The clinical ramifications of polycystic ovarian morphology in oocyte donors

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Abstract

Objective To determine the relationship between Polycystic Ovary (PCO) morphology and In Vitro Fertilization (IVF) outcome in oocyte donation cycles.

Design Cross sectional study

Setting Private IVF clinic

Patients 164 consecutive ovum donors and their recipients were reviewed, 149 were included in the study where 113 patients had normal ovarian morphology and 36 patients had PCO morphology.

Interventions All donors underwent ovarian stimulation in conjunction with GnRH agonist or antagonist in standard fashion.

Main Outcome Measures Baseline donor characteristics were recorded, as well as details of IVF stimulation and embryo data. Recipient data on pregnancy and miscarriage were also collected.

Results Patients with PCO ovaries had significantly higher peak estradiol levels and required less gonadotropins during IVF stimulation. In addition, the baseline characteristics

between donor groups did not differ except for ovarian morphology. The number of oocytes retrieved and indicators of embryo quality did not differ between the two groups, and there was no significant difference between pregnancy and miscarriage rates in the recipients.

Conclusions Oocyte donors with PCO morphology have equivalent pregnancy rates and do not need to be excluded as potential donors.

Keywords Polycystic ovary morphology · Polycystic ovary syndrome · Oocyte donation

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disease, with a prevalence of 5–10 %, often presenting with infertility due to anovulation [4,10]. There is ongoing debate within the endocrine community about the diagnostic criteria for PCOS; with NIH criteria requiring a finding of hyperandrogenism in addition to oligomenorrhea [9] while Rotterdam criteria requiring 2 out of the 3 findings of oligomenorrhea, polycystic ovaries on ultrasound, and hyperandrogenism [18]. The Androgen Excess Society criteria require hyperandrogenism in addition to either polycystic ovary morphology or oligomenorrhea [3].

Inclusion of the ultrasound finding as part of the PCOS diagnosis has led to some debate within the endocrine community because a high antral follicle count (AFC) itself is relatively common, occurring in approximately 20–30 % of younger women [17]. For diagnostic purposes, the ultrasound finding of polycystic ovaries, or “PCO morphology” has been defined as an AFC of ≥ 12 (2–9 mm) in at least one ovary, or an ovarian volume of ≥ 10 cm³. While patients with PCO in addition to oligomenorrhea or hyperandrogenism have been shown to have similarly elevated levels of insulin resistance as compared to PCOS patients defined by NIH

Capsule Oocyte donors with PCO morphology do not need to be excluded as potential donors, but need more conservative stimulation due to high antral follicle count.

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criteria [6], the clinical significance of the isolated finding of PCO is less clear. This high incidence of “polycystic appearing” ovaries questions its clinical significance in an ovulatory patient. There is some evidence, however, that patients with PCOS and PCO morphology may share the same metabolic derangements. For instance, both patients with PCOS and PCO morphology with normal ovulation have been shown to have decreased insulin like growth factor binding protein 1 (IGFBP-1) as compared to controls, even after adjusting for weight [5]. In addition, ovulatory patients with PCO morphology have been shown to have higher androgen levels and insulin resistance as compared to normal controls [2].

For infertility patients undergoing IVF with normal appearing versus polycystic ovaries, the patients with PCO morphology produce more oocytes, but have equivalent fertilization and pregnancy rates as compared to controls with normal appearing ovaries [12,21]. In addition to producing more oocytes, patients with polycystic ovaries require less gonadotropins and are more likely to have ovarian hyperstimulation syndrome (OHSS) [21,24]. Another concern with PCO morphology is whether these patients share the same increased risk of miscarriage as seen in patients with PCOS, reported to be as high as 40 % in some studies [16]. There is, however, limited literature evaluating the miscarriage risk in patients with PCO morphology ovaries.

Another complicating factor is that the majority of the literature focuses on infertile patients with PCO morphology undergoing IVF [12]. To our knowledge, there is only one older study in the literature with a very small number of patients looking at the relationship between PCO morphology ovaries and cycle outcome in ovum donation cycles [24]. Therefore the aim of our study is to gain additional information on oocyte donors with PCO morphology, to characterize their cycle stimulation and outcomes and to assess whether they are an optimal donor choice.

Materials and methods

Patient population

A total of 164 consecutive ovum donation cycles from Southern California Reproductive Center in Beverly Hills, California were identified from January 2006 to March 2011. Baseline donor and stimulation characteristics of the cycles were recorded. One hundred and forty nine cycles were included in the study. Fifteen cycles were excluded due to cancellations or lack of information such as AFC. Oocyte donors were characterized as having polycystic ovary (PCO) morphology if AFC was ≥ 12 on at least one of the ovaries. There were 113 and 36 patients in the normal and PCO morphology groups respectively. All oocyte donors were evaluated with a full history and physical exam, which

included questioning on menstrual cycles and regularity. No baseline androgen levels were drawn.

All donors underwent ovarian stimulation in conjunction with either GnRH agonist or GnRH antagonist, although only 3 cycles were stimulated with an antagonist. Oocyte donors were pretreated with oral contraceptive pills (OCPs) for 10–30 days with a 5 day overlap with GnRH agonist (1 mg/day) prior to OCP discontinuation. Patients then presented to clinic 3 days after discontinuation of OCPs for baseline estradiol levels to check for suppression as well as ultrasound. One to two days after ultrasound, GnRH agonist dose was decreased to 0.5 mg/day and gonadotropins were initiated, usually at a dose of FSH 150 IU and HMG 75 IU. However, the starting gonadotropin dose was adjusted according to physician preference depending on the donor's age, antral follicle count, and if relevant, prior stimulation history. If the patient was on an antagonist protocol, OCP pretreatment was used and after discontinuation of OCPs, the donor presented on cycle day 2 of their menses for baseline labs and ultrasound. Gonadotropins were started usually that evening, and GnRH antagonist was initiated once follicle sizes reached 13–14 mm in mean diameter or when estradiol levels were >400 pg/ml, and then was continued until day of trigger.

HCG was used to trigger ovulation once >2 dominant follicles >18 mm in size were present, at a dose of 4,000–10,000 IU depending upon physician preference. In the case of GnRH agonist trigger for two patients undergoing antagonist protocols, the dose initiated was 4 mg, at two doses 12 hours apart. Oocyte retrieval was performed 36 hours after ovulation was triggered with HCG or after the first GnRH agonist dose. Recipients were pretreated with OCPs, overlapping with GnRH agonist (1 mg/day) for 5 days prior to OCP discontinuation. Recipients continued GnRH agonist and presented to clinic 3–4 days after OCP discontinuation for baseline ultrasound and estradiol to check for suppression. GnRH agonist was decreased to 0.5 mg/day and Estrace (Warner Chilcott) was initiated at 2 mg/day in conjunction with donor stimulation. ASA 81 mg was also initiated with Estrace. Estrace was increased to 4 mg/day after 4 days, and then 6 mg for the following 3–4 days. Recipients then presented for ultrasound to check endometrial lining thickness, with a goal of >7.5 mm. On the day of egg retrieval, progesterone was initiated at 50 mg IM daily, with supplemental Endometrin (Ferring) 100 mg vaginal suppositories given twice daily starting the day after retrieval. The day after oocyte retrieval, Medrol (Pharmacia or UpJohn) 16 mg once daily as well as Anaprox DS (Roche) 550 mg twice daily were initiated and continued until the day before transfer. Claritin (Schering-Plough) 10 mg once daily started on the day of transfer was continued until pregnancy test, which was performed 14 days after oocyte retrieval. All embryos were transferred on day 5.

Embryo scoring

Embryos were assessed for stage of development and morphologic grade on days 1, 3, 5, and 6. The Vitrolife Media System was used for the entire period of the study to culture the embryos. GIVF sequential media was used for insemination/ICSI until fertilization check, G1.5 was used after fertilization until day 3 check, and the media was then switched to G2.5 from day 3 until transfer, cryopreservation, or discarding. The incubator conditions were 37 °C, 6.0 % CO₂, 5.0 % O₂, and 90 % humidity.

Outcome measures

Embryo data including number of oocytes retrieved, number of embryos fertilized on Day 1, number of day 3 embryos, and blastocysts seen on day 5 and day 6 were all retrieved from chart review. Fertilization rate was defined as the ratio of 2PN embryos on day 1 of culture over total number of oocytes retrieved. Blastulation rate was defined as total number of blastocysts on day 5 and 6 of culture divided by total number of day 3 embryos. Number of embryos transferred and number of embryos frozen were also included in the analysis for each group. Mild hyperstimulation was defined as bilateral ovarian enlargement while moderate hyperstimulation included documentation of patient discomfort; bloating, ascites or nausea. Severe hyperstimulation was defined as requiring hospitalization. Implantation rate was defined as number of gestational sacs visualized divided by the number of embryos transferred. Biochemical pregnancy (mIU/ml) was defined as pregnancy with hCG >20 measured 10 days after embryo transfer. Clinical pregnancy was defined by the presence of a gestational sac on the recipient's ultrasound. Miscarriage was defined as both loss of biochemical and clinical pregnancies.

Statistical analysis

Logarithmic scale was used for values that did not have a normal Gaussian distribution as the transformation yielded a better Gaussian distribution thus allowing the use of parametric tests for analysis. Two way student t-test was used to compare the average numbers between the 2 groups and chi square was used to compare pregnancy and miscarriage rates. For all comparisons, a statistical significance was determined to be a p value of <0.05. A post hoc power analysis was performed, and to detect a 20 % difference in pregnancy rate given a baseline pregnancy rate of 65 %, to achieve 80 % power, a sample size of 70 patients in each group would have been required.

Results

A total of 149 patients were included in this analysis. The average donor age was 26 in the normal appearing ovary group and 25 in the PCO appearing ovary group (Table 1). There were also no differences in the recipient and paternal age between the two groups as shown in Table 1. Baseline FSH levels were similar between the two groups. Only two donors reported irregular menses on history; one was on continuous active OCPs while the other had a Mirena IUD in situ. No clinically apparent hirsutism or virilization was noted on physical exam, which was performed on every donor.

Response to stimulation is shown in Table 2. Patients with PCO appearing ovaries required significantly less gonadotropins and had significantly higher levels of peak estradiol (E2) than patients with normal appearing ovaries. As a result of higher peak E2 levels, they were also more likely to be coasted additional days and had on average 3 more follicles ≥14 mm. Both groups, however, required the same number of days of stimulation. Despite higher levels of E2 in PCO morphology group, mild to moderate OHSS was observed equally in both groups, and there were no cases of severe OHSS in either group. Patients with PCO morphology ovaries also had on average two more oocytes retrieved, but this difference did not reach statistical significance. We did not find any differences between the groups in proportion of mature oocytes, fertilization rates and blastulation rates. Lastly, number of embryos transferred and frozen were also not significantly different between the 2 groups, although PCO morphology group had on average 1.7 more embryos frozen (Table 2).

Due to use of surrogates, some patients had incomplete data regarding follow up obstetric ultrasounds and delivery, and only 106 patients with normal appearing ovaries and 33 patients with PCO morphology were analyzed for pregnancy outcomes. Clinical pregnancy rate was not significantly different between the groups at 62 % and 67 % in control and PCO morphology patients respectively. There was also no significant difference between live birth rate and miscarriage rate between the two groups (Table 3).

Discussion

Consistent with concerns from the literature that patients with the finding polycystic ovaries may be metabolically similar to patients with PCOS, we found that our oocyte donors stimulated differently for their IVF cycles as compared to controls. However, some elements of the response to ovarian stimulation in our study are different from what has been shown in the past for patients with PCOS or PCO morphology. Increased sensitivity to gonadotropins has

Table 1 Baseline Characteristics of oocyte donors with PCO and normal ovarian morphology

Mean Values $\pm$ standard deviation	Normal ovaries $n=113$	PCO appearing ovaries $n=36$	p value (2 tailed)
Donor Age	26 $\pm$ 3.4	25 $\pm$ 3.2	0.44
Recipient Age	43.6	42.0	0.36
Paternal Age	44.2	42.6	0.37
ICSI (%)	5.3 (6/113)	5.5 (2/36)	NS
Day 3 FSH	5.6 $\pm$ 2.6	5.5 $\pm$ 1.8	0.87

been demonstrated in the literature in patients with PCOS [20] and also with PCO morphology in an older study [24], likely due to a larger cohort of FSH sensitive follicles [23]. Our study also agrees with the above literature showing that donors with PCO morphology are more responsive to gonadotropins. Interestingly, a more recent study looking at infertility patients with PCO morphology did not demonstrate this increase in responsiveness observed by others [12]. Our study also showed significantly higher serum E2 concentrations and more follicles in the PCO morphology group compared to controls. These findings are again consistent to what has been demonstrated in the literature in both PCOS and PCO morphology patients [12,20,24]. We also observed that women with PCO morphology had on average 2 more oocytes retrieved than controls, but this difference did not reach statistical significance. It is possible that we were underpowered to discover this difference, and that with a larger number of patients, we would have been

able to demonstrate a statistically significant difference in number of oocytes retrieved.

Another concern with PCO morphology is the elevated risk of ovarian hyperstimulation syndrome (OHSS) which has been demonstrated at similar, elevated rates as with PCOS patients undergoing IVF [21]. While studies have demonstrated a decreased rate of OHSS with metformin administration for PCOS patients undergoing IVF [22], a randomized placebo controlled study did not show decreased rates of severe OHSS for patients with polycystic ovarian morphology [20]. Still, other techniques used to control for OHSS in PCOS patients such as agonist trigger have been shown to be successful in decreasing OHSS risks PCO patients [11]. In our study, despite the hypersensitivity to gonadotropins and higher serum E2 levels, none of the donors developed severe OHSS and the occurrence of mild to moderate OHSS was similar between the 2 groups. Similar findings have also been reported in the literature looking

Table 2 Characteristics of ovarian response in oocyte donors with PCO and normal morphology

Mean Values $\pm$ standard deviation	Normal ovaries $n=113$	PCO appearing ovaries $n=36$	p value (2 tailed)
FSH (IU) used	1,684 $\pm$ 714	1,114 $\pm$ 488	<0.05
FSH (IU) used (log)	3.19 $\pm$ 0.03	3.01 $\pm$ 0.04	<0.05
HMG (IU) used	699 $\pm$ 365	490 $\pm$ 312	<0.05
Peak E2 (log)	3.59 $\pm$ 0.29	3.68 $\pm$ 0.24	<0.05
Peak E2 (ng/dl)	4,320 $\pm$ 2,001	5,524 $\pm$ 3,202	
Patients Coasted (%)	29 % $n=33$	44 % $n=16$	0.30
Days Coasted	0.45 $\pm$ 0.8	1 $\pm$ 1.6	0.05
Duration of Stimulation (days)	11.0 $\pm$ 1.6	10.9 $\pm$ 1.6	0.81
Follicles >14 mm	14.0 $\pm$ 5.0	17.0 $\pm$ 5.0	<0.05
Oocytes Retrieved (total)	17 $\pm$ 6.3	19 $\pm$ 7.4	0.19
% Mature oocytes	86 %	86 %	0.94
Fertilization Rate (log)	1.01 (log)	1.34 (log)	0.19
Fertilization Rate (%)	70 %	74 %	
Day 3 embryos $\geq$ 6 cells	9.9 $\pm$ 4.7	12.2 $\pm$ 6.2	0.08
Blastulation rate %	58 $\pm$ 24	65 $\pm$ 18	0.09
Embryos Transferred	1.6 $\pm$ 0.8	1.6 $\pm$ 0.8	0.66
Embryos Frozen	4.6 $\pm$ 4.0	6.3 $\pm$ 5.8	0.1
Mild OHSS	41 (38 %)	14 (39 %)	0.86
Mod OHSS	3 (2.6 %)	2 (5.5 %)	0.88
Severe OHSS	0	0	NA

Table 3 Clinical cycle outcome data between PCO and normal morphology oocyte donors

Mean Values	Normal ovaries <i>n</i> =106	PCO appearing ovaries <i>n</i> =33	p value (2 tailed)
Clinical Pregnancy Rate ¹ (%)	62 <i>n</i> =66	67 <i>n</i> =22	0.65
Implantation rate ² (%)	49	49	0.95
SAB (%)	17 <i>n</i> =18	6 <i>n</i> =2	0.12
Live Birth Rate to date (%)	49 <i>n</i> =52	52 <i>n</i> =17	0.81

¹ Clinical pregnancy rate was defined as gestational sac visualized on ultrasound per embryo transfer

² Implantation rate was defined as number of gestational sacs divided by the number of embryos transferred

at donors with PCO morphology [24]. One should keep in mind, however, that donors are unique in that they do not become pregnant after a stimulation which minimizes their risk of developing severe OHSS in general, thus this data should not be extrapolated to infertile patients with PCO morphology [13].

Women with PCOS have been reported to produce lower quality oocytes with lower fertilization rates than controls [1,8]. However, these findings have not been replicated in women with PCO morphology [12,20,24]. Consistent with earlier reports, we did not see any differences in number of mature oocytes, fertilization rates, day 3 embryos and progression to blastocyst in PCO morphology and control groups. In fact, we observed a trend towards higher number of day 3 embryos, increased blastulation rates and higher number of embryos frozen in the PCO morphology group compared to controls (Table 2).

PCOS has also been associated with an increased rate of pregnancy loss, some studies showing miscarriage rates as high as 40 % [16]. Speculation has centered on the deleterious effects of high concentrations of luteinizing hormone (LH) on the maturing oocytes and endometrium [14,15]. Interestingly, PCO morphology without evidence of hypersecretion of LH (by single random serum assay) have also been reported to be associated with increased pregnancy loss [19]. Lastly, it has also been demonstrated that ovulatory women with PCO morphology may have elevated androgen levels as compared to controls [2]. Given these conflicting reports on the literature, we wanted to examine the effect of PCO morphology alone on pregnancy outcome.

We realize that a weakness of this study is that we did not fully classify the possible PCOS characteristics that our PCO morphology group of donors may have had, as they did not have baseline androgen levels or metabolic studies performed. This could have resulted in inclusion of PCOS patients by Rotterdam criteria if hyperandrogenemia was discovered. However, given that donors received a thorough history and physical exam, with no clinically apparent hirsutism or virilization noted, this is less likely. This study is unique because we look at donors with PCO morphology thus eliminating any possible endometrial effects of PCOS and solely focusing on oocyte quality. Indeed, our findings

suggest that donors with PCO morphology do not differ in implantation and pregnancy rates, miscarriage rates or live birth rates. We realize that we were underpowered to detect these differences, and a larger study with more patients might be able to demonstrate this difference. Also, as in the case of OHSS, our findings do not rule out the possibility that increased miscarriage rates could exist in infertile patients with PCO morphology since these patients might share some metabolic similarities with PCOS patients [5]. The few studies evaluating PCO morphology infertile patients often do not address the issue of miscarriage, thus more studies are needed to further elucidate whether infertile patients with PCO morphology are also at increased risk of miscarriage.

Without detailed blood work to further characterize our PCO morphology group, we cannot fully determine which proportion of these patients may have had some metabolic similarities to PCOS patients. However, in asymptomatic patients with no evidence of hyperandrogenism, we did not appreciate any detrimental aspects to their IVF stimulation and recipient outcomes, albeit in a limited number of patients.

As the controversy over how to best define or diagnose PCOS continues [7], it is possible that eventually age adjusted ovarian antral follicle count will replace prior definitions. Given that oocyte donors in the PCO morphology group had a median of 15 antral follicles on one side and were in their mid-twenties, it is likely that a reformulation of the definition of PCO morphology would redefine all of our donors as normal. However, the fact that we have demonstrated stimulation differences between our two groups underscores the importance of a thorough evaluation of antral follicle count given its correlation with stimulation response.

In conclusion, visualizing PCO morphology on ultrasound in otherwise non-hirsute, ovulatory women does not appear to affect cycle outcomes such as pregnancy, miscarriage and live birth rates in recipients. The appearance of PCO morphology on ultrasound does, however, predict increased sensitivity to gonadotropins and higher serum E2 levels. Thus these donors should be given a more conservative stimulation protocol with closer monitoring, but they should not be excluded as potential donors.

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