Menstrual abnormalities effects on clinical features and in vitro fertilization pregnancy outcomes in women with polycystic ovarian syndrome

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BACKGROUND: The diagnostic criteria and phenotypes in polycystic ovary syndrome are heterogeneous. Currently, it is unclear how to assess a patient's prognosis based on the onset time of menstruation disturbance. Evidence on this topic is scarce and has mainly focused on menstrual patterns.

OBJECTIVE: This study aimed to assess the association between the onset time of menstrual disturbance and clinical features and in vitro fertilization pregnancy outcomes in patients with polycystic ovary syndrome.

STUDY DESIGN: Our study was a secondary analysis of data collected as part of a randomized controlled trial conducted to compare live birth rates between fresh embryo transfer and frozen embryo transfer in 1508 individuals with polycystic ovary syndrome. Here, 1500 participants were classified into 2 groups according to the onset time of menstrual disturbance: immediately after menarche (early group) and after at least 1 year of regular menstruation (late group). We compared the prepregnancy clinical features, variables of ovarian stimulation, pregnancy outcomes after the initial cycle of embryo transfer, and perinatal and neonatal complications in the 2 groups.

RESULTS: Compared with the late group, the early group had more antral follicles (32.00 [range, 27.25–39.50] vs 28.00 [range, 24.00–36.00]; *P*<.001), an elevated level of antimüllerian hormone (7.02 ng/mL [range, 3.60–11.47] vs 5.66 ng/mL [range, 3.65–8.92]; *P*=.024), a higher level of baseline luteinizing hormone (10.01±5.93 vs 8.51±5.53 IU/l; *P*<.001) and luteinizing hormone–to–follicle-stimulating hormone ratio (1.51 [range, 1.00–2.32] vs 1.45 [range, 0.92–2.13]; *P*<.001), lower levels of fasting glucose (5.47 mmol/L [range, 5.11–5.73] vs 5.50 mmol/L [range, 5.17–5.76]; *P*<.001), and insulin at 2 hours after 75-g oral glucose tolerance test (56.85 μU/mL [range, 34.63–94.54] vs 59.82 μU/mL [range, 33.56–94.67]; *P*=.027), a higher level of high-density lipoprotein (1.26 mmol/L [range, 1.04–1.37] vs 1.21 mmol/L [range, 1.07–1.45]; *P*=.006). During in vitro fertilization, the early group had a higher level of peak estradiol (4596.50 pg/mL [range, 2639.25–6321.00] vs 3954.00 pg/mL [range, 2378.75–6113.50]; *P*=.013), and luteinizing hormone (2.52 IU/L [range, 1.40–4.21] vs 1.93 IU/L [range, 0.91–3.32]; *P*=.010) on the day of human chorionic gonadotropin trigger. There was no statistically significant difference observed in the number of oocytes and embryos, the rates of pregnancy and live birth, and the risks of obstetrical and neonatal between the 2 groups.

CONCLUSION: An early onset of menstrual disturbance in patients with polycystic ovary syndrome may be associated with slightly more severe reproductive features and slightly milder metabolic features. Nonetheless, the outcomes of in vitro fertilization and the initial cycle of embryo transfer were comparable between the 2 groups.

Key words: embryo transfer, metabolic feature, onset time of menstrual disturbance, polycystic ovary syndrome, pregnancy outcomes

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Why was this study conducted?

Currently, there is confusion over the classification of menstruation issues in patients with polycystic ovarian syndrome (PCOS). It is unknown whether the timing of the onset of menstrual disturbance has an effect on the clinical features and in vitro fertilization (IVF) pregnancy outcomes in individuals with PCOS.

Key findings

Early onset of menstrual disturbance in patients with PCOS had more severe reproductive features, better glucose and lipid metabolic profiles, and similar pregnancy outcomes after IVF compared with late onset of menstrual disturbance.

What does this add to what is known?

Our study has important clinical implications for the individualization of care for patients with PCOS, as it can provide relevant counseling to patients.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition with endocrine and reproductive alterations. The prevalence of PCOS is 8% to 13% in reproductive-aged women.[1,2] There have been several diagnostic criteria and various phenotypes described with different combinations of diagnostic items.[3–5] The precise classification of patients with PCOS into various subgroups based on clinical manifestations and/or genetic analysis is still controversial and subject to intense study.[6,7]

Currently, the etiology of PCOS remains unclear, but there is increasing evidence supporting a genetic basis,[7] with interactions with environmental factors.[8–10] It is hypothesized that PCOS originates from puberty or even from in utero.[11,12] However, the occurrence of clinical symptoms varies greatly among patients with PCOS.[13–15] Menstrual disturbance is the most common clinical presentation of PCOS, with approximately 80% of patients experiencing oligomenorrhea.[16] However, the onset time of menstrual disturbance in patients with PCOS varies from menarche to adulthood.[17,18] A previous comparison between 49 women whose menstrual irregularity started at menarche and 40 women whose menstrual irregularity started in adult life showed no difference in hormonal and metabolic profiles.[17] However, the association between the onset time of menstrual disturbance and metabolism has not been investigated in studies involving larger cohorts.

Most females can establish a regular menstrual cycle within 1 to 3 years after menarche.[19–21] Regular and predictable ovulatory cycles usually occur within 5 years after menarche as the hypothalamic-pituitary-ovarian (HPO) axis matures.[22] In addition, the HPO axis is influenced by metabolic factors, such as insulin resistance, hyperinsulinemia, dyslipidemia, and metabolic syndrome.[23] Even after the establishment of a regular menstrual cycle, metabolic alterations can still lead to ovulation and menstrual irregularities.[24] Therefore, menstrual patterns are suggested to reflect the severity of metabolic disorders.[13] Unfortunately, it is still unclear whether the timing of the onset of menstrual disturbance is associated with clinical features and pregnancy outcomes.

We previously conducted a randomized trial in 1508 patients with PCOS who underwent their first cycle of in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI). Menstruation-related variables, prepregnancy clinical features, and pregnancy outcomes after the first embryo transfer cycle were prospectively collected using standard case report forms. Here, we compared the clinical features and IVF pregnancy outcomes between individuals with early and late onset of menstrual disturbances.

Materials and Methods

Study design

This was a secondary analysis of a multicenter randomized trial. The original trial compared the live birth rate between fresh embryo transfer and frozen embryo transfer in 1508 patients with PCOS (registration number: NCT01841528; registered on April 26, 2013). It has been approved by the ethics committee of the Center for Reproductive Medicine Affiliated with Shandong University and all other study sites (ethical approval number: 2012-15; approved on April 15, 2012). Written informed consent forms were signed by all participants. Both the study's protocol and its main findings have already been published.[25,26]

Study population

A total of 1508 patients with PCOS from 14 Chinese reproductive medical centers were enrolled to undergo their first IVF cycle between June 2013 and May 2014. Here, the participants were between the ages of 20 and 35 years old. PCOS was diagnosed by modified Rotterdam criteria, that is, presence of menstrual disorder, which is an essential condition along with either hyperandrogenism (either hirsutism or hyperandrogenemia) or polycystic ovaries on ultrasound. Other exclusion criteria included couples with abnormal karyotypes, recurrent spontaneous abortion characterized as 3 or more previous spontaneous pregnancy losses, women with a history of unilateral oophorectomy, women with uterine anomalies, or women with contraindications to assisted reproductive technology and/or pregnancy.

Patients were classified into 2 groups according to the onset time of menstrual disturbance. In the early-onset group (early group), menstrual irregularities occurred from menarche, whereas, in the late-onset group (late group), the irregularities occurred after at least 1 year of regular menstruation.

Study procedures

The menstruation and medical history were collected using a standard form. The age of menarche, the age of onset

of menstrual irregularity, and the pattern of menstruation were reported by patients and were recorded in face-to-face interviews by investigators. Waist circumference was measured at the level of the umbilicus, and hip circumference was measured at the widest diameter. A hirsutism assessment was made via the modified Ferriman-Gallwey hirsutism score[27] by trained investigating doctors.

All of the participants received a standardized recombinant follicle-stimulating hormone or gonadotropin-releasing hormone (GnRH) antagonist ovarian stimulation protocol and human chorionic gonadotropin (hCG) trigger for final oocyte maturation because the randomization was performed on the day of oocyte retrieval in the original trial. GnRH antagonist at a daily dose of 250 ug started when at least 1 follicle is ≥12 mm in mean diameter until trigger day. An hCG trigger was administered when there were 2 or more follicles with a diameter ≥18 mm, and approximately 36 hours later, a standard ultrasound-guided oocyte retrieval procedure was performed. Eligible patients with 3 to 30 oocytes who did not have a high risk of ovarian hyperstimulation syndrome (OHSS) were randomized to either frozen or fresh embryo transfer on the day of oocyte retrieval.

Both groups received up to 2 cleavage-stage embryo transfers. Individuals in the fresh embryo transfer group received daily intramuscular progesterone administrations of 80 mg from the day of oocyte retrieval. In the frozen embryo transfer group, endometrial preparation was performed using a programmed regimen. Intramuscular progesterone at a dose of 80 mg per day was administered when endometrial thickness reached 8 mm. On the fourth day of progesterone administration, embryo transfer and thawing were performed. If pregnancy was confirmed, luteal phase support was continued until 10 to 11 weeks of gestation.

Outcome measures

The outcomes included clinical features and pregnancy outcomes. The conception rate was defined as a blood β-hCG level of 10 IU/L 2 weeks after embryo transfer. Clinical pregnancy was defined as the detection of an intrauterine gestational sac by transvaginal ultrasonography after 6 weeks of embryo transfer. According to national standards of care and government guidelines for the management of preterm infants and to ensure consistency in tracking pregnancy outcomes during the original trial, live birth was defined as the delivery of a viable infant after 28 weeks of gestation, whereas miscarriage was defined as the loss of pregnancy at <28 weeks of gestation.

In addition, obstetrical and neonatal complications were assessed. This included preterm birth, defined as delivery before 37 weeks of gestation, diagnosis of a hypertensive disorder of pregnancy (HDP), gestational diabetes mellitus (GDM), and premature rupture of membranes (PROM) based on data obtained from obstetrical medical records. Large for gestational age was defined as a birthweight above the 90th percentile of the birthweight for the gestational age. Small for gestational age was defined as a birthweight below the 10th percentile of birthweight for the gestational age. Birthweight percentiles were based on Chinese population data based on recent birthweight surveys.[28−30]

Statistical analysis

Continuous variables conforming to a normal distribution were presented as mean±standard deviation; otherwise, they were presented as median and interquartile range. Categorical variables were expressed as number and percentage. Continuous variables that conform to a normal distribution were analyzed using the Student t test, whereas those that do not conform to a normal distribution were analyzed using the Mann-Whitney U test. Categorical variables were assessed using χ^2 analysis. Multivariable logistic regression was used to assess the between-group difference in pregnancy outcomes, adjusting for potential confounding factors, including maternal age, body mass index (BMI), antral follicle count (AFC), luteinizing hormone (LH), LH-to-follicle-stimulating hormone (FSH) ratio, thyroid-stimulating hormone (TSH), fasting blood glucose, high-density cholesterol (HDL), total cholesterol (TC), estradiol level on hCG administration day, endometrial thickness on the day of hCG administration, fertilization mode, endometrial thickness before embryo transfer, the number of embryos transferred, and the types of embryo transfer. All statistical analyses were performed using SPSS software (version 26.0; SPSS Inc, Chicago, IL). A P value of <.05 was considered as statistically significant.

Results

A total of 8 patients with an unknown history of menstrual disturbance were excluded, and a total of 1500 individuals with PCOS were included in the study. The early group had 540 patients (36%), whereas the late group had 960 patients (64%).

The clinical characteristics and variables during the IVF process in groups with different onsets of menstrual disturbance are displayed in Tables 1 and 2, correspondingly. Patients in the early group were slightly older than the late group (27.5 years [range, 25.0−30.0] vs 27.0 years [range, 25.3−30.0], respectively; P=.014). There was no statistical significance in BMI, waist-to-hip ratio, age of menarche, or duration of infertility. Patients in the early group had a greater number of antral follicles (32.0 [range, 27.3−39.5] vs 28.0 [range, 24.0−36.0]; P<.001) and higher levels of the antimüllerian hormone (AMH; 7.0 ng/mL [range, 3.6−11.5] vs 5.7 ng/mL [range, 3.7−8.9]; P=.024), LH (10.0±5.9 vs 8.5±5.5 IU/L; P<.001), LH-to-FSH ratio (1.5 [range, 1.0−2.3] vs 1.4 [range, 0.9−2.1]; P<.001), TSH (2.6 μIU/mL [range, 1.8−3.5] vs 2.4 μIU/mL [range, 1.7−3.2]; P=.001), TC (4.7 mmol/L [range, 4.2−5.2] vs 4.6 mmol/L [range, 4.1−5.1]; P=.021), and HDL (1.3 mmol/L [range, 1.0−1.4] vs 1.2 mmol/L [range, 1.1−1.5]; P=.006) than people in the late group (Table 1).

Lower levels of prolactin (PRL) (16.6 ng/mL [range, 11.6−22.8] vs 17.5 ng/mL [range, 12.9−22.5]; P=.009), fasting glucose (5.5 mmol/L [range, 5.1−5.7] vs 5.5 mmol/L [range, 5.2−5.7]; P<.001), and 2-hour insulin (56.9 μU/mL [range, 34.6−94.5] vs

TABLE 1
Baseline clinical characteristics

Characteristic	Early group n=540	Late group n=960	*P* value
Age (y)	27.5 (25.0–30.0)	27.0 (25.3–30.0)	.014
BMI (kg/m^2)	24.1 (21.5–27.3)	23.7 (21.1–26.1)	.064
Waist-to-hip ratio	0.86±0.06	0.86±0.06	.640
Age of menarche (y)	14.0 (14.0–15.0)	14.0 (13.0–15.0)	.100
Age of onset of menstrual irregularity (y)	14.0 (13.0–15.0)	22.0 (19.0–24.9)	.877
Duration of menstrual irregularity (y)	14.0 (12.0–16)	5.0 (3.0–8.0)	.544
Duration of infertility (y)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	.673
Indications for IVF, n (%)			.267
PCOS	90 (16.7)	188 (19.6)	
PCOS combined with tubal factors	310 (57.4)	509 (53.0)	
PCOS combined with male factors	105 (19.4)	208 (21.7)	
PCOS combined with tubal and male factors	35 (6.5)	55 (5.7)	
AFC	32.0 (27.3–39.5)	28.0 (24.0–36.0)	<.001
Baseline FSH (IU/L)	6.1±1.4	6.0±1.5	.206
Baseline LH (IU/L)	10.0±5.9	8.5±5.5	<.001
LH-to-FSH ratio	1.5 (1.0–2.3)	1.4 (0.9–2.1)	<.001
Baseline estradiol (pg/mL)	36.2 (30.1–45.6)	36.5 (26.8–44.5)	.628
Baseline progestin (ng/mL)	0.6 (0.5–0.7)	0.6 (0.4–0.8)	.088
Baseline testosterone (ng/dL)	42.2±20.8	43.0±23.9	.514
PRL (ng/mL)	16.6 (11.6–22.8)	17.5 (12.9–22.5)	.009
AMH (ng/mL)	7.0 (3.6–11.5)	5.7 (3.7–8.9)	.024
TSH (μIU/mL)	2.6 (1.8–3.5)	2.4 (1.7–3.2)	.001
PCOS phenotypes, n (%)			.865
PCOS-A: HA + OD + PCOM	442 (82.8)	806 (83.6)	
PCOS-B: HA + OD	3 (0.6)	4 (0.4)	
PCOS-C: HA + PCOM PCOS-D: OD + PCOM	0 (0) 89 (16.7)	0 (0) 154 (16)	
Metabolic profiles			
FBG (mmol/L)	5.5 (5.1–5.7)	5.5 (5.2–5.7)	<.001
2-h glucose concentration after OGTT (mmol/L)	6.5 (5.7–7.4)	6.4 (5.4–7.5)	.055
NG (%)	393 (72.8)	693 (72.2)	.857
Isolated IFG (%)	18 (3.3)	31 (3.2)	1.000
Isolated IGT (%)	81 (15.0)	177 (18.4)	.101
IFG + IGT (%)	14 (2.6)	15 (1.6)	.175
DM (%)	34 (6.3)	44 (4.6)	.182
Fasting insulin concentration (μU/mL)	11.9 (7.9–18.3)	12.1 (8.6–18.1)	.202
2-h insulin concentration after OGTT (μU/mL)	56.9 (34.6–94.5)	59.8 (33.6–94.7)	.027
Triglyceride (mmol/L)	1.2 (0.9–1.7)	1.1 (0.8–1.7)	.145
High-density cholesterol (mmol/L)	1.3 (1.0–1.4)	1.2 (1.1–1.5)	.006
Total cholesterol (mmol/L)	4.7 (4.2–5.2)	4.6 (4.1–5.1)	.021

Data are presented as median (interquartile range) or mean±standard deviation for continuous variables and number (percentage) for categorical variables.

AFC, antral follicle count; *AMH*, antimüllerian hormone; *BMI*, body mass index; *DM*, diabetes mellitus; *FBG*, fasting blood glucose; *FSH*, follicle-stimulating hormone; *HA*, hyperandrogenism; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *IVF*, in vitro fertilization; *LH*, luteinizing hormone; *NG*, normal glucose; *OD*, ovulatory dysfunction; *OGTT*, oral glucose tolerance test; *PCOM*, polycystic ovarian morphology; *PCOS*, polycystic ovary syndrome; *PRL*, prolactin; *TSH*, thyroid-stimulating hormone.

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TABLE 2
IVF treatment characteristics

Characteristic	Early group n=540	Late group n=960	*P* value
Duration of ovarian stimulation (d)	10.0 (9.0−11.8)	11.0 (9.0−12.0)	.380
Dosage of gonadotrophins (IU)	1406.3 (1200.0−1940.5)	1500.0 (1125.0−2175.0)	.243
Estradiol level on the day of hCG trigger (pg/mL)	4596.5 (2639.3−6321.0)	3954.0 (2378.8−6113.5)	.013
Progesterone level on the day of hCG trigger (ng/mL)	1.0±0.5	1.0±0.6	.803
LH level on the day of hCG trigger (IU/L)	2.5 (1.4−4.2)	1.9 (0.9−3.3)	.010
Endometrial thickness on the day of hCG trigger (cm)	1.1±0.2	1.0±0.2	.012
No. of oocytes retrieved	14.7±6.0	14.1±5.8	.068
OHSS	21 (3.9)	43 (4.5)	.690
Type of embryo transfer			.063
Fresh embryo transfer	278 (52.6)	456 (48.3)	
Frozen embryo transfer	261 (47.4)	489 (51.7)	
Type of fertilization			.342
IVF	410 (75.9)	734 (76.5)	
ICSI	110 (20.4)	205 (21.4)	
Half IVF or half ICSI	12 (2.2)	11 (1.1)	
No. of 2 PN	8.5 (6.0−12.8)	9.0 (6.0−12.0)	.549
No. of good-quality embryos on day 3	5.5 (3.3−8.0)	5.0 (3.0−8.8)	.065
No. of embryos transferred			.605
1 embryo	26 (4.9)	41 (4.3)	
2 embryos	503 (95.1)	904 (95.5)	
Stage of embryo transferred			.377
Cleavage stage	506 (95.7)	899 (95.1)	
Blastocyst stage	23 (4.3)	46 (4.9)	

Data are presented as median (interquartile range) or mean±standard deviation for continuous variables and number (percentage) for categorical variables.

hCG, human chorionic gonadotrophin; *ICSI*, intracytoplasmic sperm injection; *LH*, luteinizing hormone; *OHSS*, ovarian hyperstimulation syndrome; *PN*, pronucleus.

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59.8 μU/mL [range, 33.6−94.7]; *P*=.027) after 75-g oral glucose tolerance test (OGTT) were noted in the early group than in the late group. There was no statistically significant difference between the 2 groups in terms of indications for IVF, PCOS phenotypes, baseline estradiol, baseline progestin, or baseline testosterone.

Compared with the late group, the early group had higher levels of estradiol (3954.0 pg/mL [range, 2378.8−6113.5] vs 4596.5 pg/mL [range, 2639.3−6321.0], respectively; *P*=.013) and LH (1.9 IU/L [range, 0.90−3.3] vs 2.5 IU/L [range, 1.4−4.2], respectively; *P*=.010) and a thicker endometrium (1.0±0.2 vs 1.1±0.2 cm, respectively; *P*=.012) on hCG trigger day (Table 2). The percentage of fresh and frozen embryo transfers was not statistically significant in the 2 groups. There were no statistically significant differences in the number of oocytes retrieved, the number of good-quality embryos, the incidence of moderate or severe OHSS, and the number of embryo transfers between the 2 groups.

The pregnancy outcomes were presented in Tables 3 and 4. There was no statistically significant difference found in live birth rates (45.7% vs 44.9%; adjusted odds ratio [aOR], 0.95; 95% confidence interval [CI], 0.75−1.22; *P*=.699), clinical pregnancy rates (57.6% vs 57.3%; aOR, 0.91; 95% CI, 0.71−1.16; *P*=.449), conception rates (65.9% vs 64.9%; aOR, 0.95; 95% CI, 0.74−1.23; *P*=.715), and miscarriage rates (18.9% vs 17.5%; aOR, 1.08; 95% CI, 0.78−1.51; *P*=.648) between the 2 groups. There was no statistically significant difference in PTB (15.5% vs 17.9%), HDP (2.6% vs 1.3%), GDM (6.5% vs 5.9%), and PROM (10.4% vs 11.5%) between the 2 groups. We did not find statistically significant differences in gestational age, gender of newborn, weight of newborn,

TABLE 3
Pregnancy outcomes and obstetrical and perinatal complications

Characteristic	Early group n=540	Late group n=960	*P* value
Conception rate (%)	356 (65.9)	623 (64.9)	.693
Clinical pregnancy rate (%)	311 (57.6)	550 (57.3)	.914
No. of gestational sacs in clinical pregnancies			.748
Singleton pregnancy	166 (67.2)	295 (67.5)	
Twin pregnancy	141 (32.8)	141 (32.3)	
Triplet pregnancy	0 (0)	1 (0.2)	
Live birth rate (%)	247 (45.7)	437 (44.9)	.787
Miscarriage rate (%)	102 (18.9)	168 (17.5)	.603
PTB rate (%)	48 (15.5)	98 (17.9)	.396
GDM rate (%)	20 (6.5)	32 (5.9)	.766
HDP rate (%)	8 (2.6)	7 (1.3)	.180
PROM (%)	32 (10.4)	63 (11.5)	.651
Fetal malformation rate (%)	1 (0.3)	7 (1.3)	.270
Gestational week at delivery (wk)	37.79±2.32	37.59±2.47	.300
Newborn sex			.469
Male	136 (55.3)	255 (58.4)	
Female	110 (44.7)	182 (41.6)	
Birthweight (g)	3137.8±648.6	3134.9±735.0	.959
Macrosomia rate (%)	25 (10.1)	53 (9.9)	.895
LGA rate (%)	30 (12.1)	72 (16.5)	.146
SGA rate (%)	26 (10.5)	57 (13.1)	.394
Neonatal mortality (%)	0 (0)	2 (0.5)	.538
Neonatal congenital anomalies (%)	7 (2.8)	11 (2.5)	.808

Data are presented as mean±standard deviation for continuous variables, and number (percentage) for categorical variables.

GDM, gestational diabetes mellitus; *HDP*, hypertensive disorders of pregnancy; *LGA*, large for gestational age; *PROM*, premature rupture of membranes; *PTB*, spontaneous preterm birth; *SGA*, small for gestational age.

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neonatal malformation, and neonatal mortality rate between the 2 groups.

Comment

Principal findings

The timing of the onset of menstrual disturbance in patients with PCOS did not affect the success of their IVF pregnancy outcomes.

Results

This study suggested that early onset of menstrual disturbance in patients with PCOS was associated with more severe reproductive features, such as more AFC; higher levels of AMH, LH, and LH-to-FSH ratio; and milder metabolic features, such as lower levels of fasting glucose and 2-hour insulin and a higher level of HDL, than late onset of menstrual disturbance. However, the outcomes of IVF and the initial cycle of embryo transfer were comparable between the 2 groups.

Clinical implications

Few studies focus on the association of the onset time of menstrual disturbance with clinical characteristics and pregnancy outcomes in patients with PCOS. A previous study of 89 individuals with PCOS suggested that the onset time of menstrual irregularities was not associated with hormonal or metabolic profile and ovarian ultrasound morphology.[17] In this study with a much larger sample size, we found that an early onset of menstrual disturbances was related to more antral follicles and higher AMH, LH, LH-to-FSH ratios, TC, and TSH levels. These findings supported the neuroendocrine basis in the etiology of PCOS with an early onset of menstrual disturbance.[31] Approximately half of adolescents with oligomenorrhea are diagnosed with PCOS.[17,32,33] In addition, dysregulation of the HPO axis, represented by the raised LH levels, was found to be presented in most adolescents with oligomenorrhea.[17] In adolescents with oligomenorrhea, those with normal plasma LH levels at 2 years after menarche had a greater probability of spontaneous ovulation within the following 40 months than those with high LH levels.[34] However, the effect of elevated LH on the quality of oocytes and embryos and pregnancy outcomes remains unclear. Our findings are consistent with a recent study that found that basal LH levels did not affect the pregnancy outcomes after IVF in patients with PCOS.[35] Moreover, the current study showed that patients with PCOS and an early-onset time of menstrual disturbance had a higher level of AMH. AMH is one of the predictors of ovarian reserve[36] and ovarian response in assisted reproductive technology.[37] Moreover, AMH is suggested to be related to the severity of PCOS.[38,39] A previous study found that AMH levels are higher in patients with PCOS and amenorrhea or oligomenorrhea than in those without dysmenorrhea,[40] suggesting a role for AMH in the pathogenic mechanism of anovulation.[41] Furthermore, we found that patients with a late onset of menstrual disturbance exhibited slightly higher serum PRL levels than those with an early onset of menstrual disturbance. However, the difference may be clinically insignificant.

We found that the late onset of menstrual disturbance in patients with PCOS was associated with poor glucose and lipid metabolic profiles and a higher 2-hour insulin level after 75-g OGTT. The

TABLE 4
Multivariable logistic regression analysis

Variable	aOR	95% CI	*P* value
Conception pregnancy rate	0.95	0.74–1.23	.715
Clinical pregnancy rate	0.91	0.71–1.16	.449
Live birth rate	0.95	0.75–1.22	.699
Miscarriage rate	1.08	0.78–1.51	.648

The aOR and 95% CI were obtained via multiple logistic regression analyses. Analyses were adjusted for age, body mass index, antral follicle count, luteinizing hormone, luteinizing hormone—to—follicle-stimulating hormone, thyroid-stimulating hormone, fasting blood glucose, high-density cholesterol, total cholesterol, estradiol level on hCG day, endometrial thickness on hCG day, fertilization mode, number of embryos transferred, and type of embryo transfer.

aOR, adjusted odds ratio, *CI*, confidence interval; *hCG*, human chorionic gonadotrophin.

Miao. Timing of menstrual disturbance and in vitro fertilization outcomes in polycystic ovarian syndrome women. Am J Obstet Gynecol Glob Rep 2024.

findings suggested that metabolic factors may play a greater role in patients with a late onset of menstrual disturbance than in patients with an early onset of menstrual disturbance. However, the absolute between-group differences in the levels of glucose and insulin were slight, and the clinical significance of these small differences should be confirmed in further studies. Previous studies indicated that the prevalence of metabolic syndrome in people with polycystic ovaries was nearly 2-fold higher than in the general population.[42] The prevalence of metabolic syndrome in patients with PCOS was 27.2%,[43] which supported the relationship between metabolic alteration and PCOS.

Insulin resistance can disrupt the HPO axis, exert a direct effect on ovarian follicle development, induce elevated androgen levels, and, finally, result in ovulation dysfunction.[14] The main biochemical characteristics of PCOS are elevated LH and hyperinsulinemia, which independently affect hyperandrogenism and ovarian follicle development.

PCOS is associated with a higher risk of adverse perinatal outcomes, including GDM, PROM, and hypertensive disorders than non-PCOS.[44–46] There is still a lack of evidence on the relationship between the onset time of menstrual disturbance and IVF and ICSI pregnancy outcomes. There are studies on the effect of menstrual patterns on pregnancy outcomes in patients with PCOS.[47] A prospective cohort study revealed that the presence of hyperandrogenism + menstrual dysfunction + polycystic ovary was associated with increased risks of GDM, preeclampsia, and low birthweight neonates compared with other phenotypes.[48,49] Patients with PCOS with amenorrhea experienced a significantly higher risk of adverse pregnancy outcomes than patients with PCOS with normal menstruation.[50] Another study has demonstrated that variation in the length of menstrual cycles may serve as a risk indicator for GDM or impaired glucose tolerance.[51] However, a retrospective cohort study demonstrated that patients with PCOS with different menstrual patterns had similar clinical pregnancy and live birth rates after IVF treatment. We did not find a significant correlation between the onset time of menstrual disturbance and pregnancy outcomes after IVF or ICSI and the initial embryo transfer in this study. Of note, 1 possible reason is that IVF as an effective measure to treat infertility may overcome the adverse effect of HPO axis dysregulation and certain metabolic alterations on reproduction. Alternatively, although 1500 patients with PCOS were included, the sample size may still be underpowered to detect the small difference in pregnancy outcomes, especially for obstetrical complications.

Research implications

Further research is needed to assess the generalizability of our findings beyond Chinese patients with PCOS. In addition, this trial was constrained by its reliance on hCG as the exclusive trigger drug, which increased the risk of OHSS to some extent. The routine transfer of 2 cleavage-stage blastocysts is associated with higher rates of multiple pregnancies and preterm birth.

Strengths and limitations

There are strengths in this study. First, the data were prospectively collected during a multicenter randomized trial with a standard case report form, which ensured the accuracy and completeness of the data. The patients were enrolled from 14 study centers in the original trial, which increased the generalizability of the study. Second, besides the clinical features of PCOS, we also evaluated the pregnancy outcomes after IVF and the first embryo transfer cycle, which provided further information for clinicians. However, there are also limitations in this study. First, as a secondary analysis of the previous trial, the study population was restricted by the inclusion criteria of the original trial. Only women aged 20 to 35 years were included in the original trial and the current study. Thus, the findings may not be extrapolated to older patients with PCOS. Second, as this was a cohort study, we could not rule out the effect of potential confounders during IVF treatment on pregnancy outcomes. Third, the pregnancy outcomes were from the initial embryo transfer cycle. The results may be different from the cumulative pregnancy outcomes after all embryos were transferred or varied with the pregnancy outcomes of ovulation induction and timed intercourse. Further studies are needed to confirm our findings.

Conclusion

The findings of the current study suggest that patients with an early onset of menstrual disturbance seemed to have more severe reproductive features but milder metabolic features than those with a late onset of menstrual disturbance in reproductive-age participants with PCOS, whereas the obstetrical and neonatal complications after IVF and

the initial cycle of embryo transfer were comparable between the 2 groups. ■

CRediT authorship contribution statement

Haozhe Miao: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Huiming Yang:** Validation, Investigation, Formal analysis, Data curation. **Mengfei Yin:** Validation, Investigation, Formal analysis, Data curation. **Yixuan Wang:** Validation, Investigation, Formal analysis, Data curation. **Yuan Fang:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Min Yang:** Visualization, Methodology, Investigation, Data curation, Conceptualization. **Jialin Zou:** Visualization, Methodology, Investigation, Data curation. **Wenwen Zhang:** Visualization, Validation, Methodology, Investigation, Data curation. **Lingling Zhang:** Visualization, Validation, Methodology, Investigation, Data curation. **Chendan Liu:** Visualization, Methodology, Investigation, Data curation. **Yue Wang:** Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Ze Wang:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Conceptualization. **Yunhai Yu:** Supervision, Software, Resources, Project administration, Conceptualization. **Daimin Wei:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization. ■

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