Intrauterine insemination in natural cycle may give better results in older women

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Abstract *Background:* Controlled ovarian hyper-stimulation (COH) in combination with intrauterine insemination (IUI) has been shown to result in significantly higher pregnancy rates compared to un-stimulated (natural cycle) IUI [1]. This may however not be true in all ages.

Methods: We performed a retrospective cohort study and analysed data collected prospectively on 1759 IUI cycles in couples with unexplained infertility. The results were analysed to show the outcome of IUI with COH, and IUI in natural cycle (unstimulated), in younger women compared to their older counterparts.

Results: In women age 37 and younger, COH resulted in a significantly higher pregnancy rate (13.0% vs 6.5%) and live-birth rate (10.7% vs 5.2%) compared to natural cycle IUI ($p = 0.025$, $p = 0.045$ respectively). However for older women age > 37 years, natural cycle (unstimulated) IUI, resulted in a significantly higher pregnancy rate (12.0% vs 8.5%) live-birth rate (7.5% vs 3.5%) than IUI with COH ($p = 0.0037$). This difference is even more significant when COH was performed with clomiphene citrate (7.5% vs 2.1%) ($p = 0.0017$).

Conclusion: COH was associated with a lower live birth rate in older women, irrespective of the agent used, and it seems to be worse when the anti-oestrogenic drug clomiphene citrate was used for COH. Older women may benefit more from natural cycle (unstimulated) IUI. A

randomised controlled trial is required to confirm this observation.

Keywords Intrauterine insemination · Controlled ovarian hyper-stimulation · Natural cycle · Infertility

Introduction

Controlled ovarian hyper-stimulation (COH) in combination with intrauterine insemination (IUI) has been shown to result in significantly higher pregnancy rate compared to un-stimulated (natural cycle) IUI [1]. However a meta-analysis of 4 trials including 479 completed cycles found no significant difference between IUI in cycles with COH and IUI in natural cycle [2]. Age is an important confounding factor that may affect the outcome of stimulated or un-stimulated IUI. This important factor was not taken into consideration in these studies. The National institute of Clinical Excellence recommends the use of un-stimulated IUI as against IUI with COH, in couples presenting with male factor or unexplained infertility, to minimise the risks of multiple pregnancy [3]. To assess the effect of age on treatment, we performed a retrospective cohort study and analysed data collected prospectively to determine treatment outcome of IUI with and without COH, in young women, and their older counterparts.

Materials and methods

Study population

Between July 1997 and August 2005, 1759 cycles of IUI were performed at the Lister Fertility Clinic on women with unexplained infertility between the ages of 25 and 40 years.

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Table 1 Pregnancy and live birth rate in each group

	Frequency	Pregnancy rate	Live birth rate
Natural	288	9.0% (26/288)	6.3% (18/288)
Clomid	478	12.6% (60/478)	8.2% (39/478)
Gonadotrophin	935	10.8% (101/935)	7.2% (67/935)

Information on 58 cycles was incomplete and these were excluded from the study. IUI with COH constituted the majority of the cycles (1413). 478 cycles were stimulated with clomiphene citrate and 935 with gonadotrophin. 288 cycles were un-stimulated. The choice of agent used for COH was at the clinicians' discretion in consultation with the patient. All the couples had been trying to conceive for at least twelve months. Baseline fertility investigations in all couples include confirmation of ovulatory cycle by ultrasound scan and/or mid-luteal serum progesterone, a normal semen analysis and a post wash sperm concentration of at least 10 millions motile sperms. Tubal patency was established either by hysterosalpingogram or laparoscopy.

IUI treatment protocol

Controlled ovarian stimulation was performed with clomiphene citrate or FSH. The aim of COH was to achieve two or three dominant follicles with a diameter of at least 18 mm. Where COH was performed with FSH, baseline transvaginal ultrasound scan was carried out on cycle day 2–3, to exclude ovarian cysts. Thereafter patients injected themselves with 75iu of FSH, Puregon, (Organon Ltd) or Gonal F (Serono), daily until transvaginal scan showed at least one follicle with a diameter of 18 mm. HCG (1000 IU Pregnyl or 250 mcg of Ovitrelle) was administered and a single insemination was performed 36 to 40 hours thereafter. If there was no response or if more than 3 follicles were recruited, the dose of FSH was adjusted in the next cycle. If COH was performed with clomiphene citrate, the patient took 100 mg for 5 days, from cycle day 2 to 6, following a baseline transvaginal ultrasound scan. When at least one follicle of diameter 18 mm was seen on ultrasound scan, HCG was administered and insemination performed as above. The administration of HCG was withheld and the cycle was cancelled in both stimulation regimes when more than three follicles with diameter of at least 18 mm, or more than four follicles with a diameter of 14 mm were present.

In un-stimulated IUI cycles, detection of ovulation was performed with either urine LH tests or by trans-vaginal ultrasound scan. Patients were inseminated 24–36 h following the LH surge, or 36–40 h following the administration of HCG, where follicular growth was monitored by ultrasound scan. A urine pregnancy test was performed two weeks after IUI.

Data analysis

Data were collected in Medical System for IVF (MedicalSys, London, UK) and analysed with Statistics Package for Social Sciences (SPSS, Surrey, UK). We performed regression analysis at different age cut offs, and significant difference in outcome was noticed from age 37. Pregnancy rates and live birth rates in each treatment and age groups were examined with Chi-square Cross Tabulation test. Statistical significant was set at $P < 0.05$.

Results

The overall pregnancy rate from IUI was 10.99% (187/1701) and the live birth rate was 7.29% (124/1701). For women age ≤ 37 the pregnancy rate was 12.3% and the live birth rate was 9.6% per cycle. For women age > 37 the pregnancy rate was 9.2% and the live birth rate is 4.0% per cycle.

The pregnancy and live birth rates following natural cycle IUI (unstimulated) and IUI with COH are shown on Table 1. In women age 37 and younger, COH resulted in a significantly higher pregnancy rate and live-birth rate compared to natural cycle IUI ($p = 0.025$, $p = 0.045$ respectively) (Table 2). In these women, there was no significant difference in pregnancy rate and live-birth rate when COH was performed with either FSH or clomiphene. In this group IUI-COH was however associated with a multiple pregnancy rate of 10.8%, and a 1.6% higher order pregnancy (triplets).

However for older women age > 37 years, natural cycle (unstimulated) IUI, resulted in a significantly higher live-birth rate than IUI with COH ($p = 0.0037$). This difference is even more significant when COH was performed with clomiphene citrate ($p = 0.0017$) (Table 2). There were no multiple pregnancies in this group of women.

Table 2 Pregnancy and live birth rate in each age and treatment group

Age groups	Frequency		Pregnancy rate		Live birth rate	
	≤ 37	> 37	≤ 37	> 37	≤ 37	> 37
Natural	155	133	6.5% (10/155)	12.0% (16/133)	5.2% (8/155)	7.5% (10/133)
Clomid	338	140	13.9% (47/338)	9.3% (13/140)	10.7% (36/338)	2.1% (3/140)
gonadotrophin	509	426	13.0% (66/509)	8.2% (35/426)	10.2% (52/509)	3.5% (15/426)

Discussion

Even in this era of rapid advancements in assisted reproductive technologies, intrauterine insemination (IUI) is still widely offered to sub-fertile couples, as a cheaper and less invasive treatment option before proceeding to IVF [4]. IUI is superior to timed intercourse [2] because in IUI, motile spermatozoa, which are morphologically normal, are concentrated in small volumes and placed directly into the uterus, close to the released oocyte. In theory the probability of conception can be further improved by increasing the number of available oocytes at the site of fertilization, hence the role of COH. Controlled ovarian hyper-stimulation in combination with intrauterine insemination has been shown to result in significantly higher pregnancy rate when compared to un-stimulated (natural cycle) IUI [1, 5]. Our data is consistent with these studies, but only among younger women. In this group (<37) COH was associated with a significantly higher pregnancy rate as well as live-birth rate. Consistent with other studies [6] this was true irrespective of whether clomiphene citrate or gonadotrophin was used for COH.

Our data however showed the contrary in older women (>37). Here there was no significant difference in the pregnancy rate when IUI was performed with or without COH. In addition there was a significant difference in the live-birth rate. COH was associated with a lower live birth rate irrespective of the agent used, and seems to be worse when the anti-oestrogenic drug clomiphene citrate was used for COH.

Age differences may account for the inconsistent reports in the literature on the effect of COH on IUI. A meta-analysis of 4 trials including 479 completed cycles found no significant difference between IUI in cycles with COH and IUI in natural cycle [2]. However when the results of the two trials using gonadotropins were combined, gonadotropins significantly increased the probability of conception [2]. Whether this applies to women of all ages was not stated. Our results suggest that this may not apply to older women.

Why natural cycle IUI is associated with better outcome in older women is not entirely clear. As the ovarian follicular pool diminishes with age, a dominant follicle selected naturally may be the best in the cohort, hence increasing the likelihood of fertilisation and implantation. COH may encourage the recruitment of suboptimal follicles that may otherwise not have developed.

That COH (especially with clomiphene) in older women is associated with a significantly lower live birth rate is an interesting observation. Clomiphene citrate has been shown to have an adverse effect on early embryonic development [7, 8], on the endometrium, as well as implantation. Its antagonistic effect on the endometrium is well recognised [9]. Why the adverse effects of clomiphene should be more pronounced in older women than their younger counterparts, as suggested by our results is difficult to explain.

Our results have also confirmed the association of COH and the risks of multiple pregnancy. It is interesting to note that all the twins and triplets in our series occurred in younger women under-going IUI with COH. There were no multiple pregnancies in women under going IUI in natural cycle. Multifolliculogenesis in young women increases the number of oocytes available for fertilisation and hence the higher pregnancy and live birth rate compared to natural cycle IUI. This increase in pregnancy and live birth rate is however upset by the high incidence of twins and higher order multiple pregnancies associated COH [10], with the attendant health risks to the mother and babies as well as the overall increase in cost [3].

Our study is unique because of the large number of cycles and stratification according to age and treatment modality. However the non-randomised nature of the study requires that the results be interpreted with caution. The retrospective design means that treatment biases can not be entirely excluded although the large number of cycles involved may compensate for this.

Our results highlight the need for a randomised controlled trial to confirm or refute the main findings. There is also the need for future research to try to answer the question which couples benefit most from IUI in natural cycles and which couples would benefit from the addition of COH.

While the question remains unanswered, IUI in natural cycle should be one of the treatment options discussed with women in the older age group, as the results may be better.

Conclusion

In conclusion the result of our study suggests that, unlike younger women, older women have a better outcome from unstimulated IUI cycle.

References

1. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni L, Buster JE, Nakajima ST, Vogel DL, Canfield RE. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. *N Engl J Med* 1999;340:177–83
2. Cohlen BJ, Vandekerckhove P, te Velde ER, Habbema JDF. Timed intercourse versus intrauterine insemination with or without ovarian hyperstimulation for subfertility in men. *Cochrane Database Sys Rev* 2000; (2):CD000360
3. NICE (National Institute for Clinical Excellence). Fertility: Assessment and treatment for people with fertility problems. Clinical guidelines published by RCOG press. RCOG, 2004:75–80
4. Paterson CM, Hatasaka HH, Jones KP, Poulson AM, Carrell DT. Ovulation induction with gonadotropins and intrauterine insemination compared with invitro-fertilisation and no therapy: A prospective, non-randomised, cohort study and meta-analysis. *Fertil Steril* 1994;62:535–44

5. Steures P, Van Der Steeg JW, Verhoeve HR, Van Dop PA, Hompes PGA, Bossuyt PMM, Van Der Veen F, Habbema JDF, Eijkemans MJC, Mol BWJ. Does ovarian hyperstimulation in intrauterine insemination for cervical factor subfertility improve pregnancy rates? *Hum Reprod* 2006;19:2263–6
6. Attaullah N, Proctor M, Johnson NP. Oral versus injectable ovulation induction agents for unexplained subfertility. *Cochrane Database of Sys Rev* 2002; (3):CD003052
7. Birkenfeld A, Beier HM, Schenker JG. The effect of clomiphene citrate on early embryonic development, endometrium and implantation. *Hum Reprod*, 1986;1:387–93
8. Laufer N, Prat BM, DeCherny AH, et al. The in-vivo and in-vitro effects of clomiphene citrate on ovulation, fertilisation and development of cultured mouse oocytes. *Am J Obstet Gynecol*. 1983;147:633
9. Rogers PA, Polson D, Murphy CR et al., Correlation of endometrial histology, morphometry, and ultrasound appearance after different stimulation protocols for in-vitro fertilisation. *Fertil Steril* 1991;55:583–7
10. Gleicher N, Oleske DM, Tur-kaspa I, Vidali A, Karande V. Reducing the risk of higher order multiple pregnancy after ovarian stimulation with gonadotropins. *N Engl J Med*. 2000;1(343):2–7