

Trans-Atlantic In Vitro Fertilization Cold War

To the Editor:

In reference to the paper by Edelstein et al.,¹ we wish to point out that their study, soundly constructed and clearly presented, confirmed the previous findings of a randomized crossover study of follicle-stimulating hormone against human menopausal gonadotropin after pituitary suppression with a luteinizing hormone-releasing hormone agonist published over a year earlier,² but was not referred to at all in their discussion. Since our study was discussed (after presenting the preliminary findings³) in 1986 with Dr. Jones, one of the co-authors with Dr. Edelstein, the Norfolk team could not be unaware of our study.

It appears that an "In Vitro Fertilization Cold War" is developing across the Atlantic, with failure to acknowledge work on "the other side." I hope that this trend does not continue, as in the end the integrity and reputation of assisted conception can only suffer.

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Reply of the Authors:

We appreciate the comments of Drs. Bentick and Shaw concerning our manuscript.¹ Though the literature regarding ovarian stimulation for in vitro fertilization is vast, we do regret not having referenced their excellent article² which demonstrated similar cycle characteristics in patients pretreated with the gonadotropin-releasing hormone agonist buserelin acetate, and then administered human menopausal gonadotropin or pure follicle-stimulating hormone.

We certainly do not want to initiate a Cold War between the Colonies and our brethren across the Atlantic. In fact, a number of the articles referenced in our paper were from non-American authors. With the spirit of friendship, cooperation, and *glasnost* permeating all aspects of global society, let us leave the "Cold War" to those debating improved cryopreservation techniques.

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Reproductive Roulette—Prognosis for Ovarian Failure

To The Editor:

We read, with interest, the article by Check et al.¹ in which the authors described their experience with 100 consecutive women with hypergonado-

tropic amenorrhea and were impressed that 8 women achieved viable pregnancies. We wish to report a most unusual successful pregnancy in a woman with premature ovarian failure that was diagnosed 14 years previously. Doctor Check, in his report, noted that the mean time of diagnosis to the initiation of treatment in the women who conceived was 2.2 years.

This 31-year-old woman developed premature ovarian failure after a spontaneous abortion at the age of 17 with generally persisting elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Chromosomal analysis was normal, work-up for polyglandular and autoimmune diseases were negative, and at the age of 22 there was no response to large doses of Pergonal or a 6-month trial of Danocrine. The patient was first seen by us in January, 1988 with elevated gonadotropins, and conceived using donor eggs and delivered a normal female infant at term. Eight weeks after delivery, while nursing, the patient did demonstrate some endogenous estrogen secretion followed by a spontaneous menses in January 1989. Of interest, immediately after her delivery, the patient developed symptoms of myasthenia gravis that responded to Mestinon treatment. These symptoms remitted and did not require treatment after approximately 10 months. Because of her one spontaneous menses with low FSH and LH levels in January 1989 the patient was started, immediately after this menses, with increasing doses of Pergonal up to a total dose of 40 ampules over 7 days without any measurable increase in estradiol levels. Over the next month, her FSH and LH rose to postmenopausal levels. The patient was then placed on replacement estrogen treatment for the past 16 months. The patient had her last menstrual period on July 1, 1990 and was started on her Estrace 2 mg/d at the same time. The patient took her usual Provera dose (10 mg) on the 16th to 25th but did not have her usual withdrawal bleeding. The patient subsequently demonstrated a positive serum pregnancy test and a fetal heart beat was seen on ultrasound examination on August 14. At the present time, the pregnancy is proceeding unremarkably.

This conception, we believe, represents the longest interval between the diagnosis of the premature ovarian failure and successful pregnancy, and also is probably the first natural pregnancy in a woman who previously had a pregnancy with donor eggs.

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Reply of the Authors:

The case by Jacobson et al. reporting a woman conceiving spontaneously while on estrogen-progestin replacement therapy despite a 15-year history of premature ovarian failure is certainly very interesting. Though we did find an average of 2.2 years from time of diagnosis to treatment in those who conceived compared with 4.8 years for those not achieving a pregnancy,¹ exceptions could certainly occur. In fact, we have reported a case with a 20-year history from diagnosis of ovarian failure to delivery.² This case was not included in the data of our first 100 cases since the patient spontaneously lowered her own elevated gonadotropins by developing a huge prolactinoma (serum prolactin 975 ng/mL), and a macroadenectomy was performed. The woman delivered a healthy boy at age 38 after human menopausal gonadotropin (hMG) therapy and she conceived again with hMG and has completed her second trimester at age 41. Her case was excluded also from the first 100 since it is also possible (though very unlikely in the author's opinion) that she had a very rare gonadotropin secreting tumor making inactive but immunogenic follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which converted to a prolactinoma.

There are 2 basic types of findings when a woman has hypergonadotropic hypogonadism. Type 1 is the most common type, where there are a paucity of follicles left (or none) and type 2, where there are plenty of follicles left. The pathological cause of type 1 problems may be varied: chromosomal abnormalities, autoimmune damage, prior surgery, endometriosis, infection, and idiopathic causes. No matter what the etiology, one theory behind the occasional success in making these

woman ovulate centers on restoration of down-regulated gonadotropin receptors in the few remaining follicles by lowering serum LH and FSH or improving responsiveness of the receptors by adding estrogen.³ One theoretical etiology for type 2 problems is autoimmune folliculitis in which trigger antigens are present in only maturing follicles so that primordial follicles are spared.⁴ Suppressing gonadotropins in their group theoretically inhibits the autoimmune response and subsequent ovulation may occur because of a delay in re-establishing the secretion of antibodies. I suspect both of these very long interval cases probably represent type 2 mechanisms. Indeed, another autoimmune condition, myasthenia gravis followed the pregnancy. Remission of the autoimmune folliculitis in this case may have been secondary to prolonged suppression of the gonadotropins during the pregnancy and the immunosuppressive effect of the pregnancy itself. Even in type 2 problems there is still probably some excess follicle atresia and may account for the temporary reversion back to hypogonadism after Pergonal therapy (down-regulation of gonadotropin receptors by increased sera LH and FSH levels from the hMG) and the fact that a very high dose of hMG was required to achieve ovulation in the patient with the macroadenoma, and yet multiple follicles were usually not possible in most cycles.

This case by Jacobsen et al is probably the first natural pregnancy in a woman who previously had a pregnancy with donor oocytes. A case of a natural pregnancy after an unsuccessful oocyte donation cycle was recently reported.⁵

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Editorial Comment

Occasionally nature provides us with unique exceptions to her universal laws. These exceptions should be treasured because they provide clues to the inner workings of biology. The syndrome of androgen resistance is a good example of nature's attempt to help us unravel the pivotal role of the androgen receptor in her grand design. In a more satirical mood, she may provide biological decoys or outlyers to help maintain our scientific rigor. The duel between correspondents and authors to record the longest interval between the diagnosis of ovarian failure and viable pregnancy is the impish side of nature at work. The authors have the last word and hence the license to speculate about the different etiologies and categories of ovarian failure in humans. Nevertheless, nature can still marvel at a collection of 100 subjects with ovarian failure and thoughtfully observe the frustrating attempts to reverse the process.

To date, the true prognosis surrounding ovarian failure is confounding because of the large numbers of anecdotal and isolated case reports. Although Check et al. do not provide a control group, they do describe two different treatment regimes in 100 unstudied subjects with ovarian failure (FSH > 35 mIU/mL, E₂ < 25 pg/mL). In spite of the record breaking cases of the correspondents and authors it is clear from the Check manuscript that a long time interval from diagnosis selects against successful pregnancy. One might have suspected such an outcome in humans from studies of fertile 45,X mice. Such mice, though fertile, have reduced litter size. Given similar genetic conditions, the life span of mice compared with humans is not sufficiently long to result in oocyte depletion. The countdown to ovarian failure is clearly a function of initial germ cell endowment and father time.

This study of 100 treated subjects reveals a 2.2% viable pregnancy rate and a 50% spontaneous abortion rate. I might similarly speculate and assume

that these figures could be subverted and applied equally well to an untreated group. The treatment of ovarian failure may be part science, but it is also part lottery. The small chance of a viable pregnancy and the high spontaneous abortion rate is offset by the high incidence of successful pregnancy with donor oocytes and gamete intrafallopian transfer (85%) or embryo transfer-in vitro fertilization.¹ The latter is fortunate because our knowledge of causation in 46,XX ovarian failure has changed very little in the last several years. Although restriction fragment length polymorphisms (RFLPs) for Multiple Endocrinopathy Syndrome (MEN) I and MEN 2A have been mapped to 11p and 10q, respectively, their mapping has not clarified the etiology nor the reason ovarian failure occasionally occurs in these multiple endocrinopathy syndromes. The study of ovarian failure in some homozygotes with classical galactosemia has been similarly uninformative in understanding the pathophysiology of premature ovarian failure.² The recent identification of mutations in a G-protein resulting in parathyroid hormone resistance suggests that similar mutations in the follicle-stimulating hormone and luteinizing hormone receptors leading to gonadotropin resistance may exist.³ Studies of unique X-autosomal translocations in humans leading to ovarian failure and similar balanced translocations in eugonadal individuals by DNA hybridization subtraction techniques may elucidate the molecular basis for ovarian failure. Clinical investigation and further pursuit of hormone profiles are unlikely to be helpful. Emphasis should be appropriately placed on the molecular analysis of these rare translocations and continued studies of mutations that are likely to affect intracellular signaling systems.

Paul G. McDonough, M.D., Editor, Letters

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Who Inherits the Embryo?

To the Editor:

As a participant in the Davis v. Davis case involving the disposition of seven cryopreserved pre-embryos, I wish to make some comments and observations. These are prompted by an article, "Seven Embryos in Search of Legitimacy."¹

Mr. and Mrs. Davis had undergone four previous IVF cycles (not 6 as mentioned in the article) when cryopreservation was not available at the location of our program. They wished to attempt another cycle and delayed initiating that cycle until the program was moved to another institution that would permit cryopreservation of pre-embryos. Their expressed desire was to increase the chances of a successful pregnancy and possibly additional pregnancies utilizing the cryopreservation technology. This was discussed in detail.

When initiating our cryopreservation program, multiple sources were used to draft the consent form. After thorough discussion with our legal counsel, it was decided to use the following statement:

"We understand that in-vitro fertilization and embryo transfer, gamete intrafallopian transfer, and cryopreservation are new areas in which all of the legal principles and requirements have not been fully established. Based upon currently accepted principles regarding legal ownership of human sperm and ova, we have been advised that each embryo resulting from the fertilization of the wife's ovum and the husband's sperm should be joint property of both of us as husband and wife, and that we would be deemed to be the legal owners."

None of the medical or legal persons felt we could accord pre-embryos the status of personhood; therefore, the only other current legal status would be property.

Failure to obtain the signed consent form was based on several factors. They were "old" patients with previous signed consent forms even though those did not include cryopreservation; logistically at that time, our retrieval facility and laboratory were remote from our office location and the procedures were done on days when neither the nurse nor I were to be at the office location (an oversight on the part of myself and the nurse). One has to have been in a transitional working situation to understand how such an oversight could happen.