Association Between Menstrual Patterns and Adverse Pregnancy Outcomes in Patients with Polycystic Ovary Syndrome Undergoing in Vitro Fertilization/Intracytoplasmic Sperm Injection Embryo Transfer Cycles with The Long-Acting Long-Term Follicular Phase: A Retrospective Analysis

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Research

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Abstract

Background

Menstrual patterns of patients with polycystic ovary syndrome (PCOS) is considered to be related to metabolism, but no study has analyzed the outcome of in vitro fertilization in patients with PCOS who have different menstrual patterns. This study aimed to observe the outcomes of in vitro fertilization in patients with PCOS with different menstrual patterns and infertility who used the long-acting long-term follicular phase

Methods

This was a retrospective analysis of the first cycle of in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) at the Reproductive Medicine Center of the First Affiliated Hospital of Zhengzhou University from January 2017 to December 2019. The clinical data of 1620 patients with PCOS with oligomenorrhea or amenorrhea in the long-acting regimen. According to menstrual patterns, they were divided into the oligomenorrhea group and the amenorrhea group. Clinical characteristics, pregnancy outcome and fetal birth weight were compared between both groups. According to the pregnancy outcome of clinical pregnancy, participants were divided into the normal pregnancy group and the unfavorable pregnancy group. Logistic regression was used to analyze the relationship between menstrual patterns and the relevance of adverse pregnancy outcomes.

Results

Clinical pregnancy rates of patients with PCOS treated using long-acting long-term follicular phase were similar between the two groups (76.86% vs. 76.86%, p = 0.999). However, the incidence of adverse pregnancy outcomes in the amenorrhea group was higher than that in the oligomenorrhea group (p = 0.009). The incidences of macrosomia and very low birth weight in infants were also higher. Adjustment for confounding factors showed that menstrual patterns could influence the occurrence of adverse pregnancy outcomes (odds ratio = 0.643; 95% confidence interval, 0.406–0.961; p = 0.045). The body mass index, endometrial thickness on the day of hCG administration, and the number of eggs harvested were also independent predictors of poor pregnancy outcomes.

Conclusion(s):

Among PCOS patients with different menstrual patterns, IVF/ICSI assisted pregnancy can achieve similar pregnancy rates. However, patients with PCOS who have amenorrhea have a higher incidence of adverse pregnancy outcomes than those with oligomenorrhea. Perinatal surveillance should be strengthened during pregnancy to reduce the incidence of maternal and neonatal adverse outcomes.

Background

Polycystic ovary syndrome (PCOS) is a common reproductive and endocrine disease among women of childbearing age. It is characterized by abnormal ovulation (sparse ovulation or anovulation [ANOV]), changes in polycystic ovary, and hyperandrogenism (HA) [1]. Studies have shown that the incidences of abortions, premature births, and pregnancy complications among PCOS patients are relatively high; therefore, it is necessary to strengthen clinical perinatal monitoring [2]. Currently, conclusions on related risk factors that lead to adverse pregnancy outcomes in patients with PCOS are not completely consistent. Some of these risk factors include age, body mass index (BMI), and the application of assisted reproductive technology [3]. Patients with PCOS have heterogeneous clinical presentations. The commonest menstrual manifestation is oligomenorrhea or amenorrhea, and there are differences in the levels of sex hormones and metabolic factors among patients with different menstrual patterns [4]. Studies have shown that menstrual disorders in patients with PCOS are caused by insulin resistance and HA, which indicates that menstrual patterns may be used as a direct clinical observation index of the severity of metabolic disorders [5]. Currently, there is no research on the outcomes of in vitro fertilization (IVF) in patients with PCOS that have different menstrual patterns, and it is unclear whether menstrual patterns affect the pregnancy outcomes of patients. In recent years, due to improvements in endometrial receptivity and the pregnancy rate of fresh cycle embryo transfer, prolonged follicular phase programs have been applied at some reproductive medicine centers in China [6]. The present study retrospectively analyzed the pregnancy outcomes of patients with PCOS that have oligomenorrhea or amenorrhea during prolonged follicular phases assisted by IVF/intracytoplasmic sperm injection (ICSI), and the related risk factors for adverse pregnancy outcomes. This analysis further aims to enable clinicians to strengthen the treatment of high-risk groups, as perinatal monitoring can reduce the incidence of maternal and infant adverse outcomes.

Materials And Methods

Study design and patients

This retrospective cohort study was approved by the Ethics Review Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was waived due to the retrospective nature. The selected patients underwent IVF/oocyte therapy at the Reproductive Medicine Center of the First Affiliated Hospital of Zhengzhou University from January 2017 to December 2019. The inclusion criteria were: (1) patients receiving IVF/ICSI in the first cycle, (2) long-acting long-term follicular phase, (3) age < 40 years, and (4) patients with oligomenorrhea or amenorrhea diagnosed with PCOS according to the Rotterdam criteria. The exclusion criteria were: (1) patients who did not undergo egg harvesting due to personal reasons, (2) preimplantation genetic diagnosis or preimplantation genetic screening (PGD/PGS), (3) endometriosis, adenomyosis, intrauterine adhesions, uterine malformations, surgical history of ovarian cyst, hydrosalpinx, pelvic tuberculosis, diabetes, and thyroid dysfunction, and (4) receipt of donor eggs. We classified PCOS according to menstrual patterns as documented in the new classification of the causes of abnormal uterine bleeding in non-pregnant women of childbearing age (PALM-COEIN) system

published by the International Federation of Gynecology and Obstetrics in 2011 [7]. The patients were classified into the oligomenorrhea group (menstrual cycle > 35 days) and amenorrhea group (menstrual cycle > 180 days) (Fig. 1).

Ivf/icsi Protocols

Downregulation regimen

On the second to third days of the menstrual cycle, 3.75 mg of a long-acting gonadotropin-releasing hormone agonist (GnRH-a; The Ipsen Group, Dauphine, France) was administered to achieve downregulation. After 30–42 days, the down-regulating standard was reached (no ovarian cyst with diameter > 10 mm, an estradiol level of < 183 pmol/L, and a luteinizing hormone [LH] level < 3 IU/L), and controlled ovarian hyperstimulation was performed.

Ovulation induction

Ovarian induction therapy was administered according to BMI and the level of anti-Müllerian hormone (AMH) was used to determine the dosage of gonadotropins (Gonal-f; Merck Serono, Switzerland or Plycon; Organon, Netherlands). According to follicle size and hormone levels, we adjusted the dosage of gonadotropins and decided whether to add on human menopausal gonadotropin (LeBold, Zhuhai Livzon Pharmaceutical, China).

HCG injection and corpus luteum support standard

We administered 250 μg of Azer (Merck Serono, Italy) and 2000 IU of hCG (Zhuhai Livzon Pharmaceutical) when the diameter of one dominant follicle was ≥ 20 mm, the diameters of three follicles were ≥ 17 mm, or two-thirds of the follicles had diameters ≥ 16 mm. The eggs were harvested under vaginal ultrasound guidance 36–37 h after the injections were administered.

Follow-up of patients

In terms of following up pregnancy outcomes, 14 days after embryo transfer, blood was drawn for β-hCG determination, and follow-up was continued until 35 days after transplantation. Clinical pregnancy was diagnosed when an ultrasonic examination revealed a gestational sac. Fetal nuchal translucency examination was performed at 12 weeks of pregnancy (9–10 weeks after embryo transfer) and prenatal care was provided at the department of obstetrics. During the perinatal period, trained nurses provided follow-up via telephone. Standardized questionnaires were used to collect information on perinatal complications, gestational age, birth date, mode of delivery, neonatal sex and birth weight, diseases among newborns, treatment, and prognosis. The follow-up information was recorded in detail and stored in the electronic medical records together with the previous treatment information. The research data were extracted from the electronic database of our hospital.

Laboratory results and Clinical outcomes

The main outcomes of this study were adverse pregnancy outcomes, which included premature delivery, miscarriage, and complications of pregnancy (gestational diabetes, hypertension in pregnancy, and premature rupture of membranes). Hypertension in pregnancy included elevated blood pressure during pregnancy (blood pressure ≥ 140/90 mmHg recorded at least twice after 20 weeks of pregnancy, more than 4 hours apart), pre-eclampsia (hypertension in pregnancy and the concurrent onset of proteinuria and/or other organ dysfunction), and eclampsia [8]. Gestational diabetes mellitus was defined as abnormal glucose metabolism during pregnancy, without a pre-pregnancy diagnosis of diabetes [9]. Premature rupture of membranes referred to the spontaneous rupture of membranes before labor. Babies with low birth weight (LBW) and very LBW (VLBW) were born with birth weights less than 2500 g and 1500 g, respectively. Macrosomia referred to a birth weight of more than 4000 g.

Statistical analysis

Data with normal distributions are reported as means and standard deviations, and between-group comparisons were performed using the *t*-test. Count data are expressed as proportions (%) and between-group comparisons were performed using the chi-squared test. Variables with statistically significant results in the univariate *t*-tests and chi-squared tests were included in the multivariate logistic regression analysis. All statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA). Analysis items with p-values of < 0.05 were considered statistically significant.

Results

Comparison of patients' general characteristics and ovulation induction information

A total of 1620 patients were enrolled in this study. Among them, 1402 were included in the oligomenorrhea group and 218 patients were included in the amenorrhea group. The primary infertility rate, duration of infertility, BMI, LH/FSH level, AMH level, gonadotropin use time, and the total amount of gonadotropin administered were significantly greater in the amenorrhea group ($p < 0.05$). The daily intima thickness after hCG administration was significantly lower in the amenorrhea group ($p < 0.05$), and there were no significant differences in the remaining indicators between the two groups ($p > 0.05$) (Table 1).

Table 1
Comparison of patients'general characteristics and ovulation induction information

Item	oligomenorrhea group (n = 1402)	amenorrhea group (n = 218)	P value
Age (year)	28.61 ± 3.54	28.84 ± 3.679	0.358
Type of infertility			0.038
Primary infertility	916(65.34)	158(72.48)	
Secondary infertility	486(34.66)	60(27.52)	
Duration of infertility (year)	3.82 ± 2.53	4.31 ± 2.80	0.010
BMI(kg/m2)	24.16 ± 3.31	24.75 ± 3.25	0.015
E2(pg/ml)	49.47 ± 47.80	53.38 ± 49.09	0.280
P(ng/ml)	0.76 ± 1.86	0.75 ± 1.83	0.926
T(ng/ml)	0.87 ± 5.19	0.70 ± 3.63	0.651
LH/FSH (mIU/ml)	1.75 ± 1.26	2.19 ± 1.24	< 0.001
AMH(ng/ml)	7.93 ± 3.95	9.85 ± 4.87	< 0.001
Antral follicular count (n)	22.26 ± 4.83	22.52 ± 4.43	0.461
Starting dose of Gn(IU)	107.61 ± 18.03	108.20 ± 18.18	0.653
Length of stimulation (d)	14.48 ± 2.61	15.13 ± 2.78	0.001
Total dosage of Gn used (IU)	2117.23 ± 842.65	2308.54 ± 894.45	0.002
hCG injection day			
Endometrial thickness(mm)	12.43 ± 2.43	11.76 ± 2.16	< 0.001
E2 (pg/ml)	4022.39 ± 2261.54	4060.75 ± 2013.99	0.814
LH (mIU/ml)	0.72 ± 0.94	0.63 ± 0.65	0.168
P (ng/ml)	0.83 ± 0.54	0.81 ± 0.53	0.547

Numbers are mean ± standard deviation or N (% of response group); Gn = gonadotropin; BMI = body mass index; Gn = gonadotropin; E2 = estradiol; LH = luteinizing hormone; FSH = follicle stimulating hormone; P = progesterone; hCG = human chorionic gonadotropin

Laboratory results and Clinical outcomes

There was a significantly higher rate of pregnancy outcomes in the amenorrhea group than in the oligomenorrhea group (p = 0.009), as was the incidence of gestational diabetes mellitus (p = 0.014). The incidences of abortions, premature births, pregnancy-induced hypertension, and premature rupture of

membranes were higher in the amenorrhea group than in the oligomenorrhea group, but without statistical significance ($p > 0.05$). The incidences of macrosomia and VLBW in the amenorrhea group were significantly higher than those in the oligomenorrhea group ($p < 0.05$); however, there were no significant differences in the other indicators ($p > 0.05$) (Table 2).

Table 2
Laboratory results and Clinical outcomes

Item	oligomenorrhea group (n = 1402)	amenorrhea group (n = 218)	P value
No. of oocytes retrieved(n)	18.47 ± 7.686	18.69 ± 7.582	0.685
No. of 2PN(n)	11.23 ± 5.519	11.14 ± 5.567	0.835
No. of 2PN cleavage(n)	11.09 ± 5.474	11.02 ± 5.534	0.867
No. of good-quality embryo(n)	6.90 ± 4.46	6.95 ± 4.515	0.858
2PN fertilization rate (%)	15448(59.66)	2418(59.34)	0.694
cleavage rate (%)	15260(98.78)	2392(98.92)	0.110
good-quality embryo rate (%)	9488(62.18)	1509(63.08)	0.393
Egg retrieval cycle outcome			
Abnormal fertilization rate(%)	2(0.14)	1(0.46)	0.313
Rate of none transplantable embryo(%)	22(1.57)	4(1.83)	0.772
Embryo transfer cancelation rate for OHSS (%)	450(32.10)	72(33.03)	0.784
Implantation rate (%)	821(60.15)	133(62.44)	0.524
Clinical pregnancy rate (%)	651(76.86)	103(76.86)	0.999
adverse pregnancy	200(30.72)	45(43.69)	0.009
abortion rate (%)	66(10.29)	16(15.53)	0.102
premature births rate(%)	91(13.98)	18(17.48)	0.348
GDM rate(%)	35(6.10)	12(13.79)	0.014
PIH rate(%)	33(5.75)	7(8.05)	0.467
PROM(%)	24(4.18)	6(6.90)	0.302
Live birth rate (%)	574(67.77)	87(64.93)	0.514
Gestational week of childbirth (d)	37.83 ± 2.06	37.45 ± 2.67	0.127
Macrosomia rate (%)	64(8.96)	16(15.38)	0.039

Numbers are mean ± standard deviation or N (% of response group); 2PN = 2PN fertilization,OHSS = ovarian hyperstimulation syndrome; adverse pregnancy (including abortions, premature births, gestational diabetes mellitus, pregnancy-induced hypertension, and premature rupture of membranes); GDM = gestational diabetes mellitus; PIH = pregnancy-induced hypertension; PROM = premature rupture of membranes; LBW = low birth weight, VLBW = very low birth weight

Item	oligomenorrhea group (n = 1402)	amenorrhea group (n = 218)	P value
LBW rate (%)	123(17.23)	21(20.19)	0.458
VLBW rate (%)	9(1.26)	4(3.85)	0.049

Numbers are mean ± standard deviation or N (% of response group); 2PN = 2PN fertilization,OHSS = ovarian hyperstimulation syndrome; adverse pregnancy (including abortions, premature births, gestational diabetes mellitus, pregnancy-induced hypertension, and premature rupture of membranes); GDM = gestational diabetes mellitus; PIH = pregnancy-induced hypertension; PROM = premature rupture of membranes; LBW = low birth weight, VLBW = very low birth weight

Logistic regression assessment of perinatal outcomes

According to pregnancy outcomes, 754 clinically pregnant patients were divided into a normal pregnancy group and an adverse pregnancy group (including women who experienced abortions, premature births, gestational diabetes mellitus, pregnancy-induced hypertension, and premature rupture of membranes). Of these, 509 patients were included in the normal pregnancy group, while the adverse pregnancy group comprised 245 patients. There were no significant differences in age, duration of infertility, BMI, basic endocrinological characteristics, and gonadotropin dose between the two groups ($p > 0.05$). Compared with the normal pregnancy group, the amenorrhea rate was significantly higher in the adverse pregnancy outcome group, while the endometrial thickness and the number of eggs harvested on the day of hCG administration were significantly lower ($p < 0.05$). The multivariate analysis included variables from the univariate analysis of adverse pregnancy outcomes with statistically significant differences in menstrual patterns, endometrial thickness on the day of hCG administration, number of eggs harvested, and BMI, none of which were shown to present collinearity (variance inflation factor < 10). Upon incorporation into the binary logistic regression analysis, these variables were found to be statistically significant ($p < 0.05$) (Table 3).

Table 3
Logistic regression assessment of perinatal outcomes

	normal pregnancy (n = 509)	adverse pregnancy (n = 245)	OR(95%CI)	P value	aOR(95%CI)	P value
menstrual patterns(%)			0.572 (0.374,0.873)	0.010	0.624 (0.406,0.961)	0.032
oligomenorrhea	451(88.61)	200(81.63)				
amenorrhea	58(11.39)	45(18.37)				
Age (year)	28.44 ± 3.45	28.86 ± 3.44	1.036 (0.991,1.082)	0.119		
BMI(kg/m^2)	24.24 ± 3.36	24.75 ± 3.33	1.046 (1.000,1.095)	0.052	1.053 (1.005,1.103)	0.029
Duration of infertility (year)	3.90 ± 2.58	4.00 ± 2.91	1.013 (0.957,1.073)	0.653		
E_2 (pg/ml)	46.64 ± 41.63	50.53 ± 50.22	1.002 (0.999,1.005)	0.274		
P(ng/ml)	0.77 ± 1.85	0.70 ± 1.86	0.980 (0.898,1.069)	0.647		
T(ng/ml)	0.86 ± 4.95	0.94 ± 5.75	1.003 (0.975,1.032)	0.844		
LH/FSH(mIU/ml)	1.68 ± 1.10	1.74 ± 1.31	1.047 (0.920,1.192)	0.485		
AMH(ng/ml)	7.42 ± 3.66	7.38 ± 3.77	0.997 (0.956,1.039)	0.878		
Antral follicular count (n)	22.25 ± 4.54	21.72 ± 5.36	0.978 (0.949,1.009)	0.159		
Length of stimulation (d)	14.44 ± 2.67	14.60 ± 2.52	1.024 (0.966,1.085)	0.423		

Numbers are mean ± standard deviation or N (% of response group); adverse pregnancy (including abortions, premature births, gestational diabetes mellitus, pregnancy-induced hypertension, and premature rupture of membranes)

	normal pregnancy (n = 509)	adverse pregnancy (n = 245)	OR(95%CI)	P value	aOR(95%CI)	P value
Total dosage of Gn used (IU)	2162.23 ± 900.59	2284.08 ± 862.93	1.000 (1.000,1.000)	0.078		
hCG injection day						
Endometrial thickness (mm)	12.68 ± 2.25	12.21 ± 2.35	0.912 (0.853,0.976)	0.008	0.910 (0.849,0.975)	0.007
E_2 (pg/ml)	3475.94 ± 1815.78	3228.54 ± 1536.82	1.000 (1.000,1.000)	0.068		
LH(mIU/ml)	0.77 ± 1.06	0.71 ± 0.78	0.931 (0.784,1.106)	0.416		
P(ng/ml)	0.73 ± 0.47	0.73 ± 0.45	1.039 (0.746,1.446)	0.822		
No. of oocytes retrieved(n)	16.12 ± 5.60	15.22 ± 5.81	0.972 (0.945,0.999)	0.040	0.968 (0.941,0.995)	0.020
Numbers are mean ± standard deviation or N (% of response group); adverse pregnancy (including abortions, premature births, gestational diabetes mellitus, pregnancy-induced hypertension, and premature rupture of membranes)						

Discussion

The characteristics of PCOS, such as androgen excess, obesity, insulin resistance, and abnormal metabolism, may increase the risk of obstetric and neonatal complications [11]. Many studies have shown that PCOS is related to adverse perinatal outcomes, such as gestational diabetes mellitus [12], premature rupture of membranes [13], and pregnancy-induced hypertension [14]. In addition, PCOS in pregnancy is also associated with adverse neonatal outcomes, and an increase in the incidences of premature delivery, intrauterine growth restriction, abnormal birth weight (smaller or greater than gestational age infants), and admission to the neonatal intensive care unit [15]. After adjusting for confounding factors in the logistic regression analysis, we identified BMI, menstrual pattern, endometrial thickness on the day of hCG administration, and the number of eggs harvested among PCOS patients who received IVF/ICSI-assisted pregnancy, as well as the incidences of abortions, premature births, and pregnancy complications, as independent risk factors for adverse pregnancy outcomes.

Among patients with PCOS, excessive androgen levels interfere with normal follicular development and result in the stagnation of follicular development or even atresia. Excessive androgen levels typically lead

to oligomenorrhea or amenorrhea [16], and excessive levels of testosterone or its metabolites can also cause insulin resistance in female adipocytes through androgen receptors [17]. This further reduces the secretion of insulin-sensitive fat factor and adiponectin, and leads to fat accumulation and obesity [18]. In our study, the BMI of patients with amenorrhea was higher than that of patients with oligomenorrhea, and BMI was an independent risk factor for adverse pregnancy outcomes. A meta-analysis of 40 observations and investigations indicated that gestational diabetes mellitus occurred in PCOS patients with migraines with aura. The increased incidence of adverse perinatal outcomes, such as eclampsia and preterm birth is related to BMI [19], consistent with the results of our study. However, some researchers believe that perinatal complications, such as gestational diabetes mellitus and gestational hypertension in PCOS patients, are affected by PCOS itself and have nothing to do with BMI [20, 21]. To sum up, as an intuitive clinical observation index, BMI may be used as a predictor of adverse pregnancy outcomes among PCOS patients, but not in isolation.

Currently, the influence of different PCOS phenotypes on the occurrence of adverse pregnancy outcomes remains controversial [3]. A recent meta-analysis showed that the cumulative pregnancy rate of the PCO + HA + oligoovulation group was lower than that of the PCO + oligoovulation group [22]. A prospective cohort study showed that PCOS patients with a hyaluronic acid + menstrual disorder + PCO phenotype had a higher risk of adverse maternal and infant outcomes than those without the menstrual disorder phenotype [23]. A study of patients with PCOS with normal or rare menstruation and natural pregnancies showed that the risk of pregnancy complications in patients with PCOS may be affected by menstrual patterns, while the risk of pregnancy complications in patients with normal ovulation was similar to that of the normal population; however, no analysis was conducted among patients with PCOS who had amenorrhea [11]. The focus of this study was to compare patients with PCOS that had amenorrhea and those with oligomenorrhea. The results showed that the incidence of adverse pregnancy outcomes (abortions, premature births, and pregnancy complications) and abnormal newborn weight (VLBW) was higher in patients with amenorrhea than in patients with oligomenorrhea. The rates of adverse outcomes in the amenorrhea group were high, suggesting that the menstrual pattern of patients with PCOS affects maternal and fetal outcomes. Among patients with PCOS, the increased risk of pregnancy complications and abnormal birth weight may be due to placental damage during pregnancy [24]. Patients with PCOS who have abnormal menstruation, particularly those with amenorrhea, should receive more attention in terms of perinatal monitoring. Their management and follow-up should also be strengthened to avoid complications, such as gestational diabetes mellitus and abnormal weight of newborns.

The increased AMH production by granulosa cells in patients with PCOS can inhibit the expression of aromatase RNA in granulosa cells, reduce the transformation of androgens to estrogens, and increase the level of androgens in follicles [25]. In our study, patients with amenorrhea had higher AMH levels compared to those with oligomenorrhea. Studies have shown that patients with PCOS who have elevated AMH levels have more obvious endocrine and lipid metabolism disorders, suggesting that AMH can predict the severity of insulin resistance and HA [26]. Another retrospective study divided patients with PCOS into groups according to menstrual patterns (regular menstruation, hypomenorrhea, and

amenorrhea). There were significant differences in ^{18}F-fluorodeoxyglucose uptake, homeostatic model assessment of insulin resistance results, and triglyceride levels among the three groups, suggesting that menstrual patterns can be used as proxies of glucose and lipid levels among patients with PCOS. They can also be used as the simplest and most direct indicator of abnormal metabolism [27]. Metformin may improve endometriosis by upregulating the expression of glutamate transporter 4 in the endometrium of patients with PCOS [28]. Other studies have shown that the level of 20-hydroxyeicosatetraenoic acid (HETE), a metabolite of arachidonic acid, is positively correlated with obesity and insulin resistance [29], and abnormal HETE levels may lead to gestational diabetes mellitus [30] and gestational hypertension [31]. Therefore, in patients with amenorrhea, more severe metabolic disorders may cause abnormal elevations in HETE levels, leading to complications during pregnancy.

According to the National Institutes of Health standard or Rotterdam standard—a retrospective study of patients with PCOS who have different phenotypes and normal control groups [32] compared patients with the (ANOV + HA or PCO) phenotype to those with the (PCO + ANOV or HA) phenotype—compared to the normal control group, the uterine volume and endometrial thickness of the type group were smaller, and this indicated that different phenotypes of PCOS patients affected the uterine volume and endometrial thickness [33]. The results showed that after adjusting for confounding factors, the endometrial thickness on the day of hCG administration was an important factor that affected the perinatal outcome and neonatal birth weight (odds ratio, 0.89; 95% confidence interval, 0.80–0.99) [34]. Intrauterine studies of poor outcomes such as thin membrane thickness leading to fetal growth restriction, premature delivery, and an increased incidence of small for gestational age infants showed that the occurrence of these phenomena may be related to the decline in trophoblast cell invasion and abnormal spiral arterial remodeling [35].

In the present study, we found that the number of eggs harvested was an independent risk factor for adverse pregnancy outcomes. A retrospective analysis of 65,868 single live births showed that harvesting too many eggs during IVF can lead to premature birth and LBW, which may be due to abnormal ovarian function or changes in the endometrial environment caused by the high levels of physiological hormones [36]. Endometrial dysfunction and abnormal trophoblast invasion and implantation may cause abortions and pregnancy complications in patients with PCOS [37].

In this study, the relationship between menstrual patterns among patients with PCOS and IVF/ICSI-assisted pregnancy outcomes were analyzed for the first time. It was proven that menstrual patterns were an independent risk factor for adverse pregnancy outcomes (including abortions, premature births, and pregnancy complications). Furthermore, to reduce the impact of different items on pregnancy outcomes, we only included patients who received the long-acting long-term follicular phase.

Simultaneously, our study had some limitations. We performed only a retrospective study, which did not consider all confounding factors. Most newborn data were collected through telephone follow-up rather than direct access to medical records, which might have led to a lower incidence of neonatal

abnormalities than the actual incidence. Thus, large sample, multicenter, prospective studies are still needed to confirm our findings.

Conclusions

In summary, our data showed that the basic characteristics and perinatal outcomes of patients with PCOS with varying menstrual patterns are different. The adverse maternal and neonatal outcomes among patients with amenorrhea are higher than those of patients with oligomenorrhea. Thus, during assisted reproduction, individualized treatment should be carried out according to differences in patients' characteristics. Attention should also be paid to perinatal monitoring of patients with amenorrhea to reduce the occurrence of adverse outcomes among mothers and infants.

Abbreviations

PCOS: polycystic ovary syndrome

IVF/ICSI: in vitro fertilization/intracytoplasmic sperm injection

HA: hyperandrogenism

BMI: body mass index

AMH: anti-Müllerian hormone

LBW: low birth weight

VLBW: very low birth weight

PGD/PGS: preimplantation genetic diagnosis or preimplantation genetic screening

aOR: Adjusted odds ratio

CI: Confidence interval

E_2: Estradiol

hCG: Human chorionic gonadotrophin

Declarations

[Ethics approval and consent to participate]

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was waived due to the retrospective nature, and patients' data were used anonymously.

[Consent for publication]

Not applicable.

[Availability of data and materials]

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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[Authors' contributions]

JZ contributed to the conception of study. TY was responsible for work designing, statistical analyses performing and manuscript writing. DW contributed to revising the manuscript. YC contributed to collecting data. All authors contributed to the article and approved the submitted version.

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[Conflict of interest]

The authors declare that they have no competing interests.

References

1. de Medeiros SF, Rodgers RJ, Norman RJ. Adipocyte and steroidogenic cell cross-talk in polycystic ovary syndrome. Hum Reprod Update. 2021;00(0):1–26.
2. Helvaci N, Yildiz BO. Polycystic ovary syndrome and aging: Health implications after menopause. Maturitas. 2020;139:12–9.
3. Liu S, Mo M, Xiao S, Li L, Hu X, et al. In VitroPregnancy Outcomes of Women With Polycystic Ovary Syndrome for the First Fertilization Treatment: A Retrospective Cohort Study With 7678 Patients. Front Endocrinol. 2020;11:575337.
4. Li R, Zhang Q, Yang D, Li S, Lu S, et al. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Human reproduction. 2013;28(9):2562–9.
5. Ezeh U, Ezeh C, Pisarska MD, Azziz R. Menstrual dysfunction in polycystic ovary syndrome: association with dynamic state insulin resistance rather than hyperandrogenism. Fertility sterility. 2021;115 NO:6.

6. Ren J, Sha A, Han D, Li P, Geng J, et al., Does prolonged pituitary down-regulation with gonadotropin-releasing hormone agonist improve the live-birth rate in in vitro fertilization treatment? Fertility and sterility, 2014. 102(1): p. 75–81.
7. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. International journal of gynaecology obstetrics, 2011. 113(1): 3–13.
8. Gestational Hypertension and Preeclampsia. ACOG Practice Bulletin, Number 222. Obstetrics gynecology. 2020;135(6):e237–60.
9. American Diabetes Association. Standards of Medical Care in Diabetes-20202. Classification and Diagnosis of Diabetes. Diabetes Care. 2020;43:S14–31.
10. Oh KJ, Romero R, Park JY, Hong JS, Yoon BH. The earlier the gestational age, the greater the intensity of the intra-amniotic inflammatory response in women with preterm premature rupture of membranes and amniotic fluid infection by Ureaplasma species. Journal of perinatal medicine. 2019;47(5):516–27.
11. Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, et al. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015;21(5):575–92.
12. Reyes-Muñoz E, Castellanos-Barroso G, Ramírez-Eugenio BY, Ortega-González C, Parra A. The risk of gestational diabetes mellitus among Mexican women with a history of infertility and polycystic ovary syndrome. Fertility sterility. 2012;97(6):1467–71.
13. Yamamoto M, Feigenbaum SL, Crites Y, Escobar GJ, Yang J, et al. Risk of preterm delivery in non-diabetic women with polycystic ovarian syndrome. Journal of perinatology. 2012;32(10):770–6.
14. Sha T, Wang X, Cheng W, Yan Y. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. Reproductive biomedicine online, 2019. 39(2): p. 281–293.
15. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, et al. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006;12(6):673–83.
16. Mauvais-Jarvis F. Estrogen and androgen receptors: regulators of fuel homeostasis and emerging targets for diabetes and obesity. Trends in endocrinology metabolism. 2011;22(1):24–33.
17. Corbould A. Chronic testosterone treatment induces selective insulin resistance in subcutaneous adipocytes of women. J Endocrinol. 2007;192(3):585–94.
18. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981–1030.
19. Yu HF, Chen HS, Rao DP, Gong J. Association between polycystic ovary syndrome and the risk of pregnancy complications: A PRISMA-compliant systematic review and meta-analysis. Medicine. 2016;95(51):e4863.
20. Li GH, Fan L, Zhang L, Liu XW, Sun CJ, et al. Clinical characteristics and perinatal outcomes of non-overweight/obese pregnant women with polycystic ovary syndrome. Zhonghua yi xue za zhi. 2011;91(39):2753–6.

21. Bordewijk EM, Ng KYB, Rakic L, Mol BWJ, Brown J, et al. Laparoscopic ovarian drilling for ovulation induction in women with anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev. 2020;2:CD001122.
22. Ma L, Cao Y, Ma Y, Zhai J. in vitroAssociation between hyperandrogenism and adverse pregnancy outcomes in patients with different polycystic ovary syndrome phenotypes undergoing fertilization/ intracytoplasmic sperm injection: a systematic review and meta-analysis. Gynecological endocrinology, 2021: p. 1–8.
23. Foroozanfard F, Asemi Z, Bazarganipour F, Taghavi SA, Allan H, et al. Comparing pregnancy, childbirth, and neonatal outcomes in women with different phenotypes of polycystic ovary syndrome and healthy women: a prospective cohort study. Gynecological endocrinology. 2020;36(1):61–5.
24. Kelley AS, Smith YR, Padmanabhan V. Narrative Review of Placental Contribution to Adverse Pregnancy Outcomes in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2019;104(11):5299–315.
25. Du DF, Li XL, Fang F, Du MR. Expression of anti-Müllerian hormone in letrozole rat model of polycystic ovary syndrome. Gynecological endocrinology. 2014;30(12):885–9.
26. Bakeer E, Radwan R, El Mandoury A, El Rahman AA, Gad M, et al. Anti-Müllerian Hormone as a Diagnostic Marker in Egyptian Infertile Polycystic Ovary Syndrome Females: Correlations with Vitamin D, Total Testosterone, Dyslipidemia and Anthropometric Parameters. Journal of medical biochemistry. 2018;37(4):448–55.
27. Strowitzki T, Capp E, von Eye Corleta H. The degree of cycle irregularity correlates with the grade of endocrine and metabolic disorders in PCOS patients. European journal of obstetrics, gynecology, and reproductive biology, 2010. 149(2): p. 178–81.
28. Zhai J, Liu CX, Tian ZR, Jiang QH, Sun YP. Effects of metformin on the expression of GLUT4 in endometrium of obese women with polycystic ovary syndrome. Biol Reprod. 2012;87(2):29.
29. Gilani A, Pandey V, Garcia V, Agostinucci K, Singh SP, et al. High-fat diet-induced obesity and insulin resistance in CYP4a14 mice is mediated by 20-HETE. American journal of physiology. 2018;315(5):R934–44.
30. Kuhn DC, Botti JJ, Cherouny PH, Demers LM. Eicosanoid production and transfer in the placenta of the diabetic pregnancy. Prostaglandins. 1990;40(2):205–15.
31. Llinás MT, Alexander BT, Capparelli MF, Carroll MA, Granger JP, Cytochrome P-450 inhibition attenuates hypertension induced by reductions in uterine perfusion pressure in pregnant rats. Hypertension (Dallas, Tex.: 1979), 2004. 43(3): p. 623-8.
32. Rotterdam ESHRE/ASRM-Sponsored PCOS, Consensus Workshop, Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility sterility. 2004;81(1):19–25.
33. Panidis D, Tziomalos K, Papadakis E, Vosnakis C, Betsas G, et al. Uterine volume and endometrial thickness in the early follicular phase in patients with polycystic ovary syndrome. Endocrine practice. 2014;20(6):540–7.

34. Chung K, Coutifaris C, Chalian R, Lin K, Ratcliffe SJ, et al. Factors influencing adverse perinatal outcomes in pregnancies achieved through use of in vitro fertilization. Fertility sterility. 2006;86(6):1634–41.
35. Oron G, Hiersch L, Rona S, Prag-Rosenberg R, Sapir O, et al. Endometrial thickness of less than 7.5 mm is associated with obstetric complications in fresh IVF cycles: a retrospective cohort study. Reprod Biomed Online. 2018;37(3):341–8.
36. Sunkara SK, La Marca A, Seed PT, Khalaf Y. Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 singleton live birth outcomes. Human reproduction. 2015;30(6):1473–80.
37. Palomba S, Piltonen TT, Giudice LC. Endometrial function in women with polycystic ovary syndrome: a comprehensive review. Hum Reprod Update. 2020;00(0):1–35.

Figures

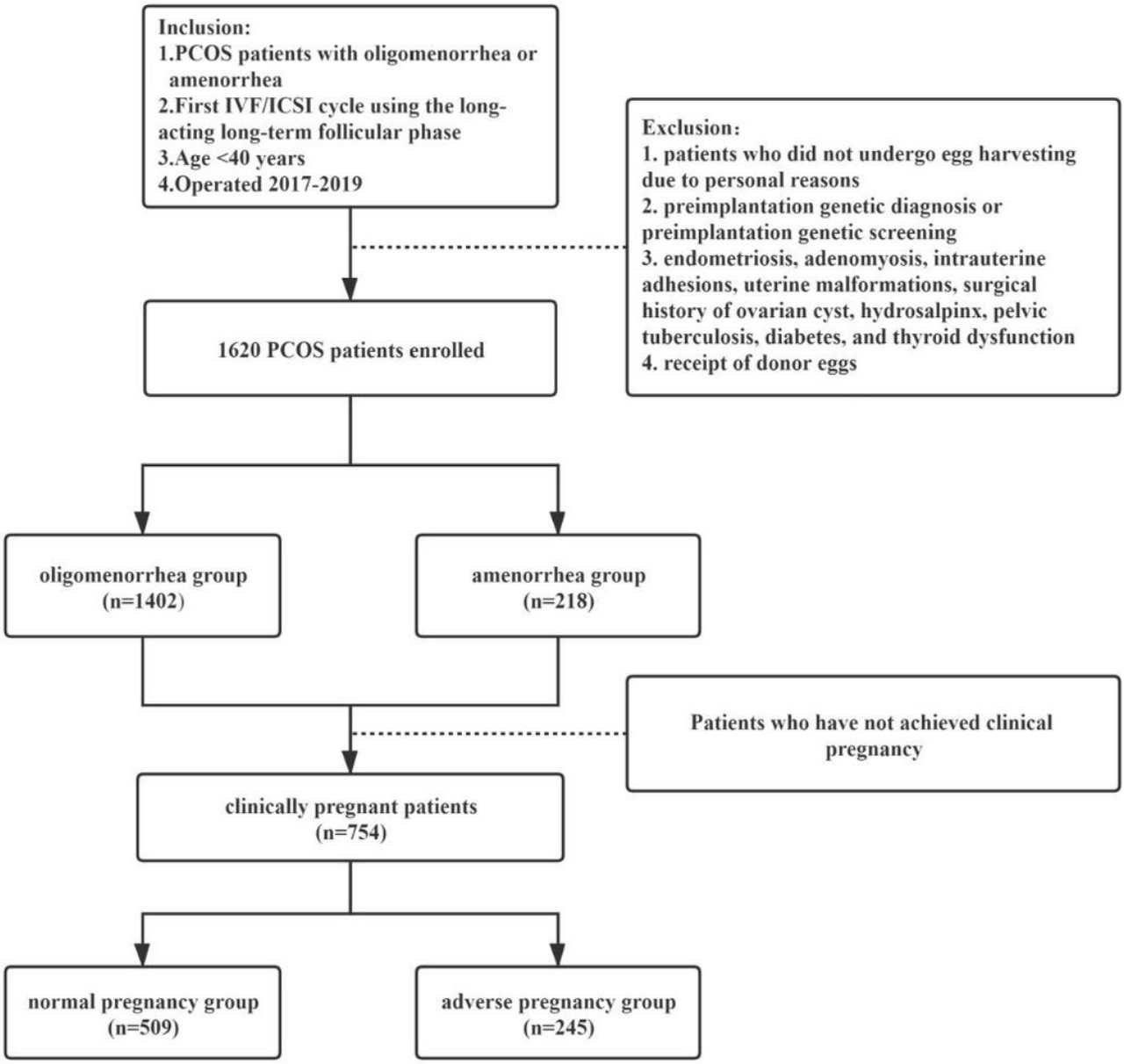

Figure 1

Flow chart depicting the patient selection.