Does High Progesterone Concentration On The Day Of Human Chorionic Gonadotropin Trigger Affect Ongoing Pregnancy In IVF/ICSI Cycles?

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Citation

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Abstract

Introduction

The influence of increased serum progesterone levels at the end of the follicular phase during in vitro fertilization/ Intracytoplasmic sperm injection (IVF/ICSI) cycles on the ongoing pregnancy rate is being of continued debate. However, various assays for progesterone measure are used and different arbitrary threshold values for defining “high” progesterone levels have been proposed in order to answer this question.

The aim of this study is to assess the relationship between trigger day progesterone levels and the ongoing pregnancy rates in an unselected population of women undergoing Controlled Ovarian Stimulation (COS) for IVF/ICSI during stimulated IVF/ICSI embryo transfer cycles.

Methods

A retrospective, observational cohort study has been conducted on all patients, during two years between January 2018 and 2020 at our center, who had been undergoing IVF/ICSI cycles with fresh embryo transfer using either gonadotropin releasing hormone(GnRH)agonist or GnRH antagonist ovarian stimulation protocols.

A single determination of serum progesterone was performed on the day of HCG administration for all patients. Patients were divided in to 4 distinct groups according to their level of progesterone p (group1: p≤1ng/ml; group2: 1<p ≤1.5 ng/ml; group3: 1.5<p≤2 ng/ml; group 4: p>2ng/ml). The pregnancy (PR) rate was compared at different progesterone thresholds.

Results

Ongoing pregnancy rates were negatively associated with serum progesterone levels on day of trigger (p<0.01). Women who had serum progesterone levels>1.5 ng/ml had a significantly lower pregnancy rate compared to those whom levels were ≤1.5 ng/ml (7.5 % vs 74 %, p=0.00)

However, there was no significant difference in PR between group1 and group2 and between group 3 and 4, but there was a high significant difference in PR between group 2 and 3, between group1 and 4, and between group1 and 3. Therefore, we identified the progesterone cut off: 1.5 ng/ml on the day of HCG administration, above which there was a decrease in ongoing PR. Ovarian reserve statistic analysis showed that antimullerien hormone values, number of oocytes and estradiol values on the day of hCG administration were positively associated with progesterone levels, respectively p=0.009 and p=0.0001, p=0.0003). Furthermore, P level on day of trigger did not differ with different stimulation GnRH protocols agonists or antagonists.

Conclusion

Elevated serum progesterone level more than1.5ng/ml on the day of trigger is more likely associated with reduced ongoing pregnancy rates following IVF/ICSI cycles. This finding confirms previous data supporting measurement of progesterone level on the day of HCG administration and cryopreservation of embryos for future frozen embryo transfer to optimize outcomes.

INTRODUCTION

Premature increases in serum progesterone (P) levels during the late follicular phase in stimulated IVF/ICSI cycles is frequent despite the routinely use of GnRH agonists and antagonists that act through suppressing the release of endogenous gonadotropins from the pituitary. However, the frequency of these elevated progesterone levels varies and its incidence is difficult to evaluate from previous studies considering the large differences in threshold definition and in assay kits [1, 2].

This premature increase in P occur even with the administration of GnRH analogues, this may be due to excessive amounts of progesterone being produced by granulosa cells as part of early luteinization. That's way; the rises in P can be attributed to an excess number of follicles. Previous data had been showing that there are no existing relationships existing between LH and P levels at the end of the follicular phase. This is because the observed rises in P may reflect the mature granulosa cell response to high FSH exposure [1, 3]. Several studies have been conducted questioning if the presence of these elevated serum P levels on the day of HCG administration can be associated with the ongoing pregnancy rate. Some studies suggest that there is no association between P levels and pregnancy rates [4, 5, 2, 6] while, others reveal have shown a negative effect of P elevation on pregnancy rates [3, 1, 7, 8, 6]. Indeed, the serum P levels>1.5ng/ml on the day of HCG administration seem to be related to a significant decrease in the ongoing pregnancy rate following IVF/ICSI embryo transfer(ET) cycles irrespective of the GnRH analogue used for pituitary down regulation[1].

The negative effect of the increase in circulating P levels on IVF outcome occurs in cleavage and blastocyst stage embryo transfer, embryo quality, and across the spectrum of ovarian response and women's ages [9]. More recent work has suggested the possibility of a negative effect of progesterone elevation on fertilization rate and embryo quality [10]. Many authors have focused on the impact of these subtle increases in serum P on IVF/ICSI outcome and live birth. Contradictory results were obtained as in most studies this was associated with a decreased probability of pregnancy [10, 11].

A recent meta-analysis has developed a prognosis model of live birth incorporating P at HCG day as a predictor. This analysis was based on a large database taking into account evidence from previously published research [12]. Some authors have demonstrated that these serum P levels are significantly lower after the GnRh antagonist than agonist protocol [13], through this was not confirmed by a subsequent study [14, 15]. In fact, the mechanism by which increased serum P concentrations may affect cycle outcome is still unclear, and some data suggest that it impairs endometrial receptivity, rather than ovocyte quality [16, 17, 18] and P elevation affects endometrial gene expression [16, 19].

In this work, we attempted to investigate the relationship between serum P concentrations on the day of trigger and the ongoing pregnancy rates in an unselected population of women undergoing IVF/ICSI cycles-ET.

METHODS

The present study is a retrospective, observational single center cohort one conducted between January 2019 and December 2020 in our IVF center. It included an unselected population of women undergoing IVF/ICSI cycles-ET who underwent COS using either a GnRH agonist long protocol (n=58), a short protocol (n=16) or a GnRH antagonist flexible protocol (n=66) for pituitary down regulation.

Ovarian stimulation was carried out with recombinant follicle stimulating hormone(r FSH)alone(Merck sereno, Geneva,Swuitzeland), rFSH combined with luteinizing hormone(r LH)(luveris, Merck sereno, Geneva,Swuitzeland), or with highly purified human menopausal gonadotropins(HP-hMG)(Menopur©,Ferring pharmaceuticals, Geneva, Switzerland). Ovulation induction was performed with recombinant hCG(Ovitrelle©250, Merck sereno, Geneva,Swuitzeland) or GnRH agonist(Decapeptil© 0.1mg x2, Ipsen Biotech) when at least two or three mature follicles reached 18mm in diameter.The choice of protocol and gonadotropins was made according to patient's characteristics and clinician preference.

After oocyte retrieval and the usual IVF and ICSI procedures, the transfer of embryos was carried out on days2/3 or day5 of the cycle based on patient age, embryo quality and rank of cycle. The luteal phase was supplemented with vaginal micronized progesterone for 14 days; it was maintained until serum beta HCG determination.

A single determination of serum progesterone was performed on the day of hCG administration for all patients, samples were tested with a microparticle enzyme

immunoassay Axsym System (Abott). During the study period, no changes in the progesterone assay had occurred. The lower limit of detection for the assay was 0.2ng/ml, and the analytical sensitivity of the assay was 0.1ng/ml. The intra-assay and inter-assay coefficients of variation for the assay were 6.7% and 7.2%, respectively.

Patients were divided into four distinct groups according to serum P levels on the day of hCG administration (group1: p≤1.00ng/ml, group2:1.00<p ≤1.5 ng/ml; group3:1.5<p≤2.00 ng/ml; group 4 p>2.00ng/ml).

The primary objective was to determinate the relationship between trigger day P levels and the ongoing pregnancy rates in women undergoing COS during stimulated IVF/ICSI – ET cycles.

The serum b-hCG was measured 14 days following oocyte retrieval. Clinical pregnancy was defined by the detection of a gestational sac in transvaginal ultrasonographic in the7thgestational week. Also, we followed all the on-going pregnancies until live delivery, which indicated live birth.

Analyses were performed using SPSS (version20). Student test, Chi-square test (Fisher's test) and logistic regression were used for statistical analyses. The significance level was set at $p < 0.05$.

RESULTS

A total of 140 women undergoing COS with ET were performed during the study period. Their demographic and infertility characteristics are presented in table 1. The average age of the patients was 38, 51 ± 5, 70 years. The majority of them experienced infertility duration of 5 years (60%). 67% of them had primary infertility. the majority of our patients had a correct basal hormonal balance with good ovarian reserve. 52.85 %(74) of them received the agonist protocol and 47.15 %(66) received the antagonist one with day-3 or day-5 ET. Serum progesterone levels on the day of hCG administration ranged from 0.33 to 11 ng/ml, and the average progesterone level among all patients was1.7ng/ml. The overall clinical pregnancy rate per cycle was 32%.

Our 4 groups were comparable regarding their demographics and infertility parameters. The average number of stimulation days, the administrated total dose of r FSH and LH, the serum E2 level on the day of trigger, the number of retrieved oocytes, and number of embryos transferred did not differ between all groups.

The PR was 92.3% (24/26) in group 1, 57.14% (16/28) in the second group, 9.67% (6/62) in group3, and 0% (0/24) in group 4, respectively. Ongoing pregnancy rates were negatively associated with serum P levels on day of trigger ($p<0.01$). Women who had serum progesterone levels>1.5 ng/ml had a significantly lower pregnancy rate compared to those whose levels were ≤1.5 ng/ml (7.5 % vs 74 %, p=0.00, table 2). However, no significant difference was registered in PR between group1 and group2 and between group 3 and 4, but there was a high significant difference in PR between group 2 and 3, between group1 and 4, and between group1 and 3. Therefore, we identified the progesterone cut off: 1.5 ng/ml on the day of HCG administration, above which there were a decrease in ongoing PR.

We further analyzed the IVF outcomes according to the different treatment protocols. The incidences of PR were 41.37% (24/58) in the GnRH agonist short protocol subgroup versus 12.5 %(2/16) in the GnRH agonist long protocol subgroup and 30.3% (20/66) in the GnRH antagonist one; but the difference was not statistically significant between the antagonist subgroup and the agonist subgroup ($p>0.05$). Notwithstanding, the average of hormonal assessment FSH, LH and AMH of the GnRH antagonist protocol subgroup patients was higher than that of the GnRH agonist subgroup patients (p=0.0039; p=0.0005 respectively).

Moreover, when we analyzed our results according to the ovarian responses. A significant association between P rises and the level of estradiol on the day of hCG administration was identified (p=0.0003). Our results showed a higher pregnancy rate when embryo transfer was made at blastocyste stage (day5) 65.21% versus that embro transfer at early cleavage stage (day 3) 34.7% (p=0.00041).

Table 1

Patient and cycles parameters characteristics

	Patients Mean ± SD	Min-max
Age (years)	38.51±5.70	29-44
BMI (kg/m²)	30.9± 7.68	27- 34
Infertility duration(years)	6± 4.0	1-20
Basal FSH (IU/ml)	7.94±3.39	2-15
Basal LH (UI/ml)	6.33±3.11	1-14
AMH(ng/ml)	2.41±2.50	0.1-10.2
GnRH protocol		
Antagonist	47.1 %(66)	
agonist	52.8 %(74)	
E2 on HCG day (pg/ml)	3083±2515.78	450-8500
Pg on HCG day (ng/ml)	1.73±1.30	0.33-11

(BMI: body mass index, FSH: follicle stimulating hormone, LH luteinizing hormone, AMH anti-Mullerian hormone, GnRH: gonadotropin releasing hormone E2: estradiol, P: progesterone)

Table 2

Ongoing pregnancy rates for participants based on serum progesterone levels≤1.5 or>1.5ng/ml

Serum progesterone level (ng/ml)	Pregnancy rate	p
P≤1.5ng/ml	74.0%	<0.000
P >1.5 ng/ml	7%	

(P-value < 0.05, significant difference)

DISCUSSION

Our study has demonstrated that premature progesterone rise can be associated with a decrease in PR. This finding is consistent with other studies suggesting that PR is significantly lower in patients with high progesterone levels [11, 20, 22].

This progesterone rise was considered responsible for the variable pregnancy outcome assessment in previously published literature. Besides the different cut-off-levels used to define premature progesterone elevation, it has to be kept in mind that different progesterone-assays have been used in those studies and differences in assay performance could have also contributed to the heterogeneous results [23].

Most studies used an absolute progesterone level on the day of hCG administration as an indicator of PR, and the cut-off values ranged from 0.8 to 2 ng/ml [20, 24, 25].

A significant negative correlation between progesterone elevation and pregnancy achievement could have already been demonstrated from progesterone levels of 1.5 ng/ml and above [3, 19] which is rather in line with our findings.

In some studies, which used new methods of serum progesterone assessment, this cut-off concentration was usually set at 1.5 ng/ml [18]. This cut-off was supported by the presence of a marked difference in endometrial gene expression profile between patients with a progesterone serum concentration above and below the threshold of 1.5 ng/ml on the day of HCG administration [19].

The overall PR per cycle in our study was 32%. The PR was 41.37% in the GnRH agonist short protocol subgroup versus 12.5% in the GnRH agonist long protocol subgroup and 30.3% in the GnRH antagonist subgroup, but the differences were not significant.

In fact , Papanikolaou et al [14], suggested that the reproductive outcomes with the two GnRH analogues were comparable, and a progesterone rise >1.5 ng/ml was noticed in 23.0% of the antagonist group, comparable with 24.1% incidence within the agonist group. However, they depicted a reduction in delivery rates when progesterone exceeded the threshold of 1.5 ng/ml, in both agonist (9.5% versus 31.8%, p= 0.03) and antagonist group (14.3 versus 34.3%, p= 0.07). The discrepancies between our series and that study were probably due to the use of a different gonadotropin or GnRH analogue and different population characteristics.

Venetis et al [4] conducted a meta-analysis of 5 published studies and they reported a lower pregnancy rate in patients with elevated progesterone on the day of hCG administration. They simultaneously pointed out that there was evidence of methodological flaws in the late-follicular-phase measurements of progesterone that may have affected the results of an unknown number of studies retained in this meta-analysis. A recent work showed that the live birth rates were significantly lower in patients with both low and high progesterone levels on the day of hCG administration [12]

In a subsequent meta-analysis of 5 studies, considering solely the impact of progesterone on GnRH antagonist cycles alone, progesterone elevation on the day of hCG administration was significantly associated with a lower probability of clinical pregnancy ($p < 0.02$) [26] which confirmed our findings. Evenly, a large retrospective study [27] concluded that ongoing PR in fresh cycle were inversely associated with serum P levels on the day of hCG

administration for all patients and proposed P levels of 1.5 ng/ml as threshold for poor responders, 1.75 ng/ml for intermediate responders, and 2.25 ng/ml for high responders. Consequently, the P threshold depends on the ovarian response in the sense that in "high" responders the negative impact on the pregnancy rate starts at higher progesterone levels compared to "normal" or "low" responders [27].

Even though a significant inverse relationship between serum P on the day of hCG administration and the success of IVF was established in many programs, the involved endocrinological mechanism was unclear. It might involve an ovarian event, with adverse effects on oocyte maturation, fertilization, or early cleavage [1, 7, 8, 28, 29]. Two retrospective studies indicated, that elevated P levels on the day of trigger also led to significantly reduced live birth rates [20, 30]. A more recent study has suggested the possibility of a negative effect of P elevation on fertilization rate and embryo quality [10]

Our results manifested that the elevation of P levels and oestradiol levels is positively associated as it is consistent with some findings [13, 15], but the negative effect of premature progesterone rise, however, is still under investigation.

The risk of this P increase appears to be associated with the number and size of follicles and the intensity of FSH stimulation. Elevated P may lead to embryo/endometrial asynchrony, reducing the probability of implantation. The possibility of cryopreserving the resulting embryos and their transfer in a subsequent frozen thawed cycle [12, 31, 32] or alternatively, administering hCG at an earlier time in the follicular phase, prior to progesterone elevation [29] needs to be put under investigation.

Besides the absolute level of P as a critical value in regards to the detrimental effect of elevated progesterone, seemingly as well as the duration of prematurely elevated serum P concentration matter. PR was found to be significantly decreased in women with longer duration of serum progesterone elevation (> 1 ng/ml), independent of the protocol used and the ovarian response [33]. Our results pinpointed a higher pregnancy rate when embryo transfer was made at blastocyste stage (day5) 65.21% versus when embro transfer at early cleavage stage (day 3) 34.7% (p=0.00041). Thus, our finding are in line with those of some study [31,34] that demonstrated that moderate increases in serum P levels have deleterious effect on pregnancy rates in IVF cycles with a GnRH-agonist protocol and day 3 embryos. Even more, extending culture to day 5, single blastocyst overcomes/ameliorates the above detrimental association between P rise and the probability of pregnancy. The authors proposed the explanation that high follicular P advances extremely the endometrium, and therefore, the replacement of a day 3 embryo (earlier than what happens in nature) in an asynchronous endometrium results in failure of establishing embryo–endometrium cross-dialogue, and in turn, in embryo demise and failure of implantation [34]

Otherwise, the definitions of premature P rise as well as the critical cut off-level are inconsistent in the literature [35]. Most published data points towards a P threshold of1.5 ng/ml and above on the day of HCG administration, which will have a negative impact on PR in fresh embryos transfer cycles.

CONCLUSION

Evidence showcased an important negative effect of progesterone at higher values of more than 1.5ng/ml on the day of trigger on pregnancy rate ongoing, independent of oocyte number or treatment protocols. This finding confirms previous data supporting measurement of progesterone level on the day of HCG administration and freeze all strategy in order to optimize IVF outcomes. However, shifting to blastocyst transfer probably can enhance the life birth during IVF/ICSI embryo transfer cycles.

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