Successful pregnancies following embryo transfer despite very thin late proliferative endometrium

E. Dix, J.H. 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, NJ (USA)

Summary

Purpose: To determine if successful pregnancies are possible following fresh or frozen embryo transfer despite a maximal endometrial thickness of only ≤ 5 mm. *Methods:* A retrospective review of all fresh and frozen embryo transfers over a seven-year period was performed. The maximum thickness either on the day of human chorionic gonadotropin injection during fresh embryo transfer or the day before the initiation of progesterone in frozen embryo transfer was performed. All embryo transfers performed with a maximum endometrial thickness of 5 mm were identified and the pregnancy rates were determined. *Results:* There were 35 embryo transfers performed with a maximum endometrial thickness of < 6 mm. There were three clinical pregnancies (8.5% per transfer), two live delivered babies (5.7% pregnancy rates per transfer). One of the live births was a fresh transfer using a minimal stimulation protocol and the endometrial thickness was 5.8 mm and the other a frozen embryo transfer with a maximum thickness of 5.0 mm (1 of 7, 14.2% of frozen embryo transfers resulted in a live delivery despite thin endometria. *Conclusions:* Live delivered pregnancies are possible despite thin endometria but the pregnancy rate is poor. Possibly the pregnancy rates may be better without controlled ovarian hyperstimulation.

Key words: Endometrial thickness; Thin endometria; Fresh and frozen transfers; Pregnancy rates.

Introduction

Lower pregnancy rates (PRs) per embryo transfer have been demonstrated in women with thin endometrium in the late proliferative phase at the time of human chorionic gonadotropin (hCG) injection [1, 2]. One review of the literature concluded that there were no successful pregnancies following in vitro fertilization-embryo transfer (IVF-ET) when the pre-ovulatory endometrium was < 6 mm (3). However subsequent to this study a successful pregnancy following IVF was reported where the maximum endometrial thickness was only 4 mm [4]. A successful delivery was also reported without IVF-ET in a natural cycle with a maximum endometrial thickness in the late proliferative phase of 4 mm [5]. The objective of the present study was to determine if these two case reports are rare or if we could find any other success in our practice in cases with very thin endometria in the proliferative phase in cycles with embryo transfer. The objective was also to determine what the likelihood of success is following embryo transfer with an endometrial thickness ≤ 5 mm.

Materials and Methods

A retrospective review of all embryo transfers fresh or frozen over a 7-year time-period was carried out. Embryo transfers were identified where maximum late proliferative phase endometrium was 5 mm. Typically the policy at our IVF center is that if the endometrium is ≤ 7 mm the fresh or frozen embryo transfer is deferred. If however on a subsequent cycle the maximal therapy to improve thickness has been provided then an embryo transfer will ensue.

Typically, for frozen embryo transfers maximal therapy consisting of taking 2-4 mg estradiol vaginally plus an oral graduated regimen of oral estradiol up to 8 mg in the proliferative phase could be extended as long as two to five days; also [6], less commonly vaginal sildenafil 25 mg 4x daily was been given during the proliferative phase [7].

Endometrial thickness was measured by placing calipers on the outer walls of the endometrium. Progesterone vaginal suppositories 200 mg twice daily and IM progesterone 100 mg per day was initiated in frozen ET cycles when maximum endometrial thickness was attained. Embryo transfers were performed on the fourth day of progesterone therapy. For fresh embryo transfers progesterone vaginal suppositories 200 mg twice daily were started the day after the 10,000 U hCG injection. Three-day-old embryos were used for transfers in both fresh and frozen ET cycles.

Results

There were 35 embryo transfers performed with the late proliferative phase endometrium at a peak thickness of 5 mm. There were two clinical pregnancies (5.7% per transfer) and two live deliveries. One of the successful pregnancies occurred in a woman who had diminished egg reserve and used a minimal gonadotropin stimulation regimen and fresh embryo transfer. Her peak endometrial thickness was 5.8 mm.

Another woman had her fresh embryo transfer deferred and her first frozen ET also because of inadequate endometrial thickness using 2 mg estradiol vaginally daily from day 2 and a graduating oral estradiol regimen of 4 mg times five days, 6 mg times four days, and 8 mg

Revised manuscript accepted for publication October 6, 2008

times five days. Her peak endometrial thickness in the next cycles only reached 5 mm. Frozen ET was performed; she conceived and delivered a healthy live baby.

Another woman with low-dose gonadotropins conceived with a maximum endometrial thickness of 4 mm. She miscarried and the fetus had aneuploidy (trisomy 18).

Thus conception occurred in 2/28 (7.1%) of fresh transfers (both minimal stimulation however) and in 1/7 (14.2%) of frozen ETs.

Conclusions

These data show that pregnancies are possible following embryo transfer despite a peak endometrial thickness in the late proliferative phase of < 6 mm.

Ten of the 28 fresh transfers were with minimal stimulation. Interestingly, the two clinical pregnancies with fresh transfer both occurred with low-dose stimulation. Thus the clinical pregnancy rate was 20% with low-dose drugs. None of the 18 women with normal stimulation conceived.

There are data supporting that in some cases the controlled ovarian hyperstimulation regimen may adversely effect embryo implantation [8, 9]. Even with low-dose gonadotropins or a graduated estrogen regimen without gonadotropins the clinical pregnancy rate in this group was lower than usual (17.6%, 3/17). The possibility exists that pregnancies would be much more rare with 4-5 mm endometrial thickness in IVF cycles with conventional controlled ovarian hyperstimulation.

Obviously one option for women with thin endometria is to use a gestational carrier. These data could suggest that one option for thin endometria in the late proliferative phase for women needing IVF-ET is either to use low-dose protocols or purposely freeze the embryos for future frozen ET [10, 11].

We did not use low-dose aspirin because we have not found it helpful in improving the endometrial thickness [12].

References

[1] Gonen Y., Casper R.F., Jacobson W., Blankier J.: "Endometrial thickness and growth during ovarian stimulation: a possible predictor of implantation in in vitro fertilization". *Fertil. Steril.,* 1989, *52*, 446.

[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] Friedler S., Schenker J.G., Herman A., Lewin A.: "The role of ultrasonography in the evaluation of endometrial receptivity following assisted reproductive treatments: a critical review". *Hum. Reprod. Update,* 1996, *2,* 323.

[4] Sundsrtom 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] 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.

[6] Check J.H., Graziano V., Lee G., Nazari A., Choe J.K., Dietterich C.: "Neither sildenafil nor vaginal estradiol improves endometrial thickness in women with thin endometria after taking oral estradiol in graduating dosages". *Clin. Exp. Obstet. Gynecol.,* 2004, *31,* 99.

[7] 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.

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

[9] Check J.H., Nazari P., Check M.L., Szekeres-Bartho J., Yuan W.: "Evidence that the adverse effect of controlled ovarian hyperstimulation on successful pregnancy outcome following embryo transfer may be related to premature trophoblast invasion". *Clin. Exp. Obstet. Gynecol.,* 2002, *29*, 83.

[10] Check J.H., Choe J.K., Nazari A., Summers-Chase D.: "Ovarian hyperstimulation can reduce uterine receptivity. A case report".. *Clin. Exp. Obstet. Gynecol*., 2000, *27*, 89.

[11] Check J.H., Summers-Chase D., Yuan W., Horwath D., Wilson C.: "Effect of embryo quality on pregnancy outcome following single embryo transfer in women with a diminished egg reserve". *Fertil. Steril*., 2007, *87*, 749.

[12] 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.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com