

Live fetus following embryo transfer in a woman with diminished egg reserve whose maximal endometrial thickness was less than 4 mm

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Summary

Purpose: To report the thinnest peak endometrial thickness to date resulting in a viable fetus following embryo transfer. **Methods:** Mild ovarian hyperstimulation was given to a 35-year-old woman with not only a family history of premature ovarian failure but she also had diminished egg reserve. **Results:** She consistently could not attain more than a 4 mm endometrial thickness in graduated estrogen replacement cycles or IVF-ET cycles. She successfully conceived on her second oocyte retrieval but first embryo transfer despite a maximum endometrial thickness of 3.7 mm; we believe this is the thinnest one to date associated with a viable pregnancy following embryo transfer. **Conclusions:** Anecdotal cases are important to help couples make appropriate choices for their therapy. A physician could simply recommend a very expensive gestational carrier. However precedents might allow a given couple to take a chance with their ideal goal despite slim odds rather than compromise with a distant second choice.

Key words: Embryo transfer; Thin endometrium; Diminished oocyte reserve.

Introduction

In the early era of in vitro fertilization-embryo transfer (IVF-ET) lower pregnancy rates were found with thinner endometria on the day of injection of human chorionic gonadotropin (hCG) [1-3]. A 10 mm thickness or greater seemed to be an ideal level in the earlier days of IVF. In the modern era newer technologies have led to heartier embryos and pregnancy rates are not so markedly diminished with a peak thickness less than 10 mm.

Nevertheless, there may be some cut-off where pregnancies are not likely to occur. To date there has only been one case published where a pregnancy was achieved following embryo transfer with a peak endometrial thickness of 4 mm [4].

When presented with a very thin endometrium one has the option of freezing the embryos and hoping that artificial estrogen replacement with graduating estrogen doses will improve the thickness. However, this is not guaranteed and then one has the disadvantage of using frozen-thawed embryos that at least in some IVF centers do not have nearly the same implantation potential as fresh embryos.

To make a decision a woman may look for anecdotal case reports to determine if there is any evidence of successful pregnancies despite an extremely thin endometrium especially if the endometrium has been consistently thin. If there are no precedents, faced with the fact that a search of the world literature failed to reveal any reports of a live delivery in a woman with a

peak endometrial thickness of a certain level, she may consider using a gestational carrier. Not only is this option extremely expensive but it denies the woman the experience of pregnancy and delivery.

There have been no published precedents for pregnancy with an endometrial thickness less than 4 mm. The present case report describes a viable pregnancy achieved following IVF-ET despite a peak endometrial thickness of only 3.7 mm.

Case Report

A 34-year-old woman with a history of Hashimoto's disease on thyroid hormone replacement presented with primary infertility of two years' duration. She was advised by a previous infertility specialist that because of pelvic adhesions from endometriosis impairing fallopian tube function bilaterally that she would require IVF-ET to achieve a pregnancy.

However, she also had a familial history of predilection to diminished oocyte reserve. Her previous infertility specialist evaluated her day 3 serum FSH level and found it to be increased. She was advised that she should consider donor oocytes.

Since our group has had extensive experience in treating women with infertility and diminished oocyte reserve, and have reported a good chance of success when IVF-ET is needed even when there is only one embryo to transfer as long as a mild ovarian hyperstimulation regimen is used, she elected to try IVF-ET with her own oocytes [5, 6].

Her baseline day 1 serum estradiol (E2) was 28 pg/ml, with a serum LH of 5.9 mIU/ml and a serum FSH of 15.2 mIU/ml. In a subsequent cycle though her serum FSH was only 9.2 mIU/ml the diminished oocyte reserve was masked because of serum FSH was brought down by her high serum E2 of 74 pg/ml. In a third evaluation cycle her serum E2 on day 3 was 80 pg/ml with a serum FSH of 8.9 mIU/ml.

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In two observation cycles it was noted that her endometrial thickness did not exceed 4 mm. Thus before attempting IVF she was placed on a graduated oral and vaginal estradiol regimen to see if under these conditions she could generate a sufficiently thick endometrium. The purpose of this test cycle was to see if a thin endometrium in the late follicular phase was found on the IVF cycle was it worth freezing the embryos and transferring the frozen-thawed embryos in a subsequent cycle with artificial estrogen preparation. Unfortunately the lining did not exceed 4 mm despite a protracted course of 25 days of oral and vaginal estrogen reaching 8 mg per day for the last two weeks.

The woman was advised that thin endometria provides an additional significant negative influence on success following embryo transfer though successful pregnancy was not unprecedented and it could be under reported [4]. In fact we informed her of another successful pregnancy that occurred with natural intercourse with a peak endometrial thickness of 4 mm [7]. It was explained that her option would be traditional surrogacy with her husband's sperm used to inseminate another woman, to perform IVF and transfer her embryos to a gestational carrier, adopt, use donor oocytes and a gestational carrier or proceed with IVF-ET herself despite low odds of success, more related to the poor endometrial development, but also related to diminished oocyte reserve.

She chose to try IVF-ET with her own eggs and with transfer back to her own uterus. Using mild ovarian hyperstimulation she attained only one dominant follicle with a serum E2 of 266 pg/ml [5, 6]. The endometrial thickness was 4 mm. One metaphase II oocyte was retrieved but it did not fertilize.

Having failed to get an embryo the first time she was re-advised of all of her options. She again chose to try IVF-ET with her own oocytes. In the second cycle though it started out similar to the first one with 150 IU FSH she did go up as high as 300 IU especially when cetrorelix 250 mcg was added with a 14 mm follicle. Her peak serum E2 was 832 pg/ml when 10,000 units of hCG were given. This was on cycle day 14 and her endometrial thickness was 3.7 mm. Three metaphase II eggs were retrieved resulting in two embryos. On day 3 an 8-cell and a 4-cell embryo with < 25% fragmentation were transferred. A pregnancy resulted and she successfully completed the first trimester with a live fetus. She was age 35 at the time of embryo transfer.

Discussion

Our patient stated that an important factor in her decision on trying with her own oocytes and her own uterus was the previous anecdotal precedents of two pregnancies with a 4 mm endometrial thickness. At least she said she knew it was possible [7].

She is another example of our disagreement in the conclusions from one of the leading IVF centers of the world that if the FSH reaches 15 mIU/ml live deliveries are not possible at any age [8]. Our data supports the concept that there are some FSH-dependent proteins needed for implantation that become reduced because of down-regulation of FSH receptors by increasing the already chronically elevated serum FSH even more by the high dosage of slow clearing exogenous FSH. Such a protein has not been identified as yet but the hypothesis would explain the 40% clinical pregnancy rate in 65% of women attaining an embryo with a minimum of six blastomeres with

women whose mean FSH clearly averaged well above 15 mIU/ml and had only one embryo to transfer [5].

Because we have had successful pregnancies especially in younger women (< age 39) who were in apparent premature menopause, we have hypothesized that there is in general a different mechanism for oocyte depletion in younger vs women of advanced reproductive age, i.e., \geq age 45 [9-14]. The very poor pregnancy rates in women \geq age 45 despite IVF-ET, even in women with normal oocyte reserve despite the transfer of normal morphologic embryos, favor the concept that with advanced reproductive age there is a natural selection of the best oocytes so what oocytes remain are of poor quality. Not that they lead to poor embryo quality but embryos that fail to result in a positive pregnancy test or live pregnancy [7, 15]. In contrast, the relatively good pregnancy rate in younger patients favors the hypothesis that the usual mechanism for diminished oocyte reserve is not a more rapid progression of oocyte atresia but related to damage to certain geographical portions. Thus they have the same quality of oocytes as their age peers but less quantity.

The one exception may be women with a familial history of early ovarian failure (mother and sister). In these cases there may be a genetic predisposition to a more rapid atresia leading to not only fewer oocytes but less quality oocytes. There is no proof for this hypothesis but my experience has been a far lower pregnancy rate in this population. The woman was made aware of this belief but still wanted to proceed with IVF-ET with her own eggs.

We had also made the woman aware that we had another unpublished case of a 47-year-old woman who successfully completed the first trimester with twins despite a maximal endometrial thickness of 4 mm but the source were donor oocytes. It is important to publish these anecdotes to help women and couples make tough decisions. Hopefully this case will encourage other colleagues having success with patients with very thin endometria to publish their experience. It is believed this is the first case report of a successful pregnancy with a peak endometrial thickness of < 4 mm.

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