Clinical assessment of fetal well-being and fetal safety indicators

UCL EGA Institute for Women's Health

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Professor and Consultant in Obstetrics and Maternal Fetal Medicine

General health

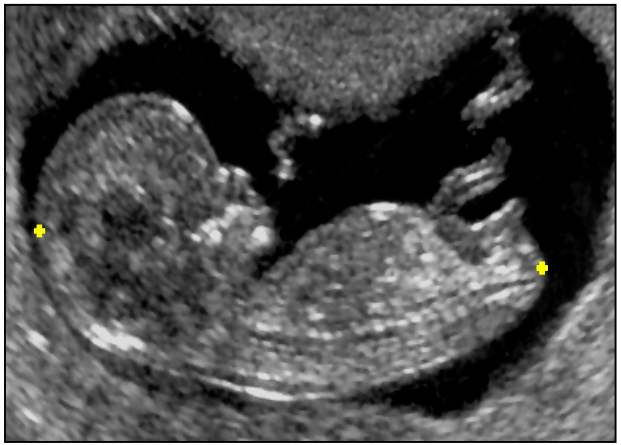
Mother
Fetus
Neonate

Pregnancy specific

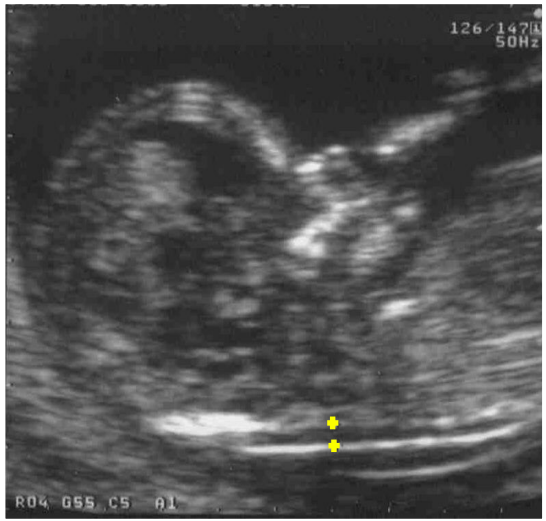
Preterm birth
Fetal growth
Placenta
Liquor
Delivery


But how can we assess fetal wellbeing?

Ultrasound: pregnancy dating, prenatal diagnosis



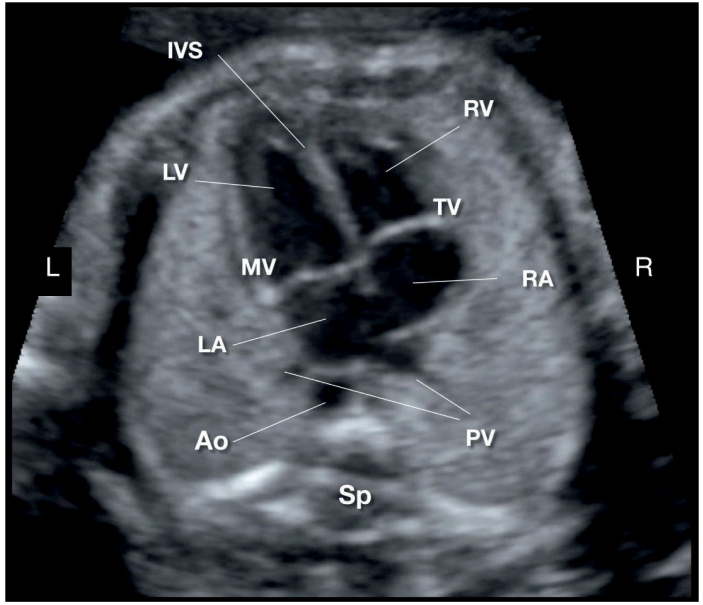
Crown Rump Length
Highly accurate pregnancy dating
Now supercedes assessment of Expected Date of Delivery from the Last Menstrual Period



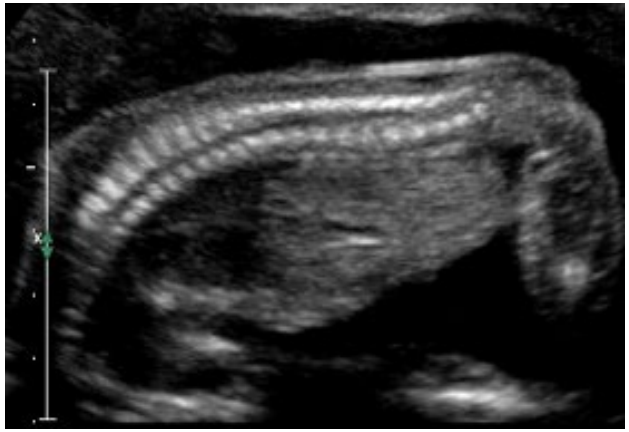
Nuchal translucency
Prenatal diagnosis of aneuploidy, single gene and cardiac disorders

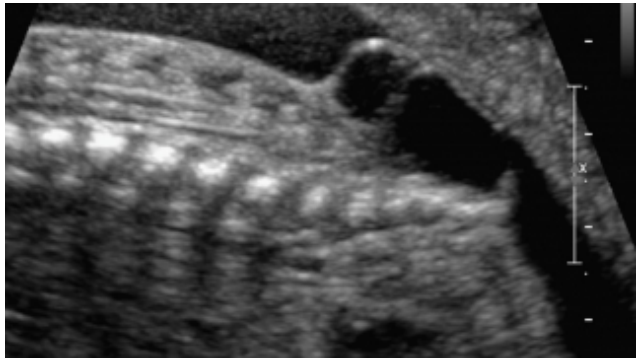
- Gestation 11-14 wks
- CRL 45-84 mm
- Mid-sagittal view
- Image size
- Calipers 0.1mm
- Neutral position
- Away from amnion
- Maximum lucency
- Callipers on-to-on

Ultrasound: fetal structure & function



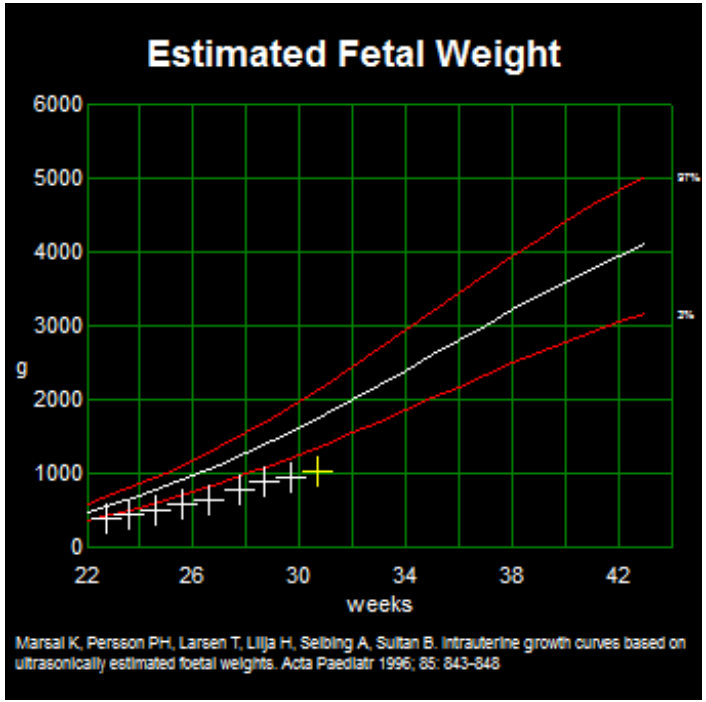
4 chamber view of the heart

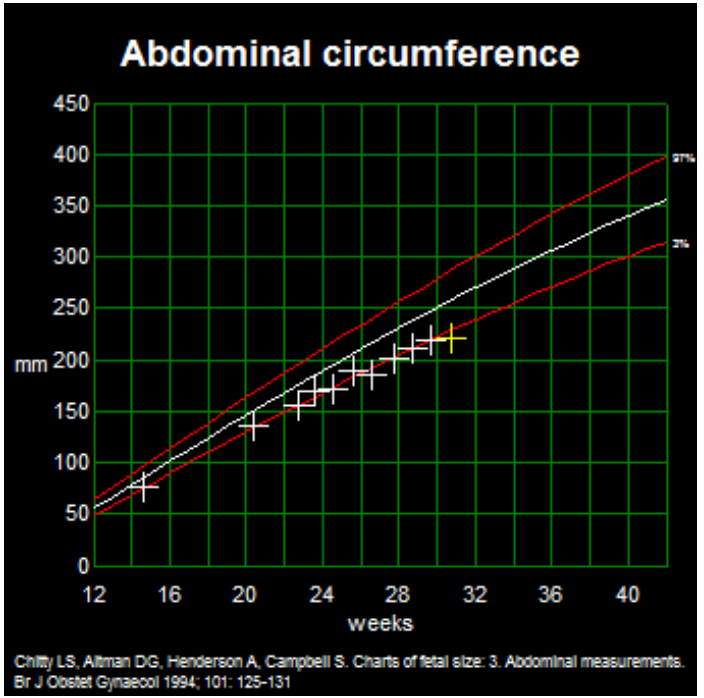




Spina bifida

Ultrasound: fetal size & wellbeing



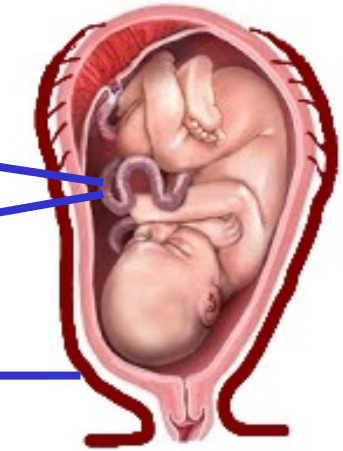


Doppler ultrasound assessment of fetoplacental circulation

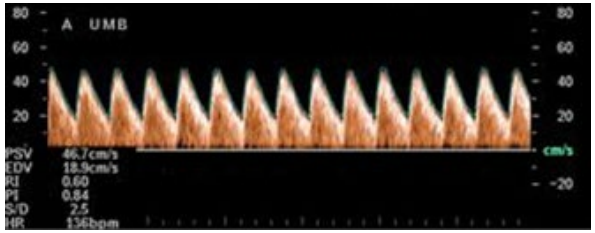
Raised Umbilical artery Pulsatility Index

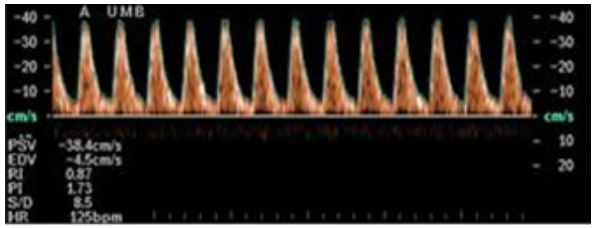
Absent or reversed End-Diastolic Flow

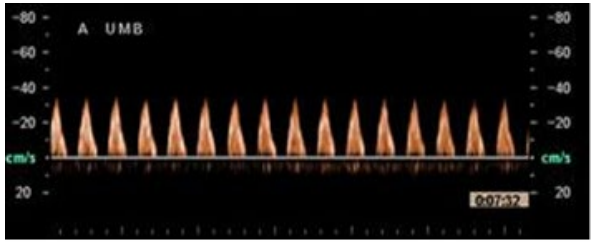
Raised Uterine artery Pulsatility Index

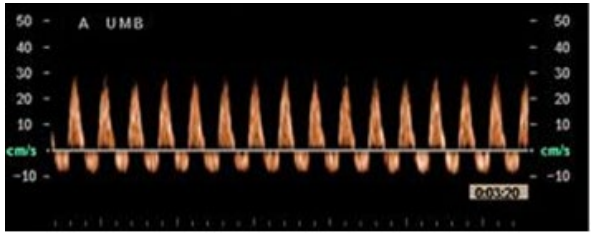


Degree of uteroplacental insufficiency

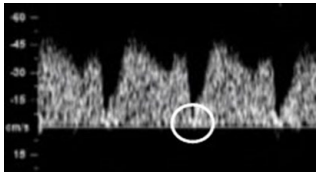


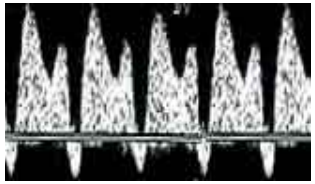




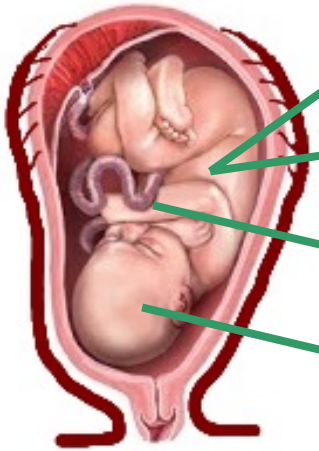


Doppler ultrasound assessment of fetal circulation





Worsening Ductus Venosus flow reflects fetal cardiac compromise and predicts acidosis



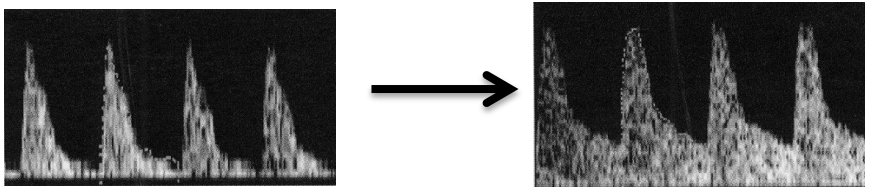
Raised Ductus Venosus Pulsatility Index

Absent or reversed ‘a’ wave

Umbilical Vein pulsation

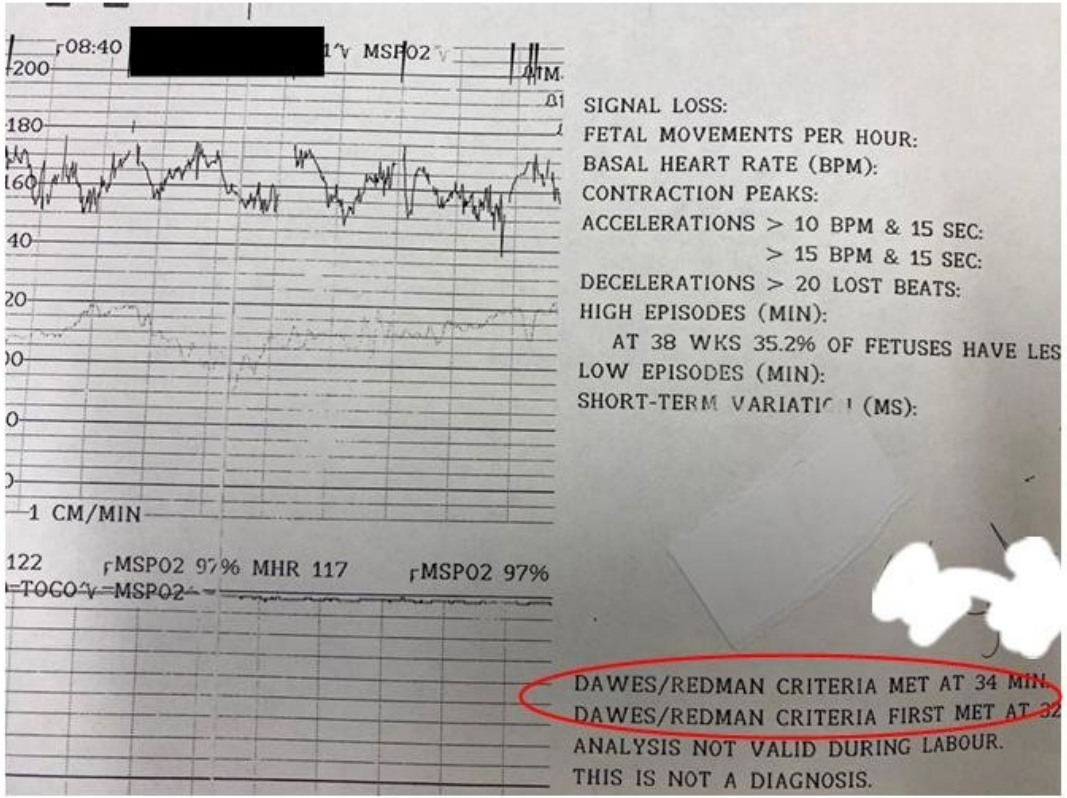
Reduced Middle Cerebral Artery Pulsatility Index

Chronic hypoxia leads to cerebral vasodilatation, associated with later neurodevelopmental delay



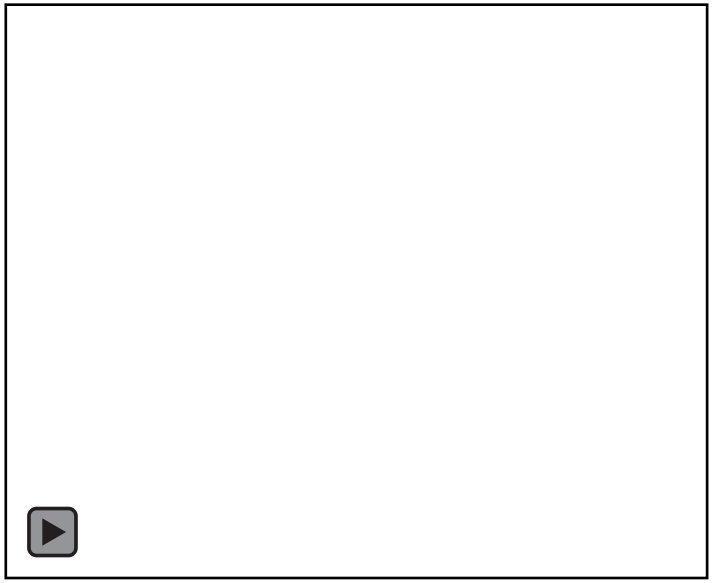
Fetal response

Antenatal Computerized Cardiotocography (CTG)



Short term variability is used to detect fetal hypoxia

Amniocentesis: sampling the amniotic fluid

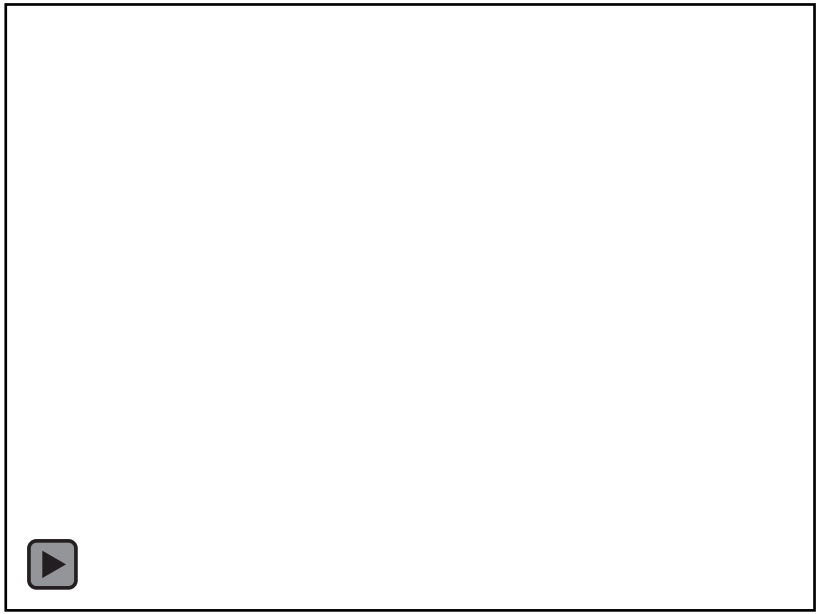


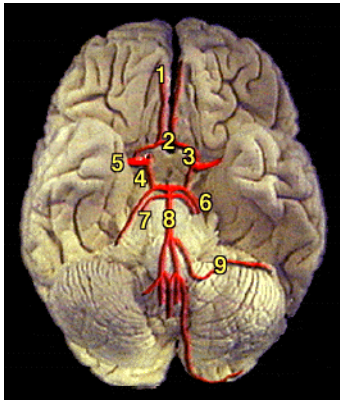
Ultrasound-guided amniocentesis to collect a sample of amniotic fluid at 16 weeks of gestation.
Used in 1980s to detect if a fetus was jaundiced due to severe anaemia.
Now superceded by Doppler ultrasound.

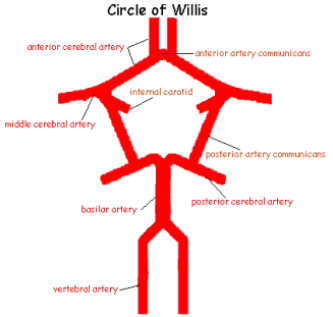
Middle Cerebral Artery Doppler to identify fetal anaemia

NONINVASIVE DIAGNOSIS BY DOPPLER ULTRASONOGRAPHY OF FETAL ANEMIA DUE TO MATERNAL RED-CELL ALLOIMMUNIZATION

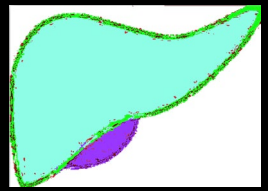
GIANCARLO MARI, M.D., FOR THE COLLABORATIVE GROUP FOR DOPPLER ASSESSMENT OF THE BLOOD VELOCITY IN ANEMIC FETUSES

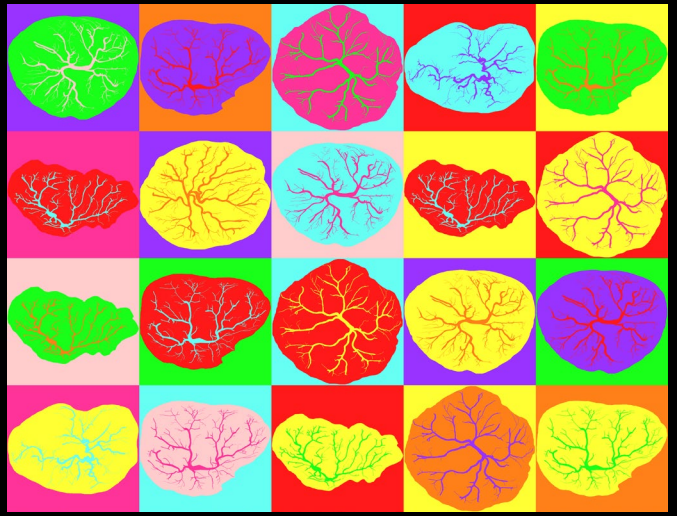


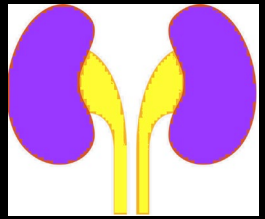




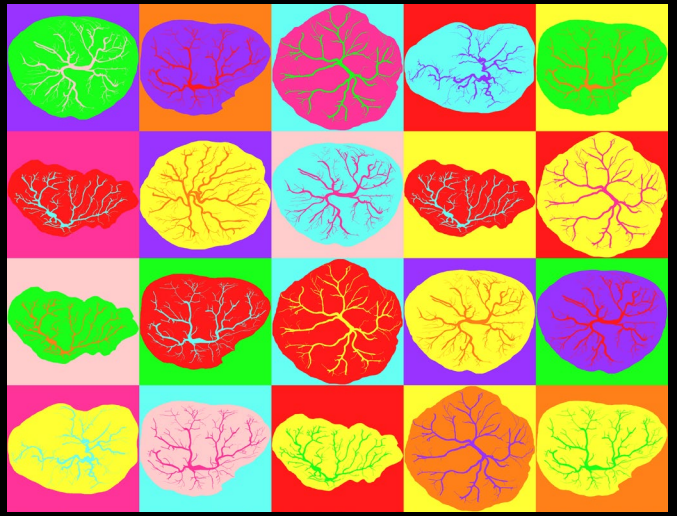
Placenta

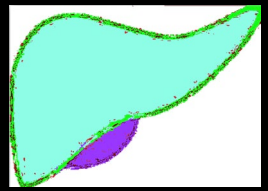


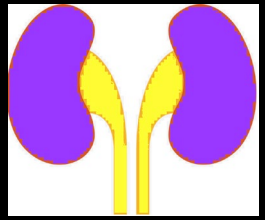


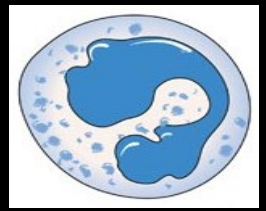


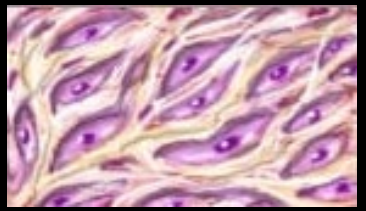
Placenta

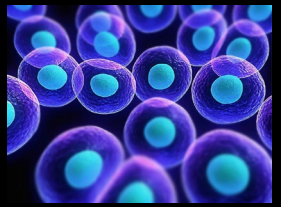




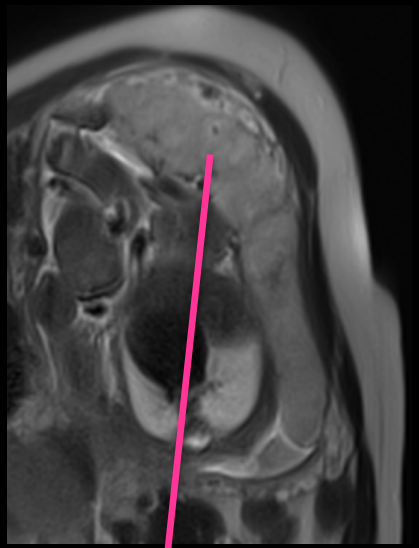




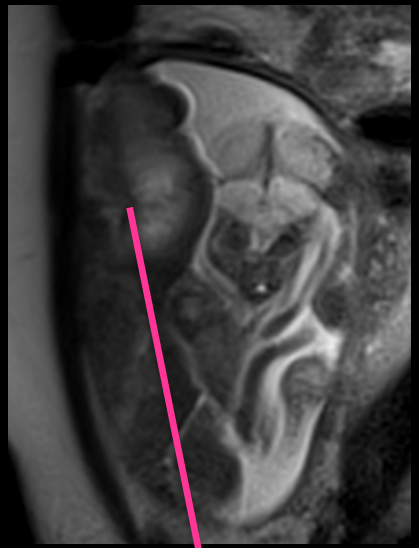




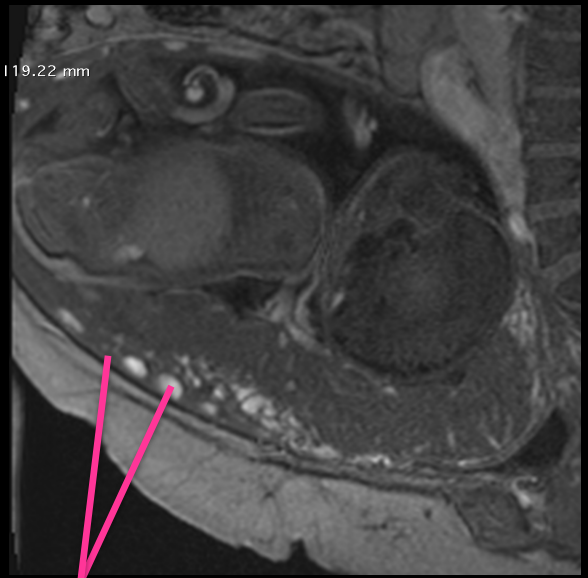
Placental MRI



Normal placenta

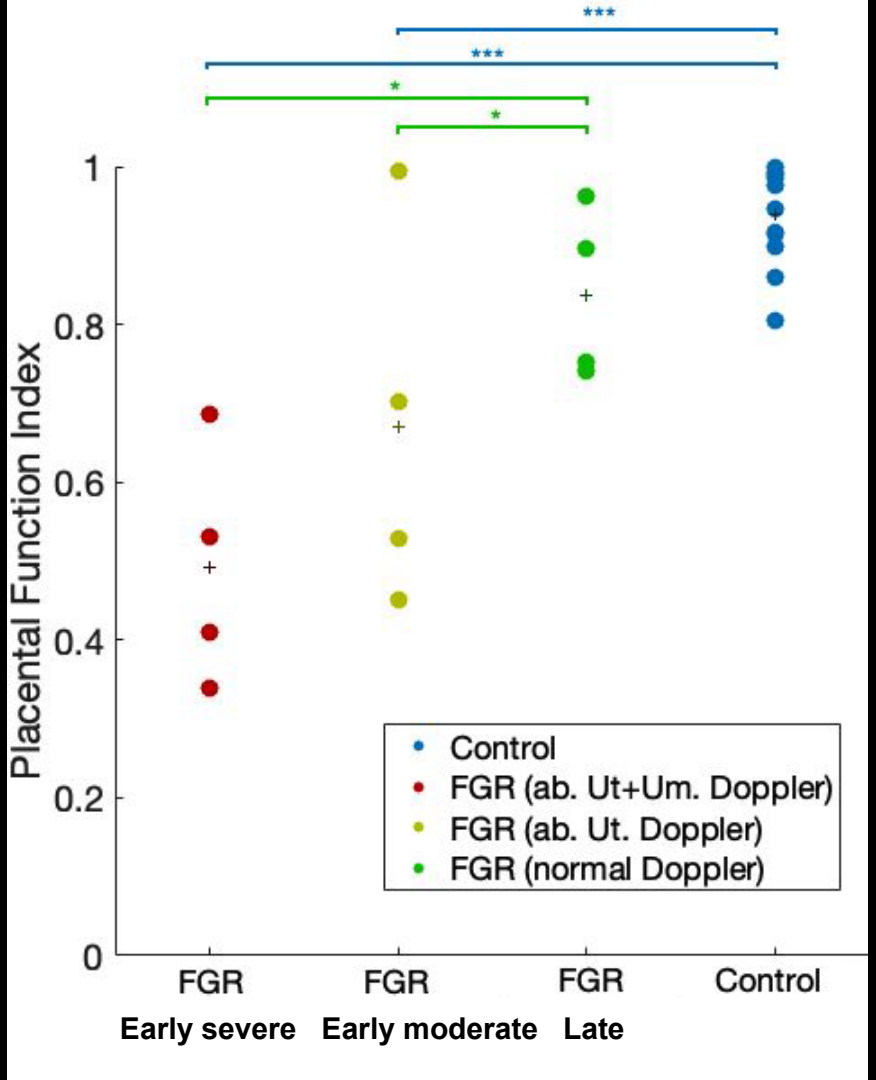


Fetal Growth Restriction



Increased Vascularisation in Placenta Accreta

Fetal MRI commonly used for imaging soft tissues such as the brain or kidneys (but not for the skeleton)



Fetal oxygenation

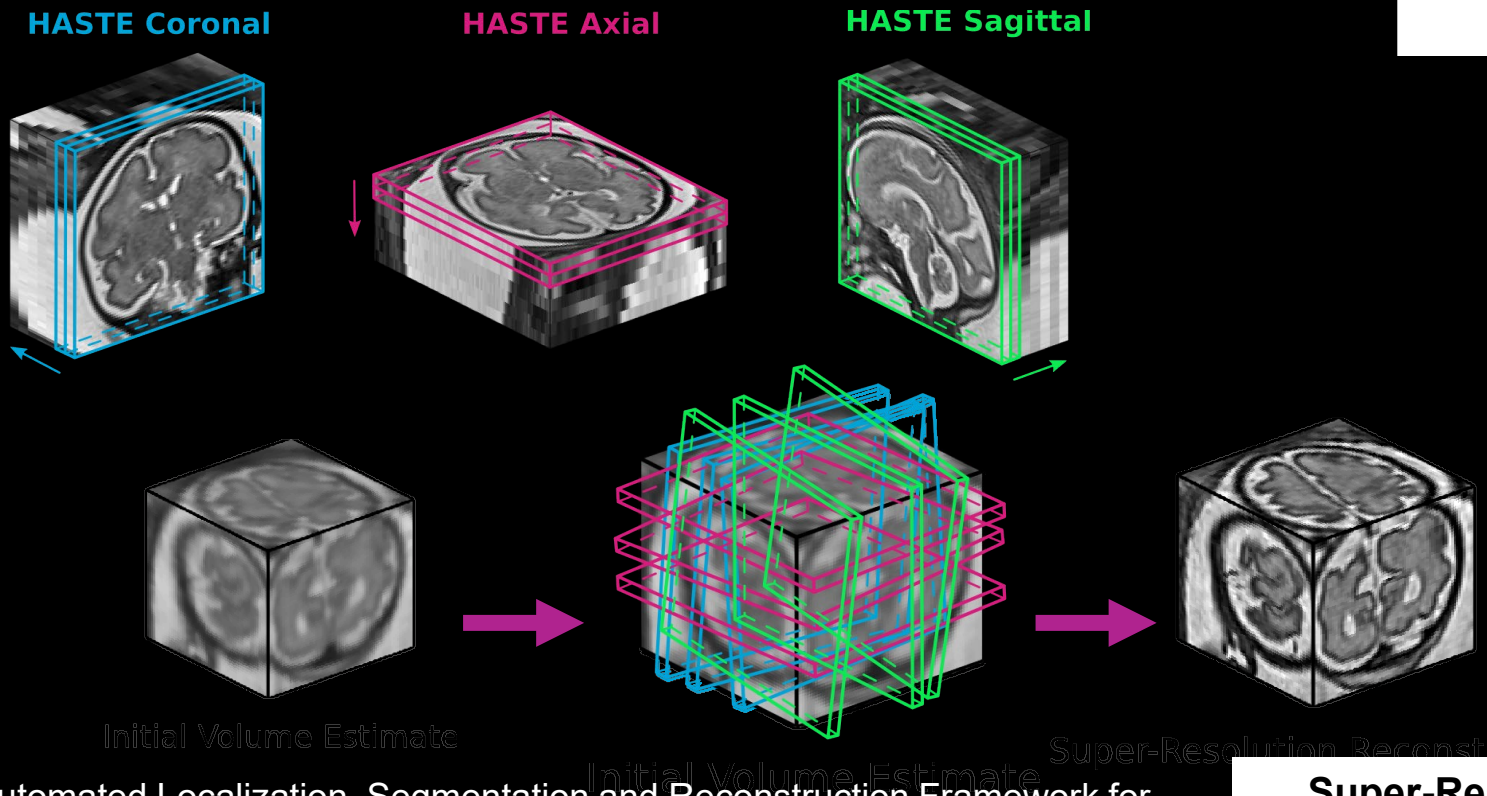
Correlation of MRI 'Placental Functional Index' with severity of Fetal Growth Restriction

* $p<0.05$, ** $p<0.005$

Placental Functional Index = fraction of placenta with mean feto-placental blood oxygen saturation >60%

Aughwane et al 2020 BJOG

MRI: 3D Reconstruction of fetal organs

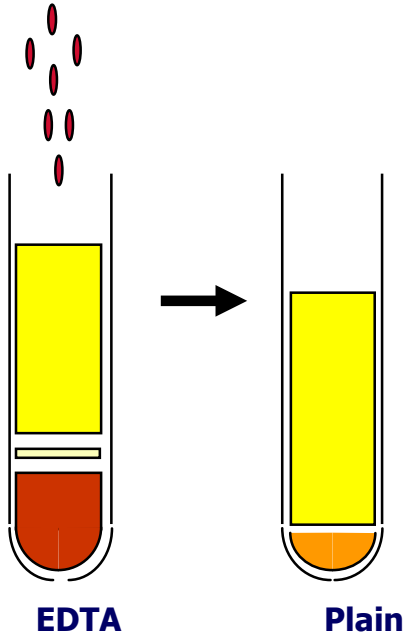


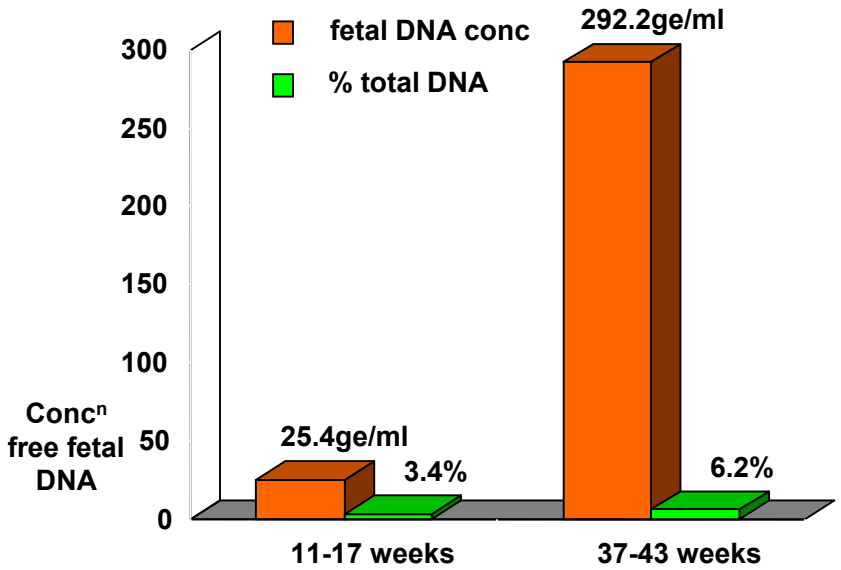
An Automated Localization, Segmentation and Reconstruction Framework for Fetal Brain MRI. Ebner & Wang et al MICCAI (1) 2018: 313-320

Super-Resolution Reconstruction

Circulating fetal DNA: non-invasive prenatal testing

DNA extracted from plasma & fetal DNA amplified with PCR





NIPT for aneuploidy

NIPD for single gene disorders, blood group & gender

Circulating fetal-derived mRNA and microRNA

Can we assess fetal safety?

Adverse Event

- Harm associated with clinical care
- Regulatory definition:
  - “Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product”

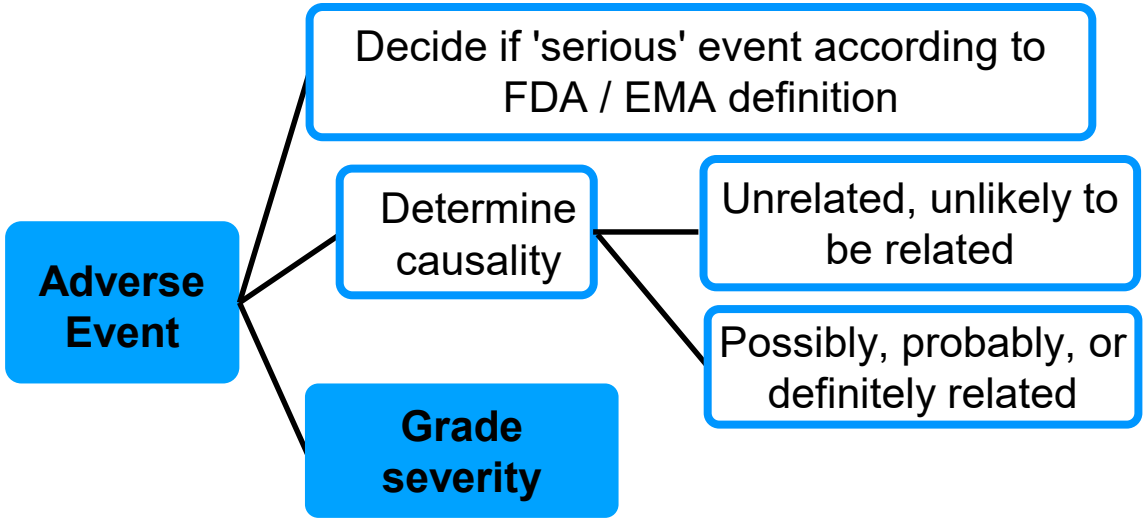
Why are Adverse Events important?

Fundamental part of clinical trial vocabulary

- Important signals in clinical trials
  - facilitate swift and responsible communication of safety data between study investigators, sponsors and regulators
- Regulatory guidelines require that AEs must be
  - recorded in medical records
  - reported to the sponsor and competent authority
  - determined if serious or related to the Investigational Medicinal Product (IMP)
- Develop clinical trial protocols

Adverse Event

- “Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product”



Adverse Event

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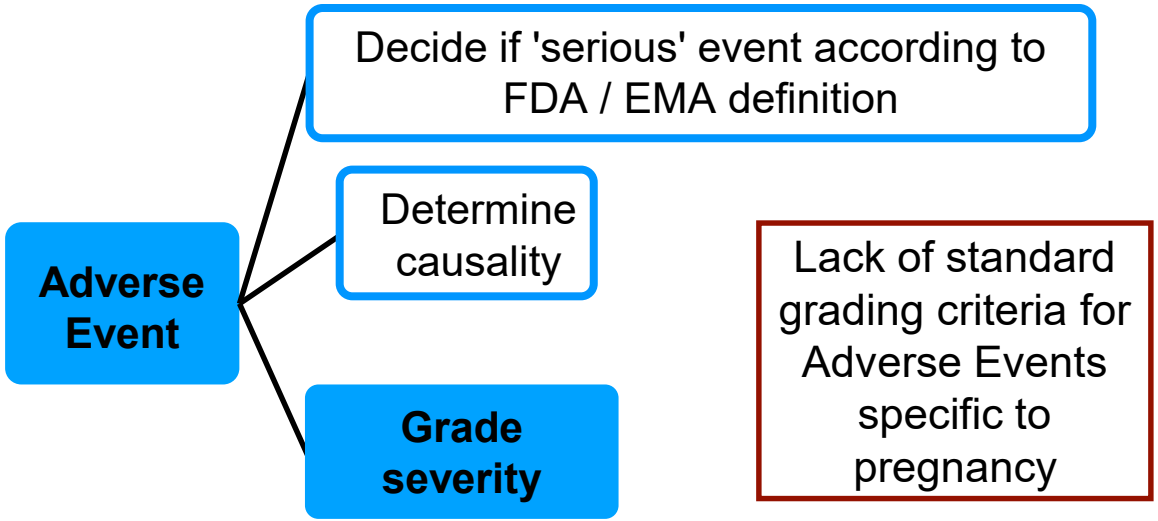

Adverse Event

- **Common Terminology Criteria for Adverse Events (CTCAE)**
- **National Cancer Institute:**
  - **Division of Cancer Treatment & Diagnosis**
  - Latest version 5.0 November 2017
  - Criteria for 837 adverse events
  - 4 events for pregnancy, puerperium & perinatal period
    - fetal death, premature delivery, fetal growth retardation
    - pregnancy, puerperium and postnatal conditions “other”

Adverse Event

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

Adverse Event

- **World Health Organisation** classifies severity of preterm birth according to the gestational age at delivery
  - extremely preterm (less than 28 weeks)
  - very preterm (28 to 32 weeks)
  - moderate to late preterm (32 to 37 weeks).

Adverse Event

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

Classification of Surgical Complications

A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey

Daniel Dindo, MD, Nicolas Demartines, MD, and Pierre-Alain Clavien, MD, PhD, FRCS, FACS

ANNALS OF SURGERY
A MONTHLY REVIEW OF SURGICAL SCIENCE SINCE 1885

Why are Adverse Events important?

Fundamental part of clinical trial vocabulary

- Important signals in clinical trials
- Regulatory guideline requirements
- Develop clinical trials:
  - Define clinical trial inclusion and exclusion criteria
  - Define decisions around dose-escalation and the Maximum Tolerated Dose (MTD) for new IMPs
  - Compare between clinical trials

Issues with AEs in pregnancy

- Events can have a very different impact on the pregnant woman and the fetus
- AE grading is often based on need for hospital admission
  - There may be a low threshold for admitting pregnant women for observation
  - Most women will already be in hospital when they give birth
- It may be difficult to assess the impact on the fetus
  - Cardiotocograph: CTG
  - Imaging
  - Fetal movements

EVERREST

- Does vascular endothelial growth factor gene therapy safely improve outcome in severe early-onset fetal growth restriction?
- Bioethics study
- Reproductive toxicology
  - Manufacture and testing of a new Drug Product
- Develop a first-in-woman phase I/IIa safety/efficacy study
  - Drug delivery by interventional radiology

PRENATAL DIAGNOSIS

https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6047

https://www.ucl.ac.uk/womens-health/research/maternal-and-fetal-medicine/prenatal-therapy/current-projects-professor-anna-david-0

ORIGINAL ARTICLE | Open Access

Development of standard definitions and grading for Maternal and Fetal Adverse Event Terminology

Rebecca N. Spencer, Kurt Hecher, Gill Norman, Karel Marsal, Jan Deprest, Alan Flake, Francesc Figueras, Christoph Lees, Steve Thornton, Kathleen Beach, Marcy Powell, Fatima Crispi, Anke Diemert, Neil Marlow, Donald M. Peebles, Magnus Westgren, Helena Gardiner, Eduard Gratacos, Jana Brodszki, Albert Batista, Helen Turier, Mehali Patel, Beverley Power, James Power, Gillian Yaz, Anna L. David

MFAET
Safety monitoring for pregnancy clinical trials

Phase 1: State of the art

Literature review

Review of existing grading criteria and relevant national and international guidelines

ACOG RCOG
RANZCOG SOGC
ISPD SMFM BMFMS
ISUOG BAPM
WHO

Development of standard definitions and grading for Maternal and Fetal Adverse Event Terminology: MFAET v1.0

Rebecca Spencer

BMFMS isuog.org

ispd International Society for Prenatal Diagnosis
Building Global Partnerships in Genetics and Fetal Care

MFAET
Safety monitoring for pregnancy clinical trials

Phase 1: State of the art

Phase 2: Developing preliminary criteria

Literature review

Steering Committee meeting 1

Review of existing grading criteria and relevant national and international guidelines

ACOG RCOG RANZCOG SOGC ISPD SMFM BMFMS ISUOG BAPM WHO

First AE Consensus Group meeting Barcelona May 2015

Draft set of 12 maternal and 19 fetal AE definitions and severity criteria

Obstetricians
Obstetric triallists
Fetal medicine experts
Fetal surgeons
Paediatric surgeons
Neonatologists
Industry representatives

MFAET
Safety monitoring for pregnancy clinical trials

Phase 1: State of the art

Phase 2: Developing preliminary criteria

Literature review

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Integration into terminology

Review of existing grading criteria and relevant national and international guidelines

ACOG RCOG RANZCOG SOGC ISPD SMFM BMFMS ISUOG BAPM WHO

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Draft set of 12 maternal and 19 fetal AE definitions and severity criteria

Liaised with Medical Dictionary of Regulatory Activities

MedDRA

17 new fetal terms added to MedDRA version 19.0 March 2016

Set up in the late 1990s by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).
A rich and highly specific standardised medical terminology.
Aims to facilitate sharing of regulatory information internationally for medical products used by humans

MFAET

Safety monitoring for pregnancy clinical trials

Phase 1: State of the art | **Phase 2: Developing preliminary criteria**

Literature review → Steering Committee meeting 1 → Integration into terminology → PPI meeting

Review of existing grading criteria and relevant national and international guidelines

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MedDRA

17 new fetal terms added to MedDRA version 19.0 March 2016

Good practice recommendations for trials of novel therapies in pregnancy

7 UK charity representatives from GIFT-Surg project

GIFT Surg

MFAET
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Patient Public Involvement recommendations

- Record antenatal decisions to terminate the pregnancy or to have only palliative neonatal care after birth
- Report mode of labour onset and mode of delivery including whether the mode of delivery is likely to impact future pregnancies
- Assess the psychological impact of the intervention on the pregnant woman including the psychological impact of any fetal AEs.
  - Evaluate using validated measures in comparison with an ‘untreated’ group with the same condition.
- Where possible, include assessment of the fetal response to an intervention, including indications of fetal pain or stress
- Record data on subsequent fertility and pregnancies over a time period proportionate and relevant to the intervention
  - Include whether women were trying to conceive, and their pregnancy outcomes and complications if they were successful

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Phase 3: Refining and finalising the criteria

Delphi round 1 → Delphi round 2

Separate online surveys for maternal and fetal AEs (definitions and severity criteria)

Clinicians
Scientists
Industry, Midwifery & Patient/Charity representatives

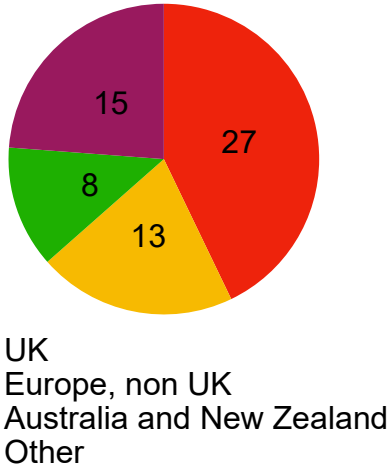
Fetal AEs

- First round - 63
- Second round - 54

Belgium, Netherlands, Spain, Ireland, Switzerland, Czech Republic

USA, Canada, Argentina, South Africa, Israel, India, Hong Kong, China, Singapore

Fetal AEs: country



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Phase 3: Refining and finalising the criteria

Delphi round 1 → Delphi round 2

Separate online surveys for maternal and fetal AEs (definitions and severity criteria)

Clinicians
Scientists
Industry, Midwifery & Patient/Charity representatives

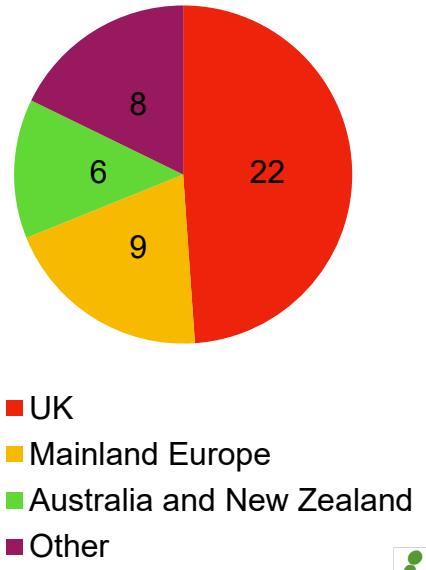
Maternal AEs

- First round - 45
- Second round - 39

Belgium, Netherlands, Switzerland, Czech Republic

Canada, Argentina, South Africa, Hong Kong, China, Singapore

Maternal AEs: country



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Phase 3: Refining and finalising the criteria

Delphi round 1 → Delphi round 2

Consensus (>70% agreement) achieved for

- **all 31 definitions**
- **74/76 (97%) of the maternal severity criteria**
- **68/74 (92%) of the fetal severity criteria**

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Phase 3: Refining and finalising the criteria

Delphi round 1 → Delphi round 2 → Steering Committee meeting 2

Consensus (>70% agreement) achieved for

- **all 31 definitions**
- **74/76 (97%) of the maternal severity criteria**
- **68/74 (92%) of the fetal severity criteria**

Face-to-face meeting and remote discussion to address eight outstanding issues

Final maternal and fetal AE definitions and severity criteria agreed
Maternal Fetal Adverse Event Terminology "MFAET" Version 1.0

MedDRA

MFAET
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General principles of MFAET v1.0: grading

- AE severity graded independently for the pregnant woman and fetus
- Pregnancy conditions can affect the mother and the fetus separately
  - For example chorioamnionitis, haemorrhage in pregnancy
- Generic fetal AEs based on CTCAE generic criteria

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)	Grade 5 (death)
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated **CTCAE generic criteria**	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death related to AE

MFAET
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General principles of MFAET v1.0: grading

- AE severity graded independently for the pregnant woman and fetus
- Pregnancy conditions can affect the mother and the fetus separately
  - For example chorioamnionitis, haemorrhage in pregnancy
- Fetal AEs were defined as being diagnosable *in utero* with potential to cause detriment to the fetus

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)	Grade 5 (death)
Clinical observation of uncertain significance Resolves spontaneously Low risk of long-term consequences **Fetal AEs**	Likely to resolve spontaneously Low risk of long-term consequence Requires increased frequency of monitoring, but less than once a week Requires additional tests	Requires increased frequency of monitoring, once a week or more; Likely to lead to significant neonatal morbidity	Likely to lead to fetal injury or permanent disability Likely to lead to neonatal death Requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery	Fetal death

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Maternal Fetal Adverse Event Terminology "MFAET" Version 1.0

Maternal AEs	Fetal AEs
Haemorrhage in pregnancy	Haemorrhage in pregnancy
Preterm premature rupture of membranes	Preterm premature rupture of membranes
Chorioamnionitis	Chorioamnionitis
Anaemia of pregnancy	Anaemia of pregnancy
Gestational hypertension	Fetal fluid collection*
Pre-eclampsia	Fetal bradycardia: non-labour*
Eclampsia	Fetal tachyarrhythmia*
Premature labour	Cardiac function abnormalities*
Puerperal infection	Fetal brain scan abnormal*
Postpartum haemorrhage (primary)	Fetal gastrointestinal tract imaging abnormal*
Retained placenta or membranes	Fetal musculoskeletal imaging abnormal*
Amniotic fluid embolism	Fetal renal imaging abnormal*
	Fetal movement disorders*
	Fetal neoplasm*
	Fetal structural abnormalities: not otherwise classified*
	Abnormal fetal growth*
	Procedural haemorrhage*
	Post-procedural haemorrhage*

*Added to MedDRA terms list

MedDRA = Medical Dictionary for Regulatory Activities

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Adverse Event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Anaemia in pregnancy: maternal	Haemoglobin 7.0-10.5 g/dL; 4.4-6.5 mol/L; 70-105 g/L and no intervention indicated	Haemoglobin 7.0-10.5 g/dL; 4.4-6.5 mol/L; 70-105 g/L and haemodynamically stable but oral iron indicated	Haemoglobin <7.0 g/dL; <4.4 mmol/L; <70 g/L; transfusion indicated	Urgent intervention indicated; imminent cardiac compromise
Anaemia in pregnancy: fetal	-	-	-	Pathological cardiotocograph; fetal indication for delivery
Definition: Disorder characterised by a reduction in the amount of haemoglobin in the blood occurring during pregnancy or the puerperium, in the absence of haemoglobinopathies				

Grade 5 = maternal or fetal death

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Fetal Adverse Event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
***Fetal fluid collection*:** Definition: The collection of non-haemorrhagic fluid in one or more fetal compartments (pericardial space, pleural space, peritoneal cavity, skin)	-	New onset isolated pericardial, pleural, or peritoneal fluid collection or skin oedema, which is not life-threatening	New onset accumulation of fluid in at least two fetal compartments (hydrops) which resolves spontaneously	New onset accumulation of fluid in at least two fetal compartments (hydrops) which is sustained; life-threatening isolated pericardial, pleural, or peritoneal fluid collection
Fetal cardiac function abnormalities: Definition: An abnormality in fetal cardiac function	-	-	Non-life-threatening signs of cardiac failure, including cardiomegaly and valve regurgitation	Likely to lead to fetal injury or permanent disability; requiring a substantive change in management including changing the course of an interventional procedure or necessitating delivery

Grade 5 = fetal death

Future of MFAET V1.0

- Disseminate and promote system
  - Working with regulatory authorities
- Version 1.0 will undergo revision as the terminology develops
- Vision: to include in all protocols of all trials in pregnancy
- Not just for clinical trials!
  - Use terminology to grade maternal and fetal Adverse Events in observational studies
  - Compare drug and surgical interventions
- Resources page: https://www.ucl.ac.uk/womens-health/research/maternal-and-fetal-medicine/prenatal-therapy/current-projects-professor-anna-david-0

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Conclusions

- Fetal wellbeing can be assessed using a variety of techniques
  - New techniques in development
  - Circulating maternal fetal-derived mRNA and micro RNA
  - Accelerometer assessment of fetal movements

- Fetal safety assessment can now be done using a comprehensive standardized system to define and grade maternal and fetal Adverse Events
  - Definitions adopted by MedDRA
  - Grading system developed through international consensus

EVERREST Adverse Event Steering Committee

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Patient Public Advisory Group Charities

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NIHR UCLH Biomedical Research Centre

Resources page: https://www.ucl.ac.uk/womens-health/research/maternal-and-fetal-medicine/prenatal-therapy/current-projects-professor-anna-david-0

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Safety monitoring for pregnancy clinical trials

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