

Is the use of a GnRH antagonist effective in patients with polycystic ovarian syndrome? A South African perspective

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Introduction. Polycystic ovarian disease (PCOS) can account for up to 35 - 40% of the female factor causes of infertility. These patients present as medically complex cases and are challenging to manage and treat successfully. They are resistant to treatment and are often offered controlled ovarian stimulation (COS) and *in vitro* fertilisation (IVF) technology.

Aim. The aim of this study was to assess whether there was a difference in the pregnancy outcomes of women with PCOS when a standard gonadotrophin-releasing hormone (GnRH) antagonist (cetorelix) protocol was used for ovarian stimulation, compared with non-PCOS patients undergoing IVF.

Methods. A retrospective patient record audit was performed on 142 patients with PCOS and 501 non-PCOS patients undergoing a similar cetorelix-based COS treatment protocol during a specified time period.

Results. The main primary outcome was an ongoing pregnancy at 12 weeks, achieved in 34% of patients in the PCOS group and 27% in the non-PCOS group. This was not significantly different ($p=0.07$). No patient in the PCOS group experienced severe hyperstimulation syndrome.

Conclusion. There was no significant difference in pregnancy rates in patients with PCOS undergoing GnRH-antagonist ovarian stimulation compared with non-PCOS patients. The fact that no hyperstimulation syndrome occurred makes this an attractive option for women with PCOS.

At least 25% of couples experience some delay in achieving a desired or planned pregnancy, and 10% remain involuntarily childless before seeking medical assistance.¹ Ovulatory dysfunction and tubal and peritoneal factors are prevalent at all ages, and male factors and unexplained causes are more common in older couples.² Anovulation and oligo-ovulation account for approximately 40% of female infertility factors, and in this group polycystic ovarian disease (PCOS) is the predominant factor (80%).^{3,4} A definite diagnosis of PCOS can be made in 70 - 80% of anovulatory infertility.⁵ Standardised diagnostic criteria for PCOS have been accepted following a consensus meeting in Rotterdam in 2003.⁶

Induction of ovulation for the purposes of infertility management in the typical PCOS patient with concomitant metabolic syndrome should be preceded by weight loss and lifestyle modification. Clark *et al.* and Norman *et al.* found that 90% of patients who lost 5% or more of body weight returned to ovulation, with 60% becoming pregnant within 18 months.^{7,8} Insulin sensitisation using drugs such as metformin, a biguanide, has been used as both an adjunct and an alternative to clomiphene citrate in patients who are not successful in achieving ovulation or pregnancy.⁹⁻¹¹ A recent review concluded that metformin is highly effective in achieving ovulation in the clomiphene citrate-resistant PCOS patient, but should not be used as a first-line treatment modality.¹² *In vitro* fertilisation (IVF) technology is an effective treatment option after repeated ovulation induction failure using clomiphene citrate and gonadotrophin

therapy. The initial gonadotrophin-releasing hormone (GnRH) analogues used in controlled ovarian stimulation were the GnRH agonists. Problems caused by GnRH agonists were mid-cycle gonadotrophin flares, a high incidence of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).¹³

The introduction of newer GnRH analogues, the GnRH antagonists, created the potential for milder stimulation protocols that are better tolerated and less costly, have a quicker onset of action, result in a lower incidence of luteinising hormone (LH) surge, and are associated with a lower multiple pregnancy rate.¹⁴⁻¹⁷ Reviews and meta-analyses have recently compared the two GnRH analogues – the agonists with the antagonists – and have found no significant difference in fertilisation rate and pregnancy outcome.¹⁶⁻¹⁹ Two recent meta-analyses of pregnancy and neonatal outcome after IVF in PCOS patients versus non-PCOS patients have shown an increased cycle cancellation rate, more oocytes retrieved per retrieval, a lower fertilisation rate, and increased pregnancy and neonatal complications in patients with PCOS.^{17,19} From an assisted reproduction technology (ART) perspective, pregnancy and live birth rates per cycle were similar in the two groups.¹⁶

Patients with PCOS undergoing ART usually show an increased response to gonadotrophins and consequently produce large numbers of follicles and oocytes. Furthermore, they also tend to have higher serum oestradiol levels, resulting in an increased risk of OHSS.²⁰

Literature on the comparative effect and pregnancy outcome of the use of GnRH antagonists for ovulation induction in PCOS patients is limited.²¹ A Medline literature search yielded three limited studies, which were presented as abstracts, comparing IVF outcomes of patients with and without PCOS when GnRH antagonists were used for pituitary down-regulation.²²⁻²⁴ In summary, they reported that pregnancy outcome with GnRH antagonist use in PCOS patients undergoing controlled ovarian stimulation did not differ from pregnancy outcome in non-PCOS patients. In a very recent study,²⁵ a GnRH antagonist was compared with a GnRH agonist in PCOS patients. No differences were found in outcome in the two groups with regard to number of oocytes retrieved, number of embryos transferred, and clinical pregnancy rates. There was also no case of OHSS in the antagonist group.

Study aim

We aimed to compare the stimulation characteristics and IVF (embryo transfer (ET)) pregnancy outcomes of women with PCOS using a standard GnRH antagonist (cetorelix) protocol for ovarian stimulation with non-PCOS patients undergoing IVF using a similar protocol. Essentially the study question was whether GnRH antagonists work equally well in PCOS and non-PCOS patients.

Materials and methods

Study design and patient characteristics

The study was a retrospective observational cohort clinical audit and patient record review of two groups of patients who entered an ART programme between January 2005 and December 2007 (3 years). The entire data set available was collected for both groups. The first group included all patients during this time period ($N=142$) diagnosed as having PCOS and requiring controlled ovulation induction using a GnRH antagonist (cetorelix) regimen for IVF/intracytoplasmic sperm injection (ICSI) purposes (cetorelix-PCOS group). Before inclusion in this study group, a documented diagnosis of PCOS was made according to the Rotterdam criteria,⁸ and other causes of hirsutism/anovulation were excluded.

The second group ($N=501$) included all patients during the same period who did not have a diagnosis of PCOS but did require controlled ovulation induction using a cetorelix regimen (cetorelix-non-PCOS group). Both groups were part of a controlled ovarian stimulation protocol for the purposes of either IVF or ICSI. The demographic characteristics of the two groups are set out in Table I.¹

As set criteria for ICSI, the following thresholds were used for male factor: count less than 10 million/ml, motility less than 30%, and morphology less than 5.

Controlled ovulation induction

The general controlled ovulation induction protocol used in our patients can be outlined as follows, allowing for some slight individual but not significant variation. The patients were all given the GnRH antagonist cetorelix (Cetrotide; Serono International, Geneva, Switzerland) for the purposes of LH surge inhibition. Cetorelix was usually given as a fixed depot dose of 3 mg on day 8, occasionally following a flexible protocol. Ovarian stimulation was achieved by administering follicle-stimulating hormone (FSH)/human chorionic gonadotrophin (HCG) (Menopur) or FSH (Gonal F) alone. This was mainly done using a step-up protocol, starting

with 2 units a day on day 4 and increasing the dose after day 8 if needed. The patients were then followed up with serial ultrasound determination of follicle development. The criteria for triggering ovulation were based on follicle data, triggering when the leading follicle achieved 18 mm and at least two other follicles achieved 16 mm or more. ET was performed between days 2 and 5, depending on the number of good-quality embryos. Progesterone 600 mg per day was given for luteal phase support after transfer.

Outcome measurement

On days 10 - 14 after ET, a blood sample was taken to assess the β hCG value: if this was >10 IU/l, the test was repeated 4 days later to confirm pregnancy. Pregnancy was defined as a 66% rise in serum β hCG in 48 hours. In the case of a positive pregnancy, ultrasound was performed at 7 weeks after ET to assess the number of fetal sacs and heart activity. Clinical pregnancy was defined as the presence of a fetal sac, with or without heart activity. As a second primary outcome, ongoing pregnancy was defined as positive heart activity at a gestational age of 12 weeks. In this study we report the ongoing pregnancy rate.

Statistics

The primary outcome measures possible with the data collected were total number of oocytes retrieved and pregnancy rates. The patient population used for the analyses of the primary efficacy endpoints were defined as all patients with either a diagnosis of PCOS or not, undergoing a cetorelix-based controlled ovarian stimulation procedure without major deviation from the protocol described above. Microsoft Excel 2002 software was used for data collection and statistical analysis.

Discrete data were compared with the chi-square test or Fisher's exact test where the expected value in any cell of a two-by-two table was less than 5. The means of normally distributed continuous data were compared by analysis of variance, while the medians of continuous data that were not distributed normally were calculated using the non-parametric Mann-Whitney U-test. A p -value of <0.05 was considered to be statistically significant, where applicable.

This study was exempt from the institutional ethics and review committee because of its retrospective, non-intervention nature, and the maintenance of total confidentiality. Data were accessed as part of an ongoing clinical audit.

Results

Table I sets out the demographic characteristics of the two groups, broken up as the two main study groups (PCOS and non-PCOS), as well as within-group assessment according to the assisted reproduction technique used (IVF and ICSI). There was no difference between the groups with regard to age. The main reasons for infertility in the non-PCOS group were male factor 40%, idiopathic 29%, endometriosis 18%, tubal factor 11% and other 2%.

In the groups described above, the number of oocytes retrieved was assessed as being different or not. The result of this analysis is presented in Table II. Similar numbers of oocytes were retrieved in both IVF groups and in both ICSI groups. Furthermore, there was no difference in oocyte retrieval between the PCOS and the non-PCOS groups. Two embryos were strictly transferred in all patients in the PCOS group as well as in the non-PCOS group.

The second primary outcome measure was a successful ongoing pregnancy. This outcome was also compared in the different study groups, and the results of the analysis are presented in Table III. There was no significant difference between the IVF ongoing pregnancy rate (46.3%) and the ICSI pregnancy rate (29.7%) in the PCOS group ($p=0.979$). The same was true of the non-PCOS group (IVF 30.95% v. ICSI 24.92) ($p=0.27$) (Table III).

There was also no difference between total pregnancy rates in the PCOS group (34.5%) and the non-PCOS group (26.95%) ($p=0.19$) (Table III).

No case of severe OHSS was reported in either the PCOS or the non-PCOS group.

In the PCOS group, there were 49 pregnancies. Seven of these ended in a miscarriage (14.3%). The miscarriage rate in the control group was 12.7%. This difference was not significant. The twin pregnancy rate in the PCOS group was 15.4% and in the non-PCOS group 14.8%.

Discussion

Infertility patients requiring controlled ovarian stimulation (COS) may be managed with three different options: (i) FSH with a GnRH antagonist; (ii) clomiphene/FSH with a GnRH antagonist; or (iii) the long-course GnRH agonist protocol.²⁶ The use of a GnRH agonist to suppress elevated LH and androgen levels and to prevent premature

LH surges in COS has been successful in reducing the miscarriage rate and improving the pregnancy rate.²⁴ It has been proposed that the newer GnRH antagonists may even be better for COS in the difficult patient subgroup.¹⁴ Antagonists have been shown to be better than agonists in general and PCOS infertility patients in that antagonists require the use of less gonadotrophin, result in better patient compliance and are associated with a lower rate of OHSS.^{22,23} The main purpose of this study was to assess whether PCOS patients had similar infertility treatment outcomes to patients with infertility problems other than PCOS when using a GnRH antagonist protocol for COS.

The data for our two main groups, PCOS and non-PCOS, were generally comparable. Age and endometrial thickness did not differ significantly (Table I). The sample size was different, but this simply reflected the study population, i.e. all patients undergoing COS treatment. Approximately 22% of the infertility patients had a formal clinical diagnosis of PCOS, which corresponds with the proportion of infertility patients with PCOS.^{3,4}

The total number of oocytes retrieved per cycle was not significantly different in the PCOS and the non-PCOS groups (Table II). This lack of significant difference is contrary to the finding that PCOS patients generally produce larger numbers of oocytes per stimulated cycle^{17,18} and may be a result of the less complex COS and IVF/ICSI protocols used in our unit. It was also very encouraging to note that

Table I. Characteristics of patients in the two study groups

| | PCOS | | | Non-PCOS | | |
|---|-------------------------|-------------------------|----------------------------|-------------------------|-------------------------|----------------------------|
| | IVF | ICSI | Total | IVF | ICSI | Total |
| Group size (N) | 41 | 101 | 142 | 168 | 333 | 501 |
| Age (yrs) (mean (SD), range) | 34.24 (3.74) 28 - 43 | 33.89 (4.20) 26 - 44 | 33.99 (4.06)* 26 - 44 | 34.48 (4.43) 21 - 43 | 34.86 (4.58) 20 - 44 | 34.73 (4.53)* 20 - 44 |
| Endometrial thickness [‡] (mm) (mean (SD)) | 26.75 (36.56) | 24.98 (35.11) | 25.49 (35.41) [†] | 17.78 (27.15) | 18.03 (27.56) | 20.24 (30.23) [†] |

*No significant difference ($p>0.05$).
[†]Significantly different ($p=0.079465$).
[‡]Endometrial thickness at embryo transfer.

Table II. Oocytes retrieved

| | PCOS | | | Non-PCOS | | |
|------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | IVF | ICSI | Total | IVF | ICSI | Total |
| Oocyte quantity (mean (SD))* | 7.19 (4.85) | 7.46 (5.83) | 7.38 (5.55) | 7.26 (4.96) | 7.16 (4.40) | 7.19 (4.59) |

*No significant difference in any category analysis ($p>0.05$).

Table III. Ongoing pregnancy rate

| | PCOS | | | Non-PCOS | | |
|------------------------|-------------------------------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|----------------------------------|
| | IVF | ICSI | Total | IVF | ICSI | Total |
| Ongoing pregnancy rate | 19/41 (46.3%) ^a | 30/101 (29.7%) ^b | 49/142 (34.5%) ^c | 52/168 (30.95%) ^d | 83/333 (24.92%) ^e | 135/501 (26.95%) ^f |

(a) v. (b) $p=0.1979$; (d) v. (e) $p=0.27$; (c) v. (f) $p=0.19$.

there was no case of severe hyperstimulation in either of the two groups.

The primary endpoint of this study was a successful ongoing pregnancy. Table III summarises the success rates in the two main groups. Each of these groups, i.e. PCOS and non-PCOS, was further divided into patients having IVF or ICSI after COS. The overall pregnancy success rate was higher for the PCOS group (34%) than the non-PCOS group (27%), although this difference was not statistically significant ($p=0.0785$). Certainly the PCOS patient does not suffer a decline in pregnancy outcome when the antagonist-based protocol is used. These overall pregnancy rates achieved in our treatment protocols are similar to those achieved in published fertility programmes – approximately 35%.²⁷ It is also interesting to note that IVF has better results than ICSI in terms of pregnancy outcome. This may be explained by the fact that other pathology may be involved with the infertility diagnosis, especially when resorting to ICSI in an assisted reproduction programme. The miscarriage rates in the PCOS (14.3%) and the non-PCOS (12.7%) groups were not significantly different.

With the limits of a retrospective study, our analysis still enables us to conclude that there were no significant differences in procedural and pregnancy success in patients with PCOS undergoing GnRH-antagonist ovarian stimulation compared with non-PCOS patients in whom the same controlled ovarian stimulation was used. Of importance is the fact that there was no case of severe hyperstimulation syndrome in the PCOS group, making the use of the GnRH antagonist an attractive option in this high-risk group of patients. In the South African setting the use of cetrorelix for PCOS patients is definitely a safe option.

1. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007;22:1506-1512.
2. Speroff L, Fritz MA. *Clinical Gynecologic Endocrinology and Infertility*. 7th ed. Baltimore: Lippincott Williams & Wilkins, 2005.
3. 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(6):1416-1425.
4. Sohrabvand F, Ansari Sh, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. *Hum Reprod* 2006;21(6):1432-1435.

5. Franks S. Polycystic ovary syndrome. *Medicine* 2005;33(11):38-40.
6. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19-25.
7. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998;13:1502-1505.
8. Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. *Trends Endocrinol Metab* 2002;13(6):251-257.
9. Balen A. Ovulation induction. *Curr Obstet Gynaecol* 2004;14:261-268.
10. Kovaks GT. Polycystic ovarian disease: an overview. *Reviews in Gynaecological Practice* 2004;4:97-104.
11. Neveu N, Granger L, St-Michel P, Lavoie HB. Comparison of clomiphene citrate, metformin, or the combination of both for first line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome. *Fertil Steril* 2007;87:113-120.
12. Siebert TI, Kruger TF, Steyn DW, Nosarka S. Is the addition of metformin efficacious in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome? A structured literature review. *Fertil Steril* 2006;86(5):1432-1437.
13. Balen A, Tan SL, Jacobs HS. Hypersecretion of luteinising hormone: a significant cause of infertility and miscarriage. *Br J Obstet Gynaecol* 1993;100:1082-1089.
14. Griesinger G. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. *RMB Online* 2006;13(5):628-638.
15. Heijnen EMEW, Eijkemans MJC, Hughes EG, Laven JSE, Macklon NS, Fauser BCJM. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12(1):13-21.
16. Eijkemans MJC, Heijnen EMEW, de Klerk C, Habbema JDF, Fauser BCJM. Comparison of different treatment strategies in IVF with cumulative live birth over a given time period as the primary end-point: methodological consideration on a randomised controlled non-inferiority trial. *Hum Reprod* 2006;21(2):344-351.
17. Kolibianakis EM, Collins J, Tarlatzis BC, Devroey P, Diedrich K, Griesinger G. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. *Hum Reprod Update* 2006;12(6):651-671.
18. Doldi N, Persico P, Di Sebastiano F, Marsiglio E, Ferrari A. Gonadotropin-releasing hormone antagonist and metformin for treatment of polycystic ovary syndrome patients undergoing in vitro fertilization-embryo transfer. *Gynecol Endocrinol* 2006;22(5):235-238.
19. Boomsma CM, Eijkemans MJC, Hughes EG, Visser GHA, Fauser BCJM, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12(6):673-683.
20. Abhoulgar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. *Hum Reprod Update* 2003;9:275-289.
21. Elkind-Hirsh KE, Webster BW, Brown C, Vernon MW. Concurrent Antagon™ and Follistim therapy for ovulation induction in women with polycystic ovary syndrome (PCOS). *Fertil Steril* 2002;77(suppl 3):S9.
22. Bracero N, Jurema M, Vlahos N, Kolp L, Garcia J. Polycystic ovarian syndrome (PCOS) patients have a favorable response to ganirelix acetate during controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF)-embryo transfer (ET). *Fertil Steril* 2002;78(3) suppl 1:S150.
23. Detti L, Khoder W, Ambler DR. IVF outcomes in patients with PCOS down-regulated with GnRH-antagonists. *Fertil Steril* 2007;88(suppl 1):S184.
24. Balen AH, Tan SL, MacDougall J, Jacobs HS. Miscarriage rates following in-vitro fertilisation are increased in women with polycystic ovaries and reduced by pituitary desensitisation with busserelin. *Hum Reprod* 1993;8:959-964.
25. Tehraminejad ES, Rashidi B, Haghollahi F, Ataie M. Comparison of GnRH antagonist with long GnRH agonist protocol after OCP pretreatment in PCOS patients. *Arch Gynecol Obstet* 2010;282:319-325.
26. Cardone V. GnRH antagonists for treatment of polycystic ovarian syndrome. *Fertil Steril* 2003;80(suppl 1):S25-31.
27. Hwang JL, Seow KM, Lin YH. Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomised study. *Hum Reprod* 2004;19(9):1993-2000.