

Safety and quality aspects of IVF - neonatal and maternal outcomes following advanced techniques

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras på Hälsovetarbacken, Hus 2, sal 2119, Arvid Wallgrens backe 5, den 8 maj, klockan 09.00

av Erica Ginström Ernstad

Fakultetsopponent:

Professor Marie Blomberg

Institutionen för klinisk och experimentell medicin

Avdelningen för barns och kvinnors hälsa

Linköpings Universitet

Avhandlingen baseras på följande delarbeten

- I. Ginström Ernstad E, Bergh C, Khatibi A, Källén K, Westlander G, Nilsson S, Wennerholm UB. Neonatal and maternal outcome after blastocyst transfer: a population-based registry study. *Am J Obstet Gynecol.* 2016 Mar;214(3):378.e1-378.e10
- II. Ginström Ernstad E, Wennerholm UB, Khatibi A, Petzold M, Bergh C. Neonatal and maternal outcome after frozen embryo transfer: Increased risks in programmed cycles. *Am J Obstet Gynecol.* 2019 Aug; 221(2):126.e1-126.e18
- III. Ginström Ernstad E, Spangmose AL, Opdahl S, Henningsen AK, Romundstad LB, Tiitinen A, Gissler M, Wennerholm UB, Pinborg A, Bergh C, Malchau SS. Perinatal and maternal outcome after vitrification of blastocysts: a Nordic study in singletons from the CoNARTaS group. *Hum Reprod.* 2019 Nov 1;34(11):2282-2289
- IV. Ginström Ernstad E, Hanson C, Wånggren K, Thurin Kjellberg A, Hulthe C, Syk Lundberg E, Petzold M, Wennerholm UB, Bergh C. Perinatal, maternal and early childhood outcome following preimplantation genetic testing: a national register-based study. *In manuscript.*

SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER



Safety and quality aspects of IVF - neonatal and maternal outcomes following advanced techniques**Erica Ginstrom Ernstad**

Avdelningen för obstetrik och gynekologi, Institutionen för kliniska vetenskaper, Sahlgrenska akademien, Göteborgs universitet, Sverige, 2020.

Abstract

Background: Singletons born following assisted reproductive technology (ART) have adverse neonatal outcome compared to singletons born following spontaneous conception (SC). Moreover, the women undergoing ART are at an increased risk of hypertensive disorders in pregnancy (HDP) and placental complications.

Aim: To study the neonatal and maternal outcomes following the introduction of advanced techniques in ART.

Material and methods: All papers were population-based register studies in Sweden with cross linkage of the national ART registers and national health data registers. In *paper III* also Danish register data were included. *Paper I* Singletons born after blastocyst transfer (n=4819), singletons born after cleavage stage transfer (n=25,747) and singletons born after SC (n=1,196,394) were included. The main outcome was birth defects. Moreover, other neonatal and maternal outcomes were assessed. *Paper II* Neonatal and maternal outcomes in different cycle regimens in frozen embryo transfer (FET) (n=6297 in natural cycles, n=1983 in stimulated cycles, n=1446 in programmed cycles) were studied. FET was also compared to fresh embryo transfer and to SC. The primary outcomes were preterm birth (PTB, <37 weeks), low birth weight (LBW, <2500 grams), HDP and postpartum hemorrhage (PPH, >1000 mL). *Paper III* Singleton pregnancies following transfer of vitrified blastocysts (n=3650) were compared to singleton pregnancies following slow-frozen cleavage stage transfer (n=8123) and fresh blastocyst transfer (n=4469). Main outcomes were PTB, LBW, macrosomia, HDP and PPH. *Paper IV* Singletons born following preimplantation genetic testing (PGT) (n=267) were compared to singletons born following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) (n=55,355) and to SC (n=26,535). Main outcomes were PTB and LBW. Moreover, maternal outcomes and early childhood outcome were assessed.

Results: *Paper I* No difference in the rate of birth defects were observed between the groups. However, there was an increased risk of placenta previa and placental abruption following blastocyst transfer compared to transfer of cleavage stage embryos and SC. *Paper II* Programmed cycles were associated with a higher risk of HDP (adjusted odds ratio [AOR] 1.6-1.8), PPH (AOR 2.6-2.9), post term birth (AOR 1.6-2.0) and macrosomia (≥ 4500 grams) (AOR 1.4-1.6) compared to other cycle regimens. The rates of PTB and LBW were similar independently of cycle regimen. *Paper III* Transfer of vitrified blastocysts was associated with a higher risk of PTB (AOR 1.3). No other differences were found. *Paper IV* For PGT singletons no differences in PTB and LBW were observed in comparison to other IVF/ICSI singletons yet higher rates compared to SC. The early childhood outcomes were reassuring but should be interpreted cautiously due to few cases and short follow-up time.

Conclusion: Blastocyst transfer is associated with a higher risk of placenta previa and placental abruption compared to cleavage stage transfer. Programmed cycles were associated with higher risks of HDP and PPH compared to other cycle regimens. The freezing technique or the embryo biopsy used for PGT do not seem to alter the neonatal and maternal outcomes.

Keywords: blastocyst transfer, frozen embryo transfer, vitrification, preimplantation genetic testing, neonatal outcome, maternal outcome