Original Articles

Reproductive Biology Section

Evidence that high serum progesterone (P) levels on day of human chorionic gonadotropin (hCG) injection have no adverse effect on the embryo itself as determined by pregnancy outcome following embryo transfer using donated eggs

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Summary

Purpose: To determine if too high of a level of progesterone at the time of peak follicular maturation of donors adversely affects pregnancy or implantation rates of recipients. *Methods:* A retrospective cohort analysis was performed on donor egg recipients. Pregnancy rates were calculated according to ranges of five serum progesterone (P) levels based on two standard deviations before and above the mean. *Results:* No adverse effect was found in recipients whose donors had serum P levels between 2.47 and 3.41 ng/ml. There may have been a slightly lower pregnancy rate in recipients whose donors had seen P levels over 3.41 but there were only seven patients in that group and there still was a live delivered pregnancy rate of 28.6% per transfer. *Conclusions:* The main adverse effect of a premature rise of progesterone in women making multiple follicles with gonadotropin stimulation seems to be on the endometrium. There appear to be enough follicles not affected by the progesterone to recommend proceeding with oocyte retrieval in the donor so as not to waste money on expensive medication and monitoring.

Key words: Serum progesterone; Late follicular phase; Oocyte donor, recipients.

Introduction

Premature luteinization in which luteinizing hormone (LH) surges result in a rise in progesterone before follicular maturation is achieved, is a recognized problem in women in natural cycles, or milder stimulation protocols aimed at inducing single follicular maturation [1-3].

It is not clear whether the adverse effect of the production of progesterone (P) by the granulosa-theca cells in natural cycles is on the oocyte contained within or on the endometrium. However even in women making multiple follicles premature rise of P has been associated with failure to achieve pregnancies.

When multiple follicular maturation is induced premature rise in progesterone also adversely effects the achievement of a successful pregnancy [4]. It is not clear if all of the follicles are producing P or one or some but not all of them are the source. If the adverse effect of a premature increase in P is on the oocyte within and the endometrium then it would be merely an academic exercise rather than a clinically important distinction to make in a woman trying to conceive naturally since whatever the mechanism pregnancy is not likely to happen.

However, the knowledge as to whether some of the eggs within the follicles, especially those that have not luteinized during in vitro fertilization (IVF) cycles, have potential to allow normal pregnancies, has clinical value. This has a special value for women who are egg donors. The recipient has spent a great deal of money on the medication and cost of follicular monitoring of the donor. Thus if the majority of eggs from the donor can still produce viable pregnancies it would be cost effective for the recipient not to cancel the cycle but to proceed with giving human chorionic gonadotropin to the donar when the follicles are mature and then do egg retrieval.

The present study evaluated the pregnancy rates in recipients according to the P levels of their respective donors to see if this is a certain level where pregnancy rates are significantly lower and thus should suggest that the recipient cancels the donor's cycles.

Materials and Methods

A retrospective cohort analysis was conducted. The serum P levels of oocyte donors were recorded on day of hCG injection. Recipients were told the serum P levels and informed of the existing evidence of low pregnancy rates associated with higher P levels in women who themselves are having oocyte retrieval and embryo transfer but that these effects may be on the endometrium. Only transfers with at least two embryos were included.

The data were stratified into five ranges of P based on standard deviation from the mean, and the pregnancy rates were determined.

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The recipients were advised that we were not sure whether the adverse effect of a rise of P adversely effects the egg or the endometrium so they were given the option of canceling the cycle or not.

Results

The pregnancy and implantation rates according to five serum P level ranges is given in Table 1. Interestingly, the highest clinical and live delivered and implantation rates were found in the group where the P ranged from 2.47 to 3.41 ng/ml.

The data suggest that if an adverse effect associated with higher P levels does exist (especially > 2 ng/ml), this does not effect the pregnancy rates of recipients. Possibly serum P levels > 3.41 in oocyte donors may adversely effect subsequent implantation and pregnancy rates in recipients but there were only seven (3.4% of the donor cycles) with serum P levels that high. If this small data set proves to be truly reflective of a larger population these data could suggest that with very high serum P levels more follicles have luteinized thus possibly affecting the egg itself.

Table 1. — *Pregnancy and implantation rates according to five serum progesterone (P) levels*.

Donor P level day of hCG	≤ .59	.59-1.53	1.53-2.47	2.47-3.41	3.41-4.35
# transfers ≥ 2 ET	16	105	60	17	7
Avg. age of donor	31.5	31.6	30.7	30.9	29.8
Mean E2 level day of hCG donor	2831.5	3058.3	3862.5	4082.8	3166.1
Mean P level day of hCG donor	0.4	1.0	2.0	2.9	3.8
# clinical pregnancies	7	62	33	12	4
% clinical pregnancy/ transfers	43.8	59.0	55.0	70.6	57.1
# viable	5	55	29	10	2
% viable/transfers	31.3	52.4	48.3	58.8	28.6
Implantation rate (%)	30.0	31.8	29.8	38.6	19.0

Discussion

Previous studies have found a correlation with lower pregnancy rates and high P levels on the day of hCG injection following controlled ovarian hyperstimulation [5, 6]. Though other studies have failed to confirm the importance of very low serum progesterone levels prognosticating higher pregnancy rates, certain higher progesterone levels that would prognosticate low chances of conception are still considered [7]. This level is frequently considered over 2 ng/ml.

By not finding a lower pregnancy rate in recipients receiving eggs from the donor with higher serum P levels these adverse effects seen in women undergoing IVF-ET themselves appear to be on the endometrium and not on the embryos per se.

These results have practical importance since some IVF centers would cancel the retrieval and not give the hCG injection to advance meiosis if the serum P of the donor exceeded a certain level. Gonadotropins are expensive and the money spent (usually by the recipient) would be wasted if the cycle was cancelled – not to mention the expense and inconvenience of monitoring serum hormone levels and follicular development by ultrasound.

The conclusions of this study could extend to women undergoing IVF-embryo transfer (IVF-ET). For IVF centers with good frozen ET pregnancy rates a women with elevated serum progesterone at the time of peak follicular maturation could consider – instead of canceling the cycle – to take the hCG injection and freeze all the embryos since it seems the main adverse effect of increased progesterone is on the endometrium.

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