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The Methods Used to Avoid Ovarian Hyperstimulation Syndrome Do Not Negatively Effect Pregnancy Success Rates Following In vitro Fertilization in Young Women with High Anti-Mullerian Hormone Levels

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Abstract

Objective: To determine if two methods to avoid the ovarian hyperstimulation syndrome (OHSS) in young women undergoing in-vitro fertilization embryo transfer with high serum antimullerian hormone (AMH) levels, namely deferring fresh embryo transfer (ET) in favor of subsequent frozen ET (FET) and substituting leuprolide acetate for human chorionic gonadotropin (hCG) to advance meiosis, negatively affects pregnancy outcome.

Material and Method: Retrospective comparison of frequency of using these two techniques to avoid OHSS in women aged <35 for women with normal ovarian reserve (serum AMH 1 to <5 ng/ml) and high-responders defined as those likely to stimulate a high number of dominant follicles (20 or more) or attaining serum estradiol (E2) levels on day of trigger shot of >4000 pg/ml based on serum AMH >5 ng/ml. Live delivered pregnancy rates (LDPRs) were determined according to the pregnancy rate per transfer and per given oocyte harvest (i.e. counting subsequent FET cycles if the first transfer did not work as long as they did not go through another oocyte retrieval). Only one live delivery per patient was included.

Results: For the majority of women, there was no adverse effect on LDPR in the high AMH group when choosing leuprolide acetate to advance meiosis vs hCG. Only a minority of women used leuprolide in the normal oocyte reserve group which did not negatively affect pregnancy outcomes either. Deferring fresh ET was more common in the high AMH group than the normal group, but it had no negative impact on pregnancy outcome.

Conclusion: Since there were not any patients that developed severe OHSS requiring hospitalization, physicians should not be afraid to use GNRHa vs hCG in controlled ovarian hyperstimulation (COH) as it not only helps to avoid severe OHSS, but also has no negative impact on pregnancy rates in patients undergoing IVF.

Keywords: Polycystic ovarian syndrome; Anti-mullerian hormone; Ovarian hyperstimulation syndrome; Embryo freezing; Leuprolide acetate; Human chorionic gonadotropin

Introduction

Women with high serum anti-mullerian hormone (AMH) levels (>5ng/nl), with or without polycystic ovarian syndrome, are more prone to ovarian hyperstimulation syndrome (OHSS) when treated with gonadotropins with the use of human chorionic gonadotropin (hCG) to allow advancement of meiosis to the metaphase II stage [1]. The severity of OHSS is worse and more prolonged in

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women treated with FSH for follicular recruitment followed by an hCG injection if they become pregnant [2]. One way to decrease the risk of OHSS in women trying to conceive naturally but requiring FSH therapy to achieve ovulation, is to increase the ratio of LH to FSH by either using gonadotropin stimulation that has LH activity or using low dosage hCG with FSH stimulation [2].

Another method to avoid OHSS in natural cycles is to substitute a gonadotropin releasing hormone agonist (GNRHa) e.g., leuprolide acetate, to advance meiosis and release the egg related to the short acting effect of the GNHRa vs the prolonged effect of hCG [3]. The purpose of the GNHRa is to induce a surge of endogenous LH and FSH to advance follicular maturation and release the egg [3]. Besides substituting a GNHRa instead of hCG, another method to avoid OHSS in natural cycles is to use the lowest dosage of FSH/LH to achieve ovulation [4].

All of these methods also apply to trying to avoid OHSS following in vitro fertilization- embryo transfer (IVF-ET) cycles. One other advantage of IVF is that if there is considered a risk of OHSS one could cryopreserve the embryos rather than immediately transfer in the controlled ovarian hyperstimulation (COH) cycle since the hCG secreted by the fetal placental unit magnifies the OHSS by constant hCG stimulation.

The question arises as to whether any of these techniques to avoid OHSS is at the sacrifice of live delivered pregnancy rates (LDPRs) following IVF-ET. There are some studies that find a lower LDPR in women whose serum anti mullerian hormone (AMH) levels are >5 [5,6]. Those findings by Fallat et al and La Marca et al could have been related to stopping the FSH stimulation prematurely related to fear of causing OHSS thus leading to oocytes that were not sufficiently advanced to the metaphase II stage.

The purpose of this study was to determine in younger women aged (<35) with a serum AMH >5ng/ml undergoing IVF-ET whether freezing all embryos and deferring fresh ET or using leuprolide injection in lieu of hCG for allowing progression of follicular maturation has any negative effect on LDPRs following IVF.

Materials and Methods

A retrospective analysis was performed to evaluate a subgroup of women whose serum AMH was > 5ng/ml and compare their outcome to women undergoing IVF-ET with serum AMH of 1 to <5ng/ml. Our normal objective with COH is to obtain at least 2 follicles with an average diameter of 20mm. For the group of women with high serum AMH levels, in general, they would receive recombinant FSH plus recombinant FSH with LH activity (e.g., menopur) (with LH activity levels generally at least 50% of the total amount of FSH). Alternatively, these women would receive exclusive recombinant FSH with low dosage hCG (generally 20 IU/day).

If there are more than 20 dominant follicles and/or the serum estradiol (E2) levels were >4000 pg/ml, the women were given leuprolide acetate 1mg every 12 hours x3 doses and/or fresh ET would be deferred.

Sometimes these same measures may have been used for women with less than 20 dominant follicles or serum AMH <5 ng/ml. Thus, not only was the outcome of the IVF procedure evaluated in this group with potential severe OHSS as a consequence of embryo transfer, according to whether they had fresh vs frozen ET, or took hCG vs leuprolide acetate for advancement of meiosis, but they were compared to women with serum AMH <5 ng/ml to determine how much does the presence of high serum AMH levels influence the decision to freeze embryos and defer fresh transfer and to use a GNRHa trigger vs hCG. Furthermore, the study would determine if these alternate choices had a greater negative impact, (if any), in the group with normal oocyte reserve (serum AMH 1 to <5pg/nl) vs supra normal oocyte reserve (AMH>5ng/ml).

Our practice tends to favor the transfer of day 3 embryos, but for various reasons, sometimes the embryos were cultured to blastocyst before transfer (fresh or frozen). Super numerous embryos were frozen on day 3 if the fresh ET was on day 3 rather than cultured to blastocyst and then frozen.

Live delivered pregnancy rates were determined in two ways. The first was the pregnancy rate per first transfer (i.e., fresh or frozen). The second measure was the LDPR per harvest defined as the pregnancy rate in achieving one live delivery counting a subsequent live baby from a frozen embryo transfer if the first transfer failed as long as those embryos were obtained from the egg retrieval cycle. If a second live delivery from the supernumerary frozen embryos was obtained, they would not be counted in the statistics.

Results

The LDPRs women with serum AMH 1 to <5 vs ≥5 ng/ml per first transfer and per oocyte harvest according to whether fresh ET or FET was performed and according to which trigger shot was used is seen as in Table 1. For the normal AMH group, there were 258 oocyte retrievals evaluated which led to 177 (68.6%) fresh transfers and 81 (31.4%) frozen ETs (FETs). This was compared to fresh ETs in 54 of 114 (47.3%) oocyte retrievals in women with high serum AMH level and 60 (52.7%) FETs.

Whereas the leuprolide acetate trigger was used in 53.5% of women with high serum AMH levels, it was only used in 20.1% of those women with normal serum AMH levels. There were no significant differences in pregnancy outcome in any comparisons e.g., GNRHa trigger vs hCG in either normal or high AMH groups, or whether fresh vs frozen first transfers were performed, or comparing pregnancy outcomes

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Table 1: Pregnancy outcome for women with serum AMH 1 to <5 vs > 5ng/nl according to whether a method was used to avoid hyperstimulation syndrome or not.

	AMH 1-4.99	**AMH ≥ 5 ng/ml**		
	Leuprolide trigger	HCG trigger	LA trigger	hCG trigger
Total	42 (20.1%)	216 (79.9%)	53 (53.5%)	61 (46.5%)
LDPR/1st transfer	31.0% (13/42)	41.2% (89/216)	45.3% (24/53)	39.3% (24/61)
LDPR/ oocyte harvest	71.4% (30/42)	61.1% (132/216)	73.6% (39/53)	62.3% (38/61)
LDPR fresh embryo transfer	36.7% (65/177)		37.0% (20/54)	
LDPR frozen embryo transfer	45.7% (37/81)		45.0% (27/60)	

in women with normal vs high serum AMH levels. If one looks for a possible trend that could achieve significance with more power, the LDPR per first transfer was about 20% lower in those taking leuprolide vs hCG in the NOR group. However, the LDPR per first transfer was about 10% higher in the women in the high AMH group who took leuprolide vs hCG.

If one looks for a trend there was about a 20% higher LDPR with frozen vs fresh IVF ET for women in both groups. Regardless of whether the women had normal vs increased serum AMH levels there was a trend for about a 20% higher LDPR using leuprolide vs hCG.

Discussion

This study shows that methods used to avoid OHSS in women with higher serum AMH levels, e.g. using a GNRHa trigger instead of hCG injection or deferring fresh ET does not have a negative impact on success rates following IVF. There are some more recent studies in addition to those which we referred to in the introduction (of Fallot et al and La Marca et al) where the options of deferring fresh ET or using a GNRHa trigger were now available have reached similar conclusions as Fallot et al and La Marca et al that patients with PCOS and higher serum AMH levels either produce inferior quality embryos or lower LDPRs [5-10].

There are other studies, however, that do not find that high serum AMH levels with or without PCOS negatively affects IVF-ET outcomes [11-14]. The difference may be related to how far the follicular maturation is taken before adding the trigger shot and possibly differences in the success rates of the respective frozen embryo program. It should be noted that none of the patients in this study where methods to avoid OHSS required hospitalization for severe OHSS.

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