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Risk of congenital anomalies in children born after IVF / ICSI: what to tell your patient?

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Children born after ART

BRITAIN'S BIGGEST EVENING SALE

Evening News

LATE SPECIAL CITY PRICES

LONDON: THURSDAY JULY 27 1978

Meet Louise, the world's first test-tube arrival

SUPERBABE

Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three

eshre

SCIENCE MOVING
PEOPLE
MOVING SCIENCE

>5 million babies born after ART

Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. Lancet **1978**;2(8085):366

Nygren KG *et al.:* International Committee for Monitoring Assisted Reproductive Technology (ICMART) world report: assisted reproductive technology 2003. Fertil Steril 2011;95:2209–22.

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Congenital anomalies

World Health Organization

eurocat
european surveillance of congenital anomalies

Definition

Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations.

Congenital anomalies can be defined as structural or functional anomalies(for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or may only be detected later in infancy, such as hearing defects.

Congenital anomalies IN VITRO fertilization

SIR,—In analysing further data from the register of in-vitro fertilisation (IVF) and gamete intrafallopian transfer (GIFT) pregnancies in Australia and New Zealand,[1] we found more infants than expected with two types of congenital malformation—namely, spina bifida and transposition of the great vessels.

Lancaster PAL. Congenital malformations after in-vitro fertilization. **The Lancet December 12, 1987**

Congenital anomalies

IN VITRO fertilization

Infants conceived with use of intracytoplasmic sperm injection or in vitro fertilization have **twice as high a risk of a major birth defect** as naturally conceived infants.

Hansen et *al.* The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. **N Engl J Med 2002**; 346: 725-30.

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Congenital anomalies

ART vs. Non ART infants

Reported meta-analyses on birth defects and assisted reproductive technologies

Early meta- analyses	Number of articles	Number ART Infants	Pooled estimate (95% CI)
Rimm et *al* (2004)	19	35 578	**1.29** (1.01 – 1.67)
Hansen et *al* (2005)	25	28 638	**1.29** (1.21 – 1.37)

Recent meta- analyses	Number of articles	Number ART Infants	Pooled estimate (95% CI)
Wen et *al* (2012)	46	124 468	**1.37** (1.26 – 1.48)
Hansen et *al* (2013)	45	92 671	**1.32** (1.24 – 1.42)

ARTs increase risk of birth defects by about 30%

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Congenital anomalies

Effect of type of ART

- ART: 6 163
- Controls: 308 974

Birth defects

IVF RR: 1.07 (95%CI 0.90-1.26)
ICSI RR: 1.57 (95%CI 1.30-1.90)

ICSI: increases risk of birth defects
IVF: Does not increase risk of birth defects

Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive technologies and risk of birth defects. N Engl J Med. 2012; 366: 1803-13

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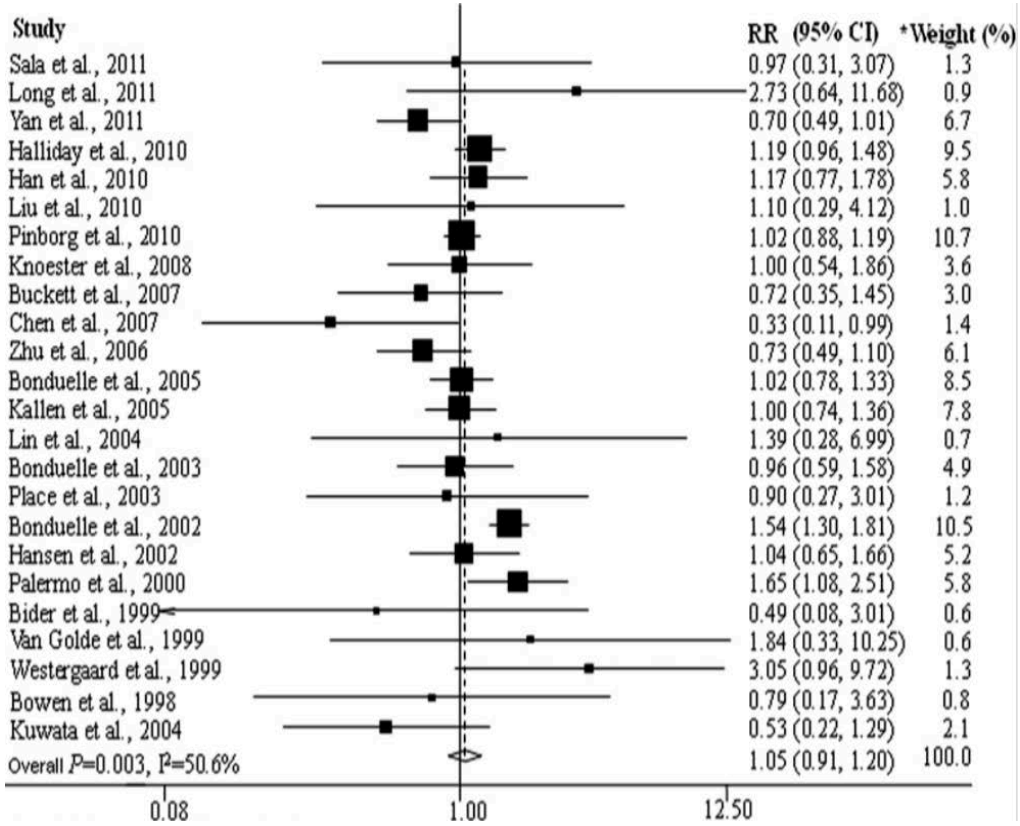
Congenital anomalies

Effect of type of ART



- **IVF:** 46 890
- **ICSI:** 27 754
- **RR:** 1.05 (95%CI 0.91-1.20)

No difference in congenital anomalies between IVF and ICSI

Wen *et al.* Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis. Fertil Steril 2012;

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Congenital anomalies

Effect of type of ART

OR (95% CI) for severe malformations after IVF:

• Fresh ejaculated ICSI	0.90 (0.78-1.04)
• Fresh IVF	1.00 reference
• Cryopreserved ejaculated ICSI	1.01 (0.76-1.33)
• Fresh ejaculated ICSI	1.00 reference
• Cryopreserved ejaculated ICSI	0.75 (0.53-1.06)
• Cryopreserved IVF	1.00 reference
• Fresh epididymal ICSI	1.07 (0.41-2.92)
• Fresh testicular ICSI	1.00 reference
• Fresh non-ejaculated ICSI	1.13 (0.72-1.87)
• Fresh ejaculated ICSI	1.00 reference
• Cryopreserved non-ejaculated ICSI	0.95 (0.30-2.99)
• Fresh non-ejaculated ICSI	1.00 reference

Congenital malformations in infants after IVF:

- Central nervous system
- Cardiovascular system
- Urogenital system
- Limb reduction defects

No difference between different types of IVF

Kallén *et al.* Congenital Malformations in Infants Born after In Vitro Fertilization in Sweden. Birth Defects Res A Clin Mol Teratol 2010

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Congenital anomalies

Singleton & multiple pregnancies

Singletons

- ART: 4 064
- Other ART: 9 589
- Controls: 1 090 154

RR = 1.43; 95% CI (1.19–1.72)

Twins and higher order multiples

- ART: 3 056
- Other ART: 2 301
- Controls: 28 008

RR = 1.26; 95% CI (1.01–1.57)

Heisey *et al.* Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments. Birth Defects Res A Clin Mol Teratol 2015

Maternal factors and the risk of birth defects after IVF / ICSI

Conception	n	Age ≥35 y
•IVF:	2 211	34.4%
•ICSI:	1 399	30.3%
•Controls:	301 060	12.1%

Davies MJ, et *al.:* Maternal factors and the risk of birth defects after IVF and ICSI: a whole of population cohort Study. BJOG. 2016 Oct 17. doi: 10.1111/1471 -0528. 14365.

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Miscarriage from amnio / CVS

Royal College of Obstetricians & Gynaecologists

Amnio 1%

CVS 1-2%

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

Amnio 0.3-0.5%

CVS 0.3-0.5%

THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

Amnio 0.2-1.5%

CVS 0.2-1.5%

RCOG: *Amniocentesis and Chorionic Villus Sampling. Green Top Guideline No.8. London: RCOG, 2010.*

ACOG: *Invasive prenatal testing for aneuploidy. ACOG Practice Bulletin No. 88. Obstet Gynecol 2007; 110: 1459-1467.*

SOGC: *Mid-trimester amniocentesis fetal loss rate. J Obstet Gynaecol Can 2007; 29: 586-595.*

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Miscarriage from amnio / CVS

King's College hospital study

Singleton pregnancies with combined screening at 11-13 w

- Expectant management
- Livebirth n = 33,310; Miscarriage n = 404 (1.2%)
- Regression model to predict miscarriage

Variable	OR	95% CI
Age (per year)	0.870	0.766-0.988
Delta nuchal translucency	1.778	1.496-2.114
Ductus venosus: reversed a-wave	2.208	1.508-3.232
Log10 PAPP-A MoM	0.356	0.233-0.543

CVS n = 2,396

Miscarriage

Observed: 44 (1.8%)

Expected: 45 (95% CI 32-58)

Akolekar R, Bower S, Flack N, Bilardo K, Nicolaides KH: Prediction of miscarriage and stillbirth at 11-13 weeks and the contribution of chorionic villus sampling. Prenat Diagn 2011:31:38.

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Miscarriage from amnio / CVS

Danish study

- 147,987 singleton pregnancies
- All had first trimester combined screening
- Propensity score stratification

Miscarriage risk difference:	CVS	**-0.2%**
	Amniocentesis	**0.6%**
Stillbirth risk difference:	CVS	**-0.3%**
	Amniocentesis	**0.1%**

Wulff CB, Gerds TA, Rode L, Ekelund CK, Petersen OB, **Tabor A**: Risk of fetal loss with invasive testing following first trimester screening: national cohort of 147,987 singleton pregnancies. Ultrasound Obstet Gynecol **2016**; 47: 38-44.

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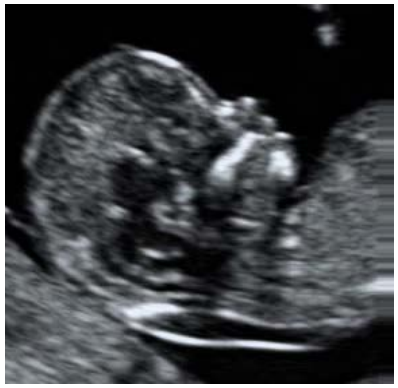
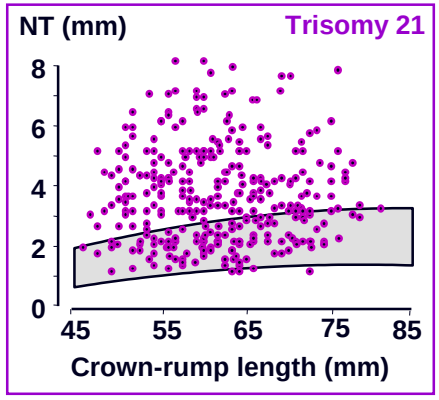
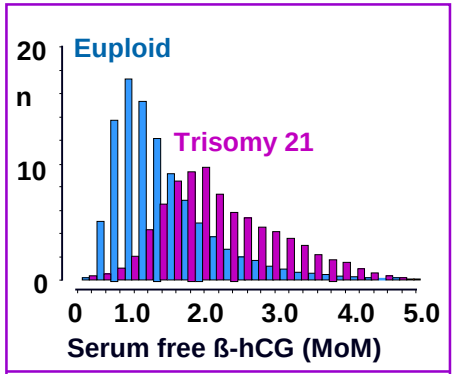
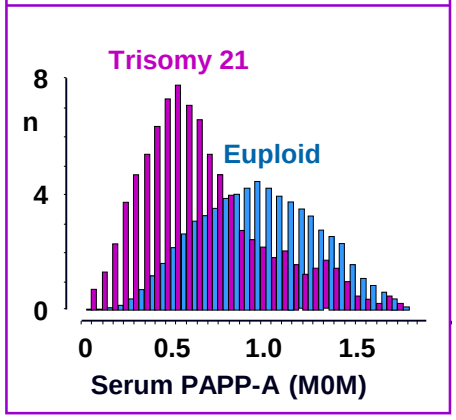
Screening for Down syndrome

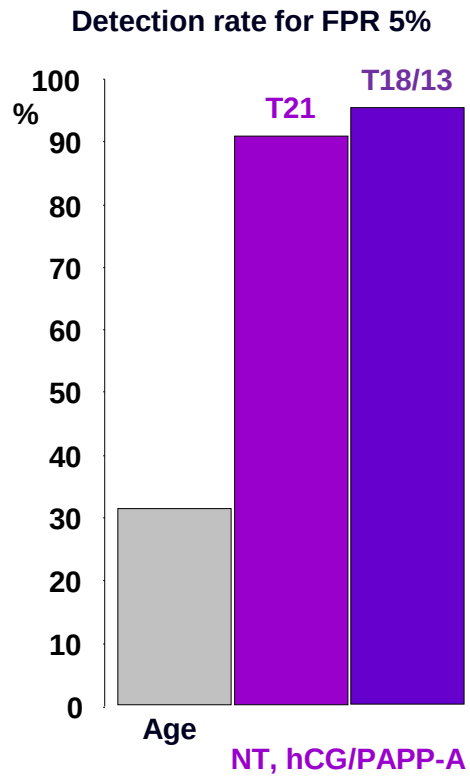
1st trimester combined test











- Nicolaides KH, Azar GB, Byrne D, Mansur CA, Marks K. Nuchal translucency: ultrasound screening for chromosomal defects in the first trimester of pregnancy. BMJ **1992**; 304:867
- Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Lancet **1998**; 352:343
- Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol **1999**; 13:231.
- Kagan KO, Wright D, Valencia C, Maiz N, Nicolaides KH. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free ß-hCG and pregnancy-associated plasma protein-A. Hum Reprod **2008**; 23:1968-75.

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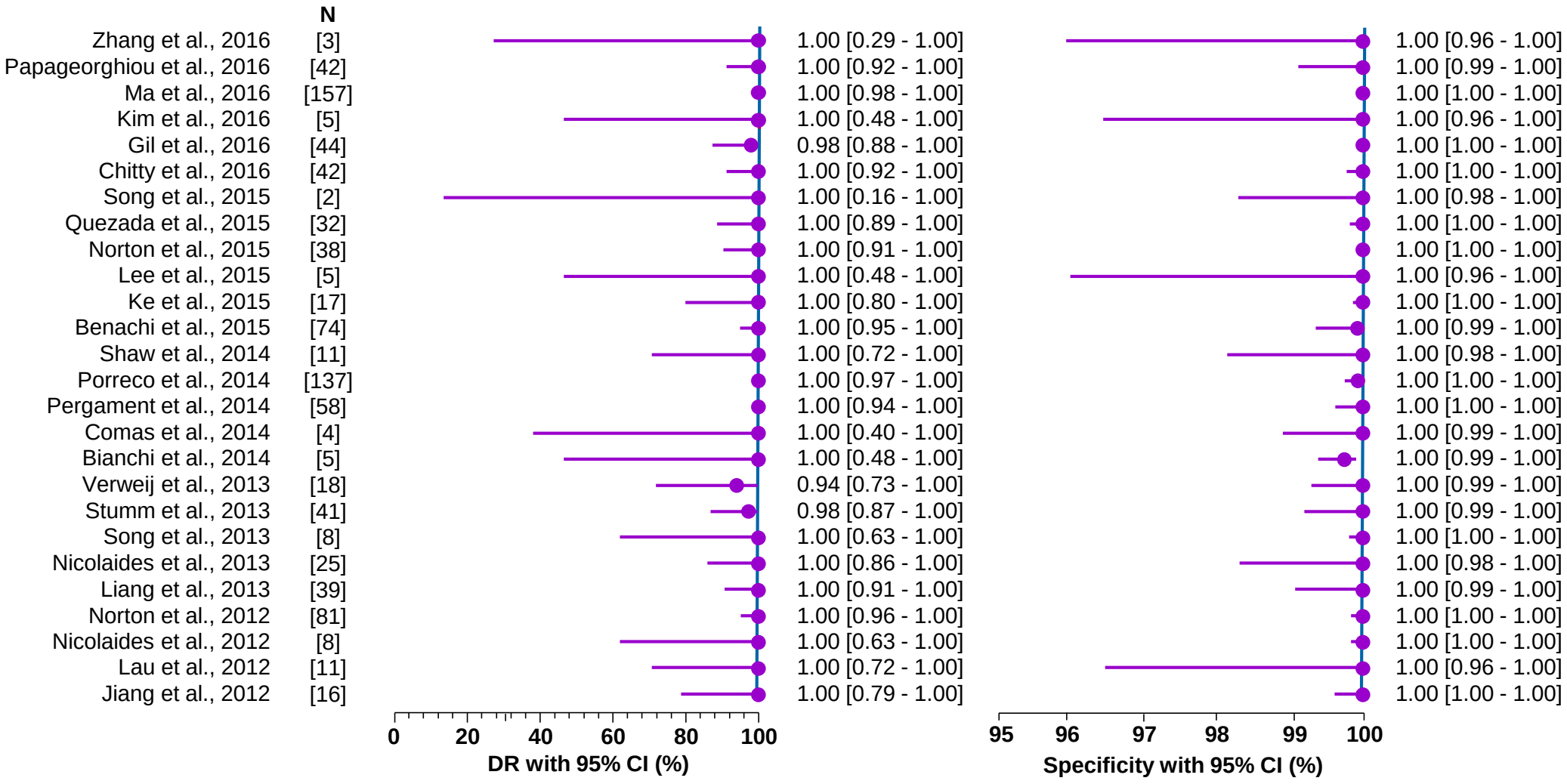
Cell-free DNA in maternal blood

Trisomy 21



Estimated DR 99.8% (920/923: 99.7%)

Estimated FPR 0.04% (25/54,359: 0.05%)

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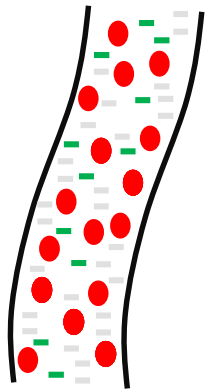
Screening for trisomies

Cell-free DNA in maternal blood



	DR	FPR
Trisomy 21 n= 923	99.8% (99.2)	0.04% (0.09)
Trisomy 18 n= 290	97.6% (96.3)	0.05% (0.13)
Trisomy 13 n= 212	96.5% (91.0)	0.02% (0.13)

Mar Gil : Updated meta-analysis December 2016

Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, Wainscoat JS. Presence of fetal DNA in maternal plasma and serum. Lancet **1997**; 350:485-7.

Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies Ultrasound Obstet Gynecol **2015**;45:249

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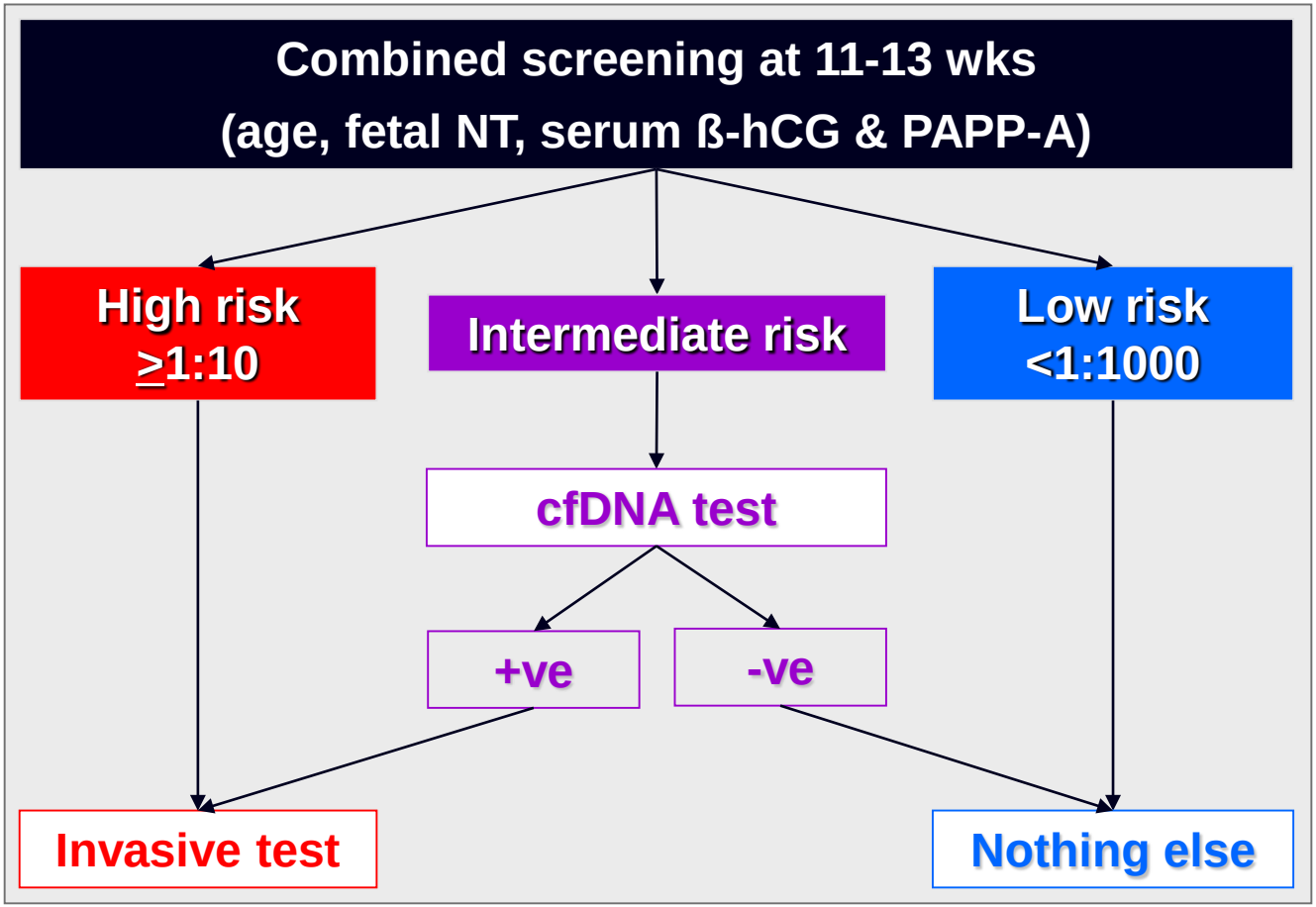
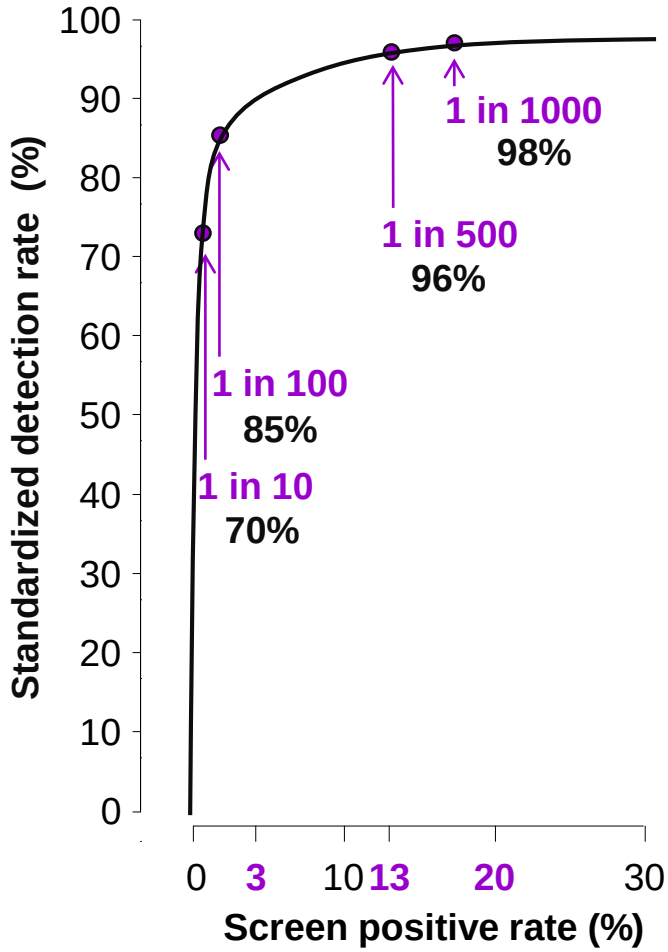
Cell free DNA test

Model of clinical implementation





Santorum M, Wright D, Syngelaki A, Karagioti N, Nicolaides KH. Accuracy of first trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol **2016**; doi 10.1002/uog.17283

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Congenital anomalies

ART: Type of defects

Singletons

- ART: 9 653
- Controls: 1 090 154

RR = 1.43; 95% CI (1.19–1.72)

Multiples

- ART: 5 357
- Controls: 28 008

RR = 1.26; 95% CI (1.01–1.57)

Increased risk of congenital defects in ART:

Most commonly affected organs:

Cardiovascular
Genitourinary
Musculoskeletal

Most common defects:

Hypospadias
Omphalocele
Neural tube defects

Heisey *et al.* Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments. Birth Defects Res A Clin Mol Teratol 2015

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Early detection of fetal defects

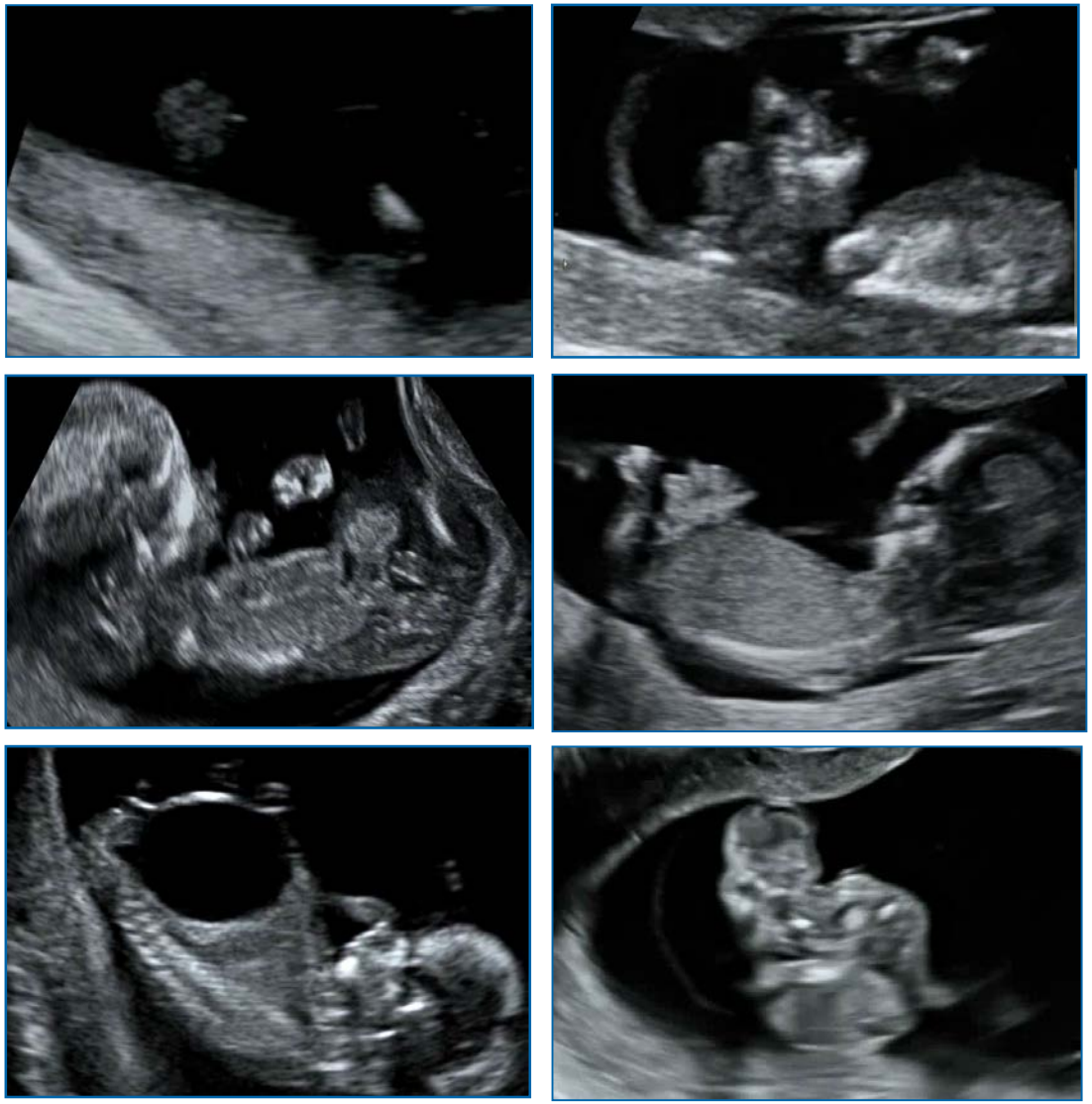
11-13 weeks

Major defects

↓

Always detected 31%

- Acrania
- Holoprosencephaly
- Exomphalos
- Gastroschisis
- Megacystis
- Body stalk anomaly



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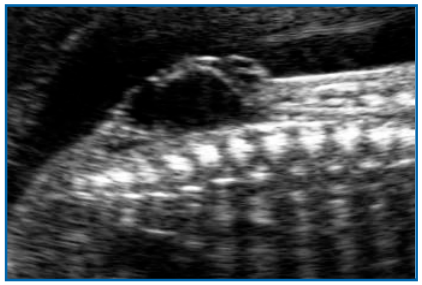
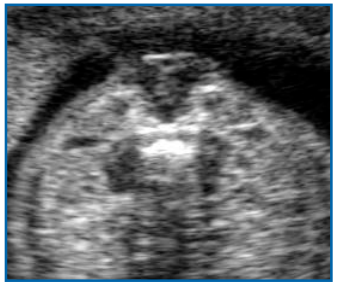
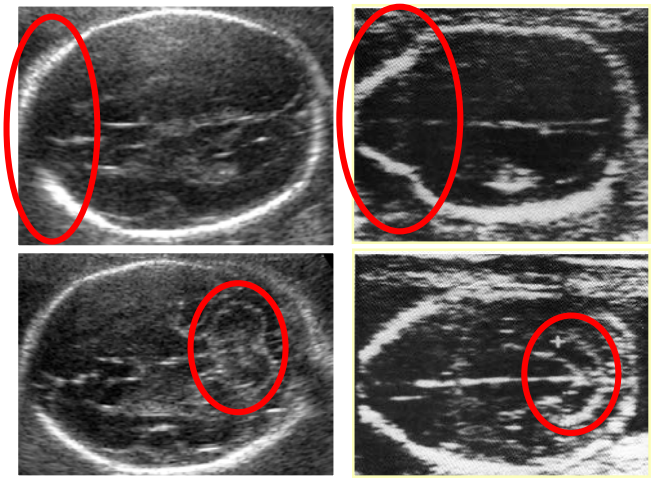
Early detection of Open spina bifida

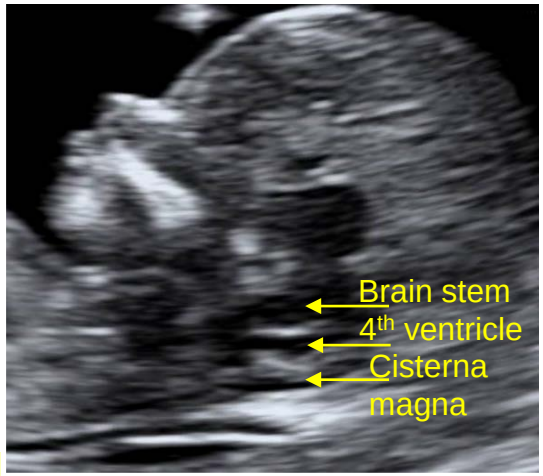
11-13 weeks

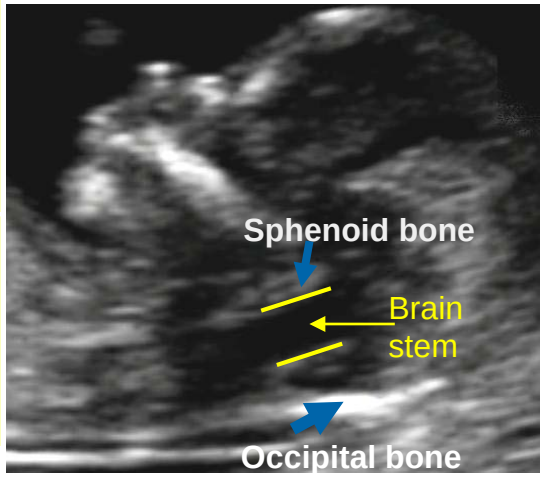


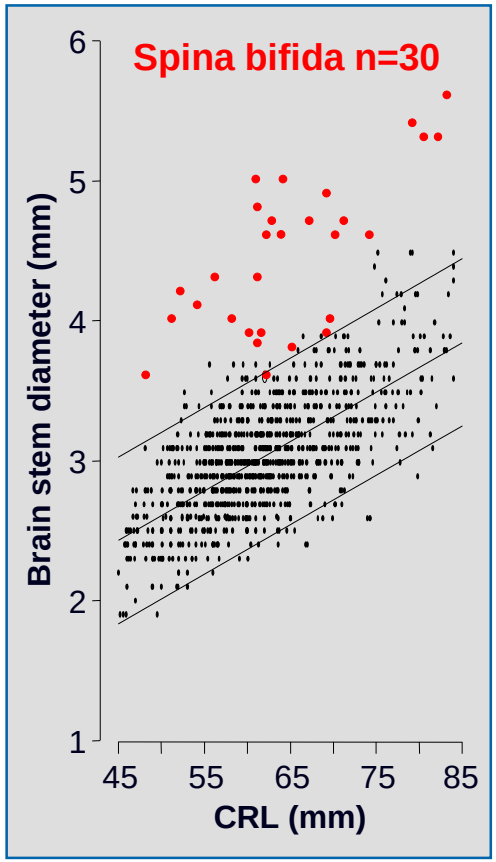


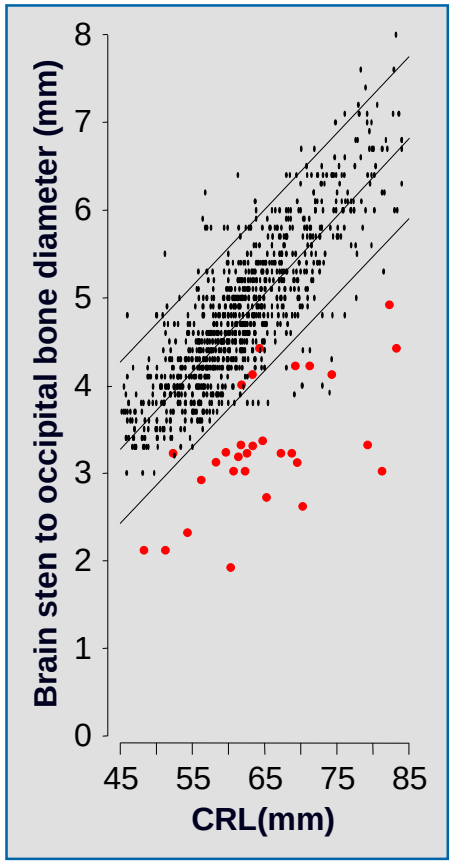


Nicolaides *et al.*, 1986









Chaoui *et al.*, 2009; Lachman *et al.*, 2011

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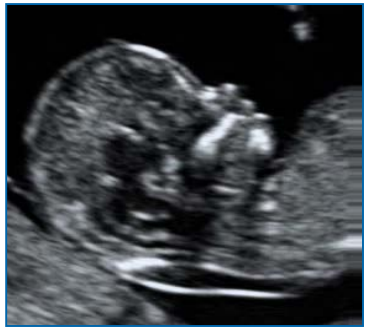
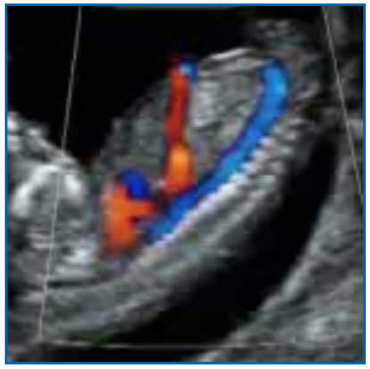
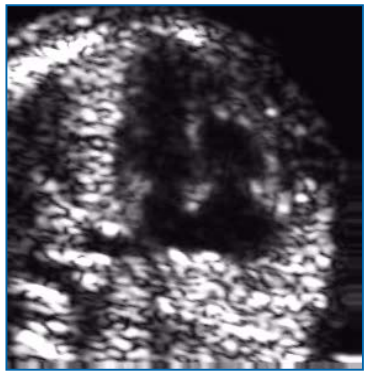
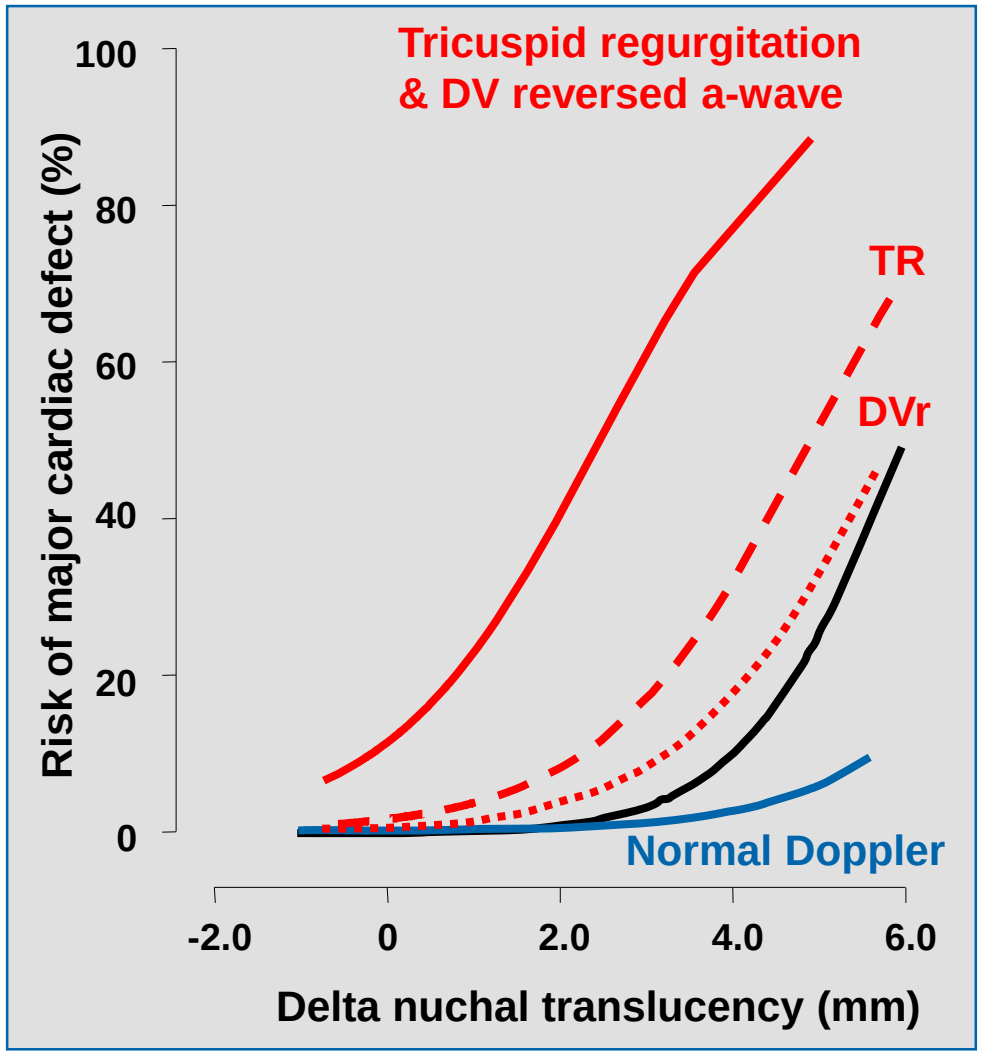
Early detection of Major cardiac defects

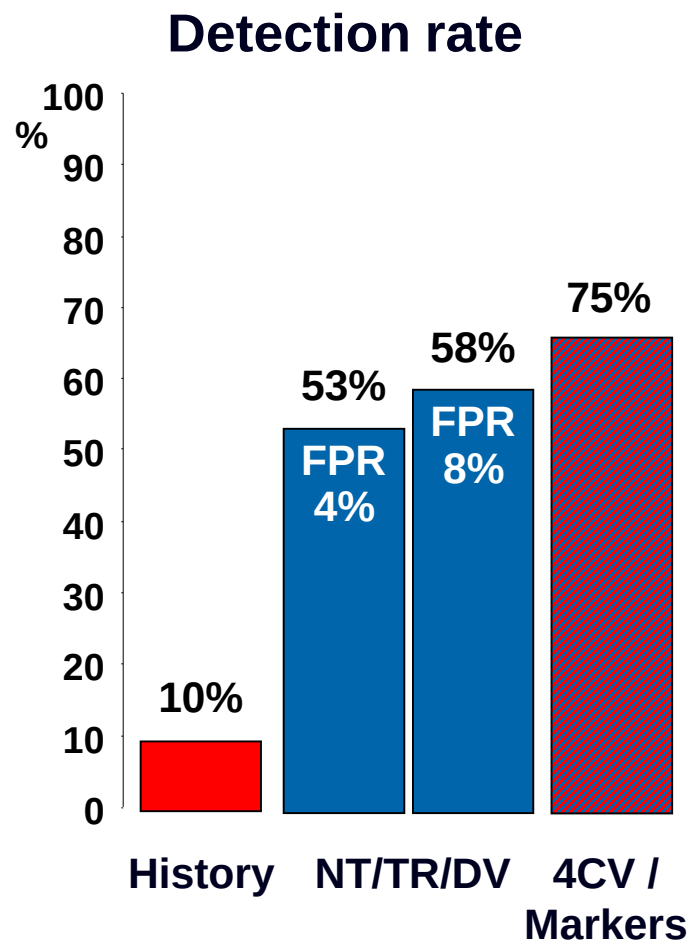
11-13 weeks











Cheleman 2011; Pereira 2011; Rembouskos 2012

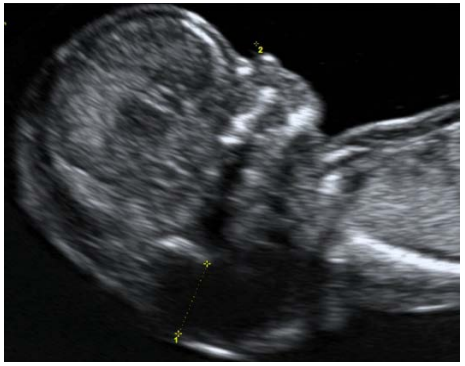
Discordance for fetal abnormality

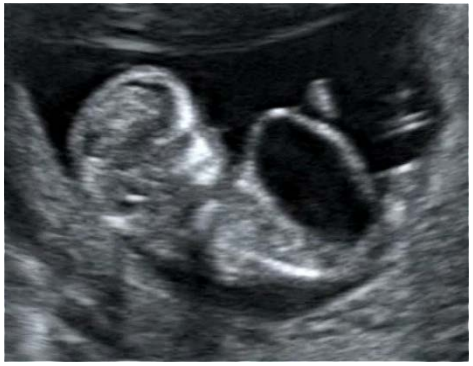
Prevalence DC : MC = 4 : 1

Defects in DC: 1 x singleton

Defects in MC: 4 x singleton

Discordance for defects: MC=DC





Management options

- DC: 1 euploid and 1 trisomy 21
- DC: 1 euploid and 1 trisomy 18
- DC: 1 euploid and 1 anencephaly
- MC: 1 normal and 1 abnormal

Timing of selective termination

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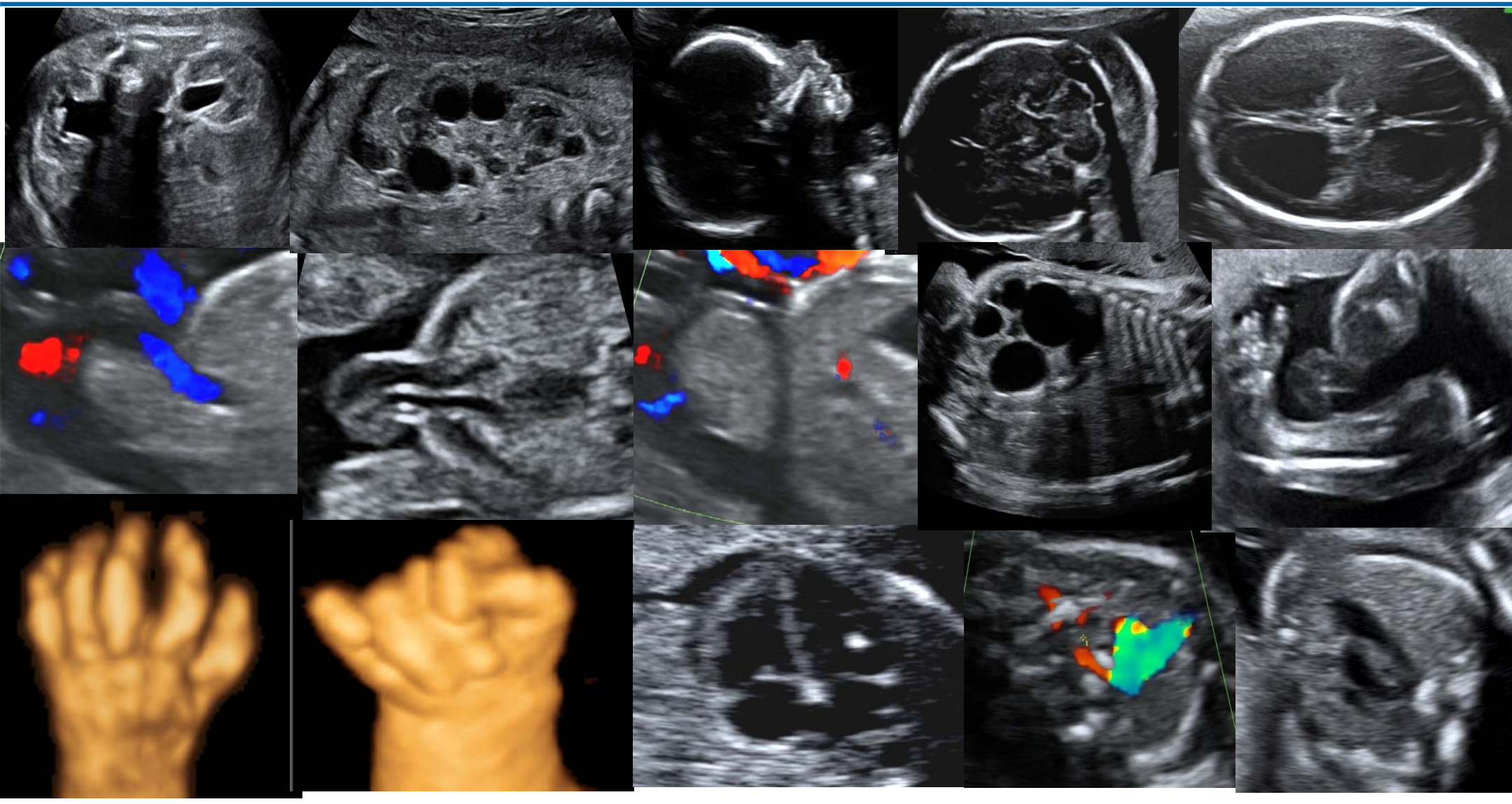
Congenital anomalies

Second trimester



Conclusions

1.Increased risk of congenital defects in ART pregnancies

2. Equal risk of congenital defects between all types of ART pregnancies

3. Management of ART pregnancies:

- ↗ Counselling with specialist in Reproductive medicine
- ↗ Counselling with specialist in Fetal medicine

4. Need for randomized studies

Thank you