



## Antepartum care and prenatal diagnosis in pregnancies after IVF

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ESHRE Campus Lübeck 18th January 2008

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### Lecture overview

1. antepartum care
  1. IVF/ICSI pregnancies
  2. PGD pregnancies
2. prenatal diagnosis
  1. IVF/ICSI pregnancies
  2. PGD pregnancies

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### 1. Antepartum care

#### IVF/ICSI pregnancies

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## 1. antepartum care - IVF/ICSI pregnancies

increased risk of obstetric morbidity following IVF/ICSI

- miscarriage
  - ectopic pregnancy
  - premature delivery
  - low birthweight
  - infants small for gestational age
  - perinatal mortality
  - Instrumental delivery

Wisanto et al 1995, Aytoz et al 1998 Doyle et al 1992, Olivennes et al 1993, Buitendijk et al 2000



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## 1. antepartum care - IVF/ICSI pregnancies

- Risk increased
  - Placenta praevia
  - Gestational diabetes
  - Preeclampsia

Maman 1998, Tallo, 1995

→ Risk not increased

Reubinoff 1997, Koudstaal 2000



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## 1. antepartum care - congenital malformations

Palermo/USA	578	1.6% <sup>1</sup>
Wennerholm/Sweden 1.8) <sup>6</sup>	1139	3.3% <sup>2</sup> OR 1.19 (CI 0.8-
Loft/Denmark	730	2.2% <sup>2</sup>
Bonduelle/Belgium	2840	3.4% <sup>3</sup>
Hansen/Australia 3.2) <sup>6</sup>	301	8.6% <sup>4</sup> RR 2.0 (CI 1.3-
Ludwig/Germany	3372	8.6% <sup>5</sup> RR 1.25 (CI 1.1-

$1.4)^6$   
1st birth major malformations

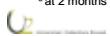
<sup>1</sup>at birth major malformations

<sup>3</sup> at birth – 2 months major

<sup>4</sup> at 1 year ICD 9

<sup>5</sup> at 2 months EUROCAT coding system

<sup>6</sup> compared to the general population



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## 1. antepartum care - IVF/ICSI pregnancies

### • obstetric morbidity following IVF/ICSI

→ Reports

- maternal complications
- congenital malformations
- obstetric complications

→ preexisting disorders

→ genetic conditions

→ risk factors

- age > 35 and delivering their first child
- multiple pregnancy

Waterstone et al, 2001



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## 1. antepartum care - IVF/ICSI pregnancies

### • Early pregnancy

- Follow up by fertility team up to 12/40
- Direct referral to high risk obstetric team

### • Increase awareness

### • Individual risk assessment



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## 1. Antepartum care

### Preimplantation genetic diagnosis pregnancies



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## 1. antepartum care - PGD pregnancies

### • Limited data

- PGD is associated with a risk of multiple gestation, cesarean section and placenta previa
- poor statistics  
→ Strom CM et al 2000.



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## 1. antepartum care - PGD pregnancies

treatments	PGD	%	PGD-AS	%	total	%
patients	535		663		1198	
age	319		363		342	
cycles	1177	mean 22 cycles/patient	102	mean 16 cycles/patient	2219	mean 18 cycles/patient
deliveries	205		164		369	
children	250		193		443	

PGD 1993-2004 - overall results



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## 1. antepartum care - PGD pregnancies

reatments	PGD	IGDAS	IGDta	confid. 95% ICSI/IVF		Bmtlthesgroup n=13399cycle	Bmtlthesgroup n=6403FICSIcycle
				OR 0.7299*	OR 0.7299*		
noICG	23.7% (23.6% of 23.7% OPU)			OR 0.7299*	OR 0.7299*	30.2% OPU	
	32.2%*	32.2%*	32.5%*	OR 0.8309*	OR 0.8309*	35.7%*	
bishmik	10.75%	15.75%	13.12%	OR 1.361	OR 1.361	10.55%	10.08%
microinc	15.05%	13.77%	13.69%	OR 1.061	OR 1.061	14.77%	13.54%
cryo(indirect)	1.43%	4.86%	3.04%	OR 1.051	OR 1.051	2.20%	1.92%
TOP	0.36%	0.81%	0.57%	OR 0.951	OR 0.951	0.07%	0.63%
luteofixup						2.48%	



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## 1. antepartum care - PGD pregnancies

treatments	PGD	PGD-AS	total n=370	control group ICSI/IVF 1998-2004 n=2904
normal delivery	60,68%	56,10%	58,65%	54,64%
instrumental delivery	8,25%	8,54%	8,38%	11,09%
cesarean section	31%	35,37%	32,97%	34,27%
cesarean section rate singletons	25,15%	29,93%	27,33%	27,64%
cesarean section rate twins	53,66	64,00%	57,57%	56,40%
cesarean section rate triplets	50%	50%	50%	90%

Mode of delivery



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## 1. antepartum care - PGD pregnancies

group	overall PGD+PGS	PGD only	PGS only	control group	PGD+PGS vs control
mean age	34.2	31.9	36.3	34.2	
children	443	250	193	2415	
perinatal mortality	<b>19 (4.3%)</b>	<b>13 (2.2%)</b>	<b>6 (0.1%)</b>	<b>11 (1.7%)</b>	<b>95% CI 1.5-4.5</b>
perinatal death singletons (% of singletons)	3 (1.0%)	2 (1.2%)	1 (0.7%)	30 (1.9%)	
perinatal death twins (% of twins)	14 (10.6%)	9 (10.9%)	5 (10.0%)	11 (1.3%)	
perinatal death triplets (% of triplets)	2 (16.7%)	2 (33.3%)	0 (0%)	0 (0%)	
obstetric complications					
overall hypertensive disorders	<b>29 (7.8%)</b>	<b>18 (8.7%)</b>	<b>11 (6.7%)</b>	<b>220 (11.3%)</b>	<b>95% CI 0.45-1.0</b>
pregnancy induced hypertension	19 (5.1%)	12 (5.8%)	7 (4.3%)	132 (6.8%)	
preclampsia	7 (1.9%)	4 (1.9%)	3 (1.8%)	77 (4.6%)	
HELLP syndrome	3 (0.8%)	2 (0.97%)	1 (0.6%)	11 (0.4%)	
gestational diabetes	<b>11 (2.97%)</b>	<b>6 (2.9%)</b>	<b>5 (3.1%)</b>	<b>55 (2.8%)</b>	<b>95% CI 0.55-2.1</b>



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## 1. antepartum care - PGD pregnancies

1. perinatal mortality rate high after PGD  
multiple pregnancy rate not higher
2. risk of hypertensive disorders not higher in PGD
3. risk of diabetes not significantly higher

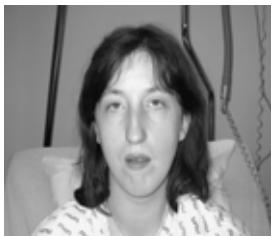
However risk assessment is extremely important  
In individual genetic indications



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## eg myotonic dystrophy



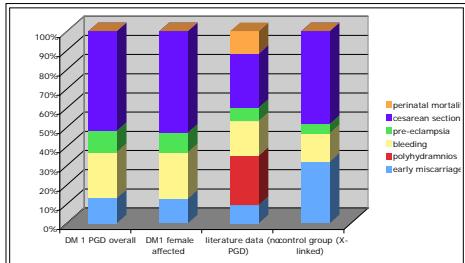
- frontal balding
- masseter, sternocleidomastoid and temporalis atrophy
- fertility issues
- obstetric risks



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## myotonic dystrophy complications



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## 1. antepartum care - PGD pregnancies

### • Examples

- Osteogenesis imperfecta/achondroplasia
- Marfan syndrome
- Sickle cell anemia
- Thalassemia
- Cystic fibrosis
- Following
  - Heart transplant
  - Renal transplant



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## 1. antepartum care - conclusion

- preconceptional risk assessment
- preconceptional optimisation
- multidisciplinary antepartum care
  - Geneticists
  - Physicians
  - Anaesthetists
  - perinatologists



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## 2. Prenatal diagnosis

### IVF/ICSI pregnancies



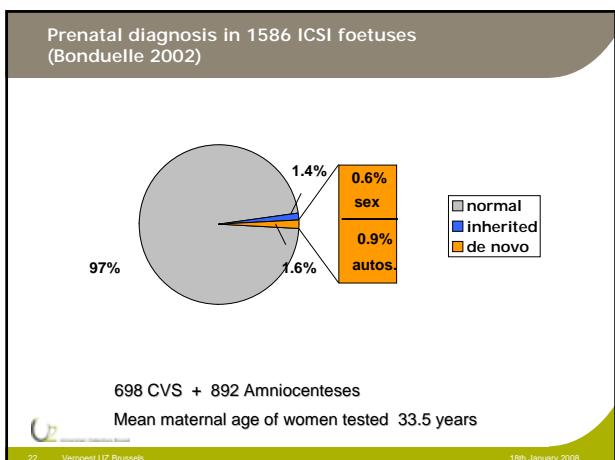
## 2. prenatal diagnosis - IVF/ICSI pregnancies

- the risk of finding an abnormality
  - IVF
  - ICSI
  - >36
  - >40
  - azoospermia
  - recurrent miscarriage
- the risk of miscarriage following
  - CVS
  - amniocentesis



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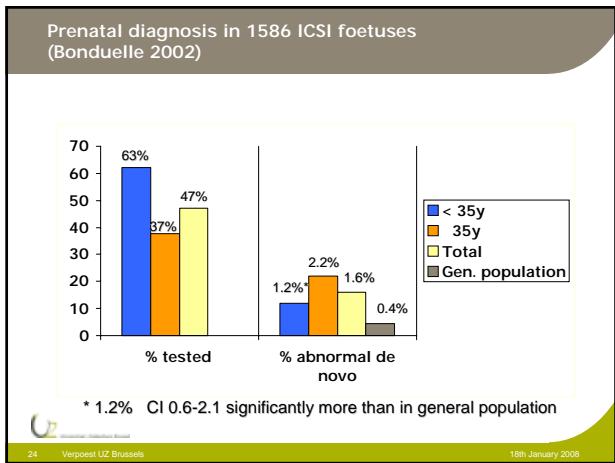
Prenatal diagnosis in 1586 ICSI foetuses  
(Bonduelle 2002)

Abnormal results	n	%	Confidence Interval	% normal population <sup>1,2,3</sup>
■ De novo	25	<b>1.6%*</b>	1.02 - 2.32%	0.45 - 0.87%
Sex chrom	10	<b>0.6%*</b>	0.30 - 1.16%	0.19 - 0.27%
Autosomal	15	0.9%	0.53 - 1.56%	0.26 - 0.60%
Numerical	8	0.5%	0.22 - 0.99%	0.14 - 0.33%
Structural	7	0.4%	0.18 - 0.91%	0.11 - 0.22%
■ Inherited	22	<b>1.4%*</b>	0.87 - 2.09%	0.47 - 0.37%
Total	47	3.0%	2.19 - 3.92%	0.92%

<sup>1</sup> Jacobs et al., 1992 on 34 910 newborns  
<sup>2</sup> Ferguson-Smith et al., 1984 on 52 965 prenatal samples  
<sup>3</sup> Hook et al., 1981, 1984, 1987 on prenatal samples

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Prenatal diagnosis in 1586 ICSI foetuses:  
*de novo* anomalies, sperm parameters / origin

- Sperm count (72%)  
< 20.10<sup>6</sup> / ml ⇒ 2.1 % chromosomal abnormalities (vs 0.24% > 20.10<sup>6</sup>/ml)  
Fisher Exact 2 tailed test p < 0.05
- Sperm motility (83%)  
< 50 % N motility ⇒ 1.9% chromosomal abnormalities  
Fisher Exact 2 tailed test p < 0.05
- Sperm morphology and origin ⇒ no influence



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Prenatal diagnosis in 1586 ICSI foetuses  
(Bonduelle 2002)

### Inherited abnormalities 1.4%

- Known risk related to the chromosomal anomalies in the parents (6.3%)
- 17/22 cases paternally inherited
- Preimplantation > prenatal diagnosis

⇒ Informed choice of the parents  
prior to the procedure



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Prenatal diagnosis in 1586 ICSI foetuses  
(Bonduelle 2002)

### Non-inherited (*de novo*) anomalies 1.6%

- Significantly higher than general population, but absolute risk low
- Related to sperm characteristics
- Severity is variable (termination not always chosen)  
→ Sex chromosomal, structural anomalies
- Detectable from 11th week of pregnancy

⇒ Informed choice of the parents  
<50% agree to do a prenatal test



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## 2. Prenatal diagnosis - IVF/ICSI pregnancies

key message:

Significant risk of chromosomal abnormalities  
under  $20 \times 10^6/\text{ml}$  sperm  
and <50% type A+B sperm motility

Bonduelle et al, 2002



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## 2. Prenatal diagnosis - cryo pregnancies

	ICSI	IVF		
	Cryo ICSI N=200	Fresh ICSI N=1586	p-value	Cryo IVF N=72
<b>Prenatal</b>				
<i>De-novo</i>	7 (3.5) <sup>b</sup>	25 (1.5)	0.080	7 (1.4) <sup>b</sup>
Sex	3	10		
Klinefelter		8		
Autosomal numerical				
Trisomy 18				1
Trisomy 21	3			
Autosomal structural	1	7		
<i>Inherited</i>	1 (0.5)	22 (1.4)	0.629	1 (1.4)
from mother	1	1		1
Prenatal total	8 (4)*	47 (2.9)	0.424	2 (2.8)*
<b>Postnatal</b>	<b>N=81</b>	<b>N=38</b>	<b>N=40</b>	
<i>De-novo</i>	2	7		
Sex		2		
Autosomal numerical		3		
Trisomy 21	1			
Autosomal structural	1	2		
<i>Inherited</i>	1	6		
from father	1			
Postnatal total	3 (3.7)	13 (3.8)	.....	0
<b>Overall (prenatal and postnatal) anomalies in tested group</b>	<b>N=281</b>	<b>N=1924</b>		<b>N=112</b>
<i>De-novo</i>	9 (3.2)	32 (1.7)	.....	1 (0.9)
Total	11 (3.9)	60 (3.1)	.....	2 (1.8)



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## 2. Prenatal diagnosis - IVF/ICSI pregnancies

amniocentesis for singleton pregnancies

CVS for twin pregnancies +

Kolibianakis et al, 2003



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**2. Prenatal diagnosis**

PGD pregnancies

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**2. PGD pregnancies - prenatal diagnosis**

	PGD-AS	PGD
n	272	314
Prenatal	34 (11 %)	138 (44 %)
Postnatal	56	32
Misdiagnosis	0	1(+3)

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**2. PGD pregnancies - prenatal diagnosis**

	Indication	Pregnancy	Prenatal	Outcome
1	MD	S	affected	TOP
2	CMT1A	S	none	Born
		Tw	affected	TOP

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## 2. PGD pregnancies - prenatal diagnosis

- Patient 1 : real misdiagnosis
- Patient 2 : erroneous linkage analysis leading to selection for affected embryos
- Misdiagnosis rate:
  - $4 / 123 = 3.2\% \quad 1 / 123 = 0.8\%$
  - $4 / 249 = 1.6\% \quad 1 / 249 = 0.4\%$



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## 2. PGD pregnancies - prenatal diagnosis

	n	%
Verlinsky et al.	663	0.5
VUB	170	0.6
	314	0.3



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## Antepartum care and prenatal diagnosis - conclusion

- Data are inconsistent
- Overall increased risk
- Individual risk assessment
- Antepartum care: increased awareness
- Prenatal diagnosis: advice to patient and obstetrician
- PGD: multidisciplinary antepartum care



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