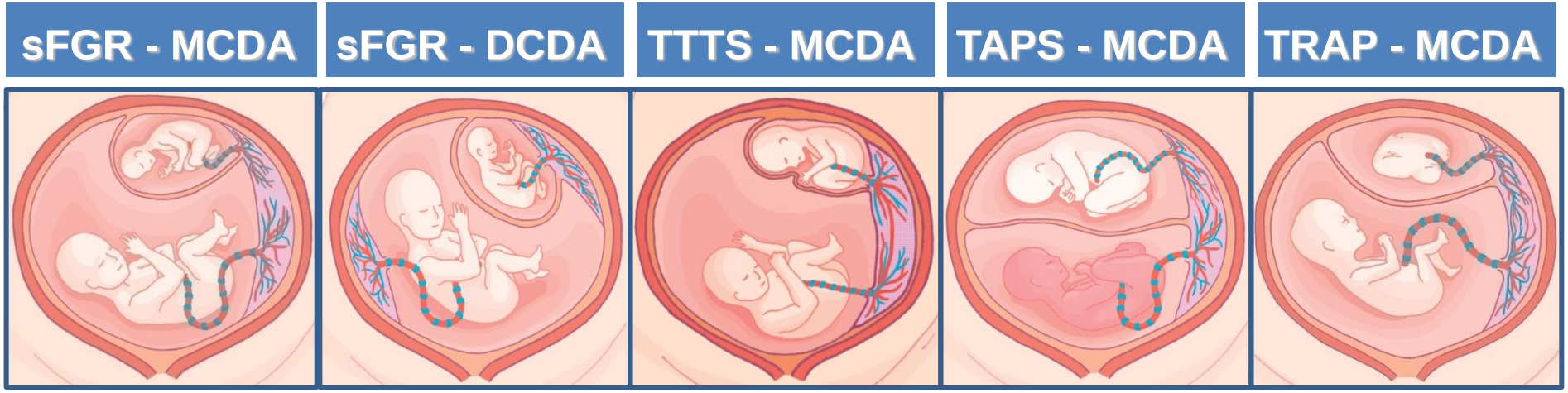
ISUOG Clinical Standard: Twin Pregnancy



Asma Khalil
St George's Hospital, University of London, UK

ISUOG Clinical Standard: Twin Pregnancy

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[13]Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Greece.

ISUOG Clinical Standard: Evidence level

- 1++ High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
- 1– Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
- 2++ High-quality systematic reviews of case–control or cohort studies or high-quality case control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
- 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
- 2- Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
- 3 Non-analytical studies, e.g. case reports, case series
- 4 Expert opinion

ISUOG Clinical Standard : Grades of recommendations

- **A** At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
- **B** A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
- **C** A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
- **D** Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
- **GPP** Recommended best practice based on the clinical experience of the guideline development group

ISUOG Clinical Standard: Scope

- Dating of the pregnancy
- Determining chorionicity and amnionicity
- Twin labelling
- Timing, frequency and content of ultrasound assessment
- Screening for aneuploidy
- Prenatal diagnosis of aneuploidy
- Screening for structural abnormalities
- Diagnosis and management of discordant twin pregnancy
- Fetal reduction/selective termination
- Screening for preterm birth
- Screening, diagnosis and management of FGR
- Management of multiple pregnancy complicated by single in utero death
- Complications unique to monochorionic twin pregnancies
    - Screening, diagnosis and management of TTTS
    - Screening, diagnosis and management of TAPS
    - Management of TRAP sequence
    - Management of MCMA twin pregnancy
    - Diagnosis and management of conjoined twins

Twin Pregnancy: Dating

How should twin pregnancies be dated?	
• **Twin pregnancies should ideally be dated when the CRL measurement is between 45 and 84 mm.**	**D**
• **In spontaneously conceived pregnancies, the larger of the two CRLs should be used.**	**C**

IVF: oocyte retrieval date or the embryonic age from fertilization



Twin Pregnancy: Chorionicity

How should the chorionicity/amnionicity be determined?

- **Chorionicity should be determined <13^{+6} weeks using:** **D**
  - **Membrane thickness at the site of insertion of the amniotic membrane into the placenta**
  - **T sign or Lambda sign**
  - **Number of placental masses**
- **An ultrasound image demonstrating the chorionicity should be kept in the records for future reference.**

- DC twins: placental masses are commonly adjacent
- MC twins: 3% have two placental masses on ultrasound



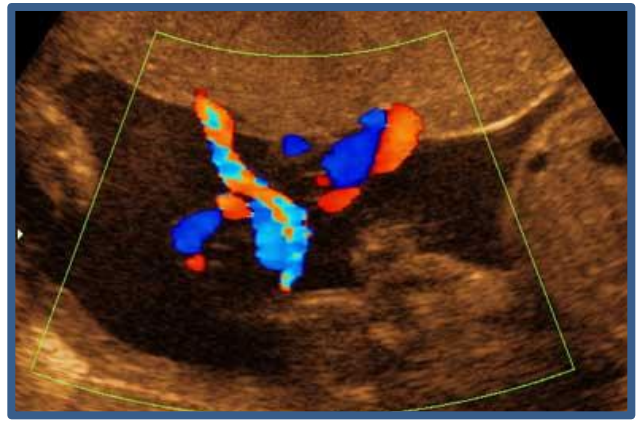


Twin Pregnancy: Chorionicity

How should the chorionicity/amnionicity be determined?

- If it is not possible to determine chorionicity by TA or TV scan, a second opinion should be sought from a tertiary referral center. ☑
- At the same time as chorionicity is determined, amnionicity should also be determined and documented. ☑
- MCMA twin pregnancies should be referred to a tertiary center with expertise in their management.

- Absence of the inter-twin membrane is best confirmed by transvaginal scan
- Color and pulsed wave Doppler: two distinct arterial waveform patterns with different heart rates are seen within the same sampling gate



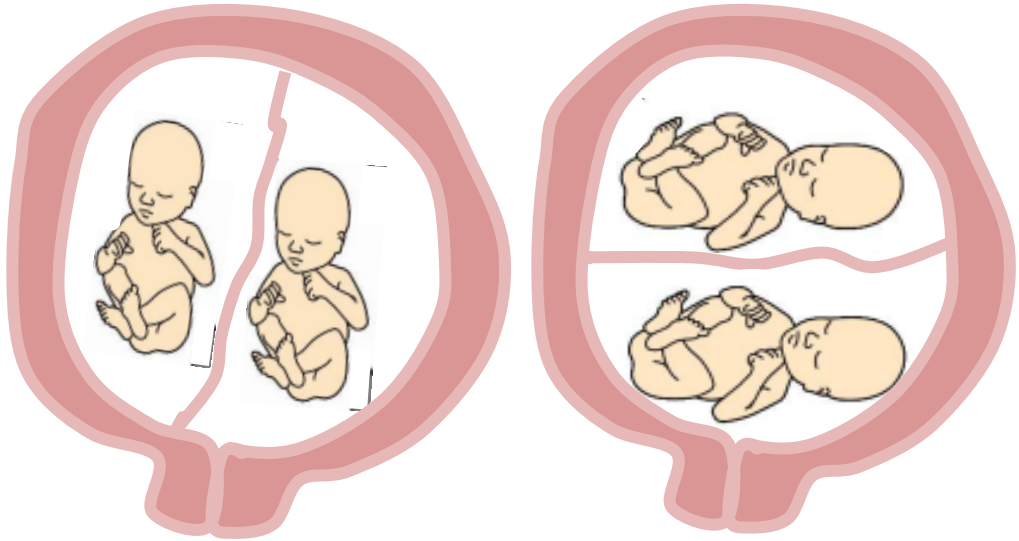
Twin Pregnancy: Labelling

How should twin fetuses be labeled?

- **The labeling of twin fetuses should follow a reliable and consistent strategy and should be documented clearly in the woman's notes** ☑

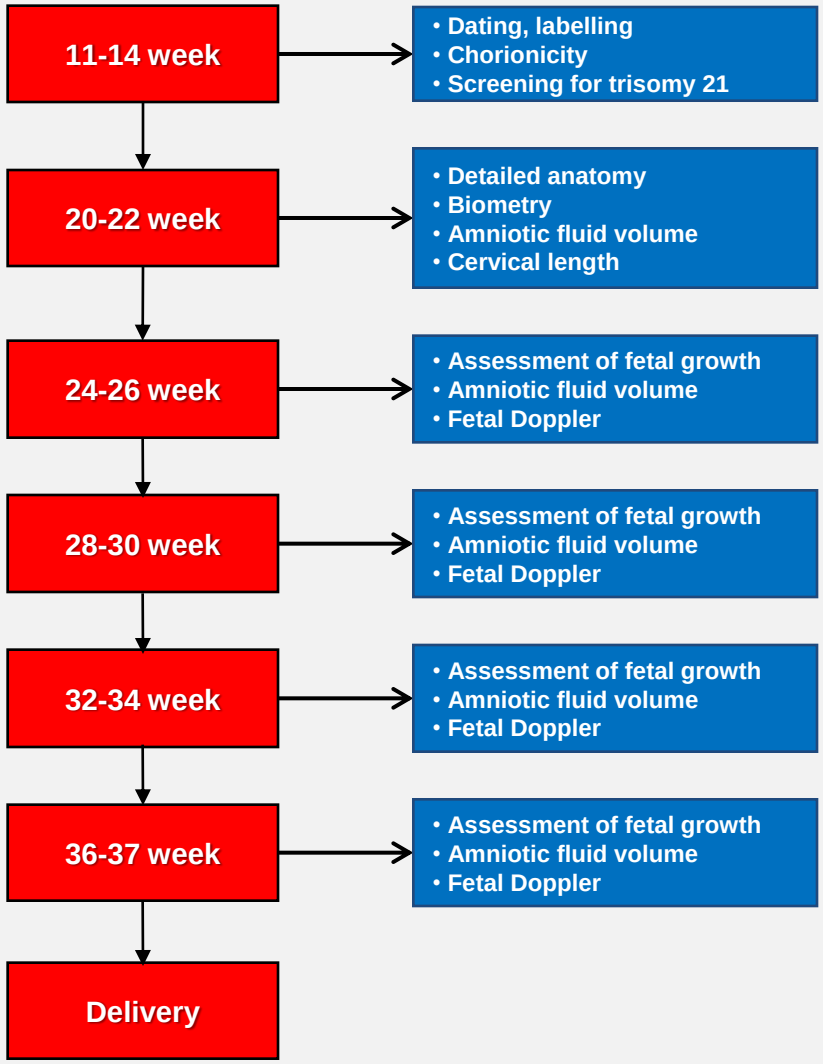
- **Twin A (female) is on maternal right with a posterior placenta and marginal cord insertion.**
- **Discordant twin: twin A, potential recipient**
- **MCMA twins**

- **Perinatal switch phenomenon**

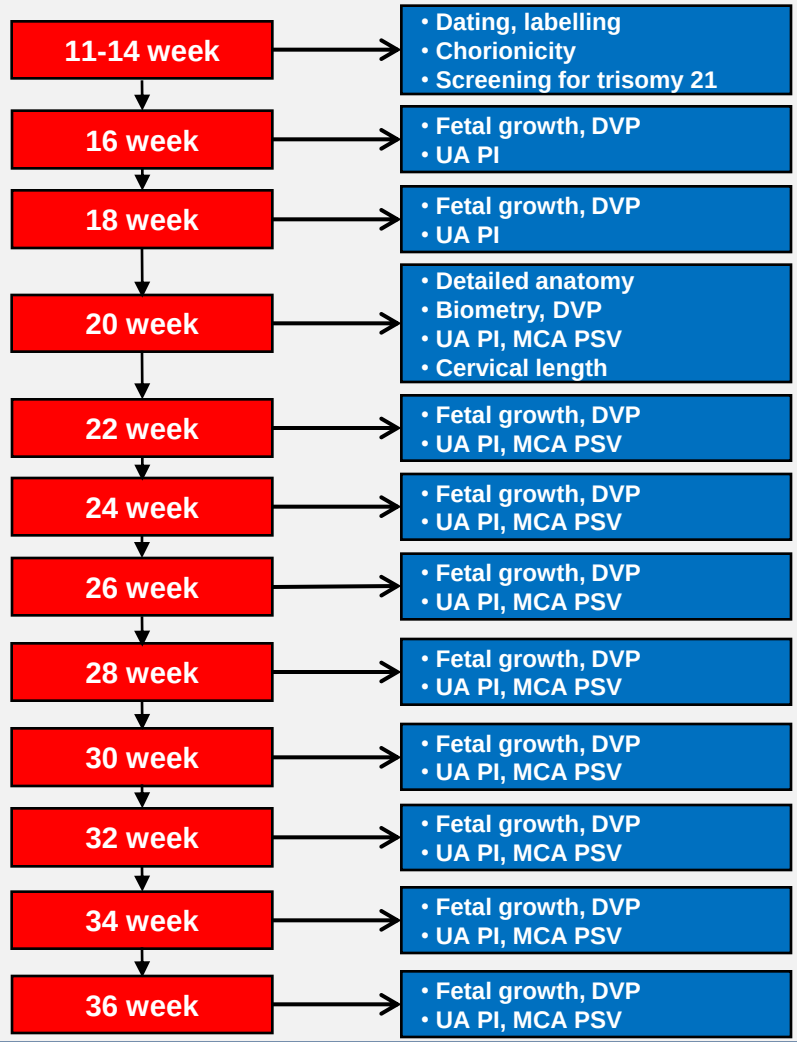


Twin Pregnancy: ultrasound monitoring

Dichorionic Twin Pregnancy



Monochorionic Twin Pregnancy



Twin Pregnancy: aneuploidy

How to screen for chromosome abnormalities?	
• Screening for trisomy 21 can be performed in the first trimester using *the combined test*. An alternative is the combination of maternal age + NT only.	B
• In case of a vanished twin, if there is still a measurable fetal pole, NT alone, in combination with maternal age, should be used for risk estimation.	B
• The DR of NIPT for trisomy 21 may be lower in twins than in singletons, but the data are still limited.	B

- Singleton: DR 99% for a FPR of 0.1%
- Twins: DR 94.4% for a FPR of 0%

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Twin Pregnancy: aneuploidy

Systematic review of screening for trisomy 21 in twin pregnancies in first trimester combining nuchal translucency and biochemical markers: a meta-analysis

Pilar Prats[1]*, Ignacio Rodríguez[1], Carmina Comas[1] and Bienvenido Puerto[2]

[1]Fetal Medicine Service, Department of Obstetrics, Gynecology and Reproductive Medicine, Hospital Universitari Quirón Dexeus, Barcelona, Spain
[2]Department of Maternal Fetal Medicine, Institut Clinic de Ginecologia, Obstetrícia I Neonatologia, Hospital Clínic, Barcelona, Spain
*Correspondence to: Pilar Prats. E-mail: pilpra@dexeus.com

Combined test in twins

	Pooled DR	Pooled FPR
Dichorionic	86.0% (72.8-93.6)	5% (4-6)
Monochorionic	87.4% (52.6-97.7)	5% (4-6)

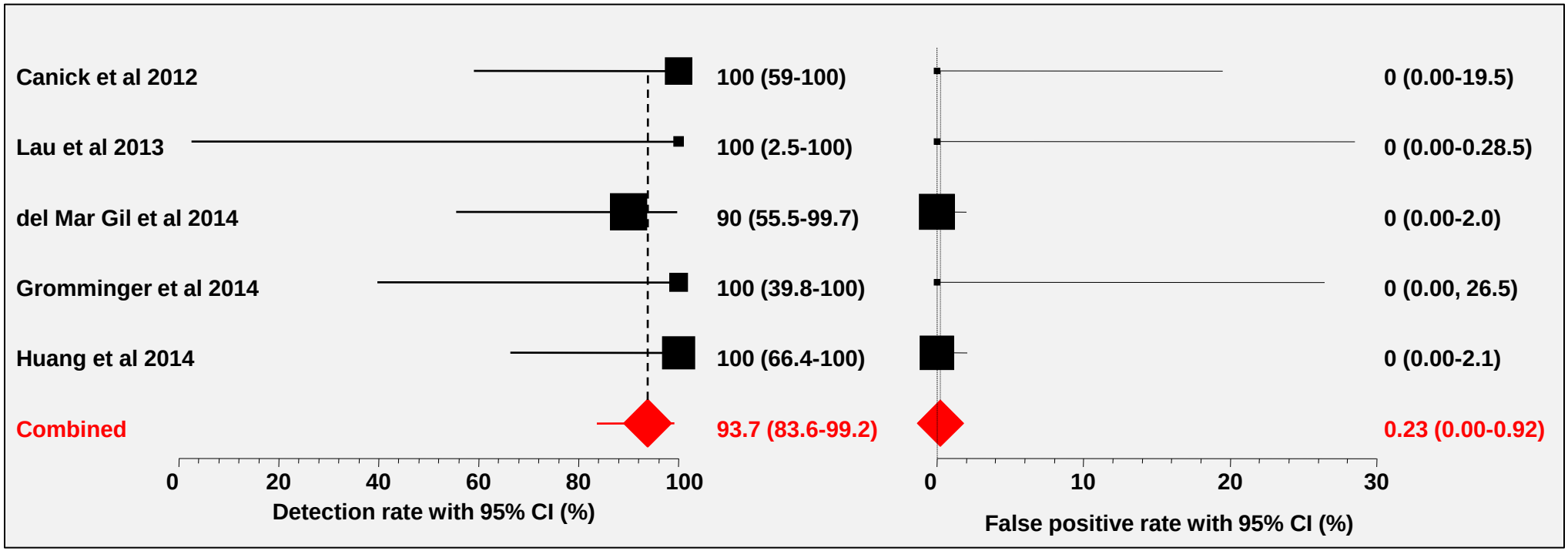
Prats et al *Prenat Diagn* 2014

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The challenges of cfDNA screening in twins

cfDNA in Twin Pregnancies

Trisomy 21



Canick et al 2012; Lau et al 2013; Gil et al 2014; Gromminger et al 2014; Huang et al 2014; Gil MM et al. *UOG* 2015

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The challenges of cfDNA screening in twins

cfDNA in Twin Pregnancies

	Total	Trisomy 21	Detection
Sehnert et al 2011	5	2	all
Canick et al 2012	25	7	all
Lau et al 2013	12	1	all
Gil et al 2014	192	10	all
Xuan et al 2014	189	9	all

- Stored samples
- Dichorionic vs monochorionic
- Other trisomies
- Fetal fraction (DZ vs MZ)
  - 6% in twin
  - 4% in singleton

Sehnert et al., 2011; Canick et al 2012; Lau et al 2013; Gil et al 2014; Xuan et al 2014; Gil MM et al *UOG* 2015

Twin Pregnancy: aneuploidy

Invasive Prenatal Diagnosis in Twin Pregnancy	
• CVS is preferred in DC twin pregnancies.	D

- Discordant MCDA twins: Double amniocentesis (heterokaryotypic)
- DC twins: selective termination in the first compared to the second trimester (7% risk of miscarriage, and14% risk of PTB <32 weeks
- MC twins: cord occlusion from 16 weeks (>80% survival)



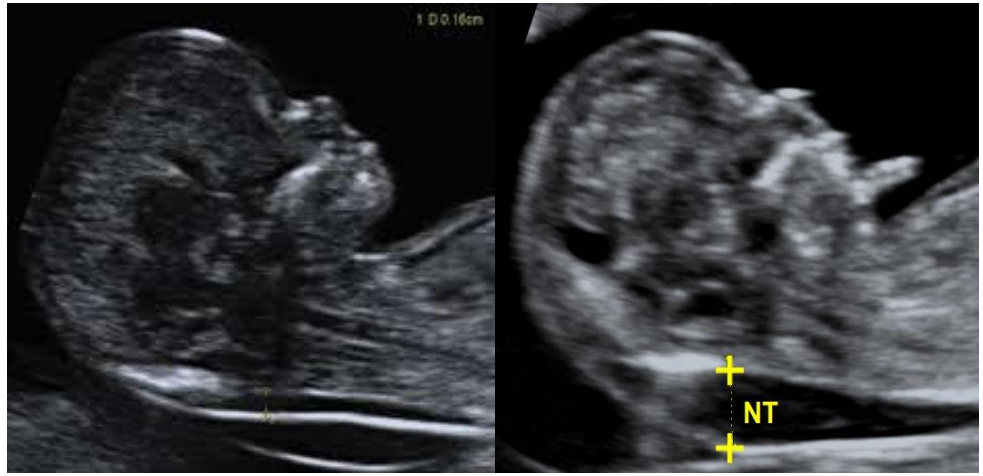
Twin Pregnancy: aneuploidy

What are the implications of discordance in NT or CRL?

- **The management of twin pregnancies with CRL discordance ≥10% or of NT discordance ≥20% should be discussed with a fetal medicine expert.** **B**

- **Detailed ultrasound assessment**
- **karyotype/array-CGH**

Risk of fetal abnormalities 25% with CRL discordance ≥10%, compared with 4% in pregnancies with CRL discordance <10%



CRL discordance at 7+0 to 9+6 weeks is a predictor of the risk of single fetal demise in the first trimester (DR of 74% for an FPR of 5%)

Twin Pregnancy: Structural abnormalities

Ultrasound screening for structural abnormalities

- **The fetuses should be assessed for the presence of any major anomalies at the first trimester scan, and routine second trimester (anomaly) scan should be performed at around 20 (18-22) weeks.** ☑
- **Cardiac assessment should be performed in MC twins.** ☑



Twin Pregnancy: Discordant anomaly

How should twin pregnancies discordant for fetal anomaly be managed?	
• Twin pregnancies discordant for fetal anomaly should be referred to a regional fetal medicine center.	☑

- lethal abnormality with a high risk of intrauterine demise:
  - DC twins: conservative management
  - MC twin: selective termination to protect the healthy cotwin against the adverse effects of spontaneous demise.



Twin Pregnancy: Discordant anomaly

Selective Feticide in Twin Pregnancies	
• In DC pregnancies, ultrasound-guided intracardiac or intrafunicular injection of KCl or lignocaine, preferably in the first trimester.	B
• When the diagnosis is made in the second trimester, women might opt for late selective termination in the third trimester, if the law permits.	☑
• MC twins: cord occlusion, intrafetal laser ablation or radiofrequency ablation.	B

- Survival >80%
- Premature rupture of the membranes and PTB <32 weeks 20%
- Adverse neurological sequelae

Twin Pregnancy: Preterm birth

What is the best method to screen for the risk of preterm birth in twin pregnancies?	
• Cervical length measurement is the preferred method of screening for preterm birth in twins; 25 mm is the most commonly used cut-off in the second trimester.	B

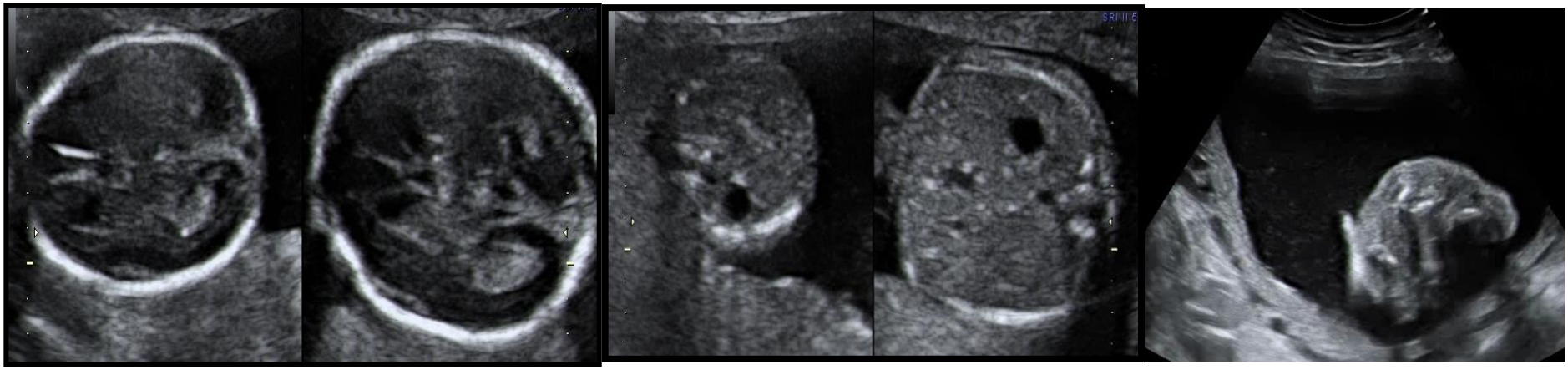
- Cervical length ≤25 mm at 20-24 weeks: pooled +ve LR 9.6 for PTB <28 weeks

- Cervical length ≤25 mm at 20-24 weeks: moderate predictor of PTB <34 weeks, but not <37 weeks



Twin Pregnancy: Fetal Growth Restriction

What are the diagnostic criteria and investigations for selective FGR?	
• sFGR: one fetus with EFW <10th centile + inter-twin EFW discordance >25%.	☑
• A discordance cut-off of 20% seems acceptable to distinguish pregnancies at increased risk of adverse outcome.	B



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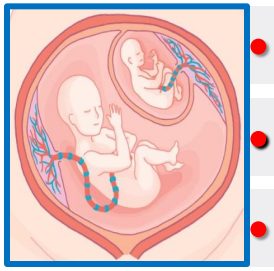
sFGR Delphi

Diagnostic features

DC twins

Solitary: EFW <3rd centile

Contributory: at least 2/3



- EFW <10th centile
- EFW discordance ≥25%
- Umbilical PI >95th centile

MC twins

Solitary: EFW <3rd centile

Contributory: at least 2/4



- EFW <10th centile
- EFW discordance ≥25%
- Umbilical PI >95th centile
- AC <10th centile

Twin Pregnancy: Fetal Growth Restriction

How best to screen for FGR in twin pregnancy?	
• A combination of head, abdomen and femur measurements performs best in calculating the EFW.	B
• If inter-twin discordance is ≥25%, a referral should be made to a tertiary fetal medicine center.	☑

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Multiple pregnancy

Screening for IUGR in Twins

NHS
National Institute for Health and Clinical Excellence

Issue date: September 2011

Multiple pregnancy

The management of twin and triplet pregnancies in the antenatal period

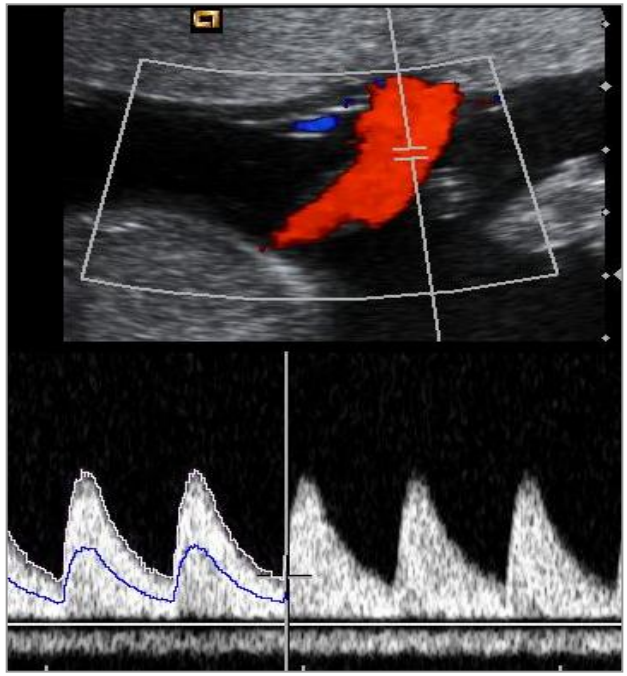
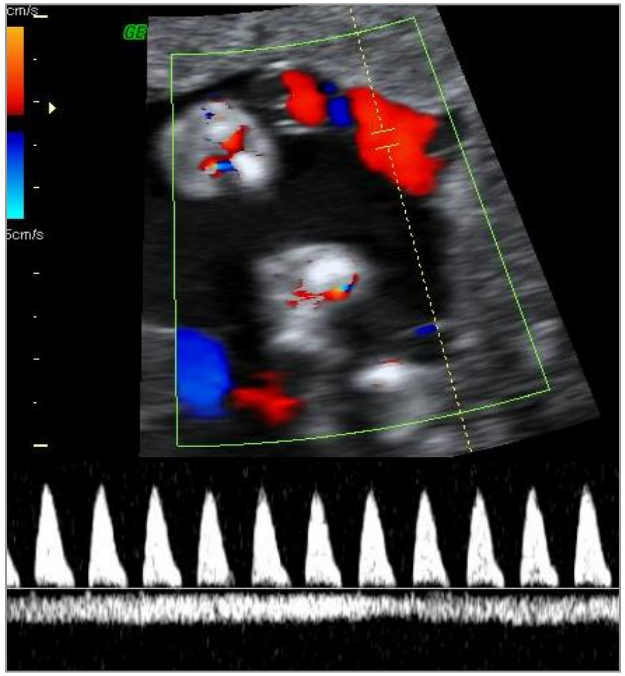
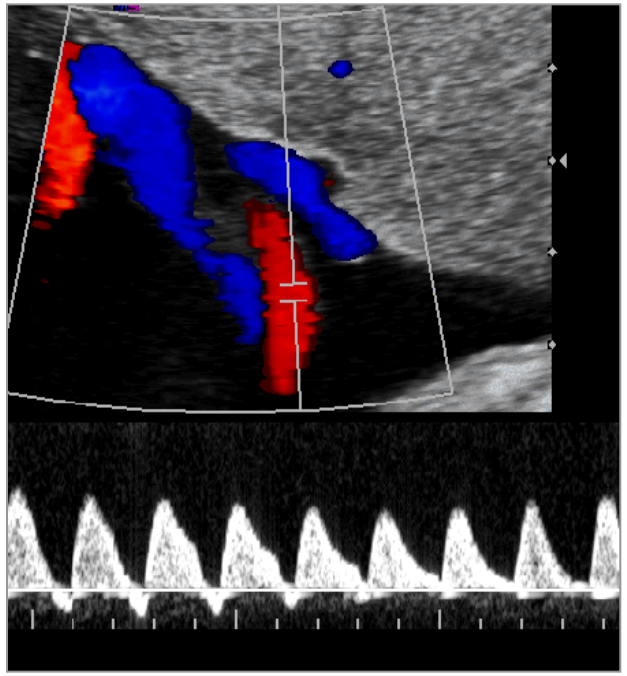
- Estimate fetal weight discordance at each scan from 20 wk.
- Do not scan more than 28 days apart.
- Consider a ≥ 25% difference in size as clinically important and refer woman to a 3ry level fetal medicine centre.

NICE 2011

Twin Pregnancy: Fetal Growth Restriction

How should monochorionic twin pregnancies complicated by sFGR be classified?

- **depends on the pattern of the end-diastolic velocity in the umbilical artery Doppler.** ☑

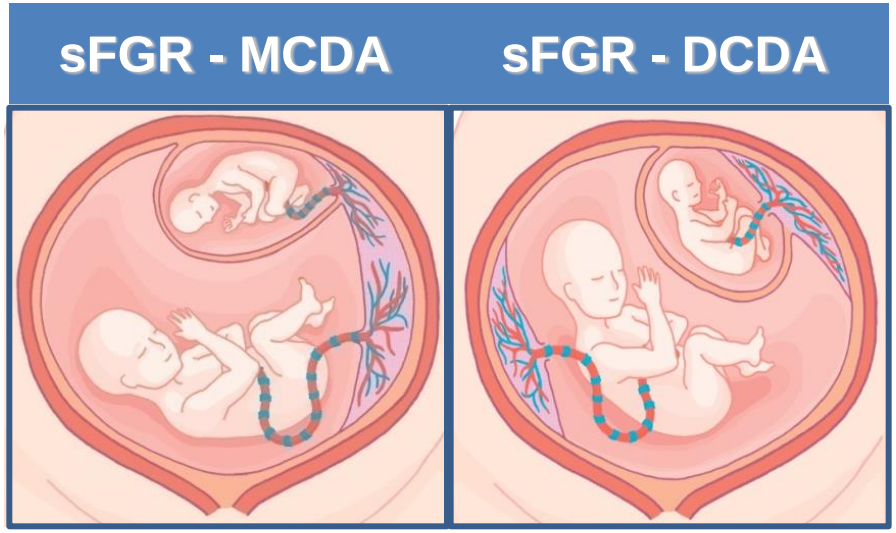
Type 1	Type 2	Type 3
		

Twin Pregnancy: Fetal Growth Restriction

What is the management of twin pregnancies complicated by sFGR?	
• In dichorionic pregnancies, sFGR can be followed as in growth-restricted singletons.	☑
• There is limited evidence to guide the management of monochorionic twins affected by sFGR.	☑

Options include:

- Conservative management followed by early delivery
- Laser ablation
- Cord occlusion



Twin Pregnancy: sFGR

What is the follow-up protocol for sFGR?

- In DC sFGR fetal Dopplers should be assessed every two weeks depending on the severity. In *MC* sFGR pregnancies fetal Dopplers should be assessed *at least weekly*. ☑

- If there is a substantial risk of fetal demise of the smaller twin (e.g. reversed a-wave in DV) **D**
  - >26 weeks: consider delivery
  - <26 weeks: consider selective termination

Delivery

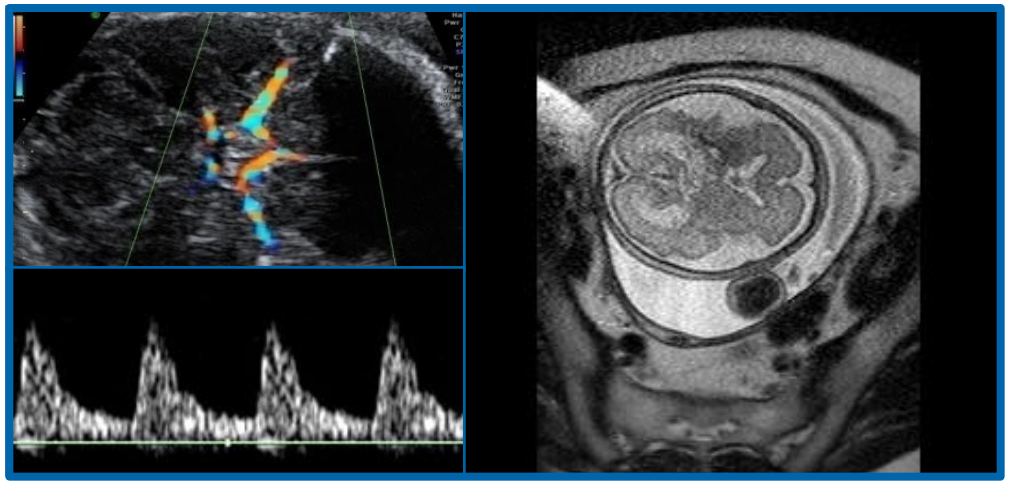
- sFGR type 1: 34-36 weeks
- sFGR type 2 and 3: 32 weeks or earlier if deterioration

Twin Pregnancy: Single fetal death

How should the surviving twin be managed after the demise of its co-twin?

- **When single fetal death occurs in a twin pregnancy, the woman should be referred to a tertiary level center with relevant expertise.** ☑

	MC	DC
Death of co-twin	15%	3%
Preterm delivery	68%	54%
PN brain abn	34%	16%
Neurological abn	26%	2%



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Twin Pregnancy: Single fetal death

Death of one fetus

sIUD in MC twin pregnancy

↓

Referral to Fetal Medicine Centre:
- **Detailed scan**
- **umbilical, MCA PSV, DV Doppler**
- **Counselling** (15% IUD, 25% neurological morbidity vs 2% in DC)

↓

Fetal biometry + Dopplers /2weeks

↓

Fetal brain MRI 4-6 weeks after sIUD →
- **TOP if abnormal**
- **PM (fetus + placenta)**

↓

Delivery at 34-36 wk after steroids

Senat MV et al. AJOG 2003

Hillman SC et al. Obstet Gynecol.2011

Hillman SC et al. Semin Fetal Neonatal Med 2010

What is the staging of TTTS?

- **Although Quintero staging does not always accurately predict outcome or chronological evolution of TTTS, it still remains the most commonly used classification system.** ☑

Stage	Classification
I	Polyhydramnios oligohydramnios sequence: DVP >8cm in the recipient and DVP < 2cm in the donor
II	Bladder in the donor twin not visible on ultrasound scan
III	Absent or reversed umbilical artery diastolic flow, reversed ductus venosus a-wave flow, pulsatile umbilical vein flow in either twin
IV	Hydrops in one or both twins
V	Death of one or both twins



Twin Pregnancy: TTTS

What is the treatment of choice for TTTS?	
• Laser ablation is the treatment of choice for TTTS at Quintero stage ≥II.	A
• Conservative management with close surveillance or laser ablation can be considered for Quintero stage I.	B
• When laser expertise is not available, serial amnioreduction is an acceptable alternative after 26 weeks.	A

Centres performing Laser for TTTS: at least 15 procedures/year

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Twin Pregnancy: TTTS

Evolution of Stage 1 TTTS: Systematic Review and Meta-Analysis

Progression 27%

	Expectant	Amnioreduction	Laser
Overall survival	79%	77%	68%
Double survival	70%	67%	54%
At least 1 survival	87%	86%	81%

Khalil *et al* TRHG 2016

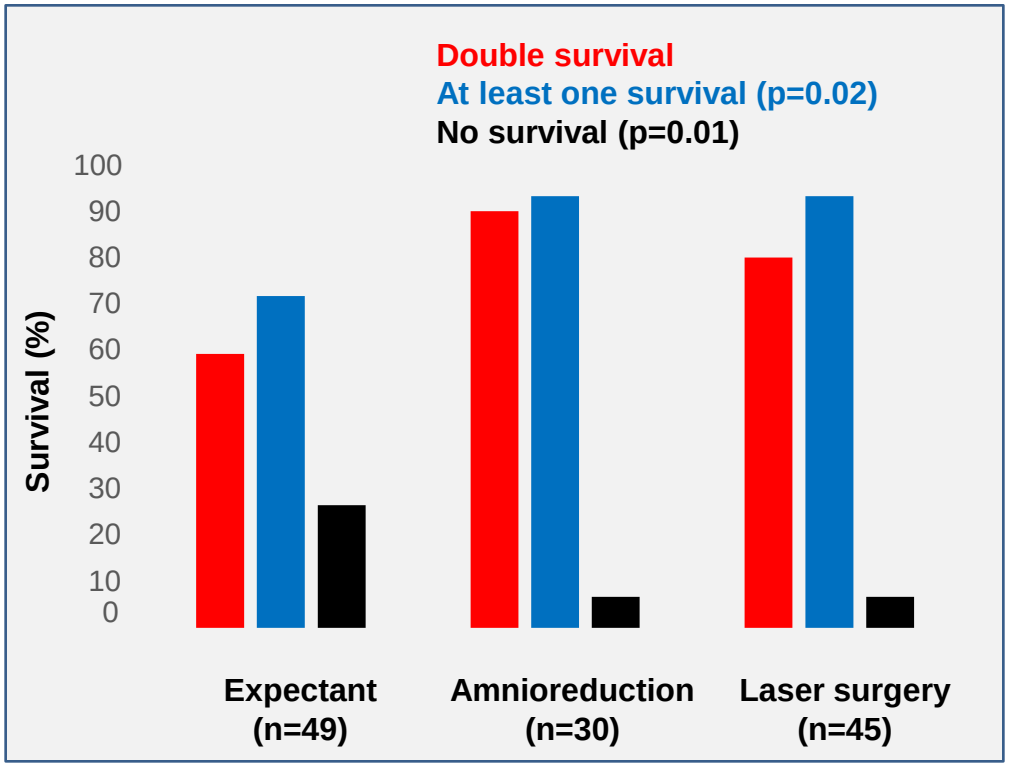
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Twin Pregnancy: TTTS

North American Fetal Therapy Network: intervention vs expectant management for stage I twin-twin transfusion syndrome

- Retrospective multicentre cohort study
- Stage I TTTS was associated with substantial fetal mortality
- Progression in 30%
- Both amnioreduction and laser therapy ↓ the chance of no survivors
- Laser was protective against poor outcome independent of multiple factors



Emery *et al* AJOG 2016

Twin Pregnancy: TTTS

What is the protocol for screening for TTTS?	
• Start at 16 weeks and repeat every 2 weeks thereafter	☑

What is the prognosis for MC twin pregnancies with amniotic fluid discordance?	
• Follow up on a weekly basis for progression to TTTS	☑

- Good outcome (93% overall survival)
- Low risk of progression to severe TTTS (14%)

Twin Pregnancy: TTTS

How should TTTS be followed-up and what is the optimal GA for delivery?	
• Weekly ultrasound assessment for the first two weeks after treatment, reducing to alternate weeks following clinical evidence of resolution.	☑

• In case of sIUD (post-laser)
  • Brain imaging in 4-6 weeks
  • Neurodevelopmental assessment at 2 years of age
	☑

GA at delivery: 34 weeks

Stirnemann et al *AJOG* 2012

Twin Pregnancy: TTTS

What is the risk of brain abnormalities and neurodevelopmental delay?

- **TTTS, sIUD, sFGR or TAPS: neurodevelopmental disability**

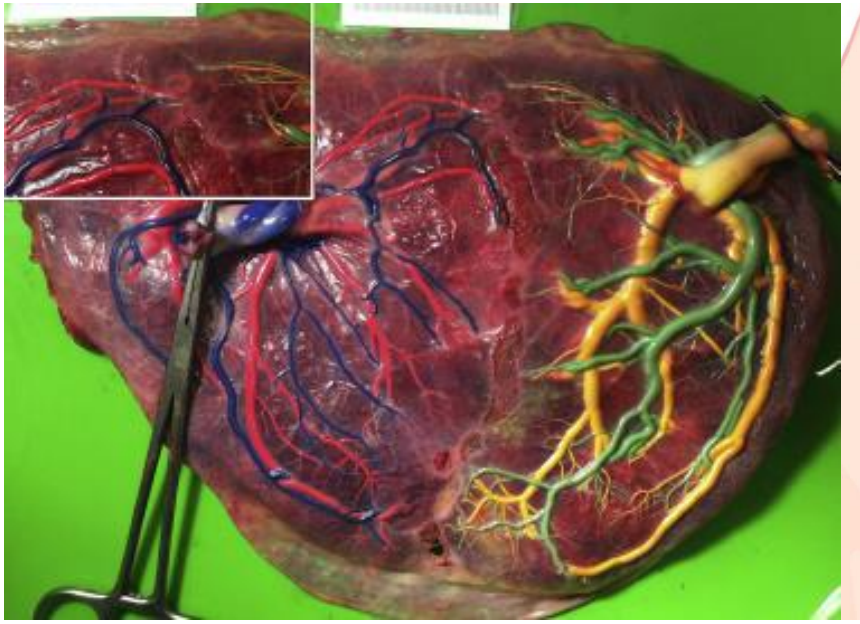
- **In TTTS, cerebral abnormalities reported in:**
  - **5% laser coagulation, 14% amnioreduction, 21% expectant management**
  - **Both donors and recipients are at risk**
  - **Mainly ischemic or hemorrhagic lesions**

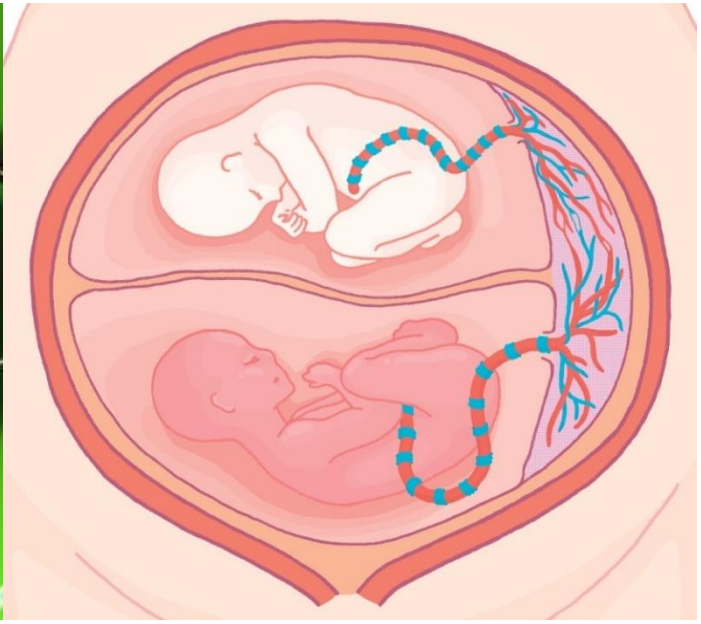
- **In TTTS, major neurological abnormalities:**
  - 7% at 34 months
  - 9% at 6 years

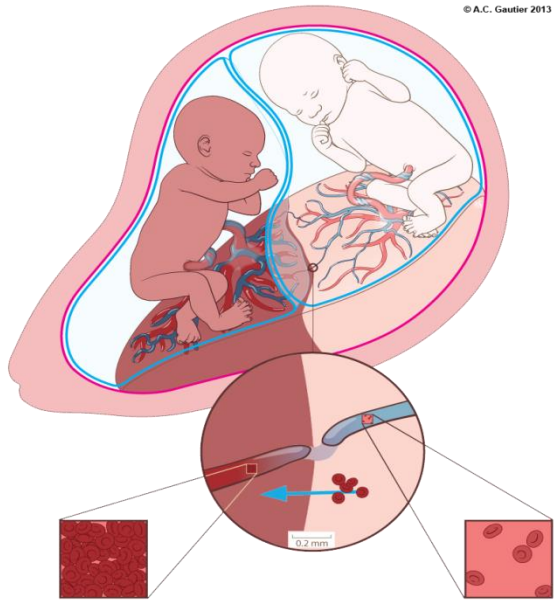
Hoffmann *et al* AJNR 2013
Quarello *et al* JMFNM 2007
Hillman *et al* Obst Gyn 2011
Inklaar *et al* Prenat Diagn 2014
Banek *et al* AJOG 2003
Graef *et al* AJOG 2006
Graeve *et al* Acta Pediat 2012

Twin Pregnancy: TAPS

• The prenatal diagnosis of TAPS is based on the finding of discordant MCA Doppler abnormalities.	D
• Little evidence about the outcome and optimal management of TAPS; therefore treatment options should be individualized and discussed with parents.	☑

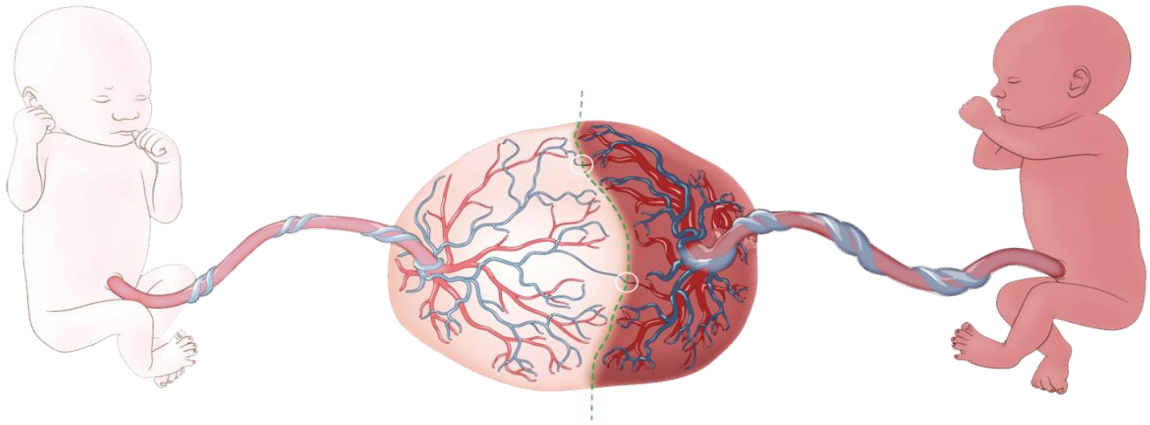






Management

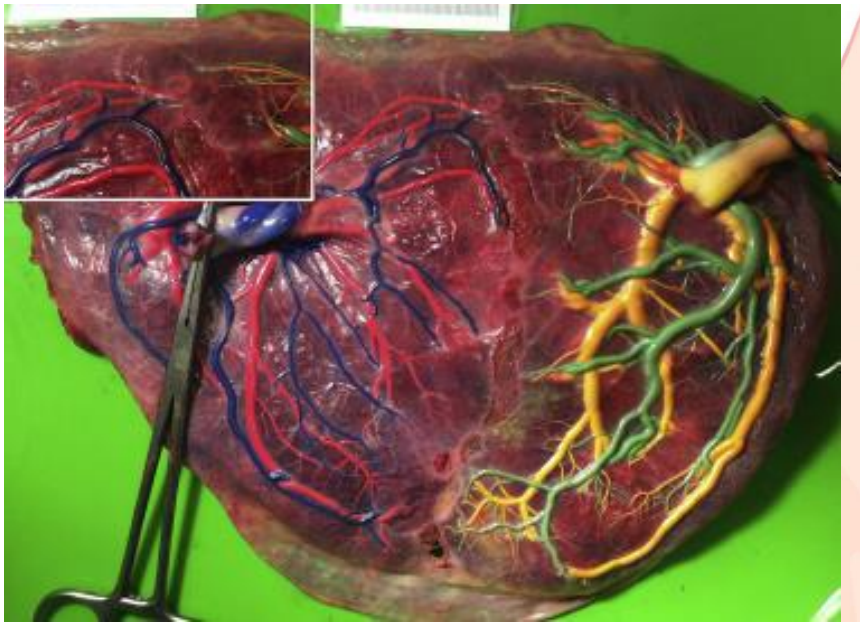
- Expectant
- Delivery
- Intrauterine transfusion
- Selective feticide
- Fetoscopic laser

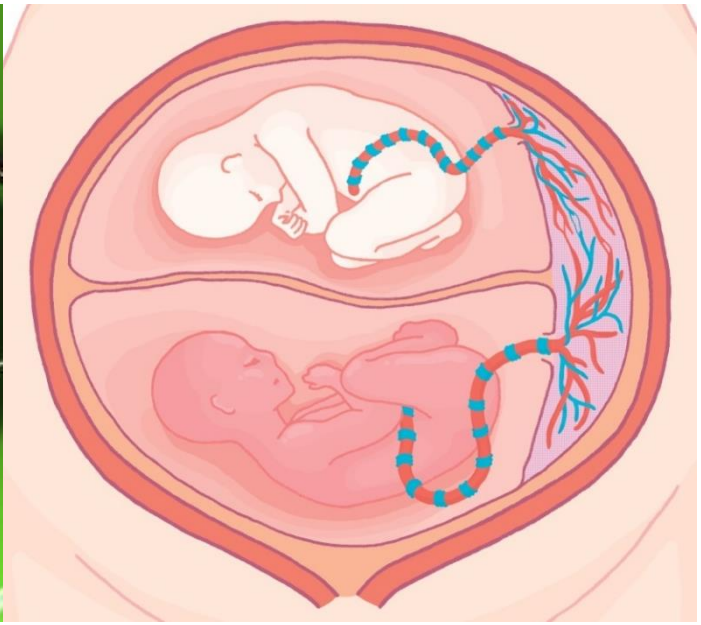


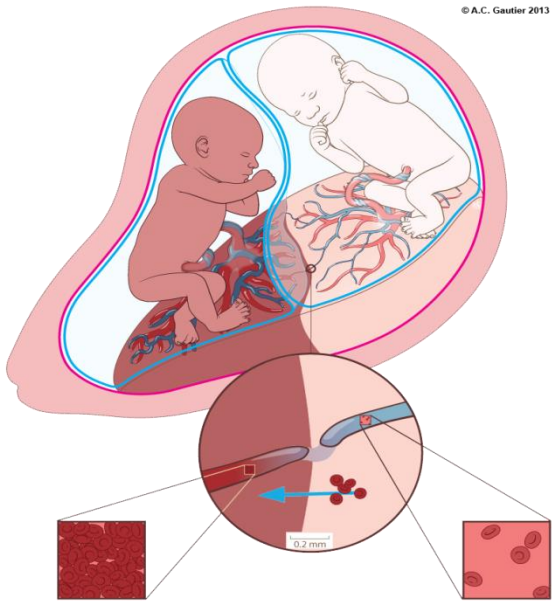
Lopriore et al, AJOG 2008
Herway et al, UOG 2009
Slaghekke et al, Fetal Diagn Ther 2010
Lopriore et al, Placenta 2007
Genova et al, Fetal Diagn Ther 2013
Slaghekke et al, UOG 2014
Lopriore et al, Prenat Diagn 2010

Twin Pregnancy: TAPS

- Screening: MCA PSV should be measured in all MC twins and during the follow-up of treated TTTS cases
- Prevention: Solomon fetoscopic laser ablation technique







Management of TRAP

- The chances of survival of the pump twin are increased by the use of minimally invasive techniques (preferably <16 weeks) **D**
  - Intrafetal Laser
  - Cord coagulation/ligation
  - Laser photocoagulation of the anastomoses







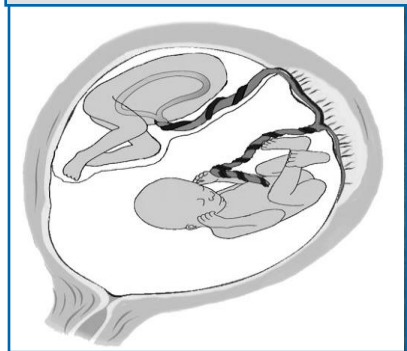


St George's University of London

TRAP sequence

Controversy on timing of intervention

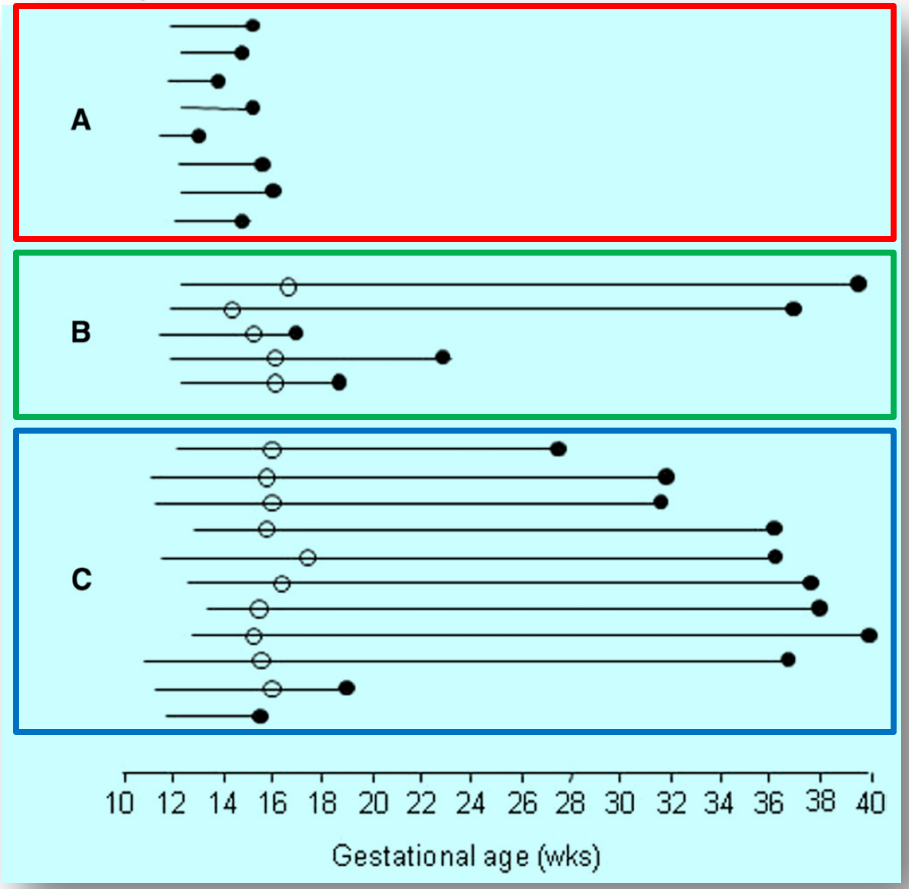
- Risks: demise of the co-twin; preterm birth
- Spontaneous cessation of the flow in the acardiac twin
- High loss rate (54%) between diagnosis in the first trimester and planned intervention at 16 weeks
- Prenatal intervention: 80% survival rate
- Lower very preterm birth rates with early vs late intervention





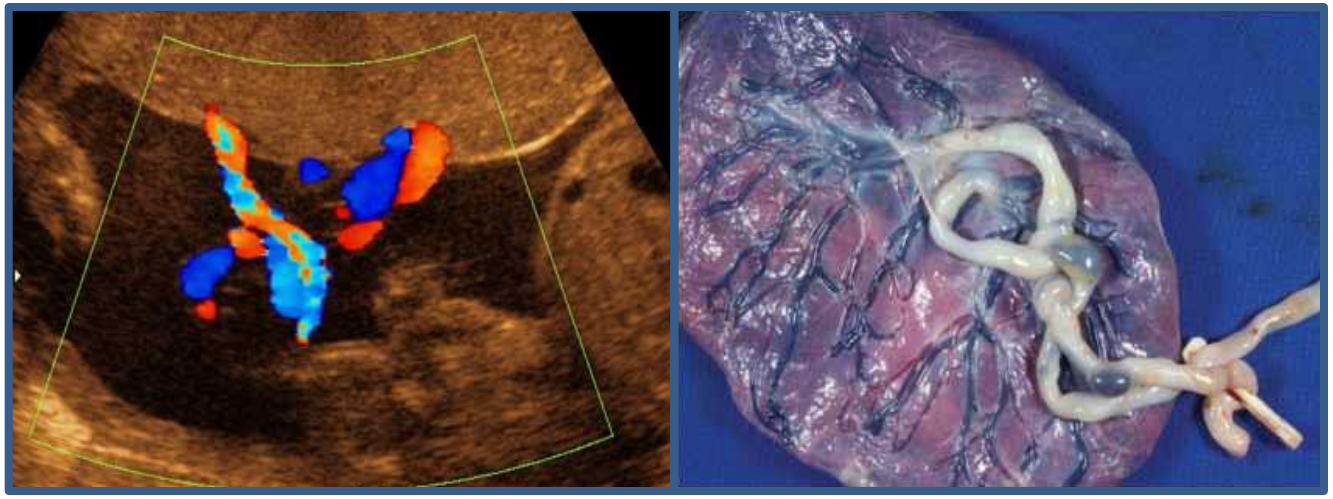


A: Spontaneous demise at 13-16 week
B: Spontaneous arrest of flow at 14-17 week
C: Pump twin alive at 16-18 week with reversed flow



Lewi L, *AJOG* 2010;
Chaveeva P, *Fet Diagn Ther* 2014
Pagani G, *UOG* 2013

MCMA twins	
• Umbilical cord entanglement is almost always present and it does not appear to contribute to their morbidity and mortality.	D
• Delivery by CS is recommended at 32-34 weeks.	D



ISUOG Clinical Standard: Scope

- Dating of the pregnancy
- Determining chorionicity and amnionicity
- Twin labelling
- Timing, frequency and content of ultrasound assessment
- Screening for aneuploidy
- Prenatal diagnosis of aneuploidy
- Screening for structural abnormalities
- Diagnosis and management of discordant twin pregnancy
- Fetal reduction/selective termination
- Screening for preterm birth
- Screening, diagnosis and management of FGR
- Management of multiple pregnancy complicated by single in utero death
- Complications unique to monochorionic twin pregnancies
    - Screening, diagnosis and management of TTTS
    - Screening, diagnosis and management of TAPS
    - Management of TRAP sequence
    - Management of MCMA twin pregnancy
    - Diagnosis and management of conjoined twins

ISUOG Clinical Standard: Twin Pregnancy



