



Original Article

Frequency and clinical manifestation of prenatal cytogenetic diagnosis of chromosomal polymorphisms in Northeast China



Li-Li Luo, Zhu-Ming Hu, Lei-Lei Li, Hong-Guo Zhang, Yu-Ting Jiang, Rui-Zhi Liu, Rui-Xue Wang*

Center of Reproductive Medicine, Center of Prenatal Diagnosis, First Hospital, Jilin University, Changchun 130021, China

ARTICLE INFO

Article history:

Accepted 17 February 2020

Keywords:

Prenatal diagnosis
Chromosomal polymorphisms/
chromosomal variants
Karyotype/phenotype
Amniocentesis
Second trimester maternal serum screening

ABSTRACT

Objective: To retrospectively analyze the incidence of chromosomal polymorphisms in prenatal cytogenetic diagnostic cases and the effect of the clinical manifestation of these fetuses.

Materials and methods: 490 fetuses with chromosomal polymorphisms among 9996 pregnant women who underwent prenatal cytogenetic diagnosis were included in this study and were set as group 1. Other 500 pregnant women, whose fetuses were with normal karyotypes, were randomly selected from the remaining pregnant women and set as group 2. Clinical information and outcomes and maternal serum screening results of group 1 were compared with group 2.

Results: The frequency of fetal chromosomal polymorphism was 4.90% (490/9996). The most common variants observed were 1/9/16 qh± (2.27%, 227/9996), followed by inv(9) (0.90%, 90/9996). 94.62% (264/279) of fetal chromosomal variants were inherited from parents. No statistical difference was found in clinical information and outcomes and maternal serum screening results between group 1 and group 2.

Conclusion: The fetus with chromosomal polymorphism has no impact on serum markers of second trimester screening and does not play an important role for the clinical outcome of the current pregnancy either, whether it is inherited from the parents or a de novo mutation.

© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Chromosomal polymorphism, also known as chromosomal variation, refers to the differences in size or staining of chromosome segments in the population [1]. Chromosomal polymorphisms include variations in heterochromatic segments, satellites and satellite stalks [2]. Mainly in chromosome (Chr) of 1, 9, 16, Y and D/G groups (chromosomes 13, 14, 15, 21 and 22), no phenotypic effects in clinical manifestation had been reported [3]. However, surveys showed that the genetic effects of chromosomal polymorphisms may result in the corresponding clinical phenotype or pregnancy abnormality under the influence of certain internal and external environments [4]. It has been reported that the difference of overall polymorphism rate was statistically significant between patients with recurrent miscarriage and the control group [5]. When the fetus' karyotype showed chromosomal polymorphism, a scientific and reasonable explanation to the pregnant couples and their family need to be given.

Prenatal maternal serum screening for Down syndrome (DS) is recommended for all pregnant women under 35 years of age between 11 and 13⁺⁶ or 15–20⁺⁶ weeks of gestation (menstrual age) in China. The following familiar serum markers were utilized in DS screening risk calculations: alpha-fetoprotein (AFP), free beta-human chorionic gonadotropin (f-βhCG), unconjugated oestriol (uE3), pregnancy-associated plasma protein (PAPP-A), while ultrasonic nuchal translucency (NT) measurement was added in the first trimester screening [6–10]. If the likelihood ratio belongs to the high risk group, amniocentesis is advised to confirm the diagnosis through cytogenetic examination then.

In order to add more evidences whether the chromosomal polymorphisms influence clinical phenotype or fetal abnormality, we analyzed the frequency of chromosomal polymorphisms among high-risk cases that underwent maternal serum screening followed by amniocentesis for the study of fetal chromosome. Furthermore, this study also compared the difference of the value of maternal serum screening markers in pregnant women who had fetuses with chromosomal polymorphisms with the control group, because it had been reported these cases might change the DS screening marker levels by affecting placental function [11]. At present, the

* Corresponding author.

E-mail address: wang_rx@jlu.edu.cn (R.-X. Wang).

relationship between chromosomal polymorphisms and clinical manifestation is still controversial.

Materials and methods

Case collection

From 17 March 2011 to 24 August 2018, a retrospective cohort of 9996 pregnant women were performed amniocentesis with high risk factors (Table 1), such as maternal serum screening (MSS) positive, noninvasive prenatal testing (NIPT) positive, adverse pregnancy outcome, abnormal ultrasonographic findings, fetus' parent was chromosomal abnormality carrier, advanced maternal age (AMA) and others. We excluded pregnant women with multiple pregnancies and those who did not consider to undergo the invasive tests. A total of 490 (4.9%) fetuses (239 males, 213 females, and 38 unknowns) with chromosomal polymorphisms were included in this study and were set as group 1 (Fig. 1). These pregnant women and their husbands had been advised to take karyotype analysis in order to confirm the origin of fetal chromosomal polymorphisms. Finally, only 279 pregnant couples accepted their chromosomal examinations. On the other hand, a total of 500 pregnant women were randomly selected from the remaining pregnant women whose fetuses were normal karyotypes and set as group 2. Appropriate written voluntary consent was obtained from all the individuals and the study was approved by the Chinese Association of Humanitarianism and Ethics. In group 1, we obtained the MSS tests of 292 women (11 women had first trimester screening, 281 women had second trimester screening), and 30 pregnant women took the nuchal translucency (NT) measurements. In group 2, 273 women had MSS test results (7 women had first trimester screening, 266 women had second trimester screening), and 38 pregnant women took the NT measurements. Second trimester screening markers' values (MoM) were compared between group 1 and 2. However, the number of pregnant women both in group 1 and 2, who undertook the first trimester screening, was too small to conduct statistical comparison.

Sample collection

Collection of exfoliated fetal cells by amniocentesis

Under ultrasonographic guidance, the insertion angle and direction of the needle were determined at the best point where fluent amniotic fluid and limbs of the fetus were observed, avoiding the placenta and umbilical cord. Amniotic fluid samples were collected and transferred directly to the laboratory for culture and to analyze the karyotype finally.

Collection of parental peripheral blood lymphocytes

Karyotype analysis of 279 couples were performed. Briefly, 3–5 ml peripheral blood was collected and peripheral blood

lymphocytes were cultured in lymphocyte culture medium and used for karyotype analysis.

Classification of chromosomal polymorphisms [12]

Increase or decrease in lengths of the stalks on the short arm of chromosome of the acrocentric chromosomes (D/G groups) was recorded as 13/14/15/21/22 pstk±. Double and increase satellites on the short arm of 13/14/15/21/22 could also be observed and were designated as pss and ps+. The pericentric inversions of chromosomes 9 were also considered as chromosomal polymorphism [13]. Increase or decrease in length of the heterochromatin on the long arm of chromosome 1/9/16/Y were designated as 1/9/16/Y qh+ or qh-. Increase in lengths of heterochromatin region on the centromere of D/G groups was recorded as 13/14/15/21/22 cenh+. Multiple variations were consisted of more than one kind of variant. All karyotypes were examined independently under light microscope by three laboratory technicians at different times in the laboratory to avoid uncertainty and various results.

Second trimester screening (STS) for down syndrome (DS)

STS was performed at 15–20⁺6 weeks of gestation using maternal age and maternal serum concentrations of AFP, f-βhCG and uE3 for risk calculation. Gestational age was determined by fetal crown rump length (CRL) or biparietal diameter (BPD). The serum marker levels of STS were measured by AutoDELFIA (PerkinElmer, Finland). All marker levels were converted into MoM, which is used to calculate the risk of DS, based on different gestational week. Information on earlier pregnancy with DS, maternal weight, maternal age, and smoking habits were also taken into account for risk calculation on DS. Screening positive at a term risk cut-off is 1/270 for STS.

Statistical analysis

Statistical analysis was performed with SPSS® version 23.0 statistical package (SPSS Inc., Chicago, IL, USA) for Windows®. Independent Sample t-test was used to analyze numerical data. Pearson chi-squared test or Fisher's exact test was used to analyze categorical data. With a two-sided p-value less than 0.05, the statistical difference had significance.

Results

The most commonly observed polymorphic variant was qh± (n = 227, 2.27%), and the most common chromosome with qh± was 1 qh+ (n = 123, 1.23%) followed by 16 qh+ (n = 64, 0.64) and 9qh± (n = 39, 0.39%). The second commonest polymorphic variant was inv(9) (n = 90, 0.90%), and the most common polymorphic variant was inv(9)(p11q13) (n = 82, 0.82%) followed by inv(9)(p11q12) and inv(9)(p12q13). Frequency distributions of the other polymorphic

Table 1

Distribution of indications of 9996 amniocentesis cases.

Indications of Prenatal Diagnosis	Cases (percentage)	Cases of chromosomal polymorphisms (frequency)
Maternal serum screening positive	4500 (45.02%)	209 (4.64%)
Noninvasive prenatal testing positive	117 (1.17%)	2 (1.71%)
Adverse pregnancy outcome	317 (3.17%)	18 (5.68%)
Abnormal ultrasonographic findings	742 (7.42%)	25 (3.37%)
Chromosomal abnormality carrier	73 (0.73%)	9 (12.33%)
Advanced maternal age	1743 (17.44%)	90 (5.16%)
Multiple	797 (7.97%)	44 (5.52%)
Others	1707 (17.08%)	93 (5.45%)

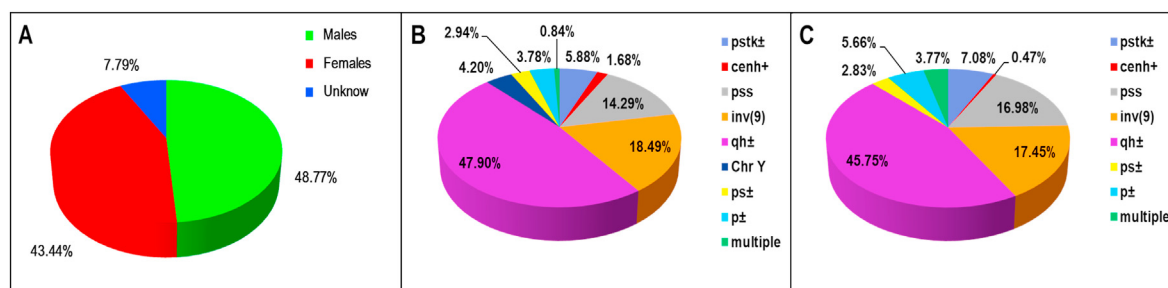


Fig. 1. The major categories of chromosomal polymorphisms among 490 fetuses: (A) distribution of chromosomal polymorphisms in fetal sex; (B) distribution of major categories of chromosomal polymorphisms in male fetuses; (C) distribution of major categories of chromosomal polymorphisms in female fetuses.

variants are shown in Table 2. The most and the second most commonly observed polymorphic variants in different sex of babies were the same as the above (Fig. 1). The commonest chromosomal polymorphism was 1 qh + both in male ($n = 67$, 1.45%) and female ($n = 47$, 1.09%) fetuses followed by inv(9)(p11q13) [$n = 41$ (0.89%) and $n = 35$ (0.81%), respectively] (Table 2). The frequency distributions of various categories of chromosomal polymorphisms were similar in male and female fetuses.

In the 9996 cases with high risk of prenatal diagnosis, there were 490 fetuses with chromosomal polymorphisms, including 239 males, 213 females, and 38 unknown of sex. The incidence of total polymorphisms was 4.90% (490/9996). The basic characteristics of subject investigated are shown in Table 3. Only a few pregnant women were advanced maternal age, and more gestational age were restricted within this study. There was no statistical difference in terms of maternal age between group 1 and 2 (31.09 ± 5.32 vs

Table 2

Frequency of chromosomal polymorphisms of prenatal diagnosis.

Classification	Karyotypes	Total (n = 9996) ^a	Frequency (%)	Male fetus (n = 4607) ^b	Frequency (%)	Female fetus (n = 4308) ^c	Frequency (%)
pstk+		32	0.32	14	0.30	15	0.35
	13pstk+	6	0.06	2	0.04	4	0.09
	14pstk+	5	0.05	2	0.04	2	0.05
	15pstk+	6	0.06	2	0.04	3	0.07
	21pstk+	6	0.06	3	0.07	3	0.07
	22pstk+	9	0.09	5	0.11	3	0.07
cenh+		7	0.07	4	0.09	1	0.02
	13cenh+	2	0.02	2	0.04	0	0
	15cenh+	4	0.04	2	0.04	0	0
	21cenh+	1	0.01	0	0	1	0.02
pss		75	0.75	34	0.74	36	0.84
	13pss	16	0.16	11	0.24	5	0.12
	14pss	12	0.12	8	0.17	4	0.09
	15pss	21	0.21	6	0.13	12	0.28
	21pss	14	0.14	4	0.09	9	0.21
	22pss	12	0.12	5	0.11	6	0.14
inv(9)		90	0.90	44	0.96	38	0.88
	inv(9)(p11q12)	5	0.05	1	0.02	3	0.07
	inv(9)(p11q13)	82	0.82	41	0.89	35	0.81
	inv(9)(p12q13)	3	0.03	2	0.04	0	0
qh±		227	2.27	115	2.50	98	2.27
	1qh+	123	1.23	67	1.45	47	1.09
	9qh±	39	0.39	14	0.30	22	0.51
	16qh+	64	0.64	34	0.74	29	0.67
	22qh+	1	0.01	0	0	0	0
Chr Y		10	0.10	10	0.22	/	/
	Yqh±	4	0.04	4	0.09	/	/
	Y ≥ 18	5	0.05	5	0.11	/	/
	Y < 21	1	0.01	1	0.02	/	/
p±		14	0.14	7	0.15	6	0.14
	13ps-	1	0.01	1	0.02	0	0
	14ps+	2	0.02	1	0.02	0	0
	15ps+	7	0.07	3	0.07	4	0.09
	21ps+	4	0.04	2	0.04	2	0.05
p±		22	0.22	9	0.20	11	0.26
	13p±	4	0.04	4	0.09	0	0
	14p±	2	0.02	0	0	2	0.05
	15p±	11	0.11	3	0.07	6	0.14
	21p±	3	0.03	1	0.02	2	0.05
	22p±	2	0.02	1	0.02	1	0.02
Multiple		13	0.13	2	0.04	8	0.19

Chr = chromosome.

^a Total number of pregnant women undergoing amniocentesis during the study period.

^b ^c Total number of boys and girls confirmed by follow-up results, respectively.

Table 3
Baseline characteristics and pregnancy outcomes.

Characteristic	Group 1 (n = 490)	Group 2 (n = 500)	p-value
Maternal Age(mean ± SD)	31.09 ± 5.32	30.55 ± 5.16	>0.05
Identification of Prenatal Diagnosis (%)			
Maternal serum screening positive	209 (42.65)	208 (41.60)	>0.05
Noninvasive prenatal testing positive	2 (0.41)	7 (1.40)	>0.05
Adverse pregnancy outcome	18 (3.67)	26 (5.20)	>0.05
Abnormal ultrasonographic findings	25 (5.10)	30 (6.00)	>0.05
Chromosomal abnormality carrier	9 (1.84)	4 (0.80)	>0.05
Advanced maternal age	90 (18.37)	83 (16.60)	>0.05
Multiple	44 (8.98)	29 (5.80)	>0.05
others	93 (18.98)	113 (22.60)	>0.05
Abnormal ultrasound findings (%)	146 (29.80)	121 (24.20)	>0.05
Complications of Amniocentesis (%)	8 (1.63)	2 (0.40)	>0.05
Fetal sex			
Boy (%)	239 (48.78)	244 (48.80)	>0.05
Girl (%)	213 (43.47)	227 (45.40)	>0.05
Unknown (%)	38 (7.76)	29 (5.80)	>0.05
Born			
Health (%)	450 (91.84)	469 (93.80)	>0.05
Abnormal (%)	3 (0.61)	4 (0.80)	>0.05
Termination and abortion (%)	21 (4.29)	23 (4.60)	>0.05
Lost to follow-up (%)	16 (3.27)	4 (0.80)	<0.01

Continuous variables are summarised with mean ± SD and categorical variables with n(%).

30.55 ± 5.16 years, $p > 0.05$). The main indication of cytogenetic prenatal diagnosis was MSS positive both in group 1 and 2 (42.65% vs 41.60%, $p > 0.05$). The other indications were similar in group 1 and 2.

474 cases (96.73%) were successfully followed up in group 1, and 16 cases (3.27%) were lost to follow-up. 496 cases (99.20%) were successfully followed up in group 2, and only 4 cases (0.80%) were lost. The missing rate of group 1 was significantly higher than that of group 2 ($p < 0.01$). Complications occurred after amniocentesis in 10 pregnant women (8 cases in group 1 vs 2 cases in group 2, $p > 0.05$), including abdominal pain (5 cases in group 1, 2 cases in group 2), vaginal bleeding (1 case in group 1), uterine contraction occurred (1 case in group 1), and abortion (1 case in group 1) (Table 1). Follow up results showed that 453 and 473 babies were born in group 1 and group 2 respectively. In group 1, 450 babies were born healthy (238 boys and 212 girls) and 3 babies (A boy with congenital hypospadias, a girl with atrial septal defect, and another fetus was born prematurely and died) were born with abnormalities. In group 2, 469 babies (243 boys and 226 girls) were born healthy and 4 babies (A boy with congenital heart disease and severe anemia, a girl with biliary obstruction, and other two babies were born prematurely and died) were born with abnormalities.

Therefore, 91.84% (450/490) of fetuses with chromosome polymorphism were born healthy, 3 (0.61%) fetuses were born abnormal, elective termination of pregnancy in 21 (4.29%) and 16 (3.27%) pregnant women were lost to follow-up. Atrial septal defect (ASD) was found in a female fetus with multiple polymorphic variants (46,XX,16qh+,21pss), congenital hypospadias was found in a male fetus with polymorphic variant of 1qh+, and another fetus with polymorphic variant of 1qh+ was born prematurely and died. Twenty pregnant women with chromosomal polymorphisms chose to terminate their pregnancy, and one was with spontaneous abortion. Among termination cases, ultrasound suggests fetal malformation [1 case of 22pstk+], congenital heart disease [1 case of inv(9)(p11q13)] and cardiac abnormalities [1 case of inv(9)(p11q13)].

279 pregnant couples were recalled to take chromosomal karyotype analysis because of their fetuses with chromosomal polymorphisms. Chromosome karyotype analysis result is showed in Table 4. 133 cases were inherited from father (67 male fetuses, 59 female fetuses and 7 unknowns), 132 cases inherited from mother

(62 males, 61 females and 9 unknowns), and 15 cases were de novo mutations (6 males, 8 females and 1 unknowns). Fetal chromosomal polymorphism inherited from the parents was far higher than that of de novo variant (94.62% vs 5.38%)(Table 4).

There was no significant difference in terms of AFP, f-βhCG, and uE3 MoM between group 1 and group 2 ($p > 0.05$) (Table 5). Furthermore, no statistical difference was found in different types of polymorphisms compared with group 2 or with other types of polymorphisms ($p > 0.05$). However, the mean of f-βhCG MoM of group 1 was higher than that of group 2 as 14 percentage points.

Discussion

Our results showed that the incidence rate of chromosomal polymorphisms in prenatal diagnosis was 4.9%. The percentage was lower than our previous research in 2015 which was 6.28% [14]. However, it was significantly higher than another study (2.06%) [15]. The reason for this difference was the prevalence of some chromosome polymorphism variants varies in different populations. In similar studies, the incidence of fetal chromosomal polymorphism was 5.7% [16] and 5.3% [11].

In the present study, the most common variants observed were 1/9/16 qh± and inv (9). Changing of highly repetitive DNA sequences leads to the increase or decrease in the length of the secondary constriction in the long arm of chromosomes 1, 9 and 16. It is currently controversial in the opinion that whether 1/9/16 qh± can cause abortion, stillbirth, and infertility [4,17,18]. Consider an influential research point that the repeat segments may cause clinical symptoms because of increased highly repetitive DNA

Table 4
Fetal sex and origins of chromosomal polymorphism.

Origin	Boy	Girl	Unknown	Total (%)
Inherited	129	120 ^a	16	264 ^a (94.62)
Paternal	67	59	7	133
Maternal	62	61	9	132
De novo	6	8	1	15 (5.38)
Unclear	104	86	21	211 (43.06)

^a Include a female fetus with two types of polymorphic variants origin of paternal and maternal, respectively.

Table 5

The markers in the second trimester maternal serum screening tests (values are expressed as MoM).

MoM	Group 1 (n = 281)	Group 2 (n = 266)	p-value
AFP			
Mean (SD)	1.09 (2.73)	0.92 (0.7)	0.337
Median (Q1, Q3)	0.77 (0.6, 1.01)	0.77 (0.56, 1.05)	
f-βhCG			
Mean (SD)	3.41 (6.38)	2.98 (2.26)	0.303
Median (Q1, Q3)	2.47 (1.66, 3.88)	2.62 (1.41, 4.0)	
uE3			
Mean (SD)	0.94 (0.56)	0.93 (0.79)	0.849
Median (Q1, Q3)	0.82 (0.61, 1.08)	0.83 (0.61, 1.05)	

f-βhCG: free beta human chorionic gonadotropin; AFP: alpha-fetoprotein; uE3: unconjugated estriol; MoM: multiples of median; SD: standard deviation; Q1: first quartile; Q3: third quartile.

sequences [19]. Heterochromatin in chromosomal polymorphism variations can regulate gene expression by reversible transformation between heterochromatin (non-coding DNA sequences) and euchromatin (expressed DNA sequences) [20,21]. However, previous studies by our research team showed that there was still a difference between DNA sequence studies and actual phenotypic effects in clinical [15]. In this study, 227 cases (46.33%) with qh± were observed, and 123 pregnant couples (54.19%) were recalled to perform chromosomal karyotype analyses. Results showed that 117 cases (95.12%) were inherited from parents and only 6 cases (4.88%) were de novo mutations. As in our previous studies [14], very few pregnant women had history of adverse pregnancies before the present pregnancy (No data). Furthermore, there was no abnormal clinical phenotype observed in these pregnant couples. It is concluded that 1/9/16 qh± is not the direct cause of miscarriage, stillbirth or infertility.

Inversion of chromosome 9 [inv(9)] is a common chromosomal structural change. It belongs to the polymorphism of chromosome structure. At present, most studies suggest that inv(9) usually has no pathological and clinical phenotypic effects [16,22]. But few earlier studies found that it was related to reproductive failure [23]. In the present study, a total of 90 fetuses' karyotype were diagnosed as inv(9), and parents of 55 fetuses among them were recalled to perform chromosomal karyotype analyses. Results showed that all fetal inv(9) were inherited from father or mother; meanwhile, no abnormal clinical phenotype was observed in these pregnant couples. Therefore, according to the results, we speculate that inv(9) cannot lead to abnormal clinical phenotype unless pregnant couples have other conditions that can lead to an adverse pregnancy outcome and even infertility. For example, Boue J et al. reporting on the mechanisms of reproductive failure couples with an inv (9) carrier suggested that crossing over in an inversion loop during meiosis leads to an unbalanced genetic composition of each chromosome [24].

We did the same analysis on the remaining chromosomal polymorphisms, and the conclusion was the same. However, it was a pity that only 3 cases with Y-chromosomal polymorphism were recalled to perform chromosomal karyotype analyses for pregnant couples. The results of parental karyotype showed that Y-chromosomal polymorphism of all 3 fetuses were inherited from the father (46,XY,Y > 18, 46,X,Yqh+, and 46,X,Yqh-), and chromosomal karyotypes of all three mothers were normal (46,XX). This study did not conduct Y-chromosome microdeletion analyses of fetuses' and their fathers' because of the number of cases and the limitations of some conditions.

In this study, follow-up results of fetuses with chromosomal polymorphism showed that the rate of lost to follow-up was significantly higher than group 2. Among the lost to follow-up pregnant women, one refused to be followed up directly. It seemed that pregnant women might have conflicting feelings

about their fetuses with chromosomal polymorphisms because they did not understand this situation very well. Therefore, we should pay more attention to fetal chromosomal polymorphic cases for genetic counseling in order to avoid unnecessary termination of pregnancy and psychological burden to the parents. In the present study, 94.62% inherited from parent and only 5.38% were de novo mutation. However, both fetal chromosomal polymorphisms inherited from the parents and de novo mutations can achieve good pregnancy outcomes. In summary, according to our research findings, continuing pregnancy should be advised to pregnant women with fetal chromosomal polymorphism unless adverse conditions occurs, such as congenital malformation, intrauterine growth retardation (IUGR), dead fetus in uterus and so on.

In our study, we also compared the MoM of maternal serum markers for DS screening between those who had fetuses with polymorphism and those who had normal karyotype to examine the possible effect of fetal polymorphism on screening test results. To the best of our knowledge, there was only one literature investigated this association before our research [11]. Unlike the previous report, no significant difference was found in terms of screening markers' MoM. But our study found that the values of f-βhCG in pregnant woman who had fetuses with polymorphism was higher than that of control group. Although the pathophysiological mechanisms underlying the increased f-βhCG levels are not clear yet, but increased f-βhCG levels may be related to the change of placental function [25,26].

Our research team was once the first time to analyze the relationship between reproductive failure and chromosomal polymorphisms through pedigrees in China. And we concluded that chromosomal polymorphisms did not play a role in reproductive problems [15]. On the other hand, our team also conducted a more in-depth study of the outcomes of assisted reproductive outcomes in infertile couples with chromosomal polymorphisms. The results showed that chromosomal polymorphic variations of either men or women had no adverse effects on good quality embryo rate, pregnancy rate, clinical pregnancy rate or live birth rate [27]. Right now, this study further confirmed that chromosomal polymorphisms had no significant effect on fertility and pregnancy outcome based on prenatal diagnosis of fetal chromosomal polymorphisms.

Funding

This work was supported by the Special Funds for Projects of Independent Innovation and New & Hi-tech Industry Development of Jilin Province (2017C025), China.

Declaration of Competing Interest

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

Acknowledgements

The present study group would like to thank all of the members of the research group in the Center for Reproductive Medicine and Prenatal Diagnosis, The First Hospital of Jilin University.

References

- [1] Wyandt HE, Tonk VS. Human chromosome variation: heteromorphism and polymorphism. Berlin: Springer; 2012.
- [2] Shaffer LG, Slovak ML, Campbell LJ. ISCN 2009: an international system for human cytogenetic nomenclature. Basel: Karger; 2009. p. 53–4.
- [3] Brothman AR, Schneider NR, Saikevych I, Cooley LD, Butler MG, Patil S, et al. Cytogenetic heteromorphisms: survey results and reporting practices of giemsa-band regions that we have pondered for years. *Arch Pathol Lab Med* 2006;130(7):947–9.
- [4] Sahin FI, Yilmaz Z, Yuregir OO, Bulakbasi T, Ozer O, Zeyneloglu HB. Chromosome heteromorphisms: an impact on infertility. *J Assist Reprod Genet* 2008;25(5):191–5.
- [5] Caglayan AO, Ozyazgan I, Demiryilmaz F, Ozgun MT. Are heterochromatin polymorphisms associated with recurrent miscarriage? *J Obstet Gynaecol Res* 2010;36(4):774–6.
- [6] Tu S, Rosenthal M, Wang D, Huang J, Chen Y. Performance of prenatal screening using maternal serum and ultrasound markers for Down syndrome in Chinese women: a systematic review and meta-analysis. *BJOG* 2016;123(Suppl 3):12–22.
- [7] Gong M, Shi H, Zhang YG, Ming L. Prenatal screening at 11–13+6 weeks in assisted reproductive technology singleton pregnancies and those conceived naturally. *J Obstet Gynaecol Res* 2015;41(10):1514–9.
- [8] Okuyama T, Yotsumoto J, Funato Y. Survey of second-trimester maternal serum screening in Japan. *J Obstet Gynaecol Res* 2013;39(5):942–7.
- [9] Lan RY, Chou CT, Wang PH, Chen RC, Hsiao CH. Trisomy 21 screening based on first and second trimester in a Taiwanese population. *Taiwan J Obstet Gynecol* 2018;57(4):551–4.
- [10] Lee FK, Chen LC, Cheong ML, Chou CY, Tsai MS. First trimester combined test for Down syndrome screening in unselected pregnancies – a report of a 13-year experience. *Taiwan J Obstet Gynecol* 2013;52(4):523–6.
- [11] Inan C, Sayin NC, Dolgun ZN, et al. Prenatal diagnosis of chromosomal polymorphisms: most commonly observed polymorphism on Chromosome 9 have associations with low PAPP-A values. *J Matern Fetal Neonatal Med* 2019;32(10):1688–95.
- [12] McGowan-Jordan J, Simons A, Schmid M. An international system for human cytogenomic nomenclature. Basel: S Karger; 2016.
- [13] Hong Y, Zhou YW, Tao J, Wang SX, Zhao XM. Do polymorphic variants of chromosomes affect the outcome of in vitro fertilization and embryo transfer treatment? *Hum Reprod* 2011;26(4):933–40.
- [14] Hu Zhu-Ming, Zhu Yu-Zhuo, Zhang Xin-Yue, Yang Yu, Liu Rui-Zhi, Li Fu-Biao. Clinical analysis of chromosome polymorphism in amniotic fluid of 60 fetuses. *Chin J Med Genet* 2015;32(5):741–4 [In Chinese].
- [15] Dong Y, Jiang YT, Du RC, Zhang HG, Li LL, Liu RZ. Impact of chromosomal heteromorphisms on reproductive failure and analysis of 38 heteromorphisms pedigrees in Northeast China. *J Assist Reprod Genet* 2013;30(2):275–81.
- [16] Dana M, Stoian V. Association of pericentric inversion of chromosome 9 and infertility in Romanian population. *Maedica (Buchar)* 2012;7(1):25–9.
- [17] Brothman AR, Schneider NR, Saikevych I, et al. Cytogenetic heteromorphisms: survey results and reporting practices of giemsa-band regions that we have pondered for years. *Arch Pathol Lab Med* 2006;130(7):947–9.
- [18] Akbas H, Isi H, Oral D, et al. Chromosome heteromorphisms are more frequent in couples with recurrent abortions. *Genet Mol Res* 2012;11(4):3847–51.
- [19] Broccoli D. Function, replication and structure of the mammalian telomere. *Cytotechnology* 2004;45(1–2):3–12.
- [20] Frenster JH, Herstein PR. Gene de-repression. *N Engl J Med* 1973;288(23):1224–9.
- [21] Nakatsu SL, Masek MA, Landrum S, Frenster JH. Activity of DNA templates during cell division and cell differentiation. *Nature* 1974;248(446):334–5.
- [22] Sipek Jr A, Panczak A, Mihalova R, et al. Pericentric inversion of human chromosome 9 epidemiology study in Czech males and females. *Folia Biol (Praha)* 2015;61(4):140–6.
- [23] Uehara S, Akai Y, Takeyama Y, Takabayashi T, Okamura K, Yajima A. Pericentric inversion of chromosome 9 in prenatal diagnosis and infertility. *Tohoku J Exp Med* 1992;166(4):417–27.
- [24] Boue J, Taillemite JL, Hazael-Massieux P, Leonard C, Boue A. Association of pericentric inversion of chromosome 9 and reproductive failure in ten unrelated families. *Humangenetik* 1975;30(3):217–24.
- [25] Yinon Y, Kingdom JC, ProctorLK, et al. Hypospadias in males with intrauterine growth restriction due to placental insufficiency: the placental role in the embryogenesis of male external genitalia. *Am J Med Genet A* 2010;152A:75–83.
- [26] Alkazaleh F, Chaddha V, Viero S, et al. Second-trimester prediction of severe placental complications in women with combined elevations in alpha-fetoprotein and human chorionic gonadotrophin. *Am J Obstet Gynecol* 2006;194(3):821–7.
- [27] Liang J, Zhang Y, Yu Y, Sun W, Jing J, Liu R. Effect of chromosomal polymorphisms of different genders on fertilization rate of fresh IVF-ICSI embryo transfer cycles. *Reprod Biomed Online* 2014;29(4):436–44.