Human Reproduction Vol.19, No.10 pp. 2263–2266, 2004
Advance Access publication August 27, 2004
DOI: 10.1093/humrep/deh435

Does ovarian hyperstimulation in intrauterine insemination for cervical factor subfertility improve pregnancy rates?

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BACKGROUND: Intrauterine insemination (IUI) can be performed with or without controlled ovarian hyperstimulation (COH). Studies in which the additional benefit of COH on IUI for cervical factor subfertility is assessed are lacking. We assessed whether COH in IUI improved pregnancy rates in cervical factor subfertility. METHODS: We performed a historical cohort study among couples with cervical factor subfertility, treated with IUI. A cervical factor was diagnosed by a well-timed, non-progressive post-coital test with normal semen parameters. We compared ongoing pregnancy rate per cycle in groups treated with IUI with or without COH. We tabulated ongoing pregnancy rates per cycle number and compared the effectiveness of COH by stratified univariable analysis. RESULTS: We included 181 couples who underwent 330 cycles without COH and 417 cycles with COH. Ongoing pregnancy rates in IUI cycles without and with COH were 9.7% and 12.7%, respectively (odds ratio 1.4; 95% confidence interval 0.85–2.2). The pregnancy rates in IUI without COH in cycles 1, 2, 3 and 4 were 14%, 11%, 6% and 15%, respectively. For IUI with COH, these rates were 17%, 15%, 14% and 16%, respectively. CONCLUSIONS: Although our data indicate that COH improves the pregnancy rate over IUI without COH, IUI without COH generates acceptable pregnancy rates in couples with cervical factor subfertility. Since IUI without COH bears no increased risk for multiple pregnancy, this treatment should be seriously considered in couples with cervical factor subfertility.

Key words: cervical factor/controlled ovarian hyperstimulation/intrauterine insemination/ongoing pregnancy/subfertility

Introduction

Intrauterine insemination (IUI) is a common treatment in subfertile couples. Intrauterine insemination can be performed with or without controlled ovarian hyperstimulation (COH). COH carries the risk of ovarian hyperstimulation syndrome and multiple pregnancy (Levene *et al.*, 1992). Moreover, IUI with COH is both a burden to the patient and costly due to the use of gonadotrophins and the need for monitoring of follicular development and growth. In view of these drawbacks, IUI without COH would be preferable over IUI with COH if the pregnancy rate for IUI without COH was more or less comparable.

The effectiveness of IUI is well established in couples in whom subfertility is due to a male factor or when subfertility is unexplained (Hughes, 1997; Cohlen *et al.*, 2000). In male factor subfertility, IUI without COH has been proven to be equally as effective as IUI with COH, and should therefore be the first choice of treatment (Cohlen *et al.*, 2000). In the treatment of unexplained subfertility, IUI with COH doubles pregnancy rates compared with IUI without COH (Guzick *et al.*, 1994, 1999).

In contrast to the former two indications, data on the effectiveness of IUI in cervical factor subfertility are conflicting. Five randomized studies have reported on the effectiveness of IUI compared with timed intercourse in couples with cervical factor subfertility. Three of these studies clearly indicated a beneficial effect of IUI (te Velde *et al.*, 1989; Kirby *et al.*, 1991; Check and Spirito, 1995), whereas two others did not report such an effect (Glazener *et al.*, 1987; Friedman *et al.*, 1989). In all of these studies, IUI was performed without COH. Studies, randomized or non-randomized, in which the additional benefit of COH on IUI for cervical factor subfertility is assessed are lacking.

The aim of this study was therefore to assess whether controlled ovarian hyperstimulation in IUI is of additional benefit in cervical factor subfertility.

Materials and methods

Patients

We performed a historical cohort study among consecutive couples with cervical factor subfertility who had been treated with IUI. The data had been collected between 1986 and 2002 in the Onze Lieve Vrouwe Gasthuis and the Vrije Universiteit Medical Centre, both located in Amsterdam, The Netherlands.

All couples had been trying to conceive for at least 12 months, and all had undergone a fertility work-up consisting of a medical history, confirmation of an ovulatory cycle either by basal body temperature, ultrasound and/or mid-luteal serum progesterone, semen analysis and a post-coital test. Tubal patency of both tubes and absence of endometriosis or uterine anomalies were confirmed by hysterosalpingography and/or laparoscopy.

All women diagnosed with cervical factor subfertility who had started IUI were included in the study. Cervical factor was diagnosed by means of a well-timed, non-progressive post-coital test, and was defined as the absence of at least one progressive motile spermatozoon in good cervical mucus at a magnification of 400×, despite normal semen parameters. The timing was performed with transvaginal sonography, and usually the post-coital was repeated in a second cycle. Intercourse would have taken place between 6 and 18 h prior to the test. Since a cervical factor can only be diagnosed in the presence of normal semen, the diagnoses of male and cervical factor were mutually exclusive.

For each couple, we registered female age, duration of subfertility, whether subfertility was primary or secondary, number of follicles and cycle number. Furthermore, we registered whether the IUI was performed with or without COH.

IUI protocol

The choice for IUI with or without COH was based on local protocols in the participating centres. If IUI was performed without COH, ovulation detection was performed with urine LH tests (a semi-quantitative monoclonal antibody-based kit; OvuQuick; Quid, San Diego, CA, USA) with a detection level of 40 IU, or by transvaginal sonography. Patients tested their urine samples once or twice a day, starting on an individually calculated cycle day. Patients were inseminated 20–30 h after the endogenous LH surge had been detected in the urine sample. In cases where follicular growth was monitored by transvaginal sonography, HCG (Pregnyl; Organon, Oss, The Netherlands) was administered when the dominant follicle had a diameter of at least 16 mm. Semen was inseminated 36–40 h thereafter. A maximum of 0.3 ml suspension of processed spermatozoa was introduced into the uterine cavity with a catheter 10 cm in length (International Medical, Zutphen, The Netherlands).

COH was performed with clomiphene citrate or FSH to achieve the growth of two or three dominant follicles. In cases where hyperstimulation was performed with FSH, baseline transvaginal sonography was carried out at cycle day 3 to exclude ovarian cysts >20 mm. Thereafter, patients injected themselves subcutaneously with 1 ampoule (75 IU) of FSH, Gonal F (Serono Benelux BV, Den Haag, The Netherlands) or Puregon (Organon), daily until transvaginal sonography showed at least one follicle with a diameter of 16 mm. In the event of such a follicle, 5000 IU HCG (Pregnyl; Organon) was given and patients were inseminated 36 h later. If hyperstimulation was performed with anti-estrogenic tablets, the patient took 100 mg clomiphene citrate on cycle day 5 for 5 days. On cycle day 10 the first transvaginal sonography was performed. When at least one follicle with a diameter of 16 mm was seen, 5000 IU HCG was given subcutaneously, and the patients were inseminated 36 h later.

The administration of HCG was withheld and IUI was not carried out in both stimulation protocols when more than three follicles with a diameter of at least 16 mm, or more than four follicles with a diameter of at least 14 mm, were present.

Semen preparation

In general, semen samples were produced and prepared <2 h prior to insemination. The semen was processed using a density gradient centrifugation (15 min at 750 *g*) and a washing step (7 min at 300 *g*) with 2 ml culture medium containing 1% HAS (CLB, Amsterdam, The Netherlands). Less than 15 min before insemination the spermatozoa suspension was centrifuged (7 min at 200 *g*) and the cell pellet resuspended in 200–250 μl culture medium.

Data analysis

The analysis was performed at cycle level, i.e. each cycle was considered as a separate unit of analysis. We used ongoing pregnancy as the end-point of the study. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography at a gestational age of at least 12 weeks. We compared the distribution of the baseline characteristics over the two treatment groups using a χ^2-test or a Wilcoxon test where appropriate. For each group, we calculated ongoing pregnancy rates per cycle. The treatment effect was expressed as an odds ratio (OR) with 95% confidence interval (CI).

The outcome of IUI is dependent on various prognostic characteristics of the couple (Steures and van der Steeg, 2004). An unequal distribution of such characteristics might influence the results and conclusion of this study. To control for the bias generated by potential confounders, we performed a multivariate logistic regression analysis, in which we calculated ORs and 95% CIs. Baseline characteristics included in this analysis were female age, duration of the subfertility, whether subfertility was primary or secondary and cycle number. As follicle growth is an effect of the use of COH, we felt that correction of this baseline characteristic was not appropriate. Because multiple cycles from the same patient were included, the data analysed were interrelated. Therefore, ORs and 95% CIs were corrected by taking into account the clustering of data (Huber, 1967). Data were collected over a period of >15 years in two fertility centres in The Netherlands. Thus, changes in IUI practice over time, as well as practice differences between the two locations, might have affected the results. Therefore, we performed a multivariate analysis in which we controlled for differences over time and between centres to control for these potential biases. To assess whether the treatment effect after COH was dependent on the number of follicles, we tabulated the ongoing pregnancy rate per cycle as a function of the number of follicles.

Subsequently, we simulated the ongoing pregnancy rate per couples for four cycles of treatment. To do so, we used the ongoing pregnancy rate per cycle for IUI with and without COH obtained from the univariable analysis.

Results

Overall, 181 couples were included who underwent 747 cycles. There were 330 IUI cycles without COH (44%) and 417 cycles with COH (56%). Of the 417 stimulated cycles,

Table I. Baseline characteristics on cycle level

	IUI without hyperstimulation ($n = 330$)	IUI with hyperstimulation ($n = 417$)	*P*-value
Female age (years) [mean (range)]	34 (24–43)	34 (22–43)	0.02
Duration of subfertility (years) [mean (range)]	3 (1–14)	4 (1–10)	<0.001
Primary subfertility (%)	251 (65)	290 (70)	0.20
Secondary subfertility (%)	115 (35)	127 (30)	
Cycle number [*n* (%)]			<0.001
Cycle 1	100 (30)	81 (19)	
Cycle 2	83 (25)	65 (16)	
Cycle 3	65 (20)	57 (14)	
Cycle 4	33 (10)	61 (15)	
Cycle 5	20 (6)	54 (13)	
Cycle ≥6	29 (9)	99 (23)	
Number of follicles [*n* (%)]			<0.001
1	323 (97)	100 (24)	
2	6 (3)	82 (20)	
3	1 (0.5)	27 (7)	
≥4	0 (0)	4 (1)	
Not registered	0 (0)	204 (48)	

298 were stimulated with clomiphene citrate (71%) and 119 were stimulated with FSH (29%).

The baseline characteristics of the IUI cycles in each group, except for whether subfertility was primary or secondary, were not equally distributed between the two groups (Table I). In the IUI group without COH the mean female age was higher, the mean duration of subfertility was lower and more inseminations were performed in cycles 1–3. Data on multifollicular growth were not registered in 27% of cycles. Of the registered cycles, multifollicular growth was achieved in 53% of the IUI cycles with COH (113/213), as compared with the 2% of the IUI cycles without COH (7/330) (Table I).

The total pregnancy rates in IUI without and with COH were 11% (36/330) and 14% per cycle (60/417), respectively. The miscarriage rates in IUI without and with COH were 1.2% (4/330) and 1.7% per cycle (7/417), respectively. The ongoing pregnancy rates in IUI without and with COH were 9.8% (32/330) and 12.3% per cycle (53/417), respectively (OR 1.4; 95% CI 0.85–2.2).

Multivariable regression analysis did slightly alter the OR of COH on the outcome of IUI, to 1.6 (95% CI 0.99–2.6) (Table II). This implies that the effect of COH on an ongoing pregnancy was slightly influenced by the unequal distribution

Table II. Multivariate analysis on the baseline characteristics

	Unadjusted		Adjusted for confounders	
	OR	95% CI	OR	95% CI
Without COH	1.0		1.0	
With COH	1.4	0.85–2.2	1.6	0.99–2.6
Female age			0.9	0.90–1.0
Duration of subfertility			1.0	0.88–1.2
Primary subfertility			1.0	
Secondary subfertility			1.2	0.73–1.9
Cycle number			0.81	0.70–0.94

Table III. Ongoing pregnancy rates in each cycle and stratified univariate analysis

Cycle	IUI without hyperstimulation [% (*n*)]	IUI with hyperstimulation [% (*n*)]	Univariate analysis	
			OR	95% CI
Cycle 1	14 (14)	17 (14)	1.3	0.57–2.9
Cycle 2	11 (9)	15 (10)	1.5	0.57–3.9
Cycle 3	6 (4)	14 (8)	2.5	0.71–8.8
Cycle 4	15 (5)	16 (10)	1.1	0.34–3.5
Cycle 5	0 (0)	7 (4)	2158	0.00–∞
Cycle ≥6	0 (0)	7 (7)	2053	0.00–∞

Table IV. Percentages of cycles of IUI with COH and ongoing pregnancies depending on number of follicles

Number of follicles	IUI with COH [*n* (%)]	Ongoing pregnancies [*n* (%)]
1	100 (24)	11 (11)
2	82 (20)	10 (12)
3	27 (7)	5 (18)
≥4	4 (1)	2 (50)
Not registered	204 (48)	25 (12)

of the baseline characteristics. In the analysis performed to control for the potential bias over different time periods and between the two participating centres we found no change in the direction or magnitude of the effect of COH on IUI (data not shown).

Table III shows the ongoing pregnancy rates in each cycle number and the stratified univariable analysis on cycle level. The pregnancy rates in IUI without COH in cycles 1, 2, 3 and 4 were 14%, 11%, 6% and 15%, respectively. For IUI with COH, these rates were 17%, 15%, 14% and 16%, respectively. In the first four cycles, ORs varied from 1.1 to 2.5, indicating an additional effect of COH on the ongoing pregnancy rates varying from almost no effect to a 2.5 times higher ongoing pregnancy rate. Table IV shows the impact of the number of follicles on the ongoing pregnancy rates. Two follicles at the time of insemination did not increase the ongoing pregnancy rate in cervical factor subfertility compared with one follicle. No conclusion could be drawn on the effect of higher numbers of follicles because of lack of data.

Discussion

In this study, the first to report on the additional effect of COH on IUI in couples with cervical factor subfertility, we found a 1.6 times higher ongoing pregnancy rate after IUI with COH compared with IUI without COH in the first four cycles. However, pregnancy rates in IUI without hyperstimulation were on average still almost 10% per cycle.

In general, four cycles of IUI were given over 6 months. If we extrapolate the ongoing pregnancy rate per cycle obtained in this study to a 6-month treatment strategy, the ongoing pregnancy rate for IUI with COH would be 52%, and for IUI without COH 32%.

Our study has several limitations. First, we analysed retrospective data on non-randomized patients, with an unequal distribution of the baseline characteristics in the two

treatment modalities; however, multivariate regression analysis controlled for this bias and we corrected the results accordingly. Secondly, the choice of treatment, i.e. IUI with COH or without COH, was based on local protocols. This might create a bias, as couples with a good prognosis might have received IUI without COH more often than couples with a poor prognosis. Correcting for this potential bias by multivariate regression analysis did not change the results. Thirdly, the pre-ovulatory follicle number was only available for 73% of cycles, as one centre did not record this item. Since this item was missing in all cycles regardless of the result, pregnancy or not, data were missing at random and therefore not subject to bias (Greenland and Finkle, 1995). Finally, data were only entered in the local databases when insemination was performed, thus hampering an analysis with the number of started cycles as the denominator. Others have reported 3% and 10% cancellation rates in IUI with and without COH, respectively (Guzick *et al.*, 1999). If we take such cancellation rates into account in our analysis, the average ongoing pregnancy rates of the started IUI cycles without and with COH would have been 9% (32/330 + 33 cancelled cycles) and 12% (53/417 + 13 cancelled cycles), respectively, which is a marginal change compared with our findings.

In the couples treated with COH, two different stimulation protocols were used, clomiphene citrate and FSH. Since we found similar results when analysis was performed for separate stimulation protocols (data not shown), we pooled these data into one COH group in the final analysis. Moreover, in a previous study we did not find an effect of different types of COH protocols on ongoing pregnancy rates in IUI (Steures and van der Steeg, 2004).

Although IUI with COH is more effective than IUI without COH, in clinical decision-making the risks of these two treatment policies should also be taken into account. In daily practice, COH carries the risks of multiple pregnancy and ovarian hyperstimulation syndrome. In case of multifollicular growth, which is the primary aim of COH, patients are forced to trade off between the risks of a multiple pregnancy and cancellation of the IUI cycle, the latter obviously implying no pregnancy at all. Moreover, the risk of multiple pregnancies cannot always be foreseen, because in IUI with COH these pregnancies can also arise from borderline or small follicles in cycles that are not cancelled based on existing guidelines. In contrast, IUI without COH bears no increased medical risk at a lower financial cost.

In conclusion, the present study indicates that in patients with cervical factor subfertility, IUI with COH is more effective compared with IUI without controlled ovarian hyperstimulation. Nevertheless, since the average ongoing pregnancy rates were almost 10% per cycle in the first four IUI cycles without COH, IUI without COH should be considered as a treatment option in couples with cervical factor subfertility. Such a policy avoids side effects from ovarian hyperstimulation, i.e. multiple pregnancies and ovarian hyperstimulation syndrome, and decreases costs. Moreover, randomized clinical trials on the subject are needed to confirm this finding.

Acknowledgements

This study was presented in part as an oral presentation at the 19th Annual Meeting of the European Society of Human Reproduction and Embryology, Madrid, 2003.

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Submitted on March 29, 2004; accepted on July 2, 2004