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Cumulative pregnancy rates in couples with anovulatory infertility compared with unexplained infertility in an ovulation induction programme

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Using a retrospective analysis, we compared cumulative pregnancy rates, early pregnancy failure rates and multiple pregnancy rates in couples with polycystic ovarian syndrome (PCOS) (n = 148), hypogonadotrophic or eugonadotrophic hypogonadism (n = 91) and unexplained infertility (n = 117), who were treated in an ovulation induction clinic between January 1991 and December 1995. The women were treated with either human menopausal gonadotrophin (HMG) or purified follicle stimulating hormone (FSH). The cumulative pregnancy rate (derived from life-table analysis) after four ovulatory treatment cycles was 70% in the PCOS group, 74% in the hypogonadism group and 38% in the unexplained infertility group. The cumulative pregnancy rate in the unexplained infertility group was significantly lower than the other groups ($P < 0.001$) but there was no significant difference between PCOS and hypogonadism using the log rank test. The early pregnancy failure rate was 25% in the PCOS group, 27% in the hypogonadism group and 26% in the unexplained infertility group (χ^2 = 0.132, not significant). The multiple pregnancy rate was 20% in the PCOS group, 30% in the hypogonadism group and 17% in the unexplained infertility group (χ^2 = 2.105, not significant). Treatment of anovulatory infertility using HMG or FSH is effective irrespective of the cause. Couples with unexplained infertility are less successfully treated using HMG: correction of unexplained infertility may involve more than simple correction of possible subtle ovulatory defects.

Key words: eugonadotrophic hypogonadism/fecundity/hypogonadotrophic hypogonadism/PCOS/unexplained infertility

Introduction

The ovulation induction clinic at the Prince Henry's Institute of Medical Research, Melbourne, Australia was founded in 1970. It treated couples who were infertile due to anovulation. These women had a diagnosis of polycystic ovarian syndrome (PCOS) and had previously failed clomiphene citrate therapy or had a diagnosis of hypogonadotrophic or eugonadotrophic hypogonadism. From 1970 until 1985, the ovulation induction medication was human pituitary gonadotrophin (Healy *et al.*, 1980; Kovacs *et al.*, 1984). From 1985, human menopausal gonadotrophin (HMG) or purified urinary gonadotrophin (follicle stimulating hormone, FSH) was used.

From 1991, couples with unexplained infertility were treated with up to four cycles of ovarian stimulation prior to either in-vitro fertilization (IVF) or gamete intra-Fallopian transfer (GIFT). None of the couples in any of the groups had intrauterine insemination (IUI) performed as part of their treatment.

By performing a retrospective analysis, we tested whether application of the same method of treatment (ovulation induction) known to be effective in couples with anovulatory infertility would be beneficial to couples with unexplained infertility receiving ovarian stimulation. The aims of our study were to compare: (i) the cumulative pregnancy rates in couples with PCOS, hypogonadotrophic hypogonadism, eugonadotrophic hypogonadism or unexplained infertility, (ii) the early pregnancy loss rates in these groups and (iii) the multiple pregnancy rates between the groups.

Materials and methods

Subjects

Data from couples treated between January 1991 and December 1995 were examined. There were 148 couples with a diagnosis of PCOS. Polycystic ovarian syndrome was diagnosed if an infertile woman with oligomenorrhoea and/or hirsutism had polycystic ovaries on vaginal or abdominal ultrasound examination, that is $\geqslant$10 peripheral ovarian cysts measuring $\leqslant$8 mm in diameter with increased ovarian stromal echogenicity with or without ovarian enlargement (Franks 1986; Adams *et al.*, 1986); without or with endocrine testing revealing a luteinizing hormone (LH):FSH $\geqslant$3, serum testosterone concentration >3.5 nmol/l and/or DHEAS >7.5 nmol/l (Chang, 1984). All these women had both ultrasound and endocrine assessment prior to beginning treatment. These patients had consistently failed to ovulate on clomiphene up to a dose of 150 mg daily for 5 days or had failed to conceive despite six ovulatory cycles of clomiphene.

There were 91 couples who had either hypogonadotrophic or eugonadotrophic hypogonadism. Hypogonadotrophic hypogonadism was diagnosed in women who had low gonadotrophin concentrations (FSH <3 IU/l) in the early follicular phase of the ovarian cycle and who had primary hypothalamic or pituitary dysfunction or weight loss [body mass index (BMI) (kg/m^2) <18]. Eugonadotrophic hypogonadism was diagnosed in women who had normal serum concentration of FSH (>3 IU/l) and normal prolactin profiles but who did not ovulate and who did not have the clinical, ultrasound or laboratory features of PCOS.

There were 117 couples with unexplained infertility. This was

diagnosed in couples when the semen analysis was normal [volume 2–5 ml, concentration $>20\times10^6$/ml, >50% total motility, >15% normal forms (WHO 1992)], including a negative immunobead test (IBT) (<50% antibody binding). These patients had patent uterine tubes and there were no significant intrauterine or pelvic abnormalities demonstrated on laparoscopy and hysteroscopy; the women's mid-luteal progesterone concentration was >30 nmol/l.

All couples in the PCOS and hypo/eugonadotrophic hypogonadism groups had two semen analyses and one IBT performed to exclude male factor infertility. The female partner had a laparoscopy or hysterosalpingogram to exclude tubal or pelvic factor infertility and endometriosis. These couples did not have male factor infertility or tubal or pelvic abnormalities.

Treatment protocols

Two to five days after the commencement of a natural or progestagen-induced menstrual bleed, the ovulation induction or ovarian stimulation treatment was begun. Prior to the start of therapy, serum LH, oestradiol and progesterone concentrations and transvaginal ultrasound (Aloka 500, Tokyo, Japan) were performed to obtain baseline levels. Treatment was not commenced if the serum oestradiol concentration was >300 pmol/l, or if there was an ovarian cyst >20 mm on ultrasound. Treatment, in couples with PCOS or hypo/eugonadotrophic hypogonadism, was commenced with HMG (Pergonal®: Serono, Sydney, Australia or Humegon®, Organon, Sydney, Australia) or purified FSH (Metrodin®, Serono) at a dose of 75 IU. In couples with unexplained infertility, our starting dose was 75 IU if the woman's BMI was <18 and 150 IU if her BMI was >18. This standard starting regimen then varied in succeeding cycles depending on the patient response.

Three to 4 days after commencing treatment, serum oestradiol concentration and pelvic ultrasound were obtained to assess ovarian follicular response. The dose of medication was adjusted according to response and monitoring continued on a daily, second daily or third daily basis. When the lead follicle was >16 mm in diameter, and provided the serum oestradiol concentration was between 500 and 3000 pmol/l, 3000 IU of human chorionic gonadotrophin (HCG) (Profasi®; Serono or Pregnyl®; Organon) was administered. The couples were advised to have sexual intercourse on the day of HCG administration and for the following 3 days.

The cycle was cancelled (no HCG administered) if there were more than three follicles >14 mm in diameter and/or the serum oestradiol concentration was >3000 pmol/l because of the risk of multiple pregnancy and hyperstimulation respectively. In these cases the couples were advised to refrain from sexual intercourse for 10 days. On days 3, 6 and 9 after HCG administration, serum oestradiol and progesterone concentrations were measured. Luteal phase support in the form of 1500 IU HCG was administered if the serum oestradiol concentration was <1000 pmol/l and the progesterone was <50 nmol/l. In all couples, if ovulation did not occur with 3000 IU HCG, the dose in the next treatment cycle was increased to 6000 IU and if ovulation still did not occur the dose was increased to 10 000 IU.

A pregnancy test was performed 15 days after HCG administration if the expected menses was delayed. Pregnancy was defined as a rising concentration of serum βHCG and a gestational sac with fetal pole and heart beat on ultrasound at 6 weeks gestation. An ongoing pregnancy was defined as a pregnancy after 20 weeks gestation.

Hormone assays

Serum FSH, LH, oestradiol, progesterone and prolactin concentrations were measured as previously described (Burger *et al.*, 1994). Serum testosterone and DHEAS concentrations were also measured as previously described (Burger *et al.*, 1995).

Table I. Clinical characteristics and pregnancy outcome in couples with polycystic ovary syndrome (PCOS), hypogonadotrophic or eugonadotrophic hypogonadism and unexplained infertility

	PCOS	Hypogonadism	Unexplained infertility
No. of couples	148	91	117
No. of cycles started	460	251	284
No. of ovulatory treatment cycles	399[d]	219[e]	270[d,e]
Age (years, mean ± SD)	30.1 ± 3.6[a,b]	31.0 ± 3.6[a]	32.0 ± 4.1[b]
BMI (kg/m^2, mean ± SD)	27.9 ± 5.9[b,c]	24.0 ± 5.7[c]	23.4 ± 3.7[b]
Fecundity rate (%)	25[d]	25[e]	11[d,e]
Early pregnancy loss (%)	25	27	26
Ongoing pregnancy rate/cycle	19[d]	18[e]	9[d,e]
Multiple pregnancy (%)	20	30	17

Values with the same superscripts within rows were significantly different: [a]$P < 0.05$; [b]$P < 0.001$; [c]$P < 0.001$; [d,e]$P < 0.005$.

Statistical analysis

In all groups, a particular couple may be represented more than once if they completed a course of treatment that culminated in a pregnancy (whether it ended in an early pregnancy loss or a live birth), and then re-presented for treatment, or, if they returned for treatment after a period of 12 months or more. Only ovulatory cycles were included in the statistical analyses.

The cumulative pregnancy rates were derived from life-table analysis. The life-table analysis and log rank tests allow maximum utilization of the available data obtained sequentially on each patient and overcome the problem of comparing fecundity rates which may be influenced by declining rates with time. Stolwijk *et al.* (1996) have drawn attention to the possibility of misleading interpretations of cumulative pregnancy rates derived from life-table analysis when these are quoted without regard to causes of patient dropout from further treatment or the wide confidence limits of the estimates at extreme times when there are few patients remaining and few pregnancies occurring. However, life-table analysis provides a valid method for estimating the pregnancy rates at each treatment for those who continue treatment and the log rank test is appropriate for comparing the pregnancy rates between groups. In the present study, the dropout rates were low (see below) and evenly distributed over the cycles. Analysis of the fecundity rates gave the same results.

Statistical analysis was carried out using the log rank test (cumulative pregnancy rates), χ^2 test, analysis of variance (ANOVA) and proportional hazards (Cox) regression where appropriate, using the statistical package SPIDA (Macquarie University, Sydney, Australia).

Results

Patient characteristics

A total of 356 couples had a total of 995 cycles initiated. Women with PCOS were typically younger and heavier than the other two groups (Table I).

Cycle characteristics

There were 460 cycles initiated in the PCOS group. Twenty-six of these cycles (6%) were cancelled prior to the

administration of HCG. Of these 26 cancelled cycles, 20 (4%) were cancelled because of multiple pregnancy/hyperstimulation risk. The other six cycles were abandoned for reasons unrelated to the treatment. Of the 434 remaining cycles, 399 cycles were ovulatory treatment cycles (92%). There were 251 cycles initiated in the hypo/eugonadotrophic group. Eight of these cycles (3%) were cancelled prior to HCG administration. Of these eight cycles, four (2%) were abandoned because of a multiple pregnancy/hyperstimulation risk. The other four cycles were abandoned for reasons unrelated to treatment. Of the remaining 243 cycles, 219 were ovulatory treatment cycles (90%). There were 284 cycles initiated in the unexplained infertility group. Twelve of these cycles (4%) were cancelled prior to the injection of HCG. Of these 12 cycles, eight (3%) were abandoned because of hyperstimulation/multiple pregnancy risk and the other four cycles were cancelled for reasons unrelated to treatment. Of the remaining 272 cycles, 270 cycles were ovulatory treatment cycles (99%), which was significantly higher than in the PCOS/hypo/eugonadotrophic groups ($P < 0.005$). There was no difference in the ovulatory rates between the PCOS and hypo/eugonadotrophic groups.

A total of 101 pregnancies occurred in 148 couples in the PCOS group, 55 pregnancies in 91 couples in the hypo/eugonadotrophic group and 31 pregnancies in the 117 couples in the unexplained infertility group. The total pregnancy rate was 68% in the PCOS group, 60% in the hypo/eugonadotrophic group, and 26% in the unexplained infertility group. The fecundity rate or pregnancy rate per ovulatory treatment cycle was 25% in the PCOS group, 25% in the hypo/eugonadotrophic group and 11% in the unexplained infertility group (Table I). The fecundity rate was significantly lower in the unexplained infertility group than in the PCOS/hypo/eugonadotrophic groups ($P < 0.005$). There was no difference in the rates between the PCOS and hypo/eugonadotrophic group.

The cumulative pregnancy rate after four ovulatory treatment cycles was 70% in the PCOS patients and 74% in the hypo/eugonadotrophic subjects. After seven cycles of ovulation induction the cumulative pregnancy rate was 85% in the PCOS group and 83% in the hypo/eugonadotrophic group. After four ovulatory cycles of ovarian stimulation in the unexplained infertility group the cumulative pregnancy rate was 38%. There was no statistically significant difference between the cumulative pregnancy rates for those with PCOS compared with those with hypo/eugonadotrophic hypogonadism. A significant difference was present in the cumulative pregnancy rates between the PCOS and unexplained infertility groups after four cycles ($P < 0.001$) and between the hypo/eugonadotrophic and unexplained infertility groups after four cycles ($P < 0.001$).

The early pregnancy failure rate was 25% in the PCOS patients, 27% in the hypo/eugonadotrophic subjects and 26% in the unexplained infertility group. There was no significant difference between the groups with regard to early pregnancy loss rates. There were four cases of ectopic pregnancy: two in the PCOS group, and one in each of the hypo/eugonadotrophic and idiopathic groups. The ongoing pregnancy rate per ovulatory cycle was 19% in the PCOS group, 18% in the hypo/eugonadotrophic group and 9% in the idiopathic group. There was a significant difference in this rate between the PCOS/hypo/eugonadotrophic groups and the idiopathic group ($P < 0.005$). There was no significant difference in the rate of ongoing pregnancy between the PCOS and the hypo/eugonadotrophic groups (Table I).

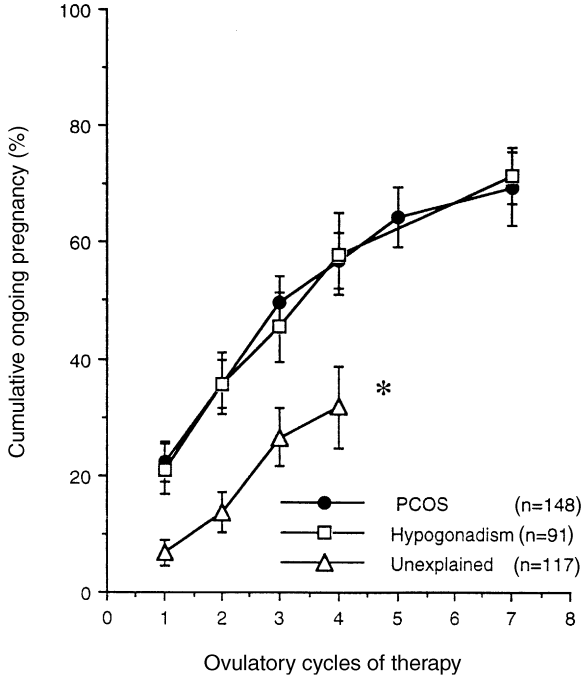

Figure 1. Cumulative ongoing pregnancy rates versus ovulatory cycles of therapy in couples with polycystic ovarian syndrome (PCOS), hypogonadotrophic/eugonadotrophic hypogonadism and unexplained infertility. Data are presented as the means ± SEM. *$P < 0.001$ versus PCOS and hypogonadism.

For ongoing pregnancies, the cumulative pregnancy rate after four ovulatory treatment cycles was 57% in the PCOS group, 58% in the hypo/eugonadotrophic group and 32% in the unexplained infertility group of patients. After seven cycles, the cumulative ongoing pregnancy rate was 70% in the PCOS group and 72% in the hypo/eugonadotrophic group. There was no statistically significant difference between the cumulative pregnancy rates for those with PCOS compared with those with hypo/eugonadotrophic hypogonadism after four or seven cycles, and a significant difference was present in the cumulative pregnancy rates between the PCOS and idiopathic groups after four cycles ($P < 0.001$) and between the hypo/eugonadotrophic and idiopathic groups after four cycles ($P < 0.001$) (Figure 1).

The combined effects of diagnosis, age and BMI on pregnancy rates were examined by Cox regression analysis. In the whole group of patients only the diagnosis was significant: the unexplained infertility group had significantly lower pregnancy rates than the other two groups combined ($r = –0.826$, SE = 0.198, $P < 0.001$). Age was not significant ($r = –0.037$, SE = 0.019, $P = 0.054$). In the patients with the diagnosis of hypogonadism, there was a significant negative effect of BMI on ongoing pregnancy rates ($r = –0.121$, SE = 0.046, $P < 0.01$).

There were 15 multiple pregnancies (13 twins and two triplets) in the PCOS group (multiple pregnancy rate 20%), 12 in the hypo/eugonadotrophic group (10 twins and two triplets) (multiple pregnancy rate 30%), and four in the unexplained infertility group (three twins and one triplets) (multiple pregnancy rate 17%). There was no significant difference in the multiple pregnancy rate between the groups. Of the multiple pregnancies in the PCOS group, one set of twins delivered at 23 weeks gestation with death of both fetuses, and in two other sets of twins, there was a fetal death of one twin each. Of the multiple pregnancies in the hypo/eugonadotrophic group, there was a fetal death *in utero* of one twin at term in one set of twins. Of the multiple pregnancies in the unexplained infertility group there were no fetal deaths.

No woman experienced ovarian hyperstimulation syndrome (mild, moderate or severe), as defined by the clinical symptoms of pain, abdominal distension, nausea, vomiting and weight gain and the clinical signs of ovarian enlargement >8 cm and the presence of ascites or hydrothorax.

Discussion

The treatment of anovulatory infertility, whether it is due to PCOS or due to hypo/eugonadotrophic hypogonadism, is known to be effective using HMG or FSH (Baird and Howles, 1994; Balen *et al.*, 1994). Our results show that cumulative pregnancy rates, both total and ongoing, are similar for PCOS and hypo/eugonadotrophic patients and that these rates are significantly greater than the rates for couples with unexplained infertility receiving ovarian stimulation. This reflects the fact that in the former two groups, the only factor in infertility is anovulation in the woman, which once corrected results in a similar cumulative pregnancy rate to that in normal couples. Similar results have also been reported by Balen *et al.* (1994) and Hull *et al.* (1979).

The treatment of couples with unexplained infertility is less successful using this treatment. These couples may have other as yet uncharacterized defects which may only be partially corrected with ovarian stimulation. At present, we know of no further investigations, other than those which we have performed, that reliably contribute to the diagnosis of these uncharacterized factors (ESHRE, 1996).

As expected, the ovulation rate was significantly greater in the unexplained infertility groups compared with the PCOS or hypo/eugonadotrophic groups. This reflects the fact that the primary disorder in the latter couples is anovulation which in some cases may be refractory to treatment.

The cumulative pregnancy rate after six cycles in our patients with PCOS compares very favourably with other reported series after six cycles of treatment (Abdel Gadir *et al.*, 1990; Hamilton-Fairley *et al.*, 1991; Balen *et al.*, 1994). Our fecundity rate for couples with unexplained infertility is greater than that in other reported series of women receiving ovarian stimulation. Serhal *et al.* (1988) reported a 6% fecundity rate for the treatment of these couples with ovulation induction alone and Chaffkin *et al.* (1991) reported a 5.5% rate. However, others have reported an increase in the fecundity rate when IUI was also performed in these couples. Aboulgar *et al.* (1993) reported a cycle fecundity rate of 20% with HMG and IUI treatment in such couples. Similarly, Serhal *et al.* (1988) reported a rate of 26%, Chaffkin *et al.* (1991) a rate of 20% and Nulsen *et al.* (1993) a rate of 19%. The data from a number of randomized clinical trials addressing the use of IUI with or without HMG in couples with unexplained infertility have been evaluated (ESHRE, 1996). The results reported were that the effects of IUI and HMG treatment were similar in that each treatment significantly increased the likelihood of conception by 2 fold (ESHRE, 1996). Chung *et al.* (1995) prospectively randomized couples with unexplained infertility to ovarian stimulation with or without IUI. All couples were treated with long-course luteinizing hormone-releasing hormone agonists (LHRHa) prior to ovarian stimulation with FSH. They reported a significantly higher cycle fecundity rate (21.8% versus 8.5%) and cumulative pregnancy rate after three cycles (42 versus 20%) in the group who had an IUI. The conclusion of the investigators was that ovarian stimulation alone in such couples was a redundant procedure. Since 1996, we now routinely perform an IUI in couples who have the diagnosis of unexplained infertility and are undergoing ovarian stimulation.

We found the PCOS patients were younger than the other two patient groups. Even though this statistical difference exists, it is unlikely to be the clinically significant factor in accounting for the difference in fecundity rates between the anovulatory groups and the unexplained infertility group as these women were still under the mean age of 35 years. Female fecundity rates have been shown to decrease after the age of 35 years (Stovall *et al.*, 1991; Hull *et al.*, 1996).

BMI was significantly elevated in the PCOS individuals compared with the hypo/eugonadotrophic and the idiopathic patients. At least in this cohort of women, the increase in the BMI is unlikely to be of clinical significance as the fecundity and cumulative pregnancy rates were no different when compared with the hypo/eugonadotrophic group and the early pregnancy loss rates were also no different. The BMI, however, appears to be important in those with hypo/eugonadotrophic hypogonadism where a BMI $\geqslant 24$ was associated with a greater early pregnancy loss rate.

In our group of patients we used either HMG or purified FSH. The preferential use of FSH compared with HMG in those patients with PCOS in particular remains a controversial issue. There is, however, ample evidence to suggest that one is not superior to the other in women with PCOS as well as in those with other causes for anovulation or in those with unexplained infertility (Larsen, 1990; Kelly and Jewelewicz, 1990; Homburg *et al.*, 1990; Sagle *et al.*, 1991; Balen *et al.*, 1993b; Olive, 1995).

We found no difference in the early pregnancy loss rates between any of the groups studied. Others have reported an increase in the miscarriage rate in those with PCOS treated with HMG (Wang and Gemzell, 1980; Farhi *et al.*,

1993). It has been postulated that this increase in the miscarriage rate occurs because of a hypersecretion of LH (Balen *et al.*, 1993a). Homburg *et al.* (1993) in a retrospective analysis compared women with PCOS who were treated by ovulation induction with and without LHRHa. They found that the cumulative live birth rate for the LHRHa treated group was 64% compared with 26% for the ovulation induction group. The miscarriage rate in the LHRHa and ovulation induction group was 18% compared with 39% for the other group. However, a previously reported randomized controlled trial in a small number of couples showed the opposite result (Homburg *et al.*, 1990). This brings into question the hypothesis that hypersecretion of LH contributes to the higher miscarriage rate in PCOS couples, especially as we did not show a higher rate. This question will only be answered by a large prospective randomized controlled trial that examines ovulation induction with and without the use of LHRHa in these couples.

We also found no difference in the multiple pregnancy rates between the groups. However, despite the strict criteria for cancellation if more than three mature follicles were present, our multiple pregnancy rate was 17–30%. Others have found similar results in couples with PCOS (Balen *et al.*, 1994) and in couples with hypogonadotrophic hypogonadism (Baird and Howles, 1994). Multiple pregnancy is obviously an undesired consequence of ovulation induction and ovarian stimulation because of the subsequent increase in perinatal mortality and morbidity.

To reduce our multiple birth rates further, we may have to be stricter in our cancellation criteria and cancel cycles when more than two follicles >14 mm in diameter are present. This may, however, be at the expense of pregnancy rates. In IVF programmes in Australia there has been a reported decrease in the multiple pregnancy rate from 21% in 1990 to 17% in 1993. This has been attributed to a decrease in the numbers of embryos transferred (Lancaster *et al.*, 1995). Ovulation induction and ovarian stimulation programmes may need to follow similar lines. Alternatively, at least for those with hypogonadotrophic hypogonadism, pulsatile gonadotrophin releasing hormone (GnRH) may be an option as the multiple pregnancy rate is lower (Hurley *et al.*, 1984; Martin *et al.*, 1994), although in the Australian context this is a much more expensive option for the couple. For those with PCOS an alternative mode of treatment may be the use of low dose gonadotrophin regimens. A recent report by White *et al.* (1996) reported a multiple pregnancy rate in PCOS couples using this regimen of 6% with a cycle fecundity rate of 16%. This contrasts with our multiple pregnancy rate of 20% with a cycle fecundity rate of 25%. The advantage of a lower multiple pregnancy rate, however, is offset by the lower pregnancy rate. Ultimately it may be a decision that is made by the couple, as to which regimen is chosen, after they have had extensive counselling as to the advantages and disadvantages of the low dose and conventional regimens for ovulation induction.

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