Clinical assessment of fetal well-being and fetal safety indicators

Professor Anna David,
Director of the UCL Institute for Women’s Health
Professor and Consultant in Obstetrics and Maternal Fetal Medicine
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
- Calipers on-to-on
Ultrasound: fetal structure & function

4 chamber view of the heart

Spina bifida
Ultrasound: fetal size & wellbeing

**Estimated Fetal Weight**

- **Estimated Fetal Weight** graph showing weight progression over weeks.
- **Abdominal Circumference** graph showing abdominal circumference progression over weeks.

References:
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.

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

- Raised Ductus Venosus Pulsatility Index
- Absent or reversed ‘a’ wave
- Umbilical Vein pulsation
- Reduced Middle Cerebral Artery Pulsatility Index

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 Now superceded by Doppler ultrasound.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 OF FETAL ANEMIA DUE TO MATERNAL RED-CELL ALLOIMMUNIZATION

Giacomo Mari, M.D., for the Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses
Fetal MRI commonly used for imaging soft tissues such as the brain or kidneys (but not for the skeleton)
Correlation of MRI ‘Placental Functional Index’ with severity of Fetal Growth Restriction

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

HASTE Coronal  HASTE Axial  HASTE Sagittal

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”

Decide if 'serious' event according to FDA / EMA definition

Determine causality

Unrelated, unlikely to be related

Possibly, probably, or definitely related

Grade severity

Adverse Event
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”

- Decide if 'serious' event according to FDA / EMA definition
- Determine causality
- Grade severity

Lack of standard grading criteria for Adverse Events specific to pregnancy
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

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth (report using mother’s participant ID)</td>
<td>NA</td>
<td>NA</td>
<td>Fetal death occurring at $\geq$ 20 weeks gestation</td>
<td>NA</td>
</tr>
<tr>
<td>Report only one</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm Birth (report using mother’s participant ID)</td>
<td>Live birth at 34 to $&lt; 37$ weeks gestational age</td>
<td>Live birth at 28 to $&lt; 34$ weeks gestational age</td>
<td>Live birth at 24 to $&lt; 28$ weeks gestational age</td>
<td>Live birth at $&lt; 24$ weeks gestational age</td>
</tr>
<tr>
<td>Spontaneous Abortion or Miscarriage* (report using mother’s participant ID)</td>
<td>Chemical pregnancy</td>
<td>Uncomplicated spontaneous abortion or miscarriage</td>
<td>Complicated spontaneous abortion or miscarriage</td>
<td>NA</td>
</tr>
<tr>
<td>Report only one</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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).
# 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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>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.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Intervention not under general anesthesia.</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Intervention under general anesthesia.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ICU management.</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Single organ dysfunction (including dialysis).</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multiorgan dysfunction.</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient.</td>
</tr>
</tbody>
</table>
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
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 Crispí, Anke Diemert, Neil Marlow, Donald M. Peebles, Magnus Westgren, Helena Gardiner, Eduard Gratacos, Jana Brodskzi, Albert Batista, Helen Turier, Mehali Patel, Beverley Power, James Power, Gillian Yaz, Anna L. David


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
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

- First AE Consensus Group meeting Barcelona May 2015

Phase 2: Developing preliminary criteria

- 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
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

Phase 2: Developing preliminary criteria

- Steering Committee meeting 1
- First AE Consensus Group meeting Barcelona May 2015
- Liaised with Medical Dictionary of Regulatory Activities
- Draft set of 12 maternal and 19 fetal AE definitions and severity criteria
- 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.
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

Phase 2: Developing preliminary criteria

- Steering Committee meeting 1
  - First AE Consensus Group meeting Barcelona May 2015
- Integration into terminology
  - Liaised with Medical Dictionary of Regulatory Activities
- PPI meeting
  - Good practice recommendations for trials of novel therapies in pregnancy
  - 7 UK charity representatives from GIFT-Surg project

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

17 new fetal terms added to MedDRA version 19.0 March 2016
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
Phase 3: Refining and finalising the criteria

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

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

- UK
- Europe, non UK
- Australia and New Zealand
- Other
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)

Maternal AEs

- First round - 45
- Second round - 39

Belgium, Netherlands, Switzerland, Czech Republic

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

Clinicians
Scientists
Industry, Midwifery & Patient/Charity representatives

Maternal AEs: country

- UK: 22
- Mainland Europe: 9
- Australia and New Zealand: 6
- Other: 8

Other

Canada, Argentina, South Africa, Hong Kong, China, Singapore
Phase 3: Refining and finalising the criteria

Consensus (>70% agreement) achieved for
- all 31 definitions
- 74/76 (97%) of the maternal severity criteria
- 68/74 (92%) of the fetal severity criteria
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
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

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

CTCAE generic criteria
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

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

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

*Added to MedDRA terms list

MedDRA = Medical Dictionary for Regulatory Activities
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
<th>Grade 4 (life-threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anaemia in pregnancy: maternal</strong></td>
<td>Haemoglobin 7.0-10.5 g/dL; 4.4-6.5 mol/L; 70-105 g/L and no intervention indicated</td>
<td>Haemoglobin 7.0-10.5 g/dL; 4.4-6.5 mol/L; 70-105 g/L and haemodynamically stable but oral iron indicated</td>
<td>Haemoglobin &lt;7.0 g/dL; &lt;4.4 mmol/L; &lt;70 g/L; transfusion indicated</td>
<td>Urgent intervention indicated; imminent cardiac compromise</td>
</tr>
<tr>
<td><strong>Anaemia in pregnancy: fetal</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Pathological cardiotocograph; fetal indication for delivery</td>
</tr>
</tbody>
</table>

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
<table>
<thead>
<tr>
<th>Fetal Adverse Event</th>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
<th>Grade 4 (life-threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetal fluid collection:</strong></td>
<td>-</td>
<td>New onset isolated pericardial, pleural, or peritoneal fluid collection or skin oedema, which is not life-threatening</td>
<td>New onset accumulation of fluid in at least two fetal compartments (hydrops) which resolves spontaneously</td>
<td>New onset accumulation of fluid in at least two fetal compartments (hydrops) which is sustained; life-threatening isolated pericardial, pleural, or peritoneal fluid collection</td>
</tr>
<tr>
<td>Definition: The collection of non-haemorrhagic fluid in one or more fetal compartments (pericardial space, pleural space, peritoneal cavity, skin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fetal cardiac function abnormalities:</strong></td>
<td>-</td>
<td>-</td>
<td>Non-life-threatening signs of cardiac failure, including cardiomegaly and valve regurgitation</td>
<td>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</td>
</tr>
<tr>
<td>Definition: An abnormality in fetal cardiac function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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
Albert Batista
Kathleen Beach
Jana Brodski
Fatima Crispi
Anna David
Jan Deprest
Anke Diemert
Francesc Fíguerass
Alan Flake
Helena Gardiner
Eduard Gratacós
Kurt Hecher
Angela Huertas Ceballos
Christoph Lees
Neil Marlow
Karel Marsal
Gill Norman
Donald Peebles
Marcy Powell
Rebecca Spencer
Steve Thornton
Magnus Westgren

Patient Public Advisory Group Charities


Funding
European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 305823
The EGA Hospital Charity
Innovative Engineering for Health award (GIFT-Surg) from Wellcome Trust [WT101957] and Engineering and Physical Sciences Research Council (EPSRC) [NS/A000027/1]
NIHR UCLH Biomedical Research Centre
UCL. Where ambitious innovators, visionary trendsetters and disruptive thinkers call home.

Find out more: ucl.ac.uk

Professor Anna David,
Director of the UCL Institute for Women’s Health
Professor and Consultant in Obstetrics and Maternal Fetal Medicine