

Original Research

Coexistence of Elevated Maternal Body Mass Index and Polycystic Ovary Syndrome May be Associated With Increased Risk of Neonatal Complications and Caesarean Section Delivery Following Intrauterine Insemination: A Retrospective Cohort Study

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Abstract

Background: The birth outcomes of neonates born to mothers with polycystic ovary syndrome (PCOS) following intrauterine insemination (IUI) remain unclear, as do the correlations with pregravid maternal characteristics, thus warranting further investigation. **Methods:** Data were collected on mothers with PCOS (PCOS group, $n = 101$), including the birth outcomes of their offspring. Mothers without PCOS (non-PCOS group, $n = 204$) and their offspring served as the control group. The two groups were analyzed for correlations between neonatal birth outcomes and pregravid maternal characteristics using univariate analysis, Spearman rank correlation, and logistic regression models. **Results:** In the PCOS group, maternal body mass index (BMI) was a positive predictor of neonatal complications, independent of confounding factors (unadjusted odds ratio [OR] = 1.28, $p = 0.03$; adjusted OR = 1.30, $p = 0.04$). However, no significant association was found between maternal BMI and neonatal complications in the non-PCOS group (unadjusted OR = 1.06, $p = 0.34$; adjusted OR = 1.02, $p = 0.71$). Compared to non-PCOS mothers, each one-unit increase in the BMI among PCOS mothers was associated with a 1.30-fold increased risk of adverse neonatal complications. Secondly, maternal BMI was a positive predictor of caesarean section delivery in the PCOS group, independent of confounding factors (unadjusted OR = 1.25, $p = 0.006$; adjusted OR = 1.28, $p = 0.005$). Maternal BMI was also a positive predictor for caesarean section delivery in the non-PCOS group, independent of confounding factors (unadjusted OR = 1.15, $p = 0.004$; adjusted OR = 1.14, $p = 0.014$). However, the adjusted OR in the PCOS group was higher than that observed in the non-PCOS group (OR = 1.28 vs. OR = 1.14). **Conclusions:** The co-occurrence of elevated maternal BMI and PCOS may be associated with an elevated risk of neonatal complications and delivery by caesarean section following IUI. Mothers with PCOS are advised to maintain a healthy pregravid BMI in order to minimize the risk of adverse neonatal complications.

Keywords: birth outcome; body mass index; intrauterine insemination; neonate; polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder often present in females of reproductive age. This syndrome accounts for 5%–10% of all cases of infertility in women [1,2], with environmental pollutants thought to play a vital role in its etiology [3]. Oligo-anovulation is the primary underlying cause of PCOS-associated infertility [4]. With the rapid progress of reproductive medicine, controlled ovarian stimulation (COS) has emerged as a promising therapy for PCOS women who intend to resume ovulation and conceive their own children [5,6].

Intrauterine insemination (IUI) is a commonly used assisted reproductive technology (ART) that enhances the likelihood of pregnancy. IUI is usually the first option recommended for infertile PCOS patients before switching to the more sophisticated *in vitro* fertilization (IVF) therapy,

since it is easy to perform, patient-friendly, and inexpensive [7]. Therefore, IUI and COS are currently recognized as first-line treatments for infertile PCOS patients [8].

The clinical practice guidelines for infertile PCOS patients recommend at least three cycles of IUI treatment [9]. An observational study reported that the cumulative live birth rate per PCOS patient can reach up to 31% after three IUI attempts [9]. A considerable number of neonates are now born each year to PCOS mothers following IUI. It is therefore clinically important to assess the birth outcomes of this particular cohort of neonates.

Several previous studies have investigated the birth outcomes of neonates born to PCOS mothers following ART, although the reported findings are somewhat conflicting [10–13]. Moreover, the context of these studies was mainly in regard to IVF. The birth outcomes for neonates born to PCOS mothers following IUI, as well as their cor-



relations with pregravid maternal characteristics, have remained largely unexplored. Additional research on this topic is clearly warranted.

The current study retrospectively evaluated birth outcomes for neonates born to PCOS mothers who underwent IUI in our center. Furthermore, we investigated possible associations between neonatal birth outcomes and pregravid maternal characteristics. Mothers without PCOS and their offspring served as the control in this study. The results of correlation analyses identified maternal duration of infertility, maternal body mass index (BMI), neonatal complications, and delivery by caesarean section as four indicators of interest. These indicators subsequently formed the focus of our study. Logistic regression analysis confirmed the predictive value of maternal BMI for neonatal complications and caesarean section delivery. More importantly, PCOS mothers with high BMI showed increased risks of neonatal complications and caesarean section delivery compared to non-PCOS mothers.

2. Materials and Methods

2.1 Study Subjects and Design

This study included PCOS women who underwent COS and IUI treatments at the Reproductive Center, First Affiliated Hospital, Shantou University Medical College, from 1 January 2016 to 31 December 2021. Patients with oligomenorrhea caused by congenital adrenal hyperplasia, hypothyroidism, or hyperprolactinemia were actively screened and excluded. Demographic and clinical data were extracted from electronic medical files. Diagnosis of PCOS was per the Rotterdam Consensus of 2003 [14]. Initially, 109 PCOS women and 221 non-PCOS women who underwent COS and IUI treatments and delivered a live singleton were enrolled into either the study (PCOS) or control (non-PCOS) groups. Exclusion criteria were abnormalities in spousal sperm, endometriosis, uterine abnormalities, karyotypic abnormalities, and missing data. Following screening, 101 PCOS women and 204 non-PCOS women were included in the final study cohort (Fig. 1). Prior to starting COS and IUI therapies in our hospital, all participants underwent a standard infertility check-up. Tests for basal serum hormone levels were performed on days 3–5 of the menstrual cycle. Information concerning neonatal birth outcomes was obtained through follow-up.

2.2 Protocols for COS and IUI

Briefly, criteria for clomiphene protocol include infertility caused by PCOS, infertility caused by insufficient luteal function, infertility caused by ovulatory dysfunction and unexplained infertility. Criteria for the letrozole protocol include infertility caused by PCOS, infertility caused by ovulatory dysfunction and unexplained infertility. Criteria for human menopausal gonadotropin (HMG) protocol include infertility caused by ovulatory dysfunction (particularly the hypothalamic-pituitary-ovarian axis dysfunction),

infertility caused by PCOS, infertility caused by poor ovarian reserve and unexplained infertility. Selection of ovulation induction protocol was codetermined by fertility doctor and patient after a thorough discussion.

The starting dose for ovarian stimulation was personalized by a fertility doctor following a full assessment of the age and BMI of each patient, their current ovarian reserve, and their prior history of ovarian response. Ovarian stimulation was generally initiated 3–5 days following menstruation.

For ovarian stimulation with HMG, we used a step-up protocol with a starting dose of 37.5–150 IU HMG (H20033042, Renjian Pharmaceutical Group, Ningbo, Zhejiang, China). The ovarian response was then evaluated by transvaginal ultrasonography (TVU), and the HMG dose was individually adapted according to follicular growth. After the emergence of a dominant follicle, the dose of HMG was not changed until its diameter had grown to ≥ 18 mm.

For stimulation with clomiphene or letrozole, women were administered either 50–100 mg clomiphene (H20140618, Codal Synto, Changzhou, Jiangsu, China) once per day, or 2.5–5 mg letrozole (H20084597, Haizheng Pharmaceutical Group, Changzhou, Jiangsu, China) once per day for 5 consecutive days, followed by monitoring of the ovarian response with TVU. For cases that were insensitive to stimulation by clomiphene or letrozole, an individualized dose of HMG was administered to promote follicle development until a dominant follicle ≥ 18 mm in diameter emerged.

After at least one dominant follicle had reached ≥ 18 mm, cycles were triggered with: (I) 10,000 IU human chorionic gonadotropin (HCG) (H44020672, Livzon, Zhuhai, Guangdong, China), or 250 μ g recombinant HCG (S20130091, Merck Serono, Geneva, Switzerland); or (II) 0.1–0.2 mg gonadotropin-releasing hormone agonists (GnRH-a) (H20140298, IPSEN PHARMA, Paris, France) plus 6000 IU HCG. Cycles with >3 dominant follicles were terminated in order to prevent ovarian hyperstimulation syndrome and multiple pregnancy. IUI was performed 24–36 h after administration of the trigger drug using a disposable catheter. Following IUI, women were instructed to rest for 30 minutes in the supine position. To detect pregnancy, serum β -human chorionic gonadotropin (β -hCG) was evaluated two weeks after IUI [15].

Luteal support was initiated the day after IUI with 10 mg tablets of Dydrogesterone (H20130110, Abbott Laboratories, Chicago, IL, USA) taken 2–3 times daily for 15–16 days. This was extended for another 10–12 weeks once a viable intrauterine pregnancy was detected [16].

2.3 Hormone Assessment

Hormone levels were quantified in the Department of Clinical Laboratory at our hospital as described previously by our group [16]. This technique is based on the detection

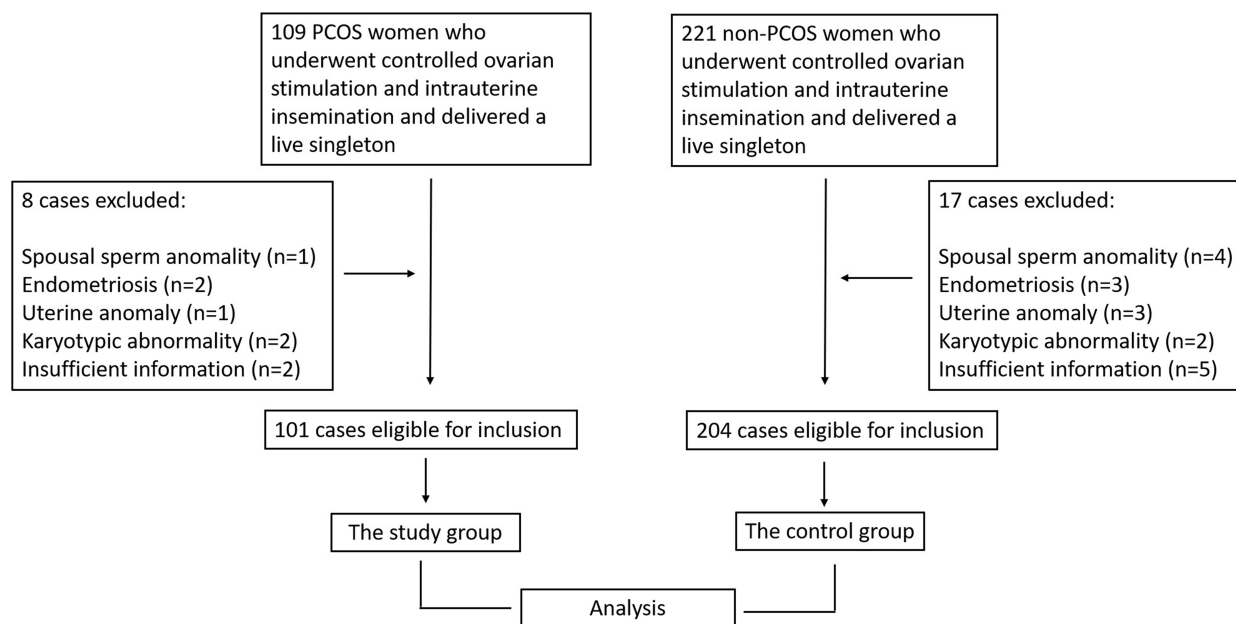


Fig. 1. Flow diagram illustrating subject selection and study design. PCOS, polycystic ovary syndrome; n, number of samples.

of chemiluminescence by the ARCHITECT ci8200 system (Abbott Biologicals B.V., Weesp, Netherlands), as recommended by the manufacturer. Inter- and intra-assay coefficients of variation were less than 10% in all assays.

2.4 Follow-up

Follow-up interviews were carried out two weeks after the IUI, followed by alternate months. Trained nurses phoned participants to collect data regarding health conditions, pregnancy, and neonatal birth outcomes. The interviews were stopped after one of the following events: (1) the serum β -hCG test performed 14 days after IUI was negative; (2) early miscarriage; or (3) delivery of a live infant. All women in this study received adequate follow-up care.

2.5 Neonatal Birth Outcomes

Pre-term delivery was defined as delivery before 37 weeks of gestation, low birthweight as a newborn weighing <2500 g, and macrosomia for a newborn weighing >4000 g [15]. Fetal growth restriction was defined as a birthweight less than the 10th percentile for gestational age [15]. Neonatal complications included admission to the neonatal intensive care unit (ICU), fetal asphyxia, fetal growth restriction, pre-term birth, oligohydramnios, low birthweight, macrosomia, an Apgar score <7, and other minor congenital defects [15].

2.6 Statistical Analyses

Statistical analyses were performed using Statistics Package for Social Sciences (SPSS Version 20.0, IBM, Armonk, NY, USA). The distribution of continuous data was assessed with the Kolmogorov-Smirnov normality test. Depending on its distribution, continuous data were shown as

either the mean $\pm$ standard deviation or the median (Q1–Q3). Continuous data showing a normal distribution was analyzed using the *t*-test, while data showing a non-normal distribution was analyzed using the Mann-Whitney *U* test. Categorical data were presented as a number or percentage, and analyzed with Fisher's exact or Pearson's Chi-square tests. Possible correlations between two specific indicators were investigated by Spearman's rank correlation analysis. A logistic regression model was constructed to identify factors that were predictive of a specific type of birth outcome. The listwise deletion method was used to deal with missing data, as recommended by SPSS. Two-tailed *p*-values < 0.05 were considered statistically significant. *Post hoc* power analysis with the G*power program (Version 3.1.9.7, University of Kiel, Kiel, Germany) indicated the statistical power was 98.36% using the following parameters: two independent groups, two-tailed test, effect size $d = 0.5$, α error = 0.05, sample size of PCOS group = 101, sample size of non-PCOS group = 204.

3. Results

3.1 Baseline Characteristics of the PCOS and Non-PCOS Groups

The baseline characteristics of women with PCOS are compared to those without PCOS in Table 1. PCOS women were significantly younger (28 years vs. 30 years, $p < 0.01$). As expected, the PCOS group had significantly higher antral follicle count, basal luteinizing hormone (LH) level, ratio of basal LH/follicle-stimulating hormone (LH/FSH), and testosterone level compared to the non-PCOS group. However, no significant differences were observed for the other characteristics shown in Table 1 (all $p > 0.05$).

Table 1. Baseline characteristics of women in the PCOS and non-PCOS groups.

Characteristic	PCOS	Non-PCOS	<i>p</i> -value
	n = 101	n = 204	
Age (years)	28 (26–30)	30 (28–33)	<0.01
Duration of infertility (years)	3 (2–4)	3 (2–4)	0.98
Etiology of infertility			
Primary	73 (72.27%)	141 (69.11%)	0.57
Secondary	28 (27.72%)	63 (30.88%)	
IUI cycle			
First cycle	52 (51.48%)	113 (55.39%)	0.69
Second cycle	36 (35.64%)	63 (30.88%)	
Third cycle	11 (10.89%)	20 (9.80%)	
Cycles after 3 attempts	2 (1.98%)	8 (3.92%)	
BMI (kg/m ²)	21.60 (19.57–23.73)	20.90 (19.10–23.30)	0.17
Antral follicle count	26.00 (22.00–31.00)	15.00 (11.00–21.00)	<0.01
Basal LH (mIU/mL)	8.99 (5.35–12.84)	3.89 (2.73–5.57)	<0.01
Basal FSH (mIU/mL)	6.34 (5.40–7.58)	6.20 (5.00–7.60)	0.26
Basal LH/FSH ratio	1.32 (0.86–1.99)	0.63 (0.45–0.99)	<0.01
Basal estradiol (pg/mL)	45.00 (33.00–59.00)	42.00 (32.00–55.00)	0.35
Basal progesterone (ng/mL)	0.33 (0.20–0.59)	0.38 (0.23–0.62)	0.46
Testosterone (ng/dL)	53.89 (38.88–70.60)	37.19 (26.59–50.58)	<0.01
Total Gn dosage used (IU)	400.00 (262.00–678.00)	450.00 (275.00–713.00)	0.37
No. of mature follicles on trigger day	1 (1–2)	1 (1–2)	0.49
Endometrial thickness on trigger day (mm)	10.00 (8.80–11.00)	10.00 (8.70–11.15)	0.98

Note: PCOS, polycystic ovary syndrome; IUI, intrauterine insemination; LH, luteinizing hormone; FSH, follicle-stimulating hormone; Gn, gonadotrophin; BMI, body mass index. Results are shown as the median (Q1–Q3), or number (%). Percentages may not sum to 100% due to rounding.

Table 2. Birth outcomes of singletons in PCOS and non-PCOS groups.

Characteristic	PCOS	Non-PCOS	<i>p</i> -value
	n = 101	n = 204	
Gender			
Male	50 (49.50%)	101 (49.50%)	0.99
Female	51 (50.49%)	103 (50.49%)	
Full-term or pre-term birth			
Full-term	97 (96.03%)	192 (94.11%)	0.66
Pre-term	4 (3.96%)	12 (5.88%)	
Mode of delivery			
Spontaneous labor	58 (57.42%)	91 (44.60%)	0.03
Caesarean section	43 (42.57%)	113 (55.39%)	
Birthweight (g)	3050 (2700–3500)	3050 (2850–3450)	0.60
Birth length (cm)	50 (49–50)	50 (50–50)	0.60
Apgar score			
7 to 10	100 (99.00%)	202 (99.01%)	1.00
<7	1 (0.99%)	2 (0.98%)	
Singletons with complications ¹			
Yes	14 (13.86%)	33 (16.17%)	0.59
No	87 (86.13%)	171 (83.82%)	

¹Complications include admission to the neonatal intensive care unit (ICU), fetal asphyxia, fetal growth restriction, preterm birth, oligohydramnios, low birthweight, macrosomia, Apgar score <7, and other minor congenital defects. Results are shown as the median (Q1–Q3), or number (%). Percentages may not sum to 100% due to rounding.

3.2 Birth Outcomes of Singletons in PCOS and Non-PCOS Groups

We next compared birth outcomes of live singletons between PCOS and non-PCOS groups following IUI treatments (Table 2). The PCOS group underwent fewer caesarean sections than the non-PCOS group ($p = 0.03$). However, the two groups showed no significant differences in any of the other characteristics investigated, including gender, full- or pre-term birth, birth length, birthweight, Apgar score, and cases of singletons with neonatal complications.

The effect of different ovulation induction agents on birth outcomes was also explored using subgroup analysis. No significant effect of different ovulation induction agents on birth outcomes was observed in the PCOS group (Supplementary Table 1). However, in the non-PCOS group, 80% of women in which clomiphene was used to induce ovulation underwent caesarean section during childbirth (Supplementary Table 2).

We also performed more analyses on detailed composition of neonatal complications in PCOS group and non-PCOS group respectively. As indicated in Supplementary Table 3, we reported 3 cases of preterm delivery, 7 cases of low birth weight, 2 cases of macrosomia, 1 case of fetal asphyxia and 1 case of pathological icterus in PCOS group. In comparison, we discovered 7 cases of preterm delivery, 11 cases of low birth weight, 7 cases of macrosomia, 1 case of fetal growth restriction, 1 case of oligohydramnios, 1 case of fetal asphyxia, 1 case of pathological icterus and 4 cases of congenital defects. Prevalence rates of individual complications and their counterparts reported in general IUI population and natural conception population were also shown in Supplementary Table 3.

3.3 Correlations of Duration of Infertility and Maternal BMI With Neonatal Complications, Delivery by Caesarean Section, and Neonatal Gender in PCOS and Non-PCOS Groups

Spearman rank correlation analyses were performed to investigate possible correlations between neonatal birth outcomes and pregravid characteristics of the mothers (Table 3). In the PCOS group, duration of infertility was correlated with neonatal complications in offspring ($p = 0.04$). Furthermore, pregravid maternal BMI was positively correlated with neonatal complications ($p = 0.03$), delivery by caesarean section ($p < 0.01$), and neonatal gender ($p = 0.04$). No other significant correlations were found for the PCOS group. For the non-PCOS group, duration of infertility and pregravid maternal BMI were positively correlated with delivery by caesarean section (both $p < 0.01$). No other significant correlations were found in the non-PCOS group.

3.4 Predictive Values of Duration of Infertility and Maternal BMI for Neonatal Complications and Delivery by Caesarean Section of Singletons in PCOS Mothers Following IUI

We next performed logistic regression analysis to further confirm whether maternal duration of infertility and BMI were predictors of neonatal complications in singletons born to PCOS mothers after IUI. As shown in Table 4, the unadjusted odds ratio (OR) of duration of infertility for neonatal complications was 1.42 ($p = 0.02$), with an adjusted OR of 1.06 ($p = 0.79$). For maternal BMI, the unadjusted OR for neonatal complications was 1.28 ($p = 0.03$), while the adjusted OR was 1.30 ($p = 0.04$).

We also examined the predictive values of duration of infertility and maternal BMI on the delivery by caesarean section of singletons born to PCOS mothers. As shown in Table 5, the duration of infertility was not a predictor of caesarean section delivery of singletons, independent of statistical adjustment (unadjusted OR = 1.18, $p = 0.200$; adjusted OR = 0.93, $p = 0.690$). However, maternal BMI was a significant positive predictor for caesarean section delivery, even after adjustment (unadjusted OR = 1.25, $p = 0.006$; adjusted OR = 1.28, $p = 0.005$).

3.5 Predictive Values of Duration of Infertility and Maternal BMI for Neonatal Complications and Caesarean Section Delivery of Singletons Born to Non-PCOS Mothers Following IUI

Next, logistic regression analysis was performed on data from the non-PCOS group. As shown in Table 6, neither the duration of infertility nor maternal BMI was a predictor for the risk of neonatal complications in singletons born to non-PCOS mothers, independent of statistical adjustments.

As shown in Table 7, the duration of infertility was a significant positive predictor for increased risk of caesarean section delivery of singletons born to non-PCOS mothers, although this was no longer significant after statistical adjustment (unadjusted OR = 1.18, $p = 0.020$; adjusted OR = 1.10, $p = 0.230$). Maternal BMI was also a significant positive predictor for caesarean section delivery of singletons born to non-PCOS mothers, independent of statistical adjustment (unadjusted OR = 1.15, $p = 0.004$; adjusted OR = 1.14, $p = 0.014$).

4. Discussion

Although many studies have investigated the birth outcomes of neonates who were born to mothers with PCOS, these were mainly carried out in the context of IVF [10–13]. IVF is an assisted reproductive technique in which fertilization and early embryo development occur independently of the PCOS maternal environment (i.e., hypersecretion of luteinizing hormone, hyperinsulinemia, and hyperandrogenism) [17–19]. It is believed that fertilization and early embryogenesis play critical roles in determining birth outcomes of neonates [20]. Therefore, findings from the

Table 3. Correlations of duration of infertility and maternal BMI with neonatal complications, caesarean section and neonatal gender in PCOS and non-PCOS groups.

Investigated characteristics		PCOS (n = 101)			Non-PCOS (n = 204)		
		Neonatal complications ¹	Caesarean section	Neonatal gender	Neonatal complications ¹	Caesarean section	Neonatal gender
Duration of infertility	Correlation coefficient	0.19	0.13	0.07	0.05	0.19	0.01
	p-value	0.04	0.16	0.43	0.42	<0.01	0.87
Maternal BMI	Correlation coefficient	0.21	0.26	0.19	0.08	0.23	0.04
	p-value	0.03	<0.01	0.04	0.23	<0.01	0.53

¹Complications include admission to the neonatal ICU, fetal asphyxia, fetal growth restriction, oligohydramnios, low birthweight, preterm birth, macrosomia, Apgar score <7, and other minor congenital defects.

Table 4. Predictive values of duration of infertility and maternal BMI for neonatal complications in singletons born to mothers with PCOS following IUI insemination.

Factors investigated	Complications of singletons born to PCOS mothers ¹ (n = 101)			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Duration of infertility	1.42 (1.04–2.10)	0.02	1.06 (0.67–1.67) ²	0.79
Maternal BMI	1.28 (1.02–1.60)	0.03	1.30 (1.01–1.67) ³	0.04

OR, odds ratio; CI, confidence interval.

¹Complications include admission to neonatal ICU, fetal asphyxia, fetal growth restriction, oligohydramnios, low birthweight, preterm birth, macrosomia, Apgar score <7, and other minor congenital defects.

²Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and BMI.

³Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and duration of infertility.

Table 5. Predictive values of duration of infertility and maternal BMI for caesarean section delivery of singletons born to mothers with PCOS following IUI.

Factors investigated	Caesarean section delivery of singletons born to PCOS mothers (n = 101)			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Duration of infertility	1.18 (0.91–1.54)	0.200	0.93 (0.65–1.32) ¹	0.690
Maternal BMI	1.25 (1.06–1.48)	0.006	1.28 (1.07–1.53) ²	0.005

¹Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and BMI.

²Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and duration of infertility.

Table 6. Predictive values of duration of infertility and maternal BMI for neonatal complications in singletons born to mothers without PCOS following IUI.

Factors investigated	Complications of singletons born to non-PCOS mothers ¹ (n = 204)			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Duration of infertility	1.01 (0.84–1.21)	0.86	1.08 (0.88–1.32) ²	0.43
Maternal BMI	1.06 (0.94–1.19)	0.34	1.02 (0.89–1.17) ³	0.71

¹Complications include admission to neonatal ICU, fetal asphyxia, fetal growth restriction, oligohydramnios, low birthweight, pre-term birth, macrosomia, Apgar score <7, and other minor congenital defects.

²Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and BMI.

³Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and duration of infertility.

Table 7. Predictive values of duration of infertility and maternal BMI for caesarean section delivery of singletons born to mothers without PCOS following IUI.

Factors investigated	Caesarean section delivery of singletons born to non-PCOS mothers (n = 204)			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Duration of infertility	1.18 (1.02–1.37)	0.020	1.10 (0.93–1.30) ¹	0.230
Maternal BMI	1.15 (1.04–1.27)	0.004	1.14 (1.02–1.27) ²	0.014

¹Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and BMI.

²Adjusted for type of protocol for ovulation induction, infertility etiology, maternal age, previous IUI history, and duration of infertility.

previous studies may not accurately reflect the interplay between embryonic development and the PCOS maternal environment. On the other hand, IUI is an assisted reproductive technique that allows fertilization and embryo development to occur within the PCOS maternal environment. The present results were obtained in the context of IUI and are therefore more likely to mirror the interplay between embryonic development and the PCOS maternal environment.

IVF is a complex, costly and invasive approach that is normally used as an alternative for infertile PCOS women who fail to conceive after several attempts with IUI treatments [7]. In contrast, IUI is a simple, economical and patient-friendly technique for enhancing the likelihood of pregnancy. IUI is currently considered to be the first-line treatment for infertile PCOS women [7]. Specialists in reproductive medicine recommend that infertile PCOS women undergo at least three attempts with IUI treatment before switching to IVF [9]. A retrospective cohort study reported a cumulative live birth rate per PCOS patient of up to 31% after three cycles of IUI [9]. Because of this success, a considerable number of neonates are now born to PCOS mothers following IUI.

The above observations demonstrate the clinical importance of evaluating birth outcomes for neonates born to PCOS mothers following IUI. This, and possible correlations with pregravid maternal characteristics, have so far remained largely unknown. In the present study, Spearman correlation analysis and logistic regression analysis revealed that pregravid maternal BMI was positively associated with a heightened risk of neonatal complications in singletons born to PCOS mothers after IUI, but not in those born to non-PCOS mothers after IUI. This finding suggests that an elevated pregravid BMI affects the growth and development of offspring differently in PCOS mothers compared to non-PCOS mothers. However, until now it has been uncertain whether the increased risk of neonatal complications in singletons born to PCOS mothers with high BMI was due to the PCOS or the high BMI, or indeed to an interaction between PCOS and high BMI.

The influence of high pregravid BMI on the adverse complications of neonates born to PCOS mothers is still only partly understood, with further research still needed. A previous study showed that obesity can aggravate hyperin-

sulinemia and hyperandrogenism, both of which are important features of PCOS [17]. This aggravating effect is significantly intensified following conception in women with PCOS. Insulin can promote a prothrombotic and profibrotic environment, as well as facilitate vascular vasoconstriction, resulting in increased blood pressure [17]. This environment, together with changes in uterine artery blood flow in women with PCOS, may eventually affect fetal growth and development [18].

A hyperandrogenic or hyperinsulinemic environment can also exert proinflammatory effects [17,19], leading to increased levels of serum C-reactive protein, inflammatory cytokines, white blood cells, and cell adhesion molecules [21]. This inflammatory environment, in concert with adverse placental changes caused by PCOS (e.g., changes in spiral arteries, placental vascular lesions, and inflammation), can cause a decrease in embryo implantation, miscarriage, detrimental pregnancy outcomes, and transgenerational effects on the offspring [19,22]. These previous studies suggest that elevated maternal BMI may act in concert with PCOS to synergistically affect the growth and development of neonates born to PCOS mothers, presumably in a more robust way than non-PCOS mothers.

We also discovered that maternal BMI was positively associated with an elevated risk of caesarean section delivery of singletons, irrespective of PCOS in the mother. However, the adjusted OR and p-values for caesarean section delivery of singletons born to PCOS mothers (OR = 1.28, $p = 0.005$) were higher and more significant, respectively, compared to those of non-PCOS mothers (OR = 1.14, $p = 0.014$). This observation suggests that elevated maternal BMI confers additional risk for caesarean section delivery of neonates born to PCOS mothers. Previous authors have reported positive associations between maternal obesity and an increased risk of delivery by caesarean section [23,24]. A meta-analysis by Qin *et al.* [25] found that PCOS was also associated with delivery by caesarean section. However, it is unclear whether there are any interactions between obesity and PCOS in terms of their influence on caesarean section delivery. Several authors have proposed that certain obesity-related pathophysiological events, such as lipid abnormalities, metabolic syndrome and hypertension may predispose obese women with PCOS to an elevated

risk of caesarean section delivery [26–28]. Peeva *et al.* [29] concluded the high rate of deliveries by caesarean section in obese women with PCOS could in part be linked to increased resistance to insulin and impaired tolerance to glucose, both of which are common in PCOS. Our findings are consistent with the above hypothesis and suggest that elevated maternal BMI may act in synergy with PCOS to further increase the risk of caesarean section delivery.

Furthermore, as shown in **Supplementary Table 3**, prevalence rates of individual neonatal complications observed herein were lower as compared to those reported in the general IUI population and natural conception population [30–35]. This discrepancy might be due to differences in the constitution of the study subjects among different studies. For those referenced studies [30–35], they either included cases with male mild infertility or did not exclude cases with male infertility. However, cases with male infertility or karyotypic abnormality were strictly excluded in our study, which might partly explain the lower prevalence rates of individual neonatal complications observed herein.

Limitations

This study has a number of limitations. First, its retrospective design and relatively small sample size necessitate caution when interpreting the results. Second, our study was based on data from a single center, and further multicenter, prospective and randomized investigations with sufficient cases are necessary to confirm the observed associations. Third, another limitation is the lack of analysis of maternal pregnancy complications, such as gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia, preterm premature rupture of membranes and infections during pregnancy. Therefore, residual confounding effects from maternal pregnancy complications could not be appropriately adjusted and might have affected our findings. Lack of analysis of maternal pregnancy complications limits the interpretability of the associations reported between pregravid BMI, PCOS, and neonatal complications. At the conceptual stage of our study, we meant to include maternal pregnancy complications in our study. Initial data assessment found that data concerning maternal pregnancy complications are few and incomplete, making it infeasible to investigate this topic and draw a convincing conclusion. However, as an extension of this study, we will continue to investigate this topic once we have collected sufficient data. Moreover, the possible synergistic effect between elevated maternal BMI and PCOS found here warrants further *in vivo* verification using mouse models of obesity and PCOS.

5. Conclusions

The coexistence of elevated maternal BMI and PCOS may be associated with an elevated risk of neonatal complications and caesarean section delivery following IUI. Our study underscores the importance of basic care and of the

need to screen for perinatal complications in neonates born to obese mothers with PCOS. It is also advised to maintain a healthy pregravid BMI in PCOS mothers so as to minimize the risk of adverse neonatal complications in their offspring.

Abbreviations

ART, assisted reproductive technology; HCG, human chorionic gonadotropin; β -hCG, β -human chorionic gonadotropin; BMI, body mass index; CI, confidence interval; COS, controlled ovarian stimulation; FSH, follicle-stimulating hormone; Gn, gonadotrophin; IUI, intrauterine insemination; IVF, *in vitro* fertilization; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; GnRH-a, gonadotropin-releasing hormone agonists.

Availability of Data and Materials

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Author Contributions

BW and SL contributed to the design, data collection, supervision, and compilation. ZL was responsible for the organization, conceptualization, methodology, and revision of the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Institutional Ethics Committee of The First Affiliated Hospital of Shantou University Medical College approved this study (Ethical Approval Number: B-2025-185). All participants gave written informed consent. This study was carried out according to the principles of the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/CEOG42801>.

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