inserted into both ureters. The VRT method employed in this case was based on the Schauta-Stoeckel technique and was described previously [2]. To begin the procedure, laparoscopic dissection of pelvic lymph nodes (26 nodes) was carried out, followed by a

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frozen section examination to ensure their true-negative status. Resection of the vaginal region commenced at a distance of at least 2 cm from the vaginal cuff, and the paravesical and pararectal spaces were developed through vaginal opening to identify the ureter in the uterovesical ligament. Half of the cardinal and uterosacral ligaments were excised to separate them from the adjacent tissue. Due to the limited space of the nullipara vaginal canal, the above procedures were performed slowly. The cervix was then transected at the lower uterine segment with a margin of at least 5 mm, but the cervix was torn (Fig. 1). The lower uterine segment was sutured. The vaginal mucosa was also sutured to the lower uterine segment, and an 8-French rubber catheter was inserted into the endocervical canal and left in place for three weeks. During this procedure, 26 lymph nodes were removed and were found to be free of metastasis upon examination. The histological examination of the sutured fragmented cervical tissue up to 5.5 × 4.0 × 1.5 cm with tumor size measuring 2.0 × 1.0 × 0.7 cm; showed a moderately differentiated squamous cell carcinoma, located 7 mm away from the surgical margin of the endocervix and 10 mm away from the surgical margin of the vagina. The parametrium was measured up to 2 × 2 × 0.8 cm. Cystofix was inserted into the bladder for suprapubic drainage of urine. She underwent bladder training one week after the operation. She recovered well from the surgery, and normal menstruation resumed six weeks post-operatively.

One year after the procedure, she underwent preconception counseling, including discussions about fertility, pregnancy management options, and expected outcomes. Due to left tubal occlusion and hydrosalpinx, in vitro fertilization was indicated. After two cycles of controlled ovarian stimulation and oocyte retrieval, she had two euploid blastocysts. A laparoscopic left proximal tubal ligation was performed before embryo transfer, followed by a diagnostic hysteroscopy that revealed mild cervical stenosis. She became pregnant after an ultrasound-guided frozen single embryo transfer. At 11 weeks of gestation, a cervical ultrasound showed a length of 2.6 cm (Fig. 2) and remained stable over the following weeks. Prophylactic cervical cerclage was performed at 14 weeks of gestation. At 35 weeks of gestation, she delivered a healthy male newborn weight 2030 gm via cesarean section after evaluating fetal lung maturity. There was no evidence of cervical cancer recurrence in the past three years since her trachelectomy.

Discussion

Cervical cancer is one of the most common types of cancer in women worldwide. Treatment options for cervical cancer include surgery, radiation therapy, and chemotherapy. Radical trachelectomy and pelvic lymphadenectomy are surgical procedures that are commonly performed as part of the treatment for early-stage cervical cancer [2]. The impact of these procedures on future fertility and the possibility of successful pregnancy after treatment is an important concern for many women.

Radical trachelectomy is a standard treatment for selected patients with early-stage cervical cancer and can be performed through several surgical approaches including vaginal, abdominal, laparoscopic, and robotic. Although the oncologic outcomes, such as the recurrence rate, death-related disease, recurrence-free survival, and overall survival, are not significantly different among the surgical approaches, pregnancy rates and obstetric outcomes of the vaginal approach appear to be superior to the abdominal approach [1]. Additionally, many doctors and researchers worldwide view minimally invasive surgery (MIS) as a favorable approach for treating cervical cancer, due to its benefits such as fertility preservation, reduced morbidity, and faster recovery compared to open surgery [3,4].

Vaginal radical trachelectomy (VRT) and laparoscopic approaches can be used for patients with lesions 2 cm or less in diameter, as the recurrence risk increases for patients with larger lesions [5–7]. Vaginal radical trachelectomy becomes relatively difficult in nullipara because of the limited vaginal canal as demonstrated in the present case. Abdominal radical trachelectomy (ART) is a technically easier option and can be performed in women with anatomic distortion or when vaginal access is not possible [8,9]. It provides a broader resection of the parametria than the vaginal approach. However, the disadvantages of ART include the need for a longitudinal laparotomy incision, increased blood loss, longer hospital stays, and uterine artery injury, which can lead to endometrial atrophy, cervical stenosis, scarring, and low birth weight in future pregnancies [9,10]. The choice between VRT and ART should be based on the surgeon experience, available resources, and tumor size. Laparoscopy-assisted vaginal radical trachelectomy and pelvic lymphadenectomy is a suitable treatment options for women with early-stage cervical cancer who desire to preserve their fertility [11–13].

In the study by Bernardini et al. [10], the largest series on the topic, 41 % (16 out of 39) of the patients attempting pregnancy faced infertility. This infertility was mainly due to a cervical factor (75 %), with anovulation being a contributing factor in 12.5 % of the cases, and the remaining 12.5 % being idiopathic [14]. Cervical stenosis is a potential cause of infertility following radical trachelectomy and has been reported to occur in 15 % of patients [14–16]. Stenosis can

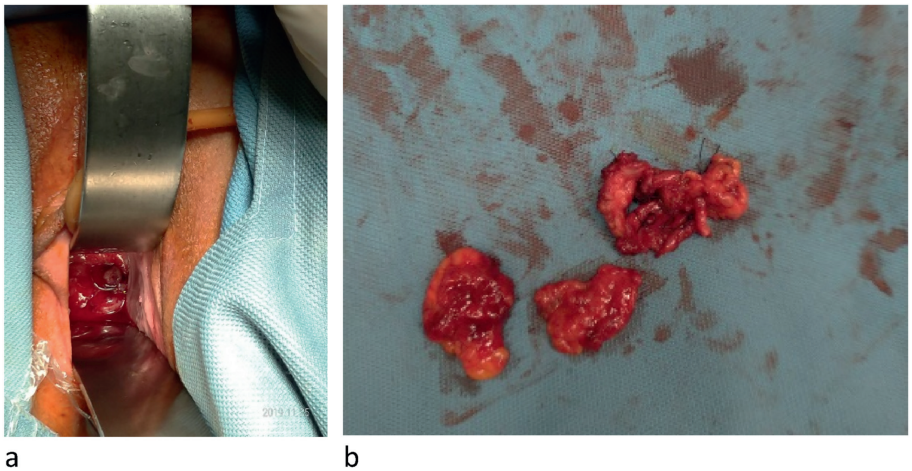

Fig. 1. (a) The cervix before surgery. (b) The fragmented cervix.

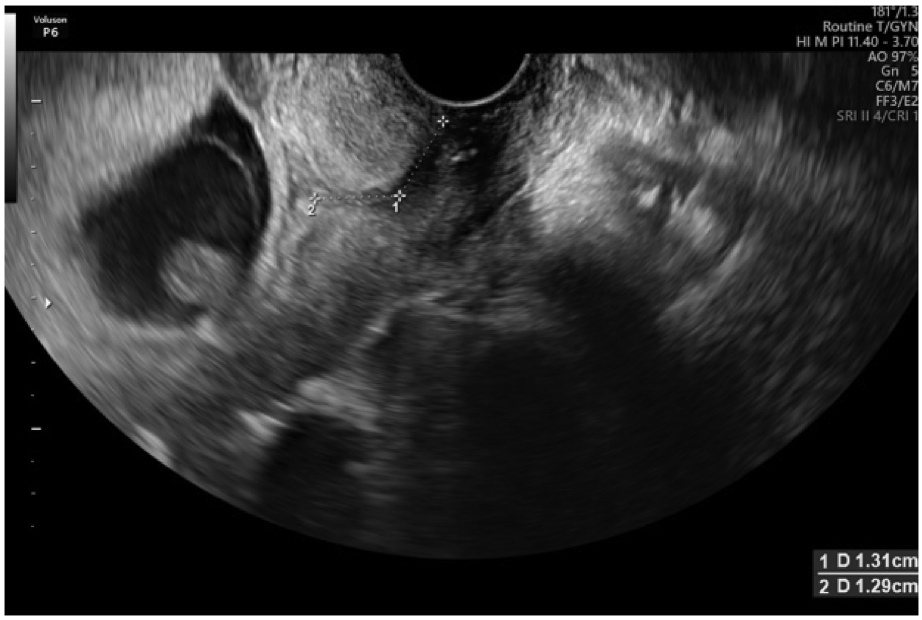

Fig. 2. The transvaginal ultrasound revealed a cervical length of 2.6 cm at 11 weeks of gestation.

be resolved by surgical expansion but may need to be repeated. Preterm labor and preterm premature rupture of membranes have also been reported following radical trachelectomy [16]. Interventions, such as routine screening for genital tract infections, prophylactic antibiotics, bed rest and/or reduced physical activity, and routine administration of glucocorticoids in the event of preterm delivery, have been proposed to prevent or mitigate these adverse effects.

In conclusion, this case report provides evidence that IVF after radical trachelectomy and pelvic lymphadenectomy may be a feasible and effective option for selected women with stage IB1 cervical cancer who desire future fertility. However, the applicability of these findings to other cases of cervical cancer treatment may vary, and individualized counseling is necessary to discuss the risks and benefits. Future research should aim to investigate the long-term outcomes of pregnancy after cervical cancer treatment and the impact of these treatments on fertility.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Case Report

Para-aortic lymphadenectomy in endometrial cancer patients with left-sided inferior vena cava: A case report and literature review

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ABSTRACT

Objective: The incidence of left-sided inferior vena cava (IVC) is extremely low. However, without a preoperative diagnosis of left-sided IVC, the risk of intraoperative vascular injury during para-aortic lymph node (PAN) lymphadenectomy is high.

Case report: Herein, we present two cases in which left-sided IVCs were diagnosed using preoperative imaging. PAN lymphadenectomies were safely performed in these patients with endometrial cancer. In the first case, the left-sided IVC crossed the abdominal aorta after the left renal and gonadal veins had drained into it and joined the right renal vein. In the second case, the left-sided IVC crossed the abdominal aorta after the left renal and gonadal veins flowed into it and the ascending lumbar vein flowed into the right side.

Conclusion: These cases demonstrate that even in the presence of vascular malformations, PAN lymphadenectomy can be performed safely by employing preoperative anatomical imaging analysis and judicious intraoperative surgical maneuvers to avoid vascular injury.

Introduction

Lymph node metastasis is an important prognostic factor for endometrial cancer, and lymphadenectomy is the standard treatment procedure [1,2]. This involves para-aortic lymph node (PAN) lymphadenectomy, which alters the peripheries of the aorta and inferior vena cava (IVC). As vascular injury can be fatal, detailed knowledge of the anatomy of the PAN region is necessary to avoid accidental injury [3,4]. For example, the IVC originates from the cardinal vein, which is typically symmetrical during the fetal stage, with most veins on the left side disappearing to form the IVC on the right side. Duplication of the IVC on both sides and left-sided IVC are sometimes observed, but the latter is extremely rare among IVC malformations, with an incidence of 0.2%–0.5 % [5]. If an undiagnosed preoperative left-sided IVC is present, the risk of vascular injury caused by PAN lymphadenectomy is high. Preoperative imaging for detecting left-sided IVC before PAN lymphadenectomy is essential due to the risk of vascular injury.

Few cases of PAN lymphadenectomy involving left-sided IVC have been reported in endometrial cancer patients thus far, and there are no reports of PAN lymphadenectomy in patients with lumbar vein inflow into the left-sided IVC. Therefore, here we report two cases of endometrial cancer in which left-sided IVCs were diagnosed using preoperative contrast-enhanced computed tomography (CT) and three-dimensional imaging CT (3D-CT), and PAN lymphadenectomies were safely and successfully performed through open and laparoscopic surgery.

Case report

Case 1

A 67-year-old woman (gravida 4, para 2) presented with the chief complaint of abnormal genital bleeding. Her height, weight, and body mass index (BMI) were 147 cm, 73.3 kg, and 33.8 kg/m^2, respectively. She had a history of hypertension but had not undergone any previous surgeries and was referred to our hospital due to positive endometrial cytology. The initial examination revealed a hen egg-sized uterus with good mobility, with endometrial histology revealing serous carcinoma. Magnetic resonance imaging (MRI) then showed endometrial cancer with >1/2 myometrium invasion, while contrast-enhanced CT showed no lymph node metastasis or distant metastasis; however, a left-sided IVC (Fig. 1a) was observed. At our institute, 3D-CT is performed when

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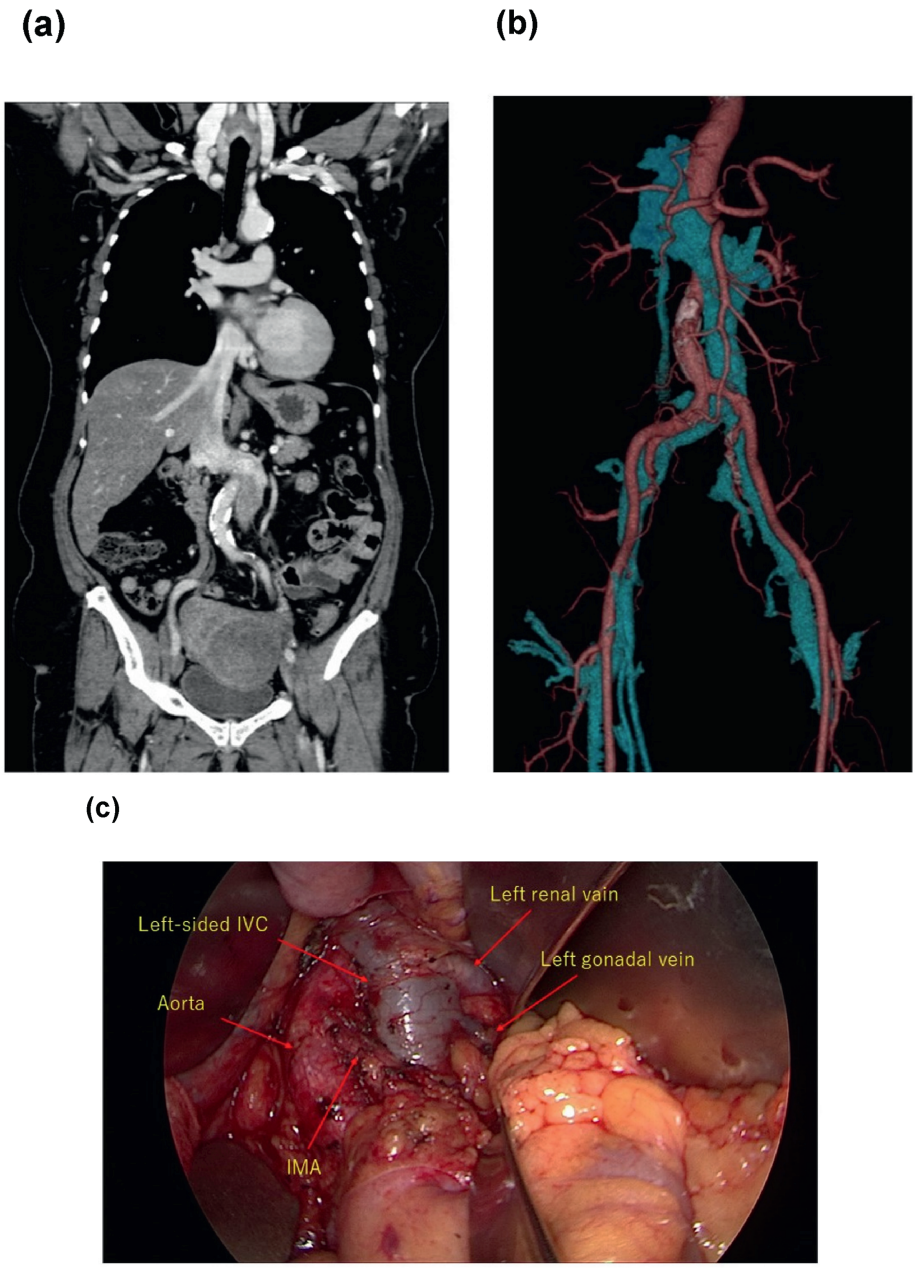

Fig. 1. **(a)** Contrast-enhanced computed tomography image showing a left-sided inferior vena cava (IVC). **(b)** Three-dimensional computed tomography image showing a left-sided IVC. **(c)** The left-sided inferior vena cava crosses the abdominal aorta after the left renal and gonadal veins drain into it.

contrast-enhanced CT confirms a malformation of the great vessels. After the presence of a left-sided IVC (Fig. 1b) was confirmed using 3D-CT in this case, total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), pelvic lymph node lymphadenectomy (PLND), PAN lymphadenectomy (PAND), and partial omentectomy were performed. Preoperative 3D-CT images revealed that the left-sided IVC crossed the abdominal aorta after the left renal and gonadal veins drained into it and joined the right renal vein. The operation time was 280 min with a blood loss of 535 mL. The PANs were dissected with careful attention to the left-sided IVC (Fig. 1c), and the patient was discharged on postoperative day 10 without intraoperative or postoperative complications. The final pathological diagnosis was International Federation of Gynecology and Obstetrics (FIGO) stage IA endometrial cancer with serous carcinoma. Postoperatively, the patient was administered 6 courses of paclitaxel and carboplatin (TC) therapy, and there was no evidence of recurrence 71 months after surgery.

Case 2

A 65-year-old woman (gravida 3, para 2) presented with abnormal genital bleeding. Her height, weight, and BMI were 158 cm, 55.8 kg, and 22.4 kg/m^2, respectively. The patient had a history of posterior lumbar interbody fusion surgery for lumbar spondylolisthesis and was referred to our hospital for endometrial cancer. The initial examination revealed a hen egg-sized uterus with good mobility, with endometrial histology revealing clear cell carcinoma. An MRI showed endometrial cancer without myometrial invasion, and contrast-enhanced CT showed no lymph node metastasis or distant metastasis. However, a left-sided IVC (Fig. 2a) was

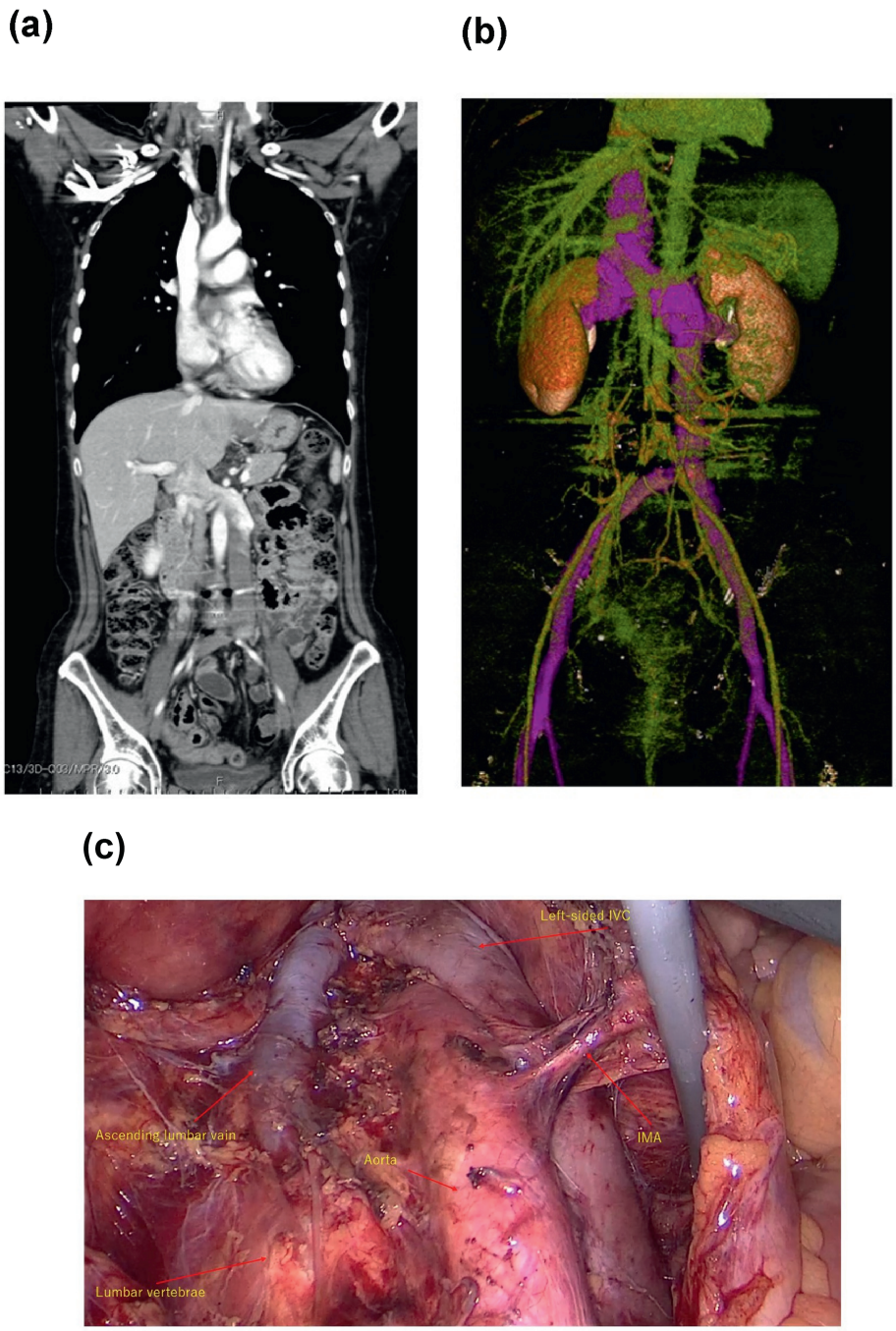

Fig. 2. **(a)** Contrast-enhanced computed tomography image showing a left-sided inferior vena cava (IVC). **(b)** Three-dimensional computed tomography image showing a left-sided IVC. **(c)** The left-sided inferior vena cava crosses the abdominal aorta, and the ascending lumbar vein flows into its right side.

observed. After the presence of the left-sided IVC (Fig. 2b) was confirmed using 3D-CT, total laparoscopic hysterectomy, BSO, PLND, PAND, and partial omentectomy were performed with a diagnosis of stage IA endometrial cancer. Preoperative contrast-enhanced CT revealed that the left-sided IVC crossed the abdominal aorta after the left renal and gonadal veins flowed into it and the ascending lumbar vein flowed into the right side. The operation time was 305 min, and blood loss was 5 mL. PANs were dissected with careful attention to the left-sided IVC (Fig. 2c), and the patient was discharged on postoperative day 4 without intraoperative or postoperative complications. The final pathological diagnosis was FIGO stage IA endometrial cancer with clear cell carcinoma. Postoperatively, the patient was administered six courses of TC therapy, and there was no evidence of recurrence 68 months after surgery.

Discussion

This study reported two cases of endometrial cancer with left-sided IVCs that were successfully treated with open and laparoscopic surgeries for PAN lymphadenectomy. In recent years, minimally invasive surgery for early-stage endometrial cancer has increased, and minimally invasive procedures have been reported to be technically and oncologically no different from open surgery [6]. In Japan, PAN lymphadenectomy for endometrial cancer of stage IB

or higher is not covered by insurance, and thus the procedure is performed by laparotomy. Therefore, the open or laparoscopic surgery is changed according to the preoperative image evaluation; however, the previous study showed that preoperative MRI and CT imaging resulted in a high rate of successful diagnosis of Stage IA endometrial carcinoma [7]. As PAN lymphadenectomy involves the resection of lymph nodes around the abdominal aorta on the distal side of the left renal vein, there is a risk of vascular injury to the IVC and other vessels. Therefore, malformation of the great vessels, especially the IVC, necessitates the highest attention as the presence of a malformation is a major risk factor for vascular injury. Studies on cadaveric autopsy specimens in the United States have reported a prevalence of 0.2%–0.5 % for left-sided IVC [8]. Additionally, Kim et al. analyzed the CT scans of 1000 healthy individuals who underwent medical checks and found IVC anomalies in 1.8 %. [9], with the highest frequencies noted in duplicate (1 %) and left-sided IVCs (0.4 %). In normal presentations, the left-sided IVC is joined by the left renal and gonadal veins, which cross the anterior abdominal aorta to join the right renal vein [10]. However, different degrees of regression produce different subtypes [11]. In the two cases described in this report, the left-sided IVC flowed into the left renal and gonadal veins, which then crossed the anterior abdominal aorta and joined the right renal vein. However, in the second case, the left-sided IVC crossed the abdominal aorta and the ascending lumbar vein flowed into the right side. Similarly, Ang et al. reported that in the few reports where the lumbar veins were mentioned, the veins drained into the left-sided IVC in a variable manner [12]. In our case, contrast-enhanced CT was better at identifying the presence of the ascending lumbar vein than 3D-CT. Here, the difficulty in identifying the ascending lumbar vein on 3D-CT may have been due to artifacts from the plate as the patient had a history of lumbar spondylolisthesis surgery. Thus, to avoid intraoperative vascular injury, close attention must be paid to the presence of subtype vessels such as the ascending lumbar vein and left-sided IVC.

Even in the absence of great vessel malformations, there has been one case of late retroperitoneal hematoma with abscess formation following Laparoscopic PLND for endometrial cancer previously reported [13]. In this study, we were able to perform PAN lymphadenectomy without any complications in two cases of endometrial cancer with left-sided IVC. PAN lymphadenectomy for gynecologic cancer patients with left-sided IVC has been reported previously [14–16]. In those cases, surgery was performed safely, but there was no inflow from the right lumbar vein similar to that observed in the second case in the present study. When performing PAN lymphadenectomy for left-sided IVC, caution should be exercised. While the diagnosis of left-sided IVC on preoperative imaging is a prerequisite, it should be assumed that there are many variations of left-sided IVCs, with some reported cases of lumbar vein inflowing into the left-sided IVC, as seen in our case, while others involve the azygos vein [17]. A detailed assessment of the veins around the left-sided IVC during preoperative imaging can help to avoid vascular injury. Additionally, the height of the kidney may vary and overlapping ureters or abnormal ureteral migration may be observed, which should be noted during PAN lymphadenectomy, as Gonzalez et al. have reported that varying degrees of regression and associated ureteric anomalies create a wide variety of configurations [11]. Furthermore, when dissecting the left IVC, caution should be exercised as the mesenteric and inferior mesenteric arteries can interfere with the visual field. Thus, attention should be paid to these factors to ensure safe PAN lymphadenectomy in patients with left-sided IVC.

Left-sided IVC is a rare vascular malformation. However, when left undiagnosed, the presence of this anomaly prior to PAN lymphadenectomy carries a high risk of vascular injury. Therefore, all cases of PAN lymphadenectomy should be evaluated preoperatively using contrast-enhanced and 3D-CT for detecting potential vascular malformations. Even if vascular malformations are identified, PAN lymphadenectomy can be performed safely with detailed preoperative anatomical analysis and careful surgical maneuvers to avoid vascular injury.

Ethics statement

Written informed consent was obtained from both patients.

Funding source

None.

Author contributions

Yuriko Higashi: Design, planning, investigation, and manuscript writing.
Shinichi Togami: Design, planning, revising the manuscript.
Hiroaki Kobayashi: Design, planning, and manuscript writing.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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Research Letter

Craniorachischisis in a stillbirth associated with maternal smoking

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Dear Editor,

A 25-year-old, gravida 6, para 2, woman was referred to the emergency room because of lack of fetal movement for three days. Ultrasound at admission showed a dead fetus with transverse lie and an estimated gestational age of 25 weeks. The pregnancy was subsequently terminated, and a 554-g dead female fetus was delivered with the phenotype of craniorachischisis with anencephaly and spina bifida (Figs. 1 and 2). The woman had a body weight of 74 Kg and a body height of 154 cm. She did not have proper prenatal care during this pregnancy. She smoked 10 cigarettes per day. She was anemic. Her hemoglobin was 7.7 g/dL, and hematocrit was 23.7 %. Her HbA1c was 5.4 %. Array comparative genomic hybridization (aCGH) on the DNA extracted from umbilical cord revealed arr (1–22, X) × 2, Y × 0 with no genomic imbalance.

With the advent of modern technology, craniorachischisis can be easily detected by ultrasound in the first trimester and in the second trimester [1,2]. The peculiar aspect of the present case is the stillbirth detected at 25 weeks of gestation in a pregnancy without proper prenatal care and with maternal smoking. Craniorachischisis is the most severe form of all neural tube defects (NTDs) with anencephaly and spina bifida and complete closure failure along the entire neural tube [3]. Craniorachischisis has a prevalence ranging from 0.1/10,000 to 11.7/10,000 live births [4,5]. Johnson et al. [4] reported a prevalence variation based on gestational age from 0.28/10,000 at 20 weeks of gestation or greater to 0.51/10,000 in the overall prevalence in population along the Texas-Mexico border.

Suarez et al. [6] reported that the NTD odds ratio among women who smoked less than half a pack a day during the first trimester was 2.2 (95 % CI = 1.0, 4.8) and 3.4 (95 % CI = 1.2, 10.0) among those who smoked a half pack or more, and suggested that maternal smoking may interfere with neural tube closure in the developing embryo. Yin et al. [7] reported that smoke may cause cell apoptosis, accelerate placenta maturation, inhibit embryonic development and lead to NTDs via down-regulating the expression of noggin and dis-inhibition of BMP2. In a meta-analysis of the association of maternal smoking and passive smoking during pregnancy with NTDs, Meng et al. [8] concluded that compared with smoking, exposure to passive smoking during pregnancy carries a higher risk of having infants with NTDs. Maternal smoking has the adverse effects of intrauterine growth restriction, poor fetal brain development, placental abruption and intrauterine fetal death [9–11]. Wu et al. [10] suggested that regular multivitamin/mineral supplement use might reduce the risk of fetal death associated with maternal smoking.

In the present case, the pregnant woman was a heavy smoker and smoked 10 cigarettes per day. It is likely that there is a correlation of maternal smoking with fetal craniorachischisis and intrauterine fetal death in this case.

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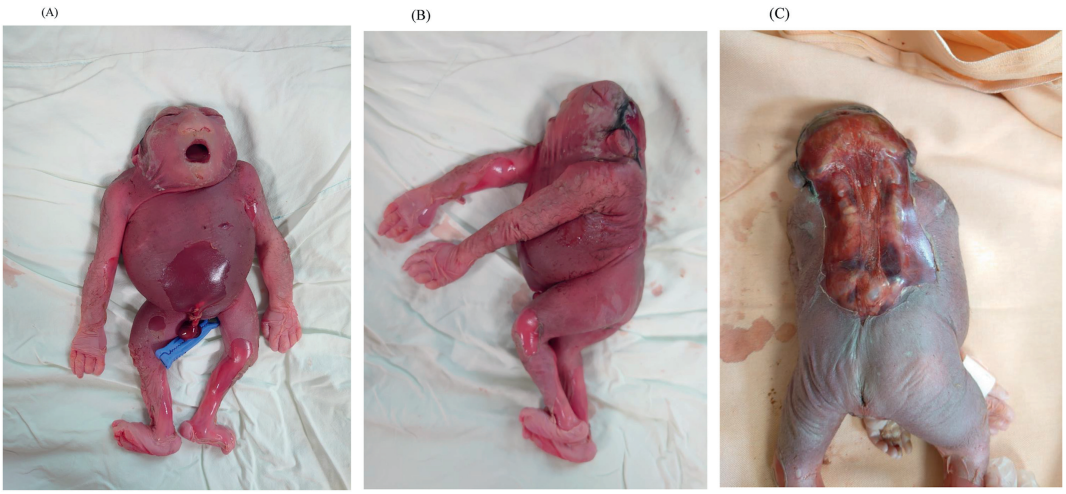

Fig. 1. (A) Anterior view, (B) lateral view and (C) posterior view of the fetus at birth at 25 weeks of gestation.

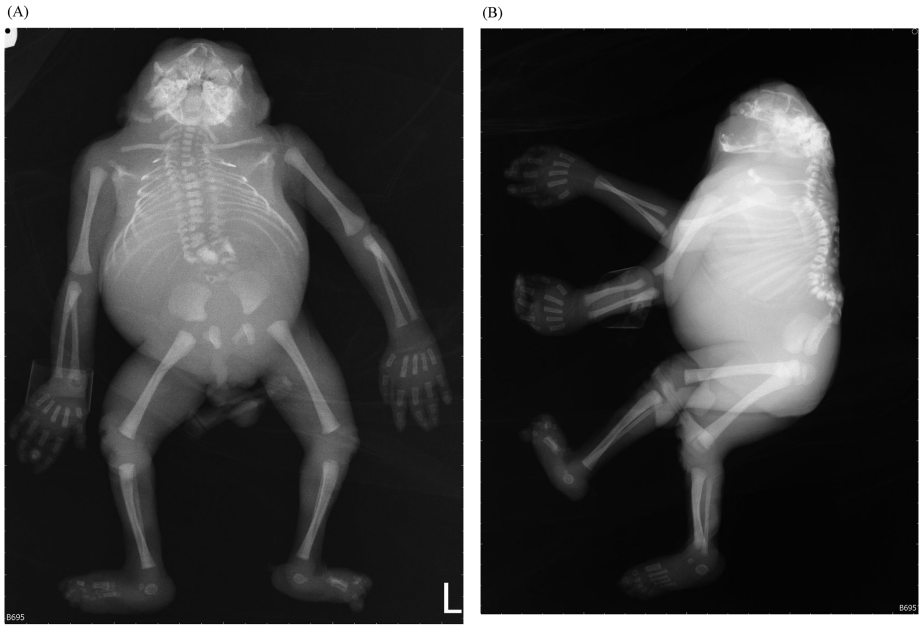

Fig. 2. (A) A-P view and (B) lateral view of the X-ray findings of the fetus.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Research Letter

Positive non-invasive prenatal testing for trisomy 13 in the first trimester in a pregnancy with fetal holoprosencephaly, cebocephaly and postaxial polydactyly

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Dear Editor,

A 41-year-old, gravida 2, para 1, woman received non-invasive prenatal testing (NIPT) at 11 weeks of gestation, and the result revealed a Z-score of 4.26 (normal: −3.0~3.0) for chromosome 13 highly suspicious of trisomy 13. She was referred for genetic counseling at 17 weeks of gestation, and prenatal ultrasound revealed alobar holoprosencephaly (HPE) and postaxial polydactyly of the hand (Fig. 1). Amniocentesis revealed a karyotype of 47,XY,+13 (Fig. 2). The parental karyotypes were normal. The pregnancy was subsequently terminated, and a 230-g malformed fetus was delivered with cebocephaly (Fig. 3) and postaxial polydactyly of the hands and feet (Fig. 4). Polymorphic DNA marker analysis using the DNA extracted from uncultured amniocytes, umbilical cord, placenta and parental bloods showed a maternal origin of the extra chromosome 13 consistent with maternal meiosis I non-disjunction (Fig. 5).

The present case was associated with HPE and polydactyly. Prenatal ultrasound is a powerful tool for detecting structural abnormalities in fetuses with trisomy 13 pregnancies [1–4]. The reported frequencies of HPE in trisomy 13 range from 16.7% to 46.7 %, and HPE has been reported to occur in an average incidence of 27.0 % (64/237 cases) in the cases with fetal trisomy 13 [2]. Trisomy 13 is the most common abnormality associated with polydactyly, and the reported frequencies of polydactyly in trisomy 13 range from 7.1 % to 21.2 % [3].

The peculiar aspect of the present case is the early diagnosis of fetal trisomy 13 by NIPT in the first trimester in association with distinctive ultrasound abnormalities in the second trimester. Chen et al. [5] previously reported low-level mosaic trisomy 13 at amniocentesis in a pregnancy associated with a positive NIPT result suspicious of trisomy 13, a chorionic villus sampling (CVS) result of mosaic trisomy 13, cytogenetic discrepancy in various tissues, normal second-trimester ultrasound findings and a favorable fetal outcome. Late first-trimester ultrasound findings can alter management after high-risk NIPT result [6]. Scott et al. [6] found that if the late first-trimester fetal ultrasound was normal, the incidence of confined placental mosaicism (CPM) was highest for those with an original NIPT high risk trisomy 13 result followed by trisomy 18 and trisomy 21. Scott et al. [6] also reported that after a normal late first-trimester fetal ultrasound, the positive predictive value (PPV) of NIPT for trisomy 21, trisomy 18, trisomy 13 and monosomy X decreased to 68 %, 57 %, 5 % and 25 %, respectively. Scott et al. [6] concluded that patients with a high-risk NIPT result for trisomy 13 and normal late first-trimester fetal ultrasound should await amniocentesis or avoid invasive testing considering the low PPV and higher rate of CPM under such a circumstance. The present case demonstrates that NIPT is a very useful tool for early suspicion of fetal trisomy 13 in the first trimester in case of trisomy 13 pregnancy.

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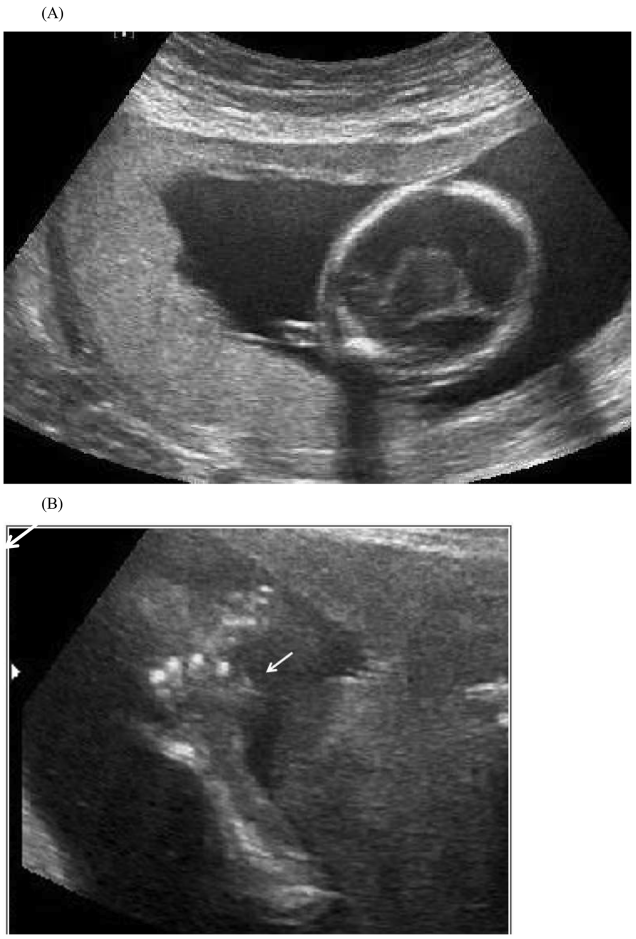

Fig. 1. Prenatal ultrasound at 17 weeks of gestation shows (A) alobar holoprosencephaly and (B) postaxial polydactyly of the hand.

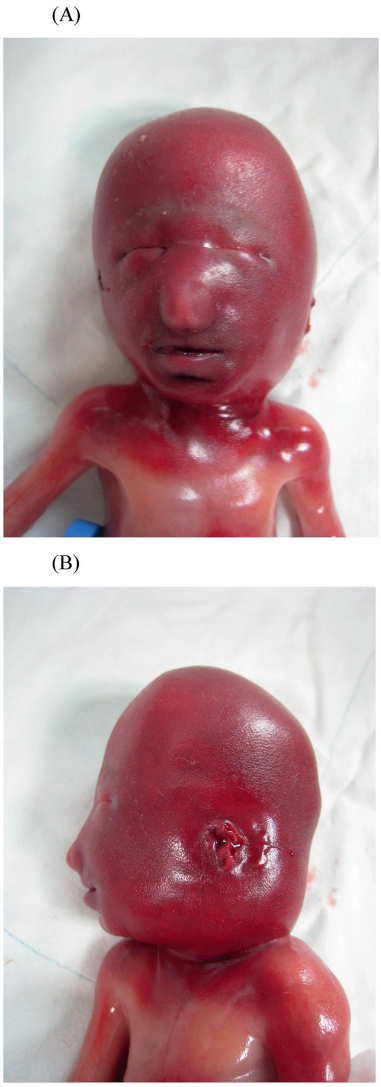

Fig. 3. The craniofacial appearance of fetus at birth. (A) Anterior view shows hypertelorism and cebocephaly with a single nostril, and (B) lateral view shows a low-set ear.

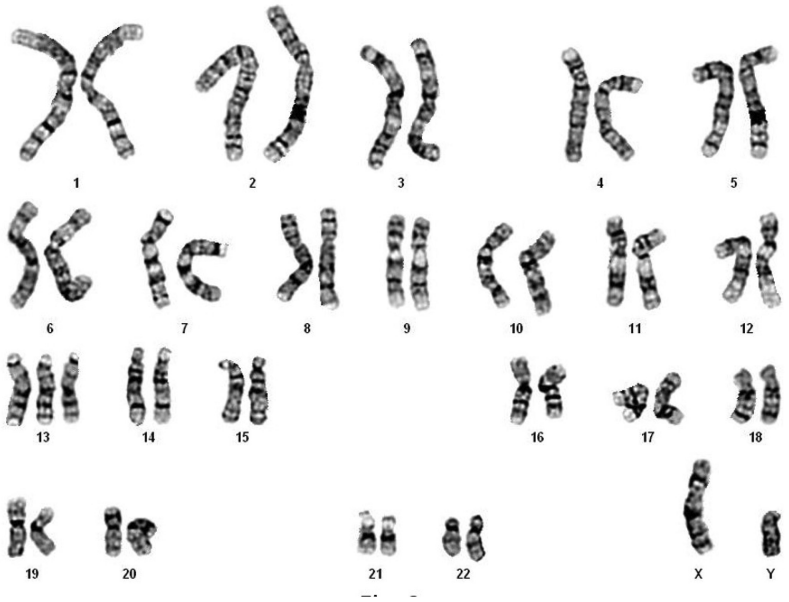

Fig. 2. A karyotype of 47,XY,+13 in the fetus.

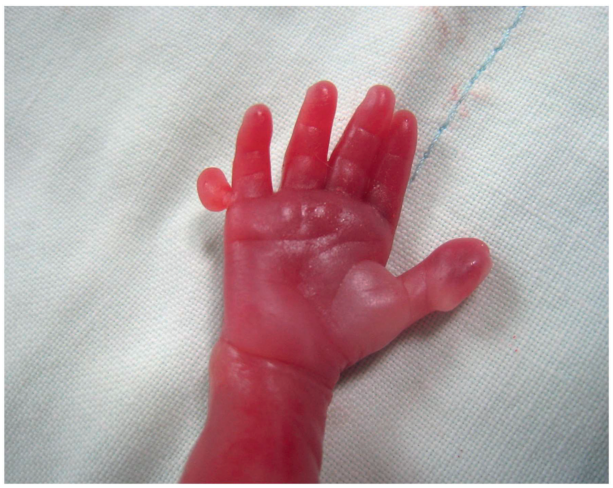

Fig. 4. Postaxial polydactyly of the hand.

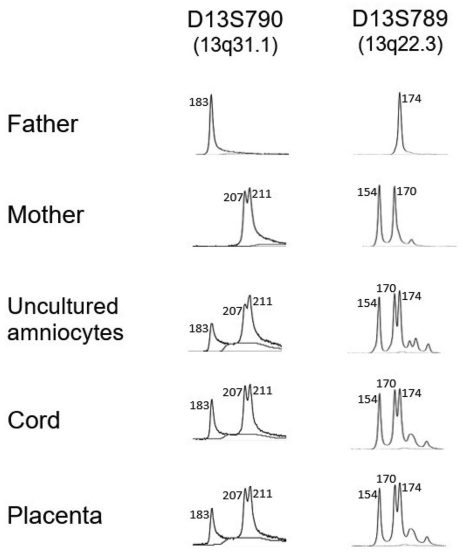

Fig. 5. Polymorphic DNA marker analysis shows a maternal origin of trisomy 13 consistent with meiosis I non-disjunction. The fetus inherits two different maternal alleles of chromosome 13 in the informative markers.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Research Letter

Rapid diagnosis of maternal origin of fetal trisomy 13 by quantitative fluorescent polymerase chain reaction in a pregnancy associated with young maternal age and omphalocele on prenatal ultrasound

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Dear Editor,

A 26-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of a small omphalocele on fetal ultrasound. Amniocentesis revealed a karyotype of 47,XY,+13 (Fig. 1). The parental karyotypes were normal. The pregnancy was subsequently terminated at 21 weeks of gestation, and a 336-g malformed fetus was delivered with postaxial polydactyly of the hands and feet (Fig. 2), a small omphalocele (Fig. 3) and craniofacial dysmorphism of low-set ears. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from cultured amniocytes, umbilical cord, placenta and parental bloods confirmed a maternal origin of the extra chromosome 13 derived from maternal meiosis I non-disjunction (Fig. 4).

Rapid diagnosis of trisomy 13 of maternal origin by QF-PCR analysis in pregnancies with abnormal fetal sonographic findings has been previous described [1–3]. The present case adds to the list of rapid diagnosis of parental origin of trisomy 13 at prenatal diagnosis.

Prenatal ultrasound is a powerful tool for detecting structural abnormalities in fetuses with trisomy 13 pregnancies [4–7]. The present case was associated with postaxial polydactyly and omphalocele. The frequencies of polydactyly in fetuses with trisomy 13 have been reported in the range from 7.1 % to 21.2 % [6]. The frequencies of omphalocele in fetuses with trisomy 13 have been reported in the range from 3.6 % to 29.4 %, and the mean frequency of omphalocele in trisomy 13, based on the six published series on second and third trimesters, is 15.5 % (22/142 cases) [6]. Prenatal sonographic diagnosis of concomitant postaxial polydactyly and omphalocele is very unusual and should alert the possibility of fetal trisomy 13.

The present case provides evidence of the usefulness of QF-PCR for rapid detection of maternal origin of fetal trisomy 13 in a pregnancy associated with young maternal age. The information acquired is very helpful for genetic counseling of the etiology of fetal structural anomaly and the parental origin of the chromosomal abnormality.

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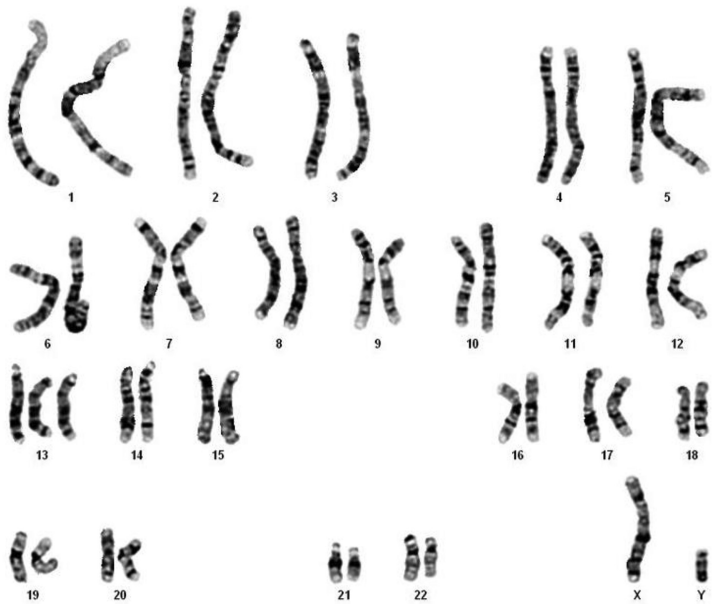
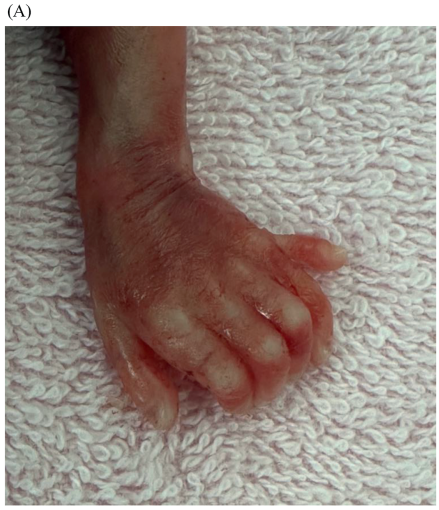


Fig. 1. A karyotype of 47,XY,+13.

(A)



(B)

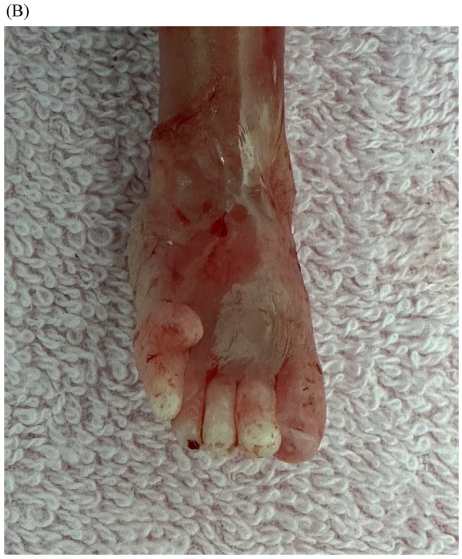


Fig. 2. Postaxial polydactyly of the (A) hand and (B) foot.

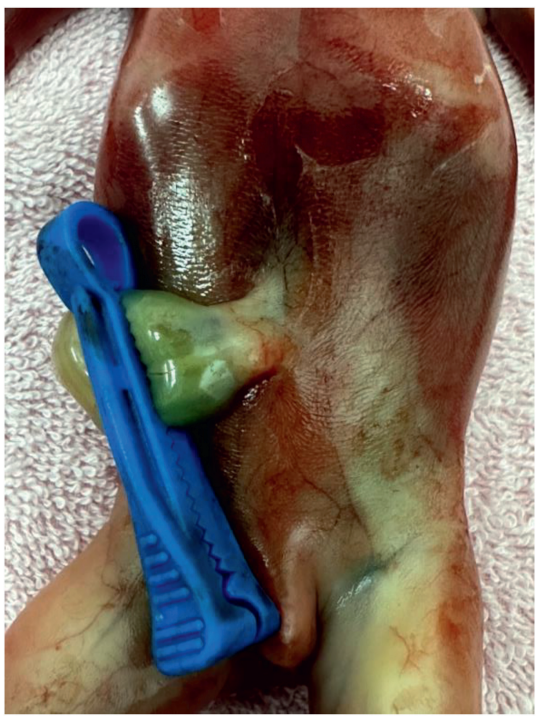


Fig. 3. A small omphalocele.

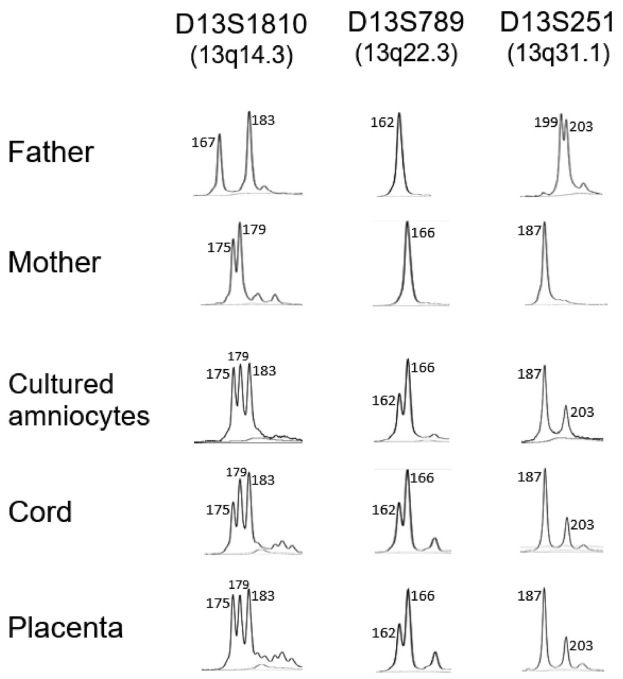


Fig. 4. Quantitative fluorescent polymerase chain reaction assays using the DNAs extracted from the cultured amniocytes, umbilical cord, placenta and parental bloods show a maternal origin of the extra chromosome 13 with two different maternal alleles in the informative marker of D13S1810, consistent with meiosis I non-disjunction.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Research Letter

Detection of 45,X/46,X,r(X)(p11.3q22.1) in a 17-year-old girl with secondary amenorrhea, short stature and normal intelligence

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Dear Editor,

A 17-year-old girl was referred for genetic analysis because of secondary amenorrhea and X chromosome abnormality. She had normal intelligence and good academic performance in college. Her menarche came at age 12 years, but later she experienced irregular menstrual cycle and secondary amenorrhea. She had a body weight of 46.7 Kg, a body height of 154 cm and an arm span of 150.3 cm. The body heights of her father, mother and the 11-year-old sister were 185 cm, 170 cm and 160 cm, respectively. She had consulted gynecological clinic, and ultrasound revealed a small uterus. Blood laboratory data then revealed testosterone = 42.8 ng/dL, progesterone = 0.28 ng/mL, estradiol (E2) = 13.88 pg/mL, prolactin = 3.37 ng/mL, luteinizing hormone (LH) = 7.98 mIU/mL, follicle stimulating hormone (FSH) = 53.46 mIU/mL, and thyroid-stimulating hormone (TSH) = 6.12 μIU/mL. Cytogenetic analysis of peripheral blood revealed a karyotype of 45,X[27]/46,X,r(X)[13] (Fig. 1). Array comparative genomic hybridization (aCGH) analysis on peripheral blood revealed arr Xp22.23p11.3 (60,701–43, 569,254) × 1.0, arr Xp11.3p11.21 (43, 571, 086–58,080,721) × 1.3, arr Xq11.1q22.1 (61, 998, 756–99,227,223) × 1.3, arr Xq22.1q28 (99, 325, 074–155,232,907) × 1.0 [GRCh37 (hg19)] (Fig. 2). Hence, the ring X chromosome revealed an Xp deletion of Xp22.33→p11.3 and an Xq deletion of Xq22.1→q28. The karyotype thus was 45,X[27]/46,X,r(X)(p11.3q22.1)[13]. *SRY* analysis of peripheral blood revealed a negative result.

The present case represents a rare case of mosaic ring X Turner syndrome or 45,X/46,X,r(X) in association with 45,X and 46,X,r(X). The r(X) chromosome has both distal Xp and Xq deletions. In the present case, the girl had a karyotype of 45,X[27]/46,X,r(X)[13] with the ratio of X: X,r(X) being 67.5:32.5 and manifested short stature, secondary amenorrhea and normal intelligence, and the ring chromosome X had an Xp deletion of Xp22.33→p11.3 and an Xq deletion of Xq22.1→q28. In the present case, the ring chromosome X contains the *XIST* gene (OMIM 314670) which is located at Xq13.2, and the patient did not have abnormal phenotype of physical and mental defects. *XIST* gene is responsible for inactivation of X chromosome. In case of tiny ring X syndrome with the karyotype of 45,X/46,X,r(X), the patient may manifest severe phenotype of physical and mental defects due to a functional disomy caused by the ring X chromosome lacking the *XIST* locus [1–3]. The present case does not belong to the tiny ring X syndrome and manifested normal intelligence.

The present case had a deletion of Xp22.33→p11.3 encompassing the *SHOX* gene (OMIM 312865) which is located at Xp22.33 and was associated with short stature. Absence of the *SHOX* gene is responsible for growth failure in Turner syndrome females.

The present case demonstrates the usefulness of conventional cytogenetic analysis and aCGH in the delineation of mosaic ring X Turner syndrome, secondary amenorrhea and normal intelligence in a 17-year-old girl.

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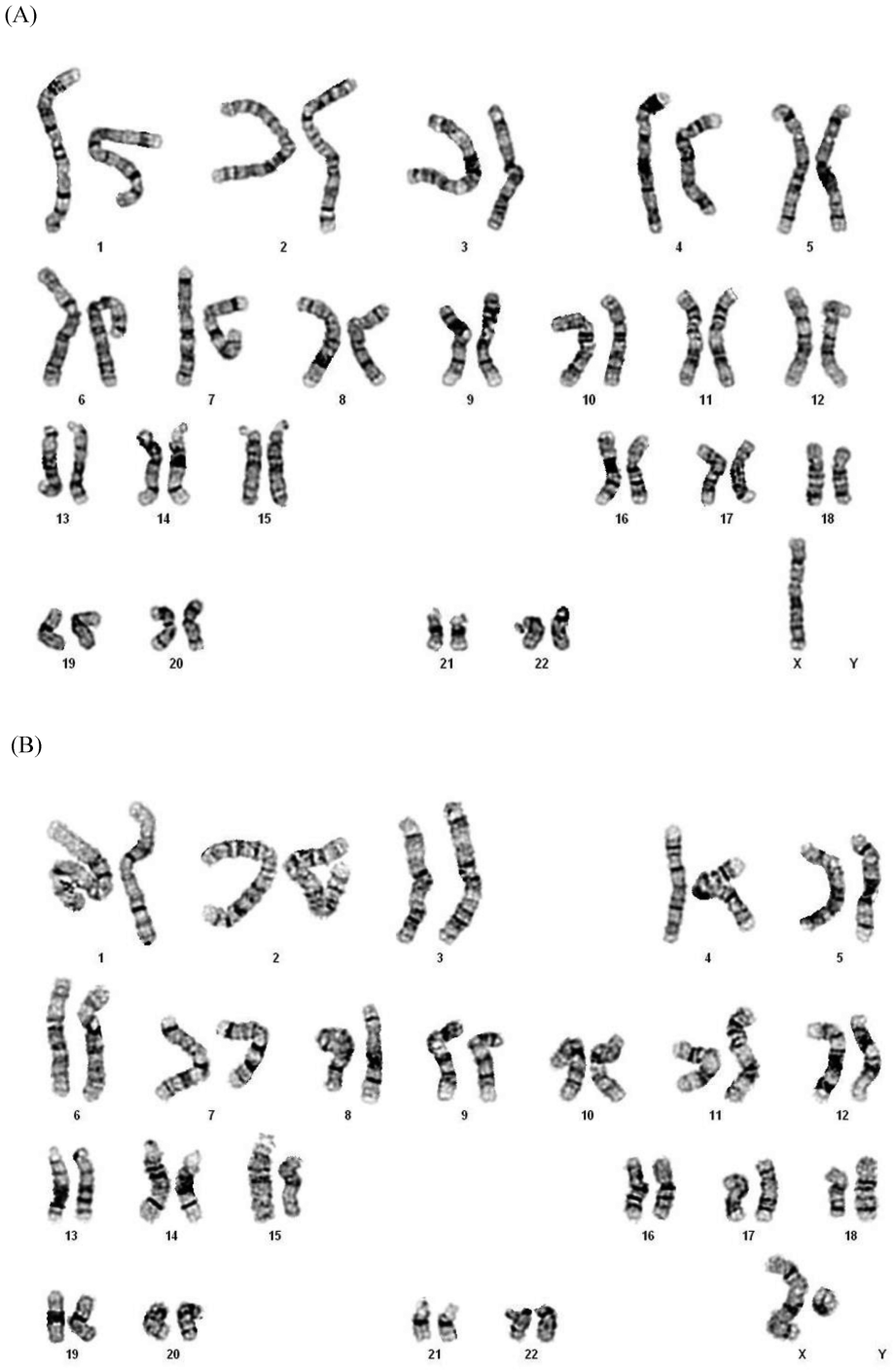

Fig. 1. (A) A karyotype of 45,X and (B) A karyotype of 46,X,r(X). r = ring.

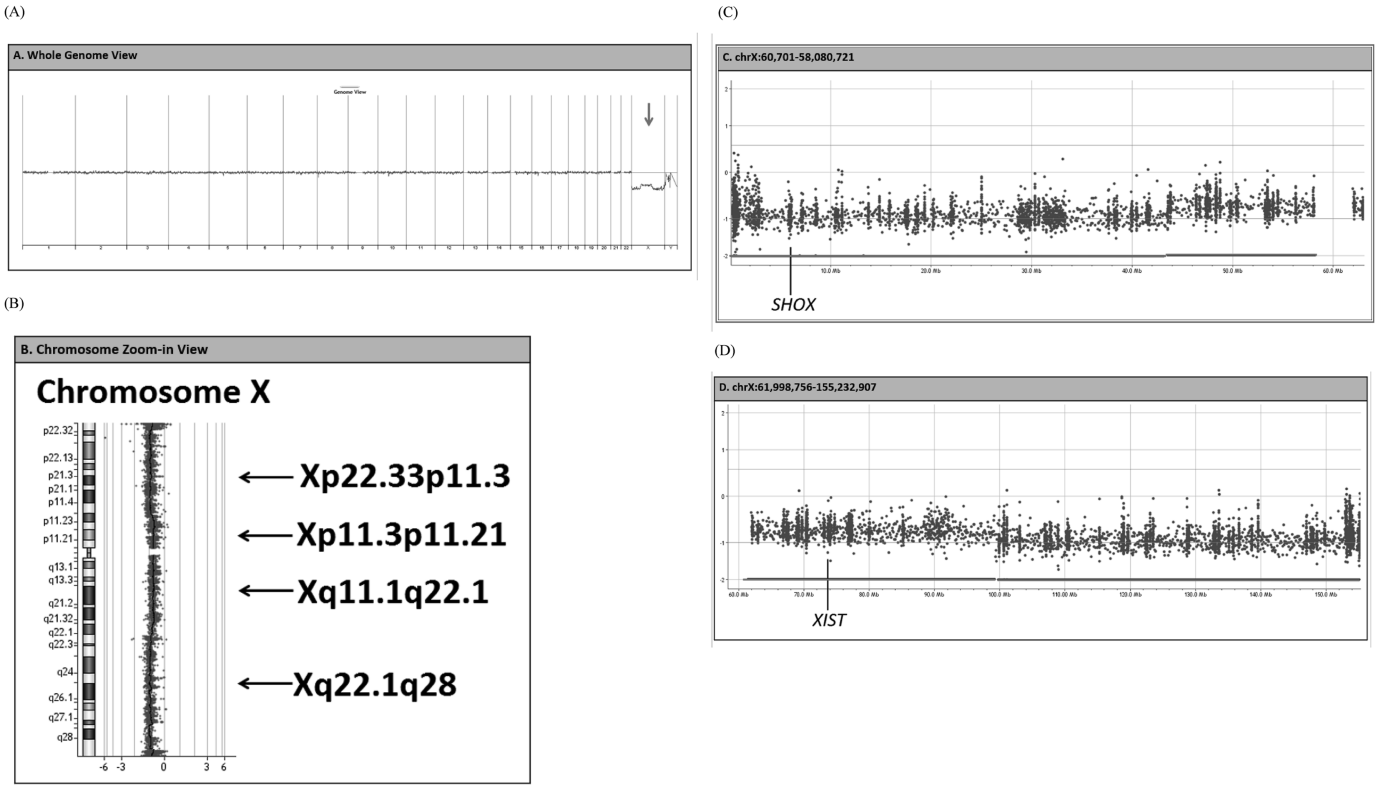

Fig. 2. Array comparative genomic hybridization (aCGH) analysis by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, Santa Clara, CA, USA) on the DNA extracted from peripheral blood shows (A), (B), (C) and (D) arr Xp22.23p11.3 (60,701–43,569,254) × 1.0, arr Xp11.3p11.21 (43, 571, 086–58,080,721) × 1.3, arr Xq11.1q22.1 (61, 998, 756–99,227,223) × 1.3, arr Xq22.1q28 (99, 325, 074–155,232,907) × 1.0 [GRCh37 (hg19)].

Conflict of interest

The author has no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grant NSTC-112-2314-B-195-001 from the National Science and Technology Council, Taiwan.

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Research Letter

Low-level mosaicism for 45,X in 45,X/46,XX at amniocentesis in a pregnancy with a favorable fetal outcome and postnatal decrease of the 45,X cell line

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Dear Editor,

A 41-year-old, gravida 3, para 1, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 45,X[3]/46,XX[12]. Prenatal ultrasound was unremarkable. She was referred for genetic counseling at 23 weeks of gestation. No repeat amniocentesis was suggested, and continuing the pregnancy was advised. A phenotypically normal 2880-g female baby was delivered at 39 weeks of gestation. The cord blood at birth had a karyotype of 45,X [5]/46,XX[35]. When follow-up at age five months, the neonate was normal in development. The peripheral blood had a karyotype of 45,X[1]/46,XX[39], and interphase fluorescence *in situ* hybridization (FISH) analysis on 110 buccal mucosal cells showed only 6.4 % (7/110 cells) had monosomy X.

45,X/46,XX at amniocentesis associated with a favorable outcome and perinatal progressive decrease of the 45,X cell line has been previously described [1–5]. The present case adds to the cases of 45,X/46,XX at amniocentesis with postnatal decrease of the 45,X cell line and provides evidence that 45,X/46,XX at amniocentesis can be a benign and transient condition. The information is very useful for genetic counseling of the parents who have very advanced maternal age, who have undergone assisted reproductive technology, and who wish to keep the baby under such a circumstance.

In the present case, amniocentesis at 18 weeks of gestation revealed a karyotype of 45,X[3]/46,XX[12], consistent with 20 % mosaicism for 45,X in 45,X/46,XX. Since the prognosis is good, and the aneuploid cell line can progressively decreased, repeat amniocentesis is not necessary. At birth, the karyotype of cord blood was 45,X[5]/46,XX[35], consistent with 12.5 % mosaicism for 45,X in 45,X/46,XX, and at age five months, the mosaic 45,X level decreased to only 2.5 %, with a karyotype of 45,X[1]/46,XX[39]. The buccal mucosal cells had only 6.4 % (7/110 cells) mosaicism for 45,X,

In conclusion, it is evident that low-level mosaicism for 45,X in 45,X/46,XX at amniocentesis is a benign and transient condition. Therefore, repeat amniocentesis is not necessary, and termination of the pregnancy should not be advised under such a circumstance.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grant NSTC-112-2314-B-195-001 from the National Science and Technology Council, Taiwan.

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https://doi.org/10.1016/j.tjog.2023.10.010

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Research Letter

High-level mosaicism for 45,X in 45,X/46,XX at amniocentesis in a pregnancy with a favorable fetal outcome and postnatal decrease of the 45,X cell line

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Dear Editor,

A 25-year-old, gravida 3, para 2, woman underwent elective amniocentesis at 17 weeks of gestation because of anxiety. Amniocentesis revealed a karyotype of 45,X[26]/46,XX[12]. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed arr (X) × 1–2, (1–22) × 2, consistent with 56 % mosaicism for 45,X. Prenatal ultrasound findings were unremarkable. She was referred for genetic counseling at 20 weeks of gestation. No repeat amniocentesis was suggested, and continuing the pregnancy was strongly advised. A phenotypically normal 2320-g female baby was delivered at 37 weeks of gestation. The karyotypes of cord blood, umbilical cord and placenta were 45,X[18]/46,XX[22], 45,X[27]/46,XX[13] and 45,X [26]/46,XX[14], respectively. When follow-up at age 11 months, the neonate was normal in development. The peripheral blood had a karyotypes of 45,X[11]/46,XX[29], and interphase fluorescence *in situ* hybridization (FISH) analysis on 118 buccal mucosal cells showed 17.8 % (21/118 cells) had monosomy X.

High-level mosaicism for 45,X in 45,X/46,XX at amniocentesis associated with a favorable outcome and postnatal progressive decrease of the 45,X cell line has been previously reported [1]. Genetic counseling of high-level mosaicism for 45,X in 45,X/46,XX at amniocentesis remains difficult and challenging because of the concern of Turner syndrome phenotype after birth, and the genetic counselors may overemphasize the possibility of postnatal occurrence of Turner syndrome that leads to the parental decision to terminate the pregnancy. However, the present case and the report of Chen et al. [1] provide evidence that high-level mosaicism for 45,X in 45,X/46,XX at amniocentesis can be a benign and transient condition. Therefore, repeat amniocentesis is not necessary, and termination of the pregnancy should not be advised. The information is very useful for genetic counseling of the parents who have very advanced maternal age, who have undergone assisted reproductive technology, and who wish to keep the baby under such a circumstance.

In the present case, amniocentesis at 17 weeks of gestation revealed 68.4 % mosaicism for 45,X in 45,X[26]/46,XX[12] in cultured amniocytes, and aCGH analysis on uncultured amniocytes revealed 56 % mosaicism for monosomy X. However, at birth, the cord blood had 45 % mosaicism for 45,X or 45,X[18]/46,XX[22], and at age 11 months, the peripheral blood had 27.5 % mosaicism for 45,X or 45,X[11]/46,XX[29], and FISH revealed 17.8 % (21/118 cells) mosaicism for monosomy X.

The fact that postnatal progressive decrease of the 45,X cell line in the present case with high-level mosaicism for 45,X in 45,X/46,XX at amniocentesis implies that genetic counseling of the prognosis of high-level mosaicism for 45,X in 45,X/46,XX at amniocentesis simply based on the prenatal cytogenetic result is not reliable and not feasible.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Research Letter

Positive non-invasive prenatal testing for Turner syndrome and low-level mosaicism for 45,X in 45,X/46,XX at amniocentesis in a pregnancy associated with a favorable fetal outcome and a normal 46,XX karyotype at birth

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Dear Editor,

A 32-year-old, gravida 3, para 2, woman received first-trimester non-invasive prenatal testing (NIPT) for aneuploidy at 12 weeks of gestation, and the result showed a Z-score of −4.64 for sex chromosome suspicious of Turner syndrome. She underwent amniocentesis at 16 weeks of gestation, and the result was 45,X [3]/46,XX [17]. Prenatal ultrasound was unremarkable. She was referred for genetic counseling at 19 weeks of gestation. Continuing the pregnancy was advised, and no repeat amniocentesis was suggested. At 39 weeks of gestation, a 3080-g phenotypically normal female baby was delivered. The cord blood at birth had a karyotype of 46,XX (40/40 cells). When follow-up at age seven months, the neonate was normal in development.

In the present case, the NIPT at 12 weeks of gestation showed a positive result for Turner syndrome, and amniocentesis at 16 weeks of gestation showed 15 % mosaicism for 45,X in 45,X/46,XX. However, at birth, the cord blood had a normal karyotype of 46,XX. Mosaic 45,X/46,XX at amniocentesis associated with a favorable outcome and perinatal progressive decrease of the 45,X cell line has been previously described [1–5]. The present case shows that positive NIPT for Turner syndrome may be associated with low-level mosaic 45,X/46,XX at amniocentesis. It is evident that low-level mosaicism for 45,X in 45,X/46,XX at amniocentesis is a benign and transient condition. Therefore, repeat amniocentesis is not necessary, and termination of the pregnancy should not be advised under such a circumstance. The information is very useful for genetic counseling of the parents who have very advanced maternal age, who have undergone assisted reproductive technology, and who wish to keep the baby in case of positive NIPT for Turner syndrome and 45,X/46,XX at amniocentesis.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grant NSTC-112-2314-B-195-001 from the National Science and Technology Council, Taiwan.

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and postnatal progressive decrease of the 45,X cell line in a mosaic 45,X/46,XX fetus with a favorable outcome. Taiwan J Obstet Gynecol 2022;61:876–9.
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Research Letter

Rapid diagnosis of maternal origin of *de novo* fetal Robertsonian translocation down syndrome of 46,XY,der(13;21)(q10;q10),+21 by quantitative fluorescent polymerase chain reaction in a pregnancy associated with increased nuchal translucency and an abnormal result of first-trimester maternal serum screening

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Dear Editor,

A 29-year-old, primigravid woman underwent amniocentesis at 16 weeks of gestation because of an abnormal first-trimester maternal serum screening result indicating a Down syndrome risk of 1/4 calculated from maternal serum free β-hCG (human chorionic gonadotropin) = 0.692 multiples of the median (MoM), PAPP-A (pregnancy-associated plasma protein A) = 0.251 MoM and nuchal translucency (NT) thickness of 4.5 mm at 12 weeks of gestation. Amniocentesis revealed a karyotype of 46,XY,der(13;21)(q10;q10),+21 (Fig. 1). The parental karyotypes were normal. The pregnancy was subsequently terminated, and a 350-g malformed male fetus was delivered with characteristic facial dysmorphism of Down syndrome. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from cord blood and parental bloods showed a maternal origin of the extra chromosome 21 (Fig. 2).

Prenatal diagnosis of Robertsonian translocation Down syndrome is very uncommon. In a study of 31,194 amniocenteses, Chen et al. [1] detected only two cases (2/31194 = 0.006 %) of Robertsonian translocation Down syndrome including one case of rob(14q21q),+21 and one case of rob(13q21q),+21. Chen et al. [2] previously reported prenatal diagnosis of 46,XX,der(13;21)(q10;q10),+21 in a pregnancy with fetal transient abnormal myelopoiesis, hepatosplenomegaly, spontaneous resolution of fetal ascites and maternal balanced rob(13q21q) translocation. The present case adds to the list of prenatal diagnosis of Robertsonian translocation Down syndrome in a young woman associated with increased NT and abnormal first-trimester maternal serum screening result.

The peculiar aspect of the present case is the association of *de novo* Robertsonian translocation Down syndrome and rapid detection of the maternal origin by QF-PCR analysis. The information acquired is very helpful for genetic counseling under such a circumstance. Robertsonian translocation Down syndrome is rare and accounts for only 4 % of Down syndrome cases, and *de novo* Robertsonian translocation Down syndrome is triple as many as familial Robertsonian translocation Down syndrome (3 % vs. 1 %) [3].

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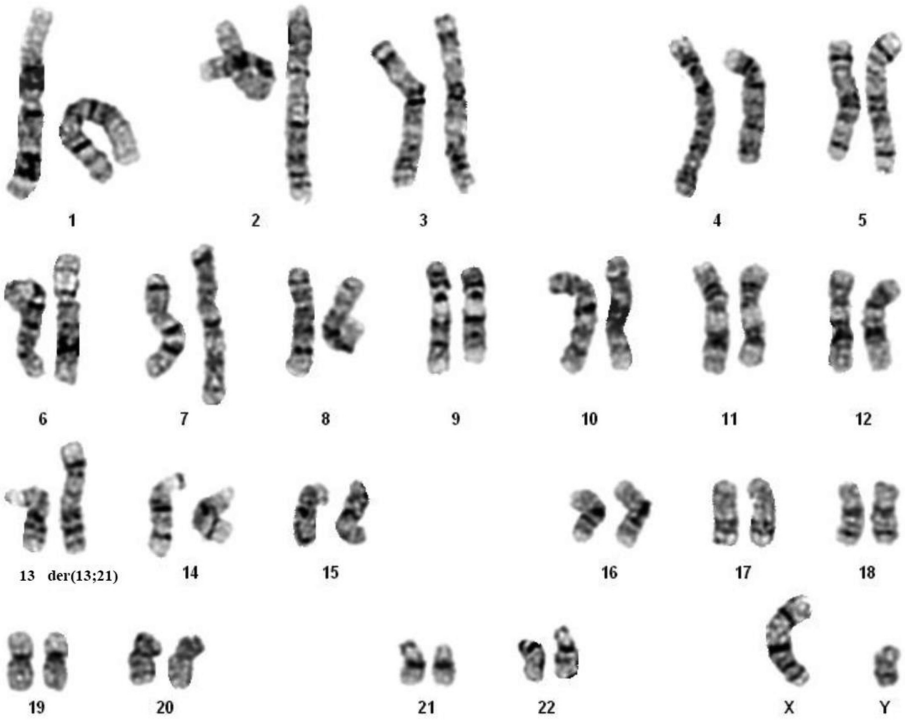

Fig. 1. A karyotype of 46,XY,der(13;21)(q10;q10),+21.

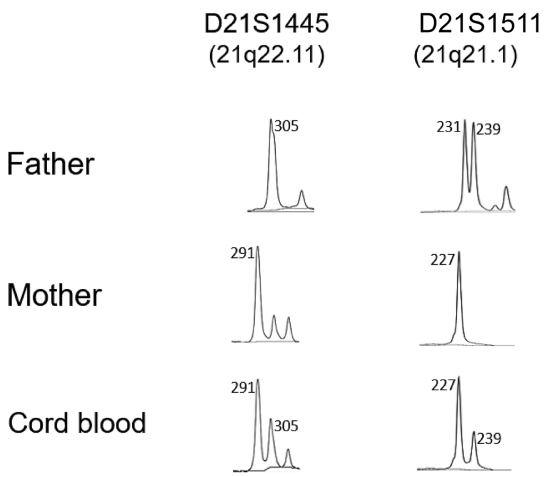

Fig. 2. Quantitative fluorescent polymerase chain reaction assays using the DNA extracted from the cord blood and parental bloods show a maternal origin of the extra chromosome 21. In the informative markers of D21S1445 and D21S1511, the cord blood shows a gene dosage ratio of 2:1 in the maternal allele: paternal allele, indicating a maternal origin of trisomy 21.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Research Letter

Mosaicism for trisomy 13 in a single colony at amniocentesis in a pregnancy associated with a favorable outcome

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Dear Editor,

A 34-year-old, gravida 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+13[1]/46,XY[15]. Among 16 colonies of cultured amniocytes, all three cells in only one colony revealed trisomy 13 (Fig. 1), whereas the other 15 colonies revealed 46,XY (Fig. 2). The parental karyotypes were normal. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis using the DNA extracted from cultured amniocytes and parental bloods excluded uniparental disomy (UPD) 13 (Fig. 3). The woman was advised to continue the pregnancy, and no repeat amniocentesis was requested. A 2974-g phenotypically normal male baby was delivered at 38 weeks of gestation. All the cord blood, umbilical cord and placenta had the karyotype of 46,XY. QF-PCR analysis on placenta and umbilical cord revealed biparental inheritance and two alleles with equal dosage, and thus excluded UPD 13 (Fig. 3). When follow-up at age two months, the neonate was normal in phenotype and development.

The present case provides evidence that mosaicism for trisomy 13 in a single colony at amniocentesis can be associated with a favorable outcome and a normal karyotype in the cord blood, umbilical cord and placenta. However, mosaicism for trisomy in a single colony at amniocentesis should alert the possibility of true mosaic trisomy associated with trisomy rescue as well as UPD. Therefore, polymorphic DNA marker analysis using the DNA extracted from cultured amnicoytes and parental bloods are helpful for rapid exclusion of UPD under such as circumstance.

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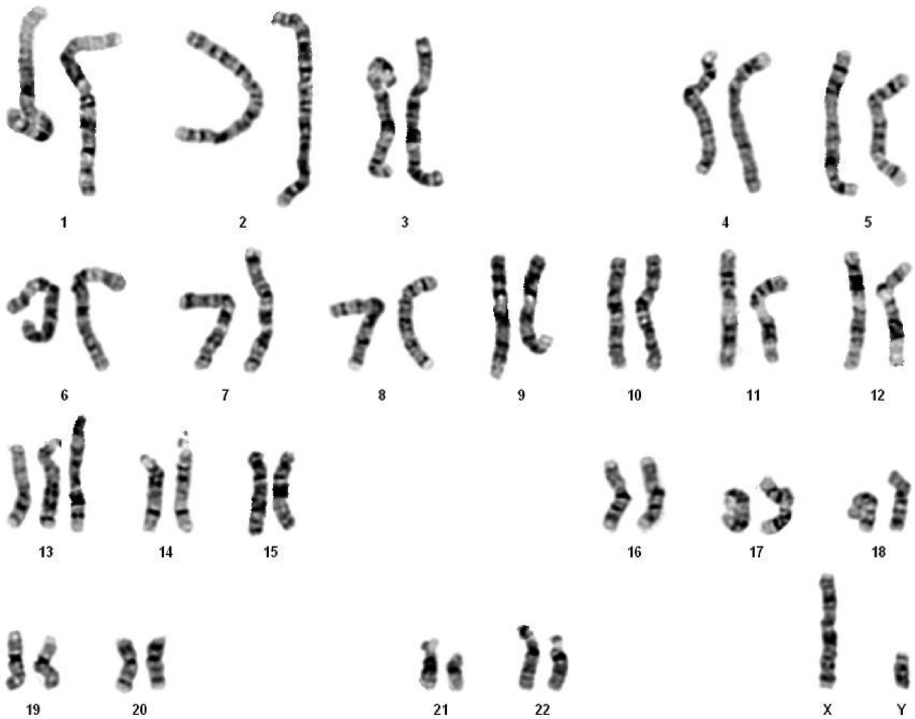

Fig. 1. A karyotype of 47,XY,+13.

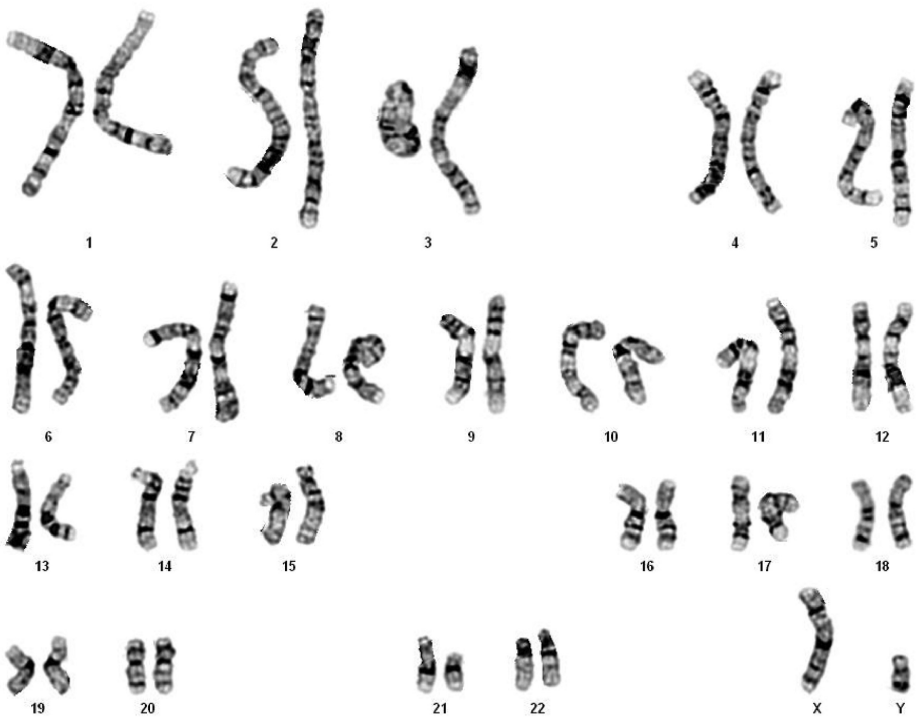

Fig. 2. A karyotype of 46,XY.

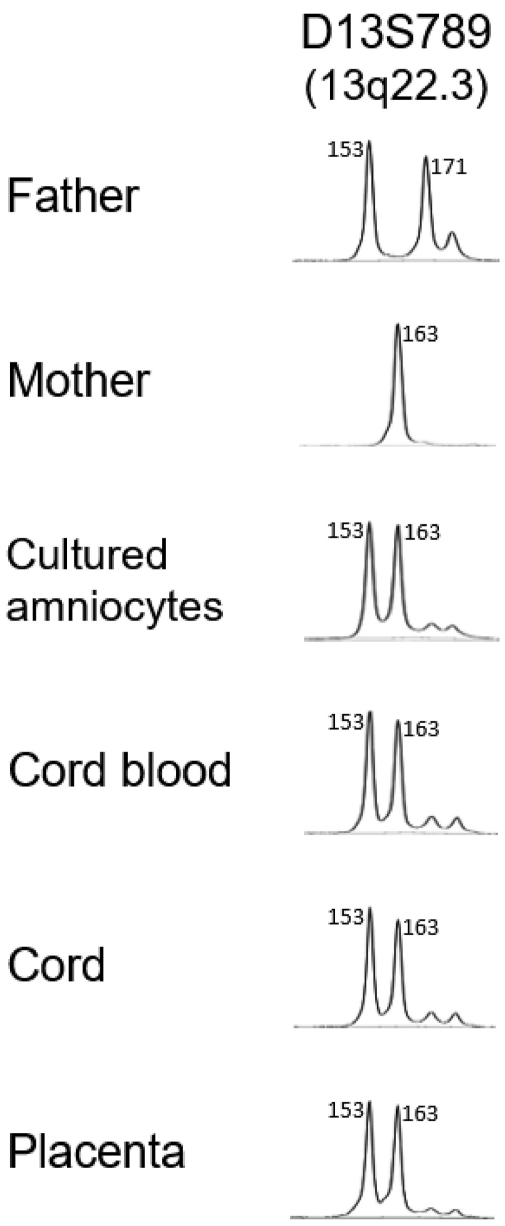

Fig. 3. Polymorphic DNA marker analysis using the informative marker of D13S789 on the DNA extracted from cultured amniocytes, cord blood, umbilical cord, placenta and parental bloods excludes uniparental disomy 13.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Correspondence

Mutational analysis of PDGFRA oncogene in high-grade neuroendocrine carcinoma of the uterine cervix in twelve Taiwanese women

Dear Editor,

We have previously demonstrated that two out of twelve cases (2/12 = 16.67 %) of high-grade neuroendocrine carcinoma (NEC) of the uterine cervix in Taiwanese women exhibited c-KIT protein overexpression. However, none carried *KIT* proto-oncogene missense mutations [1]. Despite being mutually exclusive, certain tumors, such as gastrointestinal stromal tumors (GISTs) that possess platelet-derived growth factor receptors, alpha subunit (*PDGFRA*), or *KIT* proto-oncogene activating mutations, are potential targets for selective tyrosine kinase inhibitors. An alternative mechanism of KIT/PDGFRA inhibitors was directed at the *PDGFRA* rather than the KIT molecule [2,3]. Our previous report would have been more comprehensive and valuable if we included more information about the mutational status of *PDGFRA*.

The materials and methods used in this study have been previously described [1]. We employed formalin-fixed, paraffin-embedded (FFPE) samples from 12 cases. Tumor-rich areas were identified and subsequently subjected to manual macro-dissections on 10 mm thick unstained sections. DNA extraction was performed using the QIAamp® DNA FFPE Kit (Qiagen, Valencia, CA, USA). The hotspots of the KIT proto-oncogene were sequenced using the Human Clinically Relevant Tumor GeneRead DNAseq Targeted Panel V2 (Qiagen, Valencia, CA, USA) and the next-generation sequencing (NGS) sequencer Illumina MiSeq instrument (San Diego, CA).

Our results showed that the PDGFRA proto-oncogene sequence analysis did not reveal any activating mutations. However, we did identify one polymorphic variant with a silent base substitution in exon 12, c.1701A > G p.P567, present in all 12 cases, and another silent base change in exon 18, c.2472C > T p.V824, identified in 5 cases (Table 1). In all cases (12/12 = 100 %), silent mutations were observed while no activating mutation variants were identified.

PDGFRA and *KIT* proto-oncogenes are closely linked on chromosome 4q12, share structural homology, and belong to the class III receptor protein tyrosine kinases (RTKs) family [2,3]. The mutational status of the *PDGFRA* oncogene in HGNEC Ut Cx has not been previously reported via Google and PubMed searches. Therefore, we are presenting its NGS analysis for the first time. Although no *PDGFRA*-activating mutations were found, we identified two silent variants (c.1701A > G p.P567 and c.2472C > T p.V824). The former was consistently present in all 12 tumor tissues. The clinical significance of this *PDGFRA* silent mutation, which exists in all cases, may be found in its potential diagnostic, prognostic, and research value. While the silent mutation itself may not drive cancer, it can be associated with essential clinical and biological characteristics that have implications for patient care and our understanding of this rare tumor [4].

Table 1
The mutational status of *PDGFRA* oncogene of high-grade NEC of the uterine cervix in 12 Taiwanese women.

Case number	*PDGF* mutations[a]
1	c.1701A > G p.P567; c.2472C > T p.V824
2	c.1701A > G p.P567
3	c.1701A > G p.P567
4	c.1701A > G p.P567
5	c.1701A > G p.P567
6	c.1701A > G p.P567; c.2472C > T p.V824
7	c.1701A > G p.P567
8	c.1701A > G p.P567
9	c.1701A > G p.P567, c.2472C > T p.V824
10	c.1701A > G p.P567, c.2472C > T p.V824
11	c.1701A > G p.P567
12	c.1701A > G p.P567; c.2472C > T p.V824

[a] Although no activating mutations were found, silent mutations were detected.

In summary, the absence of *KIT* and *PDGFRA* missense driver mutations may limit the current utility of KIT/PDGFRA inhibitors (such as imatinib, sunitinib, regorafenib, ripretinib, and avapritinib) as therapeutic options for high-grade NEC of the uterine cervix [5]. However, the silent mutation (c.1701A > G p.P567) in the *PDGFRA* proto-oncogene, consistently found in all 12 cases (100 %), may serve as a genetic marker for identifying potential vulnerabilities in this tumor or for tracking tumor evolution. Further research and clinical investigations are warranted to determine its significance and potential applications in patient management.

Funding

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Ethics approval

Our research was conducted under the International Conference on Harmonization (ICH) guidelines and compliant with all applicable regulations for the protection of human subjects of research,

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including review and approval by the Institutional Review Board of the Chung-Shan Medical University Hospital, Taichung, Taiwan.

Declaration of competing interest

The authors report no conflict of interest.

Acknowledgements

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Correspondence

Comment on the safety and feasibility of no-placement of urinary catheter after single-port laparoscopic surgery in patients with benign ovarian tumor: A retrospective cohort study

Dear Editor:

We read with great interest the article by Deng et al. reporting that nonplacement of the indwelling urinary catheter in patients undergoing simple gynecological surgery, resulted in reduction in the incidence of urinary tract infection and was feasible and safe in patients undergoing ovarian cystectomy or oophorectomy via single-port laparoscopic surgery. We appreciate the authors conducted a great cohort study and provided a novel perspective. However, we would like to highlight some concerns with this study [1].

First, the author declared that the length of hospital stay was not significant different between urinary catheter group and non-urinary catheter group in the result section. However, according to the Table 1, the p-value of length of hospital stay was 0.000, and showed significant different.

Secondly, although the baseline characteristics were almost similar between the groups, including age, tumor size, surgery time, and blood loss and surgery history, we are worried that some important residual confounders might exist, such as body mass index, diabetes mellitus, abdominal surgery history, and lab data between pre-operative and post-operative. The recent study by Salari have shown that urinary tract infections are highly prevalent in patients with type 2 diabetes [2]. In addition, another study found that obesity and metabolic health status were individually or collaboratively involved in urological disorders related to voiding dysfunction [3].

The study result is interesting and provocative. Yet, we recommend that residual confounders should be considered would enrich the study credibility.

Authors' contributions

Conceptualization, Y.-W.L.; Supervision, Y.-S.C.; Writing—original draft, Y.-W.L.; Writing—review & editing, Y.-S.C. and Y.-P.L. All authors have read and approved the final manuscript.

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Declaration of competing interest

The authors have no conflicts of interest that pertain to this work to declare.

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Correspondence

Common on “comparison of cesarean delivery outcome after robotic and laparoscopic myomectomy”

Dear Editor,

I read the article by Won S et al. [1] with pressure.

In the section of results, “A total of 296 patients (242 patients for LM and 54 for RM) were included in this study” But in table 1, 2, 3 and 4, there were LM 222, and RM 51. I would be interest in knowning what is it the other 20, and 3 patients respectively.

Declaration of competing interest

The author declares that there is no conflict of interest.

Reference

[1] Won S, Choi SH, Kim SJ, Lee N, Shim SH, Kim M, et al. Comparison of cesarean delivery outcome after robotic and laparoscopic myomectomy. Taiwan J Obstet Gynecol 2023;62:12–5.

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Correspondence

Whether anticoagulation is needed for ovarian vein thrombosis in non-pregnant patient?

Dear Editor,

We read with interest the article "Diagnosis and management of ovarian vein thrombosis after laparoscopic-assisted vaginal hysterectomy with bilateral salpingectomy: A case report and literature review" by Dr. Chen and colleagues [1]. Ovarian vein thrombosis (OVT) is a rare but life-threatening disorder, which is most often found in the immediate postpartum period, and may extend into the inferior vena cava (the right side) or the renal vein (the left side), even cause pulmonary thromboembolism. OVT after gynecological surgery has some differences from OVT during the postpartum period, therefore, we present our experiences to compare and increase awareness of this rare entity.

First, although the etiology of OVT is still unknown, the pathogenesis of OVT is in accordance with the Virchow's triad, which is hypercoagulable state, alterations in the vein wall, and stasis of blood flow. Bacterial infection may have caused local sepsis, producing inflammation and leukocyte infiltration that may resulted in venous intimal injury, and thermal spread to the vein wall may have caused the vessel wall injury and contributed to the risk of OVT during laparoscopic hysterectomy and salpingectomy [2]. However, the intraoperative procedures were performed in the same way to other patients. It is reasonable to speculate that there are many risk factors associated with thrombophilia, including antiphospholipid syndrome, systemic lupus erythematosus, deficiencies in proteins C and S and antithrombin III, thrombus susceptibility gene mutation (prothrombin gene, plasminogen activator inhibitor-1 gene, methylenetetrahydrofolate reductase gene), factor V Leiden mutation, hyperhomocysteinemia, paroxysmal nocturnal hemoglobinuria, etc. The thrombophilia workup should be considered in patients with OVT when available for further prophylactic anticoagulation.

Second, regarding the diagnosis of OVT, according to our experiences, not all OVT has the elevation of D-dimer, negative D-dimer could not rule out the presence of OVT. As stated in the article, OVT manifests as nonspecific symptoms such as abdominal pain, fever, and the typical findings of OVT on color Doppler ultrasonography include tubular hypoechoic adnexal masses or iliac fossa masses lateral to the great abdominal vessels, which is similar to the retroperitoneal hematoma after pelvic surgery, especially in the patient with a decreased hemoglobin level. Retroperitoneal hematoma will be suspected first in the clinical setting of pelvic surgery, not OVT. Therefore, contrast-enhanced computed tomography scan and magnetic resonance imaging are recommended to confirm the diagnosis of OVT.

Third, the incidence of pulmonary embolism (PE) increases during pregnancy and reaches its highest incidence after delivery [3]. Due to the possibility of progression to PE, it is no doubt that anticoagulants should be administered to the parturient women with OVT. However, treating OVT in the setting of hysterectomy is debatable because of lack of evidence for benefit from anticoagulation. Some authors have concluded that OVT after hysterectomy is unlikely to be treated given its appearance as a common postsurgical finding [4], but we also found some case reports of PE from OVT after hysterectomy or salpingectomy (in Table 1). Although anticoagulation for OVT in non-pregnant patients is still a controversial issue, clinicians should have a lower threshold for initiating diagnostic modality for symptoms of suspected PE in patients with OVT which need prompt diagnosis and anticoagulation.

Table 1
Clinical features of non-pregnant patients with PE from OVT.

Author	Published Year	Age(y)	History	Time of OVT	Time of PE	Treatment	Outcome
Benfayed WH [5]	2003	49	Cerebral infarct	One week later	One week later	Anticoagulation	Recovered with no complications
Wang IK [6]	2005	35	Nephrotic syndrome	6 days after RVT	6 days after RVT	Anticoagulation	Resolution of OVT and PE
Heavrin BS [7]	2008	29	Laparoscopic salpingectomy	3 weeks later	9 days after OVT	Anticoagulation	No further complications
Verde F [8]	2012	69	Metastatic pancreatic cancer	Routine follow up	Routine follow up	Anticoagulation	Resolution of OVT and PE
Takeda A [9]	2016	39	LAVH for uterine myoma	POD 5	POD 5	Anticoagulation with antibiotics	Disappearance of OVT and PE on POD 17
Li WR [10]	2021	33	Idiopathic	Abdominal pain for 2 years	Abdominal pain for 2 years	Anticoagulation and laparotomy	Ovarian vein was removed by laparotomy, abdominal pain disappeared

RVT, renal vein thrombosis; LAVH, laparoscopic assisted vaginal hysterectomy; POD, postoperative day.

https://doi.org/10.1016/j.tjog.2023.05.018

Conflicts of interest

None.

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Reply to "Successful management of cornual heterotopic pregnancy"

Dear Yang et al:

Thank you for sharing your experience and raising thought-provoking questions regarding the surgical management of ruptured cornual heterotopic pregnancy.

Firstly, we appreciate your observations and understand the importance of preserving an adequate amount of myometrium surrounding the cornual pregnancy to support its continuation and minimize the risk of uterine rupture and miscarriage, regardless of the surgical approach (laparoscopy or laparotomy). In our specific case, we encountered a bulging mass originating from the left uterine cornua accompanied by active bleeding [1] (Figure 2a). Additionally, we observed multiple blood-oozing sites on the rough surface of the left uterine cornual pregnancy site. Despite attempting bipolar electrocauterization for hemostasis, we were unsuccessful. This suggests that inadequate muscular support in the uterine cornua may have led to the rupture and subsequent bleeding during the pregnancy in the cornual region. Consequently, we made the decision to perform a wedge resection to address this issue. In cases where the bleeding can be controlled by suturing and the uterine surface is smooth, another viable option is to repair the rupture site after the extraction of the fetus and placenta.

Secondly, early diagnosis of cornual heterotopic pregnancy (CHP) poses a challenge and is frequently subject to misdiagnosis. High-resolution transvaginal ultrasound and serum β-hCG levels are indispensable tools for accurate diagnosis. In our study, tubal damage emerged as the most significant risk factor for the development of CHP [1], emphasizing the need for enhanced vigilance and meticulous examination in such cases. Early detection of cornual pregnancy leads to better prognoses.

Thirdly, we concur with the point you raised regarding the increasing incidence of heterotopic pregnancy (HP) in association with in vitro fertilization-embryo transfer (IVF-ET) and multiple pregnancies [2]. It is evident that uterine scarring represents the most significant factor in determining the risk of uterine rupture [3]. Given the theoretical heightened risk of uterine rupture during pregnancy, it is essential to engage in further discussion regarding whether to transfer one or two embryos in women who have undergone salpingectomy.

Finally, we appreciate your observation regarding the duplication of the second and sixteenth references, which indeed refer to the same article. Thank you for bringing this to our attention.

Declaration of competing interest

None.

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Correspondence

A method of laparoscopic treatment of large adnexal cysts — Two port trocar suction

Dear Editor,

We have read the article by Li, YX et al. [1] with interest and would like to know the followed questions and answers.

1. Since all the patients are from 2016 to 2019, I would be very glad to know what the condition of those (borderline tumors) LMP-mucinous patients, 4 in premenopausal, and 2 in post-menopausal. How are there follow-up clinically, any different as others. If any management have been done to them.
2. How do you define the patients accidently found? Do you do laparoscopically operation without any indications? Or you do it diagnostically (not a very good indication?).
3. In patients with endometriosis, is there any differences in the follow-up and management?

Declaration of competing interest

None.

Reference

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Correspondence

Massive blood transfusion for a pregnant woman with placenta increta at 26 weeks of gestation

Dear Editor

We read with much interest the article "A novel approach in the management of placenta accreta spectrum disorders: A single-center multidisciplinary surgical experience at Tu Du Hospital in Vietnam" by Dr. Thi Pham and colleagues [1]. The modified one-step conservative uterine surgery (MOSCUS, a combination of vascular disconnection of proliferative vessels, resection of invaded myometrial portion, bilateral uterine artery ligations, hemostasis at the placental bed site and transverse B-Lynch compression sutures) and 4P principle (patients, practitioners, places, procedures) really inspire us [1,2]. We congratulated the favorable maternal and fetal outcomes and the successful uterine preservation. The authors stated that the study included pregnant women above 28 weeks when the newborn could be alive. We also managed a pregnant woman with placenta accreta spectrum (PAS) and placenta previa at 26 weeks of gestation in May 2023 and herein describe our experience.

A 26-year-old gravida 4, para 2 woman at 26 + 4 weeks of gestational age was transferred to our department with the ultrasonographic evidence of turbulent placental lacunae with high velocity flow. She had complaint of intermittent, painless vaginal bleeding for half of day. She had two unremarkable cesarean sections and one abortion before. We administered corticosteroids for fetal lung mature and magnesium sulfate for tocolysis. After the medical treatment, the patient still had intermittent vaginal bleeding. Two days later, she was sent for magnetic resonance imaging (MRI). During waiting for MRI, she had 500 ml blood loss from vaginal bleeding. After the emergency MRI, she was sent to operating room for cesarean section without the results of MRI (Fig. 1). The patient underwent midline laparotomy. Vascular congestion on lower segment of uterine surface was obvious after laparotomy. After fetal extraction, the uterus was exteriorized from abdominal cavity promptly. We bound the para-cervical to obstruct blood supply. We administered intramuscular oxytocine 20 U, intravenous oxytocine 20 U, intramuscular carboprost tromethamine injection 250 μg twice for uterine contractions. After removing the placenta, we found the anterior lower segment of uterine wall was deficient, then we performed hemostasis at the placental bed site on the posterior lower segment of uterine wall and uterine reconstruction. The cesarean section was complicated by a loss of 4 L of blood, leading to massive blood transfusion. On the basis of the patient's strong desire to preserve her uterus before cesarean section, she was transferred to interventional radiology department for uterine artery embolization (UAE) after cesarean section for further bleeding control. The UAE was performed using gelatin sponge and took 75 min.

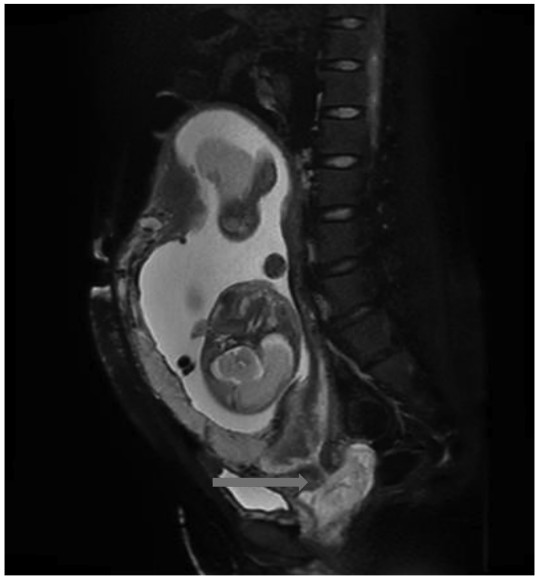

Fig. 1. Magnetic resonance imaging revealed placenta previa, the bleeding between the placenta and vagina looks like a "sandglass" (red arrow).

However, she had cardiopulmonary arrest 20 min after UAE, correction of hypovolemic shock and cardiopulmonary resuscitation was initiated immediately. The patient had return of circulation 5 min after maternal arrest and was admitted to intensive care unit. The vaginal bleeding was still present and observed, and became less and less after manual uterine massage, using uterotonics and blood transfusion. The total blood loss was in excess of 8000 ml, the patient received 22 units of packed red blood cells, 20 units of platelets, 1180 ml of fresh frozen plasma and 20 units of cryoprecipitation. The recovery was uneventful and she was discharged 5 days after operation. During follow up at the outpatient clinic, the patient had normal hemoglobin level 3 days after the discharge. Normal menstruation resumed in the patient 45 days after the discharge, and strict contraception was recommended for the patient.

Placenta increta is a life-threatening disorder that may complicate the second trimester of pregnancy. Yildirim et al. identified the changing trends in peripartum hysterectomy, the main indication for peripartum hysterectomy changed significantly from uterine atony to PAS, which is concomitantly with an increase in the rate of cesarean section [3]. As the case reported, with the rising rate

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of cesarean section, the PAS not only has been increased, but also occurred at earlier gestational age. UAE is thought as an effective intervention to achieve immediate hemostasis, however, in our case, the failure of treatment caused the persistent hemorrhage which we ignored during UAE. The rich collaterals in the pelvic circulation during pregnancy may decrease the efficacy of UAE. Chou et al. concluded that the underlying causes of UAE failure for the treatment of abnormal placentation-induced postpartum hemorrhage are associated with: iatrogenic myometrial injury caused by digital separation of the placenta; disseminated intravascular coagulopathy after massive blood loss; delayed or incomplete embolization; and unrecognized bleeding from collateral circulation [4]. Mohr-Sasson et al. also found that UAE was associated with longer operative duration and higher intraoperative blood loss compared with controls without UAE [5].

Although we saved the maternal life depended on luck, the cost of uterine-sparing management was really high. Increasing expectations regarding quality of life have shifted the management approaches for life-threatening postpartum bleeding caused by PAS and placenta previa, however, peripartum hysterectomy is still the definitive treatment [6]. In the patients with failure of UAE, hysterectomy should be regarded as a last resort, maybe earlier is better.

Declaration of competing interest

None.

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Correspondence

Successful management of cornual heterotopic pregnancy

Dear Editor,

We read with interest the article "Laparoscopic management of second trimester ruptured cornual heterotopic pregnancy with subsequent live birth delivery: A case report and literature review" by Dr. Li and colleagues [1]. We congratulated the favorable outcome of live birth after laparoscopic management of a ruptured cornual heterotopic pregnancy (HP) which is a rare but life-threatening ectopic pregnancy. We also want to share our experience of surgical management of ruptured cornual HP to compare and hope to inspire further discussion.

A 40-year-old woman, gravida 3, para 1, who complained of abdominal pain was admitted to our hospital at 12 weeks of gestation in March 2019. She had a twin pregnancy after in vitro fertilization and embryo transfer (IVF-ET) due to secondary infertility in January 2019. She had a spontaneous pregnancy and a vaginal delivery in 1998 and underwent right salpingectomy due to a right tubal pregnancy in 2014. Transabdominal ultrasonography showed a twin pregnancy and one gestational sac located in the right angle of uterus at 11 weeks of pregnancy.

After admission, physical examination revealed abdominal rebound tenderness and muscle guarding. The complete blood count revealed her hemoglobin level dropped. Transabdominal ultrasonography revealed a left intrauterine gestational sac with fetal cardiac activity, and a right cornual pregnancy also had fetal cardiac activity, the myometrium surrounding the cornual pregnancy was thin and had an irregular 32 × 17 mm anechoic mass. The rupture of cornual HP was suspected. Explorative laparotomy revealed a rupture of 1 cm in diameter at the right uterine horn and the rupture of the amniotic membrane of the cornual pregnancy, the blood loss was 1000 mL. We removed the fetus and placenta, the decidual tissue in the right uterine cornual region and repaired the rupture with continuous sutures for a water-tight closure. The patient received 3.5 units of packed red blood cells during the operation. The ultrasonography revealed the intrauterine fetus was viable after the laparotomy. Magnesium sulfate and progesterone were administered for tocolytic prophylactics. The patient had an uneventful postoperative course and was closely monitored. She was discharged on the 13th postoperative day. The continuation of the intrauterine pregnancy was unremarkable. She underwent cesarean section at 36 weeks of gestation, delivered a female infant weighing 1750 g with Apgar scores were 8 and 9 at 1 and 5 min, respectively. The baby had a normal development in a 4-year follow-up course.

First, the distance/space between the gestational sacs in dichorionic diamniotic twin pregnancy plays an important role in continuation of pregnancy after removing the cornual HP, although the ultrasound didn't show it. A wedge resection of the left cornual HP was performed and the myometrium was cut during laparoscopy [1]. However, we removed the products of conception and repaired the rupture of myometrial tissue in our case. Uterine rupture usually occurs in a scarred uterus which is secondary to salpingectomy with cornual resection, deep cornual resection, myomectomy, etc [2]. We think that left more myometrium surrounding the cornual pregnancy may provide enough space for continuation of pregnancy and lower the risk of uterine rupture and miscarriage, whether laparoscopy or laparotomy. That is why we repair the rupture after extraction of the fetus and placenta in the cornual pregnancy rather than repair directly, even the fetus had cardiac activity. Liao et al. reported a case of direct repair of cornual rupture in twin gestation at 13 weeks of gestation via laparoscopy, progressing to 30 + 5 weeks, and one of twin fetuses died 6 h after birth because of pulmonary hemorrhage which could be caused by prematurity [3]. Prematurity is also a risk factor for fetal mortality in the continuation of twin pregnancy.

Second, angular pregnancy of single pregnancy will progress to a more centric location or ultrasound normalized, the diagnosis and management of angular pregnancy is still a controversial issue. Likewise, preoperative diagnosis of cornual HP is imperative but difficult before rupture. The prognosis is associated with the timing of diagnosis of cornual HP, not mention to the ruptured cornual HP. Combination of serum β-hCG and ultrasound is an indispensable diagnostic method, and timely repeat ultrasound for suspected cornual HP is recommended.

Third, the increasing incidence of HP is associated with IVF-ET and multiple pregnancies, HP may be considered as a consequence of modern reproductive medicine [4]. It is evident that the single most important factor in determining the risk of uterine rupture is whether the uterus is scarred [3]. Due to the theoretical increase risk of uterine rupture during pregnancy, whether one or two embryos will be transferred for the salpingectomized woman warrants further discussion.

Finally, we would like to point out that the second reference and the sixteenth reference are the same article.

Declaration of competing interest

None.

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Corrigendum

Corrigendum to "Comparing the effects of two different progesterone vaginal gels, Progeson™ and Crinone™, from pharmacokinetics study to clinical applications in patients undergone fresh embryo transfer and frozen-thawed embryo transfer via natural cycle endometrial preparation protocol" [Taiwan J Obstet Gynecol 62 (2) (March 2023) 280–285]

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In the research article "Comparing the effects of two different progesterone vaginal gels, Progeson™ and Crinone™, from pharmacokinetics study to clinical applications in patients undergone fresh embryo transfer and frozen-thawed embryo transfer via natural cycle endometrial preparation protocol" by Cheng-Wei Yu, Wei-Jiun Li, Wen-Chi Hsieh, Li-Shan Chen, and Yi-Ping Li, published in the Volume 62, Issue 2, March 2023, Pages 280–285 of the Taiwanese Journal of Obstetrics & Gynecology, an error appeared in the manuscript. The Crinone trademark should be denoted with the registered trademark symbol ®, rather than the trademark symbol ™. The authors would like to apologise for any inconvenience caused.

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Corrigendum

Corrigendum to "Efficacy and safety of intravenous dexmedetomidine as an adjuvant to general anesthesia in gynecological surgeries: A systematic review and meta-analysis of randomized controlled trials" [Taiwan J Obstet Gynecol 62 (2023) 239–251]

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The authors regret the institution of this article.

The authors of the "Efficacy and safety of intravenous dexmedetomidine as an adjuvant to general anesthesia in gynecological surgeries: A systematic review and meta-analysis of randomized controlled trials" [Taiwanese Journal of Obstetrics &Gynecology 62 (2023) 239–251] would like to issue the following correction.

The authors' institution c "Mackay Medicine, Nursing and Management College, Taiwan" changed its name to" MacKay Junior College of Medicine, Nursing, and Management, Taiwan".

The authors wound like to apologize for any inconvenience caused.

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