ORIGINAL ARTICLE

Comparison of IVF/ICSI outcome in patients with polycystic ovarian syndrome or tubal factor infertility

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Abstract

Background: One of the recognized treatment options for patients with polycystic ovarian syndrome (PCOS) is *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Fears are however sometimes raised concerning the likely outcome of treatment in such patients compared with their counterparts with tubal factor infertility.
Objective: To compare the IVF/ICSI performance in women with PCOS and those with tubal factor infertility.
Materials and Methods: A retrospective analysis. Case notes of 30 patients, 35 years and below, with PCOS and who underwent 33 IVF/ICSI cycles and those of 42 age-controlled patients with tubal factor infertility and who had 43 cycles between December 2004 and April 2008 were retrieved. Data including duration of down-regulation, dose of human Menopausal Gonadotropin (hMG), number of cancelled treatments, endometrial thickness, number of oocytes retrieved and fertilization rate, in addition to the number of embryos transferred with resultant pregnancy outcome were compared between the two groups. The main outcome measures were response to gonadotropin stimulation, fertilization rate and clinical pregnancy rate.
Results: There was no significant difference between the PCOS group and the tubal factor infertility group in the hMG dose (2.7 vs. 3.4 vials, respectively), endometrial thickness (10.5 vs. 10.1 mm, respectively) and embryos transferred (3.1 vs. 2.9, respectively). The fertilization rate was significantly higher in the tubal factor infertility group, which was 81.48% as against 63.24% for the PCOS group ($P < 0.0001$). While more cases of ovarian hyperstimulation syndrome (OHSS) occurred in the PCOS group ($P = 0.049$), overall clinical pregnancy rate per embryo transfer was similar (45.45% vs. 42.85%; $P = 1$), with similar miscarriage rates.
Conclusion: IVF/ICSI performance in patients with PCOS is probably similar to their counterparts with tubal factor infertility with, however, a reduced fertilization rate and higher incidence of OHSS.

Key words: IVF, polycystic ovarian syndrome, pregnancy, tubal

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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine condition with an estimated prevalence of approximately 4–8%, but as high as 25% in some populations.[1] It is reported that over 70% of women suffering from normogonadotrophic anovulation present with ultrasound or endocrine features associated with PCOS.[2]

Ovulation induction with pharmacological agents constitutes the first-line treatment of choice in these women.[3] First-line agent of choice is the antiestrogen clomiphene citrate, while exogenous gonadotropins are commonly used as second-line intervention.[3,4] Unfortunately, multiple pregnancy rates with the above, especially with gonadotropins, are considerably high.[5] While some patients will benefit from any of these treatments, a considerable number will require

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other forms of assisted conception such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI).[6] With IVF/ICSI, the number of embryos transferred can be determined and it can therefore be possible to reduce the multiple pregnancy rates.

Several protocols exist for controlled ovarian stimulation. These include the ultra-short, short, and the long protocols.[7] The long protocol has the effect of suppressing endogenous gonadotropins. This is particularly relevant in patients with PCOS as they commonly have an elevated luteinizing hormone (LH) levels with subsequent elevation of androgens. The reversible hypogonadotropic hypogonadism so produced permits unimpeded control over follicular development, thereby allowing the oocyte containing follicles to develop in the sensitive polycystic ovary, free from the adverse environment of high tonic LH levels. These oocytes appear to fertilize better than those obtained in cycles without pituitary desensitization.[8]

Concerns have however been raised regarding the risk of ovarian hyperstimulation syndrome (OHSS), fertilization as well as pregnancy rates in this group of patients.

The aim of this study, is to compare the IVF/ICSI performance in women with PCOS with their age-matched counterparts with tubal factor infertility.

Materials and Methods

A retrospective analysis was carried out at the Port Harcourt Fertility Centre, Rivers State, Nigeria. Case notes of 30 patients, 35 years and below, with PCOS and who underwent 33 IVF/ICSI cycles and those of 42 age-controlled patients with tubal factor infertility diagnosed on hysterosalpingogram, with normal ovaries, and who had 43 cycles between December 2004 and April 2008 were retrieved. Those who had male factor infertility or combined PCOS and tubal factor infertility were excluded from the study. All patients with PCOS were placed on metformin tablets 500 mg b.d. before the commencement of pituitary down-regulation. Data including duration of down-regulation, dose of human Menopausal Gonadotropin (hMG), number of cancelled treatments, endometrial thickness, number of oocytes retrieved and fertilization rate, in addition to the number of embryos transferred with resultant pregnancy outcome were compared between the two groups. Data were analyzed with SPSS statistical package. Cycle parameters were compared using the Student's *t*-test and Fisher's exact *test*. A *P*-value of <0.05 was considered statistically significant at 95% confidence interval.

For the purpose of this study, PCOS was defined as anovulation/oligoanovulation and clinical and/or biochemical evidence of hyperandrogenism and polycystic appearance on ultrasound scan.[9] All three criteria were present in the 30 patients.

Main outcome measures were response to gonadotropin stimulation, fertilization rate, and clinical pregnancy rate.

Results

As shown in Table 1, there was no significant difference in age, hMG dose (2.7 vs. 3.4 vials), and endometrial thickness (10.5 vs. 10.1 mm) between the PCOS group and the tubal factor infertility group ($P = 0.152$, 0.137, and 0.414, respectively).

Table 2 compares the stimulation, fertilization, and clinical outcome between the two groups. Although a greater number of oocytes were retrieved from the PCOS group (12.7 vs. 9), the fertilization rate was significantly higher in the tubal factor infertility group, which was 81.48% as against 63.24% for the PCOS group ($P < 0.0001$).

While more cases of OHSS occurred in the PCOS group ($P = 0.049$), overall clinical pregnancy rate per embryo transfer was similar (45.45% vs. 42.85%; $P = 1$) with similar miscarriage rates (12.12% vs. 11.63%). Take-home baby rate was 36.41% and 30.27% for the PCOS and tubal factor infertility groups, respectively.

Discussion

The aim of every IVF program is to achieve multifollicular development resulting in the collection of several appropriately matured eggs without causing OHSS. This is especially so in women with PCOS as they usually exhibit

Table 1: Comparison of age, HMG dose, and endometrial thickness between the PCOS and tubal factor groups

Cycle parameters	PCOS ($n = 33$)	Tubal factor ($n = 43$)	*P* value
Age (years)	30.24 ± 3.99	30.65 ± 2.68	0.152
hMG dose (vials)	2.7 ± 0.88	3.4 ± 1.14	0.137
Endometrial thickness (mm)	10.5 ± 2.45	10.1 ± 2.15	0.414

Table 2: Stimulation, fertilization, and clinical outcome

Cycle parameters	PCOS ($n = 33$)	Tubal factor ($n = 43$)	*P* value
Oocytes retrieved	12.7 ± 7.69	9 ± 6.27	0.021*
Fertilization rate (%)	265/419 (63.24)	242/297 (81.48)	<0.0001*
Embryos transferred	3.1 ± 1	2.9 ± 0.89	0.169
OHSS rate (%)	6 (18.18)	3 (6.98)	0.049*
Clinical pregnancy (%)	15 (45.45)	18 (42.85)	1
Miscarriage rate (%)	4 (12.12)	5 (11.63)	0.926

*Significant

greater sensitivity than women with normal ovaries to exogenous stimulation.[10] In our study, although fewer ampoules of hMG were used for stimulation of the patients with PCOS compared to those with normal ovarian function, the difference was not statistically significant ($P = 0.137$). Despite this, significantly more patients with PCOS had OHSS ($P = 0.049$). This again might be a reflection of the extreme sensitivity of patients with PCOS to gonadotropins as already alluded to. In a study by Urman *et al*.,[11] patients with PCOS used a significantly lower dose of hMG compared to those with normal ovaries. In another study, despite using the same dose of hMG, significantly more cycles were cancelled in the PCOS group because of imminent OHSS (6% vs. 1%).[12]

While gonadotropin-releasing hormone (GnRH) antagonist protocol is associated with lower incidence of OHSS,[13] we still prefer the long protocol of pituitary desensitization with GnRH agonist as it allows for better flexibility necessary for batching our patients.[14] With the long protocol, we are able to commence controlled ovarian stimulation in all batched patients at the same time following variable periods of pituitary down-regulation.

Patients with PCOS have higher estradiol levels compared with their counterparts with normal ovarian function.[15] Estradiol levels give an indication of the risk of OHSS, and the higher the estradiol level, the greater is the risk of OHSS. Unfortunately, we rely solely on endometrial thickness on transvaginal ultrasound scan for cycle monitoring during ovarian stimulation and so cannot comment on the estradiol levels in our patients. This is not out of place as there are reports that estradiol levels are a poor predictor of treatment success and, when done routinely, do not reduce the incidence of OHSS.[16] Estradiol levels are probably only necessary in patients at risk of OHSS on ultrasound scanning.[16] Endometrial thickness also has a good correlation with estradiol levels, while the number of developing follicles can predict the risk of OHSS.[17,18] All our patients with suspected risk of OHSS based on the number of developing follicles, especially if more than 20, were "coasted" for 1–2 days. There are reports that this reduces the serum estradiol levels and subsequently reduces the risk of OHSS.[19] Prolonged coasting for more than 3 days might, however, be associated with poor clinical outcome.[20,21] Despite this measure, we still recorded a higher OHSS rate in the PCOS group, though none was severe. There was no statistically significant difference in the endometrial thickness at the point of human chorionic gonadotropin (hCG) administration between the two groups of patients ($P = 0.414$).

Oocyte recovery was significantly more in the PCOS group, as observed in other studies.[22-24] It is our practice to carry out ICSI in patients with previous history of fertilization failure from IVF or whenever we use frozen or overnight semen sample from those previously identified to be at risk of psychogenic anejaculation. Oocyte quality was not compared between the two groups in our study. Fertilization rate was, however, significantly more in the tubal factor infertility group ($P < 0.0001$). We cannot conclude if this is a reflection of poorer egg quality or as a result of significantly more immature eggs in the PCOS patients. While significantly more oocytes were recovered by Plachot and coworkers[23] (12.1 vs. 9.6), a significantly greater percentage of the oocytes were immature (13.8 vs. 5.8%). Another recent study did not observe any difference in the maturity of the oocytes or oocyte dysmorphism between patients with PCOS and those with normal ovarian function.[15] The role of premature administration of hCG because of the fear of OHSS, as a possible reason for the occurrence of significant number of immature oocytes in patients with PCOS, needs to be investigated. Importantly though, reduction of the adverse hormonal milieu of the developing follicle in PCOS would ultimately lead to better quality oocytes. While there are reports that pituitary desensitization for up to 14 days might be enough to achieve this, some investigators recommend a longer period of desensitization for up to 30 days, especially for patients with PCOS.[25]

The cumulative clinical pregnancy rate was the same for the two groups of patients ($P = 1$) as was observed in other studies.[26] There was no significant difference in miscarriage rates between the two groups contrary to some reports.[15,27] This observation might be as a result of the application of our protocol which involves placing all patients with PCOS on metformin prior to commencing treatment. Metformin has been shown by various studies to reduce the miscarriage rates in patients with PCOS undergoing IVF treatment.[28,29] While reports show that PCOS patients demonstrate a significantly increased chance of cycle cancellation (12.8% vs. 4.1%),[26] no cycle was cancelled in our study. While our practice of coasting such patients might have played a role, our sample size was, however, small.

Our study suggests that IVF/ICSI performance in patients with PCOS might be as good as their counterparts with tubal factor infertility. The small sample size, however, limits a more definitive conclusion. Further randomized controlled studies are required.

References

1. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010;8:41.
2. Laven JS, Imani B, Eijkemas MJ, Fauser BC. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstet Gynaecol Surv 2002;57:755-67.
3. Beck J, Boothroyd C, Proctor M, Farquhar C, Hughes E. Oral anti-estrogens and medical adjuncts for subfertility associated with anovulation. Cochrane Database Syst Rev 2005;(1):CD002249.
4. Nugent D, Vandekerckhove P, Hughes E, Arnot M, Lilford R. Gonadotrophin

therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2000;(4)CD000410.

5. Eijekemans MJ, Imani B, Mulders AG, Habbema JD, Fauser BC. High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2). Hum Reprod 2003;18:2357-62.
6. Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005;365:1807-16.
7. Bhathena RK, Patel S, Shah D. Superovulation strategies in assisted conception. In: Rao K, editor. The infertility manual. 2nd ed. Jaypee Brothers Pubishers. New Delhi 2004. 285-90.
8. Abdalla HI, Ahuja KK, Leonard T, Morris NN, Honour JW, Jacobs HS. Comparative trial of luteinizing hormone-releasing hormone analog/human menopausal gonadotropin and clomiphene citrate/human menopausal gonadotropin in an assisted conception program. Fert Steril 1990;53:473-8.
9. Chang J, Azziz R, Legro R, Dewailly D, Franks S, Tarlatzis R, *et al*. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome: The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Fertil Steril 2004;81:19-25.
10. Schenker JG, Ezra Y. Complications of assisted reproduction techniques. Fertil Steril 1994;61:411-22.
11. Urman B, Fluker MR, Yuen BH, Fleige-Zahradka BG, Zouves CG, Moon YS. The outcome of *in vitro* fertilization and embryo transfer in women with polycystic ovary syndrome failing to conceive after ovulation induction with exogenous gonadotropins. Fert Steril 1992;57:1269-73.
12. Kodama H, Fukuda J, Karube H, Matsui T, Shimizu Y, Tanaka T. High incidence of embryo transfer cancellations in patients with polycystic ovarian syndrome. Hum Reprod 1995;10:1962-7.
13. Lainas TG, Sfontouris IA, Zorzovillis IZ, Petsas GK, Lainas GT, Alexopoulou E, *et al*. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated to IVF: A prospective randomized controlled trial (RCT). Hum Reprod 2010;25:683-9.
14. Okohue JE, Onuh SO, Ikimalo JI, Onuh SO. Challenges in running/establishing an assisted conception centre in the Niger-Delta region of Nigeria. West African Journal of Assisted Reproduction 2011;1:1-17
15. 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.
16. Thomas K, Searle T, Quinn A, Wood S, Lewis-Jones I, Kingsland C. The value of routine estradiol monitoring in assisted conception cycles. Acta Obstet Gynecol Scand 2002;81:551-54.
17. Okonofua FE, Onwudiegwu U, Smith W, Thomas N, Craft I, Dandona F. Correlation of ultrasound assessment of endometrial growth and plasma steroid concentration during superovulation for *in vitro* fertilization. Afr J Med Sci 1993;22:89-93.
18. Verwoerd GR, Mathews T, Brinsden PR. Optimal follicles and oocyte numbers for cryopreservation of all embryos in IVF cycles at risk of OHSS. Reprod Biomed Online 2008;17:312-7.
19. Moon HS, Joo BS, Moon SE, Lee SK, Kim KS, Koo JS. Short coasting of 1 or 2 days by withholding both gonadotropins and gonadotropin releasing-hormone agonist prevents ovarian hyperstimulation syndrome without compromising the outcome. Fert Steril 2008;90:2172-8.
20. Egbase PE, Al-Sharhan MA, Grudzinskas JG. 'Early coasting' in patients with polycystic ovarian syndrome is consistent with good clinical outcome. Hum Reprod 2003;17:1212-6.
21. Nardo LG, Cheema P, Gelbaya TA, Horne G, Fitzgerald CT, Pease EA, *et al*. The optimal length of 'coasting protocol' in women at risk of ovarian hyperstimulation syndrome undergoing *in vitro* fertilization. Hum Fertil (Camb) 2006;9:175-80.
22. MacDougall MJ, Tan SL, Balen A, Jacobs HS. A controlled study comparing patients with and without polycystic ovaries undergoing *in vitro* fertilization. Hum Reprod 1993;2:233-7.
23. Plachot M, Belaisch-Allart J, Mayenga JM, Chouraqui A, Tesquier A, Serkine AM, *et al*. Oocyte and embryo quality in polycystic ovary syndrome. Gynecol Obstet Fertil 2003;31:350-4.
24. Esinler I, Bayar U, Bozdag G, Yarali H. Outcome of intracytoplasmic sperm injection in patients with polycystic ovary syndrome or isolated polycystic ovaries. Fertil Steril 2005;84:932-7.
25. Salat-Baroux J, Alvarez S, Antoine JM, Tibi C, Cornet D, Mandelbaum J, *et al*. Comparison between long and short protocols of luteinising hormone releasing hormone agonist in the treatment of PCOD by *in vitro* fertilization. Hum Reprod 1988;3:535-9.
26. Heijinen EM, Eijekemans 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;12:13-21.
27. Kaya C, Pabuccu R. Assisted reproduction techniques in the treatment of polycystic ovary syndrome. Turkiye Klinikleri J Gynecol Obst 2007;17:454-65.
28. Tang T, Glanville J, Orsi N, Barth JH, Balen AH. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod 2006;21:1416-25.
29. Khattab S, Mohsen IA, Foutouh IA, Ramadan A, Moaz M, Al-Inany H. Metformin reduces abortion in pregnant women with polycystic ovary syndrome. Gynecol Endocrinol 2006;22:680-4.

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