

# A case report demonstrating that follicle maturing drugs may create an adverse uterine environment even when not used for controlled ovarian hyperstimulation

J. H. Check, M. L. Check

*The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey (USA)*

## Summary

**Purpose:** To evaluate whether follicle maturing drugs used in lower dosages for luteal phase defects rather than controlled ovarian hyperstimulation may have an adverse effect on successful implantation.

**Methods:** Unique case report.

**Results:** A 40-year-old woman who failed to conceive after six years of follicle maturing drugs with or without progesterone supplementation and four years of in vitro fertilization with embryo transfer (92 embryos transferred in 10 cycles) successfully conceived with the first cycle after the exclusive use of vaginal progesterone in the luteal phase.

**Conclusions:** This case provides convincing evidence that for some women follicle maturing drugs, even when used in lower dosages, can adversely affect the uterine environment.

**Key words:** Follicle maturing drugs; Adverse uterine environment; Refractory infertility; Progesterone supplementation.

## Introduction

The majority of gynecologists and infertility specialists empirically prescribe follicle maturing drugs, e.g., clomiphene citrate or gonadotropins for luteal phase defects. However, a study in 1988 found that the majority of women with luteal phase defects attain mature follicles, and those with mature follicles have a much higher viable six-month pregnancy rate with progesterone supplementation in the luteal phase than with follicle maturing drugs (74.2% vs 3.7%) [1].

It was not clear from that study whether the very poor pregnancy rate with follicle stimulating drugs was merely due to the fact that the follicle stimulating drugs, by raising the serum progesterone, also increase contra-progesterone hormones and thus did not correct the luteal phase defect, or the possibility exists that the follicle maturing drugs created a hostile uterine environment for implantation, or both [1].

Evidence has been presented that the use of follicle maturing drugs for the purpose of controlled ovarian hyperstimulation (COH) can create a hostile uterine environment for implantation [2-5]. One case report clearly supported the concept that COH per se can inhibit successful pregnancy since the patient failed to conceive after ten in vitro fertilization-embryo transfer (IVF-ET) cycles including 92 transferred embryos [6]. Interestingly, a second pregnancy by this same woman also provides strong evidence that follicle maturing drugs can create a hostile uterine environment even when used in

dosages merely aimed at attaining just one or few mature follicles [6]. Furthermore, this case illustrates the importance of supplemental progesterone in the luteal phase as an important fertility promoting drug.

## Case Report

A case of a woman with ten years of primary infertility who failed to conceive after ten IVF-ET cycles involving the transfers of 92 embryos but who conceived on her first attempt at frozen ET in an artificial estrogen-progesterone replacement cycle was described [6]. She failed to conceive even though she transferred 12 embryos each time for her last six fresh ETs, but conceived her first time with transfer of five frozen-thawed embryos [6].

Before attempting IVF-ET, this woman with polycystic ovaries and oligomenorrhea, but no other known infertility factor, failed to conceive after 65 cycles of ovulation induction with clomiphene citrate or gonadotropins. At least half of these cycles were supplemented with either oral or vaginal progesterone. Once she started IVF-ET, she used should be IVF exclusively and no longer merely tried ovulation induction.

One year from delivery of a full term healthy baby, she returned at the age of 40 for transfer of four of the remaining 20 frozen embryos. She stated that her last nine cycles had been 28-30 days apart. She presented on day 17 of her cycle and by ultrasound she appeared to have recently ovulated based on the presence of a corpus luteum by ultrasound. This was confirmed by her serum progesterone level of 4.2 ng/ml. She was started on progesterone vaginal suppositories and she conceived that cycle. The pregnancy this time was achieved with her own natural ovulation rather than transfer of frozen-thawed embryos. She has successfully delivered.

Revised manuscript accepted for publication March 10, 2001

## Discussion

The establishment of regular menses after delivery or oral contraceptives in a woman with polycystic ovarian syndrome and oligomenorrhea is not unusual. Despite many previous cycles even at a much younger age that included progesterone therapy along with ovulation inducing drugs, she failed to conceive, yet did so easily now at the age of 40. However, since this was the first non-IVF-ET cycle with the use of progesterone therapy alone, this report strongly suggests that in some women follicle maturing drugs may cause a uterine environment not conducive for implantation even with the smaller doses used in non-IVF cycles. Most of the previous studies, including the previous case report of this same woman, only provided evidence that the very high dosages of the ovulation inducing drugs used for the purpose of COH may create a hostile uterine environment [2-6].

Thus, this case report lends more credence to the concept that the very poor pregnancy rate seen when follicle-maturing drugs were used to treat luteal phase defects despite the apparent attainment of mature follicles may have been secondary not only to not treating with progesterone, but the establishment of a hostile uterine environment even with small dosages of follicle maturing drugs used [1]. Hopefully, this case report will restore interest in trying exclusive use of progesterone in the luteal phase for women with regular menses as first-line therapy rather than follicle maturing drugs. Alternatively, if follicle maturing drugs and progesterone supplementation were used and failed to achieve a pregnancy, the treating physician might consider treating exclusively with progesterone in the luteal phase [7-9] rather than proceeding with IVF-ET.

Other options for this patient with polycystic ovarian syndrome who did not have regular menses following pregnancy, might have been to try treating with medications aimed at restoring down-regulated insulin receptors, e.g., metformin; and if this enabled the women to make mature follicles, then to merely supplement with progesterone in the luteal phase. If the menses became regular,

but the egg released before the follicle matured in this hypothetical scenario, the woman could be allowed to develop her dominant follicle and then later in the follicular phase boost the follicle to maturity by the use of a short course of low-dose gonadotropins to minimize the potential establishment of a toxic uterine environment by the usual dosage of these follicle maturing drugs.

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Address reprint requests to:  
 JEROME H. CHECK, M.D., Ph.D.  
 7447 Old York Road  
 Melrose Park, PA 19027 (USA)