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Original Article

Diminished ovarian reserve in patients with psoriasis

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ABSTRACT

Objective: Psoriasis is a multi-systemic chronic inflammatory skin disease. Previous data suggests that women with some chronic inflammatory diseases have diminished ovarian reserve. This study explores ovarian reserve in patients with psoriasis.

Materials and methods: We prospectively analyzed 14 female patients with psoriasis and 35 healthy age and body mass index matched controls. An interview explored demographic characteristics, obstetrical history and menstrual characteristics. Psoriatic area severity index (PASI) in patients was assessed. Estrogen, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone and with gynecologic ultrasonography, ovarian volume and antral follicular count (AFC) were measured in both study and control groups. These values were analyzed with changes of the PASI in the patient group.

Results: Patients with psoriasis had significantly higher levels of FSH and FSH/LH ratio than healthy controls ($p = 0.039$, $p = 0.005$ respectively). AFC of psoriasis patients were significantly lower than healthy controls ($p = 0.002$).There were no significant difference among other hormone levels and ovarian volumes ($p > 0.05$). The hormone levels, ovarian volume and AFC were not correlated with PASI of the patients.

Conclusion: The results of the study suggest that patients with psoriasis may have diminished ovarian reserve.

Introduction

Psoriasis is a complex, chronic relapsing skin disease. Among the psoriasis patients, about 50% are female, whereas the majority of them have onset of the disease in childbearing years [1,2].

The disease of psoriasis is characterized by an immuno-mediated inflammatory process that affects the skin and joints but leads to systemic inflammatory conditions and contributes to pathological mechanisms of other chronic inflammatory diseases [2,3].

Current evidence suggests that women with chronic inflammatory diseases like systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome (PAPS) have diminished ovarian reserve [4—6].

Ovarian reserve (OR) provides an indirect estimate of a reproductive aged woman's remaining follicular pool. A spectrum of markers to detect the ovarian reserve consists of basal follicle stimulating hormone (FSH), estrogen (E2), FSH/luteinizing hormone (LH) ratio, Inhibin B, antimullerian hormone (AMH). Ovarian morphometric markers include ovarian volume (OV) and antral follicle count (AFC). However, the availability of multiple ovarian reserve markers suggests that none is ideal and age is known to be the most important factor in determining the fertility potential of a regularly cycling women [7].

Accumulating data suggests that the female hormonal status during pregnancy, has an affect on the course of psoriasis and in contrast psoriasis has an impact on pregnancy outcomes. Despite the data relating psoriasis with pregnancy, ovarian reserve and functions have not been studied yet in psoriatic patients [2,8—10].

Therefore, our primary objective was to assess ovarian reserve tests in reproductive aged psoriatic women without previous systemic treatment and in age-matched, healthy females to determine whether the ovarian reserve is reduced. Secondly, we aimed to

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determine whether the severity of disease correlates with ovarian reserve or not. Furthermore, we analyzed the association of psoriasis with the number of births and miscarriages, and with the menstrual cycle regularity.

Materials and methods

In this prospective analytic case–control study, we included 14 female patients with psoriasis and 35 age and body mass index (BMI) matched women as healthy controls who are all in reproductive age. The study was performed between January and September 2014 in Aksaray University Research and Training hospital. The protocol of the study was designed in accordance with the Helsinki declaration and implemented after receiving approval from the local ethics community. After written consent was obtained, patients and controls were screened for eligibility.

Healthy controls were selected from the routine gynecological examined women without any complaint. Eligibility criteria for patients selection were determined by a dermatologist based on clinical findings and histopathological studies. The following data of the patients were documented: type of psoriasis, presence of hair and nail psoriasis, the severity of the disease using psoriatic area severity index (PASI) which was conducted by a dermatologist. Participants that were enrolled in the study, were also questioned for demographic characteristics, confounding morbidities, obstetrical and gynecological history, such as pattern of menstrual cycle and age of menarche.

The exclusion criteria for both groups includes infertility, pregnancy, the presence of gynecological pathologies, polycystic ovarian syndrome (PCOS), breastfeeding, history of gynecological surgery, chronic renal or liver failure, smoking, malignancy or other dermatologic, inflammatory, physical and psychiatric disorders. Patients who had ever received any systemic treatment and hormone medication were also excluded to avoid possible affects on ovarian function.

To assess ovarian function tests, venous blood sampling was performed from all participants in the early follicular phase (days 2–4) of the menstrual cycle at approximately 9:00 a.m. Levels of early follicular phase hormones; E2, FSH, LH and thyroid stimulating hormone (TSH) were assayed from the samples. Serum levels of FSH, LH, E2 and TSH were measured with electrochemiluminescence assay (Elecsys 2010, Hitachi/Roche Diagnostic). Following the blood collection, each patients were also evaluated by a gynecologist to determine ovarian volume and total antral follicles measuring 2–10 mm in diameter were measured by transvaginal ultrasonography. Clinical data of each participant were kept as blinded to avoid any possible bias. The measurements were conducted using a high resolution ultrasound machine (Logic Q7, General Electric, USA) with a 7.5 mHz mechanical sector transducer. PASI score of each participant of study group were assessed, in the same day with gynecological investigation.

Mann Whitney U test were used to analyze the collected data from independent samples. To determine correlation between variables, Spearman test was used. Numerical variables were presented as median interquartile range (IQR). The level of statistical difference was $p < 0.05$. The power of the analysis was 87%. All analyses were performed with the Statistical Package for the Social Sciences, version 20.0 (SPSS, Chicago, IL, USA).

Results

Among the 14 patients with psoriasis, 9 had plaque type, 3 had guttat type and 2 had palmoplantar type psoriasis and in contrast none of them had psoriatic arthritis. Patients who had disease duration less than one year were only confined to 14.3 percent. The

Table 1
Psoriasis types and disease duration of the patients.

	N	Percent
Plaque type	9	64,28
Guttat type	3	21,42
Palmoplantar type	2	14,28
Patients with nail psoriasis	3	21,42
Patients with scalp psoriasis	11	78,57
Disease duration more than one year	12	85,7

distribution of types and features among psoriasis patients are shown in Table 1.

Median age of the psoriasis group was 31 (13.5) years (range 16–48 years) with a median BMI of 27.39 (10.5) (range 19.37–36.75) kg/m^2. There was no statistically significant difference between groups in terms of age and BMI. The median age of menarche was 13 (2) in psoriasis patients same as in the control group. Also gravidity, parity and miscarriage numbers of groups were statistically analyzed. A summary of demographic characteristics and obstetrical history of each group is showed in Table 2.

Patients with psoriasis had significantly higher levels of FSH than healthy controls (6.76 (1.96); 5.71 (2.24) respectively, $p < 0.05$). AFC of psoriasis patients were significantly lower than healthy controls (5 (2.5); 7 (4.5) respectively, $p < 0.05$). FSH/LH ratio was significantly higher in patients with psoriasis than healthy controls (1.52 (0.86); 0.92 (0.54) respectively, $p < 0.05$). There were no significant differences among other hormone levels, ovarian and uterus volumes ($p > 0.05$) (Table 2).

Median value of the PASI was 4.69 (5.9) with a range 2–19.8. According to the Spearman's rho test, there was no correlation

Table 2
Demographic, hormonal, and ultrasonographic parameters of the groups.

	Patients (N:14)	Healthy controls (N:35)	p
Median (IQR) age, years	31 (13,5), range 16–48	29 (10), range 17–43	0,535
BMI (kg/m^2)	27,39 (10,50)	24,24 (6,33)	0,150
Median (IQR) age at menarche, years	13 (2)	13 (2)	0,731
Gravidity	2 (3)	2 (3)	0,568
Parity	1,5 (2)	1 (3)	0,982
Spontaneous abortions, n (%)	5 (35,7%)	4 (11,5%)	0,050
Menstrual irregularity, n (%)	0 (0%)	4 (8,2%)	0,312
TSH (mIU/L)	2,67 (1,38)	2,32 (1,18)	0,140
FSH (mIU/mL)	6,76 (1,96)	5,71 (2,24)	**0,039**
LH (mIU/mL)	4,74 (3,53)	5,73 (3,46)	0,475
FSH/LH	1,52 (0,86)	0,92 (0,54)	**0,005**
E2 (pg/mL)	27,58 (18,16)	34 (27,31)	0,143
Total AFC	5 (2,5)	7 (4,5)	**0,002**
Total OV (cm^3)	10,92 (5,22)	11,66 (8,26)	1000

BMI, body mass index; TSH, tiroid stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; AFC, antral follicle count; OV, ovarian volume; IQR, interquartile range.
P-values numbers marked in bold indicate numbers that are significant on the 95% confidence limit.

Table 3
Correlation of psoriatic area severity index (PASI) with ovarian reserve tests in patients with psoriasis (FSH, follicle-stimulating hormone; (LH) luteinizing hormone; E2, estradiol; AFC, antral follicle count; OV, ovarian volume; IQR:interquartile range).

		E2	FSH	LH	FSH/LH	AFC	OV
PASI median (IQR:4,65(5,9) (range 2 –19,8)	Correlation coefficient	–,011	,108	–,178	0,402	–,238	,011
	p value	,970	,714	,543	0,154	,412	,970
	N	14	14	14	14	14	14

between the severity of psoriasis vulgaris, as exhibited by the PASI score and hormone levels, antral follicle count and ovarian volumes (Table 3).

Discussion

Average age of diagnosis in women with psoriasis is 28, a prime age for pregnancy [11]. Therefore, many female patients with psoriasis are concerned about adverse effects of the disease on their future fertility. Diminishing ovarian reserve is a phenomenon noted in women during mid to late thirties and at times earlier, and is well substantiated by the declining follicular pool and oocyte quality [12]. Thus, age is known to be the most important factor in determining the pregnancy potential in regularly cycling women [7]. A woman's cumulative hypothetical pregnancy chance is mathematically reflected in her complete follicle pool, her total ovarian reserve [13]. The development and use of ovarian reserve tests have become prevalent because chronological age alone has a limited value in predicting individual ovarian responses [14,15].

Predictive values of ovarian reserve tests have been frequently considered, but none is ideal alone [7]. Ovarian evaluation with FSH, LH, E2, ovarian volume and AFC is the preferential method for the disease-affected ovarian reserve [16,17]. Basal follicle stimulating hormone (FSH) levels measured on the third day of the menstrual cycle is the most widely used ovarian reserve test. The increase in FSH levels occurs due to follicle depletion [18] and the elevated FSH:LH ratio can be a signal of diminished OR [19]. Since FSH begins rising before LH as OR diminishes, using two measurements may seem more plausible [20]. The FSH:LH ratio is an early indicator of ovarian aging and could be the first marker of diminished OR [21]. Using transvaginal ultrasound to determine the AFC (the number of follicles measuring 2—10 mm in diameter) is another predictor of ovarian reserve. It is found that the number of AFC declines with age and correlates with other markers [22].

In our study, levels of FSH and FSH/LH ratio is found higher, where AFC is lower in patients than healthy women. However, there are no differences between levels of E2 and OV within patients and controls. Basal E2 and inhibin B are not found to be of any better predictive value than FSH [23] and OV remains unchanged till the perimenopausal period and does not add to the predictive value of AFC [24].

In the study, results supports diminished ovarian reserve in premenopausal women with psoriasis, however, ovarian reserve tests do not correlate with disease severity.

Compelling evidence has indicated the ovarian reserve to be effected under several specific conditions and chronic disorders, including autoimmune diseases [25]. Recent studies that have evaluated the association of reduced ovarian reserve with autoimmune diseases, reported systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome have low levels of anti-mullerian hormone (AMH), antral follicule count, and high levels of FSH [4—6]. Reduced ovarian reserve was suggested to be triggered by ovarian antibodies causing autoimmune oophoritis, which may result in premature ovarian failure (POF). The condition of POF is defined as a premature depletion of ovarian follicles/arrested folliculogenesis before the age of 40 years with high FSH levels (>40 IU/L), and hypoestrogenism [26]. Current evidence convincingly implicates that the confounding morbidities and autoimmune disorders are more common in patients with psoriasis compared to general population. The great majority of inflammatory autoimmune disorders are caused by the derangements in multiple cytokine pathways [27]. Thus, considering similar pathogenesis in autoimmune diseases, autoimmunity in psoriasis may be one of the causes of diminished ovarian reserve.

The keratinocytes in the psoriatic skin lesions were recognized as a source of pro-angiogenic cytokines which induce angiogenesis, e.g. vascular endothelial growth factor (VEGF). VEGF is an angiogenic cytokine and also a potent mitogen for vascular endothelium. The VEGF-A type was found to be associated with skin inflammation and pathogenesis of psoriasis [28], and is also positively associated with the severity of disease and increased intimal media thickness (IMT) [29]. Moreover, during reproductive life, VEGF is expressed and produced by the ovaries, which is also suggested to play a role in the cyclic growth of ovarian follicles, and maintenance of corpus luteum development by mediating ovarian angiogenesis [30]. Accumulating evidence supports the link between this vascularization and follicle dynamics [30—32]. In a recent study, this association was presented as an inverse relationship that increased superficial cortex vascularization has a negative effect on follicle dynamics, by increasing the rate of depletion of resting follicles [33]. Therefore, increased production of VEGF by keratinocytes in psoriasis may also be by ovaries, as well. Defects in angiogenesis may contribute to a variety of disorders including anovulation and infertility, pregnancy loss, ovarian hyperstimulation syndrome, and ovarian neoplasms [30]. Based on recent studies, diminished ovarian reserve in psoriasis may be due to the depletion of follicles related to increased superficial over cortex vascularization as a result of increased production of VEGF.

According to our findings, there were no differences of gravidity and parity between psoriasis and control groups, however, there was a borderline difference (p = 0.05) in incidence of spontaneous abortions between groups. Results of recent studies are also contradictory. Seeger et al. and Lima et al. reported no differences in pregnancy incidence, spontaneous abortions between psoriasis and controls groups, whereas, Cohen-Barak et al. reported psoriasis with a higher prevalence of spontaneous abortions [2,34,35]. This association was also based on the severity of disease, but compared to aforementioned study by Seeger et al. patient selection by Cohen-Barak et al. [35] included moderate to severe disease. Other inflammatory diseases like inflammatory bowel diseases, rheumatoid arthritis and systemic lupus erythematosus were also reported to pose a high risk for both total and spontaneous abortions. In larger prospective studies, impact of psoriasis on pregnancy outcomes with wide spectrum of patients who have different clinical stages may be studied.

One of the limitations of the present study was the lack of AMH level measurement which is now beginning to lead ovarian reserve assessment in clinical practice. Another limitation of the study was the patient selection, including most of the patients with mild to moderate disease. Thus, it may be due to the exclusion of patients who have had systemic treatment before because most of the patients with severe psoriasis usually have a history of systemic treatment.

Women in their mid to late 30s and early 40s constitute an important part of the infertile population that many of them require expensive treatments including assisted reproductive technologies [7]. According to our findings that supports diminished ovarian reserve in psoriasis, ovarian reserve assessment and individualized procreative counseling of all reproductive age women with psoriasis should be incorporated into routine preventive care, considering the widely prevalent onset of psoriasis in the reproductive years. Improved awareness of the effects of psoriasis on ovarian reserve besides aging and early referral to a reproductive endocrinologist or obstetrician when there is a risk of diminished ovarian reserve, can improve pregnancy planning and management especially before starting systemic treatment for psoriasis. More studies are needed to confirm the ovarian reserve of patients with psoriasis vulgaris with different stages of the disease in larger groups.

Conflicts of interest

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

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