

The effect of conventional vs. mild ovarian hyperstimulation on the total number of live babies born from a given oocyte retrieval

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Summary

Purpose: To compare pregnancy outcome in women with normal oocyte reserve according to whether they received conventional or mild follicle stimulating hormone (FSH) controlled ovarian hyperstimulation (COH) further stratified by age. **Materials and Methods:** A ten-year retrospective study including all cycles (even multiple in given patients) was performed. Mild stimulation including all cycles initiated and continued with 150 IU FSH or less from early follicular phase. Everything else was considered conventional stimulation. Mild stimulation included natural cycles or those with just a boost of 75 IU FSH from the mid to late follicular phase. Only women with normal oocyte reserve were selected – serum FSH < 12 mIU/mL and serum E2 < 50 pg/mL. Live delivered pregnancy rates within three age groups (≤ 35 , 36-39, and 40-42 years) were compared per embryo transfer and per embryo retrieval, i.e., the percentage of women having a live baby without proceeding to another IVF-ET cycle. Also compared were the average number of babies born from one retrieval. **Results:** For aged ≤ 35 there were no differences in pregnancy rates per transfer but a trend for higher pregnancy rates per retrieval with conventional stimulation. For all other age groups both pregnancy rates per transfer and retrieval were significantly higher with conventional stimulation. This was reflected with a higher average number of babies born per retrieval with conventional. **Conclusions:** For women with normal oocyte reserve in general, there is no advantage of mild vs. conventional COH other than cost saving. Of course there are exceptions, e.g., ovarian hyperstimulation with conventional COH.

Key words: Normal oocyte reserve; Controlled ovarian hyperstimulation; Mild FSH stimulation; Fresh and frozen embryo transfer; Pregnancy outcome.

Introduction

Some anecdotal case reports vividly demonstrate that in some instances the use of controlled ovarian hyperstimulation (COH) may create an adverse uterine environment preventing embryos from implanting [1, 2]. Nevertheless most IVF centers in the modern era are enjoying excellent live delivered pregnancy rates with fresh embryo transfer following conventional COH.

Baart *et al.* found that despite the creation of many embryos, there is an average of only 1.8 chromosomally normal embryos that advance to the blastocyst stage [3]. There may be a selective process where the best oocytes, i.e., those that are chromosomally normal, have better FSH receptors and are more likely to respond to lower FSH stimulation. Thus it is possible that mild FSH stimulation may create less embryos but the same number of chromosomally normal embryos. It is possible in some circumstances conventional COH will create an adverse uterine environment but not with mild stimulation. It is possible that both mild and conventional COH result in a similar frequency of adverse uterine environments and thus conventional COH has the

advantage of more embryos cryopreserved for future embryo transfer. If one does develop more normal embryos with conventional vs. mild COH, the former may have the advantage of more children derived from one given oocyte retrieval.

The objective of the present study was to compare the number of babies born from a given oocyte retrieval considering whether a conventional or mild COH protocol was used in women with normal oocyte reserve.

Materials and Methods

A retrospective cohort comparison study over ten years was conducted. In vitro fertilization cycles were eliminated if day 3 serum FSH was >12 mIU/mL or serum E2 was > 50 pg/mL. The data were stratified according to three age groups: ≤ 35 , 36-39, and 40-42 years. Data were stratified according to whether they had full vs. mild stimulation. Mild stimulation was considered if the woman started on no more than 150 IU FSH with an increase of 75 IU only when a GnRH antagonist was used. Significance was determined by Chi-square analysis.

The reason for choosing mild over conventional COH may have been related to: saving money not only on medication but the price

Table 1. — Effect of full vs. mild stimulation on live delivered pregnancy rates and number of babies born following IVF-ET in women with normal oocyte reserve.

Age	Full stimulation			Mild stimulation		
	≤35	36-39	40-42	≤35	36-39	40-42
No. retrievals	1349	708	406	391	393	408
No. transfers (fresh or frozen)	2138	916	473	504	447	444
No. viable (fresh or frozen)	966	331	117	216	104	74
Percentage viable/transfers (fresh or frozen)	45.2%	36.1%	24.7%	42.9%	23.3%	16.7%
No. deliveries	902	302	99	205	91	64
Percentage delivered/fresh or frozen transfer	42.2%	33.0%	20.9%	40.7%	20.4%	14.4%
Percentage delivered/retrieval (fresh and frozen)	66.9%	42.7%	24.4%	52.4%	23.2%	15.7%
Implantation rate	29.9%	22.5%	13.8%	29.6%	18.0%	11.4%
Average no. babies per retrieval	0.91	0.55	0.28	0.69	0.30	0.19

of the IVF-ET procedure is less when mild stimulation is used, previous failure to conceive with conventional stimulation (mild stimulation used to cover the possibility of high stimulation causing an adverse uterine environment), fear of the ovarian hyperstimulation syndrome, and desire not to have the dilemma of extra frozen embryos in case only one more child was desired.

Viable per transfer referred to live fetus at 12 weeks. If a fresh ET was not performed related to risk of OHSS or inadequate endometrial thickness, the category viable per transfer included that retrieval cycle but all transfers were frozen ETs. Thus this category states percentage viable in live delivered per fresh or frozen transfer. The category percentage delivered per retrieval includes all women having at least one baby born including the frozen transfer (if the fresh was not successful) and represents the numerator and the number of oocyte retrievals is the denominator. If a woman had an oocyte retrieval and she proceeded to another IVF-ET cycle without using her cryopreserved embryo, she was excluded from this study.

Results

The live delivery rate and the number of live babies born according to fresh vs. mild COH and age is seen in Table 1. The only comparison not showing a significantly higher live delivered pregnancy rate for full stimulation was in the live delivered pregnancy rates per transfer (fresh or frozen) in the younger (≤ 35 years) age group. But even in that younger group there was a significantly higher overall live delivery rate per retrieval (67% vs. 52.4%) (chi-square, $p < 0.05$). Chi-square analysis found significantly higher rates with full stimulation in women aged 36-42 in both pregnancy rates per transfer and pregnancy rate per retrieval.

Discussion

The main disadvantage of a retrospective study is potentially inadvertent selection of better candidates in one treatment regimen vs. another. One advantage of a retrospective study is that it generally has more power in numbers than a prospective study which is generally funded. Another advantage of a large retrospective study is that, as in this one, all cycles during a specific time period were selected so there was no discrimination toward a more "ideal" group. A prospective

study sometimes may not be representative of the majority of women seeking help with fertility.

For younger women, full stimulation resulted in about a 28% greater chance of having a live baby per retrieval and a 1.32 greater number of live babies produced. For age 36-39, full stimulation provided twice the chance of a live baby per retrieval and 1.83 as many live babies. For ages 40-42, full stimulation provided a 60% increased chance of a live baby per retrieval and 1.47 greater chance of producing live babies. Though implantation rates were slightly lower for mild stimulation vs. full stimulation for women $\geq 36-42$, the main reason for higher live delivery rates per retrieval and more babies were related to more embryos formed.

Conclusions

These data show that though there may be a few cases where full COH adversely effects uterine environment; this must be in a small minority since implantation rates were slightly lower not higher with mild stimulation. Of course some bias of selection could account for a somewhat lower implantation rate since mild stimulation was frequently used for women failing to conceive in previous cycles with full stimulation.

References

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