Early and late pregnancy loss in women with polycystic ovary syndrome undergoing IVF/ICSI treatment: a retrospective cohort analysis of 21,820 pregnancies.

He Cai[1], Stephan Gordts[2], Hui Wang[1], Tao Wang[1], Na Li[1], and juanzi Shi[1]

[1]Northwest Women and Children's Hospital
[2]Life Expert Centre

August 6, 2020

Abstract

Objective To examine early and late pregnancy loss in women with and without polycystic ovary syndrome (PCOS) undergoing IVF/ICSI transfers. Design Retrospective cohort study. Setting Reproductive medicine center at a tertiary hospital. Population Records were reviewed for women with a positive β-hCG after IVF/ICSI treatment from May 2014 to April 2019. Methods Odds ratios (ORs) for early (13 [?]weeks) and late (13-24 weeks) pregnancy loss were calculated among women with and without PCOS for plurality of the pregnancy with adjustment for confounding factors. Main outcomes measures Early and late pregnancy loss. Results A total of 21,820 charts identified with a positive β-hCG, 2,357 (10.8%) subjects had PCOS, and 19,463 (89.2%) controls did not. Early pregnancy loss occurred in 12.4% of women with PCOS versus 12.8% in women with non-PCOS. Women with PCOS demonstrated a higher rate of late pregnancy loss (5.4% in PCOS vs 3.1% in non-PCOS, OR 1.79, 95%CI, 1.46-2.19, P<.001), regardless of the plurality of the pregnancy (one gestational sac: 4.1 vs. 2.7 percent, OR 1.56, 95%CI,1.18-2.05; [?] two gestational sacs: 8.1 vs. 4.1 percent, OR 2.08, 95%CI,1.54-2.82, PCOS vs. Non-PCOS, respectively). Potential negative impact of PCOS was reduced to marginal level once BMI were taken into account (aOR 1.42, 95% CI, .99-2.03). BMI and maternal comorbidities were independently associated with late pregnancy loss (aOR 1.65, 95%CI, 1.26-2.17 and aOR 2.07,95%CI,1.43-3.00). Conclusions PCOS women with overweight and preexisting comorbidities would benefit from lifestyle intervention and close surveillance throughout the whole pregnancy.

Early and late pregnancy loss in women with polycystic ovary syndrome undergoing IVF/ICSI treatment: a retrospective cohort analysis of 21,820 pregnancies

Running title

Early and late pregnancy loss in PCOS

He Cai, M.D.,[a] Stephan Gordts, M.D.,[b] Hui Wang, M.D.,[a] Tao Wang, M.D., [a] Na Li, M.D., [a] Juanzi Shi, M.D., Ph.D·[a]

Corresponding author

Juanzi Shi, M.D., Ph.D.

Assisted Reproduction Center, Northwest Women and Children's Hospital, Xi'an, People's Republic of China.

Mail: 73#, Houzaimen North Street, Xi'an, China

E-mail: shijuanziart@126.come

[a] Assisted Reproduction Center, Northwest Women and Children's Hospital, Xi'an, People's Republic of China.

[b] Leuven Institute for Fertility & Embryology, Schipvaartstraat 4, 3000 Leuven, Belgium.

Objective : To examine early and late pregnancy loss in women with and without polycystic ovary syndrome (PCOS) undergoing IVF/ICSI transfers.

Design: Retrospective cohort study.

Setting: Reproductive medicine center at a tertiary hospital.

Population: Records were reviewed for women with a positive β-hCG after IVF/ICSI treatment from May 2014 to April 2019.

Methods: Odds ratios (ORs) for early (13 [?]weeks) and late (13-24 weeks) pregnancy loss were calculated among women with and without PCOS for plurality of the pregnancy with adjustment for confounding factors.

Main outcomes measures: Early and late pregnancy loss.

Results : A total of 21,820 charts identified with a positive β-hCG, 2,357 (10.8%) subjects had PCOS, and 19,463 (89.2%) controls did not. Early pregnancy loss occurred in 12.4% of women with PCOS versus 12.8% in women with non-PCOS. Women with PCOS demonstrated a higher rate of late pregnancy loss (5.4% in PCOS vs 3.1% in non-PCOS, OR 1.79, 95%CI, 1.46-2.19, P<.001), regardless of the plurality of the pregnancy (one gestational sac: 4.1 vs. 2.7 percent, OR 1.56, 95%CI,1.18-2.05; [?] two gestational sacs: 8.1 vs. 4.1 percent, OR 2.08, 95%CI,1.54-2.82, PCOS vs. Non-PCOS, respectively). Potential negative impact of PCOS was reduced to marginal level once BMI were taken into account (aOR 1.42, 95% CI, .99-2.03). BMI and maternal comorbidities were independently associated with late pregnancy loss (aOR 1.65, 95%CI, 1.26-2.17 and aOR 2.07,95%CI,1.43-3.00).

Conclusions : PCOS women with overweight and preexisting comorbidities would benefit from lifestyle intervention and close surveillance throughout the whole pregnancy.

Keywords : Polycystic ovary syndrome, pregnancy loss, vanishing twins, overweight, comorbidity, pregnancy outcomes

Tweetable abstract

PCOS women are at increased risk of late pregnancy loss, which is associated with elevated BMI and maternal comorbidities.

Introduction

Polycystic ovary syndrome (PCOS), characterized by ovulatory dysfunction, biochemical or clinical hyperandrogenism, and polycystic ovaries, is one of the most common endocrine disorders, affecting 5.5–21% of women of reproductive age.[1-5] To conceive, many women with PCOS failing to ovulate with clomiphene citrate and low-dose gonadotropin might require assisted reproductive technology (ART).[6,7] It is estimated that in women attending infertility clinics, PCOS accounts for up to 70% of patients suffering from anovulatory infertility.[7,8]

In addition to the difficulty of conceiving, PCOS patients who are fortunate enough to become pregnant after either spontaneous or assisted conception, are still faced with the distressing issue of having increased risk for pregnancy loss. Previous studies indicate that PCOS patients are thought to have 30–50% rates of pregnancy loss which is three times higher than normal women.[9,10] However, it is still unclear if the pathology of PCOS as such increase the risk of pregnancy loss following ART treatment or if maternal characteristics such as maternal age, body mass index (BMI) or multiple pregnancies play a crucial role in the higher rates.

Available data are limited in small size and most were unable to distinguish between early and late pregnancy loss. Current evidence on the associations among maternal characteristics, pre-existing health conditions, pregnancy plurality and pregnancy loss at different gestational ages is inadequate, which is important in counseling PCOS cases about their risks of loss throughout pregnancy.

We carried out a large cohort study of pregnant women after ART to access the risk of early and late pregnancy loss in women with PCOS. Furthermore, given that multiple pregnancies are common in IVF practice, the pregnancy loss was also calculated for each gestational sac separately.

Methods

Study population

Records were reviewed for all women who underwent fresh or frozen autologous IVF/intracytoplasmic sperm injection (ICSI) cycles at the Assisted Reproduction Center of Northwest Women's and Children's Hospital, Xi'an, China. A cohort of women with positive serum β- human chorionic gonadotropin (β-hCG) after embryo transfer between May 2014 and April 2019 were included. Demographical traits, cycle characteristics, clinical and laboratory data were extracted from electronic medical records. If a clinical intrauterine pregnancy resulted, the maximum number of fetal sacs in early pregnancy, the pregnancy and perinatal outcome were included. Figure 1 shows the flowchart of patient selection and an overview of the treatment.

The diagnosis of PCOS was re-evaluated according to the Rotterdam criteria with satisfying at least two of the three criteria:[11] oligo-/anovulation (a cycle length >35 days or variation between consecutive menstrual cycles of >10 days); clinical or biochemical hyperandrogenism; ultrasound diagnosis of polycystic ovary morphology.[12]Patients with other causes of hyperandrogenism and ovulation dysfunction (congenital adrenal hyperplasia, Cushing's syndrome and androgenic-secreting tumors) were excluded. Exclusion criteria also included patients with recurrent pregnancy loss, uterine malformations, treatment with preimplantation genetic testing (PGT) and those involving donor sperms and oocytes.

The baseline characteristics were the female age, body mass index (BMI), maternal underlying medical conditions, gravidity and parity, history of prior spontaneous pregnancy loss as well as basal hormone levels. Age (years) and BMI (kg/m^2) were also categorized for the clarity of data analysis. Three age subgroups were formed: age <30 years, 30-34 years and [?]35 years. BMI subgroups were: <25 kg/m^2 (normal), 25-29.9 kg/m^2 (overweight), [?]30 kg/m^2(obesity). Infertility diagnosis (ovulation dysfunction, male and tubal factor, unexplained and multiple diagnoses) were included as categorical variables. Cycle characteristics included the insemination type (conventional IVF, ICSI or a combination of IVF and ICSI), fresh versus frozen cycle, the number and quality of transferred embryos.

Stimulation and embryos transfer protocol

For a full description of the IVF protocols, luteal phase support, and laboratory procedures please refer to our previous publication.[13] Embryos were cultured to day 3 or day 5 depending on the number of embryos of good morphological quality on day 3. The strategy of the number of embryos transferred changed gradually during the study period. From 2014 to July 2018, one or two of the best quality embryos were transferred into the uterus on day 3 or 5. Since Sep 2018, offering transfer of single-embryo is the routine in clinical care. If two embryos were transferred, the quality of the best embryo was used for analysis. Embryonic cleavage and morphologic appearance were assessed as described previously.[14] In case of high risk of OHSS or those with elevated serum progesterone levels on the day of ovulation trigger embryos were electively cryopreserved at the physician's discretion and after discussion with the patient. Embryos that were cryopreserved in 'freeze-all' cycles and supernumerary embryos which were vitrified, were transferred in artificially supplemented cycles or in natural cycles. The vitrification, warming procedure, endometrial preparation and embryos transfer procedures was done according to standard protocols.[15] If pregnancy was achieved, luteal phase support was continued until 10 weeks' gestation.

Pregnancy assessment and outcomes

Pregnancy was defined as a serum β-hCG level greater than 20 IU/L 14 days after cleavage embryo transfer or 12 days after blastocyst transfer. If the β-hCG assay yielded a positive result, the patient underwent ultrasonographic monitoring to determine the number of gestational sacs and fetal viability at the 6^{th}-7^{th} week of gestation. A biochemical pregnancy loss was defined as a pregnancy without the intrauterine gestational sac that resolved spontaneously. Clinical pregnancy was defined as an intrauterine gestational sac visible by means of transvaginal ultrasound coincident with a positive serum β-hCG concentration. The ongoing pregnancy was defined by presence of fetal heart beat on ultrasound scan at 12 weeks' gestation. Live birth was defined as delivery of a live-born infant after 24 weeks' gestational age.

The primary endpoint of interest was clinical pregnancy loss which was defined as a pregnancy ending before 24 weeks of gestation, which were further categorized based on gestation length: early pregnancy loss ([?]13 weeks), late pregnancy loss (13-24 weeks).[16,17] We also examined the rate of pregnancy loss stratified by plurality of the pregnancy, defined as the number of fetal sacs on early ultrasound. Pregnancies with two and more than two fetal sacs in the ultrasound were combined in the analysis because of low numbers. Vanishing twins was defined as pregnancy with two intrauterine gestational sacs at 6-7 weeks' gestation but that eventually delivered one infant. Fetuses dying after [?]24 gestational weeks are registered as stillborn. Ectopic pregnancies and hydatid moles were excluded from the pregnancy loss analyses due to their different etiology.

Maternal complications in the analysis included gestational diabetes mellitus (GDM) diagnosed via the 75 g 2-hour oral glucose tolerance test,[18] hypertensive disorders of pregnancy, including gestational hypertension or pre-eclampsia, placental abruption and placenta previa, premature rupture of the membranes (PROM), macrosomia (birth weight >4,000g). Neonatal outcome variables included gestational age at delivery, preterm birth (PTB; <32 and <37 weeks), low birthweight (<1,500 and <2,500 g) and macrosomia (>4,000 g). With the intention to eliminate the impact of multiple pregnancies on maternal and newborn outcomes, we restricted the analysis to only singletons.

Statistical analysis

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., USA). Categorical data were presented by the number of cases and corresponding percentage and continuous data were presented as the mean value ± SD. Categorical data and continuous data that did not show a normal distribution were analyzed by Pearson's chi-squared test/Fisher's exact test or Kruskal–Wallis test as appropriate. Binary logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) of pregnancy loss and to evaluate the effect of potential confounders. Female age and BMI were recorded as either continuous or categorical variables. Female age, BMI, number of embryo transferred, a history of previous pregnancy loss and comorbidities (hypertension and diabetes), were considered as a covariate potential confounders for the hypothesized relationships. P -values <0.05 were considered to indicate statistically significance.

Results

Of the 21820 charts identified with a positive β-hCG, 2357 (10.8%) subjects had PCOS, and 19463 (89.2%) controls did not. After excluding the biochemical pregnancies (n=1382), ectopic pregnancies (n =130) and molar pregnancies (n =3), the study population consisted of 20305 clinical pregnancies (2224 cases with PCOS; 18081 controls without) (Figure 1). Among 2224 intrauterine pregnancies with PCOS, 394 ended in pregnancy loss (17.7 %). 275 (12.4% of total pregnancies) were early pregnancy losses, 119 (5.4%) were late pregnancy losses and 5 (2.7were stillbirths. In pregnancies without PCOS (n=18081), there were 2861 pregnancy losses (12.8% in early stage and 3.1% in late stage) and 18 (1.2

Patient characteristics

Differences in women characteristics were observed between patients with and without PCOS (Table 1). Specifically, women with PCOS were more likely to be younger than the non-PCOS women (29.3±3.3 vs 30.5±4.2). PCOS patients were more often nulliparous than controls (64.7% vs 57.7%, P <.001) and over-

weight (BMI [?]25kg/m^2) and obese (BMI [?]30 kg/m^2) were more common in women with than without PCOS (33.3% vs 17.0%, and 9.2% vs 1.7%, P <.001). The prevalence of hypertensive disease and diabetes mellitus were significantly higher (5.9% and 1.2%) in women with PCOS as compared with women with non-PCOS (2.7% and 0.2%). Anovulation was recorded as the indication for fertility treatment in 930 patients (39.5%) with PCOS and male factor being mentioned as an indication in 423 (17.9%). Whereas, tubal and male factor infertility were major causes in women without PCOS (47.8% and 23.9%, respectively). Basal serum FSH level was lower in the those with PCOS as presumed, alternatively, number of antral follicle count and levels of total testosterone and LH were significantly higher adjusting for age. There was no significant difference in having a history of prior pregnancy loss (P = .060) between women with and those without PCOS. In this cohort women, more PCOS cases were treated by conventional IVF compared with of controls (81.2 vs 71.4%). Rate of high quality of transferred blastocysts was slightly higher in the PCOS group than in the control group (55.8 vs 50.0%), however, no significant difference was seen in the quality of embryo in day 3 between two groups

Female age was found to be effect modifier, so we stratified the analysis. Figure 2B displays the age-stratified association between the PCOS and pregnancy loss. We found that regardless of age and PCOS status, the risks of having pregnancy loss were higher in the first trimester. In PCOS group, the risk of pregnancy loss decreased from 12.4 percent in the first trimester to 5.4 percent during the secondary trimester. We observed that younger women (<35 years) with PCOS had higher odds of late pregnancy loss (>13 weeks) when compared with same age group without PCOS (<25 years: 6.9 vs. 2.2 percent; 25-35 years: 5.3 vs. 3.2 percent, PCOS vs. Non-PCOS, respectively). However, no significant difference was seen among those over 35 years of age (4.3 vs. 2.8 percent, P =.337). As expected, in both of the two groups, the risk of early pregnancy loss increased with increasing maternal age (P =.046 and$P$ <.001). However, the change related to maternal age became less significant during the secondary trimester. No significant differences in late pregnancy losses were seen among three age groups (Table 2).

When data were analyzed according to the type of embryo transfer procedure, increased risk of late pregnancy losses was also seen in women with PCOS using either freshly or thawed fertilized embryos (4.6 vs. 2.7 percent, OR 1.71, 95%CI, 1.21-2.40, P =.02; 5.9 vs. 3.3 percent, OR 1.81, 95%CI, 1.41-2.34, P <.001, freshly and thawed fertilized, respectively) (Table 3). No significant difference in early pregnancy loss was found between women with and without PCOS, irrespective of the type of embryo transfer procedure (Figure 2C).

We calculated the risk of early and late pregnancy loss by pregnancy plurality on early ultrasound for the 20305 clinical pregnancies. The number of pregnancy loss, partial pregnancy losses (vanishing co-twins), singletons and twin deliveries are shown in Table 4. The results indicated that there was no significant difference in early pregnancy loss between the PCOS and non-PCOS group (one gestational sac: 15.7% vs 16.0%, OR 0.98, 95%CI, .85-1.14, P=.794; [?] two gestational sacs: 5.1 vs. 4.8 percent, OR 1.06, 95%CI, .74-1.52, P=.738, PCOS vs. Non-PCOS, respectively). However, after 13 weeks' gestation, women with PCOS had significantly higher risk of pregnancy loss. For pregnancies with one fetal sac on ultrasound, the risk of loss was increased significantly for patients with PCOS (4.1% vs 2.7%, OR 1.56, 95%CI,1.18-2.05,P =.002). Among pregnancies with two or more fetal sacs, there was a tendency towards a higher incidence of pregnancy losses during the whole gestation in the PCOS group compared with non-PCOS group (93/703 (13.2%) vs 464/5215 (8.9%), OR 1.56, 95%CI,1.23-1.98, P<.001); Women with PCOS had a doubled risk of late pregnancy loss compared with women without PCOS (57/703 (8.1%) vs 212/5215 (4.1%), OR 2.08, 95%CI,1.54-2.82, P <.001).

Logistic regression to assess risk of early and late pregnancy loss

Early pregnancy loss

PCOS status did not influence the risk of early pregnancy loss, not even after adjusting for age and the other confounders (Table 5). Compared with women who were <35 years of age, women aged [?]35 years had higher early pregnancy loss risk (P <.001, 95% CI, 1.65-2.39). Overweight, comorbidities including gestational diabetes and hypertension and single-embryo transfer (SET) were also positively associated with

early pregnancy loss. Previous pregnancy loss was also not related to early pregnancy loss after adjusting for cofounders.

Late pregnancy loss

The diagnosis of PCOS was associated with late pregnancy loss in the univariate analysis (OR 1.79, 95% CI, 1.79 (1.46-2.20,P <.001) and in a multivariable regression Model 1 (adjusted OR 1.60, 95% CI, 1.13–2.28, P =.009) (Table 6). However, the effect was reduced into marginal after adjusted for BMI (Model 2), (adjusted OR 1.42, 95% CI, .99-2.03, P = .059). BMI was independently associated with late pregnancy loss in the overweight groups (adjusted OR 1.65, 95% CI, 1.26-2.17, P <.001). Regardless of PCOS, preexisting medical conditions have a significant effect on pregnancy loss rate, either before or after adjustment for confounders. Contrary to the early stage, lower risk of late pregnancy loss was seen in SET when compared to double-embryo transfer (DET) (P =.009, 95% CI, 1.06-1.49), but the effect was reduced to a non-significant level after adjustment for other confounders (P =.152, 95% CI, 0.93-1.56). As gestation developed, maternal age had no significant negative effect on late pregnancy loss (adjusted OR 1.03, 95% CI, .99-1.06, P =.109). Again, a history of prior pregnancy loss was not independently associated with late pregnancy loss.

Obstetric and Perinatal Complications

Among the 1356 live-born singletons in patients with PCOS, 1218 singletons were from singleton gestations and 138 (10.2%) were survivors of a twin conception in early weeks. In pregnancies without PCOS, 10456 singletons resulted from singleton gestations and 1245 (10.6%) were derived from vanishing twins. There is no significant difference in the rate of vanishing twins between groups (P =.600) (Table 7). To facilitate comparison of obstetric and neonatal outcome parameters between pregnancies with PCOS and without PCOS, data analysis was restricted to singleton pregnancies with confirmed outcome. Women with a diagnosis of PCOS had a higher risk of developing hypertensive disorder of pregnancy or pre-eclampsia than women with no such diagnosis (P =.001, P <.001, respectively). PCOS cases had a nearly doubled risk of GMD compared with those without PCOS (12.8 vs 6.9, P <.001). Infants born to mothers with a diagnosis of PCOS were more often suffered from preterm (10.9 vs 8.7,P =.008) and very preterm birth (1.8 vs 1.0, P =.009), but were not at increased risk of LBW and very LBW (5.9 vs 5.3,P =.266, 1.0 vs 0.7, P =.205). The average birthweight in children with PCOS mothers was greater than in controls (3.34 +- 0.57 vs 3.30 +- 0.52, P =.023) and the risk of macrosomia was also significantly increased in former group (11.7 vs 8.4,P <.001).

Discussion

Main Findings

When the pregnancy began, there was a significantly higher rate of late pregnancy loss among the PCOS population, without an increase in the rate of early clinical pregnancy loss. However, in the final adjusted model, PCOS was no longer associated with increased risk of late pregnancy loss. Adverse pregnancy outcome in PCOS may be influenced by increased BMI and underlying medical conditions rather than an independent effect of PCOS.

Strengths and limitations

There are some limitations to acknowledge. First, due to the retrospective character, information about preexisting conditions and gestation-related health issues could be incomplete and underreporting. Insulin concentrations were measured in only a few of the PCOS cases, we did not explore the correlation between the pregnancy insulin resistance and the occurrence of GDM. Secondary, the lines between spontaneous and induced abortion was not clearly distinguished. However, the proportion of induced abortion in this study is negligible, because women are conceived by ART thus artificial abortion is performed very seldom, and only on maternal medical indication. Finally, as we restricted our analyses to pregnancies conceived by ART, our results may not be generalizable to women with natural pregnancies. To draw firm conclusions on the risk of pregnancy loss in PCOS cases, multi- center studies cross country is needed.

The major strength of our study is in its real-world based data with a large sample size of women. Unlike most previous studies, we were able to distinguish between early and late pregnancy loss. Evaluating risk of pregnancy loss at different gestational ages is critical in understanding its etiology and in counseling pregnant women about their possibility of pregnancy loss. Additionally, we also calculated the risk for pregnancy loss stratified by plurality of the pregnancy sac on early ultrasound, which strengthens our findings.

Interpretation

While previous studies have shown that women with PCOS are more prone to suffer from early pregnancy loss,[19-22] we show here, as Sterling et al.[23] suggested, that risk of early pregnancy loss did not differ markedly between PCOS cases and controls. Furthermore, findings in the current study extended upon previous literature. PCOS cases in the previous study were within the normal range of BMI which does not therefore represent the whole spectrum of PCOS. They studied pregnancy outcomes after fresh embryo transfer only, whereas pregnancy losses in subsequent frozen embryo transfer were also included in our study.

An important finding of the present study was that late pregnancy loss appeared to have stronger associations with PCOS than early pregnancy loss. After 13 weeks of gestation, women with PCOS have been shown to be at higher risk of pregnancy loss, regardless the plurality of the pregnancy. In the adjusted model 1, late pregnancy loss was associated with the diagnosis of PCOS. The retrospective nature of our study design makes it difficult to elucidate the reasons for this finding. This may reflect the hypothesis of a different etiology of pregnancy loss in first and second trimester.

Some authors have argued that the risk of pregnancy loss is more related to the elevated BMI which is known to be associated with an increased risk other than PCOS status.[24-26] This is in congruence with the findings of this study. Although the cause of this association between PCOS and obesity remains unknown, overweight is present in 30%˜50%.[27-29] and in the present study 33.7% had BMI [?]25 kg/m^2 and 9.2% with BMI [?]30 kg/m^2. We noticed that the potential negative impact of PCOS was eliminated once BMI were taken into account in the fully adjusted Model 2. In line with our results, Joham et al,[3] suggested that PCOS was not independently predicts higher risk of a pregnancy loss. However, as overweight and obesity often coexisting with PCOS,[27-30] it is debatable whether data should be controlled for BMI.

Significant differences were found in maternal preexisting medical conditions with a markedly increased risks of hypertension and diabetes were noted in women with PCOS compare with women with non-PCOS, which was supported by other researches.[30-33] A recent review of PCOS patients, derived from a UK general practitioner research database with a mean age of 27 years followed for a median period of 4.7 years, demonstrated that women with PCOS had a higher systolic blood pressure.[30] Reports suggest that a woman with PCOS may have a fourfold increased risk of developing diabetes, and a 33% risk of impaired glucose tolerance.[33] Though overweight seems to be the most important predictor, the effect of comorbidities also remained statistically significant after multivariable analysis (Table 4 model 2)

Women with PCOS are prone to undergo ART, with its higher frequency of twins and multiple pregnancy. The loss of pregnancy due to multiple pregnancies have been evaluated in PCOS patients. Mikola et al.[34] found that the higher incidence of poor obstetric outcomes of PCOS pregnancies could partly explained by the increased number multiple pregnancies. As double-embryo transfer is still common, we here, subdivided the pregnancy loss rate according to the numbers of gestational sac in early ultrasound. Our results here do not suggest that the number of embryos transferred or multiple pregnancies alone increases the risk the pregnancy loss among patients with PCOS (Table 2 and Table 3). But the results should not be taken as a plea for DET or twin pregnancies for those with PCOS. On the contrary, higher rate of late pregnancy loss was observed when DET was performed in both of the two groups, confirming that SET is a logical practice.[35] In line with previous studies,[36] we found that 25.8% percent of multi gestational pregnancies that progressed to a livebirth delivery experienced loss of at least one fetus during the pregnancy. More worryingly, spontaneous reductions in IVF/ICSI twin pregnancies have been suggested to be a possible cause of the increased morbidity in IVF singletons.[36-38] Message above is critical for the whole cohort of infertility patients since they frequently ask for more embryos to be transferred to secure a maximum chance

of success.

In the present study we found women with PCOS were slightly younger than women without the diagnosis. PCOS women frequently exhibit menstrual irregularities such as oligomenorrhea, hence are more likely to require medical assistance. With the awareness of the potentially reduced fertility, they could have started trying to conceive earlier. This hypothesis is supported by an observational study, which reported that women with PCOS are also more likely to have had their first pregnancy at a younger age.[33] Advanced maternal age is strongly correlated with early pregnancy loss in the study (Table 3), although we adjusted for maternal age in the multivariate analysis, a residual effect could still be possible. However, there was no association with maternal age and late pregnancy loss in PCOS or non-PCOS cases, before and after multivariable analysis (Table 4). These findings need to be confirmed in future studies.

Various studies suggested that females with PCOS who conceive might suffer from pregnancy-related complications such as gestational diabetes,[39] pregnancy induced hypertension[39,40] to a higher extent in comparison to controls. Varies studies have shown that infants born to women with PCOS are also predisposed to many adverse health outcomes.[2,23,40] We have consistently reported an increase in maternal and neonatal complications for women with PCOS, even analysis was restricted to singletons. But we failed to find a correlation between PCOS and risk of caesarean section, which does not correspond with the findings of other studies. Differences can probably be explained by the high incidence of caesarean section in China, either caused by social or clinical factors, particular when women undergoing ART.

Conclusion

Understanding reproductive outcomes and risk of loss during the whole pregnancy for PCOS patients is important. Findings in the study, may inform a reproductive clinician on PCOS patients' risk of pregnancy loss based on maternal age, BMI, underlying medical conditions, pregnancy plurality, and gestational age of the fetus. PCOS women with obesity and comorbidities would benefit from lifestyle intervention and increased surveillance during pregnancy.

Disclosure of interests

None to declare.

Contribution to authorship

Juanzi Shi conceived the study question. He Cai and Juanzi Shi were responsible for the design of the study. He Cai and Na Li undertook the statistical analyses. Stephan Gordts, Tao Wang, and Hui Wang developed the first draft of the article, and all author contributed to the interpretation of findings and revising of drafts of the article. All authors approved the final article for publication.

Details of ethics approval

This study was approved by the Ethics Review Board of the Northwest Women's and Children's Hospital, Xi'an, China (ref. no. 2019013). Written informed consent was obtained from all patients before treatment, and the patients consented to the use of their retrospective data in scientific publications.

Funding

None.

Acknowledgments:

The authors thank Professor Ben W. Mol for language editing. We are very grateful to our volunteer patients for taking part in our research.

References

1. MarchWA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod

2010; 25:544-51.
2. Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. BMJ 2011;343:d6309.
3. Joham AE, Boyle JA, Ranasinha S, Zoungas S, Teede HJ. Contraception use and pregnancy outcomes in women with polycystic ovary syndrome: data from the Australian Longitudinal Study on Women's Health. Hum Reprod 2014;29(4):802-8.
4. Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85:2434-8.
5. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006;12: 673-83.
6. Angelica Linden Hirschberg. Polycystic ovary syndrome, obesity and reproductive implications. Womens Health 2009, 5(5):529-42.
7. Brassard M, AinMelk Y, Baillargeon JP. Basic infertility including polycystic ovary syndrome. Med Clin North Am 2008, 92, 1163-92.
8. Laven JS, Imani B, Eijkemans MJ and Fauser BC. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstet Gynecol Surv 2002; 57,755-67.
9. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 2002;87:524–9.
10. Giudice LC. Endometrium in PCOS: Implantation and predisposition to endocrine CA. Best Practice & Research Clinical Endocrinology & Metabolism 2006, 20(2):235-44.
11. Rotterdam ESHRE/SRM-sponsored PCOS Consensus Workshop Group. Revised 2003consensus on diagnostic criteria and long-term health risks related to polycystic ovarysyndrome (PCOS). Hum Reprod 2004;19:41-7.
12. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Hum Reprod Update 2003;9:505-14.
13. Shi W, Zhang S, Zhao W, Xia X, Wang M, Wang H, et al. Factors related to clinical pregnancy after vitrified-warmed embryo transfer: a retrospective and multivariate logistic regression analysis of 2313 transfer cycles. Hum Reprod 2013;28(7):1768-75.
14. Cai H, Mol BW, Li P, Liu X, Watrelot A, Shi J. Tubal factor infertility with prior ectopic pregnancy: a double whammy? A retrospective cohort study of 2,892 women. Fertil Steril 2020;113(5):1032-8.
15. Shi W, Xue X, Zhang S, Zhao W, Liu S, Zhou H, Wang M, Shi J. Perinatal and neonatal outcomes of 494 babies delivered from 972 vitrified embryo transfers, Fertil Steril 2012;97(6):1338-42.
16. National Institute for Health and Care Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management.NG126.2019. https://www.nice.org.uk/guidance/ng126.
17. Chu J, Hardy P, Beeson L, et al. What is the best method for managing early miscarriage? BMJ 2020;368:l6438
18. Thompson D, Berger H, Feig D, Gagnon R, Kader T, Keely E, et al. Diabetes and pregnancy. Can J Diabetes 2013;37(Suppl 1):S168–83.
19. Li HW, Lee VC, Lau EY, Yeung WS, Ho PC, Ng EH. Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. J Assist Reprod Genet 2014;31(2):205-11.
20. Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. J Womens Health (Larchmt) 2015;24(4):299-307.
21. Joham AE, Boyle JA, Ranasinha S, Zoungas S, Teede HJ. Contraception use and pregnancy outcomes in women with polycystic ovary syndrome: data from the Australian Longitudinal Study on Women's Health. Hum Reprod 2014;29(4):802-8.
22. Sahu B, Ozturk O, Ranierri M, Serhal P. Comparison of oocyte quality and intracytoplasmic sperm injection outcome in women with isolated polycystic ovaries or polycystic ovarian syndrome. Arch

Gynecol Obstet 2008;277:239-44.
23. Sterling L, Liu J, Okun N, Sakhuja A, Sierra S, Greenblatt E. Pregnancy outcomes in women with polycystic ovary syndrome undergoing in vitro fertilization. Fertil Steril 2016;105(3):791-7.e2.
24. Heijnen EM, Eijkemans MJ, Hughes EG, Laven JS, Macklon NS, Fauser BC. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. Hum Reprod Update 2006;12(1):13-21.
25. Hart R, Norman R. Polycystic ovarian syndrome–prognosis and outcomes. Best Pract Res Clin Obstet Gynaecol 2006;20:751-78.
26. McCormick B, Thomas M, Maxwell R, Williams D, Aubuchon M. Effects of polycystic ovarian syndrome on in vitro fertilization embryo transfer outcomes are influenced by body mass index. Fertil Steril 2008;90:2304-9.
27. Pasquali R, Gambineri A, Pagotto U. The impact of obesity on reproduction in women with polycystic ovary syndrome. Review. BJOG 2006, 113(10):1148-59.
28. Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. Hum Reprod 2001;16:226-9.
29. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. Int J Obes Relat Metabol Disord 2002; 26:883-96.
30. Morgan CL, Jenkins-Jones S, Currie CJ, Rees DA. Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study. J Clin Endocrinol Metab 2012;97:3251-60.
31. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012;33:981-1030.
32. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact.Trends Endocrinol Metab 2015;26:136-43
33. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab 2015; (3):911-9.
34. Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. Hum Reprod 2001;16(2):226-9.
35. Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005;365(9473):1807-16.
36. Dickey RP, Taylor SN, Lu PY, et al. Spontaneous reduction of multiple pregnancy: incidence and effect on outcome. Am J Obstet Gynecol 2002;186(1):77-83.
37. Pinborg A, Lidegaard O, la Cour Freiesleben N, Andersen AN. Consequences of vanishing twins in IVF/ICSI pregnancies. Hum Reprod 2005;20(10):2821-9.
38. Pinborg A, Lidegaard O, Freiesleben Nl, Andersen AN. Vanishing twins: a predictor of small-for-gestational age in IVF singletons. Hum Reprod 2007;22(10):2707-14.
39. Bruyneel A, Catteau-Jonard S, Decanter C, et al. Syndrome des ovaires polymicrokystiques: une pathologie a risque obstetrical? Gynecol Obstet Fertil 2014;42(2):104-11.
40. Naver KV, Grinsted J, Larsen SO, et al. Increased risk of preterm delivery and pre-eclampsia in women with polycystic ovary syndrome and hyperandrogenaemia. BJOG 2014;121:575-81.

Figure legends

Fig.1. Flow chart.

Fig.2. A. Early and late pregnancy loss between women with PCOS and women without PCOS. B. Risk of clinical pregnancy loss stratified by female age in relation to gestational age. C. Early and late pregnancy loss based on fresh or frozen embryo transfer.

Table 1. Baseline characteristics of the patients

Variable	Tubal Surgery (n=39)	IVF (n=95)	P value
Age, y	39.6 ± 3.2	38.8 ± 2.8	NS

Variable	Tubal Surgery (n=39)	IVF (n=95)	P value
[?]40 years, n (%)	22 (56.4)	37 (38.9)	NS
BMI (kg/m^2)	23.3 ± 2.8	22.8 ± 3.1	NS
Duration of infertility, y	5.1 ± 3.8	5.8 ± 4.8	NS
Infertility type, n (%)			
Primary	22 (56.4)	43 (45.3)	NS
Secondary	17 (43.6)	52 (54.7)	NS
History of pelvic surgery, n (%)	11 (28.2)	21 (22.1)	NS
Previous ART treatment, n (%)	16 (41.0)	59 (62.1)	0.03
AFC, n	3.9 ± 2.0	3.4 ± 1.9	NS
Basal FSH (IU/L)	9.7 ± 5.2	10.9 ± 5.1	NS
Basal estradiol (pg/ml)	41.8 ± 24.1	39.6 ± 20.4	NS

Values are presented as mean±SD or frequencies (percentage)

AFC: Antral follicle count; ART: Assisted reproductive technology; BMI: body mass index

Table 2. Risk of clinical pregnancy loss stratified by female age in relation to gestational age.

Female age, years	Early pregnancy loss ([?]13w)	Early pregnancy loss ([?]13w)	Early pregnancy loss ([?]13w)	Early p
n (%)	PCOS	PCOS	Non-PCOS	Non-P
	Total	Case (%)	Total	Case (
Total	2224	275 (12.4)	18081	2307 (
<25	159	15 (9.4)	779	83 (10.
25-35	1950	238 (12.2)	14150	1522 (
>35	115	22 (19.1)	3152	702 (2
P-value		**0.046**		**<0.00**

Table 3. Risk of clinical pregnancy loss stratified by type of transfer procedure in relation to gestational age.

	Early pregnancy loss ([?]13w)	Early pregnancy loss ([?]13w)	Early pregnancy loss ([?]13w)	Early pregnancy loss ([?]13w)	Late pregnancy loss (>13w)	Late pregnancy loss (>13w)	Late pregnancy loss (>13w)	Late pregnancy loss (>13w)
	PCOS	Non-PCOS	OR 95% CI	*P*-value	PCOS	Non-PCOS	OR 95% CI	*P*-value
Total	275 (12.4)	2307 (12.8)	.97 .84-1.10	.599	119 (5.4)	554 (3.1)	1.79 1.46-2.19	**<0.001**
Fresh embryo transfer	90 (10.1)	856 (10.6)	.94 0.76-1.185	.613	41 (4.6)	221 (2.7)	1.71 1.21-2.40	**.002**
Frozen embryo transfer	185 (13.9)	1451 (14.5)	.95 .809-1.125	.576	78 (5.9)	333 (3.3)	1.81 1.41-2.34	**<0.001**

Table 4. The number of pregnancy losses and livebirth according to the gestational sac in week 7.

Variables		One sac	One sac	[?] Two sacs[a]	[?] Two sacs[a]	[?] Two sacs[a]
n (%)	PCOS	Non-PCOS	*P*-value	PCOS	Non-PCOS	*P*-value
No. of women	1521	12866		703	5215	
Pregnancy loss	301 (19.8)	2397 (18.6)	0.273	93 (13.2)	464 (8.9)	**<0.001**?¿?
13 w	239 (15.7)	2055 (16.0)	0.794	36 (5.1)	252 (4.8)	0.738
>13 w	62 (4.1)	342 (2.7)	**0.002**	57 (8.1)	212 (4.1)	**<0.001**
Vanishing twins				152 (21.6)	1325 (25.4)	**0.029**?¿?
13w	-			138 (19.6)	1223 (23.5)	**0.024**
>13 w	-			14 (2.0)	102 (2.0)	0.949
No. of live-birth	1218 (80.1)	10456 (81.3)	0.282	607 (86.3)	4746 (91.0)	**<0.001**
Singletons	1218	10456		138 [b]	1245 [b]	
Twins	-	-		469	3501	
Still birth	2 (0.1)	13 (0.1)	0.668	3 (0.4)	5 (0.1)	0.059

a. Among the 5918 pregnancies showing two or more sacs on ultrasound, 81 were triplet pregnancies.

b. Singletons were survivors of vanishing twins.

Bold indicates *P*- value <0.05.

Table 5. Univariable and multivariable regression analysis of early pregnancy loss.

	Univariable regression	Univariable regression	Multivariable regression	Multivariable regression
	Odds radio (95% CI)	*P*-value	Odds radio (95% CI)	*P*-value
PCOS status				
No	Reference		Reference	
Yes	1.01 (0.88-1.15)	.918	1.03 (0.81-1.31)	.796
Maternal age, years	1.10 (1.09-1.11)	**<.001**	1.10 (1.08-1.12)	**<.001**
Maternal age				?¿?
35	Reference		Reference	
>35	2.33 (2.11-2.56)	**<.001**	1.99 (1.65-2.39)	**<.001**
BMI, kg/m^2	1.02 (1.01-1.03)	**<.001**	1.02 (1.01-1.04)	**<.001**
BMI				
<25	Reference		Reference	?¿?
25	1.53 (1.33-1.73)	**<.001**	1.42 (1.32-1.61)	**<.001**
Prior pregnancy loss	1.21 (1.00-1.46)	**.046**	1.03 (0.85-1.25)	.754
Comorbid conditions	1.21 (0.96-1.50)	**.103**	1.61 (1.27-2.04)	**<.001**
Embryo transferred				
SET	Reference		Reference	
DET	0.87 (0.80-0.94)	**.002**	0.86 (0.75-0.99)	**.037**

PCOS: polycystic ovary syndrome, BMI: Body mass index, SET: single embryo transfer, DET: double embryo transfer. The number of three embryo transfer is low which has been calculated in the group of DET.

Adjusted for maternal age, overweight, history of spontaneous miscarriage, number of embryos transferred and medical conditions (diabetes, hypertensive disease).

Bold indicates *P*- value <0.05.

Table 6. Univariable and multivariable regression analysis of risk of late pregnancy loss.

	Univariable regression	Univariable regression	Multivariable regression Model 1	Multivariable regression Model 1	Multivariable regression Model 2	Multivariable regression Model 2
	Odd ratio (95% CI)	*P*-value	Odd ratio (95% CI)	*P*-value	Odd ratio (95% CI)	*P*-value
PCOS status						
No	Reference		Reference		Reference	
Yes	1.79 (1.46-2.20)	**<.001**	1.60 (1.13-2.28)	**.009**	1.42 (.99-2.03)	.059
Maternal age, years	1.01 (.99-1.03)	.471	1.03 (.99-1.06)	.075	1.03 (.99-1.06)	.109
Maternal age						
[?]35	Reference		Reference		Reference	
>35	1.02 (0.82-1.27)	.863	1.21 (0.85-1.74)	.297	1.17 (0.81-1.68)	.400
BMI, kg/m^2	1.04 (1.02-1.08)	**<.001**			1.04 (1.01-1.09)	**<.001**
BMI						
<25	Reference				Reference	
[?]25	1.77 (1.36-2.30)	**<.001**			1.65 (1.26-2.17)	**<.001**
Prior pregnancy loss	1.37 (0.99-1.90)	.060	1.30 (0.93-1.81)	.127	1.28 (0.91-1.78)	.153
Comorbid conditions	1.85 (1.31-2.61)	**<.001**	2.05 (1.41-2.98)	**<.001**	2.07 (1.43-3.00)	**<.001**
Embryo transferred						
SET	Reference		Reference		Reference	
DET	1.25 (1.06-1.49)	**0.009**	1.21 (0.93-1.56)	0.154	1.21 (0.93-1.56)	0.152

PCOS: polycystic ovary syndrome, BMI: Body mass index, SET: single embryo transfer, DET: double embryo transfer. The number of three embryo transfer is low which has been calculated in the group of DET.

Model 1. Odds ratios adjusted for maternal age, history of spontaneous miscarriage and number of embryo transferred and comorbid conditions (preexisting hypertension and diabetes). Model 2. BMI is included.

Bold indicates *P*- value <0.05.

Table 7. Singleton pregnancy complication rates in PCOS group vs. Non-PCOS group.

Variables	PCOS	Non-PCOS	*P*- value
No. of singleton livebirths	1356	11701	
Survivors of a vanishing co-twin	138 (10.2)	1245 (10.6)	0.600
Maternal complications			
PROM, n (%)	35 (2.6)	261 (2.2)	0.412
Abnormal placentation, n (%)	10 (0.7)	108 (0.9)	0.494
Hypertensive disorder, n (%)	142 (10.5)	731(6.2)	**<0.001**

Variables	PCOS	Non-PCOS	*P*- value
HBP	90 (6.6)	541 (4.6)	0.001
Preeclampsia	52 (3.8)	190 (1.6)	**<0.001**
GDM, n (%)	174 (12.8)	812 (6.9)	**<0.001**
Cholestasis, n (%)	10 (0.7)	46 (0.4)	0.066
Mode of delivery[a], n (%)			
Vaginal	444 (32.7)	3601 (30.8)	0.138
Caesarean section	912 (67.3)	8100 (69.2)	
Neonatal outcomes			
PTB, n (%)			
<37 weeks	148 (10.9)	1021 (8.7)	**0.008**
<32 weeks	24 (1.8)	117 (1.0)	**0.009**
Birthweight g, n (%)	3.34 ± 0.57	3.30 ± 0.52	**0.023**
LBW, n (%)			
<2500 g	80 (5.9)	607 (5.2)	0.266
<1500 g	13 (1.0)	77 (0.7)	0.205
Macrosomia >4000 g, n (%)	158 (11.7)	984 (8.4)	**<0.001**
Newborn sex[a], n (%)			
Boy	725 (53.5)	6220 (53.2)	0.830
Girl	631 (46.5)	5481 (46.8)	

PROM: premature rupture of the membranes, Abnormal placenta: placenta previa and placental abruption. HBP: hypertensive disorders of pregnancy, GDM: diabetes mellitus, PTB: preterm birth, LBW: low birthweight.

[a]. Proportions were calculated by Pearson's chi-square test. Bold indicates *P*- value <.05.

Hosted file

`Figure 1.docx` available at https://authorea.com/users/349200/articles/474274-early-and-late-pregnancy-loss-in-women-with-polycystic-ovary-syndrome-undergoing-ivf-icsi-treatment-a-retrospective-cohort-analysis-of-21-820-pregnancies

Hosted file

`Figure 2.docx` available at https://authorea.com/users/349200/articles/474274-early-and-late-pregnancy-loss-in-women-with-polycystic-ovary-syndrome-undergoing-ivf-icsi-treatment-a-retrospective-cohort-analysis-of-21-820-pregnancies