



The Use of Advanced Reproductive Technologies while Breastfeeding: A Role for *in vitro* Maturation

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Abstract

Background: IVF (*in vitro* fertilization and embryo transfer) exposes a patient to many medications and the production of multiple follicles produces abnormal levels of growth factors and hormones. Although the benefits to mother and child of an extended period of breastfeeding are considerable, pursuing IVF for further expanding a woman's family usually involves a trade-off between the timing of working on pregnancy and the length of time a mother is able to breastfeed.

Case: This case demonstrates that *in vitro* maturation IVF, where oocytes are harvested without super-physiologic drug stimulation, can be used to enable new mothers to continue breastfeeding while using advanced reproductive technologies. The adaptation of an *in vitro* maturation IVF procedure, to enable fertility treatment without stopping breastfeeding or waiting for a patient's cycle to re-start, is presented.

Conclusion: *In vitro* maturation IVF is a technique that can be used by women who wish to utilize advanced reproductive technologies, but wish to maximize their duration of breastfeeding between children.

Keywords

Lactation, Breastfeeding, IVM, *In vitro* maturation, IVF

The potential interaction of these factors and other medications on breastfeeding and on the infant leads most practitioners to await completion of breastfeeding prior to initiating an IVF cycle.

In contrast, IVM is a more natural and a more gentle approach to advanced reproductive technologies. The amount of medications used is minimal, usually natural female hormones, and in quantities consistent with normal physiology [3]. Estrogen levels are in the normal physiologic range [4]. The largest usable follicles for IVM contain at most one million granulosa cells and thus the quantity of potentially potent growth factors produced by them is in the normal menstrual cycle range [2]. In general, IVM is a significantly easier experience for a woman with a new infant to undertake than IVF [5].

Breastfeeding provides significant health benefits for both the mother and child. There is a decreased risk of ovarian and breast cancer, the development of diabetes, and myocardial infarction for women who breastfed their child. The risk decreases even more significantly if the mother is exclusively breastfeeding without supplementation of formula and the longer the mom and baby choose to breastfeed. For the child, breastfeeding decreases the risk of childhood leukemia, childhood obesity, asthma, sudden infant death syndrome (SIDS), and acute otitis media. Studies extending to at least one year suggest that an increased duration of breastfeeding further enhances some of these benefits [6,7].

Introduction

In vitro maturation IVF (IVM) is a variant of IVF in which immature oocytes are harvested from antral follicles (small follicles that are 4 to 12 mm in diameter). Since these oocytes are immature, they must undergo maturity in the laboratory before they can be fertilized. In contrast, with conventional IVF, significant quantities of the hormone FSH are given for 10 to 12 days in order to create a large cohort of mature oocytes that can be fertilized soon after they are removed from the body. Super-physiologic quantities of estradiol are produced as a byproduct of IVF therapy. Maternal estradiol levels may be high enough that breast milk estradiol levels (the estimated serum to breast milk ratio is about 10:1) may exceed levels normally encountered by the fetus [1]. Each follicle containing a mature oocyte contains about 50 million granulosa cells [2]; each of which is producing small quantities of other growth factors and hormones.

Case

The patient was a 29 year old infertile female who conceived her first child on her third cycle of conventional IVF. She presented eight months after delivery and expressed a strong interest in proceeding with IVF to conceive her second child, but also wished to continue to breastfeed her new son as long as possible. She had had an uncomplicated pregnancy and delivery, but had yet to have her first post-delivery menstrual period.

During her prior infertility therapy and treatment, her total antral follicle count was 18 and her AMH level was 2.7 ng/ml. The number of oocytes retrieved for her three IVF cycles were 19, 13 and 18. She experienced mild ovarian hyperstimulation syndrome on her third cycle. On transvaginal ultrasound examination, although a high antral follicle count was seen, the antral follicles were almost all small.

Based on her prior IVF cycle, the patient was offered the option of IVM, which would enable her to continue breastfeeding except for 24 hours after she received anesthetic agents for her oocyte retrieval.

Without inducing a period, the patient was given FSH 75 IU daily as priming for IVM.

Ultrasound evaluations were performed 6, 7, 8 and 9 days after starting gonadotropins. During these exams, the cohort of medium and large (6 to 10 mm) antral follicles increased daily. Micronized estradiol (6 mg) was started after 5 days of gonadotropins, which increased the thickness of the endometrial lining from 6 mm with a homogeneous pattern to 8 mm with a tri-laminar pattern. On the day of the last ultrasound examination, the patient was given 10,000 IU of hCG. Retrieval of six oocytes from the eleven medium and large antral follicles present took place 38 hours later. One oocyte matured five hours after retrieval and four more within 18 hours of retrieval. Three of the four fertilized embryos (9, 8 and 5 cells) were transferred resulting in a singleton ongoing pregnancy.

Except for the day following anesthesia, the patient continued to breastfeed her son. Note that withholding breastfeeding after exposure to the anesthesia drugs: fentanyl, midazolam, and propofol, was done for physician comfort since it is likely safe for the fetus [8]. With pregnancy the patient noted a decrease in the amount of milk she was able to pump (for storage and use when she was not available), but her son appeared to be satisfied with the quantity of milk he was getting directly from the breast.

Comments

The availability of IVM enabled treatment of this patient's underlying infertility while maximizing her autonomy. Although IVM always makes fewer demands on patients than does IVF [5], this case was unusual in that the difference between IVM and IVF likely had a lifelong impact on the health risks for this patient and her child.

Although the use of FSH priming is not uniform for all IVM cycles [9], its use appeared to be essential here. Based on the quiescent ultrasound appearance of her uterus and ovaries and her eight months of amenorrhea after delivery, this patient's endocrine status was likely in a suppressed steady state. In the setting of exogenous low dose FSH, there was a progressive increase in the number of medium and large antral follicle. This made retrieval of five oocytes capable of achieving maturity possible (or at least easier). Exogenous estradiol was started due to concern about the patient's ability to develop a normal appearing endometrial lining without supplemental estrogen.

While the association of breastfeeding and maternal-fetal health benefits has been evaluated in thousands of publications as critically reviewed by Ip *et al.* [6], the association of breastfeeding with a child's cognitive development is less well accepted, but may possibly even more important to women invested in becoming mothers using advanced reproductive technologies. Kramer *et al.* reported

on a (cluster) randomized seventeen thousand patient study in the Republic of Belarus that looked at the impact of breastfeeding on IQ scores and school performance at age 6.5 years. Randomization was performed on the provision of providing instruction promoting exclusive and long-term breastfeeding in women who already planned to breastfeed. The study was evaluated by an intention to treat analysis. In spite of a breastfeeding overlap in the treatment and control groups, the treatment group children had IQ scores about five points higher than the control group and better school performance. There was more benefit for children who had a longer duration of exclusive breastfeeding [10].

The data concerning benefits for mothers and babies is sufficiently strong, that all physicians who work with pregnant women or women trying to get pregnant, should be advocates for long-term breastfeeding after delivery. The ability to offer IVM, enables physicians to advocate continued breastfeeding while a woman is trying to conceive additional children using an advanced reproductive technology. The woman can attempt pregnancy without waiting for her menstrual cycle to resume and may continue to breastfeed after a failed cycle or after pregnancy until her and her child wish to stop breastfeeding.

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