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# **Fetal management in ART pregnancy**

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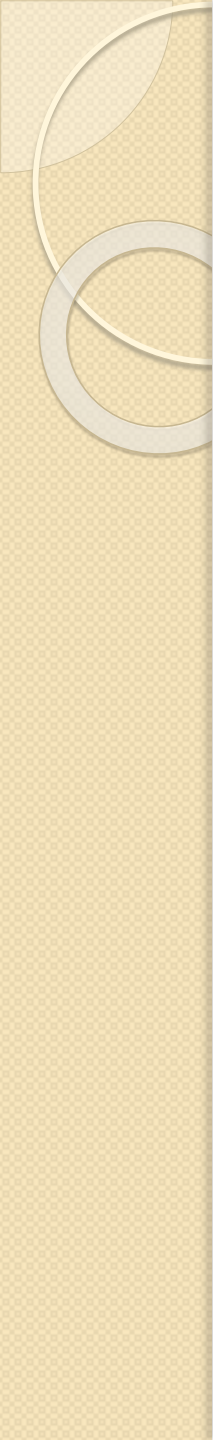
Fellowship


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- To date, more than **8 million** children have been conceived after **ART** globally
- up to **6%** of the European birth cohorts is conceived by **ART**
- **ART** involves :
  - standard in vitro fertilization (**IVF**)
  - Intracytoplasmic sperm injection (**ICSI**)
  - either fresh embryo transfer (**ET**) or
  - frozen embryo transfer (**FET**)

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- **While most births after ART are uncomplicated, ART is associated with potential adverse obstetric outcomes for both **mothers** and **infants**, including:**
    - **hypertensive disorders**
    - **preterm delivery,**
    - **low birth weight (5,6).**
    - **Increased risk of birthdefects (7,8)**
  - **Many of these adverse outcomes can be attributed to a higher rate of multiple pregnancies after ART (2,9)**

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- ART is associated with an up to **twofold** increased risk of preterm birth and LBW in singleton pregnancies.

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- most data also show that :
  - **ART singletons** have a more compromised perinatal outcome compared to singletons born after spontaneous conception, e.g.  
higher rates of:
    - **preterm birth**
    - **low birth weight**

# It could be related to

- **the ART procedure**
  - (drugs, manipulation of gametes and embryos, culture, effect of ovarian stimulation on endometrial receptivity)
- **Treatment biases in studies of IVF**  
pregnancies, as these pregnancies can be associated with excessive parental anxiety ("**premium pregnancy**")
- **Subfertility**
  - appears to have an adverse effect on pregnancy outcome, independent of its treatment.

# Higher Order Multiples

- **sixfold** increase in chance of preterm birth
- **fivefold** increased risk of stillbirth
- **sevenfold** increased risk of perinatal death
- **Preterm delivery, increases risk of**
- **intra ventricular hemorrhage,**
- **Periventricular leukomalacia**
- **cerebral palsy**





**It is important to monitor the  
safety of ART and the health of  
ART offspring**

# IVF versus ICSI

- **In summary, children born after ICSI have a better perinatal outcome compared with standard IVF**
- **A possible explanation for the better outcome may be that in ICSI the majority of the women are reproductively healthy, which could give a more favourable perinatal outcome.**

# Transfer of blastocysts versus transfer of cleavage stage embryos

- In summary, blastocyst transfer compared with cleavage transfer is associated with a **small increased risk** of adverse perinatal outcomes, particularly **preterm birth**
- a higher rate of MZT
- an altered sex-ratio have been observed after blastocyst transfer
- a higher male-to-female ratio

# Fresh versus frozen/thawed embryo transfer

- higher risks of **pre-eclampsia** after eFET (RR 1.79, 95% CI 1.03–3.09)
- mean birth weight, preterm birth, or birth defects were the same

# **Perinatal outcomes after natural conception versus in vitro fertilization (IVF) in gestational surrogates: a model to evaluate IVF treatment versus maternal effects**

- Irene Woo, M.D.,<sup>a</sup> Rita Hindoyan, M.D.,<sup>a</sup> Melanie Landay, M.D.,<sup>a</sup> Jacqueline Ho, M.D.,<sup>a</sup> Sue Ann Ingles, Ph.D.,<sup>b</sup> Lynda K. McGinnis, Ph.D.,<sup>a</sup> Richard J. Paulson, M.D.,<sup>a</sup> and Karine Chung, M.D., M.S.C.E.<sup>a</sup>**

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# Conclusion(s):

**Neonates born from commissioned embryos and carried by gestational surrogates have increased adverse perinatal outcomes, including**

- **preterm birth,**
- **low birth weight**
- **Hypertension**
- **maternal gestational diabetes**
- **placenta previa**
- **compared with singletons conceived spontaneously and carried by the same woman.**
  
- **Our data suggest that assisted reproductive procedures may potentially affect embryo quality and that its negative impact can not be overcome even with a proven healthy uterine environment.**
  
- **(Fertil Steril 2017;108:993–8. 2017 by American Society for Reproductive Medicine.)**

# Oocyte donation (OD)


- **65% of the recipients were 40 years or older**
- **In a recent SR including 23 studies, rates of:**
  - **hypertensive disorders in pregnancy**
  - **preterm birth**
  - **very preterm birth**
  - **low birth weight**
  - **very low birthweight**
  - **were increased after OD compared with IVF/ICSI with autologous oocytes**



**also in young women, aged <35 years, the use of donated oocytes A higher rate of preterm birth and low birth weight (47)**

- **no difference in the rate of preterm birth and low birth weight when adjusted for pre-eclampsia (46)**
- **The fact that the foetus is allogenic to the mother's immunological mechanisms may explain the higher risk of pre-eclampsia in OD pregnancies.**
- **There was a lower prevalence of pre-eclampsia in OD pregnancies when the donor was related to the recipient (48).**



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- Since **OD** pregnancies have nearly **three times the risk of pre-eclampsia** in comparison to spontaneous pregnancies
  - **OD pregnancies should be considered as high-risk pregnancies**
  - **single embryo transfer** is highly recommended
  - In summary, **OD** may constitute an independent risk factor for a more adverse perinatal and maternal outcome than pregnancies after **ART** with autologous oocytes.

# Birth defects

- **ART versus general population**

A Nordic cohort study from the CoNARTaS comparing ART singletons (n¼62,379) with singletons born after spontaneous conception (n¼362,215) observed :

**an increased risk for major birth defects (3.4% versus 2.9%)**

in different organ systems:

central nervous system; eye; ear, face, and neck; heart; gastrointestinal system; urinary system; and the musculo-skeletal system,

**congenital heart defects being the most common defects 1.0% versus 0.7%**

# Birth defects

- **IVF versus ICSI**
- **increase in the risk of birth defects in ICSI compared with standard IVF**
- (RR 1.12, 95% CI 0.97–1.28; and RR 1.05, 95% CI 0.91–1.20, respectively)
- **Australian study of 6163 ART children (singletons and multiples) found that**
- **IVF was associated with a reduced risk of any birth defect as compared with ICSI**
- (aOR 0.68, 95% CI 0.53–0.87)
- **The risk was reduced for fresh cycles but not for frozen cycles.**
- **An overall higher rate of urogenital defects**
- **in ICSI versus IVF was found in a SR by Massaro et al. (58).**

# **Birth defects**

- **ICSI with ejaculated versus non-ejaculated sperm**
- **Birth defects were not significantly associated with sperm origin or the cause of male factor infertility.**

# Birth defects

- **Fresh versus frozen/thawed embryo transfer**
- **no difference in the risk of birth defects between FET and fresh cycles**

# Birth defects

- **Transfer of blastocysts versus transfer of cleavage stage embryos**
- Earlier studies have claimed that blastocyst transfer is associated with an increased risk of birth defects compared with cleavage stage (32,66)
- Two recent reviews and one cohort study:
- **no increased risk compared with cleavage stage transfer, irrespective of whether any cryopreservation procedure had been used**

# Birth defects


- **Chromosomal anomalies**


In summary, based on few studies, ICSI may be related to a **modestly increased risk of chromosomal abnormalities associated with sperm parameters**

# Epigenetic Effects of Assisted Reproductive Technology in Human Offspring

- **Wei Chen** 1,2,3,4,†, **Yong Peng** 1,2,3,4,†, **Xinyi Ma** 1,2,3,4,†, **Siming Kong** 1,2,3,4, **Shuangyan Tang** 1, **Yuan 3 Wei** 1, **Yangyu Zhao** 1, **Wenxin Zhang** 1, **Yang Wang** 1,2,3,\* , **Liyang Yan** 1,2,3,\* , **Jie Qiao** 1,2,3,4,5,\*



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- **We discovered that :**
  - **IVF-ET** seemed to introduce less disturbance into the infant epigenome than **IVF- FET** or **ICSI-ET** did
  - **approximately half of the DNA methylomic changes in ART-conceived offspring could be explained by parental background biases.**

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- **ART *per se* would introduce minor DNA methylation changes locally**
  - **ART-induced epigenomic alterations were highly enriched in the processes which might contribute to increased incidence of preeclampsia during pregnancy and metabolic syndrome in offspring**
  - **an epigenetic basis for the potential long-term health risks in ART-conceived offspring**

- **Neurodevelopmental issues**
- (psychomotor, cognitive, behavioral, and socio-emotional development, as well as mental disorders (eg, mental retardation, autism, attention deficit/hyperactivity disorder))
- some data suggest **a small increased risk**
- the bulk of available evidence suggests that the neurodevelopmental outcomes of **singleton children** conceived after medically assisted reproduction **are similar to those of children conceived naturally**

# Imprinting disorders

- Genomic imprinting is a process by which genes from only one parental allele are expressed.
- **There are nine known imprinting syndromes**
- Given the rarity of these disorders, it is difficult to determine whether they may be related to some aspect of the ART procedure or subfertility itself or a combination of factors [84]
- **Beckwith-Wiedemann syndrome (BWS)** was significantly associated with IVF/ICSI, **Silver-Russell syndrome** was probably associated with IVF/ICSI,

# Cancer

- the risk of cancer in offspring has been **debated**
- overall absolute risk may be **slightly higher** than that of the general population
- Association does not establish causality

- **A 2019 retrospective Danish cohort study of over one million children**
- **similar numbers** of overall cancer cases for children (17.6 versus 17.5 per 100,000 children-years)
- **fresh** embryo IVF and ICSI **did not** have an increased risk of cancer
- children born following **FET**, the childhood cancer risk was **more than double** that of children born to fertile women (44.4 per 100,000 children-years)



**2.9 percent** of all cases of  
childhood cancer could be  
attributed to medically assisted  
reproduction

# Morbidity and mortality

- Stillbirth and perinatal mortality rates increased as much as **fourfold**
- In the United States
  - stillbirth rate after IVF is **0.6 percent**
- Denmark
  - in low-risk ART pregnancies stillbirth rates of **0.1 percent following IVF** and **0.3 percent after ICSI**




# Trends and correlates of the sex distribution among U.S. assisted reproductive technology births

(Fertil Steril 2019;112: 305–14. 2019 by American Society for Reproductive Medicine.)

- Jennifer L. Narvaez, M.D.,<sup>a,b</sup> Jeani Chang, Ph.D., M.P.H.,<sup>c</sup> Sheree L. Boulet, Dr.P.H., M.P.H.,<sup>a,c</sup> Michael J. Davies, Ph.D., M.P.H.,<sup>d</sup> and Dmitry M. Kissin, M.D., M.P.H.<sup>a,c</sup>
- <sup>a</sup> Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia; <sup>b</sup> Department of Obstetrics and Gynecology, Women and Infants Hospital, The Warren Alpert Medical School of Brown University, Providence, Rhode Island; <sup>c</sup> Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; and <sup>d</sup> University of Adelaide, Adelaide, Australia

# Conclusion(s):

- **The proportion of male live-born infants among ART population did not change during 2006–14, ranging from 50.5% to 51.2%**
- **Factors such as blastocyst transfer, intracytoplasmic sperm injection use, embryo stage, and number of embryos transferred may be associated with infant sex; further investigation is needed to understand possible underlying causes.**



# **MATERNAL AND NEONATAL OUTCOMES IN WOMEN OF ADVANCED MATERNAL AGE (AMA) UNDERGOING TWO IN VITRO FERTILIZATION (IVF) SINGLETON PREGNANCIES, AS COMPARED TO ONE IVF TWIN PREGNANCY. S.**


- **Amrane,<sup>a</sup> P. Ghosh,<sup>a</sup> D. E. Reichman,<sup>b</sup> Z. Rosenwaks,<sup>b</sup> S. E. Gelber.<sup>a</sup> <sup>a</sup>Obstetrics and Gynecology, New York Presbyterian-Weill Cornell Medicine, New York, NY; <sup>b</sup>Center for Reproductive Medicine and Infertility, Weill Cornell Medical College, New York, NY**

# CONCLUSIONS:

- In women of AMA,
- undergoing **two subsequent IVF singleton** pregnancies is less morbid than undergoing **one IVF twin pregnancy**
- However, severe morbidity and neonatal mortality were relatively rare in the twin group
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# **ACOG RECOMENDATION**

- **Couples should be informed that pregnancies conceived by ART are associated with **increased risks****
- **Every effort should be made to achieve a singleton gestation**
- **Encourage & expand use of single-embryo transfer**

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- **Before ART should complete a medical evaluation to ensure that patient are in **good health****

## Comments

- **avoiding multiple pregnancies, is the main contributor to the better outcome**
- **implementing SET as the main strategy**
- **ICSI should mainly be reserved for its original intended use, male-factor infertility**


# Comments


- as there seems to be increased risks for **hypertensive disorders** of pregnancy, **macrosomia**, and **LGA** babies after FET Therefore,
- **FET should be used in specific cases** such as high risk of ovarian hyperstimulation syndrome  
Fertility preservation, or in the context of randomised trials.



# Comments

- **Concerning management during pregnancy:**
- **closer surveillance**
- **prophylactic treatment for preeclampsia with low-dose aspirin may be indicated in high risk pregnancies such as pregnancies after OD**
- **preterm birth screening with transvaginal ultrasound measurements of cervical length in the second trimester**
- **Subsequent treatment with progesterone if the cervix is short**

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- **Continuous supervision after ART is needed**
  - **National ART registries**
  - **follow-up studies of ART children**

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- **American Institute of Ultrasound in Medicine and American Heart Association recommendation for fetal echocardiogram in ART-conceived pregnancies**

# Non-invasive prenatal testing in the context of IVF and PGT-A

Author links open overlay panel [Dana Kimelman MD, MS, RSM \(Gynecologist\)<sup>ab</sup>](#) [Mary Ellen Pavone MD MSCI \(Associate Professor,](#)

- [Best Practice & Research Clinical Obstetrics & Gynaecology](#)
- Available online 15 July 2020

# Highlights

Preimplantation genetic testing for aneuploidy (PGT-A) is not able to diagnose or rule out chromosome abnormality.




PGT-A should not be used to definitively predict chromosomal status of a fetus conceived by in vitro fertilization (IVF).



For this reason, **first trimester diagnostic testing should still be considered.**



Women achieving pregnancies from IVF-PGT may be reluctant to undergo invasive but diagnostic fetal testing.


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- In pregnancies conceived after mosaic embryo transfer, invasive diagnostic testing is highly recommended, with **amniocentesis strongly preferred** over chorionic villus sampling.

# Does a freeze-all policy lead to better IVF outcomes in first autologous cycles?

**Katherine C. Bishop a,↑, Kelly S. Acharya a, Benjamin S. Harris a, Chaitanya R. Acharya b, Douglas Raburn a, Suheil J. Muasher a**

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**Middle East Fertility Society Journal**  
**Available online 13 July 2018**

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- **In conclusion:**
  - **a freeze-all policy appears to lead to improved IVF outcomes in patients who are **high responders**, but not in patients who are low or intermediate responders**



