

Clinical Practice Guideline for Care Around Stillbirth and Neonatal Death

Section 6

Investigation of Neonatal Deaths

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Endorsed by



SECTION 6

INVESTIGATION OF NEONATAL DEATHS

6.1 Introduction

In Australia, neonatal death is defined as the death of a live born baby within 28 days of birth. Neonatal death can be further categorised as early (within 7 days of birth) or late (after 7 completed days and before 28 completed days of birth). Post neonatal death is the death of an infant occurring after day 28 and up to one year of age¹.

Neonatal deaths can result from disorders of the neonate, placenta or mother. The majority of neonatal deaths are due to major congenital anomalies and complications of preterm birth. Due to the presence of a wide range of aetiological, clinical and geographic circumstances across the spectrum of neonatal deaths, the nature of investigations undertaken following death may vary widely. For example, the investigation of the sudden collapse and death of a newborn receiving standard hospital postnatal care will require a very different investigative approach to that of an infant born at 24 weeks gestation who eventually succumbs to the complications of prematurity after a lengthy course of neonatal intensive care.

Therefore, it is not feasible or appropriate to develop a comprehensive standardised protocol for investigation of neonatal deaths that accommodates all scenarios. Decisions regarding appropriate investigations should be made by the clinical team providing care based on the individual circumstances and accessing additional specialist expertise as required. This could include a neonatologist (even if the death occurs outside a tertiary centre), a clinical geneticist and/or a metabolic physician.

However, the importance of a high quality autopsy to accurately determine the cause of a neonatal death must be stressed. Neonatal care providers are encouraged to discuss the value of an autopsy with the parents for all neonatal deaths.

For further discussion on post-mortem examination and placental pathology please refer to Section 4; Perinatal post-mortem examination and/or Section 5; Investigation of stillbirths.

This section of the update of the guideline has been undertaken through a partnership between PSANZ and the NHMRC Stillbirth Centre of Research Excellence in Stillbirth.

To view further information on the described guidelines in this section of the PSANZ PSANZ Clinical Practice Guideline for Care Around Stillbirth and Neonatal Death see *Appendices A-Q*.

6.2 Objective of this section

This section of the guideline provides a list of core investigations, based on the consensus of the Working Party, which should be undertaken at the birth of high risk newborns. Investigation of at risk neonates who subsequently die will commence shortly after birth. Investigations that may be considered in certain clinical scenarios are also provided.

For further information regarding communication with parents after a perinatal death please refer to Chapter 3 Psychological and social aspects of perinatal bereavement.

6.3 What has changed in this update?

In this update, based on the findings of an updated literature review, the recommendations have remained unchanged. We have revised the formatting and reduced duplication across the different sections of the guidelines to enhance readability.

6.4 Newborns at high risk of mortality and place of death

Newborns at high risk of mortality include those where there is:

- Extreme prematurity, either pre-viable or in grey zone of viability (≤ 24 weeks)
- Severe cardiorespiratory depression at birth, including overwhelming sepsis
- Signs consistent with congenital infection
- Severe growth restriction
- Hydrops fetalis and severe anaemia
- Lethal congenital anomalies.

A large proportion of neonatal deaths occur outside of the neonatal nurseries². Neonatal Deaths occur in a variety of settings including:

- Birth suite - predominantly in the subcategories of congenital anomaly and extreme prematurity and others with severe cardiorespiratory depression
- Babies admitted to the neonatal intensive care unit
- Postnatal ward
 - Palliative care involving parental wishes
 - Sudden unexpected death in first 48 hours
- At home - deaths after hospital discharge may be planned (palliative care) or unexpected.

Section 6 Recommendations

- 1 | Obstetric and neonatal care teams should collaborate closely to ensure that all relevant maternal (pregnancy and birth) and neonatal factors are considered in the investigation of the neonate. Comprehensive maternal medical, social and antenatal history including results of all investigations documented in the medical record by obstetric staff. A comprehensive neonatal history including death scene analysis is always required.
- 2 | A detailed external examination of the baby must be performed by a perinatal pathologist, neonatologist or paediatrician where possible.
(Please see Appendix D – Clinical examination of baby checklist).
- 3 | Accurate anthropometric parameters of birth weight, length and head circumference plotted on appropriate gender specific birth growth charts.
- 4 | A newborn screening blood sample should be taken for all neonatal deaths.
- 5 | Clinicians should discuss the value of an autopsy with parents in all cases of a neonatal death and offer the option of the procedure.
(Please see Section 4; Perinatal postmortem examination).
- 6 |

Following consent from the parents, clinical photographs should be taken for later review, particularly in the circumstance of birth in non-tertiary hospital settings. These photos are additional to the bereavement photographs, and should be clearly labelled and filed in the medical record (not given to the parents) and be available for members of expert PNM committee to view. The use of digital imaging for this purpose is optimal, however issues regarding storage and patient confidentiality must be considered.

- 7 For neonates at high risk of death at the time of birth, or in birth suite, targeted investigations based on the presenting scenario should be undertaken.
 - Detailed external examination of the baby by a neonatologist or paediatrician (where possible) with clear documentation of findings in the medical record
 - Where possible, cord blood gas analysis that includes both arterial and venous samples
 - Newborn screening blood sample
 - Detailed macroscopic examination of the placenta and cord with findings documented in the medical record by obstetric staff
 - Histopathological examination of fresh and unfixed placenta, cord and membranes.
 - Autopsy.
- 8 Clinicians should initiate investigations specific to the circumstances of the birth (*see Section 6.7 for targeted investigations*).

6.5 Further investigations for high risk newborns at the time of birth

Further investigations at the time of birth may provide valuable information in specific situations, which are detailed below, particularly in the event of neonatal death, where consent for autopsy is not obtained.

Suspected congenital infection including birth after clinical chorioamnionitis and spontaneous preterm labour and delivery and severe cardiorespiratory depression at birth

- Maternal low vaginal/anorectal culture for Group B streptococcus (GBS) and vaginal culture for other common bacterial pathogens associated with perinatal death (e.g. E coli, Klebsiella);
- Maternal blood cultures
- Infant blood samples for haematological assessment (full blood count with nucleated red cell count), CRP, and antibody screen and;
- Baby blood taken with aseptic technique for microbiological culture (cord blood not recommended)
- Placental swab taken between amnion and chorion using aseptic technique for aerobic and anaerobic bacterial and fungal culture (ideally taken by pathologist with macroscopic placental examination)

- Placental macroscopic and histological examination (*see Appendix P – Placental histopathology reporting form*) specifically for maternal and fetal inflammatory responses; and
- If viral infection is suspected a placental biopsy should be sent for appropriate PCR or viral culture
- Maternal serology for Cytomegalovirus, Toxoplasma, Parvovirus B19, Rubella, Syphilis and Zika (if not already undertaken in this pregnancy);
- If infection suspected before birth consider amniotic fluid for multiplex PCR.

Severe fetal growth restriction

Studies to identify possible thrombophilic disorders should be considered in mothers with preeclampsia or with a personal/family history of thrombosis, or following the birth of an infant with severe growth restriction^{3,4}. These should include initial testing followed by further testing at 8-12 weeks postpartum as required (see section 5 Selective screening for thrombophilic disorders following birth of a high risk neonate or a neonatal death may be helpful in assisting parents and clinicians to understand the cause of death, plan future pregnancies and give consideration to the risks and benefits of antithrombotic therapy⁵.

Screening

Please see Section 5; Stillbirth investigations algorithm for further details of screening Section 5; Investigation of stillbirth for further discussion on Thrombophilia.

Section 6 Recommendations

- 9 Clinicians should investigate possible thrombophilic disorders in mothers with preeclampsia or with a personal/family history of thrombosis, or following the birth of an infant with severe growth restriction.
- 10 Selective screening in addition to placental examination for thrombophilic disorders should be undertaken following the birth of high risk neonate or a neonatal death:
 - Anticardiolipin, lupus anticoagulant, anti-B2 glycoprotein-1 antibodies
 - Microarray/karyotype
 - Autopsy

Suspected major congenital anomalies

With the advances in Maternal Fetal Medicine the majority will have been investigated and diagnosed antenatally.

- Maternal serology for Cytomegalovirus, Toxoplasma, Parvovirus B19, Rubella and Syphilis (if not already undertaken in this pregnancy);
- Viral placental culture and placental biopsy for viral PCR if viral infection suspected
- Infant blood samples for haematological assessment (full blood count with nucleated red cell count), blood group, DCT and antibody screen and microbiological culture and CRP;

- Infant cord or peripheral blood sample for chromosomal analysis; microarray /karyotype
- placental histopathology to determine possible causes for growth restriction
- routine and specific clinical photographs to display dysmorphic features
- for hydropic infants blood test for Transferrin Isoforms for Carbohydrate deficient glycoprotein disorders (CDG), chromosomes, comparative genomic hybridization array
- Glycosylated Hb (HbA1C) may be indicated
- Consultation with geneticist and access to syndrome identification digital technology
- Consider investigation for genetic metabolic disorder.

Severe cardiorespiratory depression

- Maternal low vaginal/anorectal culture for GBS and vaginal culture for other common bacterial pathogens associated with perinatal death (e.g. E-coli, Klebsiella)(2);
- Maternal serology for Cytomegalovirus, Toxoplasma, Parvovirus B19, Rubella and Syphilis if not undertaken in this pregnancy;
- Infant blood samples for haematological assessment (full blood count with nucleated red cell count); CRP, blood group, DCT and antibody screen and microbiological culture;
- Placental swabs between the amnion and chorion using aseptic technique for aerobic and anaerobic bacterial and fungal cultures. (*See Appendix C – Placental examination; Accoucheur flow chart*); and
- Consider investigation for genetic metabolic disorder and blood sample for chromosomal analysis.

Birth trauma

While this has declined in high income countries over recent decades, deaths still occur particularly associated with instrumental and assisted deliveries. Acquired prepartum lesions rarely cause the infant to have a low Apgar score. The exception is severe damage to the brainstem and basal ganglia. Traumatic injury to the brain is most commonly subdural haemorrhage.

Careful autopsy, particularly of the neck and paravertebral tissues, spinal cord, brainstem and nerve roots is important when trauma is suspected.

These NNDs usually necessitate escalated enquiry such as Root Cause Analysis and/or Coronial investigation.

Macroscopic infant

The increased risk of perinatal morbidity and mortality with maternal diabetes is well known^{6,7}. As universal screening for diabetes is not currently implemented throughout Australia and New Zealand it is essential that the possibility of undiagnosed maternal diabetes is excluded; HbA1C monitors glycaemia over the previous 3 months by reflecting the average glucose concentration over the life of the red cells.

If there is no clear maternal diabetic history, other causes of macrosomia such as Beckwith Wiedemann syndrome with close examination for syndromic features and placental changes should be considered.

Section 6 Recommendations

- 11** Investigation for maternal diabetes, if not previously undertaken, should include:
 - Maternal HbA_{1c} level (as soon as possible after delivery); and
 - If the HbA_{1c} level is raised, a fasting blood glucose should be undertaken and, if abnormal, a glucose tolerance test performed 6-8 weeks postnatally.
- 12** Other causes of macrosomia, such as Beckwith Wiedemann syndrome, should be investigated if there is no maternal or paternal diabetic history.

Suspected genetic metabolic disorders

To ensure a precise diagnosis, peri mortem evaluation of infants suspected of genetic metabolic disorders is required. Parental consent needed for post-mortem examinations and for any tissue and blood samples taken prior to death. Clinicians need to counsel parents sensitively about the importance of an accurate diagnosis for future genetic risks in this very distressing time. Metabolic disease may cause a baby to be both weak and floppy and respiratory failure at birth or shortly afterwards and should be investigated for peroxisomal disorders, non-ketotic hyperglycinaemia, lipid and storage disorders and mitochondrial disease

Due to the complexity and number of different possible diseases, it is strongly recommended that clinicians discuss each individual case with the State Laboratory to identify the optimum tests to request. Should more expert guidance be required a clinical metabolic specialist should be consulted.

Peri-mortem investigation by the clinician should include the following:

Christodoulou and Wilcken⁸ highlight the need for an increased index of suspicion for genetic metabolic disorders (inborn errors of metabolism) in neonatal cases. The authors describe predominant clinical or biochemical presentations of genetic metabolic disorders in the neonatal period and recommend a protocol for screening for these disorders and also for a genetic autopsy.

Please see Appendix S – Components of the genetic autopsy for investigations of metabolic disorders.

The predominant clinical or biochemical presentations of genetic metabolic disorders are as follows: acute encephalopathy: hypoglycaemia, hyperammonaemia, ketosis, disorders of acid-base balance, seizures as an early predominant feature; acute hepatocellular disease; sudden death; severe hypotonia; non-immune hydrops fetalis; facial dysmorphism, with or without congenital malformations⁸.

Please see Appendix C – Placental examination; Accoucheur flow chart and Appendix H – Instructions on taking clinical photographs.

Section 6 Recommendations

- 13** In the case of a suspected genetic metabolic disorder, Clinicians should discuss individual cases with their State Laboratory to identify the optimum tests to request and consult a clinical metabolic specialist if more expert guidance required.
- 14** All tissue samples should be stored and transported to a Specialist Metabolic Laboratory for investigation.
- 15** When a lethal genetic metabolic disorder is suspected prior to birth, clinicians should:
- Seek consent from the parents for a metabolic autopsy
 - Consult a metabolic physician or a histopathologist before collecting the following samples:
 - Blood sample (0.8ml) in lithium heparin tube (refrigerate)
 - Urine sample (5-10ml)
 - Knee cartilage and/or skin biopsy (3 x 2 mm punch biopsies) (sent to cytogenetics with request for fibroblast culture and store)
 - Liver and muscle biopsies (for electron microscopy, histopathology and enzymology).

6.5.1 Sudden unexpected neonatal collapse in the first weeks of life

The sudden unexpected death of a neonate requires comprehensive investigation as to the cause of the death. Although, Sudden Infant Death Syndrome (SIDS) is rare in the neonatal period since implementation of Back to Sleep campaigns, there has been a proportionate increase in the number of cases occurring at less than one month of age^{8,9}. It is important that all unexpected deaths are investigated fully prior to designation to the category of SIDS and the role of infection/inflammation examined¹⁰. Based on epidemiological and population characteristics classification of these deaths is incorporated into the PSANZ classification systems^{11,12}. The classification includes a category for unclassified sudden death where no cause for the death was identified and where inadequate investigation was undertaken. Classification of deaths into this category will hopefully decrease in number with appropriate investigations ensuring that a diagnosis is found in most cases.

The Royal College of Pathologists and The Royal College of Paediatrics and Child Health have published a comprehensive protocol for care and investigation for sudden unexpected deaths in infancy. Please refer to this document for further details¹³.

For further details on the classification of SIDS, please refer to Section 7 Perinatal death classifications.

Section 6 Recommendations

- 16** Investigation of any sudden unexpected neonatal death should include:
- Coroner notification
 - Thorough maternal and infant medical histories

- Full autopsy examination by a forensic pathologist skilled in perinatal autopsy or a forensic pathologist in conjunction with a perinatal pathologist
 - Investigation of the various scenes where incidents leading to the death might have occurred including the infants sleeping environment.
- 17** Investigations for genetic metabolic disorders should be undertaken for all sudden unexpected neonatal deaths.
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6.6 Alternative investigations: When permission for autopsy not obtained

If permission for an autopsy is not obtained, an external examination, detailed ultrasound of the infant, babygram, and clinical photos (as described above) are important tests to perform. Other alternatives to a full post-mortem examination including Post-mortem needle biopsy; laparoscopic autopsy and small incision access are other alternatives to a full post-mortem for focussed investigation of suspected anomalies.

Magnetic Resonance Imaging (if available) may be offered to parents who decline an autopsy investigation. Clinicians should however explain to the parents that a full autopsy remains the gold standard as the MRI does not supply tissue samples and therefore important information may be missed MRI should only be offered when available and if radiologists experienced in reporting post mortem MRIs. Parents should be informed about the possibility of missing an important finding when an autopsy is not undertaken.

Please refer to Section 4; Perinatal postmortem examination for further details on alternate investigations to autopsy

6.7 References

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6.8 Section authors

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6.10 Appendices

Appendix A – Stillbirth investigations algorithm

Appendix C – Placental examination; Accoucheur flow chart

Appendix D – Clinical examination of baby checklist

Appendix H – Instructions on taking clinical photographs

Appendix P – Placental histopathology reporting form

Appendix R – Screening for genetic metabolic disorders

Appendix S – Components of the genetic autopsy for investigations of metabolic disorders