

# Review. Carmen Turnaturi Sotelo.

## Genetics Degree 2013-2014, Universitat Autònoma de Barcelona.

### INTRODUCTION

Assisted reproduction technology (ART) has been an important therapy method and a basic technique in many infertile couples to achieve a pregnancy by artificial or partially artificial means. Types of ART include in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), among others.

Since the first child conceived by IVF was born in 1978, there has been a consistent growth in the use of ART and more than 5 million babies worldwide have been born via these technologies. For this reason, the safety of ART has gained increasing attention. All these artificial procedures may harm the mother as well as the embryo.

#### OBJECTIVE

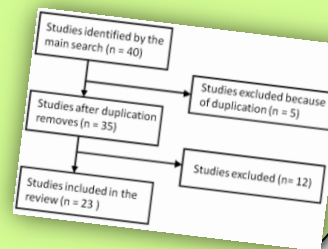
Worldwide, there are many publications on the topic of ART safety. This review tries to summarize the current evidence about whether both the mother and ART-conceived children are at an increased risk of health problems compared with natural conceptions.

### METHODS

This review was performed by literature search in different electronic databases, looking for scientific studies and reviews using the search strategy depended on various combinations of keywords and considering some criteria for the eligibility of the articles.

- **DATABASES:** Pubmed and WoK.
- **KEY WORDS:** "Assisted reproduction technology, ART, infertility treatments, in vitro fecundation, IVF, ICSI" AND "risk".
- **CRITERIA:** articles from 2008 to 2014.

Resources available on the databases such as the access to related articles were also used, as well as the manual search of references cited in the published studies.



### RESULTS

#### RISKS ASSOCIATED WITH THE MOTHER

##### RISKS DERIVED FROM OVARIAN STIMULATION

• **OVARIAN HYPERSTIMULATION SYNDROME:** is the most serious consequence of induction of ovulation, and it may occur after stimulation of the ovaries into superovulation with hCG. It results in the enlargement of the ovaries and the development of vascular hyperpermeability with the resulting shift of fluids into the third space.

• **GYNECOLOGICAL CANCER:** no study has been able to answer the question about an increased risk due to ART, and further studies are needed.

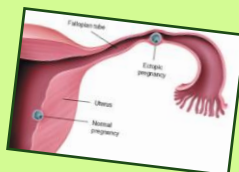


##### RISKS DERIVED FROM FOLLICULAR ASPIRATION

Ultrasound-guided transvaginal follicle aspiration is the standard technique for oocyte retrieval prior to IVF or ICSI. It can cause various potentially serious complications such as **HAEMORRHAGE, PELVIC INFECTION** and **INJURY OF PELVIC STRUCTURES**.

##### RISKS FROM PREGNANCY

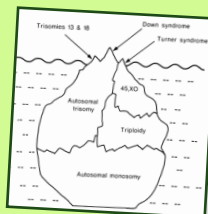
• **ECTOPIC PREGNANCY:** condition in which the fertilized egg is implanted outside the uterus. The possible risk factors are the reproductive characteristics of infertile women such as distorted tubal function and the technical issues of the embryo transfer procedure.



• **MULTIPLE PREGNANCY:** the most frequent complication of ART, which may result in a higher risk of perinatal mortality, lower birth weight, and premature delivery of ART-conceived children. Single embryo transfer has been advocated as the best strategy to prevent this complication.

• **PRETERM PREGNANCY:** giving birth to a baby of less than 37 weeks gestational age, before the developing organs of the baby are mature enough to allow normal postnatal survival. Therefore, premature infants are at greater risk for short and long term complications. Its incidence after IVF-ICSI is twice that in natural conceptions.

• **SPONTANEOUS MISCARRIAGE:** spontaneous loss of a fetus before the 20th week of pregnancy. Chromosomal abnormalities in embryos are the most important cause.



#### RISKS ASSOCIATED WITH THE CHILD

Embryo risks  
2 origins:

transmission of abnormalities  
their parents are carriers of  
ART technical procedure

##### GENETIC ANOMALIES

• **CHROMOSOMAL ABNORMALITIES** are the main cause of recurrent miscarriage, but some forms can result in live births. They can be inherited from infertile parents (especially in ICSI, which allows fertilization by abnormal sperm) or *de novo*.

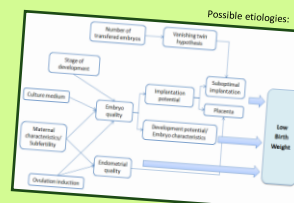


##### ADVERSE PERINATAL OUTCOMES

- **PERINATAL DEATH**
- **LOW BIRTH WEIGHT**
- **PREMATURE DELIVERY**
- **PRENATAL MOBILITY**



The main reason is multiple pregnancy. Other ones are all those factors related with the embryo quality and the endometrial quality, as well as the infertility itself.



##### CONGENITAL ANOMALIES / BIRTH DEFECTS

**Structural or functional anomalies** which are present at the time of birth. ART children have an increased risk of 30-40%; the possible causes reported are multiple births, invasive ART procedures and infertility.

##### LONG-TERM DEVELOPMENTAL ABNORMALITIES

• **NEUROLOGICAL DEVELOPMENT:** the risk of developing cerebral palsy is nearly doubled and the risk of developing epilepsy is also higher. Behavioral problems including attention deficit/hyperactivity disorder may be also more common, but the finding is uncertain. Data on autism are difficult to interpret.



• **CARDIOVASCULAR RISK:** ART children are associated with general vascular dysfunction in late childhood (up to 10 times higher risk).

• **CANCER:** there may exist a small increase in the incidence of childhood cancer, but data are uncertain.

\* The majority of these risks is mediated by neonatal complications, including prematurity and low birth weight, which after ART are most likely linked to parental subfertility and are less an effect of the ART technology.



##### IMPRINTING DISORDERS

- **ANGELMAN SYNDROME**
- **BECKWITH-WIEDEMANN S.**
- **RETINOBLASTOMA**

Gene imprinting is an epigenetic dynamic process established during germ cell development and modified after fertilization, during the early embryo development. Alterations, associated with subfertility and/or ART, may result in various epigenetic diseases and syndromes.

### CONCLUSIONS

• As evoked in this review, risks associated with the **mother** are usually clear and the cause is known: they are derived from stimulation, follicular aspiration or the pregnancy itself.

• Despite the methodological limitations and the short history of ART, numerous studies have reported increased risks of birth defects among ART-conceived **children**. Nowadays, it is difficult to determine if they are a consequence of the ART procedures or are inherent to the infertility problems.

Recent advances in ART and the knowledge of these risks have helped us to improve the techniques by maximizing the efficiency, minimizing the risks and extending its use to prevent transmission of diseases. Nevertheless, there are still many unanswered questions and further studies are required.

### RELEVANT REFERENCES:

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