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Endometriosis does not impact aneuploidy rates of products of conception in IVF population

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It has been debated whether endometriosis (EMS) adversely affects oocyte quality, potentially leading to a higher incidence of genetically unbalanced embryos or other egg factors that affect the developmental potential. In this study, we explored the effects of endometriosis on risk of chromosomally aberrant in miscarried products of conception (POC) after assisted reproductive treatment (ART), including fresh and frozen cycles. Miscarried POCs were collected from EMS patients ($N = 102$) and non-EMS patients ($N = 441$). Single nucleotide polymorphism (SNP) array analysis was conducted on all collected samples. Propensity score matching (PSM, ratio of 1:4) based on maternal age was applied in data analysis. Logistic regression analysis was performed to identify risk factors for chromosomal aberration-induced miscarriage between the two cohorts. A total of 228 (41.99% of 543) conceptuses were identified as having chromosomal aberrations. The results showed that women with EMS had a significantly lower antral follicle count (AFC) (10 ± 5 vs. 14 ± 7, $P < 0.01$) compared to the control group. Additionally, the EMS group had a relatively lower anti-Mullerian hormone (AMH), higher basal follicle stimulating hormone (FSH) and fewer oocytes, ($P > 0.05$). There was no significant difference in the chromosomal aberration rate of POCs between EMS and non-EMS groups (35.29% vs. 43.54%; odds ratio (OR) = 1.03, 95% confidence intervals (CIs) 0.79–1.35). This is the first study to show that EMS maybe associated with decreased ovarian reserve, but not related to chromosomal abnormalities in POCs. These results suggest that chromosomal abnormalities may not be the only cause of miscarriage in EMS patients.

Keywords Endometriosis, Single nucleotide polymorphism array, Miscarriage, Chromosomal abnormality, ART

Endometriosis (EMS) affects 10–15% of all women of reproductive age[1]. Women with EMS are referred for assisted reproductive treatment (ART) therapy to overcome infertility due to distorted anatomy[2] or an altered immune environment[3]. It has been debated whether EMS adversely affects oocyte quality, which could translate to a higher incidence of genetically unbalanced embryos or other egg factors affecting the developmental potential. Numerous correlation studies have been conducted on different endpoints and models during in vitro fertilization (IVF) / intracytoplasmic sperm injection (ICSI) follow-up. Previous studies have shown that EMS affects natural fertility through various mechanisms[1,4] and interferes with altered spindle configurations[5], poor oocyte quality, implantation failure and high abortion rate[6]. In contrast, more recent studies have reported that the oocyte quality and embryo quality, did not differ compared with the control groups[7]. Juneau et al. has shown that the aneuploidy rate of embryos from women with EMS were similar to those of controls[8]. A recent report suggested that there may be a minimal or no effect of oocyte quality on IVF outcomes in women with EMS in a donor oocyte cohort[9]. It remains unclear whether patients with EMS show poor reproductive outcomes due to their lower ovarian response or additional qualitative oocyte morbidity.

Previous studies have shown that 50% of pregnancy losses are due to embryonic chromosomal abnormalities[10]. Therefore, understanding the risk factors that contribute to miscarriages caused by chromosomal aberrations is vital for improving reproductive counseling and planning of ART therapy. Genetic testing has been proposed as

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1

a cost-effective reproductive screening and testing method for fetal genetic disorders in the evaluation of patients with recurrent pregnancy loss (RPL)[11–13]. It aids the patient and the physician in making joint strategies for fresh or frozen cycles of embryo transfer (ET)[14]. However, it remains unclear whether EMS affects the aneuploidy rates of products of conception (POCs) in the IVF population. Consequently, we carried out a retrospective observational cohort study to examine the rate of embryonic chromosomal anomalies in POCs from both EMS and disease-free patients using single nucleotide polymorphism (SNP) array analysis. We expected to determine the clinical value of embryonic chromosomal abnormalities in the POCs of females with EMS.

Methods

Study design

This retrospective analysis was performed using primary clinic data collected by the Clinical Reproductive Medicine Management System/Electronic Medical Record Cohort Database (CCRM/EMRCD) of Zhengzhou University Reproductive Medical Center. All data entry, management, and analyses were conducted at the same institution. The dataset included patients who experienced involuntary spontaneous miscarriage after successful ART therapy and had their miscarriage samples sent to our preimplantation genetic diagnosis (PGD) center in our fertility clinic for genetic analysis between January 2013 and January 2023. This study was approved by the Ethics Committee of the 1st Affiliated Hospital of Zhengzhou University and the written informed consent was obtained from all patients at their first consultation. The procedures used in this study adhered to the principles of the Declaration of Helsinki.

Study subjects

To reduce the influence of age-dependent chromosome anomalies, all cycles involving females aged > 38 were excluded, as were male partners aged > 45 years[15]. Additional exclusion criteria were as follows: (i) an abnormal chromosome karyotype for either member of the couple; (ii) a history of RPL (defined as 2 or more pregnancy losses according to American Society for Reproductive Medicine (ASRM) committee consensus (14); (iii) thyroid dysfunction; (iv) uterine factors such as submucosal fibroids, chronic endometritis, adenomyosis or submucosa myomas; (v) multiple pregnancies or donor oocyte cycles; and (vi) factors related to immunological disorders and genital malformations.

After exclusion, data on all women diagnosed with EMS ($n = 119$) or without EMS ($n = 1940$) were separated into two groups. Propensity score matching (PSM) (ratio of 1:4) was used in data analysis to tackle potential confounders when two groups differed systematically according to maternal age by a data manager. Due to security concerns, only the database after PSM were allowed to export from the archive. The remaining data cleansing was carried out by the researchers themselves.

SNP array analysis of POC

Spontaneous miscarriage was defined as the absence of fetal cardiac pulsation in the uterine cavity after the confirmation of clinical pregnancy. Once cautiously diagnosed, uterine cavity curettage was performed, and the obtained chorionic villi were routinely sent to the PGD center for genetic analysis to identify the etiology of this adverse reproductive outcome.

Chorionic villi were thoroughly separated from maternal decidua according to a previously published protocol[17] to avoid maternal genome contamination. DNA was extracted from the villi using an AllPrep DNA Mini Kit (Qiagen, Hilden, Germany). The extracted DNA was subjected to SNP analysis. SNP array analysis was performed using a Human CytoSNP-12v.21 Array (Illumina, San Diego, CA) as indicated by the manufacturer's instructions. Genome-Studio (Illumina 2011) and Karyo-Studio v1.4 were applied for data analysis. Copy number variants (CNVs) were mapped via the DGV database (http://dgv.tcag.ca/dgv/app/faq) to identify candidate pathogenic CNVs. All steps were double-checked by at least two experimental technicians. The interassay coefficient of variation (CV) was 3.5% (standard deviation, 2.1%). The primary outcome was frequency of genetic abnormalities in POCs.

Statistical analysis

In this study, PSM was used to balance the distributions of confounders between EMS and non-EMS groups, including maternal age, as patient age is the most influential confounder in determining the aneuploidy rate. After PSM, all demographic and IVF characteristics were compared between the two groups. Sample descriptive statistics were calculated using chi-square (χ^2) tests, t-tests, and Wilcoxon rank sum tests. Adjusted logistic regression analysis was performed to identify risk factors for chromosomal aberration-induced miscarriage between two groups. The confounders included maternal age, body mass index (BMI), basal follicle stimulating hormone (FSH), type of ET, type of embryo transferred etc. These variables were primarily selected a priori based on the clinical experience of the research team and the literature. In the multivariable model, covariates were selected if the covariate's $P < 0.1$ in univariate model. The adjusted odds ratio (aOR) for abnormal genetic rates of POCs were calculated from the logistic regression model Data were analyzed using the statistical software SPSS version 26.

Results

Flow chart of selecting patients was shown in Fig. 1, while the flow chart before applying PSM was shown in Supplementary Fig. 1. Finally, a total of 543 patients were enrolled in the final study. In EMS groups, around 94.1%) of them had previously undergone surgery for EMS. Patients in whom endometrioma was visualized in transvaginalsonography and sampled by cyst puncture, and EMS was subsequently diagnosed through histological analysis ($n = 6$)[4,16]. The remaining 441 patients were classified into the non-EMS group.
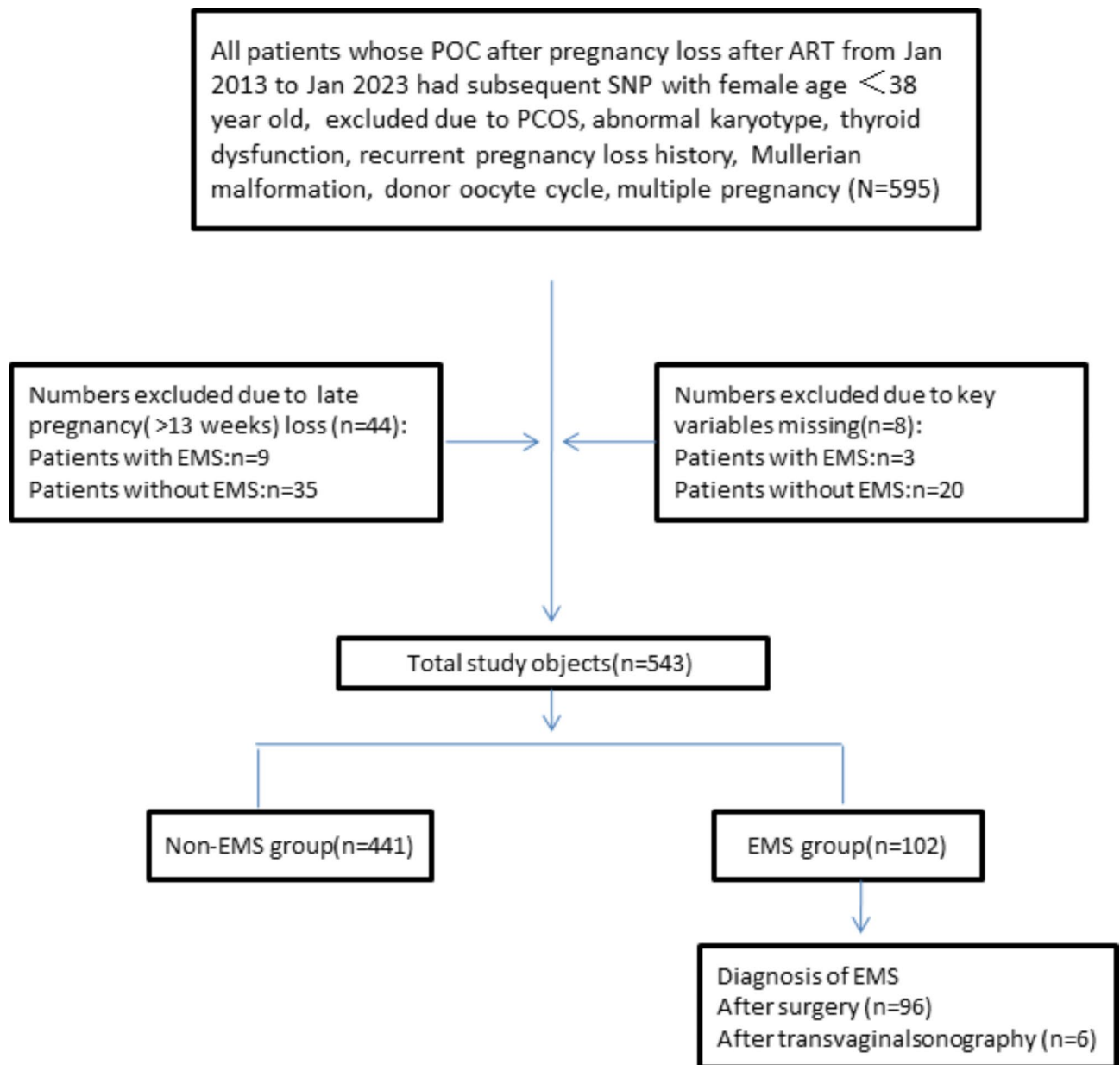
Fig. 1. Flow chart of the patients enrolled and the research framework after PSM. ART = assist reproductive technology; PCOS = polycystic ovary syndrome; POC = miscarried products of conception; SNP = single nucleotide polymorphism; EMS = endometriosis.

Demographics of all study patients

Table 1 shows the characteristics of EMS and non-EMS groups. Female age was comparable between the EMS group (31.2 ± 3.4 years) and the non-EMS group (31.3 ± 3.4 years, $P > 0.05$). No significant differences were observed for female BMI, either treating female BMI as a continuous or categorical variable (using 18.5, 25, and 30 as the cut-off values) between the two groups ($P > 0.05$). The EMS group exhibited a significantly lower basal antral follicle count (AFC) compared to the non-EMS group (10 ± 5 vs. 14 ± 7, $P < 0.01$). Additionally, the EMS group had a trend towards lower anti-Mullerian hormone (AMH) levels (2.82 ± 2.74 vs. 3.41 ± 2.10), lower number of oocytes retrieved (10.6 ± 5.7 vs. 11.9 ± 5.7), and higher basal FSH levels (7.90 ± 3.67 mIU/mL vs. 7.25 ± 6.56 mIU/mL) although those differences were not significant difference between the two groups ($P > 0.05$). They were also less likely to have a male cause of infertility (10.47% vs. 20.19%) and underwent fewer ICSI fertilization procedures (11.32% vs. 29.27%). No statistically significant differences were found in the rate of secondary infertility (49.5% vs. 54.88%), the rate of single embryo transferred (39.22% vs. 36.73%), or the proportions of cleavage embryo (64.71% vs. 62.36%) between two groups.

	EMS Group N = 102[1]	Control Group N = 441[1]	p-value[2]
Female Age			0.818
Mean ± SD	31.2 ± 3.4	31.3 ± 3.4	
Female BMI			0.287
Mean ± SD	22.5 ± 3.1	22.9 ± 3.0	
Female BMI Category, n (%)			0.536
≧ 18.5, < 25	74(72.55)	319(72.34)	
< 18.5	8(7.84)	21(4.76)	
≧ 25, < 30	19(18.63)	92(20.86)	
≧ 30	1(0.98)	9(2.04)	
AMH			0.064
Mean ± SD	2.82 ± 2.74	3.41 ± 2.10	
AFC			< 0.001**
Mean ± SD	10 ± 5	14 ± 7	
Basal FSH			0.181
Mean ± SD	7.90 ± 3.67	7.25 ± 6.56	
Oocytes Retrieved			0.146
Mean ± SD	10.6 ± 5.7	11.9 ± 5.7	
Infertility Type, n (%)			0.329
Primary Infertility	51 (50.50)	199 (45.12)	
Secondary Infertility	50 (49.50)	242 (54.88)	
Infertility Reason, n (%)			0.030*
Tube	43 (50.00)	185 (42.92)	
DOR	0 (0.00)	15 (3.48)	
Ovulation	0 (0.00)	10 (2.32)	
Male Factor	9 (10.47)	87 (20.19)	
Both	14 (16.28)	43 (9.98)	
Unexplain	20 (23.26)	91 (21.11)	
Fresh or Frozen, n (%)			0.484
Fresh Embryo	53 (51.96)	246 (55.78)	
Thawed Embryo	49 (48.04)	195 (44.22)	
Fertilization Method, n (%)			0.007**
IVF	47 (88.68)	174 (70.73)	
ICSI	6 (11.32)	72 (29.27)	
Type of Embryo, n (%)			0.658
D3	66 (64.71)	275 (62.36)	
D5	36 (35.29)	166 (37.64)	
No. of Embryo, n (%)			0.765
1	40 (39.22)	162 (36.73)	
2	62 (60.78)	279 (63.27)	
Abortion Week			0.363
Mean ± SD	8.83 ± 1.29	8.96 ± 1.34	
Chromosome of POC, n (%)			0.128
Normal chromosome	66 (64.71)	249 (56.46)	
Abnormal Chromosome	36 (35.29)	192 (43.54)	
Type of Abnormal Chromosomal Karyotype, n (%)			0.018*
Single Trisomy	20 (55.56)	125 (65.10)	
Trisomy and Dupliation/Deletion	4 (11.11)	8 (4.17)	
Continued			

	EMS Group N = 102[1]	Control Group N = 441[1]	p-value[2]
Multiple Trisomy	1 (2.78)	6 (3.13)	
Monosomy	1 (2.78)	19 (9.90)	
Mosaicism	4 (11.11)	17 (8.85)	
Complex Abnormalities	0 (0.00)	10 (5.21)	
Triploidy	6 (16.67)	7 (3.65)	

Table 1. Baseline and ART characteristics of EMS group and Control group. [1]n (%). [2]Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test. BMI = body mass index; ART = assisted reproductive technology; DOR = diminished ovarian reservation; POC = products of conception; AMH = antimullerian hormone; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; EMS = endometriosis; AFC = antral follicle count.; FSH = follicle stimulating hormone. * indicates $P < 0.05$, ** indicates $P < 0.01$.

	Univariable					Multivariable				
Characteristic	**N**	**Event N**	**OR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**OR[1]**	**95% CI[1]**	**p-value**
Female Age	543	228	1.13	1.08, 1.20	< 0.001	532	222	1.13	1.07, 1.19	< 0.001
Female BMI	543	228	0.98	0.92, 1.03	0.420	532	222	0.96	0.90, 1.01	0.142
basal FSH	532	222	0.99	0.95, 1.02	0.597	532	222	0.98	0.93, 1.01	0.279
AMH	420	158	0.98	0.89, 1.07	0.612					
GROUP										
Non-EMS	441	192	—	—						
EMS	102	36	0.71	0.45, 1.10	0.130					
AFC	537	226	0.97	0.94, 0.99	0.020					
Infertility Reason										
Tube	228	93	—	—						
Ovulation	10	3	0.62	0.13, 2.30	0.500					
DOR	15	2	0.22	0.03, 0.83	0.052					
Male Factor	96	41	1.08	0.67, 1.75	0.749					
Both	57	30	1.61	0.90, 2.90	0.108					
Unexplain	111	45	0.99	0.62, 1.57	0.965					
Infertility Type										
Primary Infertility	250	100	—	—						
Secondary Infertility	292	128	1.17	0.83, 1.65	0.367					
Fresh or Frozen										
Fresh Embryo	299	128	—	—		292	123	—	—	
Thawed Embryo	244	100	0.93	0.66, 1.31	0.668	240	99	1.27	0.86, 1.88	0.230
Type of Embryo										
D3	341	166	—	—		333	161	—	—	
D5/D6	202	62	0.47	0.32, 0.67	< 0.001	199	61	0.44	0.29, 0.65	< 0.001

Table 2. Univariate and multivariate analysis of influencing factors. [1]OR = Odds Ratio, CI = Confidence Interval. Number in data frame = 543, Number in model = 532, Missing = 11, AIC = 694.2, C-statistic = 0.66, H&L = Chi-sq (8) 11.17 ($p = 0.192$). BMI = body mass index; DOR = diminished ovarian reservation; AMH = antimullerian hormone; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; EMS = endometriosis; AFC = antral follicle count.; FSH = follicle stimulating hormone. * indicates $P < 0.05$, ** indicates $P < 0.01$.

EMS was not a risk factor for chromosomal aberrations in POCs

Univariate analysis indicated that maternal age, AFC, the type of ET (cleavage-stage or blastocyst) was significantly associated with embryonic aneuploidy in the POCs ($P < 0.05$). In contrast, EMS, BMI, AMH, and the number of embryos transferred did not show a significant association with embryonic aneuploidy in the POCs. The frequency of aneuploidy in POCs was 35.29% for EMS patients compared to 56.46% for non-EMS (aOR = 0.71, 95% confidence interval (CI), 0.45, 1.10, $P = 0.13$). Table 2 demonstrates that after multivariate analysis, only maternal age and type of ET had a significant effect on embryonic aneuploidy in the POCs.
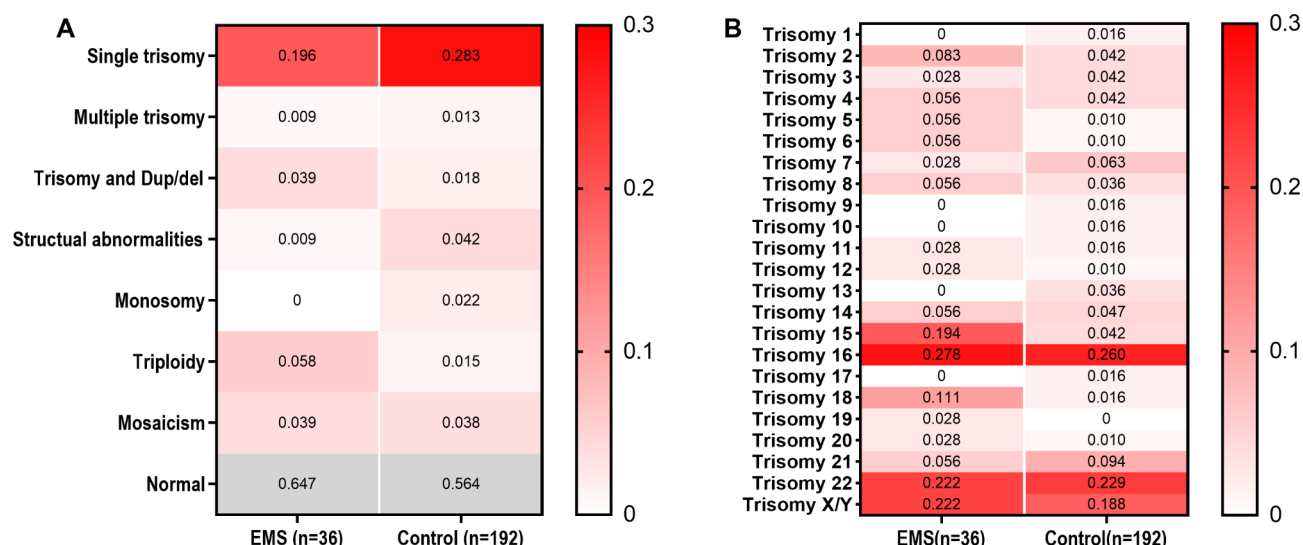
Fig. 2. Spectrum of abnormal chromosomal karyotype and frequency variation between EMS group and control group. Dup/del = duplication/deletion; EMS = endometriosis.

Overall results of the SNP array analysis of chorionic villi from spontaneous miscarriages

After cytogenetic analysis of POCs using an SNP array, 41.98% (n = 228) of the subjects showed abnormal karyotypes. The detected chromosomal abnormalities included trisomy, monosomy, triploid, structural abnormalities, and mosaicism (Fig. 2A), with trisomy as the most common type, accounting for 24.4% of the EMS group and 31.4% of the non-EMS group. Single-chromosome trisomy accounted for 80% of all trisomy cases. Trisomy 16 accounted for the most single-chromosome trisomy cases (27.8% in the EMS group and 26.0% in the non-EMS group), followed by trisomy 22 (22.2% in the EMS group and 22.9% in the non-EMS group) (Fig. 2B). Triploidy was found in 13 samples with 2 in the EMS group and 11 in the non-EMS group.

Discussion

During ART cycles, EMS is specially and cautiously managed at the time of fertilization assessment according to guidelines[4]. However, there has been significant debate over the past 30 years as to whether endometriosis is harm to oocytes and pregnancy outcome. In this study, we found that EMS did not increase the risks of above-mentioned adverse genetic outcomes in POCs. These data suggest that there may be a limited effect of oocyte quality on abortus outcomes in women with EMS.

To the best of our knowledge, the present study is the first to examine the genetic information from POCs of women with EMS using SNP array-based analysis. The examination of chorionic villi from the miscarriage samples provided evidence for a similar incidence of aneuploidy in POCs. This evidence suggests that EMS is not associated with the aneuploidy rate among POCs, and women with EMS are more likely to miscarry for reasons other than aneuploidy. EMS was not determined to be an independent risk factor for POCs to develop chromosomal aberrations, which may partly explain the comparable spontaneous abortion rates between EMS patients and non-EMS patients undergoing ART.

The hypothesis that oocyte quality might be hampered in women with EMS is not new, but the growing body of evidence is inconclusive on this point[1,17]. Our study found that EMS was not detrimental to aneuploid rate of abortion patients after ART cycles. Our finding supports previous studies on preimplantation genetic test for aneuploidy (PGT-A) outcomes comparing EMS and non-EMS, which found a lack of harmful effect to embryo outcomes[10–12]. Similar to our observations for the likelihood of chromosomal aberration in POCs, a recent report revealed no difference in reactive oxygen species (ROS) levels or the morphology of oocytes in ICSI cycles between healthy women and those with EMS[18]. Our finding supports the results from a recent report by Invernici et al.[17], who prospectively evaluated the possible detrimental effects of EMS on embryo development. They concluded that diminished follicular function due to an adjacent endometrioma and EMS does not adversely affect folliculogenesis, oocyte quality, and pregnancy outcome[19]. In a recent work based on an experimental model, the authors suggested that EMS negatively affected the meiotic spindle and chromosomes at the level of the cytoskeleton[20], and this suggestion was in agreement with our findings from this study pointing to a negative link between EMS and the formation of aneuploid gametes. In line with our results, previous studies have compared the aneuploidy rates in EMS patients with those of age-matched healthy patients[8]. Juneau et al.[8] concluded that the aneuploidy rates in EMS patients were equivalent to those of age-matched patients without EMS in a recent retrospective cohort. However, studies have reported lower pregnancy rates following IVF in women with EMS. Further exploration in needed to determine whether this low pregnancy rate could be attributable to a defect in endometrial receptivity[20] or abnormal embryo crosstalk[3]. However, based on the findings of the current study, the low pregnancy rate does not seem to be related to defective oocytes.

Emerging evidence suggest that EMS is detrimental to the ovarian reserve[21] and fertility[1]. In this study, women with EMS had a lower AMH and elevated FSH level, suggesting a decline in ovarian reserve, which was in accordance with previous literatures[19,22]. Increased oxidative stress, cytokines, the extent of cortical fibrosis were negatively correlated with the AMH levels and diminished ovarian reserve[23]. Diminished ovarian reserve and fewer eggs were harvested, resulting in limited embryos to be extended to blastocysts- after all, blastocyst formation rate is only 60%[24]. Patients with EMS were prone to transfer cleavage-stage embryos in clinics; then the EMS group had a lower proportion of D5 blastocyst-stage embryos. In addition, the primary infertility rate in the EMS group was higher. EMS can affect endometrial receptivity through abnormal immune cell populations and their abundance, steroid hormone responsiveness[3]. On the other hand, EMS causes pelvic adhesions, fallopian tube dysfunction and infertility or prolonged time to pregnancy[25].

POC's chromosomal anomalies may be related to a number of factors, especially age, a previous history of spontaneous abortion, multiple pregnancy[26], infertility factors such as polycystic ovary syndrome (PCOS), and the gestational day at which spontaneous abortion occurred[27]. In this study, we took care to avoid these confounding variables. To further adjust for confounding factors, we conducted logistic regression analyses to evaluate the association between EMS and embryonic aneuploidy. Maternal age is widely recognized as a predictive factor for aneuploid embryos[28], as is paternal age[29,30]. It is well documented that maternal age is strongly associated with a higher risk of fetal aneuploidy, an established cause of pregnancy loss[26]. Wang et al.[29] showed that paternal age was a negative risk factor for chromosomal-aberration-related miscarriages. Advanced paternal age was a suspected risk factor for increased levels of sperm deoxyribonucleic acid fragmentation, which is associated with pregnancy loss[31,32]. After we excluded aged mothers and fathers, our data still showed that maternal age (OR = 1.13, 95% CI 1.08 to 1.20) were detrimental to the aneuploidy rate of POCs. Furthermore, we took into account multiple potential confounding factors of the probability of chromosomal aberrations in POCs in our cohort. We observed similar high risks for day 3 embryos, in line with our previous results[14]. We showed that blastocysts in frozen cycles were associated with a lower incidence of aneuploidy rates in POCs than fresh cycles[14].

Our study had several strengths. Our study included a large cohort of women with singleton pregnancies, and it took into account multiple potential maternal confounding factors. Another strength of the current study was the use of a single-center registry with POCs achieved with the use of comparable ART technology, which helps ensure consistency in treatment approach within the practice. Although our sample size is limited after matching for maternal age, the data we obtained were collected through long-term and meticulous follow-up, and the POCs specimens in this study are clinically precious and difficult to obtain. Therefore, we believe that our results are reliable and stable.

A potential limitation of our study is that the EMS group included patients with either a surgical diagnosis of EMS or an ultrasound diagnosis of persistent space-occupying disease. Therefore, this study was unable to stratify aneuploidy outcomes based on the stage or severity of EMS, as not all patients had surgical history documentation, so we were unable to assess the effect of the stage of EMS on pregnancy outcomes. Additionally, patients in the non-EMS cohort had not undergone laparoscopy, so patients with mild EMS who were lack of specific symptoms may have been included in the control group. Another limitation was that we collected only data on primary infertility, not the exact history of miscarriage, which seemed to be associated with cytogenetic results of spontaneous early miscarriages[26]. This study was of retrospective design; thus, potential bias factors such as smoking, alcohol consumption cannot be fully addressed and identified. Given we only enrolled individuals who have experienced miscarriages, along with POCs that were submitted for examination, we therefore did not specifically collect data on miscarriage rates. We used SNP array analysis, not next-generation sequencing (NGS), to detect chromosomal abnormalities in POCs; therefore, the monogenic etiology of pregnancy loss may have been missed[33]. However, aneuploidy in miscarriage tissue was the leading cause of early pregnancy loss. Compared to NGS technology, SNP technology offers a superior cost-benefit analysis and is more suitable for general chromosomal aneuploidies screening. Last, SNP analysis was executed from the year 2016, all the POC test were comparable in two cohorts equally.

In conclusion, our study found that EMS may have limited negative impact on oocyte quality in abortion cycles in patients with IVF treatment. Instead, maternal factors may play more important roles in this condition. Thus, the present data provides further support for the hypothesis that EMS is associated with indicators of lower ovarian reserve. Further studies are needed to explore whether the presence of EMS is associated with a poor clinical outcome which would help with optimizing treatment outcomes.

Ethics declarations
All study methods were approved by Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and were performed in accordance with relevant guidelines and regulations. All subjects enrolled in the study gave written formal consent to participate. The procedures used in this study followed the principles of the Declaration of Helsinki.

Data availability
The datasets analyzed during the current study are available in the link: https://pan.baidu.com/s/1kaSKgxWWk o2XrkOb97J1ag with code asdf.

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Author contributions

HK contributed to the concept and design of the study; WF provided the data analysis; TY collected the data; LD interpreted the data. HK drafted the manuscript. All authors reviewed the final draft and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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