Comparison of Indices between PCOS and Non-PCOS Patients in Assisted Reproduction

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) patients are infertile in most cases, but could have progenies through assisted reproductive technology (ART). Birth weight, which has been extensively investigated recently, were used as an indicator of ART risks in offspring.

Methods: Characters of PCOS patients and their babies were compared with non-PCOS ones.

Results: PCOS patients presented abnormal hormonal levels, and higher BMI than non-PCOS ones.

Conclusion: Although PCOS patients showed no advantages in ART, their off-springs showed no abnormality in general characteristics comparing to non-PCOS ones.

Keywords: ART, birth-weight, PCOS, singletons

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 DOI: 10.7727/wimj.2016.012

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women, with 5-10% of women suffering this condition (1). Women with PCOS present with polycystic ovaries, hyperandrogenism and/or ovulatory dysfunction (2). And they sometimes show a decrease sensitivity to insulin as well as exhibit obesity (3, 4) and excessive abdominal distribution of body fat (5, 6). Moreover, some chronic diseases were shown to be associated with PCOS, such as cardiovascular disease, hypertension and diabetes (7-10).

For PCOS women with ovulation symptom, their symptom can be improved by adjusting diet or taking medicine, or conceiving naturally, On the other hand, women with anovulation can also eventually be pregnant through assisted reproductive technology (ART). Birth weight has been extensively investigated in recent studies. It was used as an indicator to predict ART risks in offspring (11, 12). Dumoulin et al (13) suggested that lower mean birth weight of singletons was more often been observed when Cook medium was used compared to the usage of Vitrolife medium. This result was also confirmed by Nelissen's study who used frozen-thawed embryos (14). In the other reports, Global and Quinn's advantage medium did not seems to affect neonatal birth-weight (15,16). Birth-weight is also being shown to be associated with PCOS symptoms (17, 18). To the best of our knowledge, there were no researches to analyze correlation of birth weight of newborn conceived from PCOS with ART treatment.

In the present study, we retrospectively analysed the effects of PCOS symptom on the birthweight of newborns based on the clinical data from our centre from 2009 to 2013.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Ethics Committee of Tianjin Center Hospital of Gynecology Obstetrics. Women with (n=849) or without PCOS (n=1639) who underwent IVF or ICSI cycles in our center between January 2009 and December 2013were involved in the present study. Women with systemic diseases, endometriosis, abnormal prolactin levels or thyroid dysfunction were excluded from this study. These women received ART for male and/or tubal factor infertility. PCOS was diagnosed based on Rotterdam criteria. These women were all administrated with controlled ovarian hyperstimulation (COH) using GnRH agonist or GnRH antagonist protocol as described previously. Follicle growth in these women was monitored by serum estrogen (E2) levels and transvaginal ultrasonographic. Urinary hCG (human chorionic gonadotropin, 10,000 u/Serono, Aubonne, Switzerland) was administered when E2 level reached 500 pg/ml and the diameter of one follicle achieved 18 mm. Then, oocyte retrieval was performed under ultrasonography guidance. Finally, each woman was prescribed 60 mg progesterone per day.

This retrospective study was approved by the Ethics Committee of Tianjin Center Hospital of Gynecology Obstetrics. Patient information was blind to researchers.

Oocyte fertilization, embryo culture and transfer

Fertilization was performed by IVF or ICSI according to laboratory's routine insemination procedures after oocyte retrieval (designated as Day 0). On day 1, 16-18 hr after insemination, pronuclei morphology was observed under stereomicroscope. The presence of two pronuclei was regarded as successful fertilization, then zygotes were cultured in a drop of

pre-equilibrated cleavage medium under condition of 6% CO_2 and 95% humidity. G1, Global HTF and Quinn's advantage cleavage medium were used, and 3-4 zygotes were distributed in one droplet. Then the embryos were observed on day 3, and graded mainly according to blastomere number and fragmentation ratio. If the women are accorded with one of following conditions, two embryos were transferred: (1) ages are more than 35 years old, (2) failed in the previous two ART cycles, (3) no high-quality embryos was found. Otherwise only one embryo was transferred on day 3.

Data collection and analysis

In present study, women who are younger than 45 years old were included. Frozen-thawed cycles would be avoided and only fresh embryo transfer cycles were included. Moreover, only singletons or twins who live until the 20^{th} week of gestation were collected and analysed further. Pre-implantation genetic diagnosis or oocytes donation were all excluded. The standards for low birth-weight (LBW) and high birth-weight (HBW) were referred to previous studies (14).

Statistical analysis

Data was analyzed using SPSS 17.0 software. The basic physiology characteristics of patients were analyzed using Student's t-tests (continuous variables) and the categorical variables were compared using χ^2 tests. The possible relationship between PCOS and birth-weight was evaluated by multiple linear regression analyses. The effects of possible confounding factors, including fertilization methods (IVF or ICSI), maternal age, paternal age, maternal

height, paternal height, maternal weight, paternal weight, subfertility types, duration of subfertility, cause of subfertility, gestational age, infant gender, number of transferred embryos, number of cycles and newborn complications (neonatal brain injury, congenital heart disease, Down syndrome, hypertrophic pyloric stenosis, icterus hepatitis or congenital cartilage disease) were all controlled. Statistical significant difference was confirmed when P value was less than 0.05.

RESULTS

There were no significant differences in Age, Prolactin, Triglyceride, Total cholesterol, LDL, HDL, Glucose, Insulin, HOMA-IR between the PCOS and non PCOS groups. However the PCOS group presented higher BMI and levels of LH, free testosterone, total testosterone than those in non-PCOS group. Moreover the level of FSH in PCOS group was lower than non-PCOS group (Table 1).

As to the outcomes of ART, PCOS group demonstrated higher mean oocytes retrieve number, more MII oocytes, fertilized oocytes and cleaved oocytes than those in non-PCOS group but less high-quality embryos than that in non-PCOS group. By contrast, there is no significant difference in rate of fertilization, rate of cleavage, number of transferable embryos, number of embryo transferred per cycle, clinical pregnancy rate per ORC and number of miscarriage per pregnancy between these two groups (Table 2).

Neonatal singletons from PCOS patients (n= 729) were compared with those who were born from non-PCOS subjects (n=1482). There is no significant difference in birth

gender, gestational age, ratio of preterm birth, birth weight, ratio of very low birth weight, ratio of low birth weight, ratio of high birth weight between these two groups. These indicate that offspring derived from PCOS patients were with normal characteristics (Table 3). Furthermore, the relationship between birth weights of singletons (n=354) with profile of PCOS patients were analyzed by linear regression analysis. TT, LDL, MII, HQE were shown to be positively correlated with birth weight of singletons, while BMI, LH, OC, CPRP, NEWCOME were negatively correlated with it (Table 4).

DISCUSSION

Our results showed that PCOS patients had abnormal hormone levels and higher BMI, in turn they ovulated more oocytes for fertilization and showed obese phenotype.

Fertilization of PCOS patients after ART were compared with non-PCOS ones. Although IVF in some PCOS patients, the rates of fertilization and cleavage did not reveal any difference between oocytes retrieved from non-PCOS patients. Notably, the rate of high-quality embryos derived from PCOS patients was less than that from non-PCOS ones. This indicates development potential impairment in oocytes retrieved from PCOS patients. Comparing off springs from PCOS patients with those from non-PCOS ones, there was no difference between the ratio of singletons born from PCOS patients with those born from non-PCOS ones.

PCOS is a common endocrine-metabolic disease of women, which could be stimulated by genetic or hormone factors (19,20). PCOS is a risk factor for infertility,

dysfunctional bleeding or obesity (21-23) therefore attracts many researches. The commonly accepted theory about the etiology of PCOS is excess androgen production by ovaries (24-26). Patients with PCOS produced higher levels of some hormones that were secreted from ovary (Table 1) than non PCOS counterparts. This is consistent with other reports (27). As most of PCOS patients were infertile naturally (28, 29), we performed ART to assist these patients to have their own babies. Therefore we checked the quality of the oocytes and their derivative embryos from PCOS patients using various of parameters. Although oocytes retrieved from PCOS women is mature and excess in number as indicated by intact fertilization rate and cleavage rate, the ratio of high-quality embryos is much lower than those from non-PCOS patients. This indicates that although embryos from PCOS patients proliferate normally, they lose development potentials which might due to deranged hormone levels. Abnormity hormone levels in POS patients might contribute to the low quality of oocytes.

To judge whether the children from PCOS women by ART were healthy or not, we assessed the general characteristics of neonatal singletons of PCOS and non-PCOS women. It was shown that neonatal singletons of PCOS patients by ART presented no abnormality compare to off springs from non-PCOS patients. ART is safe to assist PCOS patients to conceive. However, excess androgens might affect the quality of oocytes. And obesity might lead to some conditions that affect healthy pregnancy. So ART still poses some risks to neonatal babies, which was consistent to previous report (30).

In conclusion, PCOS patients present deranged hormone levels and super-ovulation, but their infertility could be rescued with ART which does not lead to any abnormality in their progenies in this study.

AUTHORS' NOTE

None of the authors declare any interest conflict.

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Table 1: Comparison of general physiological characters between PCOS and non-PCOS patients

Index	PCOS (n=849)	Non-PCOS (n=1639)	P value
Age (year)	31.4 ± 5.2	29.3 ± 4.5	N.S
BMI (kg/m^2)	26.2 ± 3.7	23.9 ± 2.5	<0.001
LH (IU/l)	10.1 ± 4.0	8.1 ± 4.3	<0.001
FSH (IU/l)	5.5 ± 3.2	6.9 ± 2.0	<0.01
Free testosterone (pg/mL)	8.0 ± 4.3	2.8 ± 0.7	<0.001
Total testosterone (ng/mL)	43.5 ± 12.8	31.2 ± 11.7	<0.001
Prolactin	9.3 ± 4.8	9.8 ± 4.2	N.S
Triglyceride (mg/dL)	90.2 ± 14.6	89.6 ± 11.7	N.S
Total cholesterol (mg/dL)	149.3 ± 17.2	142.5 ± 22.4	N.S
LDL (mg/dL)	90.1 ± 12.7	89.6 ± 14.5	N.S
HDL (mg/dL)	49.5 ± 11.2	50.4 ± 12.3	N.S
Glucose (mg/dL)	81.6 ± 5.4	79.2 ± 8.5	N.S
Insulin (U/l)	10.6 ± 5.8	11.2 ± 6.9	N.S
HOMA-IR	2.3 ± 1.6	2.6 ± 1.4	N.S

BMI body mass index; LH luteinizing hormone; FSH follicle stimulating hormone; HDL high-density lipoprotein; LDL low-density lipoprotein; HOMA-IR homeostatic model of insulin resistance index. NS non-significant.

Table 2: General characters of oocyte from PCOS patients and non-PCOS patients

Index	PCOS (n=849)	Non-PCOS (n=1639)	P value
No. of oocytes retrieved Mean	18.26 ± 7.43	13.94 ± 7.53	< 0.0001
No. of MII oocytes	16.23 ± 3.28	12.02 ± 5.11	< 0.0001
No. of oocytes fertilized (Mean)	11.85 ± 3.55	8.69 ± 5.17	< 0.0001
Rate of fertilization	73.58	75.62	N.S[a]
No. of oocytes cleaved (Mean)	8.34 ± 2.96	6.85 ± 3.84	< 0.0001
Rate of cleavage	72.83	74.26	N.S
No. of embryos that can be transferred	3.15 ± 2.12	3.68 ± 2.88	N.S
No. of high-quality embryos	2.12 ± 1.95	3.14 ± 2.68	< 0.0001
No. of embryo transferred per cycle	1.68 ± 0.74	1.73 ± 0.72	N.S
Clinical pregnancy rate per ORC [b] (%)	34.84	35.96	N.S
No. of miscarriage per pregnancy [c] (%)	14.62	13.43	N.S

Superscript “a”, N.S. means the data was not significant difference.
Superscript “b”, ORC means oocyte retrieval cycles.
Superscript “c”, Miscarriage was defined as pregnancy loss after ultrasonographic evidence of an intrauterine pregnancy.

Table 3 General characteristics of neonatal singletons from PCOS and non-PCOS patients

Index	PCOS (n=729)	Non-PCOS (n=1482)	P value
Ratio of male newborns (n)	51.6 (376)	52.3 (775)	N.S.
Gestational age (week)	37.9 ± 1.29	38.6 ± 1.35	N.S.
Ratio of preterm birth (n)	6.6 (48)	5.9 (88)	N.S.
Birthweight (g)	3246.5 ± 589.6	3309.2 ± 674.9	N.S.
Ratio Very low birthweight (<1500 g) (n)	4.5 (33)	4.3 (63)	N.S.
Ratio Low birthweight (<2500 g) (n)	0.4 (3)	0.4 (6)	N.S.
Ratio High birthweight (>4500 g) (n)	1.0 (7)	0.9 (13)	N.S

Table 4: Multiple linear regression analysis of birth-weight of 354 singletons

Model	Unstandardized coefficients		Standardized	T	Sig.
	B	Std. Error	Beta		
Constant	1472.499	210.865		6.235	0.000
BMI	-55.299	6.654	-0.318	2.315	0.001
LH	-24.300	4.615	-0.084	0.165	0.013
TT	25.026	6.894	0.361	1.941	0.001
LDL	53.035	9.132	0.909	3.512	0.000
MII	88.388	13.566	0.664	2.564	0.000
OC	-86.835	10.895	-0.247	1.657	0.000
HQE	169.373	26.465	0.537	6.254	0.000
CPRP	-71.708	10.228	-0.510	8.124	0.000
NEWCOM	-149.949	18.238	-0.523	11.658	0.000