Reproductive BioMedicine Online (2013) 27, 407–413

www.sciencedirect.com
www.rbmonline.com

ARTICLE

Risk of ectopic pregnancy following day-5 embryo transfer compared with day-3 transfer

Laura P Smith [a,b,c,d], Selwyn P Oskowitz [a,b,c], Laura E Dodge [a], Michele R Hacker [a,c,*]

[a] *Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Kirstein 3, Boston, MA 02215, USA;* [b] *Boston IVF, 130 Second Avenue, Waltham, MA 02451, USA;* [c] *Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA;* [d] *Reproductive Medicine and Surgery Center of Virginia, 595 Martha Jefferson Drive, Suite 390, Charlottesville, VA 22911, USA*
* Corresponding author. *E-mail address:* mhacker@bidmc.harvard.edu (M.R. Hacker).

Laura Smith studied medicine at the University of Virginia School of Medicine in Charlottesville, Virginia and completed her fellowship in Reproductive Endocrinology and Infertility at Beth Israel Deaconess Medical Center in Boston, Massachusetts. She currently practices reproductive endocrinology and infertility at the Reproductive Medicine and Surgery Center of Virginia and teaches obstetrics gynaecology residents at the University of Virginia Health Sciences Center. Her research interests include short-term complications of IVF, including ovarian torsion and ovarian hyperstimulation syndrome.

Abstract The incidence of ectopic pregnancy after IVF is increased approximately 2.5–5-fold compared with natural conceptions; however, the aetiology for this increased risk remains unclear. One proposed practice change to decrease the incidence of ectopic pregnancy is blastocyst embryo transfer on day 5 rather than cleavage-stage embryo transfer on day 3. A retrospective cohort study was conducted to compare the risk of ectopic pregnancy following fresh day-5 embryo transfer with day-3 embryo transfer among women who underwent IVF and achieved pregnancy from 1998 to 2011. There were 13,654 eligible pregnancies; 277 were ectopic. The incidence of ectopic pregnancy was 2.1% among day-3 pregnancies and 1.6% among day-5 pregnancies. The adjusted risk ratio for ectopic pregnancy from day-5 compared with day-3 transfer was 0.71 (95% confidence interval 0.46–1.10). Although this analysis included 13,654 cycles, with a two-sided significance level of 0.05, it had only 21.9% power to detect a difference between the low incidence of ectopic pregnancy among both day-3 and day-5 transfers. In conclusion, this study was not able to demonstrate a difference in the risk of ectopic pregnancy among day-3 compared with day-5 transfers.

KEYWORDS: blastocyst, day-3 embryo transfer, day-5 embryo transfer, ectopic

Introduction

Ectopic pregnancy continues to be a potentially life-threatening complication of IVF. It is well known that the incidence of ectopic pregnancy after IVF is increased approximately 2.5–5-fold compared with natural conceptions, although the precise aetiology for this increased risk remains unclear (Clayton et al., 2006; Revel et al., 2008; Society for Assisted Reproductive Technology, 2007). Retrograde embryo migration into the Fallopian tubes, impaired tubal function

1472-6483/$ - see front matter
http://dx.doi.org/10.1016/j.rbmo.2013.06.015

limiting tubal extrusion, alterations in uterine contractility during the window of implantation and hormonal influences on endometrial receptivity, tubal receptivity and uterine contractility have all been postulated to increase the rate of ectopic pregnancy following IVF (Fanchin et al., 1998; Jia-Rong et al., 2009; Marcus and Brinsden, 1995; Lesny et al., 1999; Paltieli et al., 2000; Schoolcraft et al., 2001). In IVF cycles, studies have shown that a history of pelvic inflammatory disease, tubal factor infertility, endometriosis and prior abdominal or pelvic surgery are related with ectopic pregnancy, but few interventions to decrease the risk of ectopic pregnancy have been suggested (Marcus and Brinsden, 1995; Clayton et al., 2006; Strandell et al., 1999).

One practice change that has been proposed to decrease the incidence of ectopic pregnancy following IVF is blastocyst embryo transfer on day 5 rather than cleavage-stage embryo transfer on day 3 (Milki and Jun, 2003). Studies of uterine contractility using high-resolution and 3-dimensional ultrasound have demonstrated that there are waves of uterine contraction propagating primarily from the fundus towards the cervix during the early follicular phase of the menstrual cycle, which then increase in frequency and switch directionality 180° to aim towards the fundus at the time of ovulation (Bulletti and de Ziegler, 2006; Fanchin and Ayoubi, 2009; Lesny et al., 1998b). In studies during IVF cycles, these retrograde uterine contractions of the early luteal phase appear to decrease in frequency and amplitude for about 6 or 7 days following human chorionic gonadotrophin (HCG) administration, with near uterine quiescence after that time (Fanchin et al., 2001; Lesny et al., 1998b). The progressive uterine quiescence is postulated to be due to the increasing serum progesterone concentrations that occur concurrently. Theoretically, due to this pattern of uterine dynamics, a day-5 embryo transfer would be expected to have a higher likelihood of in-situ uterine implantation and a lower likelihood of retrograde propulsion, with resultant ectopic implantation, than an earlier embryo transfer.

Milki and Jun (2003) investigated this hypothesis in a retrospective analysis of the incidence of ectopic pregnancy after 956 day-3 and day-5 embryo transfers at their centre from 1998 to 2003. During this period, 3.5% of clinical pregnancies following day-3 embryo transfers were ectopic compared with 3.9% following day-5 transfers, a difference that was not statistically significant. Although it was the largest study of ectopic pregnancy following day-3 and day-5 embryo transfer, there were only 35 ectopic pregnancies in this population.

This study group conducted a large, retrospective cohort study to compare the risk of ectopic pregnancy following fresh day-5 embryo transfer with fresh day-3 embryo transfer. The preliminary results were reported at the annual meeting of the American Society for Reproductive Medicine in 2009 (Smith et al., 2009).

Materials and methods

Patient characteristics

This study identified all patients who achieved pregnancy following fresh day-3 or day-5 embryo transfer at Boston IVF, Deaconess Medical Center from 1 January 1998 to 1 March 2011. Pregnancy was defined as serum βHCG >5 mIU/ml measured 14 days following vaginal oocyte retrieval. All homologous IVF and oocyte recipient cycles were included. This study excluded frozen–thawed embryo transfer cycles, gamete intra-Fallopian transfer cycles, gestational carrier cycles and cycles with embryo transfer performed on day 2, 4 or 6. Collected data included participant age, history of ectopic pregnancy, type of assisted reproduction protocol (fresh homologous or fresh oocyte recipient cycle), cycle number, number of oocytes retrieved, number of embryos transferred, day of embryo transfer (day 3 or day 5), pregnancy outcome, initial βHCG concentration, peak βHCG concentration, ultrasound results and history of tubal factor infertility, uterine factor infertility and endometriosis.

Ectopic pregnancies

Because of the need for accurate identification of ectopic pregnancies, medical records for all ectopic pregnancies were reviewed by LPS or LED to verify the diagnosis. Each ectopic pregnancy was classified into one of the following three categories based on the diagnostic criteria in **Table 1**: sonographically or surgically verified, clinically

Table 1 Diagnostic classification of ectopic pregnancies.

Classification	Description of classification criteria
Sonographically or surgically verified	(1) Definitive ultrasound visualization of an extrauterine gestational sac with or without a yolk sac or fetal pole or (2) Direct surgeon visualization at the time of operative management
Clinically verified	(3) No intrauterine gestational sac seen on transvaginal ultrasound with serum βHCG above the discriminatory zone or (4) Pathological exclusion by endometrial curettage
Clinically suspected	(5) Inappropriately rising serial serum βHCG concentrations with peak below the discriminatory zone and suspicion of ectopic pregnancy given all available data