Successful twin pregnancy in a donor oocyte recipient despite a maximum endometrial thickness in the late proliferative phase of 4 mm

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Summary

Purpose: To show that even a twin pregnancy is possible following embryo transfer despite a very thin endometrium. *Methods:* Two embryos derived from donor oocytes were transferred into a 47-year-old woman despite a peak endometrial thickness of 4 mm. *Results:* She delivered viable dichorionic twins at 30 weeks in a pregnancy complicated by HELLP syndrome. *Conclusions:* Anecdotal case reports are important to establish precedents to allow patients to make decisions when presented with treatment options. A third precedent of a successful pregnancy with endometrial thickness of only 4 mm is presented. Without precedent she would have chosen embryo freezing and subsequent transfer into a very expensive gestational carrier if thin endometrium persisted.

Key words: Thin endometrium; Twin gestation; Donor oocyte recipients.

Introduction

In the early era of in vitro fertilization-embryo transfer (IVF-ET) lower pregnancy rates were found with thinner endometrium on the day of the injection of human chorionic gonadotropin (hCG) [1-3]. With improved embryo technology the embryos are heartier and pregnancies may occur despite thin endometrium. However, in the literature there is only one case report of a successful pregnancy following IVF-ET with a 4 mm endometrium on the day of hCG injection [4].

Sometimes if during a controlled ovarian hyperstimulation IVF-ET cycle the endometrial thickness is too thin, one has the option of freezing the embryos hoping that the endometrial thickness will increase with an artificial graduated estrogen protocol. However, if a woman is already in an estrogen replacement cycle, and the dosage has already been increased and vaginal estrogen has been added with the follicular phase extended for transfer of embryos derived from donor eggs, one cannot assure the woman that other therapeutic interventions can be made in a succeeding cycle to improve the endometrial thickness. For example though there have been claims that the addition of sildenafil can significantly improve endometrial thickness, this has not been our experience [5-7]. Similarly our data does not support the conclusion that low-dose aspirin can improve endometrial thickness [8, 9]. In fact our studies suggest that low-dose aspirin given during a similar graduated estrogen protocol for transfer of frozen-thawed embryos is associated with a significant decrease in subsequent pregnancy rates [9].

Revised manuscript accepted for publication July 29, 2010

There are IVF centers who do well when they transfer fresh embryos but have a relatively poor cryopreservation program. At the Cooper Institute for Reproductive Hormonal Disorders we developed a protocol that generally provides a pregnancy rate following frozen-thawed transfer that approximates the pregnancy rate following fresh embryo transfer in IVF-ET cycles using controlled ovarian hyperstimulation [10-12]. However, even in our IVF center we have data showing that in the absence of controlled ovarian hyperstimulation the fresh embryo has a better chance to implant than frozen-thawed embryos [13].

Case Report

A 47-year-old woman with a history of two previous spontaneous abortions and a therapeutic abortion in the past with no live children presented with secondary infertility of eight years duration. A previous hysteroscopy found a normal uterine cavity.

The woman based on her age requested to be a donor oocyte recipient. After matching with an oocyte donor she was synchronized for fresh embryo with oral contraceptives, then leuprolide acetate followed by a graduated oral estradiol regimen of 2 mg x 5 days, 4 mg x 4 days, then 6 mg x 5 days along with 2 mg per day of estradiol placed vaginally.

Despite an endometrial thickness of only 4 mm (triple line echo pattern) she elected to proceed with fresh embryo transfer rather than to freeze the embryos and try in another cycle. She transferred on day 3 two 7-cell embryos (with < 25% fragmentation in one and 26-50% fragmentation in the other) on her 4th day of progesterone support (progesterone vaginal suppositories 200 mg twice daily and 100 mg progesterone in oil IM).

The woman achieved a dichorionic diamniotic intrauterine pregnancy. In her third trimester she developed HELLP syndrome and the decision was made to deliver by cesarean section at 30 weeks. A live baby girl was born with a weight of 3

pounds and 4 ounces (1.47 kg) and a baby boy with a weight of 3 pounds 2 ounces (1.41 kg). Both babies were detained for a short time in the neonatal intensive care unit and then were discharged.

Discussion

The couple was advised that although the pregnancy rate with fresh embryos derived from donor oocytes is higher with fresh vs frozen thawed embryo transfer, the pregnancy rates are still very respectable with frozen-thawed embryo transfer [13].

On the other hand they were advised that although pregnancy rates are lower with thinner endometrium, there was a previous successful pregnancy with embryo transfer at 4 mm [4]. In fact, since controlled ovarian hyperstimulation may create a hostile uterine environment, theoretically the absence of controlled ovarian hyperstimulation and the good quality oocytes from a younger donor could make it more likely for these embryos derived from donor oocytes on an estrogen-progesterone replacement cycle to implant [14].

Furthermore, the patient was advised that we were not aware of any interventions that would necessarily improve her endometrial thickness. Thus if she deferred fresh transfer she could be faced with a similar endometrial thickness in the next cycle only then with possibly less hearty frozen thawed embryos. Also she was advised of another case where a successful conception occurred with just natural intercourse and luteal phase progesterone support occurred with only a 4 mm endometrial thickness [15].

Shallow endovascular cytotrophoblast invasion in the spiral arteries and endothelial cell dysfunction are two key features in the pathophysiology of preeclampsia and HELLP syndrome [16]. Thus the question arises as to whether the thin endometrium contributed to this problem. However the twin gestation could have been the etiologic factor as well as the use of donor oocytes [17, 18].

The two previous anecdotal cases of successful pregnancies with a 4 mm endometrial thickness helped this couple decide to try fresh embryo transfer despite a very thin endometrium. Now there are three anecdotal cases to help some other couple make decisions, e.g., to freeze embryos and hope for a better cycle or even the extreme of transferring the embryos into an extremely expensive gestational carrier. Certainly showing success with twins in a 47-year-old woman provides a strong anecdotal precedent for a woman faced with the dilemma of whether to transfer embryos or not in the face of not attaining an endometrium of sufficient thickness.

References

[1] Gonen Y., Casper R.F.: "Prediction of implantation by the sonogrpahic appearance of the endometrium during controlled ovarian stimulation for in vitro fertilization (IVF)". *J. In Vitro Fert. Embryo Transf.*, 1990, *7*, 146.

[2] Check J.H., Nowroozi K., Choe J., Dietterich C.: "Influence of endometrial thickness and echo patterns on pregnancy rates during in vitro fertilization". *Fertil. Steril.*, 1991, *56*, 1173.

[3] Dickey D.P., Olar T.T., Carole D.N., Taylor S.N., Rye P.H.: "Endometrial pattern and thickness associated with pregnancy outcome after assisted reproduction technologies". *Hum. Reprod.*, 1992, *7*, 418.

[4] Sundstrom P.: "Establishment of a successful pregnancy following in vitro fertilization with an endometrial thickness of no more than 4 mm". *Hum. Reprod.*, 1998, *13*, 550.

[5] Sher G., Fisch J.D.: "Vaginal sildenafil (Viagra): a preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF". *Hum. Reprod.*, 2000, *15*, 806.

[6] Sher G., Fisch J.D.: "Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development". *Fertil. Steril.*, 2002, *78*, 1073.

[7] Check J.H., Graziano V., Lee G., Nazari A., Choe J.K., Dietterich C.: "Neither sildenafil or vaginal estradiol improves endometrial thickness in women with thin endometria after taking oral estradiol in graduating dosages". *Clin. Exp. Obstet. Gynecol.*, 2004, *31*, 99.

[8] Wada I., Hsu C.C., Williams G., Macnamee M.C., Brinsden P.R.: "The benefits of low-dose aspirin therapy in women with impaired uterine perfusion during assisted conception". *Hum. Reprod.*, 1994, *9*, 1954.

[9] Check J.H., Dietterich C., Lurie D., Nazari A., Chuong J.: "A matched study to determine whether low-dose aspirin without heparin improves pregnancy rates following frozen embryo transfer and/or affects endometrial sonographic parameters". *J. Assist. Reprod. Genet.*, 1998,*15*, 579.

[10] Baker A.F., Check J.H., Hourani C.L.: "Survival and pregnancy rates of pronuclear stage human embryos cryopreserved and thawed using a single step addition and removal of cryoprotectants". Hum. Reprod. Update 2, (CD-ROM), 1997.

[11] Check J.H., Hoover L., Nazari A., O'Shaughnessy A., Summers D.: "The effect of assisted hatching on pregnancy rates after frozen embryo transfer". *Fertil. Steril.*, 1996, *65*, 254.

[12] Check J.H., Katsoff B., Choe J.K.: "Embryos from women who hyper-respond to controlled ovarian hyperstimulation do not have lower implantation potential as determined by results of frozen embryo transfer". In: International Proceedings of the 13th World Congress on In Vitro Fertilization and Assisted Reproduction and Genetics, Monduzzi Editore, 2005, 109.

[13] Check J.H., Choe J.K., Nazari A., Fox F., Swenson K.: "Fresh embryo transfer is more effective than frozen ET for donor oocyte recipients but not for donors". *Hum. Reprod.*, 2001, *16*, 1403.

[14] Check J.H., Choe J.K., Katsoff D., Summers-Chase D., Wilson C.: "Controlled ovarian hyperstimulation adversely affects implantation following in vitro fertilization-embryo transfer". *J. Assist. Reprod. Genet.*, 1999, *16*, 416.

[15] Check J.H., Dietterich C., Check M.L., Katz Y.: "Successful delivery despite conception with a maximal endometrial thickness of 4 mm". *Clin. Exp. Obstet. Gynecol.*, 2003, *30*, 93.

[16] Roberts J.M., Redman C.W.G.: "Preeclampsia: More than pregnancy-induced hypertension". *Lancet*, 1993, *341*, 1447.

[17] Soderstrom-Anttila V., Tiitinen A., Foudila T., Hovatta O.: "Obstetric and perinatal outcome after oocyte donation: comparison with in-vitro fertilization pregnancies". *Hum. Reprod.*, 1998, *13*, 483.

[18] Salha O., Sharma V., Dada T., Nugent D., Rutherford A.J., Tomlinson A.J. *et al.*: "The influence of donated gametes on the incidence of hypertensive disorders of pregnancy". *Hum. Reprod.*, 1999, *14*, 2268.

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