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Improving Pregnancy outcome by Measures used to Prevent Premature Progesterone Increase-Individualizing Art Treatment

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Abstract

It is well known that if there is increased Progesterone(P) in the latter part of the follicular phase during controlled ovarian stimulation(COS), used for in vitro fertilization(IVF)it has a detrimental effect on the outcome of the same. Proof exists regarding acceleration of endometrial maturation, which directly effects the endometrial receptivity(ER). Also there are some studies although only

retrospective, which show premature P rise might affect the oocyte/embryo quality. Increased FSH during the latter part of COS has been identified as the main culprit. Thus important is to individualize the COS protocol, based on the patients ovarian reserve and accordingly taper down if required the dosage of FSH in the end of follicular phase. Additional options are use of corticosteroids, prevention of prolonged stimulation, and use of freeze all strategy, postponing ET in next cycle, although there are questions regarding longterm safety of childrenborn from frozen thwed embryos.

Keywords: *progesterone increase, COS, Drug used, ER, embryo oocyte quality.*

Introduction

There is evidence that there is increase in progesterone(P) prematurely in the late follicular phase in in vitro fertilization(IVF) cycles where stimulation is used very often and is not preventable by giving gonadotropin releasing hormone(Gn RH) analogues, which occurs in as high as 38%of all stimulated cycles independent of the stimulation protocol used[1]. A lot of articles have described the bad effects of premature P on assisted reproductive technologies(ART) outcome[2, 3].

Normally for embryo implantation to occur a crosstalk is needed between a functional embryo at blastocyst stage as well as receptive endometrium , which is synchronized. It is still a controversy if reduced implantation as well as live birth rates seen if P is raised at follicular phase are secondary to bad effects on viability of embryo, receptivity of endometrium or both.

So it is still important to either prevent premature P during a stimulation or in that case to act in accord. Thus need of the hour is to prevent premature P elevation during stimulation of ovaries or once it occur, to act on its basis. Thus individualization of ART treatment, based on the need of the patient will be the main way of avoiding or dealing with premature P elevation.

Effects of P Elevation

Changes in Endometrial Receptivity

To differentiate endometrial factor from the quality of oocyte cohort and hence viability of embryos, oocyte donation model and frozen embryo transfer(FET) cycles have been used in some reports to assess endometrium and the effects of increased P on cycle outcome. Meta-analysis of the studies which evaluated oocyte donation cycles in which 1649 patients were studied it was shown that there is no evidence for

an association between the presence of elevated P in donor stimulation cycle with pregnancy achievement probability in recipient cycles[3]. Same was true for all the P threshold evaluated from 0.8 to 2.5ng/ml. Further Melo et al, reviewing those receiving oocytes from 120 donors who had repeated donation cycles presented increased P or not was studied. Study results showed that no differences in terms of implantation, pregnancy and miscarriage rates in which P was high(>1.2ng/ml)and those recipients receiving oocyte from the cycle where P was below the threshhold. Moreover fertilization, cleavage rate and morphological feautures of the embryo cohorts like fragmentation, and blastulation rates of each group were comparable.

Similarly the conjoint analysis of studies which includedfrozen embryo transfer(FET), which involved a total of 5046 patients[3], did not reveal any significant differences on cycle outcome regarding, regardless of the serum P levels at the end of the corresponding stimulation cycle for any of the P threshholds, applied across the studies.

This has been further amplified in a larger multicenter matched cohort study including 2910 cycles(1455 fresh , 1458 frozen). It was revealed that ongoing pregnancies rates was significantly lower in the total fresh cycles of serum P>1.0ng/ml, irrespective of age (<=35 or >35)while no difference was seen if P was <1.0ng/ml[5]. These 2 findings give indirect evidence of a bad effect of raised P on endometrial receptivity, as pregnancy rates were not affected if embryos were obtained from cycles with increased P, but transferred to endometrium which has not been exposed to high levels of P levels as occurs in case of FET or cycle donation.

Direct Effects

Using gene expression profiles, direct effect of the increased P on endometrium has been studied [6, 7]. Here endometrium was obtained in 2 different times of the cycle i.e the day of oocyte retrieval [6]and five days after[7]. Earlier immunochemistry assays showed that the Og and P receptor expression in the endometrium on the day of HCG administration is similar to that shown in 1st days of the luteal phase in a natural cycle. This shows an accelerated maturation of endometrium, which is exposed to supraphysiological concentration of P in the late follicular phase of IVF cycles[8]. This advancement of endometrium anticipates the window of implantation which is a self limited period in which the endometrium epithelium acquires the functional capability of supporting blastocyst adhesion[9].

Endometrial biopsies(EB) from 14 patients who had undergone controlled ovarian stimulation(COS) for IVF using 200iu/day of rec FSH in a GnRH antagonist protocolwere analyzed by Van Varenbergh et al[6]. They divided patients into 3 groups based on the serum P levels on the day of HCG administration i)0.9ng/ml, (n=1), ii(1-1.5ng/ml(n=6) and iii)>1.5ng/ml(n=5).

Advanced endometrial maturation for majority of patients (13/14)was shown in histological dating. This ranged from 2-4 days. No ongoing pregnancies happened in the group having P>1.5ng/ml, but 2 ongoing pregnancies were seen in the other 2 groups. Examination of endometrial gene expression analysis revealed that a short number of differentially expressed probe sets between patients with P<0.9ng/ml and those with P of 1-1.5ng/ml.Only 5 patients upregulated and 23 downregulated in the 2nd group. Reversely a good amount of differentially expressed probe sets between the groups with between 1.01-1.5ng/ml and P>1.5ng/ml.1607 upregulated in the intermediate serum P and 212 downregulated, i.e in total 819 differentially expressed probe sets.

Analyzing the biological functions of these significantly differentially expressed genes showed that the most relevant functions were related to cellular growth, proliferation, cellular movement, development, cell-cell signaling and cell death.

Similarly EB's of 12 women who had undergone COS with 225iu/day of rec FSH for oocyte donation was studied by Labreta et al 2011[7]. 6 of whom were following a GnRH agonist long protocol, while 6 after a GnRH antagonist protocol.3of each subgroup had S.P on day of HCG >1.5ng/ml, while 3 with P <0.9ng/ml. Thus 6/12 had high P as per the cut off value.In all women a luteal phase support treatment with vaginal aministration of 400mg /day of natural micronized P starting on the day after oocyte pick up(OPU) to simulate the cycle of patient who underwent ET. The reason this study was unique, is all EB's were taken 5days after the OPU i.e during the window of implantation period. This allowed to study the actual gene expression profile of endometrium when the

blastocyst is ready to implant.

Using a parametric method showed a total of 140 genes to be expressed significantly different between both study groups (64 up and 76 down regulated). Total number of dysregulated genes were 370 if a nonparametric method was used with 161 up and 209 downregulated in the higher P level grp. Specific analysis of 25 genes previously described to be strongly related with the receptiveness and the implantation process [10], 13 showed dysregulation in women with highP levels, 7 of them over upregulated and 6 downregulated. All these genes showed higher changes than those seen in the normal menstrual cycle. The particular genes which appeared upregulated in the natural cycle, did the same more markedly in women with high P levels. 8/13 genes were seen to have putative P response elements in their regulatory sequences.

Thus from the 2 publications it is clear that Serum P levels at follicular phase end cause significant change in gene expression profile of endometrium which are already shown on the day of OPU and continues to be present on the day when blastocyst is ready for implantation.

That it is clear their is impairment in endometrial receptivity, in presence of high P.

Changes in Oocyte/EmbryoQuality

This subject has received little attention. In 1995 there was a retrospective analyses by Ubaldi et al of the characteristics of the cumulus complexes along with the nuclear maturity of the oocytes and the fertilization and cleavage rates of 53 women who presented high Serum P>1.0ng/ml on the day of HCG[11]. No differences were seen when compared to the feautures of women with P<1.ng/ml. In the same way no differences were seen in the blastulation between women with high >0.9ng/ml and low P on the day of HCG trigger as seen by Fachin et al in 1996.

Recently 2 large retrospective analysis were published by Huang et al and Vanni et al in 2016 and 2017 respectively[13, 14].

In the 1st1236 cycles where COS was done using rec FSH in a GnRH long protocol, it was seen that the top quality embryo rate i.e. embryos from 2 pronuclei correated negatively with P levels even when adjustment was done for other factors which can influence the same like basal FSH, the total gonadotropin dosage, the age of women at the time of stimulation, top quality embryo was significantly different($p<0.05$) in Serum P levels below 2ng/ml and where it was 0.2ng/ml. [13]

In the 2nd study carried out in the same vein quality of embryos were examined by Vanni et al[14], who examined 986 pts undergoing COS with rec FSH and a Gn RH antagonist protocol. All patients had a blastocyst transfer. They saw, that while P levels did not correlate significantly either with fertilization rate nor with blastulation rate , there was a significant decrease in top quality blastocyst formation rate in relation to increasing P levels which was confirmed in all the 4 cutoff used(1.0, 1.5, 2.0, 2.5ng/ml). Hence there is recent evidence that increasing serum P at end of stimulation could be associated with a poorer embryo quality .

Yet contrasting evidence is obtained from stimulation done in luteal phase and that under high Serum P levels , given the similar implantation rates than there from follicular phase as shown by Ubaldi and Kuang et al in double stimulation protocols which was used in poor responders both in follicular and luteal phase [15, 16]. Still more objective clinical evidence and doses of mechanism explaining these findings is required.

Once this mechanism is confirmed it could=> different clinical management of increasing P at end of follicular phase .

Prevention strategies

Corticosteroid use

P is not only produced in ovary but part of it comes from adrenal gland [17]. Roughly 50% cotributon to P levels is from both sourcesduring follicular phase of a natural cycle[18]. Thus treatment with glucocorticoids in a dose dependent manner=> suppression of the hypothalamic-pituitary-adrenal axis. Giving dexamethasone in the follicular phase of normal cyclessuppresses serum P levels Hence addition of corticosteroids in COS lowers baseline P levels, which may finally cause significantly lower P levels on the day of final oocyte maturation[20, 21].

Influence of stimulation Protocol on Subtle Increase in serum P

It was thought earlierthat stimulation using a Gn RH antagonist protocol may decrease the incidence of P

increase as compared to stimulation using a GnRH agonist long protocol[22, 23]. But the effect of type of GnRH analogue which was usedfor suppression during COS, on chances of clinical pregnancy during existing P Increase was only due to lower pregnancy rates in patients undergoing the flexible multidose Gn RH antagonist protocol had comparative pregnancy rates to those with P<1.5 ng/ml. Thus need for reexamining this critically is there because of retrospective nature of study.

Modification of stimulation medication and stimulation intensity

COS prior to IVF involve the administration of relatively high dose of exogenous FSH to maintain a serum FSH concentration above the threshold, which is required to get multifollicular growth [23]. HCG/LH activity might be a cause of P rise and this risk could be decreased by administration of HCG/LH activity was advocated by Switz, Weiner et al in 2014[24, 25].

Yet P synthesis by preovu latory follicles get stimulated through FSH and LH with LH providing the strongest signal[26, 27] and Theusen et al showed that adding HCG/LH activity even increased P production during follicular phase[28], instead of preventing it. There is increased data which prove that increasing FSH stimulation in ART cycles is the main cause of premature P elevation[29, 30]. Thus decrease in FSH stimulation intensity in the end of FSH stimulation may lower P increase. To investigate chances of P increase in stimulation using corifollitropin alpha (CFA) with stimulation using rec FSH was done by Kyrou et al[31]. rec FSH needs FSH injection every day to prevent drop in serum FSH levels below critical threshold for further follicle growth following every injection, the peak serum FSH levels get reached within 10-12 hand then decrease until the next injection. Steady state levels get reached after 3-5days. Instead CFA is Hybrid molecule with sustained follicle simulating activity and has interaction only with FSH receptor, and it lacks LH activity[32]. Since it has long half life (t1/2) it may function as a follicle stimulant with the capability to initiate and sustain multiple follicular growth for a full week. This pharmacokinetic profile of CFA implies that the higher FSH activity during the 1st 2days with decreasing FSH activity following that might be similar to a step down protocol[34]. Different stimulation medications use showed a significantly lower incidence of P increase on the day of final oocyte maturation

Support for this comes from the recent in vitro studies done on human ovaran cortical and a non LH, FSH responsive human mitotic granulosa cell line showed that FSH stimulates the expression of 3 β-hydroxysteroid dehydrogenase(3β-HSD) and P biosynthesis in these cells. FSH contributes to a direct stimulatory effect on the enzymatic activity of 3β-HSD and hence increased conversion of pregnenolone to P. This led to a dose dependent increase in P and E2 output from the samples which get stimulated with FSH[35].

Duration of Stimulation

Proper timing is to be decided in COS for IVF. Normally oocyte maturity is related to the size of follicles [36] and the most widely accepted approach is togive tbe trigger as soon as 3 follicles have reached a diameter of>=17mm. But decision making on the timing of HCG may also be relatedto the business of the IVF laboratory tobe sure that there is smooth work.

Influence of prolonged COS on P levels on the day of final ocyte maturation was studied by Kolibiankis in 2004 and Kyrou etal in 2011[37, 38]by delaying final oocyte Maturation they postponed HCG injection for 1 day [38]or 2days[37], after the criteria for final oocyte maturation were met. It was accepted that that patient in the late HCG group had significantly higher P levels as compared to the early HCG groups. Mean +-SD P levels increases from 0.8+-0.3to 1.1+-0.1 to 1.5+-0.1ng/ml if HCG was delayed by 1day and from 1.1+-0.1to1.5+0.1ng/ml in case of a 2day delay.

Delay of HCG injection will cause more follicular growthand hence cause subsequently higher P levels because intrafollicular P Concentrations therefore Significantly rise with the follicle size[39].

Should ET be done or not

It is clear that various increases in P has a negative effect on ART outcome, but different P thresholds =>a bad outcome is seen in literature.In the biggest metaanlysis done[3], Veneti et al divided data according to various P thresholds . P >0.8 ng/ml were already associated with significantly bad correlation between P increase and pregnancy achievement. But Bosch et. al put this threshold at 1.2ng/ml[2] or 1 5ng/ml later [1] in 2010.

Yet same threshold may not be applicable to all patients and one has to examine it .

On the basis of ovarian reserve, In 2013 Griesinger et al did a pooled analysis and found a threshhold of 1.5ng/ml is detrimental in the low and normal responders, but in high responder patients there was no effect on pregnancy rates. Other studies on high responder patients show that Serum P >1.8ng/ml and >2.25 ng/ml[40]respectively might be the values at which P has minimum effect on implantation rates in high responder patients.Besides the known negative effect of raised P level on endometrial receptivity, there was a correlation between the P levels on the day of final oocyte matura tion and the rate of top embryo quality[14, 42]. In these studies patients with an increased P level during the follicular phase are at risk for the absence of top qualiy blastocysts and the top quality rate was significantly different between serum P<2.0 ng/ml and 2.0ng/ml. Increased P levels >2.0ng/ml before oocyte maturation are detrimental for the oocyte[13].

Hence further prospective properly designed studies are required to clarify freezing all embryos and the correct strategy to avoid a bad impact on pregnancy outcome.

Timing of ET In case of increased P

Since there is endometrial advancement with increasing P[43] and decreased endometrial receptivity [7]; there is decreased pregnancy rate because of asynchrony between embryo and endometrium. Ability of extending embryo culture to day 5 and performing blastocyst transfer has been studied by various workers as a strategy to overcome the endometrium-embtyo asynchrony by allowing the endometrium to recover from the damage caused by elevated P levels[44-47].

Only study by Papanikolau et al [47]did not find a bad effect of increased P beyond 1.5ng/mlon the pregnancy rate after blastocyst transfer, whereas in study carried out by Huang et al [46] a detrimental effect on blastocyst was only seen if P concentration reached >1.75ng/ml day of final oocyte maturation. In patients undergoing planned single ET on day 5 decreased pregnancy rates were seen with increasing P levels at end of stimulation.In pts stimulated with rec FSH the P threshold =>decreased pregnancy rates was lower as compared to pts stimulated with highly purified HMG(>4nmol/l vs >7nmol/l[48].

Freeze all Strategy and Cycle Segmentation

Cryopreservation of oocytes and embryos and subsequent ET in a natural or hormonal replacement cycles will remain the ultimate in fresh COS, if there is premature P rise. Dissociating COS from ET, one can remove the bad effect of P on Endometrial receptivity completely[49]. But cycle segmentation may not be acceptable to all patients because of legal, ethical or economic reason. Further undetectable, molecular changes in key genes and transcripts might get produced from the process of cryopreservation and thawing and such modulation may have long term effects on the child conceived[50]. Still long term follow up showing longterm safety is needed.

Conclusions

Thus summarizing the optimum measures

i) During COS the addition of corticosteroids in patients with an initial higher P level has the capacity to decrease the P levels during COS.

ii) Avoidance of excessive COS towards the end of follicular phase by performing a step down approach decreases the incidence of P elevation on the day of final oocyte maturation

iii) Giving ovarian stimulation beyond the optimal stimulation i.e.when >=3follicles of a size of >=17mm should be avoided, since it will increase the risk of P elevation.

iv) There is some evidence that increased P has a negative impact on the outcome of ART, which depends on the ovarian response(a P rise of >1.5ng/ml is critical for implantation as in normal or low responder pts, whereas in high responders the critical threshhols seems to be higher.

v) Delay of ET from cleavage state embryos to blastocyst embryos is critical in overcoming the effect of P elevation, since most studies don't show an improved pregnancy rate with blastocyst transfer.

A last approach is freeze all, since cycle segmentation with ET in subsequent cycle. The impact of P increase on the endometrium gets eliminated. But it is possible that this process of freezing and thawing may lead to

epigenetic alterations, and these might have longterm consequences of the child conceived after frozen thaw embryo replacement.

Hence preventing P increase prematurely on day of final oocyte maturarion are essential as raised P is associated with reduced pregnancy rates. Cryopreservation of oocytes and embryos is not the optimal answer. The main important thing is during COS during IVF treatment, using the correct stimulation dosage based on the patients ovarian reserve parameters and adapting the stimulation dosage according to the hormonal parameters during COS.

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