

# PLACENTAL HISTOLOGY

## CLINICAL GUIDELINE MSCA.MBC.2.1

### Why does adverse pregnancy outcome often remain unexplained?

- There may be poor correlation between maternal indicators of infection (which may be false negative) and placental findings of infective causes.
- Placental causes of fetal and perinatal death may be clinically silent, e.g., maternal vascular malperfusion (MVM), delayed villous maturation (DVM) or fetal vascular malperfusion (FVM).
- Fetal growth restriction (FGR) has a multifactorial etiology related to fetal, maternal and placental pathology.

### Causes of fetal growth restriction (FGR)

- Maternal
  - Maternal vascular malperfusion (MVM): Maternal diseases, e.g., hypertension, diabetes, auto-immune disease but it can also be present in isolation
  - Drugs, toxins and teratogens, e.g., cigarette smoking and alcohol consumption, medications, recreational drugs. Other: poor nutrition, residence at high altitudes. Fetal infections: viral, parasitic.
  - Multiple gestation
  - Chromosomal: Confined Placental Mosaicism, aneuploidy (Trisomy 21)
  - Other: genetic and structural anomalies
- Placental
  - Fetal vascular malperfusion (FVM): Maternal thrombophilia, abnormal cord insertion
  - Tumors
  - Haemorrhage
  - Other: e.g., maternal floor infarction/massive perivillous fibrin deposition (associated with FGR, a very high rate of recurrence, and a significant risk of neurological handicap), villitis of unknown etiology (VUE)

## How can placental histopathology contribute?

- Determine the pathophysiology of an adverse pregnancy outcome
- Contribute to the management of the mother and neonate in short and longer term
- Contribute to the management of subsequent pregnancies in terms of recurrence risk
- Determination of timing of events may assist in assessment of medico legal claims.
- Most experts in litigation in this area have highlighted three focal points:
- Failure to identify clinically important placental lesions
- Failure to detail in the record the significance of these lesions
- Failure to communicate to the parents the cause-and-effect relationship
- Contribute to defining health policies and allocation of resources

## Cerebral Palsy (CP)

CP related to perinatal brain injury occurs in 2 to 3 per 1000 live births, of which 50- 60% involve term and near-term infants after 34 weeks. There has not been a decrease in the prevalence of cerebral palsy in the last three decades, despite several advances in fetal monitoring and neonatal ICU care.

### 1. Risk factors for CP

- Intrapartum asphyxia
- FGR (not related to hypertension)
- Cerebral anomalies
- Maternal infection
- Placental infection
- Family history of CP/neurological disorder

Only 8 - 10% of CP cases at term can be attributed to pure intrapartum hypoxia. The remainder may be related to remote antenatal processes. Most children with CP demonstrate no evidence of “fetal distress” intrapartum, yet neuroradiologic studies reveal injury consistent with an insult within hours of delivery.

Placental pathology can:

- Identify processes that directly cause or contribute to neurological damage or impairment
- Identify placental pathological processes that cause decreased placental reserve, placing the foetus at risk when entering labour
- Indicate an abnormal intrauterine environment which was present prior to onset of labour

There is no linear correlation between placental pathology and outcome, but it can be considered whether:

- The pathology in the placenta was severe enough to cause brain injury?
- This pathology been associated in the literature with brain injury?
- The adverse outcome would have been prevented /minimized if the placenta had been normal

## 2. Hypothesis

- Placental lesions decrease the threshold for brain injury so that relatively minor intrapartum insults cause severe neurological injury.
- Although placentas possess between 30 - 40% excess capacity, placentas with decreased reserve may function adequately in rest, but be unable to cope with the stress associated with labour.
- Even with sentinel events, there is a high prevalence of additional placental lesions
- Multiple independent placental lesions increase the risk for CNS injury, particularly if temporal heterogeneity.
- Perinatal asphyxia may be the CONSEQUENCE of, rather than the CAUSE of neurologic impairment.

### Placental pathology relevant to CP

#### Preterm

Placental lesions may modulate the risk for CP but may not usually be the sole cause since CNS damage may be due to developmental immaturity

Prenatal factors associated with CP and other neurological defects

- Underlying FGR
- Cardiopulmonary instability in neonatal period
- Infections in antenatal and postnatal period

Placental pathology determines causes of FGR and can identify significant fetal inflammatory response (FIR) to infection

#### Term

Often accompanied by basal ganglia injury due to inflammatory placental lesions Placental pathology identifies processes that contribute to CNS injury

#### Sentinel events/total asphyxia

- Abruptio placenta /uterine rupture
- Fetal haemorrhage

- Umbilical cord occlusion/constriction
- Maternal hypotension

### **Fetal vasculopathies**

- Fetal vascular malperfusion (FVM)
- Severe chronic villitis with obliterative fetal vasculopathy
- Meconium associated vascular necrosis of fetal vessels
- Chorioamnionitis (Grade 2 FIR)
- Eosinophilic T cell vasculitis

### **Decreased placental reserve/uteroplacental insufficiency**

- Maternal vascular malperfusion (uteroplacental insufficiency)
- Distal villous immaturity
- Massive perivillous fibrin deposition
- Critical if additional significant stresses experienced such as hypotension, metabolic stress, and hyperthermia

### **Prolonged partial asphyxia/chronic intermittent hypoxia**

- Repetitive hypoxic events over a prolonged time
- Chronic partial/intermittent umbilical cord (UC) compression
  - Abnormal cord insertion
  - Hypercoiling of the cord
  - Entanglements – nuchal /body coils or cord knots
- Subacute/chronic abruptio placentae – chorioamniotic hemosiderosis

## **Indications for requesting placental histopathology**

The following indications for placental histopathology are currently used in South Africa:

- All unexplained stillbirths after 24 weeks gestation or birthweight  $\geq 500$  g
- Signs of asphyxia in a viable baby. This group consists of all neonates who required resuscitation, unless clearly due to abruptio placentae or cord prolapse and cases who had an abnormal/suspicious CTG before and/or during labour
- If umbilical cord blood pH  $< 7$  or base excess  $\geq -12$  mmol/l
- Second or higher order mid-trimester loss
- Idiopathic preterm labour (gestational age  $< 34$  weeks or birth weight  $< 1800$  g)
- Suspected clinical chorioamnionitis or maternal pyrexia ( $\geq 38^{\circ}\text{C}$ ).
- Suspected maternal TB or confirmed maternal TB on treatment for less than 2 months

- Fetal growth restriction
- Small for gestational age
- Hydrops fetalis
- All multiple pregnancies with uncertain chorionicity at the time of birth
- Cases of severe pre-eclampsia, uncontrolled diabetes, and other maternal disease at discretion of the clinician
- Congenital abnormalities without prior diagnosis or apparent diagnosis at birth
- Abnormality of the umbilical cord e.g.
  - velamentous or hypercoiled cord as this may predispose to Fetal Vascular Malperfusion or thrombotic vasculopathy
- Any abnormal looking placenta e.g.
  - abnormal amount of fibrin on the maternal surface/very firm placenta – massive perivillous fibrin deposition/maternal floor infarction (very strong association with neurological damage and recurrence)
  - masses on maternal surface – large chorangiomas are associated with sequestration of platelets in the fetus and neonatal / intracranial bleeding

## **Procedure to request placental pathology**

### **General handling:**

At delivery all placentas (see options for management of placentas from specific ethnic/religious groups at end of document):

- Must be placed in a sealed bag (no formalin)
- Labelled with a patient hospital sticker
- The date must be indicated on the sticker
- Placentas should be kept in a refrigerator at 4° C for 24 to 48 hours before being discarded

### **A designated healthcare worker must on a daily basis:**

- Identify the placentas that should be sent for histology by checking the forms filled in by the clinicians
- REMOVE THE SELECTED PLACENTAS FROM THE PLASTIC BAGS
- Place these placentas in the buckets provided and fill with 10% buffered formalin until the whole placenta is covered.
- Use plastic containers of sufficient size that it does not distort the placenta.
- Send these placentas with their forms to the laboratory

**The following clinical information must be supplied on the request form:**

- Gestational age, birthweight and sex newborn or stillborn
- Live birth or stillbirth
- Relevant maternal history and diseases (including HIV status and Syphilis serology)
- Pertinent obstetric history
- Maternal, fetal and/or placental indications from above list

Based on the findings by the histopathologist, PCR testing for specific infectious diseases, e.g. *Toxoplasma gondii*, cytomegalovirus (CMV), and *Listeria monocytogenes* can be performed on the formalin-fixed placental tissue.

**Handling of placentas which need to be returned to patients for religious/traditional practice:**

- Obtain written informed consent from patient/parents
- Explain the need for the examination and the process
- Advise that the placenta will be treated with the necessary respect
- A defined number of samples will be taken
- Placenta will be returned to the referring laboratory for collection

**References:**

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2. Hankins, GDV, Speer M. 2003 *Defining the Pathogenesis and Pathophysiology of Neonatal Encephalopathy and Cerebral Palsy*. *Obstet Gynecol*; 102:628 –36
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5. Guttmacher AE, Maddox YT, Spong CY. 2014 *The Human Placenta Project: placental structure, development, and function in real time*. *Placenta*; 35:303-4.

## Authorship

These guidelines were drafted by a clinical team from Mediclinic and were reviewed by a panel of experts from SASOG and the BetterObs™ clinical team in 2020 and revised by the scientific committee of BetterObs™ in 2023. All attempts were made to ensure that the guidance provided is clinically safe, locally relevant and in line with current global and South African best practise. Succinctness was considered more important than comprehensiveness.

All guidelines must be used in conjunction with clinical evaluation and judgement; care must be individualised when appropriate. The writing team, reviewers and SASOG do not accept accountability for any untoward clinical, financial or other outcome related to the use of these documents. Comments are welcome and will be used at the time of next review.

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## History and version control

Author	Version	Details of update	Effective date
Dr Coen Groenewald	1	Initial Release	2020 05 23
SASOG Scientific Committee Dr C Groenewald	2	IUGR replaced by FGR Causes of FGR subdivided into Maternal and Placental The following was added: Most experts in this field of litigation highlighted three focal points: a. Failure to identify clinically important placental lesions b. Failure to detail in the record the significance of these lesions c. Failure to communicate to the parents the cause-and-effect relationship Intrapartum asphyxia added to risk factors for CP	2023 01 10

## Approval and sign-off

Department/ Area/ Group/ Forum	Representative name	Signature	Designation	Date
Clinical Department	Dr Gerrit De Villiers		Chief Clinical Officer	2023 04 27