Comparison of ectopic pregnancy risk among transfers of embryos vitrified on day 3, day 5, and day 6

Tong Du, M.S.,[a,b] Hong Chen, M.D.,[a] Rong Fu, M.S.,[c] Qiuju Chen, Ph.D.,[a] Yun Wang, M.D.,[a] Ben W. Mol, M.D., Ph.D.,[d] Yanping Kuang, M.D.,[a] and Qifeng Lyu, Ph.D.[a]

[a] Department of Assisted Reproduction, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [b] Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [c] Department of Biostatistics, Pharmaceutical Product Development, Shanghai, People's Republic of China; and [d] Robinson Research Institute, School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

Objective: To compare ectopic pregnancy risk among transfers of embryos vitrified on day 3, day 5, and day 6.
Design: Retrospective cohort study.
Setting: Academic tertiary-care medical center.
Patient(s): A total of 10,736 pregnancies after 23,730 frozen-thawed embryo transfer (FET) cycles of in vitro fertilization/intracytoplasmic sperm injection from March 2003 to May 2015.
Intervention(s): The ectopic pregnancy rate was compared among pregnancies resulting from transfers of embryos vitrified on day 3, day 5, and day 6. Generalized estimation equation regression models were used to calculate unadjusted and adjusted odds ratios and 95% confidence intervals for the association between ectopic pregnancy and selected patient and treatment characteristics. We studied this association in both the group that achieved pregnancy and the group that underwent an FET cycle.
Main Outcome Measure(s): Odds of ectopic pregnancy.
Result(s): The overall rate of ectopic pregnancy was 2.8% (304/10,736). Ectopic pregnancy rates after day-3, day-5, and day-6 vitrified embryo transfers were 3.1% (287/9,224), 2.0% (11/562), and 0.6% (6/950), respectively. After adjusting for confounders, the risks of ectopic pregnancy in day-3 and day-5 vitrified embryo transfers were both significantly higher than in day-6 vitrified embryo transfers. The associations were similar when we did calculations per cycle.
Conclusion(s): In women undergoing FET, day-6 vitrified embryo transfer is associated with a significantly lower risk of ectopic pregnancy than both day-3 and day-5 vitrified embryo transfers. (Fertil Steril® 2017;108:108–116. ©2017 by American Society for Reproductive Medicine.)
Key Words: Ectopic pregnancy, in vitro fertilization, intracytoplasmic sperm injection, frozen-thawed embryo transfer, embryo age

Ectopic pregnancy is a leading cause worldwide of maternal mortality during the first trimester of pregnancy and represents 5% and 10% of all maternal deaths in high- and low-resourced countries, respectively (1, 2). An estimated 1%–2% of all spontaneous pregnancies turn out to be ectopic, and the incidence increases to 2.1%–8.6% of pregnancies following assisted reproductive technologies (ART) (3).

Both the pathogenesis of ectopic pregnancy and the mechanism accounting for the increased risk of ectopic pregnancy following ART are not elucidated (3), and few interventions to decrease the risk of ectopic pregnancy following ART have been suggested (4). One proposal is to adopt blastocyst transfer rather than cleavage-stage embryo transfer (5). Blastocysts are reported to interact better with the endometrium than cleavage-stage embryos (6), and are routinely transferred into the uterine cavity 7 days after hCG administration, when the cervix to fundus contractions of the uterus decrease to a near-quiescent state (7). Together with a larger diameter and fewer days before implantation, theoretically, blastocyst

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Reprint requests: Qifeng Lyu, Ph.D., Department of Assisted Reproduction, Shanghai Ninth People's Hospital, Zhizaoju Road No. 639, Shanghai 200011, People's Republic of China (E-mail: lyuqifeng@126.com).

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TABLE 1

Summary of selected previous studies on the relationship between embryo stage and ectopic pregnancy risk.

Study	Region	Design	Type of ET		Embryo stage	Pregnancies, n	EP rate, %	aOR	Risk reduction stage
Ishihara et al. 2011 (9)[a]	Japan	Retrospective	Autologous	Fresh	Cleavage	4,509	2.3	NA	Blastocyst
					Blastocyst	2,713	1.6	NA	
				Frozen	Cleavage	1,324	1.8	NA	
					Blastocyst	10,312	0.8	NA	
Li et al. 2015 (11)[b]	Australia and New Zealand	Retrospective	Autologous	Fresh	Cleavage	11,511	1.9	1.30 (1.07–1.59)	Blastocyst
					Blastocyst	16,845	1.3	Reference	
				Frozen	Cleavage	6,409	1.7	NA	
					Blastocyst	9,337	0.8	NA	
Fang et al. 2015 (10)	China	Retrospective	NA	Fresh	Day 3	1,637	2.4	NA	NS
					Day 5	357	1.7	NA	
				Frozen	Day 3	259	1.9	NA	Day 5/Day 6
					Day 5	712	0.3	NA	
					Day 6	375	0.5	NA	
Santos-Ribeiro et al. 2016 (12)[c]	UK	Retrospective	Autologous	Fresh and frozen	Days 1–2	72,423	NA	Reference	Blastocyst
					Days 5–7	30,929	NA	0.73 (0.63–0.84)	
Marek et al. 1999 (13)	USA	Retrospective	Autologous	Fresh	Day 3	220	0.9	NA	NS
					Day 5	180	1.1	NA	
Milki and Jun 2003 (5)	USA	Retrospective	NA	Fresh	Day 3	615	3.5	NA	NS
					Day 5	271	3.3	NA	
Clayton et al. 2009 (16)[d]	USA	Retrospective	Autologous	Fresh	Day 3	NA	NA	Reference	NS
					Day 5	NA	NA	1.04 (0.79–1.36)	
Smith et al. 2013 (4)[e]	USA	Retrospective	Autologous and oocyte recipient	Fresh	Day 3	12,231	0.6	Reference	NS
					Day 5	1,423	0.6	0.86 (0.40–1.87)	
Wang and Sun 2014 (14)	Sweden and Belgium	Meta-Analysis	Autologous	Fresh	Cleavage	168	1.2	NA	NS
					Blastocyst	197	1.5	NA	
Cheng et al. 2015 (15)[f]	China	Retrospective	Autologous	Fresh	Day 3	574	1.2	NA	NS
					Day 5	639	1.7	NA	
Perkins et al. 2015 (17)[g]	USA	Retrospective	Autologous	Fresh	Day 3	217,891	2.0	Reference	NS
					Day 5	130,165	1.8	1.07 (0.98–1.16)	
Keegan et al. 2007 (18)	USA	Retrospective	NA	Fresh and frozen	Day 3	1,681	0.5	NA	Day 3
					Day 5	1,107	1.6	NA	
Rosman et al. 2009 (19)	USA	Retrospective	Autologous	Fresh	Day 3	1,991	0.4	NA	Day 3
					Day 5	2,195	1.3	NA	

Note: aOR = adjusted odds ratios; EP = ectopic pregnancy; ET = embryo transfer; NA = not available; NS = not significant.

[a] Data of single-embryo transfer and pregnancies of unknown outcome were excluded.

[b] Adjusted for maternal age, parity, cause of infertility, fertilization procedure, and number of embryos transferred.

[c] Adjusted for female age, infertility diagnosis, type of IVF, type of ET, number of embryos transferred, and year of treatment.

[d] Data of three or more embryos transferred and no extra embryos cryopreserved, and adjusted for age, previous spontaneous abortions, previous births, infertility diagnosis, use of assisted hatching, use of intracytoplasmic sperm injection (ICSI).

[e] Data of sonographically and surgically verified ectopic pregnancies, and adjusted for number of fertilized embryos.

[f] Data of sonographically and surgically verified ectopic pregnancies.

[g] Adjusted for age, number of previous assisted reproductive technology (ART) cycles, number of previous live births, number of previous spontaneous abortions, infertility diagnosis, year of ART procedure, use of ICSI, use of assisted hatching, number of embryos transferred, number of supernumerary embryos cryopreserved, and ovarian hyperstimulation syndrome.

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