

CASE REPORT

Hyperreactio luteinalis despite the absence of a corpus luteum and suppressed serum follicle stimulating concentrations in a triplet pregnancy

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Hyperreactio luteinalis is characterized by moderate to marked cystic enlargement of the ovaries related to multiple theca lutein cysts and is associated with very high sex steroid concentrations. It is a rare condition especially in the first trimester. The case described below is believed to be the only case of hyperreactio luteinalis reported following frozen embryo transfer. This case provides an opportunity to gain further insight into the mechanism responsible for this unusual condition. The 30 year old woman demonstrated a slightly elevated LH/FSH ratio (5 and 3 mIU/ml respectively) and normal baseline androgen concentrations. Two years following oocyte retrieval she had a second frozen embryo transfer. The ovaries were normal size when the embryos were transferred and androgens were still normal. The ovaries did not begin to enlarge until 51 days from transfer. A dichorionic intrauterine pregnancy with monozygotic twins in the left gestational sac was seen. Eventually, 86 days from transfer, the ovaries enlarged to 145×103×116 mm right; and 83×95×117 mm left. Serum oestradiol was 30 078 pg/ml, β -human chorionic gonadotrophin (HCG) 239 920 mIU/ml, serum progesterone >160 ng/ml, total testosterone 2254 ng/dl, free testosterone 42.3 pg/ml and androstenedione 7328 ng/dl. Throughout the first trimester, serum FSH was <1 mIU/ml. Thus, neither FSH nor a corpus luteum is necessary to initiate this syndrome.

Key words: frozen embryo transfer/hyperreactio luteinalis/triplets

Introduction

Hyperreactio luteinalis is a rare condition characterized by moderate to marked cystic enlargement of the ovaries related to multiple theca lutein cysts. This condition occurs more commonly in states associated with very high β -human chorionic gonadotrophin (β -HCG) concentrations, e.g. hydatidiform mole and choriocarcinoma. Hyperreactio luteinalis has been

reported even more uncommonly in pregnancies not associated with trophoblastic disease and a summary of the world literature from 1938 (first report) to 1989 has been provided (Wajda *et al.*, 1989).

There have been fewer case reports in the last 10 years probably because of a lack of new types of presentations different from those previously reported or cases that lead to a better understanding of the aetiology or the treatment (Al-Ramahi and Leader, 1998; Csapo *et al.*, 1999). One case has been reported and 51 other cases summarized which occurred with a singleton pregnancy (Schnorr *et al.*, 1996). Another case and summary of hyperreactio luteinalis and summaries of other cases have been provided (Lambers and Rosenn, 1996). A summary of many, but not all, of these cases of ovarian hyperstimulation syndrome (OHSS) in spontaneous pregnancies not associated with hydatidiform mole was also recently provided (Ludwig *et al.*, 1998).

The majority of cases (70%) of hyperreactio luteinalis occur in the third trimester or immediately postpartum (Wajda *et al.*, 1989). However, 16% present in the first trimester and thus this condition becomes difficult to distinguish from OHSS occurring in spontaneous pregnancies without the use of follicle stimulating medications (which is also a very rare event) (Fouk *et al.*, 1997; Ludwig *et al.*, 1998).

The case described below involving marked cystic enlargement of the ovaries and secretion of extremely high concentrations of sex steroids is unique in that this abnormal pathophysiological state resulted from transfer of thawed frozen embryos with suppression of hormone secretion by the corpus luteum and FSH secretion from the pituitary.

Case report

A couple with severe male factor infertility in the 51 year old male partner sought IVF with intracytoplasmic sperm injection (ICSI). The 30 year old female partner had two previous oocyte retrievals in other centres but no fertilization or embryo transfer occurred; ICSI was not available at that time. Her menstrual cycles varied between 21 and 30 days. She had mild hirsutism but not excessive for her nationality. At that time her serum oestradiol was 59 pg/ml, LH 5 mIU/ml, and FSH 3 mIU/ml (normal values 1.6–7.9 mIU/ml and 3–12 mIU/ml respectively).

The patient was started on follicular phase leuprolide acetate s.c. 0.15 mg from day 2 of the menstrual cycle and was started on day 5 with 150 IU recombinant FSH [either Follistim (Organon Inc., West Orange, NJ, USA) or Gonalf (Serono

Inc, Randolph, MA, USA) and 150 IU human menopausal gonadotrophin (HMG) [Repronex (Ferring Inc., Tarrytown, NY, USA), Humegon (Organon) or Pergonal (Serono)] on days 5 and 6 and was decreased to 150 IU HMG and 75 IU recombinant FSH for 3 days, then the dosage was decreased to 75 IU of each for 1 day, then decreased to 75 IU for 2 days of HMG only, then coasted with no gonadotrophins for 2 days when HCG 10 000 IU was given i.m. The serum oestradiol was 4462 pg/ml at the time of HCG injection and was 6535 pg/ml the next day. The serum FSH concentration was only 3 mIU/ml on the day of HCG and the peak concentration was 9 mIU/ml on days 7 and 10 of her menstrual cycle.

In all, 24 oocytes were retrieved from 59 follicles. ICSI was performed on the 19 mature oocytes; 10 fertilized, eight were cryopreserved at the two pronuclear (2PN) stage, and two were atretic. Thus, no transfer of fresh embryos occurred because of fear of OHSS. However, the patient developed no signs of OHSS following retrieval. The semen analysis on the day of egg retrieval showed a concentration of 38.7×10^6 spermatozoa/ml with 9% motility, 100% IgA antisperm antibody and a hypo-osmotic swelling test of 20%. The percentage of spermatozoa with normal morphology using strict criteria was 9% (Kruger *et al.*, 1988).

The patient failed to conceive after her first frozen embryo transfer of three embryos. Two years later, she had her second frozen embryo transfer with four embryos transferred. Baseline ultrasound located multiple follicles <3 mm on both ovaries. The right ovary measured 31×33×30 mm and the left 31×30×32 mm. The serum oestradiol was 30 pg/ml and serum LH and FSH 5 and 4 mIU/ml respectively on day 2 of her cycle. Her serum testosterone was 38 ng/dl (normal range 22–80 ng/dl). The free testosterone was 2.2 pg/ml (normal range 0.7–3.6 pg/ml) and the androstenedione was 195 ng/dl (normal range 47–268 ng/dl). She was placed on graduating doses of oral oestradiol beginning at 2 mg and finishing with 6 mg on day 15 with a 9 mm endometrial thickness and a triple line echo pattern and no follicles larger than 5 mm. The four embryos were transferred on the fourth day of progesterone replacement (100 mg i.m. daily, and 200 mg twice daily of progesterone vaginal suppositories). The oral oestradiol therapy was maintained at 6 mg/day.

Her initial β -HCG concentration was 244 mIU/ml 11 days from the transfer of the 3 day old embryos and the serum oestradiol was 1377 pg/ml. Three days later, the β -HCG increased to 969 mIU/ml and the serum oestradiol decreased to 717 pg/ml. Androgen concentrations were found to be slightly increased at this point: testosterone, 175 ng/dl, free-testosterone, 5.1 pg/ml, and androstenedione, 342 ng/dl. Even when her β -HCG reached 25 560 mIU/ml 22 days from transfer, her serum oestradiol was 1106 pg/ml and it was only 1771 pg/ml when the β -HCG was 180 200 mIU/ml. The serum oestradiol (4696 pg/ml) started to rise abruptly when the β -HCG concentration reached 332 700 mIU/ml. Serum FSH was measured each time a serum oestradiol was obtained and was <1 mIU/ml.

The first ultrasound since conception, 22 days from embryo transfer, showed a dichorionic gestation with right sac showing one yolk sac within and the left sac had two yolk sacs. The

right ovary measured 29×25×25 mm and the left ovary 22×20×20 mm. Two weeks later, the ultrasound showed a dichorionic intrauterine pregnancy with monozygotic twins in the left gestational sac. The ovaries still measured normal size.

Two weeks later (51 days from transfer) the ovaries began to enlarge (40×33×30 right; 31×23×37 mm on the left). The ovaries were markedly enlarged 66 days from embryo transfer—right ovary 73×84×70 mm and left ovary 56×78×58 mm. This was related to multiple cysts over 20 mm with the largest at 37 mm. The largest ovarian size documented was 86 days from transfer—right ovary 145×103×116 mm and the left ovary 83×95×117 mm consisting of multiple cysts <48.3 mm.

Discussion

A relatively recent publication described a case of hyperreactio luteinalis during the first trimester differentiated from severe OHSS in a spontaneously conceived pregnancy (Foulek *et al.*, 1997). It was further stated that 'without pharmacologic induction of ovulation the clinical diagnosis is severe hyperreactio luteinalis' (Foulek *et al.*, 1997). A further statement that 'hyperreactio luteinalis presents with a more indolent course and is usually seen later than OHSS which presents more acutely and earlier in the pregnancy' was made (Foulek *et al.*, 1997). In the case presented here, the cardinal feature of OHSS, increased vascular permeability as manifested by oedema, was not present. Probably most cases of hyperreactio luteinalis occurring in the first trimester can be distinguished from OHSS occurring in the first trimester despite the occurrence of a spontaneous pregnancy.

This case, because of intense monitoring at a much earlier stage than when the marked cystic enlargement of the ovaries developed, allows some extra insight into the mechanism of how this type of hyperstimulation can develop even in the absence of follicle maturing drugs or HCG injection. Ovarian enlargement did not occur soon after pregnancy diagnosis but instead after the patient was at least 8 weeks pregnant; this occurred when the β -HCG concentration was >300 000 mIU/ml and was possibly related to the greater placental surface with this multiple gestation pregnancy. However, only ~15% of cases of hyperreactio luteinalis were associated with multiple gestations and only ~2% had triplets (Wajda *et al.*, 1989; Yaper *et al.*, 1996).

There is a general belief that certain pathological ovarian states make a woman more prone to OHSS. For example, OHSS is more frequent in patients with polycystic ovarian syndrome (PCOS; Schenker *et al.*, 1994; Ben-Chetrit and Greenblatt, 1995). This patient did have mild hirsutism (but normal for her Pakistani nationality) and slight irregularity of her menses (21–30 days) and a mildly high LH:FSH ratio consistent with PCOS. However, she did not have increased baseline androgens. She did, nevertheless, demonstrate a hyper-response to a relatively low level of gonadotropin stimulation in her cycle of oocyte retrieval 2 years previously and her baseline ultrasound showed multiple follicles <3 mm in size.

One study suggested that FSH may play a role in the aetiology of hyperreactio luteinalis (White and Bradbury,

1965). These workers injected 150 IU of HMG for 5 days before elective Caesarean section in six women and caused the development of large theca-lutein cysts (Elchalal and Schenker, 1997). In another study, two women developed severe OHSS in the two cycles where they were treated with FSH exclusively, but they subsequently had no side-effects despite many cycles of HMG therapy (Check *et al.*, 1985). However, the case reported here illustrates that FSH was suppressed by exogenous oestrogen both prior to frozen embryo transfer and throughout the first trimester. Thus, this case demonstrates that FSH is not critical for the development of hyperreactio luteinalis.

OHSS is most commonly seen in situations where there are multiple corpora lutea. The case presented here indicates that hyperreactio luteinalis occurring in the first trimester can develop even without a single corpus luteum of pregnancy. Of course, two of the major hormones made by the corpus luteum, i.e. oestrogen and progesterone, were exogenously supplied, thus suggesting that other sex hormones besides oestradiol and progesterone or peptides secreted by the corpus luteum do not play an essential role in the development of hyperreactio luteinalis even if it occurs in the first trimester.

There are many different views on the pathophysiology of OHSS including some roles by substances, e.g. prorenin and the renin-angiotensin cascade (Elchalal *et al.*, 1997) or cytokines, e.g. vascular endothelial growth factor (VEGF) (Ludwig *et al.*, 1998). These substances were not measured in this patient. A recent case of OHSS occurring in a spontaneous pregnancy was associated with increased VEGF concentrations (Ludwig *et al.*, 1998). Our case, however, was not associated with fluid retention so possibly VEGF would have not been increased.

In all cases of hyperreactio luteinalis, the key histological feature is the marked luteinization and hypertrophy of the theca interna layer. The case presented here demonstrated that this condition can occur without any previous evidence of a pre-existing condition associated with increased androgen production. The mechanism causing this hypertrophy still remains to be determined. This case, which is believed to be the first pregnancy following frozen embryo transfer complicated by hyperreactio luteinalis, contributes to the understanding of the pathophysiology of this condition by demonstrating that neither a corpus luteum of pregnancy nor the presence of FSH is needed for the development of this form of ovarian hyperstimulation.

Though this pregnancy was associated with increased placental surface related to the multiple gestation and higher concentrations of β -HCG than in a singleton, it must be recalled that the serum testosterone reached male hormone values before the β -HCG reached 1000 mIU/ml when there would be very little placental surface.

These data strongly suggest that the main aetiological factor in the development of hyperreactio luteinalis is some intrinsic sensitivity to gonadotrophins causing marked hypertrophy followed by luteinization of the theca-interna layer. Unfortunately, because the patient was asymptomatic, we did not obtain hormonal concentrations after the HCG injection in the retrieval cycle performed 2 years earlier, because transfer was

withheld. Thus, some intrinsic sensitivity may exist in classic cases of OHSS following stimulation with FSH with or without LH followed by HCG injection. Though VEGF, endothelin-1, renin-angiotensin system and cytokines probably play a pivotal role in increased capillary permeability and subsequent anasarca (Elchalal *et al.*, 1997), other factors must be responsible for the marked hypertrophy and luteinization of the theca interna layer. Once the patient delivers the triplets, we plan to evaluate her for insulin resistance.

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