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Chapter 4

Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies?

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ABSTRACT

BACKGROUND Controlled ovarian stimulation (COS) with intrauterine insemination (IUI) is a common treatment in couples with unexplained non-conception. Induction of multifollicular growth is considered to improve pregnancy outcome, but it contains an increased risk of multiple pregnancies and ovarian hyperstimulation syndrome. In this study the impact of the number of follicles (>14 mm) on the ongoing pregnancy rate (PR) and multiple PR was evaluated in the first four treatment cycles.

METHODS A retrospective cohort study was performed in all couples with unexplained non-conception undergoing COS-IUI in the Academic Hospital of Maastricht. The main outcome measure was ongoing PR. Secondary outcomes were ongoing multiple PR, number of follicles of ≥14 mm, and order of treatment cycle.

RESULTS Three hundred couples were included. No significant difference was found in ongoing PR between women with one, two, three or four follicles respectively (P = 0.54), but in women with two or more follicles 12/73 pregnancies were multiples. Ongoing PR was highest in the first treatment cycle and declined significantly with increasing cycle order (P = 0.006), while multiple PR did not change.

CONCLUSIONS In COS-IUI for unexplained non-conception, induction of more than one follicle did not improve the ongoing PR, but increased the risk of multiple pregnancies. Multiple PR remained high in the first four cycles with multifollicular stimulation. Therefore, in order to reduce the number of multiple pregnancies, in all IUI cycles for unexplained non-conception monofollicular growth should be aimed at.

INTRODUCTION

Intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is a common treatment in couples with unexplained non-conception. In a randomized controlled trial in couples with unexplained non-conception, COS in combination with IUI has been shown to result in significantly higher cumulative pregnancy rates (PR) per couple (33%) as compared to unstimulated intracervical insemination (10%), COS alone (19%) or IUI alone (18%) (Guzick *et al.*, 1999). The main benefit of the addition of COS to IUI is considered to be due to the induction of multifollicular growth (Cohlen, 1998). However, stimulating excess follicles has serious drawbacks considering the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Multiple pregnancies carry medical risks for mother and offspring, and increase the likelihood of social and economic problems in families and societies.

Since assisted reproductive technologies, i.e. IUI and IVF, have become available, the number of multiple pregnancies has increased. In the USA there was an increase of 75% in twin births between 1980 and 2000. Over the same period the rate of triplet and higher order multiple pregnancies has risen 4-fold in the USA (Fauser *et al.*, 2005). Since the number of monozygotic twins has remained relatively constant (0.3–0.4% of all pregnancies) (ESHRE Capri Workshop Group, 2000), the increase in multiple pregnancies is the result of increasing numbers of dizygotic twins, triplets and higher order multiples. This is influenced by increasing maternal age, but mainly due to the use of agents for ovulation induction in assisted reproduction treatment (ESHRE Capri Workshop Group, 2000).The incidence of multiple pregnancies after COS-IUI is poorly documented, but it is estimated that the multiple PR is 10–40% per cycle, and that 30–50% of all multiples are due to COS-IUI (Fauser *et al.*, 2005). So far few studies (Nuojua-Huttunen *et al.*, 1999; Gleicher *et al.*, 2000) have investigated the relationship between multiple PR and number of follicles induced in COS-IUI.

The aim of this study was to evaluate the role of the number of follicles in COS-IUI in relation to ongoing PR and complications (multiple pregnancies) in couples treated for unexplained non-conception. Furthermore, we investigated whether increasing cycle order or patient variables influenced the outcome.

MATERIALS AND METHODS

Patients

A retrospective cohort study was performed in all couples with unexplained non-conception that had been treated with COS-IUI in the Academic Hospital of Maastricht, The Netherlands, in the period August 1993 till April 2004.

According to the local protocol, couples were offered a maximum of four cycles of COS-IUI. For IUI either fresh partners' sperm or cryopreserved donor sperm was used. All couples with unexplained non-conception had tried to conceive for ≥24 months. Couples using donor sperm had had ≥12 cycles of intracervical insemination. All had normal findings in their fertility work-up. This work-up consisted of confirmation of an ovulatory cycle by ultrasound, semen analysis, post-coital testing and evaluation of tubal function by hysterosalpingography and/or laparoscopy. Tubal status was considered to be normal if there were no adhesions and at least one tube was patent at pertubation during hysterosalpingography or laparoscopy. Minimal endometriosis was considered compatible with the definition of unexplained non-conception. For each couple, female age and duration of non-conception until start of treatment was registered, and whether unexplained non-conception was primary or secondary. Furthermore, we recorded the number of follicles measuring ≥14 mm at the time of HCG injection, the number of positive pregnancy tests and the number of ongoing singleton and multiple pregnancies. Only cycles in which HCG was given were included.

Ovarian stimulation and insemination protocol

The aim of COS was to achieve two or three dominant follicles, i.e. follicles with diameters of ≥18 mm. The preparation used for ovarian stimulation was Humegon (Organon, Oss, The Netherlands), Menogon (Ferring, Hoofddorp, The Netherlands) or Menopur (Ferring, Hoofddorp, The Netherlands). Stimulation was started on day 3 of the cycle with a fixed dose of 150 IU of HMG s.c. per day. The ovarian response was monitored by serial vaginal ultrasonographic follicular measurements. If there was no response, or if more than four follicles were recruited, the starting dose of HMG was adjusted accordingly in the next cycle. Ovulation was triggered with the injection of 5000 IU of HCG s.c. (Pregnyl; Organon, Oss, The Netherlands) when at least one dominant follicle was detected.

The administration of HCG was withheld, and IUI was cancelled in stimulation cycles with more than four follicles with a diameter of ≥14 mm, or more than three dominant follicles. IUI was performed only once, 40–48 h after administering HCG, using fresh or cryopreserved sperm samples. The suspension of processed sperm was introduced into the uterine cavity with an IUI canula (Lettix, Apeldoorn, The Netherlands). The luteal phase was supported with 200 mg intravaginal progesterone three times a day for a period of 14 days after insemination (Progestan, Organon, Oss, The Netherlands) or a total of three injections of 1500 IU HCG s.c. (Pregnyl) on day 3, 6 and 9 after insemination respectively. A pregnancy test was performed in urine 12–14 days after IUI and was considered positive when HCG level was >25 mIU/ml. An ultrasound scan was performed between 9 and 12 weeks of gestation and the number of gestational sacs with fetal cardiac activity was established. An ongoing pregnancy was defined as cardiac activity at 9–12 weeks of gestation.

Semen preparation

Either fresh partner's semen was used, produced ~4 h before IUI, or cryopreserved donor semen, which had been frozen in human sperm preservation medium with glycerol as a cryoprotectant (Mahadevan and Trounson, 1983). Before IUI, all fresh and thawed semen samples were subjected to a discontinuous density gradient centrifugation using PureSperm (Nidacon, Gothenburg, Sweden) (Laursen *et al.*, 2003). After centrifugation at 800 g for 15 min, the sperm pellet was washed twice with fresh medium by centrifugation for 10 min at 200 g, and finally resuspended in a total volume of 0.5 ml. Semen was evaluated before processing for volume, total number, motility and progressive motility, and this was combined into the progressively motile sperm density (PMSD). In our laboratory a PMSD of >3×106/ml is considered to reflect normozoospermia (Enginsu *et al.*, 1992).

Statistical analysis

For the comparison of baseline patient characteristics and outcome, a Wilcoxon test and a χ^2-test were used where appropriate. For the comparison of ongoing PR and multiple PR, a χ^2-test for linear trend was used. $P < 0.05$ was considered to reflect statistical significance. Other characteristics that potentially are associated with the occurrence of pregnancy might bias our findings by confounding. Potential confounders are previous pregnancies, female age, duration of non-conception, non-conception being primary or secondary, cycle order and semen quality. In order to control for these potential confounders, we performed a multivariable logistic regression analysis, in which pregnancy was the dependent variable, and both follicle number as well as the potential confounders were independent variables.

RESULTS

Overall, 300 couples were included, with a total of 879 cycles of COS-IUI. Cryopreserved semen was used for 34 couples in 92 cycles. There were 82 couples who had secondary unexplained non-conception. Since patient characteristics and treatment outcomes did not differ between couples using fresh semen and cryopreserved semen, these two groups have been combined for further analyses. The baseline characteristics of couples included are shown in Table I. The mean semen volume was 3.3 ml (range 0.2–9.7) and mean sperm concentration 66.3×106/ml (range 2.2–264). All couples with <24 months of unexplained non-conception had secondary non-conception, and were offered COS-IUI treatment without delay, based on findings at examination and treatment in the past.

The PR per cycle was 10.9%. The cumulative PR in four cycles was 32.0% per couple. Twenty-three couples had a miscarriage (2.6% per cycle) and one couple had an ectopic pregnancy (0.1% per cycle). The cumulative ongoing PR in four cycles was 23.0% per couple. The ongoing multiple PR in four cycles was 16.4%, of which 12.3% were twins

and 4.1% were triplets. The multiple PR per positive test was 12.5%. The odds ratio of the number of follicles for the occurrence of pregnancy was 1.0 (95% CI 0.75–1.3). This did not change in the multivariable analysis.

In Table II the ongoing and multiple PR according to the number of pre-ovulatory follicles of ≥14 mm is given. No statistically significant difference in ongoing PR was found between patients who had one or more than one follicle respectively (ongoing PR 7.9%, 95% CI 5.0–11.7 and 8.5%, 95% CI 6.4–11.0 respectively). In patients who had one follicle, no multiple pregnancies were found, whereas in patients with more than one follicle, 12/73 ongoing pregnancies were multiples.

Although COS was applied in all couples, 36.0% of the couples had only one follicle of ≥14 mm in the first cycle. In the next cycle the dose of HMG was adjusted, and none of the couples had repeated cycles with one follicle. Table III gives the outcome according to order of treatment cycle. Ongoing PR was the highest in the first treatment cycle (11.7%)

Table I. Baseline characteristics of couples with unexplained non-conception undergoing controlled ovarian stimulation with intrauterine insemination

No. of couples	300
Female age (years)	33 (20-41)
Duration of non-conception (months)	39.6 (1-137)
Primary non-conception (%)	70.7
PMSD (x106/ml)	16.4 (0.1-120)
PMSD = progressively motile sperm density.	

Table II. Ongoing and multiple pregnancy rates (PR) in couples with unexplained non-conception undergoing controlled ovarian stimulation with intrauterine insemination according to the number of pre-ovulatory follicles of ≥14 mm at the time of HCG administration.

Follicle number	Cycles	Ongoing (%) PR[a]	Singletons	Multiples	Multiple PR (%)
1	279	22 (7.9)	22	-	-
2	358	27 (7.5)	22	5	18.5
3	210	22 (10.5)	16	6	27.3
4	30	2 (-)	1	1	50
5	2	-			

[a] χ^2-Test for linear trend: $P = 0.54$.

Table III. Ongoing and multiple pregnancy rates (PR) per cycle in couples with unexplained non-conception undergoing controlled ovarian stimulation with intrauterine insemination in four cycles.

Cycle number	Couples	Ongoing (%) PR[a]	Singletons	Twins	Triplets	Multiple PR[b] (%)
1	300	35 (11.7)	31	4	-	11.4
2	242	19 (7.9)	16	-	3	15.8
3	187	12 (6.4)	9	3	-	25.0
4	150	7 (4.7)	5	2	-	28.5

[a] χ^2-Test for linear trend: P = 0.006.
[b] χ^2-Test for linear trend: $P = 0.16$.

and declined significantly with increasing cycle order (7.9% in the second cycle, 6.4% in the third and 4.7% in the fourth cycle) (P = 0.006). No statistically significant trend was noted in the multiple PR, which was 11.4% in the first, 15.8% in the second, 25.0% in the third and 28.5% in the fourth treatment cycle.

DISCUSSION

In couples with unexplained non-conception, COS-IUI is a widely used and effective treatment before resorting to IVF. In our study 32% of the couples conceived in four treatment cycles of COS-IUI, which is within the range of 20–33% reported by others (Guzick *et al.*, 1999; Ibérico *et al.*, 2004). The PR per cycle in our study was 10.9%. In the literature, PR per cycle has been reported to vary from 9 to 20% (Crosignani *et al.*, 1991; Nulsen *et al.*, 1993; Zikopoulos *et al.*, 1993; Guzick *et al.*, 1999; Dickey *et al.*, 2002; Ibérico *et al.*, 2004). Several studies have been performed to search for plausible causes for these differences in PR, and for determinants of success concerning COS-IUI therapy. It has been shown that an increasing maternal age, a longer duration of non-conception and a poor semen quality have a negative impact on the PR in couples receiving COS-IUI (Dickey *et al.*, 2002; Duran *et al.*, 2002; Ibérico *et al.*, 2004), whereas couples with unexplained or cervical factor non-conception have a more favourable outcome (Steures and van der Steeg, 2004). It has been assumed that the number of pre-ovulatory follicles and order of the treatment cycle affect the outcome of COS-IUI as well.

In our study, couples with unexplained non-conception that had one follicle at the time of HCG administration had an ongoing PR of 7.9%, and couples who had multifollicular growth had an ongoing PR of 8.5%. The difference in PR found between these two groups is not statistically significant (OR 1.1, 95% CI 0.6–2.0). A sample size of >10,000 cycles would be needed to detect a difference in PR of ≥1 percentage point over a control rate of 7.9%, with a power of 80% at a significance level of 0.05, so the difference in PR found in our study is not clinically relevant. Moreover, the absolute increase in PR of 0.6% in multifollicular cycles indicates that the number needed to treat is 166, i.e. 166 multifollicular (as opposed to monofollicular) cycles are needed for one additional pregnancy, which would result in at least 28 multiple pregnancies. Therefore, in IUI for unexplained non-conception, monofollicular stimulation is equally effective as compared to multifollicular stimulation, it is less costly and has fewer adverse effects in terms of multiple pregnancies.

In the literature, however, there is controversy concerning the number of pre-ovulatory follicles in COS-IUI and subsequent PR. Some studies show an increase in PR when follicle numbers rise (Tomlinson *et al.*, 1996; Nuojua-Huttunen *et al.*, 1999; Stone *et al.*, 1999; Dickey *et al.*, 2002; Ibérico *et al.*, 2004), whereas others found that two follicles at the

time of IUI did not increase the ongoing PR as compared to one follicle (Steures *et al.*, 2004). One of the possible causes for this heterogeneity in results reported may be due to the inclusion of couples with different causes of non-conception and different prognosis, like male factor non-conception, tubal factor nonconception and anovulation. Furthermore, in some studies clomiphene citrate was used for ovulation induction, while in others gonadotrophins were administered. Although there is still insufficient evidence for a statistically significant difference in PR (Althaullah *et al.*, 2002), gonadotrophins seem to be superior to clomiphene citrate.

Although induction of multifollicular growth is considered to improve pregnancy outcome in COS-IUI, it contains the risk of multiple pregnancies. In unexplained non-conception a multiple PR of 9–36% per couple has been reported (Zikopoulos *et al.*, 1993; Guzick *et al.*, 1999; Nuojua-Huttunen *et al.*, 1999; Ibérico *et al.*, 2004). Guzick *et al.* (1999) did not report on the number of follicles, but had 17 sets of twins (7.4% per couple), four triplets (1.7% per couple) and three quadruplets (1.3% per couple). In the study by Zikopoulos *et al.* (1993) the mean follicle number was 3.8 per cycle, and the multiple PR was 36%. Nuojua-Huttunen et al. (1999) reported a multiple PR of 13.7%, but found no correlation between the number of large follicles and the multiple PR. In our study the aim of COS was to achieve two or three dominant follicles, and in 68.3% of the treatment cycles multifollicular growth was obtained. In these multifollicular cycles nine twins and three triplets occurred, and the multiple PR in multifollicular cycles was 17.1%.

In COS-IUI cycles one decides either to administer HCG or to cancel the cycle, by estimating the risk for multiple pregnancies and OHSS by the number of pre-ovulatory follicles. Pregnancies are considered to originate from dominant follicles, but smaller follicles have been shown to have a substantial contribution as well (Navot *et al.*, 1991; Valbuena *et al.*, 1996; Richmond *et al.*, 2005). In order to prevent multiple pregnancies in COS-IUI the total number of pre-ovulatory follicles >14 mm at the time of HCG injection should be taken into consideration.

In our study, a statistically significant decrease in ongoing PR was found with increasing order of treatment cycle in COS-IUI in couples with unexplained non-conception. This is confirmed by Aboulghar *et al.* (2001), who reported a cumulative PR of 39.2% in the first three cycles and a PR of only 9.3% in the next three cycles. In the study by Nuojua-Huttunen *et al.* (1999) 97% of pregnancies occurred within the first four treatment cycles, and Ibérico *et al.* (2004) reported that 74.2% of pregnancies occurred within the first two treatment cycles. These studies indicate that there appears to be an upper limit to the number of successful treatment cycles, beyond which additional pregnancies are less likely to occur. Although the overall PR was found to decrease significantly with increasing cycle order, in our study the multiple PR was not influenced by the order of treatment cycle, since multiples were present in every rank number. No studies were identified in the literature that examined the occurrence of multiple pregnancies in relation to the rank of the treatment cycle.

In conclusion, in COS-IUI for unexplained non-conception, induction of more than one dominant follicle did not improve the ongoing PR significantly, but increased the risk of multiple pregnancies. In subsequent cycles with multifollicular growth, multiple PR remained high. Therefore, in order to reduce the number of multiple pregnancies, in all IUI cycles for unexplained non-conception, monofollicular growth should be aimed at. It remains to be established whether the cumulative PR levels off after four treatment cycles in monofollicular IUI, as it seems to do in multifollicular COS-IUI.

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