DISCREPANCY IN β-hCG LEVELS IN TWO SEPARATE PREGNANCIES RESULTING FROM FERTILIZATION OF A COMMON POOL OF OOCYTES

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ABSTRACT

A unique donor oocyte recipient program where oocytes were shared by the female (who herself is having IVF) with a recipient (diagnosed with ovarian failure) provides an opportunity to evaluate the rise of **β-hCG** level in two different pregnancies in separate uteri; two such pregnancies resulted from a common pool of oocytes, but two different sources of sperm. The **β-hCG** in the donor two weeks from retrieval was 49 MIU/ml, and was almost identical in the recipient, suggesting that not only did fertilization occur on the same day but implantation established at approximately the same time. This was further confirmed by similar **β-hCG** levels 3 weeks from retrieval (1371 for donor; 1210 for recipient). At 3.5 weeks there was a change in the rate of rise with the donor increasing to 6790 compared to 2877 in the recipient. This difference continued as judged by **β-hCG** level of 87,000 MIU/ml in the donor and only 18,000 MIU/ml in the recipient. Ultrasonography confirmed a single viable fetus in both pregnant women without discrepancy in size. This supports the concept of constant doubling time for **β-hCG**. But the conflicting data also suggest a prolongation of the doubling time as the gestation advances.

INTRODUCTION

The level of serum **β-hCG** in pregnant women is a measure of the number of days from ovulation that the specimen was obtained. Thus, two different women ovulating on the same day would be expected to have similar **β-hCG** levels since implantation occurs at the same time in all pregnant women. Two possible suggested mechanisms for how a female who presents initially with a **β-hCG** level that seems too low for the predicted day of ovulation and yet

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progressively rising **β-hCG** levels are appropriate and fetal viability is demonstrated subsequently, include a) fertilization of another oocyte at a later time in the same cycle and b) delayed implantation.

IVF-ET has provided some new insights on implantation of human blastocysts. A woman, 40 years of age had a tubal factor etiology as the cause of her infertility. The patient conceived following **IVF-ET** when 3 embryos were transferred (Check/Chase, In Press). Her first ultrasound at 28 days post-embryo transfer demonstrated two sacs. One sac, 14 mm in diameter contained a single viable fetus. A second smaller sac (4 mm) did not demonstrate a gestational pole, suggesting a blighted ovum. However, a subsequent ultrasound 15 days later demonstrated two viable fetuses with only the second one appearing as though there was a later ovulation. The assumption at that time was that because of her tubal factor and replacement of embryos all within 24 h of each other, this event may be due to delayed implantation. The size discrepancy between the two concepts remained throughout gestation.

Our donor-oocyte program is somewhat unique in that patients who are having **IVF-ET** share half their oocytes with a designated recipient in exchange for shared monetary costs. When both donor-recipients conceive in the same cycle and both pregnancies are viable, this would provide an opportunity to compare sequential **β-hCG** levels and ultrasound in two separate individuals in whom the same pool of oocytes were divided and then fertilized by sperm from 2 different male partners and the embryos then transferred into 2 different females (the oocyte donor and recipient) at the same time.

MATERIALS / METHODS

Medical History of Donor

The donor is a 30 year-old female who decided to have **IVF-ET** for a male factor problem. The couple failed to conceive after one year of progesterone (**P**) therapy for a luteal phase defect. The endometrial biopsy that had been 4 days out of phase initially was only 1 day out of phase following **P** therapy. Sperm concentration was 18 x 10^6/ml with 38% sperm motility, but only 2% normal sperm using the STRICT CRITERIA of **Kruger** (Kruger et al, 1988) **IVF-ET** was thus suggested for a male factor problem and/or unexplained infertility. Tubal patency was previously established by laparoscopy. The patient conceived at first attempt with **IVF-ET**.

Medical History of Recipient

The recipient, a 33 year-old female; her last menstrual period was 2.5 years earlier and had premature ovarian failure based on a serum E_2 < 20 pg / ml, with a serum LH of 73 mIU/ml and FSH of 101 mIU/ml. The patient's mother had a history of autoimmune/endocrine anomaly but our patient had no other endocrinopathies at this time. The patients complete blood count, general health studies, thyroid profile and antinuclear antibody tests were all normal or negative. She conceived at her first attempt with donor oocyte fertilization.

Hyperstimulation Protocol for Donors

The long leuprolide acetate/hMG stimulation protocol was used (Meldrum, 1989). A specific protocol is generally followed for oocyte donors. Each patient was started with leuprolide acetate, 1 mg subcutaneously on day 21 of the cycle and continued for 10 days, at which time a serum estradiol (E_2) and progesterone (**P**) were obtained. If E_2 was suppressed below 25 pg/ml and the **P** < 1 ng/ml, the leuprolide acetate is then reduced to 0.5 mg subcutaneously daily and hMG was started at 300 IU daily in two divided doses. Gonadotropin therapy was not initiated if either E_2 or **P** were not adequately suppressed (E_2 < 25 pg/ml; **P**< 1 ng/ml). Leuprolide acetate was continued for a few more days when the patient was retested.

If sera E_2 and **P** had not adequately risen after 7 days, increments to 375 or 450 IU, hMG were given. **hCG** was administered at 10,000 units when two dominant follicles attained an 18 mm size by transvaginal ultrasonography (using a 5 MH_Z endovaginal transducer) with a minimum sera E_2 of 600 pg/ml and a **P** of <2 ng/ml. Retrievals were performed 34 to 36 h after **hCG** and transfers were made 48 h after retrieval.

Hormone Replacement for the Recipient

Oral micronized estradiol at a dosage of 2 mg (Estrace-2) was given to the recipient twice daily beginning on the 6th day of the donor's leuprolide. There was an increment of 2 mg every 4th day until 8 mg estradiol when the dosage was maintained. The dosage was decreased to 6 mg when the donor received her **hCG**. Progesterone at a daily dosage of 50 mg IM was started with donor's **hCG** and continued until a negative **β-hCG** level two weeks later, or continued if the test was positive.

Table 1 - β hCG levels after oocyte retrieval

β hCG level	Weeks from retrieval					
(mIU/ml)	2	3	3.5	4	4.5	5
Donor	49	1371	6790	*	30,900	87,000
Recipients	51	1210	2877	7120	*	18,000

* β hCG levels not obtained

Oocyte fertilization

Oocytes were obtained via the transvaginal approach using ultrasound guidance 34-36 h after **hCG**. The oocytes were divided equally based on morphological criteria between donor/recipient. Fresh specimens were collected from the male partners of both the donor/recipient, and 60 x 10^3 motile sperm were incubated with each oocyte.

RESULTS

Eleven follicles were punctured, and 11 oocytes were retrieved. The donor received 6 oocytes and the recipient received 5. The donor fertilized only 1 of 6 and the recipient fertilized 4 of 5. The donor had only one embryo transferred; all 4 were transferred to the recipient. There was a serial increase in **β-hCG** in donor/recipient (Table 1). Although the levels were very similar up to 3 weeks gestation, the **hCG** level rose much more abruptly in the donor than the recipient after this time.

Ultrasonography of the recipient was first performed at 5 weeks from retrieval. The crown/rump length was 8-9 mm consistent with 6.9 weeks ± 5 days. The sac diameter was 19 mm consistent with 6.7 weeks ± 5 days. The **β-hCG** level was 18,000 MIU/ml. Ultrasonography was performed one week later on the donor. The crown/rump length was 16 mm, consistent with 7.9 weeks ± 5 days. The sac diameter was 29 mm, consistent with 7.8 weeks ± 5 days. Subsequent ultrasonograms on both patients showed appropriate growth; both completed the second trimester without any complication.

DISCUSSION

In contrast to the case of twins (mentioned previously) with possible delayed implantation responsible for different mean sac diameters and fetal pole measurements, in this case the ultrasound evaluation was quite similar. However, for unknown reasons, the **β-hCG** levels began to accelerate much more rapidly by 3.5 weeks from retrieval in the donor (Table 1). The fact that the **β-hCG** levels were similar up to 3 weeks from retrieval provides more evidence against delayed transfer to explain the difference in the **β-hCG** levels.

There has been controversies about the doubling time (**DT**) of the **β-hCG** levels as to whether they are constant (Kadar, 1990), or whether prolongation of the **DT** occurs with advanced gestation (Pittaway, 1985; Check/Weiss, In Press). Perhaps different pregnancies can follow either pattern and that is why, after three weeks, these two pregnancies resulting from the same pool of oocytes transferred at the same time had such vastly different doubling times. This case may support either theory.

REFERENCES

Check JH, Chase JS, Nowroozi K, Goldsmith G, Dietterich C (In Press). Evidence that differences in sizes of fraternal twins may originate from early gestation - A case report. *Int J Fertil.*

Check JH, Weiss R (In Press). Evidence against a constant β-hCG doubling time during first trimester pregnancy. *Fertil Steril.*

Kadar N, Freedman M, Zacher M (1990). Further observations on the doubling time of human chorionic gonadotropin in early asymptomatic pregnancies. *Fertil Steril* **54**:783-787.

Kruger TF, Acosta AA, Simmons KF, Swanson RJ, Oehinger S (1988). Predictive value of abnormal sperm morphology in *in vitro* fertilization. *Fertil Steril* **49**:112-117.

Meldrum DR, Wisot A, Hamilton F, Gutlay AL, Kepton W, Huynh D (1989). Routine pituitary suppression with leuprolide before ovarian stimulation for oocyte retrieval. *Fertil Steril* **51**:455-459.

Pittaway DE, Reish RL, Wentz AC (1985). Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies. *Am J Obstet Gynecol* **152**:299-302.