

**INTERNATIONAL FEDERATION OF FERTILITY SOCIETIES** 

# Obstetric and paediatric outcomes following assisted reproduction

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Int@FedFertilitySoc

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### No declarations or conflicts

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## **Educational objectives**

- Maternal outcomes
- Neonatal outcomes
- Singleton vs Multiple pregnancy
- Does ART increase the risk of birth defects?
- Long term outcomes

### **Ectopic pregnancy**



### **Heterotopic pregnancy**



0.3-1% of ART pregnancies Rizk et al. Am J Obs & Gyn(1991);164:161-164

## Vanishing twin

10.5% singletons originate from twin pregnancies Significantly higher rate of preterm delivery cf singleton **Zhou et al EJOG (2016) 203:35-39** 

Mean gestational age 35.1+/-3.7 versus 38.2+/-2.6 weeks (P=0.001) cf singleton controls Almog. Reprod Biomed Online (2010) 20(2): 255-260

Prevalence 10.4% of IVF singletons Birth weight <2500 g: OR 1.7 Cl 1.2-2.2 Birth weight <1500 g: OR 2.1 Cl 1.3-3.6 **Pinborg Human Reprod (2006) 21(5):1335** 

## **Key Practice Points**

- 1. Always suspect ectopic pregnancy after ART
- 2. If more than one embryo is replaced at IVF the presence of intrauterine pregnancy does not exclude ectopic think heterotopic
- 3. Diagnosis of vanishing twin increases risk of preterm labour

# Maternal Outcome of singleton pregnancies conceived following ART

#### Severe maternal morbidity

ART cf Fertile deliveries. Cesarean Section: OR, 1.67; Cl, 1.40-1.98 ART cf Subfertile deliveries. Cesarean Section: OR, 1.75; Cl, 1.30-2.35 Luke. Am J Obstet Gynecol. 2017

#### APH

IVF vs NC n= 6730 – regional retrospective cohort OR 2.0; Cl 1.8-2.3. Healy. Hum Reprod 2010 Systematic review n=20807. OR 2.49; Cl 2.30-2.69. Pandey Hum Rep Up 2012

#### Hypertensive disease

Systematic review, n=16923 OR 1.49; Cl 1.39-1.59 Pandey. Hum Reprod Update 2012

#### **Gestational diabetes**

Systematic review, 16 studies. **RR 1.69; CI 1.19-2.42**. Systematic review n = 13399. **OR 1.48; CI 1.33-1.66**. **Pandey Hum Rep Up 2012** 

#### **Prevalence of placental incidents in ART pregnancies**



Healy et al Hum Reprod. 2009;25(1):265-274.

## **Key Practice Points**

1. IVF pregnancies are higher risk related to the underlying demography and maternal health

2. Careful imaging of placental site is indicated

3. Access to MRI



## Neonatal outcome – singleton ART

- **Congenital abnormalities** slight but significant increase
- Hospitalisation 0-5 years OR 1.3
- Stillbirth / PNM OR: 1.82; Cl 1.34-2.48. Davies J Dev Orig Health Dis (2017) 8(4):443-447 – S Australian birth cohort. OR 4.44, Cl: 2.38-8.28 Danish national cohort Wisborg Hum Reprod 2010; OR 1.90, Cl 1.57-2.30. Ombelet. Facts Views Vis Obgyn (2016) 8(4) 193-204. Belgian national cohort
- NND OR: 2.04; Cl 1.27-3.26 Davies J Dev Orig Health Dis (2017) 8(4):443-447
- CP OR: 2.30, Cl 1.12-4.73 after adjustment for preterm birth and multiplicity Zhu, Hum Reprod 2010

### **Pre-term labour - Singleton pregnancies**

17 studies n= 31,032

#### RR 1.84; CI 1.54, 2.21

#### McDonald et al. EJOG (2009) 146;2:138-146

#### Systematic review; 2 studies eSET singletons cf NC singletons



#### Grady et al. Fertil and Steril (2012) 97: 324-331

 IVF/ICSI vs NC (subfertile) TTP > 1 year :
 OR 1.55; CI 1.30, 1.85

 IVF/ICSI vs non-ART siblings:
 OR 1.27; CI 1.08, 1.49

Pinborg et al Hum Reprod Update. 2013;19(2):87-104



Li et al Lancet, 385;9966: 430-440 (January 2015)

#### Multiple pregnancy and LBR following ART global data



Sources: HFEA(2016); SART(2017); NPEU, Australia (2016); EIM (2016); RedLARA (2017); ANARA (2017); JSRM (2017)





#### Severe maternal consequences of twins cf singletons



Santana et al Obstetrics & Gynecology (2016) 127(4):631-641

## Neonatal risks of multiple pregnancy

- Pre-term labour OR 9.9, Cl 8.7-11.3 Pinborg AOGS 2004 Danish Cohort. 18.7x cf singletons. Chambers JAMA Paediatric 2014 168 (11): 1045-53
- SFD 3.6x Chambers JAMA Paediatric 2014 168 (11): 1045-53
- SB 2.0x Pinborg AOGS 2004 Danish Cohort; 5.0x Cheong-See BMJ (2016); 354:i4353 GONet Collaboration
- NND 6.4x
- Readmissions 1-5y OR 1.3 (1.2-1.4) Chambers JAMA
   Paediatric 2014 168 (11): 1045-53

## **Cerebral Palsy**

CP – small cohort study twins cf singletons OR 10.2 Petridou et al, 1996

Swedish national cohort Prevalence: <28 weeks 71.4/1000 births; 39.6 at 28-31 weeks; 6.4 at 32-36 weeks and 1.41 >36 weeks. Himmelmann Act Paediatric (2014) 103(6): 618-624

3.5 x cf singletons birthweight <1,000 g, 25x cf normal Smithers-Sheedy Dv Med Child Neurol (2016) 58 Supp 2:5-10

#### OR 2.18 CI: 1.71-2.77

Hvidtjorn et al Arch Pediatric Adoles Med 2009 163(1):72-83



### **Frozen vs fresh ET singletons**

Antepartum hemorrhage Preterm birth Small for gestational age Perinatal mortality

hage RR = 0.67, CI 0.55-0.81RR = 0.84, CI 0.78-0.90age RR = 0.45, CI 0.30-0.66RR = 0.68, CI 0.48-0.96

Maheshwari et al Fertil and Steril (2012) 98(2):368-

LBW PTB **Post-term birth** LGA Macrosomia Perinatal mortality OR 0.81, CI 0.71-0.91 OR 0.84, CI 0.76-0.92 OR 1.40, CI 1.27-1.55 \*\* OR 1.45, CI 1.27-1.64 \*\* OR 1.58, CI 1.39-1.80 \*\* OR 1.49, CI 1.07-2.07 \*\*



Wennerholm et al. Hum Reprod (2013) 28(9):2545-53

 Preterm birth
 OR = 1.14, 95 % CI: 1.02, 1.28 (higher risk with fresh)

 Low birth rate
 OR = 1.48, 95 % CI: 1.37, 1.60 (higher risk with fresh)

 Cesarean section rate
 OR = 0.85, 95 % CI: 0.80, 0.91\*\*

 Zhao et al. Reprod Biol Endocrinol (2016); 14(1):51

## **Key Practice Points**

- 1. Multiple pregnancy substantially increases risks to mother and babies
- 2. Infertility practitioners should make every effort to reduce the likelihood of multiple pregnancy and advise their patients of the risks

# Evidence for birth defects following ART?

**Bergh et al, Lancet; 1999** - retrospective cohort study, Sweden – 5856 IVF singletons, (1982-95) malformations occurred in 5.4% of all babies in the in-vitro-fertilisation group (1.39 [1.25-1.54]), rates of neural-tube defects and oesophageal atresia were higher cf to controls.

Hansen et al, N Eng J Med, 2002 – population based study, Australia. 1038 offspring – OR 2.0; Cl 1.3-3.2

Halliday et al, Hum Reprod; 2010 – population study, Australia OR 1.36 (1.19-1.55) 1991-2004

Yan et al, Fertil and Steril; 2011 – population based study, China; 15,405 offspring – cf NC - no difference

Studies biased by ascertainment due to more stringent follow-up of ARTconceived babies, are confounded by many other influences, have lacked proper controls, may be based on extrapolation hypotheses and are often of insufficient sample size.

## **Birth defects in ART conceptions**

	ART	NC	Un OR	Adj OR
Any defect	361 (8.3)	16,989 (5.8)	1.48 (1.32–1.65)	1.30 (1.16–1.45)
IVF				
All	105/1484		1.25 (1.02–1.52)	1.06 (0.87–1.30)
Fresh	71/1005		1.25 (0.98–1.59)	1.05 (0.82–1.35)
FET	34/479		1.24 (0.88–1.76)	1.08 (0.76–1.53)
ICSI				
All	91/939		1.72 (1.38–2.15)	1.55 (1.24–1.94)
Fresh	76/713		1.95 (1.53–2.48)	1.73 (1.35–2.21)
FET	15/226		1.17 (0.70–1.97)	1.10 (0.65–1.85)

Infertile but no history of treatment with assisted reproductive technology 52/600 1.54 (1.15–2.05) 1.37 (1.02–1.83)

#### Davies et al; N Eng J Medicine 366;19 2012

### **ART singletons and birth defects**

Relative weight 0.03 0.08 0.22 1.32 0.98 7.89 9.78 1.68 1.51

> 26.54 2.27 14.32

5.48 10.71 11.20

1.85
 0.23
 0.41
 1.40
 0.22
 1.40
 0.12
 0.39

Study name	Subgroup within study	Statistics for each study			Risk ratio and 95% Cl				
		RR	Lower limit	Upper limit					
Verlaenen 1995	IVF	6.11	0.30	123.10			+		
Apantaku 2008	Both	3.50	0.60	20.42			┼╺┼	$\rightarrow$	
Isaksson 2002	Both	2.17	0.74	6.36			┢╸┼		
Sagot 2012	Both	2.00	1.30	3.09			+ − 1		
Wen 2010	Both	1.61	0.97	2.67			+		
Katalinic 2004	ICSI	1.53	1.28	1.83			.		
Hansen 2012	Both	1.53	1.30	1.80			÷		
Olson 2005	Both	1.44	0.98	2.12			+		
Westergaard 1999	Both	1.43	0.95	2.16			+		
Kallen 2005	Both	1.39	1.26	1.53					
Dhont 1999	Both	1.36	0.98	1.90			-		
Halliday 2010	Both	1.36	1.19	1.55					
Klemetti 2005	Both	1.30	1.05	1.61		- <b>-</b> -			
Pinborg 2010	Both	1.27	1.09	1.48		-			
Davies 2012	Combined	1.26	1.08	1.46					
Fujii 2010	Both	1.17	0.81	1.69		-∔∎			
Koivurova 2002	IVF	1.13	0.40	3.17			<u>+</u> ─		
Palermo 2008	ICSI	1.06	0.49	2.33			+		,
Ombelet 2005	ICSI	1.02	0.67	1.56					
Koudstaal 2000a	IVF	1.00	0.35	2.89		- <b>- -</b>	<u>+</u> − 1		
Wang 2002	Both	0.95	0.63	1.46				′	
Bowen 1998	Both	0.93	0.22	3.84	<u> </u>		<b>↓ /</b>		
Shevell 2005	Both	0.90	0.40	2.01		- <b></b>	-//		
Pooled estimate sing Chi <sup>2</sup> =19.61, P=0.607	gletons n=23 , l <sup>2</sup> =0%	1.36	1.30	1.43		•			
				0.1	1 0.2	0.5 (1)	2 5	10	



Hansen M et al. Hum. Reprod. Update 2013;19:330-353

More birth defects ART

Fewer defects ART

## **Urogenital abnormalities**

### **Danish National Cohort Study**

Fedder et al: Hum. Reprod. (2013) 28 (1): 230

**Hypospadias** 1.37 (0.14-4.02) p=0.22



**Testicular maldescent** 1.37 (0.35–4.87) p=0.04

## **Imprinting disorders**



- Variable phenotype
- Facial recognition
- Macroglossia
- Macrosomia third Tri
- Abdominal wall defects
- Heart (20%)
- Renal tract
- Hyperinsulinaemia 30%
- Embryonal cell tumours (7.5%)

### **Cardiac anomalies**

Outflow tracts and ventriculo-arterial connections adjusted OR 1.7 95% (CI 1.1–2.8)

Cardiac neural crest defects and double outlet right ventricle without ventricular hypoplasia (adjusted OR 1.8 95% (CI 1.0–3.3). OR included null value when multiples were excluded. Tararbit et al. European Heart Journal (2011) 32, 500–508

TOF adjusted OR 2.4, 95% (CI: 1.5–3.7); adjusted OR: 3.0, 95% (CI: 1.0–8.9) (ICSI). Tarabit et al, Human Reproduction (2013) 28, 2: 367–374

41 studies n=25000 All types CHD, singleton pregnancies OR, 1.55; 95% Cl, 1.21–1.99; *P* = 0.0005 Giogiorne et al Ultrasound in Obstets & Gynaecol (2018) 51: 33-42

## **Cancer risk**

Kallen et al, Paediatrics. 2010 126, 2 Swedish Cancer Registry RR 1.42 (Cl 1.09-1.87)

Hargreave et al, Fertil and Steril 2013; 100: 150-161 Systematic Review RR = 1.33 (Cl 1.08–1.63)

Williams et al N Eng J Med. 2013 369; 19 UK HFEA: 106,013 1992-2008 108 cancers cf 109.7 expected RR 0.98 (0.81-1.19)

## **Key Practice Points**

- 1. Babies born following IVF/ICSI have a small but significant increased likelihood of birth defect
- 2. Reassure patients that this risk is small and is likely to due in part to underlying fertility
- 3. Routine imaging for fetal abnormality is indicated

# Long term cardiovascular consequences for offspring conceived through ART



#### Xiao-Yan et al. Fertil & Steril (2017)107;3:622-631

### Long term mental health and neurodevelopment following ART

Mental health outcomes in adolescence	Summary of effect
Cognitive function	$\uparrow$ $\leftrightarrow$ cognitive scores
School performance	$\leftrightarrow$ educational achievement
Neuromotor development	$\leftrightarrow$
Social functioning and behaviour	$\leftrightarrow$ both at home and at school
Attention-deficit disorder	$\leftrightarrow$
Autism	$\leftrightarrow$
Depression	$\uparrow \leftrightarrow$
Binge drinking	↑ $\bigcirc$ more than $\bigcirc$
Smoking	$\leftrightarrow$
$\uparrow$ increased: $\leftrightarrow$ no effect: $\bigcirc$ female: $\bigcirc$	male

"Reassuring evidence re mental health outcome. Potential associations with risk of CP and developmental delay, appears to be explained by obstetric factors rather than IVF"

#### Hart and Norman. Hum Reprod Update(2013) 19, 3: 244–250

## Long term development

Denmark (Aarhus) Cohort study All treatments cf NC with (subfertility) or without delay (fertile) in conception

School difficulties age 9-11 (n=211): 9<sup>th</sup> Grade – age 16 (n=203): Senior grade – age 19 (n=154): Intelligence – age 19 (n=90):

RD 1.0 (0.7–1.4) all subjects NS all subjects NS RD 0.5 (–1.6 to 2.5)

Bay et al. Fertil & Steril (2016); 106: 1033-1040

## **Key Practice Points**

- 1. Long term monitoring of children conceived following ART is not required per se
- 2. The importance of universal collection of data on ART processes and outcomes is stressed

## Conclusions

- ART singleton pregnancies are at increased risk and necessitate additional care
- Multiple pregnancy substantially increases the risks for both mother and baby and should be avoided
- Preterm labour is the major risk to the newborn
- National registries facilitate systematic follow up especially important with increased complexity of treatments



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