Case Report

Progesterone Hypersensitivity: A Challenge for Luteal Support

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Abstract

Progesterone hypersensitivity is a rare phenomenon which can occur after both endogenous and exogenous exposures. We present a case of hypersensitivity to various forms and routes of exogenous progesterone. A 27-year-old female presented with primary infertility. Investigations revealed Grade 1 endometriosis and polycystic ovary syndrome. Three cycles of intrauterine insemination were attempted which were unsuccessful and *in vitro* fertilization was proceeded. Six blastocysts of Grade A were formed and cryopreserved. Artificial cycle was used for endometrial preparation for frozen embryo transfer (FET). However, due to failure to use exogenous progesterone due to hypersensitivity reaction, Modified Natural Cycle (MNC) was used. A follicle was formed using ovulation induction with tamoxifen and human menopausal gonadotropin. Ovulation was induced by human chorionic gonadotropin (hCG), and natural progesterone from corpus luteum was used. FET was done when endometrium was 8 mm. Pregnancy was confirmed by transvaginal ultrasound and β-hCG levels and continued uneventfully. Endogenous progesterone can be used as an alternative for endometrial preparation for FET in patients with exogenous progesterone hypersensitivity.

Keywords: *Frozen embryo transfer, hypersensitivity, luteal-phase support, progesterone*

Introduction

Luteal-phase support (LPS) is a routine procedure after embryo transfer in both fresh and frozen transfer *in vitro* fertilization (IVF) cycles. LPS is a term used for the administration of medications to support implantation and pregnancy, which mainly consist of human chorionic gonadotropin (hCG) and progesterone. As the use of hCG is associated with a high risk of ovarian hyperstimulation syndrome, progesterone is the agent of choice.[1] It is available in intramuscular, oral, vaginal, and subcutaneous forms. Progesterone hypersensitivity is a rare entity which is a challenge for infertility clinicians. We present a rare case of hypersensitivity to various routes and forms of exogenous progesterone.

Case Report

A 27-year-old female, married for 2 years, presented with an inability to conceive for 1 year. She had spontaneous abortion at 6 weeks of gestation 1 year back. Her menstrual cycle length was of 1–3 months' duration with bleeding for 4–5 days. Medical and surgical histories were insignificant. Transvaginal ultrasound (TVS) showed polycystic ovary, and antral follicle count was 26. Hysterosalpingography showed bilateral patent tubes and karyotype of the couple was normal. The patient's husband's semen analysis was normal.

Hysterolaparoscopy showed Grade 1 endometriosis and bilateral positive chromopertubation. Three cycles of intrauterine insemination were performed which were unsuccessful and therefore a decision for IVF was taken. Stimulation was done for 12 days using antagonist protocol with injection human menopausal gonadotropin (hMG) 225 IU. Antagonist cetrorelix acetate 0.25 mg was added when leading follicle was 14 mm. Trigger was given by a gonadotropin agonist, triptorelin acetate 0.1 mg. Transvaginal oocyte retrieval was done

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35 h after trigger. Six blastocysts of Grade A were formed and cryopreserved. In the next menstruation, endometrial preparation was started for frozen embryo transfer (FET) with oral estradiol valerate. Once endometrium was 8 mm, exogenous injectable natural micronized progesterone 100 mg was added (Hald; Intas). Two hours after injection, the patient developed burning and pain at the injection site associated with fever and breathlessness. She was managed with injectable hydrocortisone. Next day, aqueous progesterone 25 mg (Pregcert AQ; Koye) was given following which similar symptoms developed. Vaginal progesterone gel (Emprogest 8% w/w; Emcure) and 300 mg capsules (Hald; Intas) were tried. Vaginal blisters developed and similar symptoms reappeared. The cycle was cancelled due to failure to administer progesterone.

As there was no previous history of endogenous progesterone hypersensitivity, we decided to use Modified Natural Cycle (MNC).

In the next cycle, follicular growth was initiated by tamoxifen 40 mg for 5 days and 75 IU HMG daily. Follicular monitoring showed monofollicular development. As the follicle size reached 19 mm, endometrial thickness was found to be 8.2 mm. Ovulation was triggered with recombinant hCG 250 µg for natural progesterone secretion from corpus luteum. Progesterone measured 48 h after trigger was found to be 4.59 ng/ml. Ovulation was further confirmed by corpus luteum and homogenous endometrium on TVS. Embryo transfer was done after 7 days of trigger (5 days after ovulation). Progesterone level on the day of transfer was 20 ng/ml. Luteal support was given as recombinant hCG 250 µg starting on the day of ovulation and continued every 72 h. Ten days posttransfer, β-hCG was 174.37 mIU/ml and progesterone was 21.78 ng/ml. TVS done 17 days after transfer (5 weeks of gestation) showed a gestational sac of 3.5 mm and yolk sac of 1.1 mm, with β-hCG of 1733.44 IU/ml and progesterone level of 11.82 ng/ml. At 7 weeks, TVS confirmed a single intrauterine pregnancy with crown rump length of 5.5 mm corresponding to 6 weeks and 6 days and cardiac activity of 118 beats/min and progesterone level of 11 ng/ml. LPS was withdrawn at 10 weeks and pregnancy is now continuing uneventfully at 16 weeks.

Discussion

The luteal phase is defined as the period from the time of ovulation till the occurrence of a pregnancy or the resumption of menses 2 weeks later. In the normal luteal phase, hormonal production peaks 4 days after ovulation and continues for 1 week until falling before the next menstruation. After ovulation, granulosa cells undergo luteinization under the influence of luteinizing hormone (LH) and the formed corpus luteum requires regular LH stimulation to maintain adequate production of progesterone.[2] If pregnancy occurs, corpus luteum is maintained by hCG.

In artificial cycle for endometrial preparation, exogenous estrogen is used which also prevents follicular growth. Thus, there is no corpus luteum, and exogenous progesterone supplementation is required to initiate and maintain the secretory endometrium and pregnancy. Several studies have shown an increase in live birth rate after luteal-phase supplementation of progesterone in FET.[3,4] Therefore, progesterone supplementation is a necessity for FET cycles and the management of progesterone hypersensitivity is a challenge.

Progesterone hypersensitivity is a rare entity with variable presentation varying from dermatitis,[5,6] dyspnea, cough, and anaphylaxis.[7] The first case was reported by Shelley *et al*. in 1964 as a dermatitis flare after premenstrual endogenous progesterone exposure.[8] Hypersensitivity reactions have been reported after exogenous as well as endogenous progesterone exposures.[9,10] Hypersensitivity after endogenous progesterone exposure occurs during menstruation or pregnancy without additional exogenous hormone supplementation.

Hypersensitivity can occur after external progesterone exposure from natural source such as soy and yam as well as synthetic forms such as 21-carbon derivatives (medroxyprogesterone acetate, megestrol acetate, and nomegestrol) and 19-nortestosterone compounds (norethindrone, norethindrone acetate, and levonorgestrel). These patients do not have any previous history of symptoms during the luteal phase of cycle or pregnancy. Our patient belonged to this category as she did not have a history of any previous hypersensitivity reaction to endogenous exposure.

Progesterone supplementation was required for endometrial preparation for FET. However, due to failure in supplementing exogenous progesterone, MNC was used. Follicle was developed and ovulation was triggered by recombinant hCG. The normal range of progesterone after ovulation varies from 3 to 20 ng/ml.[11] In our patient, it was 4.59 ng/ml that confirmed ovulation which was further confirmed by homogeneous endometrium by TVS. Recombinant β-HCG was given every 72 h to maintain corpus luteum till 10 weeks. Corpus luteum was able to maintain normal progesterone level and pregnancy continued uneventfully.

Progesterone hypersensitivity is a dilemma for infertility clinicians. Anticipating such challenge and making

alternative protocols to deal with it is the key to success. Management of our case thus gives a hope for many such patients in achieving uneventful pregnancy and delivery after IVF cycles.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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