

Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment

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Abstract

Purpose This retrospective cohort study evaluated the cumulative live birth rate in women with polycystic ovary syndrome (PCOS) and isolated polycystic ovaries (PCO) undergoing in-vitro fertilisation (IVF) treatment.

Methods We studied 104 women with PCOS, 184 with PCO and 576 age-matched controls undergoing the first IVF treatment cycle between 2002 and 2009. The main outcome measure was cumulative live birth in the fresh plus all the frozen embryo transfers combined after the same stimulation cycle.

Results Women in both the PCOS ($n=104$) and isolated PCO groups ($n=184$) had higher ovarian response parameters compared to age-matched controls ($n=576$), and higher rates of withholding fresh embryo transfer for risk of ovarian hyperstimulation syndrome (OHSS). The actual incidence of moderate to severe OHSS was significantly higher in the PCOS (11.5 %) but not the isolated PCO group (8.2 %) compared to controls (4.9 %). The live birth rates in the fresh cycle were comparable among the 3 groups, but the PCOS group had a significantly higher miscarriage rate compared to the other 2 groups. Cumulative live birth rate was significantly higher in the isolated PCO group (60.3 %), but not the PCOS group (50.0 %), compared to controls (47.5 %).

Capsule Women in the isolated PCO group, but not the PCOS group, had a significantly higher cumulative live birth rate compared to controls. This could be explained by the quantitative effect of the higher number of transferable embryos obtained per stimulation cycle, which is uncompromised by the unfavourable embryo competence otherwise observed in PCOS.

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Conclusions Women in the isolated PCO group, but not the PCOS group, had a significantly higher cumulative live birth rate compared to controls. This could be explained by the quantitative effect of the higher number of transferable embryos obtained per stimulation cycle, which is uncompromised by the unfavourable embryo competence otherwise observed in PCOS.

Keywords Polycystic ovary syndrome · Isolated polycystic ovaries · Cumulative live birth · In-vitro fertilisation

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine problem affecting 5–10 % of women in the reproductive age. Although in-vitro fertilization (IVF) is not the first-line treatment for anovulatory subfertility secondary to PCOS, some women with PCOS may require IVF treatment because of failure of or resistance to ovulation induction treatment, or because of co-existing male or tuboperitoneal factors [1]. The IVF outcome in women with PCOS has been extensively studied, and generally their pregnancy and live birth rates were not significantly different from matched non-PCOS controls, although they had significantly higher risk of ovarian hyperstimulation syndrome (OHSS) [2].

The sonographic feature of polycystic ovaries (PCO) constitute a cardinal feature of PCOS, and is one of the diagnostic criteria for PCOS according to the Rotterdam consensus [3]. However, the finding of isolated PCO morphology does not equate to PCOS. In fact, about 20–33 % of women in the normal adult population have been reported to have PCO feature [4–8]. Some of these ovulatory PCO women may require IVF because of other reasons leading to subfertility.

There were a few studies on the IVF outcome of this group [9–15]. Some of these reported similar pregnancy or live birth rates in the isolated PCO group compared to controls [10, 12–15], whereas some reported higher pregnancy rates than controls [9, 11].

These existing reports addressed the pregnancy or live birth rates only in the fresh cycle. With the advent of embryo cryopreservation, frozen-thawed embryo transfer (FET) has become an integral part of modern-day assisted reproduction programmes. To evaluate the IVF treatment outcome, it would hence be more logical to consider the cumulative live birth rate which includes the live births from both the fresh and all FET cycles combined, instead of the fresh cycles only. We conducted this retrospective analysis to evaluate the cumulative live birth rate in women with PCOS and isolated PCO compared to age-matched non-PCO controls.

Materials and methods

Subject selection

We reviewed data on patients undergoing the first IVF treatment cycle between January 2002 and December 2009 at our Centre. Ethics approval was obtained from the Institutional Review Board of our institution for the retrospective review. Only those women undergoing their first treatment cycle on a long GnRH agonist protocol were included in this study to avoid selection and treatment bias respectively. Among them, we identified 104 women with PCOS and another 184 women who had isolated PCO, who were treated on a long GnRH agonist protocol. The PCOS group was diagnosed according to the Rotterdam criteria [3], while the isolated PCO group was defined by the presence of 12 or more antral follicles of 2–9 mm in either ovary [16] but regular menstrual cycles between 21 and 35 days and absence of hyperandrogenism. Either PCOS or PCO women did not receive metformin or other insulin sensitizing agents before and during IVF treatment. Another 576 age-matched ovulatory non-PCO women were selected systematically by consecutive chronological order as controls. Cycles carried out for pre-implantation genetic diagnosis or those using donor oocytes were excluded from this analysis. Clinical details of all their treatment cycles were retrieved from our computer database for analysis. Those women who still had frozen embryo(s) not replaced yet were excluded from the cumulative live birth analysis.

Stimulation cycle

Details of the stimulation cycle have been previously reported [17]. All patients included under this study were treated on the long GnRH agonist protocol for pituitary down-regulation. The initial dose of stimulation was determined according to

the baseline total AFC (AFC ≥ 15 : 150 IU per day; AFC between 6 and 14: 300 IU for the first 2 days followed by 150 IU daily). Fertilisation was carried out in-vitro either by conventional insemination or intracytoplasmic sperm injection (ICSI) depending on semen parameters. Fresh embryo transfer (ET) was carried out with replacement of at most two embryos of the best quality available on the second day post-insemination. Fresh embryo transfer would be withheld with all good quality embryos cryopreserved if the subject had symptoms suggestive of OHSS or if serum E2 concentration on the day of hCG injection was $>20,000$ pmol/L. OHSS was defined and classified according to the RCOG guideline [18].

Frozen-thawed embryo transfer

The details of the freezing and thawing protocols were reported previously [19]. The frozen embryos were thawed on the morning of FET. Embryos were discarded if more than 50 % of the original blastomeres were lysed or degenerated upon thawing. Frozen-thawed embryos were transferred in natural cycles in ovulatory women, or in either clomiphene-induced or hormone replacement cycles for anovulatory women. A maximum of two frozen embryos were allowed to be transferred in any one FET cycle.

Pregnancy outcome

A pregnancy test was done 16 days after the transfer. Pregnancy was defined by a positive urine hCG test or serum hCG concentration of above 10 IU/L. Pregnant women were offered an ultrasound examination 10–14 days later to confirm intrauterine pregnancy and the number of gestational sacs present. Pregnancy outcome was traced from all pregnant women by postal questionnaire or by phone.

Statistical analysis

The primary outcome measure was the cumulative live birth in the fresh and all FET cycles combined following the same index stimulation cycle. The age of the women used in analysis referred to the time of starting ovarian stimulation. Non-normally distributed continuous variables were expressed as median (interquartile range) unless otherwise stated. Continuous and categorical variables were compared between groups using Kruskal-Wallis test and Fisher's Exact test respectively. Logistic regression analysis was used to examine factors predicting cumulative live birth. Statistical analysis was carried out using the Statistical Program for Social Sciences (SPSS Inc., Version 15.0, Chicago, U.S.A.) and MedCalc (Version 12, Belgium). The two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Of the 2,556 women who underwent the first IVF cycle during the study period, we identified 864 cases who fulfilled our inclusion criteria for this analysis. These included 104 women with PCOS and 184 women with isolated PCO, and another 576 ovulatory non-PCO women who were matched with age. Among them, 565 (65.4 %) underwent conventional insemination, while 226 (34.6 %) were inseminated by ICSI, the latter including 44 (5.1 %) and 29 (3.4 %) using sperm from microsurgical epididymal sperm aspiration and testicular sperm extraction respectively.

($p < 0.05$) compared to controls. Those in the PCOS group had significantly higher AFC compared to the isolated PCO group ($p < 0.05$), and both were significantly higher than that in controls ($p < 0.05$).

Basic demographic and clinical parameters

The demographic and clinical parameters were listed in Table 1. There was no significant difference in age among the three groups. Women in the PCOS group, but not those in the isolated PCO group, had significantly higher body weight and body mass index

Ovarian stimulation characteristics

As shown in Table 2, women in both the PCOS and isolated PCO groups required significantly lower total doses of gonadotrophin, had significantly higher serum E2 level and number of follicles reaching 16 mm or above on the day of hCG trigger, and significantly higher total numbers of retrieved oocytes and transferable embryos.

Treatment outcome in the fresh cycle

Table 3 shows the treatment outcome in the fresh IVF cycle. There was no significant difference ($p > 0.05$) in the pregnancy or live birth rates among the 3 groups, both when analysed per started cycle or per transfer. There was a higher miscarriage rate in the PCOS group (34.2 %, $p =$

Table 1 Basic demographic and clinical parameters of women in the control group, polycystic ovary syndrome (PCOS) group, and isolated polycystic ovaries (PCO) group. Values are shown in median (interquartile range)

| Group | Control (n=576) | PCOS (n=104) | PCO (n=184) | P value ^a | | | |
|----------------------------------|------------------|------------------|------------------|----------------------|-----------------|----------------|-------------|
| | | | | Overall | PCOS vs control | PCO vs control | PCOS vs PCO |
| Antral follicle count | 10 (7–13) | 26 (23–35) | 23 (20–28) | <0.001* | <0.05* | <0.05* | <0.05* |
| Age (years) | 33 (31–35) | 33 (30–36) | 33 (31–35) | 0.79 | | | |
| Weight (kg) | 54 (50–58) | 57 (51–62) | 54 (50–59) | 0.003* | <0.05* | >0.05 | <0.05* |
| BMI (kg/m ²) | 21.2 (19.6–22.7) | 22.2 (20.7–24.9) | 21.3 (19.7–22.9) | <0.001* | <0.05* | >0.05 | <0.05* |
| Type of subfertility | | | | | | | |
| Primary | 400 | 63 | 119 | 0.14 | | | |
| Secondary | 176 | 41 | 65 | | | | |
| Duration of subfertility (years) | 4 (3–6) | 5 (3–7) | 4 (3–6) | 0.25 | | | |
| Cause of subfertility | | | | | | | |
| Tubal | 127 | 19 | 39 | 0.07 | | | |
| Endometriosis | 59 | 4 | 12 | | | | |
| Male factor | 291 | 56 | 97 | | | | |
| Unexplained | 34 | 3 | 12 | | | | |
| Mixed | 65 | 22 | 24 | | | | |
| Smoking | | | | | | | |
| Yes | 523 | 94 | 167 | 0.99 | | | |
| No | 53 | 10 | 17 | | | | |
| Type of insemination | | | | | | | |
| Conventional | 371 | 70 | 124 | 0.69 | | | |
| ICSI | 205 | 34 | 60 | | | | |

^a Kruskal-Wallis test with Conover’s post-hoc analysis for individual group comparisons if overall p value < 0.05 (for continuous variables) or χ^2 test (for categorical variables)

*Statistically significant

Table 2 Ovarian stimulation parameters in the control group, polycystic ovary syndrome (PCOS) group, and isolated polycystic ovaries (PCO) group. Values are shown in median (interquartile range)

| Group | Control (<i>n</i> =576) | PCOS (<i>n</i> =104) | PCO (<i>n</i> =184) | <i>P</i> value ^a | | | |
|-----------------------------------|--------------------------|-----------------------|----------------------|-----------------------------|-----------------|----------------|-------------|
| | | | | Overall | PCOS vs control | PCO vs control | PCOS vs PCO |
| Total dose of gonadotrophin (IU) | 1950 (1650–2531) | 1500 (1350–1950) | 1500 (1350–1800) | <0.001* | <0.05* | <0.05* | >0.05 |
| Serum E2 on hCG day (pmol/l) | 9876 (6254–15050) | 15328 (9026–23279) | 13420 (8722–19769) | <0.001* | <0.05* | <0.05* | >0.05 |
| Duration of stimulation (days) | 11 (10–12) | 10 (9–12) | 10 (8–11) | <0.001* | >0.05 | <0.05* | >0.05 |
| Follicles ≥16 mm on hCG day | 6 (4–8) | 8 (6–11) | 8 (6–10) | <0.001* | <0.05* | <0.05* | >0.05 |
| No. of oocytes retrieved | 9 (5–13) | 13 (9–18) | 14 (10–20) | <0.001* | <0.05* | <0.05* | >0.05 |
| Total no. of transferable embryos | 5 (2–7) | 6 (3–9) | 7 (3–10) | <0.001* | <0.05* | <0.05* | >0.05 |

^a Kruskal-Wallis test with Conover's post-hoc analysis for individual group comparisons

*Statistically significant

0.025), but not the isolated PCO group (23.3 %, $p=0.297$), compared to the controls (17.1 %). Significantly more women were required to withhold fresh ET for risk of OHSS in both the PCOS group (18.3 %, $p<0.001$) and the isolated PCO group (14.7 %, $p<0.001$) compared to controls (5.7 %). The rate of moderate to severe OHSS was also significantly higher in the PCOS group (11.5 %, $p=0.021$) than the controls (4.9 %); although that in the isolated PCO group showed a higher trend compared to controls, the difference was not statistically significant (8.2 %, $p=0.100$).

Cumulative pregnancy and live birth outcome

Combining the outcomes from the fresh ET plus all FETs deriving from the same stimulation cycle, the cumulative pregnancy and live birth rates were significantly higher in the isolated PCO group (69.1 %, $p=0.001$; 60.3 %, $p=0.003$), but not the PCOS group (62.1 %, $p=0.235$; 50.0 %, $p=0.665$), compared to the controls (55.2 % and 47.5 % respectively) (Table 3).

Table 4 shows results of analysis using the multivariate logistic regression model. The presence of PCOS or isolated

Table 3 Treatment outcome parameters in the control group, polycystic ovary syndrome (PCOS) group and isolated polycystic ovaries (PCO) group. Values are shown as absolute fractions (percentages)

| Group | Control (<i>n</i> =576) | PCOS (<i>n</i> =104) | PCO (<i>n</i> =184) | <i>P</i> value ^a | | | |
|--|--------------------------|-----------------------|----------------------|-----------------------------|-----------------|----------------|-------------|
| | | | | Overall | PCOS vs control | PCO vs control | PCOS vs PCO |
| Fresh cycle outcomes | | | | | | | |
| Pregnancy per started fresh cycle (%) | 216/576 (37.5 %) | 38/104 (36.5 %) | 75/184 (40.8 %) | 0.683 | | | |
| Live birth per started fresh cycle (%) | 174/576 (30.2 %) | 25/104 (24.0 %) | 55/184 (29.9 %) | 0.453 | | | |
| Pregnancy per transfer in fresh cycle (%) | 216/512 (42.2 %) | 38/80 (47.5 %) | 75/148 (50.7 %) | 0.156 | | | |
| Live birth per transfer in fresh cycle (%) | 174/512 (34.0 %) | 25/80 (31.3 %) | 55/148 (37.2 %) | 0.642 | | | |
| Miscarriage in fresh cycle (%) | 37/216 (17.1 %) | 13/38 (34.2 %) | 17/73 (23.3 %) | 0.048* | 0.025* | 0.297 | 0.262 |
| Moderate/severe OHSS | 28/576 (4.9 %) | 12/104 (11.5 %) | 15/184 (8.2 %) | 0.021* | 0.012* | 0.100 | 0.401 |
| Withhold ET for risk of OHSS | 33/576 (5.7 %) | 19/104 (18.3 %) | 27/184 (14.7 %) | <0.001* | <0.001* | <0.001* | 0.503 |
| Cumulative outcomes | | | | | | | |
| Cumulative pregnancy (%) | 316/572 (55.2 %) | 64/103 (62.1 %) | 125/181 (69.1 %) | 0.003* | 0.235 | 0.001* | 0.242 |
| Cumulative live birth (%) | 271/571 (47.5 %) | 50/100 (50.0 %) | 108/179 (60.3 %) | 0.011* | 0.665 | 0.003* | 0.103 |

OHSS ovarian hyperstimulation syndrome

^a Comparisons using Fisher's Exact tests

*Statistically significant

Table 4 Multivariate logistic regression analysis for the prediction of cumulative live birth. Factors included into the model using the enter method were the women's age and body mass index, total number of transferable embryos and the presence of PCO morphology

| | B | Standard error | P value | Exp(B) (95 % confidence interval) |
|--------------------------------------|--------|----------------|---------|-----------------------------------|
| Women's age | -0.016 | 0.024 | 0.501 | 0.984 (0.940–1.031) |
| Women's body mass index | -0.049 | 0.029 | 0.092 | 0.952 (0.898–1.008) |
| Total number of transferable embryos | 0.237 | 0.023 | <0.001* | 1.268 (1.211–1.327) |
| Group | | | 0.456 | |
| PCOS | -0.199 | 0.198 | 0.314 | 0.820 (0.556–1.207) |
| PCO | -0.332 | 0.286 | 0.244 | 0.717 (0.410–1.255) |

*Statistically significant

PCO feature was not a significant factor in predicting cumulative live birth after adjusting for age and body mass index of the women, and the total number of transferable embryos. Among the four parameters entered into the model, only the total number of transferable embryos was an independent significant factor in predicting cumulative live birth.

Discussion

This study adds to the few reports in the current literature on the IVF outcome in women with isolated PCO in comparison to those with PCOS and ovulatory non-PCO controls, and includes the largest sample size among all. Our results showed that women in both the PCOS and isolated PCO groups had significantly higher ovarian response parameters as illustrated by lower total dose of gonadotrophin required, higher number of follicles reaching 16 mm or above and higher serum E2 level on the day of hCG trigger, and the larger number of retrieved oocytes and transferable embryos derived per stimulation cycle. The duration of stimulation was shorter in the isolated PCO group but not the PCOS group possibly because of extra judicious step-up of gonadotrophin in certain cases perceived as high-risk in the latter.

Concurring with higher ovarian responses, the rate of withholding fresh ET for risk of OHSS was significantly higher in both the PCOS and isolated PCO groups. Moreover, the actual incidence rate of moderate to severe OHSS was significantly higher in the PCOS group (11.5 %) compared to the controls (4.9 %). Such findings are all in line with those reported by others [11, 12, 14, 15]. There was also a trend of higher rate of moderate to severe OHSS in the isolated PCO group (8.2 %) which corresponded to a 67 % risk increment compared to the controls although not reaching statistical significance. This might be due to the limited sample size of our cohort manifesting this complication, and yet this apparent increase in the risk of OHSS should not be ignored in clinical practice.

We also confirmed similar pregnancy and live birth rates in the fresh cycles, both analysed per cycle started or per transfer, in both the PCOS and isolated PCO groups compared to controls. This echoed the findings in some reported studies

[10, 12–15], while some others have reported higher pregnancy rates in women with PCO compared to controls [9, 11]. In contrast to some of the reported studies, our study made use of age-matched controls, which eliminated the confounding effect of age to the treatment outcome. Moreover, all the reported studies evaluated the pregnancy/live birth outcome in the fresh IVF cycle only. In modern-day IVF programmes, a smaller number of embryos are replaced each time to reduce the risk of multiple pregnancies and cryopreservation of surplus embryos with subsequent transfers in thawed cycles has become an integral part of an IVF programme. Hence, it would be more meaningful to study the cumulative live birth per stimulated cycle, taking into account the outcomes from both the fresh ET cycle as well as the FETs derived from the same index stimulation cycle. To our knowledge, ours is the first report comparing the cumulative pregnancy and live birth rates among women with PCOS, isolated PCO and the ovulatory non-PCO controls.

We found that the cumulative pregnancy and live birth rates were significantly higher in the isolated PCO group than controls. This was likely accountable by the significantly higher ovarian response and hence larger number of retrieved oocytes and total number of transferable embryos derived per stimulation cycle. Indeed, our multivariate logistic regression analysis suggested that it was the total number of transferable embryos which was the most important in predicting the cumulative live birth. Although the cumulative pregnancy and live birth rates were apparently higher in the PCOS group compared to controls, the difference did not reach statistical significance. We speculate that this could be due to poorer embryo competence in the PCOS group which might have offset the positive effect from the quantitative aspect. Actually it has been reflected in terms of higher miscarriage rates in the PCOS group compared to the isolated PCO and control groups, both from our findings as well as those reported by some others [12, 20]. It was suggested that this increased miscarriage rate in PCOS was not explained genetically by increased risk of embryonic aneuploidy [21]. As reviewed by Qiao and Feng [22], there is a multitude of endocrine and metabolic dysfunctions like LH hypersecretion, hyperandrogenaemia and hyperinsulinaemia, as well as altered intraovarian paracrine/autocrine factors, which are

characteristic of PCOS and could be implicated in the impaired embryo developmental competence observed in PCOS. On the other hand, some studies have revealed that women having isolated PCO, unlike those with PCOS, do not have altered endocrine and metabolic profile compared to normal controls [12, 15, 23]. As limited by the retrospective nature of our current study, however, we did not have the metabolic and endocrine data for comparison among the three groups.

Inherent to the metabolic characteristics of women with PCOS, they had significantly higher body weight and body mass index compared to the isolated PCO and control groups. However, the absolute magnitude of difference was very small, and this probably did not affect the validity of our primary conclusion on the cumulative live birth since it is not a significant factor predicting the latter as shown in our logistic regression analysis.

Another limitation inherent to the retrospective design of this study is the presence of confounders given the long study period included. During the study period, however, the treatment protocol adopted in our Centre has been consistent and unchanged. Furthermore, to reduce treatment bias, we only included in this study those women treated on the long GnRH agonist protocol, which was the standard treatment protocol that we and many others were adopting during the study period. However, in more recent years, with accumulating data suggesting significantly lower risk of OHSS and hence increased safety with the use of GnRH antagonist in women with PCOS, we have moved towards the latter as the standard protocol for women with PCO or PCOS. It would hence be warranted to repeat a similar analysis on the cumulative live birth outcome and the ovarian stimulation parameters with the use of GnRH antagonist protocol in further studies.

In conclusion, our results showed that women with isolated PCO, but not PCOS, had a significantly higher cumulative live birth rate. This could be explained by the quantitative effect of the higher number of transferable embryos obtained per stimulation cycle, which is uncompromised by the unfavourable embryo competence otherwise observed in PCOS. We also confirmed that both of the PCOS and isolated PCO groups had higher ovarian response compared to non-PCO controls, and hence both groups would require more judicious use of gonadotrophin in ovarian stimulation with more vigilant monitoring.

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