Pregnancies consequent to ART

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3rd INTERNATIONAL MEETING
"THE FUTURE OF A.R.T."

Lugano, Switzerland | 13 March 2026

TOPICS

- ART patients
- Chromosomal and genetic risk in ART
- First trimester screening tests and invasive procedures
- ART risk of adverse maternal, fetal, obstetric outcomes and the effect on the offspring health throughout life
- Informed consent and counseling
- Management of ART patients

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ART patient ?

IUI
OI
IVF
ICSI
IMSI
1 or more embryo transfer
Blastocyst transfer
Cleavage-stage embryo
Slow cryopreservation
Vitrification
Oocyte donation
Embryo-adoption
Surrogate mothers
PGT-A/PGT-M
Sperm retrivial (natural/surgical)
Sperm anomalies

Femal infertility

Maternal age
Genetic anomalies
Fallopian factor
Uterine anomalies
- Malformation
- Fibroid
- Adhenomiosis
- Scar, isthmocele

Endometrial anomalies
- Polyps
- Hyperplasia
- Hypoplasia
- Infections, Asherman

Maternal factors
- Obesity
- Endocrinal patologies
- Thrombophilia
- Immunitary diseases, Hypertension
- PCOS, POF
- Endometriosis
- Pelvic adhesions, varicocoele
- Bowel patologies/ disbiosis
- Psycological factors

Lifestyle and Environmental factors
- Smoke, alcool, drug abuse, medications
- Nutrition,

Male infertility

Varicocele
Sperm disorders
Infections
Chronic diseases (diabetes , hyperhomocysteinemia)
Lifestyle and Environmental factors
- Smoke, alcool, drug abuse, medicatis
- Exosure to toxins/radiation
- Structural and physical issues
- Hormonal imbalances (pituitary or hypothalamus gland
- Genetic conditions
- etc

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Chromosomal and genetic anomalies in ART patients

No higher prevalence of karyotipe abnormalities in ICSI vs IVF or ICSI vs SC
(adjusted for maternal age risk)

ICSI: Increased risk of imprinting disorder<1:12,000 births

- Beckwith-Wiedemann Syndrome (BWS)
- Silver-Russell Syndrome
- Angelman and Prader-Willi Syndrome

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Vermeiden et al, Fertil Steril 2013, Mussa et al. Pediatrics 2017,
Gentilini et al Clin Epigen 2018

Prof. Paolo Cavoretto, modified

First trimester screening for T 21 in ART patients

The NT measurement did not show any statistical difference between study groups (IVF and ICSI) and controls. Early anomaly scan and heart evaluation is done in expert hands at the same time with a DR of >60%

Biochemical screening gives an increased false positive rate due to

Low PAPP-A

Low PIGF for PPE screeng

Useful sign of early placental dysfunction

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Nicolaides 2004, Lee et al 2015, Tul et al 2006, etc

NIPT/ cff-DNA testing in ART

Fetal fraction is significantly lower in IVF vs SC (10.3% vs 11.9%)

Test failure rate is higher 5.2 vs 2.2%

Lee et al , Human reprod. 2018

Positive correlation of FF with PAPP-A evident in IVF/ICS pregnancies, particularly in fresh ET.

Associated with peculiar placental development: smaller placenta, placental dysfunction, lower neonatal weight

DNA fetal fraction is low both in fresh and frozen embryos vs SC but particularly low in the fresh one.

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Prof. Paolo Cavoretto, modified

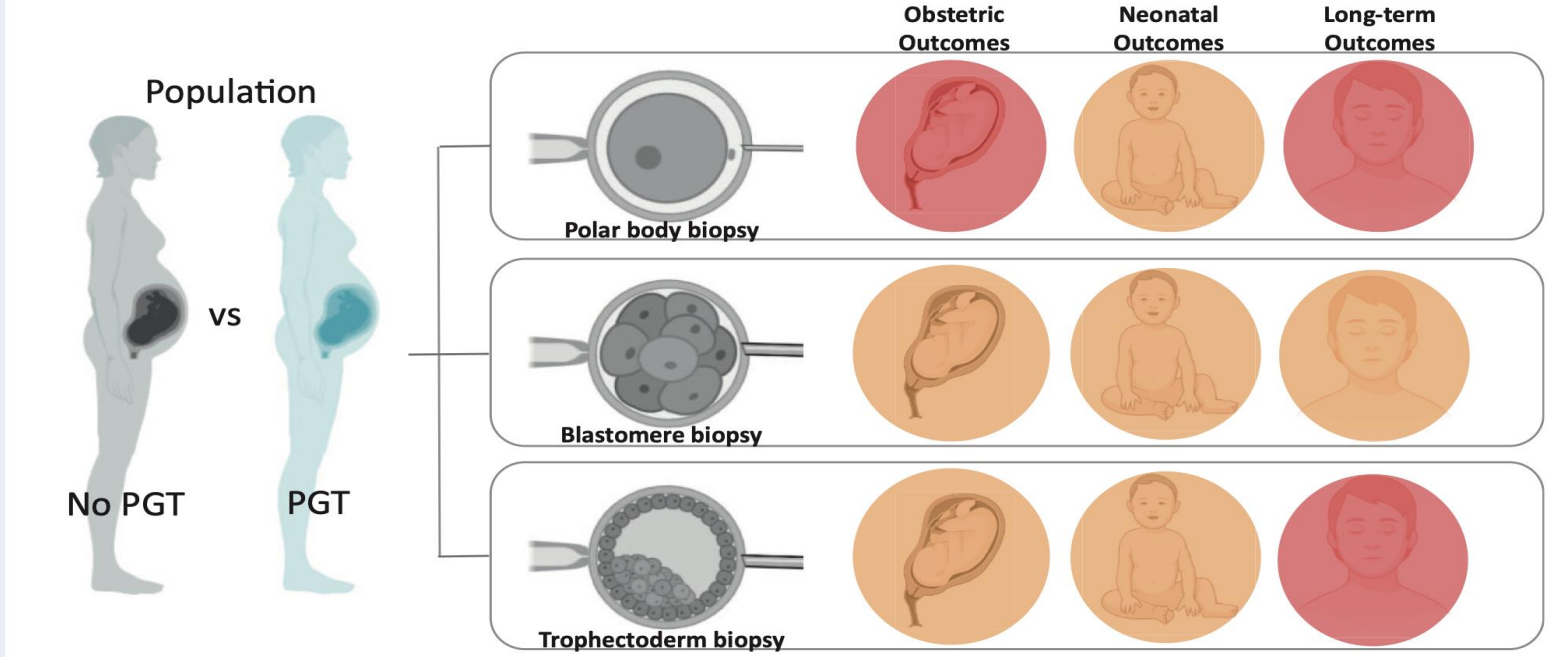
Human Reproduction Update, Vol.29, No.3, pp. 291–306, 2023
Advance Access Publication on January 19, 2023 https://doi.org/10.1093/humupd/dmad001

human reproduction update

Obstetric, neonatal, and child health outcomes following embryo biopsy for preimplantation genetic testing

Alessandra Alteri[1,2], Greta Chiara Cermisoni[1], Mirko Pozzoni[1,2], Gerarda Gaeta[1,2], Paolo Ivo Cavoretto[1,2], and Paola Viganò[3]*

GRAPHICAL ABSTRACT



No conclusive evidence for an adverse effect of PGT on outcomes. The amber symbol represents weak and/or a controversial body of safety evidence for which further research is required. The red symbol warns that no evidence of safety exists. PGT, preimplantation genetic testing.

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Does maternal age affect assisted reproduction technology success rates after euploid embryo transfer? A systematic review and meta-analysis

Amerigo Vitagliano, M.D., Ph.D.,[a] Alessio Paffoni, Ph.D.,[b] and Paola Viganò, Ph.D.[c]

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SEMINAL CONTRIBUTIONS 75 years fertility and sterility
Volume 120, Issue 2
P251-265August 2023

Conclusion and Relevance: *Increasing maternal age is associated with a decline in ART success rates independent of embryo ploidy.*

This message contributes to an appropriate patient's counseling before starting preimplantation genetic testing for aneuploidies procedures.

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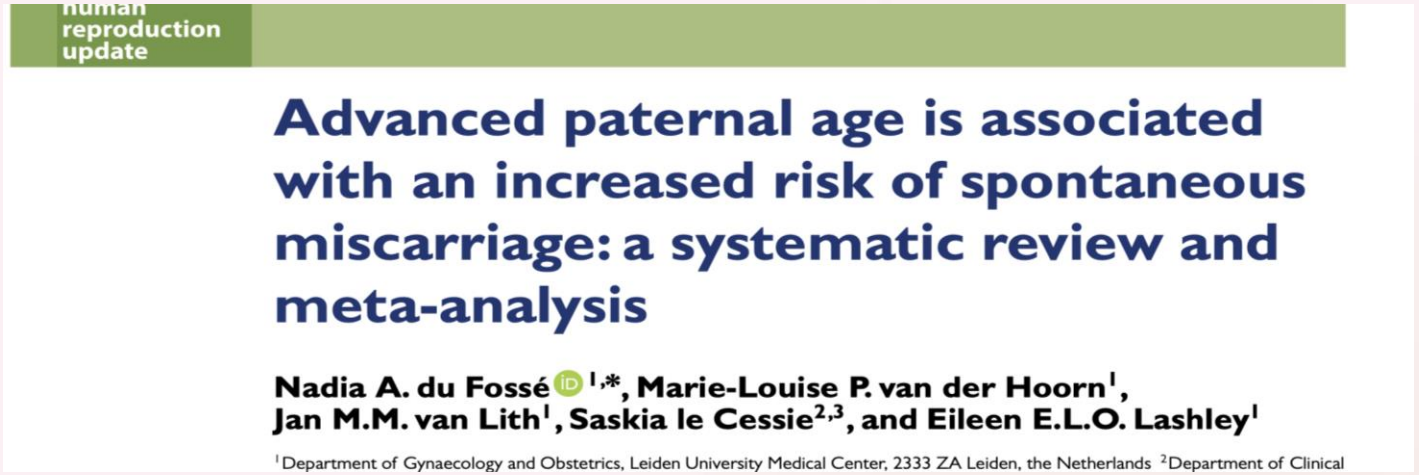

human reproduction update

Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis

Nadia A. du Fossé [1,*], Marie-Louise P. van der Hoorn[1], Jan M.M. van Lith[1], Saskia le Cessie[2,3], and Eileen E.L.O. Lashley[1]

[1]Department of Gynaecology and Obstetrics, Leiden University Medical Center, 2333 ZA Leiden, the Netherlands [2]Department of Clinical

Human Reproduction Update, Vol.26, No.5, pp. 650–669, 2020
Advance Access Publication on May 2, 2020 doi:10.1093/humupd/dmaa010

Advanced paternal age is also associated with an increased risk of spontaneous miscarriage. Although the paternal age effect is less pronounced than that observed with advanced maternal age and residual confounding by maternal age cannot be excluded, it may have implications for preconception counselling of couples comprising an older aged male.

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Congenital fetal anomalies in ART

Human Reproduction, Vol.36, No.1, pp. 116–129, 2021
Advance Access Publication on November 30, 2020 doi:10.1093/humrep/deaa272

human reproduction ORIGINAL ARTICLE *Infertility*

The risk of birth defects with conception by ART

Barbara Luke[1,*], Morton B. Brown[2], Ethan Wantman[3], Nina E. Forestieri[4], Marilyn L. Browne[5], Sarah C. Fisher[5], Mahsa M. Yazdy[6], Mary K. Ethen[7], Mark A. Canfield[7], Stephanie Watkins[8], Hazel B. Nichols[9], Leslie V. Farland[10], Sergio Oehninger[11], Kevin J. Doody[12], Michael L. Eisenberg[13], and Valerie L. Baker[14]

STUDY DESIGN, SIZE, DURATION: This was a population-based cohort study linking ART cycles reported to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) from 1 January 2004 to 31 December 2015 that resulted in live births from 1 September 2004 to 31 December 2016 in Massachusetts and North Carolina and from 1 September 2004 to 31 December 2015 for Texas and New York: these were large and ethnically diverse States, with birth defect registries utilizing the same case definitions and data collected, and with high numbers of ART births annually. A 10:1 sample of non-ART births were chosen within the same time period as the ART birth. Naturally conceived ART siblings were identified through the mother's information. Non-ART children were classified as being born to women who conceived with ovulation induction (OI)/IUI when there was an indication of infertility treatment on the birth certificate, but the woman did not link to the SART CORS; all others were classified as being naturally conceived.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study population included 135 051 ART children (78 362 singletons and 56 689 twins), 23 647 naturally conceived ART siblings (22 301 singletons and 1346 twins) and 9396 children born to women treated with OI/IUI (6597 singletons and 2799 twins) and 1 067 922 naturally conceived children (1 037 757 singletons and 30 165 twins). All study children were linked to their respective State birth defect registries to identify major defects diagnosed within the first year of life. We classified children with major defects as either chromosomal (i.e. presence of a chromosomal defect with or without any other major defect) or nonchromosomal (i.e. presence of a major defect but having no chromosomal defect), or all major defects (chromosomal and nonchromosomal). Logistic regression models were used to generate adjusted odds ratios (AORs) and 95% CI to evaluate the risk of birth defects

WIDER IMPLICATIONS OF THE FINDINGS: The use of ART is associated with increased risks of a major nonchromosomal birth defect, cardiovascular defect and any defect in singleton children, and chromosomal defects in twins; the use of ICSI further increases this risk, the most with male factor infertility. These findings support the judicious use of ICSI only when medically indicated. The relative contribution of ART treatment parameters versus the biology of the subfertile couple to this increased risk remains unclear and warrants further study.

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Fertil Steril. 2015 June ; 103(6): 1438–1445. doi:10.1016/j.fertnstert.2015.02.027.

ADVERSE PREGNANCY AND BIRTH OUTCOMES ASSOCIATED WITH UNDERLYING DIAGNOSIS WITH AND WITHOUT ART TREATMENT

Judy E Stern, PhD[1]

Results—Risk of prenatal hospital admissions was increased for endometriosis (ART 1.97, 1.38– 2.80; non-ART 3.34, 2.59–4.31), ovulation disorders (ART 2.31, 1.81–2.96; non-ART 2.56, 2.05– 3.21), tubal (ART 1.51, 1.14–2.01), and reproductive inflammation (non-ART 2.79, 2.47–3.15). Gestational diabetes was increased for women with ovulation disorders (ART 2.17, 1.72–2.73; non-ART 1.94, 1.52–2.48). Preterm delivery (AORs 1.24–1.93) and low birthweight (AORs 1.27– 1.60) were increased in all groups except endometriosis with ART.

Conclusions—The findings indicate **substantial excess perinatal morbidities associated with underlying infertility-related diagnoses in both ART-treated and non-ART-treated women.**

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Maternal co-morbidity	ART technique	Fetal issues
Endometriosis	IVF (ICSI), FET	Preterm birth, SGA, placenta previa, hypertensive disorders
Adenomyosis	IVF (ICSI), FET	Miscarriage, preterm birth, SGA, PAS, hypertensive disorders
Uterine fibroids	IVF (ICSI), FET	Miscarriage, malpresentation, preterm birth, placental abruption
PCOS	IVF (ICSI) or Ovulation induction	GDM, preeclampsia, preterm birth, LGA, SGA
Obesity	IVF (ICSI), FET	GDM, preeclampsia, anomalies, macrosomia, stillbirth
Age	Autologous IVF (ICSI), Donor oocyte	Miscarriage, preterm birth, SGA, hypertensive disorders

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Archives of Gynecology and Obstetrics (2024) 309:1323–1331
https://doi.org/10.1007/s00404-023-07002-y

MATERNAL-FETAL MEDICINE

Associations between endometriosis and adverse pregnancy and perinatal outcomes: a population-based cohort study

Amanuel T. Gebremedhin[1] · Vera R. Mitter[2,3] · Bereket Duko[1] · Gizachew A. Tessema[1] · Gavin F. Pereira[1,4,5]

Results There were 19,476 singleton livebirths among 8874 women diagnosed with endometriosis. Using a doubly robust estimator, we found pregnancies in women with endometriosis to be associated with an increased risk of preeclampsia with RR of 1.18, 95% CI 1.11–1.26, placenta previa (RR 1.59, 95% CI 1.42–1.79) and preterm birth (RR 1.45, 95% CI 1.37–1.54). The observed association persisted after stratified by the use of Medically Assisted Reproduction, with a slightly elevated risk among pregnancies conceived spontaneously.

Conclusions In this large population-based cohort, endometriosis is associated with an increased risk of preeclampsia, placenta previa, and preterm birth, independent of the use of Medically Assisted Reproduction. This may help to enhance future obstetric care among this population.

reproduction ORIGINAL ARTICLE Gynaecology

Pregnancy outcomes in women with endometriosis and/or ART use: a population-based cohort study

Ibinabo Ibiebele [1,2,*], Tanya Nippita[1,2,3], Rodney Baber[1,3], and Siranda Torvaldsen[1,2,4]

STUDY QUESTION: What is the association between endometriosis and adverse pregnancy outcomes with ART use and non-use?

SUMMARY ANSWER: Endometriosis and ART use are both associated with increased risk of preterm birth, antepartum haemorrhage, placenta praevia and planned birth (caesarean delivery or induction of labour).

WHAT IS KNOWN ALREADY: There are contradictory findings on the association between endometriosis and adverse pregnancy outcomes, and many large studies have not considered the effect of ART use.

STUDY DESIGN, SIZE, DURATION: Population-based cohort study of 578 221 eligible pregnancies during 2006–2015, comparing pregnancy outcomes across four groups (No endo/no ART, No endo/ART, Endo/no ART and Endo/ART).

PARTICIPANTS/MATERIALS, SETTING, METHODS: All female residents of New South Wales, Australia aged 15–45 years and their index singleton pregnancy of at least 20 weeks gestation or 400 g birthweight. Linked hospital, pregnancy/birth and mortality data were used. Modified Poisson regression with robust error variances was used to estimate adjusted risk ratios (aRRs) and 99% CIs, adjusting for sociodemographic and pregnancy factors.

WIDER IMPLICATIONS OF THE FINDINGS: These results suggest that women with endometriosis including those who used ART to achieve pregnancy are a higher-risk obstetric group requiring appropriate surveillance and management during their pregnancy.

LIMITATIONS, REASONS FOR CAUTION: Endometriosis is often under-diagnosed and women with a history of hospital diagnosis of endometriosis may represent those with more symptomatic or severe disease. If the effects of endometriosis on pregnancy are greater for those with more severe disease, our results may over-estimate the effect of endometriosis on adverse pregnancy outcomes at a population level. We were unable to assess the effect of endometriosis stage or typology on the study outcomes.

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Human Reproduction Update, Vol.26, No.4, pp. 514–544, 2020
Advance Access Publication on May 22, 2020 doi:10.1093/humupd/dmaa011

human reproduction update

Risk of gestational diabetes mellitus in women achieving singleton pregnancy spontaneously or after ART: a systematic review and meta-analysis

Julia K. Bosdou[1], Panagiotis Anagnostis[2], Dimitrios G. Goulis[2], Georgios T. Lainas[1], Basil C. Tarlatzis[1], Grigoris F. Grimbizis[1], and Efstratios M. Kolibianakis[1,*]

WIDER IMPLICATIONS: The present systematic review and meta-analysis, by analysing 1 893 599 women, showed a higher risk of GDM in women achieving singleton pregnancy by ART compared with those achieving singleton pregnancy spontaneously. This finding highlights the importance of early detection of GDM in women treated by ART that could lead to timely and effective interventions, prior to ART as well as during early pregnancy.

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Preterm birth in assisted reproduction: the mediating role of hypertensive disorders in pregnancy

Human Reproduction, 2025, **40(1)**, 167–177
https://doi.org/10.1093/humrep/deae261
Advance Access Publication Date: December 4, 2024

MAIN RESULTS AND THE ROLE OF CHANCE: **Pregnancies following frozen-ET had a higher risk of any preterm birth** compared to natural conception (occurrence 6.6% vs 5.0%, total effect OR 1.29, 95% CI 1.21–1.37) **and 20.7% of the association was mediated by HDP** (mediated effect OR 1.05, 95% CI 1.04–1.05). The mediation occurred primarily in medically indicated preterm births. **Pregnancies following fresh-ET also had a higher risk of any *preterm* birth** compared to naturally conceived pregnancies (occurrence 8.1% vs 5.0%, total effect OR 1.49, 95% CI: 1.45–1.53), **but none of this could be mediated by HDP** (mediated effect OR 1.00, 95%CI 1.00–1.00, proportion mediated 0.5%). Sensitivity analyses with extra confounder adjustment for body mass index and smoking, and restriction to primiparous women, were consistent with our main findings. Furthermore, the results were not driven by differences in ART procedures (intracytoplasmic sperm injection, culture duration, or the number of embryos transferred).

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Ultrasound Obstet Gynecol 2018; **51**: 43–53
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.18930

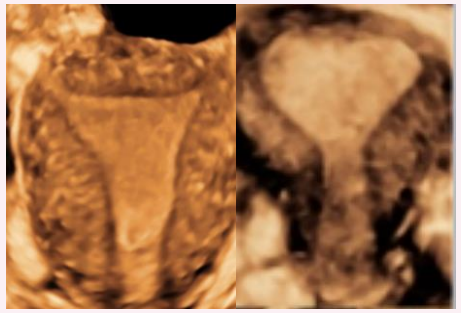
Risk of spontaneous preterm birth in singleton pregnancies conceived after IVF/ICSI treatment: meta-analysis of cohort studies

P. CAVORETTO[1], M. CANDIANI[1], V. GIORGIONE[1], A. INVERSETTI[1], M. M. ABU-SABA[1], F. TIBERIO[1], C. SIGISMONDI[1] and A. FARINA[2]

[1]*Gynecology and Obstetrics Department, IRCCS San Raffaele Hospital, Vita-Salute University, Milan, Italy;* [2]*Division of Obstetrics and Gynecology, St. Orsola-Malpighi Polyclinic, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy*

Conclusions *The risk of sPTB in singleton pregnancies resulting from IVF/ICSI is significantly greater than that in spontaneously conceived singletons. These findings should be interpreted with caution given the low quality of the available evidence.*

Congenital uterine malformation:



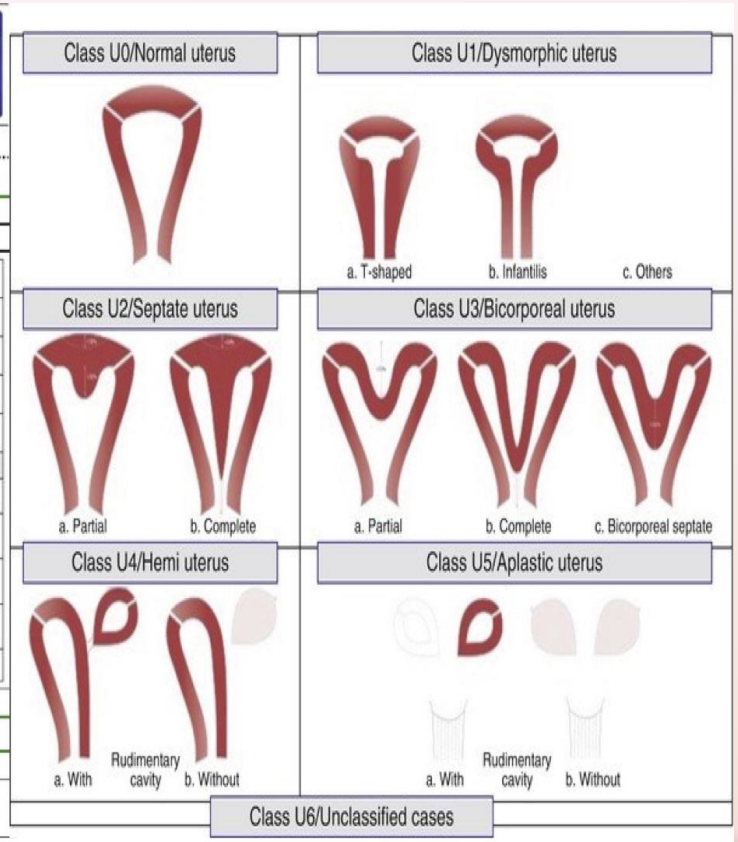
ESHRE/ESGE classification
Female genital tract anomalies

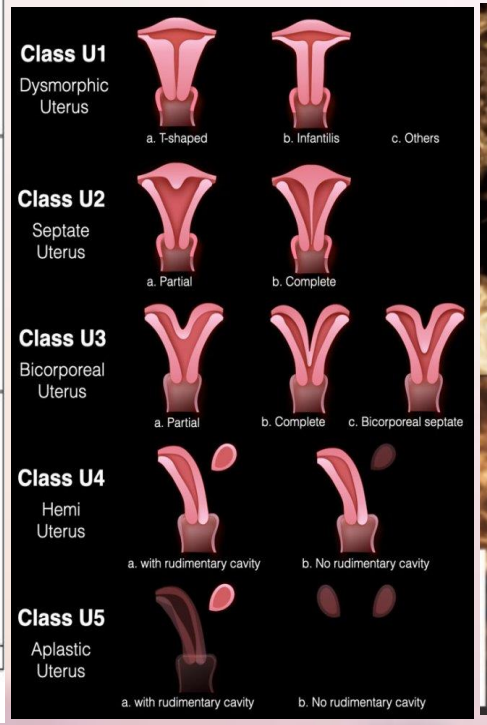
Name Birth Date:

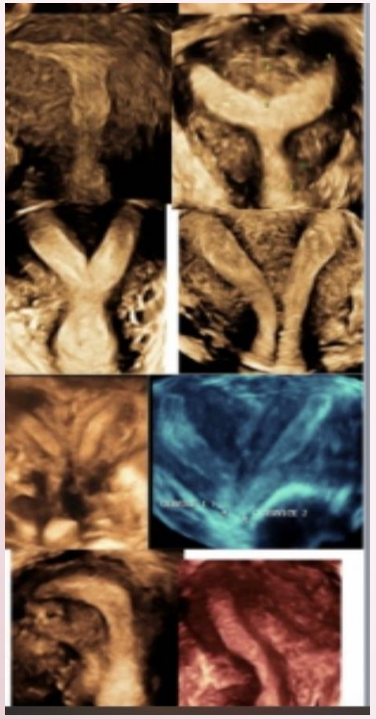
Diagnostic Method:

	Uterine anomaly		Cervical/Vaginal anomaly	
	Main class	*Sub-class*	*Co-existent class*	
U0	Normal uterus		C0	*Normal cervix*
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	C1	*Septate cervix*
U2	Septate uterus	**a.** Partial **b.** Complete	C2	*Double "normal" cervix*
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate	C3	*Unilateral cervical aplasia*
U4	Hemi-uterus	**a.** With rudimentary cavity (communicating or not horn) **b.** Without rudimentary cavity (horn without cavity/no horn)	C4	*Cervical aplasia*
U5	Aplastic	**a.** With rudimentary cavity (bi- or unilateral horn) **b.** Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	V0	*Normal vagina*
			V1	*Longitudinal non-obstructing vaginal septum*
			V2	*Longitudinal obstructing vaginal septum*
			V3	*Transverse vaginal septum and/or imperforate hymen*
			V4	*Vaginal aplasia*
U6	Unclassified malformations			
U			*C*	*V*

Associated anomalies of non-Müllerian origin:







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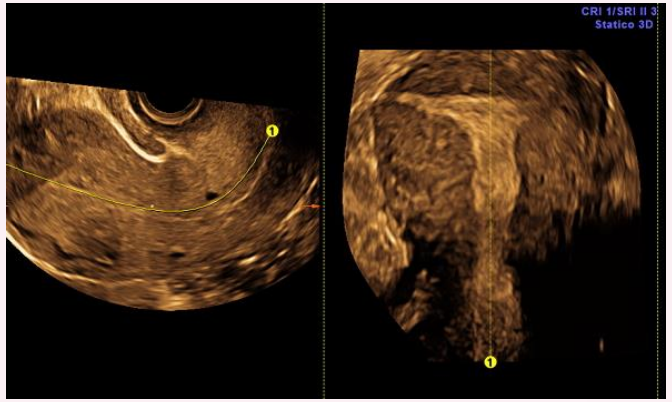

Impact on women's reproductive life and pregnancy complications:

T shaped uterus (Y, I)

	RR	IC 95%
• Infertility	0.8	0.7-1.0
• Miscarriage	1.7	1.3-2.2
• Prematurity	2.2	1.6-3.1
• malpresentation	4.8	
• IUGR	1.9	
• Mortality	2.4	

Gabbai D et al . Pregnancy outcomes among patients with recurrent pregnancy loss and uterine malformations J. Perinat. Med 2017

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Risk of pre-eclampsia in oocyte donation and natural conception

Table II. Estimated prevalence of pre-eclampsia (PE) and severe pre-eclampsia according to mode of conception, maternal age and plurality. Values are expressed as percentage (95% confidence interval).

Outcome	Age group	Pregnancy type	Oocyte Donation (OD)	Natural Conception (NC)	IVF
PE	All ages	Singleton	10.7 (6.6–15.5)	2.0 (1.0–3.1)	4.1 (2.7–5.6)
		Multiple	27.8 (23.6–32.2)	7.5 (7.2–7.8)	9.7 (6.2–13.9)
PE	Age >40 years	Singleton	17.4 (13.3–22.0)	1.3 (0.2–2.9)	1.3 (0.2–2.9)
		Multiple	17.9 (13.5–23.1)	3.6 (3.5–3.7)	3.6 (3.5–3.7)
PE (overall)	—	—	15.7 (11.3–20.6)	3.1 (2.1–4.2)	5.3 (4.0–6.8)
Severe PE	All ages	Singleton	4.0 (2.3–6.2)	0.5 (0.4–0.6)	1.0 (0.3–1.9)
		Multiple	8.5 (6.9–10.2)	0.5 (0.3–0.7)	4.7 (4.2–5.2)
Severe PE	Age >40 years	Singleton	8.8 (4.0–14.3)	1.4 (0.0–7.4)	2.9 (0.4–10.2)
		Multiple	NA	NA	NA
Severe PE (overall)	—	—	5.7 (3.3–8.6)	0.5 (0.4–0.6)	1.5 (0.3–3.2)

Keukens et al, Hum Reprod 2022

Suspected immunological mechanisms :

The embryo contains no maternal genetic material and is therefore completely allogeneic to the mother. This can trigger a stronger maternal immune response against the placenta

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RISK OF CERVICAL INCOMPETENCE

increase in :

- PCOS frozen embryo transfer +
- BMI
- low AMH
- Frequency of hysteroscopy operations
- Congenital uterine defects
- Prior pregnancies

- Fresh embryo transfer, elevated androstenedione levels

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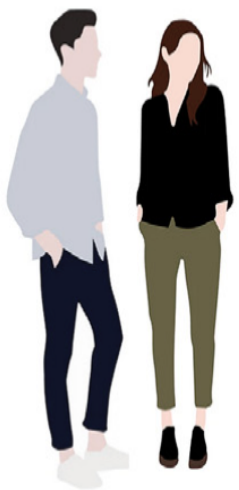
Zhao X, Ye S, Yan X, Li R and Wang Y (2025) Risk factors of cervical insufficiency in women with PCOS undergoing IVF-ET treatment: a case-control study. *Front. Endocrinol.* 16:1498443. doi: 10.3389/fendo.2025.1498443

Pregnancy complications	ART Method	References
Deleterious effects:		
Placental abruption	IVF, ICSI	(Isaksson, 2002; Katalinic, 2004; Luke, 2017; Vermey, 2019; Cochrane, 2020; Petersen, 2020)
Placenta previa	IVF, ICSI	(Isaksson, 2002; Katalinic, 2004; Luke, 2017; Vermey, 2019; Cochrane, 2020; Petersen, 2020)
Preterm rupture of membranes	IVF, ICSI	(Katalinic, 2004; Pandey, 2012)
Ante/postpartum hemorrhages	IVF, ICSI	(Pandey, 2012, Luke, 2017)
Poly/oligohydramnios	ICSI	(Katalinic, 2004)
Caesarean sections	IVF, ICSI	(Chaveeva, 2011; Pandey, 2012, Luke, 2017)
Preterm deliveries	IVF, ICSI	(Pandey, 2012; Ombelet, 2016; Luke, 2017; Hwang, 2018; Chang, 2020; Cochrane, 2020)
Preeclampsia/hypertension	IVF, ICSI	(Katalinic, 2004, Chaveeva, 2011; Pandey, 2012; Almasi-Hashiani, 2019; Petersen,2020)
Gestational diabetes mellitus	IVF, ICSI	(Chaveeva, 2011; Pandey, 2012; reviewed in Mohammadi, 2020)
Early abortion	IVF, ICSI, IUI, OI ,FET	(Brandes, 2011)
Neutral effects:		
No risk of LBW, perinatal morbidity/mortality or rate of malformations	IVF	(Vasario, 2010)
No risk of obstetric complications	IVF, ICSI, IUI, OI	(Elfituri, 2021)
Placenta outcomes		
Deleterious effects:		
Morphological changes, increased weight, efficiency & thickness	IVF, ICSI	(Daniel, 1999; Haavaldsen, 2012; Eskild, 2013)
Abnormal umbilical cord insertion	IVF, ICSI	(Daniel, 1999; Yanaihara, 2018; Cochrane, 2020)
Epigenetic changes, methylation/gene expression of imprinted genes	IVF, ICSI	(Katari, 2009; Menezo, 2010; Turan, 2010; Vermeiden, 2013; Nelissen, 2013, 2014; Choux, 2015, 2018, Sakian, 2015; Dong, 2019; Chi, 2020)
Altered expression of transmembrane transporters	IVF	(Zhang, 2010)
Neutral effects:		
Normal weight	IVF, ICSI	(Yanaihara, 2018; Dong, 2019)
Perinatal outcomes		
Deleterious effects:		
Reduced birth weight & SGA	IVF, ICSI	(Isaksson, 2002; Katalinic, 2004; Sakka, 2010; Chaveeva, 2011; Pandey, 2012; Ombelet, 2016; Luke, 2017; Hwang, 2018; Chang, 2020; Cochrane, 2020; Magnus, 2021)
Congenital anomalies	IVF, ICSI	(Hansen, 2012; Pandey, 2012; Donzelli, 2015; Hwang, 2018; Valenzuela-Alcaraz, 2019; Chang, 2020)
Infectious diseases	ART	(Hwang, 2018)
Increased perinatal mortality	IVF, ICSI	(Isaksson, 2002, Pandey, 2012; Ombelet, 2016; Hwang, 2018)
Cardiovascular changes	IVF, ICSI	(Valenzuela-Alcaraz, 2013, 2018; Guo, 2017; Hwang, 2018; Chang, 2020)
Dilated atria, cardiac and vascular remodeling	IVF, ICSI	(Valenzuela-Alcaraz, 2013, 2018)
Neutral effects:		
No risk of birth defects	IVF, ICSI	(Davies, 2012; Levi Setti, 2016)
Normal birth weight	IVF, ICSI	(Levi Setti, 2016)
No increase in perinatal mortality	IVF, ICSI	(Chaveeva, 2011)
Normal perinatal outcomes	IVF, ICSI, IUI, OI	(Elfituri, 2021)
Positive effects:		
Reduced risk of SGA	IVF, ICSI, IUI	(Glatthorn, 2021)

FIGURE 1 | The effect of the use of ART on pregnancy complications, placental and fetal adaptations, and perinatal health outcomes. Legend: SGA: Small for [illegible]nal Age. FET: Frozen Embryo Transfer. IUI: Intra-Uterine Insemination, OI: Ovulation Induction with Clomiphene citrate.

Childhood	ART Method	References
Cardiovascular & Metabolic health		
Deleterious effects:		
Elevated blood pressure & triglyceride levels	IVF, ICSI	(Ceelen, 2008a; Sakka, 2010; Pontesilli, 2015; Guo, 2017; Valenzuela-Alcaraz, 2019; Cui, 2020; Zandstra, 2020)
Elevated glucose	IVF, ICSI	(Ceelen, 2008a; Pontesilli, 2015; Cui, 2020)
Vascular dysfunction	IVF, ICSI	(Scherrer, 2012; Guo, 2017; Cui, 2020; Zandstra, 2020)
Altered growth patterns	IVF, ICSI	(Ceelen, 2008a; Green, 2013; Magnus, 2021; Roseboom and Eriksson, 2021; Magnus, 2021)
Elevated body fat	ICSI	(Belva, 2007; reviewed in Hart and Norman, 2013)
Elevated peripheral fat and skinfolds	IVF	(Ceelen, 2007)
Congenital malformations	ICSI	(Belva, 2007)
Neutral effects:		
Normal blood pressure	ART	(Scherrer, 2012)
Normal BMI, lipid profile, GTT & ITT	IVF, ART	(Sakka, 2010; Scherrer, 2012)
Favorable lipid profile and normal fat mass	IVF	(Miles, 2007)
Neurodevelopmental health		
Deleterious effects:		
Developmental delay and risk of cerebral palsy	IVF	(Strömberg, 2002)
High risk of autism	ART	(Fountain, 2015; reviewed in Liu, 2017)
Neutral effects:		
No risk of ADHD	IVF, ICSI	(Farhi, 2021a, 2021b)
Normal school performance	IVF, ICSI	(Wagenaar, 2008; Punamäki, 2016; Norrman, 2018; Luke, 2020)
Normal cognitive function and verbal skills	IVF, ICSI	(Belva, 2007; Carson, 2010; Punamäki, 2016; Farhi, 2021a)
Normal psychomotor development	IVF, ICSI	(Belva, 2007; Nekkebroeck, 2008; Carson, 2010; Sánchez-Soler, 2020)
No mental retardation or autistic disorders	IVF, ICSI	(Sandin, 2013; Lung, 2018; Jenabi, 2020; Farhi, 2021b)
Positive effects:		
Reduced risk of autism	ART	(Maimburg and Vaeth, 2007)
Lower odds of adverse neurodevelopmental (cognitive and language) outcomes	IVF, ICSI, ET, IUI	(Roychoudhury, 2021)
Adolescence		
Deleterious effects:		
High blood pressure	IVF	(Ceelen, 2008a)
High fasting glucose	IVF	(Ceelen, 2008a)
Higher LH and DHEAs in girls	IVF	(Ceelen, 2008b)
Higher bone age/chronological age in girls	IVF	(Ceelen, 2008b)
Elevated body fat in girls	ICSI	(Belva, 2012a)
Neutral effects:		
Healthy bone mineral composition/high peripheral fat	IVF	(Ceelen, 2007)
Normal height, weight and BMI	IVF, ICSI , other	(Magnus, 2021)
Healthy blood pressure	ICSI	(Belva, 2007, 2012b)
Normal metabolic outcomes	ICSI	(Belva, 2019)
Normal gonadal function/pubertal development	IVF, ICSI	(Belva, 2007, 2019; Ceelen, 2008b)



Young Adults

Deleterious effects:		
Lower glucose sensitivity after acute overfeeding	IVF	(Chen, 2014)
Increased systolic BP after acute overfeeding	IVF	(Chen, 2014)
Low HDL in men	ICSI	(Belva, 2018)
Low sperm count, abnormal exocrine function	ICSI	(Belva, 2019)
Neutral effects:		
Normal gonadal function	ICSI	(Belva, 2019)
Normal basal metabolic health	IVF, ICSI	(Chen, 2014; Halliday, 2014; Belva, 2018; Juonala, 2020)
Normal cholesterol/triglycerides/insulin & BP	IVF, ICSI	(Chen, 2014; Belva, 2018; Juonala, 2020)
Positive effects:		
Lower chance of psychiatric diagnosis	IVF, ICSI, IUI, **OI** , FET	(Rissanen, 2020)

FIGURE 2 | The effect of the use of ART on childhood, adolescent and adult health outcomes. Legend: LH: Luteinizing Hormone; DHEAS: Dehydroepiandrosterone sulfate; HDL: High-density lipoprotein; ADHD: Attention-deficit/hyperactivity disorder; BP: Blood pressure; BMI: Body Mass Index, GTT: Glucose Tolerance Test, ITT: Insulin Tolerance Test, ET: Embryo Transfer.

SCHROEDER et al (2022) ***The Consequences*** *of Assisted Reproduction Technologies on the Offspring Health Throughout Life****: A Placental Contribution****.* Front. Cell Dev. Biol. 10:906240. doi: 10.3389/fcell.2022.906240

Placenta exame: Beyond morphological changes, abnormalities in gene expression could reflect alterations in placental function in ART.

A combination of genetics, epigenetics, and the current environments in addition to the ART procedure are all involved in disease causation (Hochberg et al., 2011).
The long-term effects remain to be seen once the first- generation of ART offspring reaches an older age (i.e. > 65), a time-point where fetal programming effects may still emerge.

Though it is difficult to establish the mechanisms underlying the changes observed among ART newborns and children, it is plausible that the placenta could play a key role in the process.

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Based on the currently available literature, ART offspring until around 40 years of age do not appear to be at greater risk of developing persistent life-long health complications.

INVITED REVIEW

Assisted reproductive technology: Short- and long-term outcomes

Mary Elaine Graham[1] | Angie Jelin[2,3] | Alexander H. Hoon Jr[4,5] | Anna Maria Wilms Floet[4,6,7] | Eric Levey[8] | Ernest M. Graham[3,9]

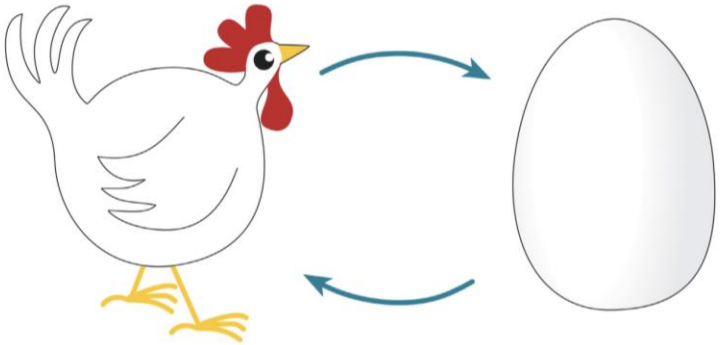
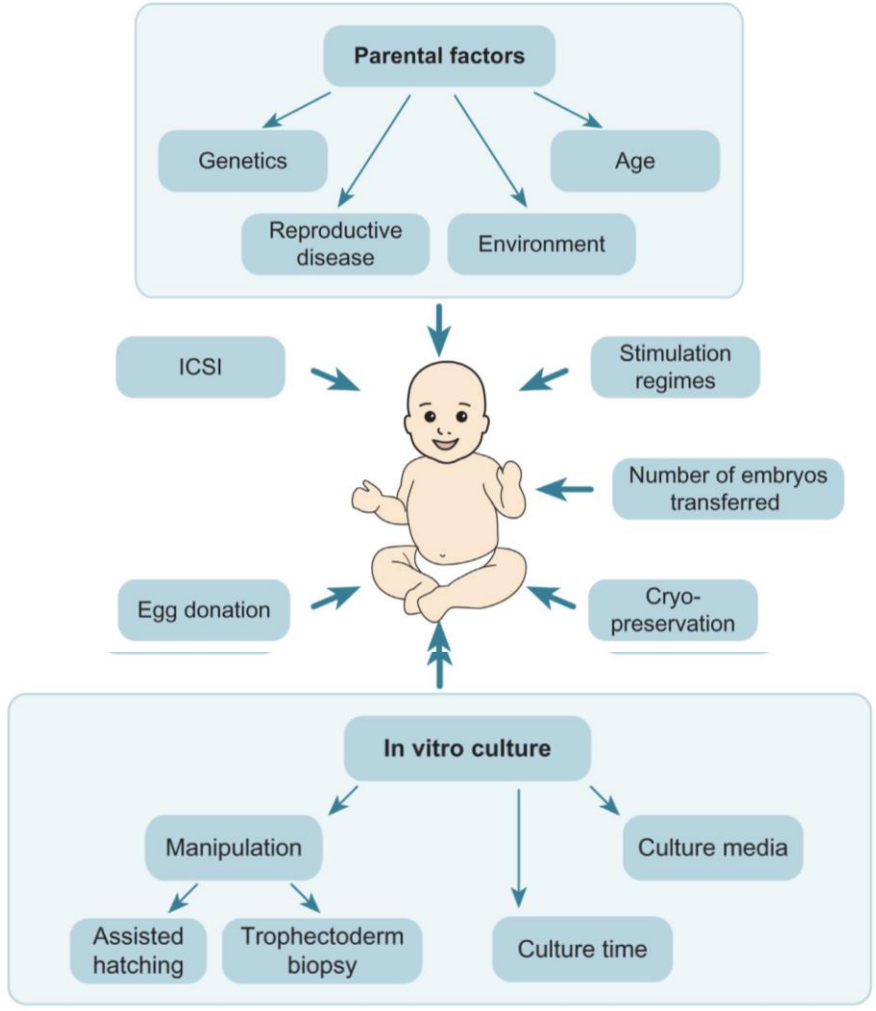


FIGURE 3 A wide range of factors can adversely affect the offspring born after assisted reproductive technology. It is difficult to definitely determine the relationship between assisted reproductive technology and outcome. Reproduced with permission from Berntsen et al.[7]



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INVITED REVIEW

Assisted reproductive technology: Short- and long-term outcomes

Mary Elaine Graham[1] | Angie Jelin[2,3] | Alexander H. Hoon Jr[4,5] | Anna Maria Wilms Floet[4,6,7] | Eric Levey[8] | Ernest M. Graham[3,9]

In general, ART has the potential to have a life-changing impact for people who are otherwise unable to conceive; however, ***parents should be counseled on the risks and benefits****.*

Although the primary risks are more strongly associated with multiple births, ***even in singleton pregnancies there is an increase risk for specific birth defects, imprinting disorders, preterm birth, low birthweight, small for gestational age, stillbirth, and perinatal mortality.***

Neurodevelopmental outcomes are overall reassuring*, with risks disappearing when adjustments are made for* ***multiple births****. Furthermore, when* ***risks persist****, it is often* ***for specific subgroups*** *such as* **IVF compared with ICSI or with fresh embryo transfer compared with cryopreservation.**

The **most well-established risk for a neurodevelopmental disorder is the implantation of more than one embryo**, with the mechanism linked to an increased risk of brain injury in association with preterm birth.

PhD, Dr Med Luisa Di Luzio

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Fertil Steril. 2022 June ; 117(6): 1223–1234. doi:10.1016/j.fertnstert.2022.02.009.

Assisted reproductive technology (ART) treatment increases obstetric and neonatal risk over that of the underlying infertility diagnosis

Judy E. Stern, et al

Capsule:

Obstetric and neonatal risk are increased by different infertility-related diagnoses compared to a fertile group. Some complications, particularly **placental problems, are further increased by ART treatment**.

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ProCrea

Ultrasound diagnosis of placental and umbilical cord anomalies in singleton pregnancies resulting from in-vitro fertilization

L Larcher [1],et al , Placenta 2022

IVF pregnancies in general and those resulting from donor oocyte in particular are at higher risk of placental and umbilical cord abnormalities compared to spontaneous pregnancies. These anomalies can be diagnosed accurately at the mid-trimester detailed fetal anomaly scan and our findings support the need for a targeted ultrasound screening of these anomalies in IVF pregnancies.

Assisted reproductive technologies (ART) and placental abnormalities

Elizabeth Cochrane [1], Et al10.1515/jpm-2020-0141

ART is associated with increased rate of placental abnormalities, including abnormal umbilical cord insertion and increased rates of adherent placentation. This information may be beneficial in planning and surveillance in patients with ART pregnancies.

PhD, Dr Med Luisa Di Luzio

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BJOG 2019 Jan;126(2):209-218.

doi: 10.1111/1471-0528.15227. Epub 2018 May 8.

Are singleton pregnancies after assisted reproduction technology (ART) associated with a higher risk of placental anomalies compared with non-ART singleton pregnancies? A systematic review and meta-analysis.

B G Vermey[4] et al

Risk of placenta praevia, placental abruption and morbidly adherent placenta was higher in ART than SC pregnancies: odds ratio (OR) (OR 3.76, 95% CI 3.09-4.59); (OR 1.87, 95% CI 1.70-2.06) and (OR 2.27, 95% CI 1.79-2.87) respectively.

Conclusions: Singleton ART pregnancies are associated with an increased risk of placental anomalies compared with non-ART singleton pregnancies.

Tweetable abstract: ***A review of over 6 million singleton pregnancies finds increased risk of placental anomalies after ART.***

PhD, Dr Med Luisa Di Luzio

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Velamentous cord insertion

J Assist Reprod Genet (2018) 35:431–434
https://doi.org/10.1007/s10815-017-1084-2

ASSISTED REPRODUCTION TECHNOLOGIES

Difference in the size of the placenta and umbilical cord between women with natural pregnancy and those with IVF pregnancy

Atsushi Yanaihara[1] · Shota Hatakeyama[1] · Shirei Ohgi[1] · Kenichirou Motomura[1] · Ryoma Taniguchi[1] · Aguri Hirano[1] · Shin Takenaka[1] · Takumi Yanaihara[1]

In velamentous umbilical cord insertion, the placental end of the cord consists of divergent umbilical vessels surrounded only by fetal membranes, with no Wharton's jelly. Thus, it is assumed to increase the risk of severe complications, including fetal death, and it is seen in 3–5% of all deliveries. In our study, even in the normal pregnancy group, the rate of velamentous umbilical cord insertion was higher (9.9%) than that previously reported, but the reason is unclear. However, there have been many reports on increases in placental and cord abnormalities in IVF pregnancies [14–17], and our results are in line with these results (20.3%).

There was no difference in the placental weight and umbilical cord size; however, the rate of velamentous insertion of the cord increased significantly with IVF pregnancy. Further studies and improvement in IVF techniques may be necessary to decrease the incidence of the velamentous insertion of the cord.

PhD, Dr Med Luisa Di Luzio

Next Fertility ProCrea

EP15.11. Ultrasound first trimester screening for anomalous umbilical cord insertion (UCI): is it time to consider it?

Luisa Di Luzio[1], Elena Maria Masi[3], Luca Mandia[1], Claudio Castagna[4], Mario Giuseppe Meroni[4], Enrico Ferrazzi[2]
1.Ostetricia e Ginecologia, ASST Fatebenefratelli Sacco, Milano, Italy; 2. Università di Milano Ospedale Vittore Buzzi, Milano, Italy.
3. Università Degli Studi di Milano, Milano, Italy. 4.Ostetricia e Ginecologia, Ospedale Niguarda Ca' Granda, Milano, Italy.

Introduction: The evaluation of umbilical cord insertion (UCI) on the placental site is not required in routine ultrasound screening during pregnancy, if the placenta is normally inserted .
Yet, it is well known that velamentous UCI is associated with adverse obstetrical and fetal outcome and requires an appropriate management.

Objectives: The aim of this study was to analyze the feasibility, the time impact and the accuracy of evaluation of the UCI on the placental site, during the nuchal translucency (NT) screening test. The second aim was to evaluate the prevalence of anomalous UCI (velamentous or marginal) in our population.

Methods: We performed a multicenter prospective study. We recruited 316 consecutive women with singleton pregnancies during the NT screening (11+3 -13+5 weeks). UCI was assessed by trans-abdominal or trans-vaginal 2D ultrasound and Power Doppler. UCI was classified into central/para-central, marginal and velamentous according to existing classification. The study was performed in 3 different referral centers, by 6 operators (2 senor and 4 junior) certified by Fetal Medicine Foundation (FMF) for NT. We than re-examined all recruited patients at 19-21 weeks to confirm the site of UCI.

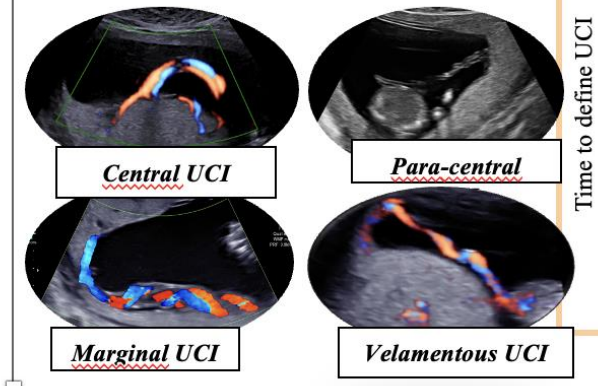

Figure 1. Umbilical cord insertion

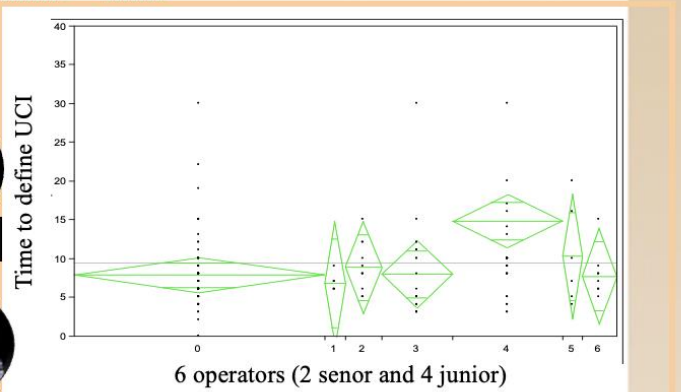

Figure 2. Time to define UCI by operator

Results: The visualization of UCI on the placenta was possible in 315 out of the 316 case recruited. The average time to define the cord insertion was 9.5 sec(±1,5). The range was 3 sec to 30 sec. There were no significant differences between senior and junior operators. In our study we found 298 central/para-central insertions (94.6 %), 13 marginal insertions (4.13 %), 3 velamentous cord insertions (0,95 %). All 16 anomalous cord insertions were confirmed at the second trimester scan..

Conclusion

We have shown that the ultrasound evaluation of UCI on the placental site at 11-13 weeks of pregnancy is a feasible, accurate, and rapid examination. Our data confirm that in a general population the prevalence of anomalous UCI is low. Yet, It is well known that velamentous UCI is associated with adverse obstetrical and fetal outcome and requires an appropriate management. The limited effort required to screen cases at risk, versus the obstetrical events that might originate from such condition, induce us to the inclusion of the evaluation of UCI on the placental site during the first trimester NT scan.

PhD, Dr Med Luisa Di Luzio

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ISUOG ROME 2016

Ultrasound Obstet Gynecol 2018; **51**: 33–42
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.18932

Congenital heart defects in IVF/ICSI pregnancy: systematic review and meta-analysis

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Conclusion *Fetuses conceived with IVF/ICSI methods are at an increased risk of developing CHD compared with those conceived spontaneously. However, this finding deserves further investigation due to heterogeneity of both ART procedures and cardiac defects.*

PhD, Dr Med Luisa Di Luzio

Next Fertility ProCrea

ESC European Society of Cardiology
European Heart Journal (2024) 45, 4840–4858
https://doi.org/10.1093/eurheartj/ehae572

CLINICAL RESEARCH
Congenital heart disease

Congenital heart defects in children born after assisted reproductive technology: a CoNARTaS study

Nona Sargisian[1], Max Petzold [2], Eva Furenäs [3], Mika Gissler [4,5,6], Anne Lærke Spangmose[7], Sara Malchau Lauesgaard[1], Signe Opdahl [8], Anja Pinborg [7], Anna-Karina A. Henningsen [7], Kjersti Westvik-Johari [8,9], Kristiina Rönö [10], Christina Bergh [1†], and Ulla-Britt Wennerholm [1*†]

Methods All 7 747 637 liveborn children in Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015), and Sweden (1987–2015), where 171 735 children were conceived after ART, were included. National ART and medical birth registry data were cross-linked with data from other health and population registries. Outcomes were major CHDs, severe CHDs, 6 hierarchical CHD lesion groups, and 10 selected major CHDs, diagnosed prenatally or up to 1 year of age (Denmark, Finland, and Sweden) and prenatally or at birth (Norway). The association between ART and CHDs was assessed with multivariable logistic regression analysis, with adjustment for available confounders.

Results Major CHDs were detected in 3159 children born after ART (1.84%) and in 86 824 children born after SC [1.15%; adjusted odds ratio (AOR) 1.36; 95% confidence interval (CI) 1.31–1.41]. Risk was highest in multiples, regardless of conception method. Severe CHDs were detected in 594 children born after ART (0.35%) and in 19 375 children born after SC (0.26%; AOR 1.30; 95% CI 1.20–1.42). Risk was similar between ICSI and IVF and between frozen and fresh embryo transfer.

Conclusions Assisted reproductive technology–conceived children have a higher prevalence of major CHDs, being rare, but severe conditions. The absolute risks are, however, modest and partly associated with multiple pregnancies, more prevalent in ART.

PhD, Dr Med Luisa Di Luzio

Next Fertility ProCrea

ISUOG ROME 2016

OP33.07 . Anomalous umbilical cord placental insertion. A possible marker for fetal cardiac defect?

Luisa Di Luzio[1], Elena Maria Masi[4], Luca Mandia[1], Gabriele Vignati[3], Stefano Marianeschi[6], Paola Francesca Corbella[5], Enrico Ferrazzi[2]

1.ASST Fatebenefratelli Sacco, Milano, Italy; 2. Università di Milano Ospedale Vittore Buzzi, Milano, Italy; 3. Cardiologia Pediatrica, Ospedale Niguarda Ca' Granda , Milano, Italy. 4. Università Degli Studi di Milano, Milano, Lombardia, Italy; 5. Ostetricia e Ginecologia, Ospedale Niguarda Ca' Granda, Milano, Lombardia, Italy.6. Cardiochirurgia Pediatrica, Ospedale Niguarda Ca' Granda, Milano, Lombardia, Italy.

Objectives

The aim of the study was to evaluate the umbilical cord insertion (UCI) on the placental site, in a prospective cohort of fetuses affected by congenital heart defects (CHD) and in a non selected population.

Methods

The study was performed by feto-maternal specialists and pediatric cardiologists. We recruited 110 women, at 19-22 weeks' gestation, carrying singleton pregnancies with fetuses affected by CHD and 183 women, referred for routine midtrimester scan, as control group. All patients underwent fetal echocardiography and evaluation of UCI, classified into central/para-central (cp.UCI), marginal (m.UCI) and velamentous (v.UCI), according to existing classification. UCI was confirmed at delivery.

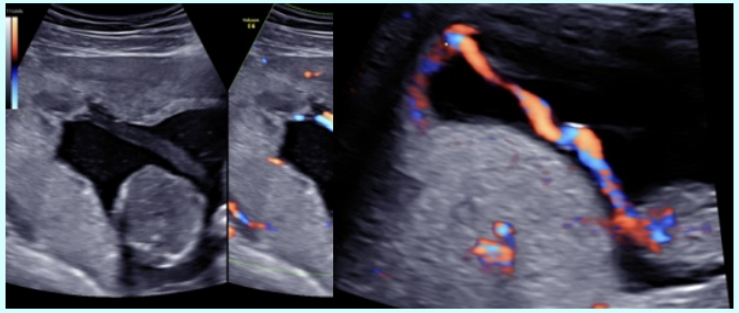
Results

The visualization of UCI was possible in all patients. In the control study group we found 9 m.UCI (4.9 %) and 3 v.UCI (1.6 %), with a total of 12 anomalous cases (6.5%). In the 110 fetuses affected by CHD, we found 22 anomalous UCI (20%, p=0.0005), 15 m.UCI (13.6 %) and 7 v.UCI (6,3 %). In the subgroup of 37 fetuses affected by conotruncal CHD, we found anomalous UCI in 16 (43.3 % p=0,0002) divided in 10 m.UCI (27%) and 6 v.UCI (16.2 %). Univariate analysis showed that anomalous UCI is associated with CHD (OR 3.9; IC95% 1.9-8.4; p<.001) and, more significantly, with cono-truncal CHD (OR 11.0; IC95% 4.9-24.9; p<.001).

Conclusion

We have shown that the prevalence of anomalous UCI is significantly higher in fetuses affected by CHD, than in a general population. It is well known that prenatal detection of CHD could improve neonatal outcome and nowadays, regardless the effort, the sensitivity of prenatal screening for CHD remains low. Ultrasound evaluation of UCI on the placental site is feasible, accurate, and fast, both in first and second trimester scans. If proved on larger cohorts, anomalous UCI could well become a screening tool for targeting fetuses at higher risk of CHD, in particular for conotruncal anomalies.

Figure 1: Marginal cord insertion
Figure 2 : Velamentous cord insertion



	Group Routine N°(%)	Group CHD N°(%)	P value	Group CHD cono truncal	P value
Anomalous cord insertion:	12 (6,5)	22 (20)	0.0005	16 (43,3)	0,0002
marginal	9 (4,9)	15 (13,6)		10 (27)	
velamentous	3 (1,6)	7 (6,3)		6 (16,2)	
Total	183	110		37	

	present	absent	OR	IC 95%	P value	AOR	IC 95%	P value
Anomalous cord insertion	34	256						
CHD	22	88	3,6	1,7-7,7	0,0009	3,53	1,7- 7,7	0,02
Anomalous cord insertion	34	256						
CHD cono truncal	16	21	10,1	4,5-22,8	<0,0001	10,32	4,6-23,7	<0,0001

Figure 3-4. Results

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CONCLUSIONS

- IVF is overall safe, but no risk free
- Absolute risks remain low despite relative increases
- Most excess risk is reduced by achieving singleton pregnancies Only SET (single embryo transfer)
- Identify individuals at risk and manage
- MATERNAL AGE LIMIT?
- Womens' co-morbidities and oocyte donation are of special concern

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Next Fertility
ProCrea

Review > Dev Med Child Neurol. 2025 Apr;67(4):443-449. doi: 10.1111/dmcn.16189.
Epub 2024 Nov 17.

Informed consent in assisted reproductive technology: Implications for pediatric clinicians

Mary E Graham [1], Shannon Blee [2], Rebecca D Pentz [3], Emily Roebuck [1], Alexander H Hoon Jr [4] [5], Mara Black [6]

Principles of clinical ethics.

Ethical	Definition
Autonomy	All persons who have capacity have intrinsic and unconditional worth, and, therefore, should have the power to make rational decisions and moral choices, and each should be allowed to exercise their capacity for self-determination.
Justice	The fair, equitable, and appropriate treatment of persons.
Beneficence	The obligation of a physician to act for the benefit of the patient, including avoiding and preventing harm and promoting patient welfare.
Nonmaleficence	The obligation of a physician not to harm the patient. This includes the rules to not kill, cause pain or suffering, incapacitate, cause offense, and not deprive others of the goods of life.

Additional ethical principles.

Ethical	Definition
Informed consent	The patient must be competent to understand and decide, receives a full disclosure, comprehends the disclosure, acts voluntarily, and consents to the proposed action.
Truth telling	A patient has the right to know their diagnosis and prognosis, but also has the option to forgo this disclosure.
Confidentiality	Physicians are obliged not to disclose confidential information given by a patient to another party without the patient's authorization.
Shared decision-making	When making a medical decision, the physician should share the best available evidence, the physician and patient discuss the options, and the patient makes the decision based on their values and preferences.[43] If the patient requests, the physician can also make a recommendation based on the best medical evidence, for the patient to consider in making a decision.

Preconceptional counseling

*This counseling can take many forms, including genetic and psychological counseling .**Genetic counseling** can help patients understand the testing process and how to navigate results in ways that align with their values. **Psychological counseling** can help patients navigate the stressful landscape and can be a valuable adjunct to the informed consent process*

*One important caution is that **counseling is a valuable addition to the process of informed consent, not a substitute for it.***

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3rd INTERNATIONAL MEETING
"THE FUTURE OF A.R.T."

Lugano, Switzerland | 13 March 2026

TAKE HOME MESSAGES

- ART are a reality and there is an increasing request in the world from infertile couples
- IVF is overall safe, but no risk free. The resulting pregnancies are associated, for several reasons, to increased fetal, maternal and obstetric risks.
- **ART patients deserve a multidisciplinary approach including a trained MFM specialist.**
- The anamnestic history of the couple and the ART procedures mast be clearly recorded, to guide the MFM specialist to an adequate management.
- **Maternal morbidity request a multidisciplinary team (including psicological support).**
- Prenatal screening of chromosomal anomalies includes NT screening and early anomaly and heart scan
- NIPT must be performed at the right time
- Direct invasive procedures are restricted to selected cases (es: in a mosaic aneuploid blastocyst an extended amnio and UPD-test for uniparental disomy is advisable)

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TAKE HOME MESSAGES
Risk and **management**

- Fetal malformations and fetal heart anomalies – **referral anomaly scan with heart scan starting at 12 weeks**
- Placental anomalies (accretio placentae, placenta previa)
- Placental dysfunction (fresh>frozen)/confined placental mosaicism)
- Fetal Growth impairement (FGR, SGA) or LGA fetus
- Umbilical cord anomalies (velamentous cord insertion, vasa previa)
- Increased risk of preeclampsia

Serial Growth assessments, including placental Doppler, fetoplacental Doppler, fetal Doppler (CPR), and monitoring of «fetal heart adaptation», in expert hands.

- Increased risk of premature birth (spontaneus versus iatrogenic): **cervical measurement.** (PE screening , UtD and EFW as indicators of increased risk)
- Intrapartum risks : **Choosing timing and mode of delivery (EFW, CPR, UCR)**

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Next Fertility ProCrea

3rd INTERNATIONAL MEETING
"THE FUTURE OF A.R.T."

Lugano, Switzerland | 13 March 2026

TAKE HOME MESSAGE

Obstetric and neonatal outcomes in patients undergoing ART also depend on adequate pregnancy management secondary to a PRECISION MEDICINE APPROACH.

We can't avoid every problem, but we have to try to manage it in the best possible way.

…thank you

PhD, Dr Med Luisa Di Luzio

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