Reproductive Biology Section

Prevention of first-trimester miscarriage with dextroamphetamine sulfate treatment in women with recurrent miscarriage following embryo transfer - case report

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Summary

Purpose: To present a novel approach to prevent miscarriage by treatment with sympathomimetic amines. *Materials and Methods:* Two women undergoing in vitro fertilization-embryo transfer (IVF-ET) with a history of recurrent miscarriage even in IVF-ET cycles were treated with dextroamphetamine sulfate prior to their next IVF-ET cycles. *Results:* Both women successfully completed their first trimester. One woman delivered a live baby and one had neonatal death related to prematurity secondary to severe pre-eclampsia. *Conclusions:* Sympathomimetic amines therapy may prove to be an effective therapy to prevent recurrent miscarriage especially in women who have failed despite progesterone therapy, and where no other etiologic factors have been determined.

Key words: Embryo transfer; Sympathomimetic amines; Recurrent miscarriage; Dextroamphetamine sulfate.

Introduction

There is a wide variety of chronic disorders described involving multiple physiological systems that are refractory to "standard" therapies, but respond quickly and effectively to treatment with sympathomimetic amines [1, 2]. These disorders include marked relief of chronic pelvic pain, whether it is of bladder origin as in interstitial cystitis or chronic pelvic pain or dysmenorrhea as seen in endometriosis [3-5].

Interstitial cystitis can be diagnosed prior to development of inflammatory changes that can be detected by cystoscopy by performing a potassium sensitivity test [6]. Installation of a potassium solution into the bladder in a person without this disorder will not evoke pain but severe burning pain ensues in a person with interstitial cystitis because the bladder mucosa no longer prevents an effective barrier to inhibit the absorption of potassium into the bladder wall [6].

One of the important functions of the sympathetic nervous system is to diminish cellular permeability [2]. Thus it is the authors' belief that the etiology for the vast variety of pain syndromes in different areas of the body, i.e., headaches, backaches, fibromyalgia, gastrointestinal system, not to mention the pelvis, and dramatic relief of these syndromes by treating these disorders with dextroamphetamine sulfate, is by correcting the cellular permeability defect and thus inhibiting the absorption of chemical toxins into the tissues which causes the pain [2, 5].

The possibility exists that increased cellular permeability may allow the absorption of chemical toxins into the endometrium which could impair implantation even following in vitro fertilization-embryo transfer (IVF-ET).

The authors describe two cases that had failed to successfully conceive following several IVF-ET cycles that were finally successful when sympathomimetic amine therapy was added.

Case Report

Case 1

The woman first presented to this reproductive endocrine practice for infertility at age 40. She had a history of one previous pregnancy with a different male partner at age 25 but had a miscarriage. She had been trying to conceive with her present husband for 3.5 years. She had failed to conceive at another infertility center after three cycles of follicle-maturing drugs and intrauterine insemination (IUI) and two cycles of IVF-ET. Her menstrual cycles were regular, her fallopian tubes were patent, and her husband had a perfectly normal semen analysis.

With her first IVF-ET cycle at our institution, she had 25 oocytes retrieved. Twenty-two were metaphase II and 17 fertilized. Three day three embryos [6, 9, 10] with very little fragmentation were transferred on day 3. Thirteen embryos were frozen (nine at the 2 pronuclear stage and four multi-cell ones). A pregnancy was achieved but she had a first-trimester spontaneous abortion related to a triploidy.

There were 15 oocytes retrieved on her second cycle and 14 were metaphase II. She fertilized 13 oocytes although six were allowed to cleave to day 3, there was only one with six blastomeres and the other two had four cells. She conceived and again had a first-trimester miscarriage.

She next had a frozen ET. This resulted in a pregnancy and the beta-human chorionic gonadotropin level doubled appropriately to 1,303 mIU/ml, but three days later only reached 1,739

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mIU/ml. Ultrasound showed an anembryonic gestational sac. She had transferred three embryos-one 8-cell and two 5-cell embryos.

She then had her third IVF-ET cycle with our group at age 41.6 and conceived. However, she had another first-trimester miscarriage. Chromosome analysis of the aborted fetus found a normal male.

Following the miscarriage of a chromosomally normal fetus, despite aggressive progesterone therapy, and the unavailability of lymphocyte immunotherapy, the authors provided the option of sympathomimetic amine therapy to accompany her next frozen ET.

She was started on dextroamphetamine sulfate extended release capsule daily and conceived again following her next frozen ET. She successfully completed her second trimester. Unfortunately she developed severe pre-eclampsia in her last trimester and delivered preterm and the baby subsequently died. She had continued the sympathomimetic amine therapy and progesterone.

Case 2

A couple had ten years of unprotected intercourse and no live babies. Once they sought the opinion of an infertility specialist because of their difficulty in conceiving, the problem was thought to be secondary to severe oligoasthenozoospermia.

When they failed to conceive after 12 cycles of IUI, they decided to do IVF-ET at another IVF-ET center. She conceived three times and had first-trimester spontaneous miscarriages each time. They could no longer afford IVF-ET, so they opted for insemination with donor sperm. She conceived three more times but also had three more first-trimester losses.

The couple came to this infertility center to consider another IVF-ET cycle with her husband's sperm using intracytoplasmic sperm injection (ICSI). However, they especially consulted the authors for a possible new consideration on how to prevent another miscarriage (i.e., so far six pregnancies and six first-trimester miscarriages. All the standard tests for recurrent miscarriage had been performed, e.g., thyroid tests and tests for coagulation disorders and infections. She was offered sympathomimetic amine therapy.

She started dextroamphetamine sulfate extended release capsules 15 mg daily. She proceeded with another IVF-ET cycle. Despite taking 300 IU of follicle-stimulating hormone (FSH) with 150 IU of luteinizing hormone (LH), she did not respond very well with only five metaphase II oocytes retrieved. Three fertilized but only two cleaved to day 3. She conceived a singleton pregnancy following ET and delivered a full-term healthy baby. She remained on the dextroamphetamine sulfate throughout the pregnancy. She was 36.8 years of age on the day of her oocyte retrieval.

Discussion

One cannot state with certainty that these successful pregnancies were the result of the treatment with dextroamphetamine sulfate. Nevertheless considering the many pregnancy losses of these two women and the clear-cut benefit of this therapy for various pain syndromes, it seems probable that it could have prevented first-trimester miscarriage. These case reports should hopefully stimulate controlled prospective studies to evaluate the potential of this novel therapy. Dextroamphetamine sulfate in normal pharmacologic dosage is not considered to be a human teratogen [7-9].

Case 1 was age 42 and was nulliparous so that she was at greater risk for pre-eclampsia. However, women with this sympathetic nervous system hypofunction defect are more prone to edema related to the inability to compensate for the increase in hydrostatic pressure by diminishing capillary permeability leading to transudation from intravascular to extravascular space [10, 11]. Thus it is possible that women who are more prone to miscarriage because of sympathetic nervous system hypofunction allow the absorption of toxic material into the endometrium. It remains to be seen in further studies if this therapy allows progression to the last trimester and if pre-eclampsia will be more frequent.

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