Cooling guidance for babies presenting with moderate to severe hypoxic ischaemic encephalopathy within the North West London Perinatal Network

1. INTRODUCTION

Perinatal asphyxia severe enough to cause neonatal hypoxic-ischaemic encephalopathy (HIE) occurs in approximately 3/1000 births in the UK[1] and despite improved obstetric management this rate has remained unchanged for the last 10 years. The risk of death or severe handicap in survivors of moderate or severe HIE is approximately 25 and 75% respectively, and children without motor impairments have lower cognitive scores on long term follow-up, poorer scholastic attainment in independent National Attainment Tests, and often need educational support [2,3]. Perinatal asphyxia thus creates a major burden for the individual, the family and for society.

Until recently no specific treatment for HIE was available. However the results of three randomised controlled trials, including the UK total body cooling trial (TOBY), comprising 767 infants confirm that 72 hours of cooling to a core temperature of 33-34 ^{o}C started within six hours of birth reduces death and disability at 18 months of age and improves a range of neurodevelopmental outcomes in survivors [4-6]. Meta analysis of these trials showed that the number needed to treat for survival without impairment at 18 months is 8 (95% confidence interval 5-17). No clinically significant adverse event was attributed cooling.

The North West London sector has approximately 31,500 live births and therefore within the NWLPN we can anticipate approximately 90 cases of moderate to severe cases of HIE per annum.

This guidance has been written to help ensure that babies born with moderate to severe hypoxic ischaemic encephalopathy within the NWLPN receive appropriate treatment including prolonged moderate hypothermia. The guidance should be used in conjunction with the *"Guideline for the management and investigation of neonatal encephalopathy*" provided by Queen Charlotte's and Chelsea Hospital (Appendix 1).

To audit treatment with cooling in the UK, a TOBY Cooling Register of cooled infants is administered by the TOBY co-ordinating centre at the National Perinatal Epidemiology Unit (www.npeu.ox.ac.uk/Toby). **All infants treated with hypothermia whether in or outside of a 'cooling centre' should be registered with TOBY Cooling Register.**

2. WHEN TO CONSIDER TREATMENT WITH COOLING

Therapeutic hypothermia (cooling) should be considered in infants that meet the following criteria:

2.1 Treatment criteria

A. ***Infants ≥36 completed weeks gestation*** *admitted to a NNU with at least* ***one*** *of the following*:

- Apgar score of ≤5 at 10 minutes after birth.
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth.
- Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord or arterial or capillary pH <7.00).
- Base Deficit ≥16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth.

Infants that meet criteria A should be assessed for whether they meet the neurological abnormality criteria (B):

B. Seizures or moderate to severe encephalopathy*, consisting of:*

- Altered state of consciousness (lethargy, stupor or coma) ***and***
- Abnormal tone (focal or general hypotonia, or flaccid) ***and***
- Abnormal primitive reflexes (weak or absent suck or Moro response)

Infants who meet criteria A and B may be considered for treatment with cooling.

NOTE: a non ventilated baby can meet treatment criteria

The criteria for defining moderate and severe encephalopathy are listed in this table:

Parameter	Moderate Encephalopathy	Severe Encephalopathy
Level of consciousness	Lethargic	Stupor or coma
Spontaneous Activity	Decreased Activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Suck	Weak	Absent
Moro	Incomplete	Absent
Pupils	Constricted	Deviated, dilated or non-reactive
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnoea

2.2 When to start cooling

Cooling should be started as soon as possible after resuscitation is completed. Current evidence suggests that cooling is unlikely to be beneficial if started more than six to eight hours after birth.

2.3 Other assessment

Encephalopathy score

The severity of encephalopathy should be assessed and recorded in the baby's medical record when cooling commenced using the criteria in the table. There is no specific score threshold that indicates treatment with cooling is required however this score provides a useful way to monitor the baby's clinical neurological signs.

This score should be **recorded when cooling in commenced** and then **daily** for the first four days after birth. (See "*UK TOBY Cooling Register data collection form"* – Appendix 2).

Sign	0	1	2	3
Alertness	Alert	Irritable	Poorly responsive	Comatose
Tone	Normal	Hypertonia	Hypotonia	
Respiratory Status	Normal	Respiratory distress * (Apnoea/ needing oxygen)	CPAP or mechanical ventilation	
Reflexes	Normal	Hyperreflexia	Hyporeflexia	Absent reflexes
Seizure	None	Suspected**	Confirmed clinical seizure***	
Feeding	Normal (Breast/bottle)	Tube/ Nil by mouth		

Please score EVERY sign (allocate highest score unless lower score can be elicited on examination)

***What is respiratory distress?**
Examples include:
Tachypnoea, recession, irregular or periodic breathing, oxygen requirement.

****What is a suspected seizure?**
Examples include:
Posturing, lip smacking, head turning, eye turning.

*****What is a clinical seizure?**
Examples include:
Generalised tonic clonic movements which do not stop when the limbs are held.
Posturing associated with apnoea > 20 seconds or signficant bradycardias.
Episodes of posturing, lip smacking, head turning, eye turning lasting more than 2 minutes on more than 2 occasions.

aEEG assessment

The amplitude integrated EEG (aEEG or CFM) **must** be recorded in all infants treated with cooling ***but cooling need not be delayed until the aEEG is initiated.***

A normal aEEG record (confirmed by assessing the underlying EEG and excluding artefact distortion of aEEG) indicates a high probability of normal outcome, and clinicians may consider that treatment with cooling is not required.

Continued aEEG recording during the treatment period is helpful clinically, to assess occurrence of seizures and monitor the severity of encephalopathy. A copy of CFM traces should be sent with the baby to the cooling centre and provided with other data to the UK TOBY Cooling Register.

IV anticonvulsant therapy may cause transient suppression of EEG activity. Ideally the aEEG should be performed before administering anticonvulsant therapy.

Information on the use of the aEEG is available from the suppliers of the cerebral function monitors, from text books and on the following website: http://neoweb.org.uk. Refer to section 8 for further information on aEEG.

Apparent improvement of the aEEG after 6 hours of age is not an indication for discontinuing cooling. However, if the aEEG becomes normal by 6 hours of age, and the infant appears to be recovering clinically, the risk of cerebral damage is low, and the need for continuing cooling can be reconsidered.

2.4 When is cooling not appropriate?

Cooling is not appropriate if:

- The infant is likely to require surgery during the first 3 days after birth
- There are other abnormalities indicative of poor long term outcome

Cooling may not be appropriate if the infant appears moribund or has persisting extremely severe encephalopathy such that further treatment is likely to be futile, for example if the aEEG/EEG is isoelectric beyond 12-24 hours of age.

Cooling may produce adverse respiratory or cardiovascular effects and should be used with caution in infants with an unstable respiratory or cardiovascular condition.

3 WHERE SHOULD INFANTS BE TREATED WITH COOLING?

Cooling is part of a range of intensive care treatments which babies with HIE may require and as such should only be carried out in centres that are appropriately staffed and resourced to deliver continuing intensive care. These centres must have received appropriate training in therapeutic hypothermia. In the NWLPN, currently, QCCH and St Mary Hospital are Treatment Centres providing active cooling (Therapeutic Hypothermia).

QCCH co-ordinates care within these 2 units.

3.1 Cooling for infants born outside treating centres

The possibility of treatment with cooling may be considered for infants that meet the clinical criteria A and B above. See Appendix 3 – *"Referral of a baby for Cooling Treatment"*.

QCCH should be contacted directly with a request to transfer the infant for specialist care, including, if appropriate, treatment with hypothermia.

If transfer to a cooling treatment centre is feasible, the local clinicians should discuss the option of treatment with parents and seek parental verbal consent for the infant to be transferred for treatment with cooling.

Following parental verbal consent, passive cooling should be commenced prior to and continued during the transfer to the cooling centre.

Cooling outside the treatment centre is started by turning off heating equipment, and removing coverings from the infant. Refrigerated (but **not** frozen) gel packs or fluid filled bags placed around the infant or a fan can help induce cooling. These can be removed or replaced as necessary to achieve and maintain target rectal temperature.
See Appendix 4 – *"Passive Cooling – How to do it".*

The infant vital signs should be monitored and recorded; continuous monitoring of heart and respiratory rate, blood pressure, rectal and peripheral temperature is advisable.

The "*UK TOBY Cooling Register data collection form*" (Appendix 2) should be downloaded from www.npeu.ox.ac.uk/tobyregister, if none are available on the neonatal unit. The first page should be **completed by the referring hospital including the HIE score** prior to cooling.
If NWLPN cooling centres are unable to accept referral of the infant for further specialist care and, if appropriate, treatment with cooling, the team at QCCH will advise the referring hospital if a cot will soon be available at either QCCH or SMH. If no cot is available the QCCH team will advise the referring hospital to contact the Emergency Bed Service (EBS) and refer to other London neonatal network cooling centres.

If EBS is unable to locate an appropriate treatment cot, the attending consultant at Queen Charlotte's and Chelsea Hospital should be consulted. It may be decided, for example, that cooling is maintained at the hospital of birth until a cot is available at the cooling centre. In that case, the infant should be monitored and data recorded according to the "*UK TOBY Cooling Register data collection form"* (Appendix 2) and the QCCH team will provide telephone advise and support to the local medical and nursing team.

4. CONSENT

Clinicians should always discuss the option of cooling treatment with parents and seek parental verbal consent as soon as practically possible. Give the parents a copy of the "*UK TOBY Cooling Register Parent Information Leaflet* (Appendix 5)

Details of all discussion with parents about their infant's treatment with cooling should be documented in the infant's notes.

Local Trust clinical governance procedures and policy for consent for treatment should be followed.

5. MANAGEMENT

5.1 Maintaining cooling (Therapeutic Hypothermia)

Active cooling (Therapeutic Hypothermia) should be maintained using only appropriately certified cooling equipment. Servo controlled equipment should be used whenever possible as these reduce nurse work load and result in better temperature control than manually adjusted equipment.

The manufacturer's instructions should be followed when using the cooling equipment.

The target rectal temperature is 33-34C maintained for 72 hours followed by slow rewarming over 8-12 hours to 37C.

The rectal probe should be inserted 3 cm into the rectum and secured to the thigh. The probe position must be checked regularly. Cooled infants at the correct temperature of 33-34C often have mild bradycardia of around 100 bpm.

It is essential that continuous rectal temperature monitoring should be performed, with hourly recordings documented.

The investigations and all monitoring listed in the "*UK TOBY Cooling Register data collection form*" (Appendix 2) and the *"Guideline for the management and investigation of neonatal encephalopathy*" (Appendix 1) should be carried out on each infant treated with cooling as this will help establish the aetiology of the neonatal encephalopathy.

5.2 Seizures

The management of seizures will be guided by local protocols and the *"Guideline for the management and investigation of neonatal encephalopathy*" (Appendix 1).

In general, symptomatic seizures or frequent subclinical (>3/hr) seizures seen on aEEG/CFM will be treated with anticonvulsants.

Cooling may affect the metabolism of several drugs, including anticonvulsants and sedatives, and toxic drug levels may occur even with normal doses. Consult the *"Guideline for the management and investigation of neonatal encephalopathy*" (Appendix 1) or QCCH neonatal formulary for the appropriate drug dosage.

The 1st line anticonvulsant is Phenobarbital. Three doses of 20mg/kg are recommended before moving on to second line drugs.

Remember treating with anticonvulsants may suppress respiration; institute mechanical ventilation via ET tube early if respiratory drive is effected.

The 2nd line anticonvulsants are Benzodiazapines such as midazolam, or clonazapam. The dose should be adjusted according to response.

Lidocaine is sometimes used as a further 3rd line anticonvulsant, but should be avoided if phenytoin has previously been administered. There is a risk of toxicity if the lidocaine infusion is continued more than 6 hours at 6mg/kg/hr, or more than 12 hours at lower doses.

Phenytoin is not an anticonvulsant of choice as has to be administered at a rate no faster than 1mg/minute, may increase the risk of cardiac arrhythmia and Lidocaine can not be used if phenytion has previously been administered.

Severe bradycardia or ventricular tachycardia has been noted following phenytoin or lidocaine administration. Treatment consists of immediately discontinuing the agent and initiating standard resuscitative measures. It is not known if the risk of arrhythmia is increased with cooling.

Neither lidocaine nor phenytoin should be used outside a unit with full intensive care provision and expertise in the management of neonatal encephalopathy and therapeutic hypothermia

5.3 Ventilation

Almost all infants treated with cooling will initially require mechanical ventilation.

Ventilatory care will be managed according to the Treatment Centre's standard policy and this may include treatment with high frequency oscillation and inhaled nitric oxide if necessary.

Blood gases will guide ventilatory requirements; as a guide PaO2 should be maintained between 6-10 KPa and the PaCO2 between 6-7 KPa. The infant's temperature should be inputted into the blood gas machine so that the appropriate adjustment is performed.

Ventilator gases should be warmed and humidified in the normal way, according to local policy.

5.4 Cardiovascular support

Alterations in heart rate and blood pressure are common during cooling. In general the heart rate is reduced and blood pressure increases with a reduction in body temperature.

Most infants with a rectal temperature of 33-34C (the target rectal temperature for whole body cooling) will have a heart rate around 100 bpm and a mean blood pressure greater than 40 mmHg.

A rapid rise in body temperature may cause hypotension by inducing peripheral vasodilatation.

Causes of hypotension should be sought and appropriate treatment provided.

Treatment with volume replacement and inotropes should be considered if the mean arterial blood pressure is less than 35-40 mmHg. A bolus of 10-20 ml/kg of normal saline should be given initially, and repeated if necessary. If the blood pressure remains low following treatment with normal saline the infant should be treated with dopamine 5-10 micrograms/kg/min, and/or dobutamine 5-10 micrograms/kg/min. Persistent failure of response may be treated by increasing the dose of dopamine and dobutamine up to 20 micrograms/kg/min.

5.5 Anti-oedema therapy

Infants being treated with cooling should not be treated with steroids (other than for treatment of hypotension), or mannitol.

5.6 Analgesic and sedative therapy

Stress may have adverse effects in asphyxiated infants and may influence the therapeutic effect of hypothermia. In addition, neonatal intensive care procedures may cause considerable stress to infants and cooling may also be associated with stress.

Signs of distress include tachycardia, facial grimacing and irritability. A heart rate consistently above 110 bpm in cooled infants suggests that the infant is distressed.

Ventilated infants may be sedated with intravenous morphine, **maximum loading dose 50 micrograms/kg over 30 minutes followed by 10-20 micrograms/kg/hour**. Morphine should be discontinued after 24-48 hours to lessen the risk of accumulation and toxicity.

Non-ventilated infants who appear distressed will also require sedative therapy, for example with chloral hydrate, 50 mg/kg. Respiratory function must be monitored in these infants.

5.7 Fluid Management

Renal function is commonly impaired following severe perinatal asphyxia. The infant's weight, blood creatinine and electrolytes and urine output will guide fluid management.

As a guide infants will require about 40-60 ml/kg/day. Infants in renal failure should receive a total of 30 ml/kg/24 hours plus any measured losses. Boluses of 0.9% saline may be required to avoid hypovolaemia if diuresis occurs in the infant or if vasodilatation occurs during rewarming.

In infants with moderate encephalopathy oral feeds may be commenced at 10 mls/kg and advanced with caution during cooling.

5.8 Sepsis

Antibiotic therapy may be given if clinically indicated.

5.9 Rewarming procedures

Cooling is concluded after 72 hours, (or earlier if clinical circumstances dictate).

The rectal temperature should be allowed to rise by no more than 0.5C per hour, to 37+/- 0.2C.

The manufacturer's instructions should be carefully followed to avoid excessive rewarming.

The infant's temperature must be carefully monitored for 24 hours after normothermia has been achieved to prevent rebound hyperthermia, as this might be detrimental.

6. DATA COLLECTION

The "*UK TOBY Cooling Register data collection form*" (Appendix 2) should be used for all infants being treated with cooling for perinatal asphyxial encephalopathy.

Data collection covers the first 4 days following induction of hypothermia, recording clinical information about the infant's condition at birth, pregnancy and delivery information, hourly temperature recordings and basic daily information summarising the care and treatments required by the infant.

CFM traces should be copied for submission to the Register.

Outcome data are also collected, including MRI information. If MRI findings are not available at the time the form is submitted then a subsequent request will be made to collect this information.

All data submitted to the Register must be anonymised, and identified only by the infant's Register PIN. Please ensure that ALL items sent to the Register are clearly marked with the PIN.

The treatment centre will send the completed forms to the TOBY Register however, if the baby is discharged back to the referring hospital before full sucking feeds are established the referring centre will be contacted for this information.

Photocopies of all completed forms, clearly marked with the Register PIN and hospital patient identifiers should be kept in the treatment centres patient records and copies sent to the referring hospital for babies discharged back to local hospitals.

7 aEEG MONITORING

A guide to aEEG monitoring for infants with hypoxic ischaemic encephalopathy is available on http://neoweb.org.uk

Adhesive or needle electrodes may be used. These should be placed in the parietal area according to the instructions specific to the cerebral function monitor (CFM) used.

Scalp needle electrodes

- Choose site of insertion and part the hair using damp gauze, then dry the area, maintaining the parting.
- Clean exposed skin according to local policy.
- Insert needle under the skin, in line with the parting.
- If infant is to wear a hat for securing ET tube, direct the leads to the front of the head so that they sit easily leading away from the hat towards the forehead.
- Using collodion (supplied in a tube, not the liquid variety from a bottle) place a spot on the hub of the needle and exposed skin, and hold in place until the collodion is dry. Once the collodion is dry this is very secure, it can be easily inspected and there is no need for tape. Acetone (or substitute) will aid removal.

Adhesive electrodes

The skin needs meticulous preparation to result in a good trace with low impedance.

- Part any hair using a wet swab and clean the application site according to local policy.
- Gently rub the skin using abrasive paste such as Nu-Prep or use the edge of an “orange stick”.
- Apply the electrode and hold in place for about 30 seconds.
- Check impedance. If impedance is greater than 5Kohms, gently dribble some sterile water through a syringe to edge of electrode to improve conduction.
- Place a bonnet over head to help keep electrodes in place.

Needle electrodes will probably be quicker to insert, and more likely to result in a good trace. If the electrodes cannot be attached on the parietal area because of hair, they can be attached at the hair line in the fronto-temporal area but the trace may be artefacted by muscle movement.

Artefacts

Artefacts are common during long term monitoring of aEEG. Always inspect the underlying EEG for artefact at the start of a recording or if the aEEG trace alters.

A common artefact is elevation of the baseline due to ECG signal. The underlying EEG will display a regular artefact with the same frequency as the heart rate.

Common movement artefacts are due to head movement due to gasping or caused by mechanical ventilation. This type of artefact often causes widening of the aEEG trace.

Examples of artefacts affecting the EEG are provided in the aEEG guide at http://neoweb.org.uk

8. COOLING EQUIPMENT

Please refer to the manufacturer's specific instructions

Guidelines on the management of infants nursed on the Tecotherm cooling mattress

All infants being treated with cooling need to have continuous rectal temperature monitoring for the period including induction of hypothermia, maintenance of hypothermia and rewarming.

- The rectal probe needs to be inserted 2-3 cm and secured to the thigh.
- The rectal probe position must be checked regularly, especially if the infant is not behaving as expected clinically , for example:
  If the infant has been over-cooled the heart rate will be lower than anticipated.
- Cooled infants at the correct temperature of 33-34C often have mild bradycardia of around 100bpm.
- "Normal" heart rate of >120bpm in cooled infants may be an indication of distress and sedation should be considered or increased if appropriate.
- If cooled infants are slow to adjust their temperature and are too cold, it might be helpful to lighten sedation, to make the infant more responsive.
- The adjustment of the mattress set temperature to maintain the infant's target temperature must be done manually by the nurse caring for the infant, it is not a servo-controlled system.
- Regulation of the mattress set temperature needs to anticipate variations in the infant's temperature. If the infant temperature starts to show a trend in one direction, counteract it by adjusting the mattress set temperature, in steps of at least 1C, or even 2C. Changes of less than 1C will not produce a change quickly enough to have the desired effect.
- Larger infants may take longer to adjust their temperature than small-for-dates infants, but may be more stable once at target temperature.
- To initiate cooling, set the mattress at 20C. This may be reduced if necessary, for example for a large infant who is rather warm at the commencement of cooling.
- When the infant reaches 35C start bringing the set mattress temperature up, to avoid overcooling. The maintenance setting will be around 28-30C.
- For rewarming raise the mattress temperature gradually to result in an increase of the infant's temperature of 0.5C an hour, rewarming should not be completed more quickly than this.

9. MAGNETIC RESONANCE IMAGING

An MRI should be done in all infants within about 2 weeks of birth. MRI is the imaging modality of choice for assessing the distribution of injury, and likely prognosis and to support a diagnosis of hypoxic ischaemic encephalopathy.

10. LONG TERM OUTCOME

Infants should be followed up regularly after discharge and a formal neurological examination and psychomotor assessment should be carried out at approximately 2 years of age.

Anonymised data from the 2 year follow-up assessment should be submitted to the TOBY Register, on the *"UK TOBY Cooling Register Follow-up assessment at 2 years of age"* form (Appendix 7), and using the infant's Register PIN as identification.

A reminder will be sent to the hospital that provided the cooling treatment at birth when 2 follow-up data is due to be collected.

DEFINITIONS OF TERMS IN DATA COLLECTION FORM

Active cooling
Therapeutic hypothermia maintained by using appropriately certified cooling equipment to keep the rectal temperature within the target range 33-34C for 72 hours.

Arrhythmia
Sinus bradycardia below 80 bpm and other arrhythmias identified on ECG

Coagulopathy
Any disorder requiring treatment in order to maintain or recover normal haemostasis

***Delivery complications*.** This can include prolapsed cord, abruption, shoulder dystocia, ruptured uterus, head entrapment etc.

Diabetes
Existing diagnosis of diabetes, or gestational diabetes requiring treatment.

EDD Use the best estimate (dates or ultrasound) based on a 40 week gestation.

Head entrapment
Delayed second stage during breech delivery, vaginally or at caesarean section

Hypoglycaemia (infant)
Blood glucose below 2.6mmol/litre

Hypotension (infant)
Persistent mean blood pressure of < 40mmHg

Illicit drug use
Recorded drug or alcohol use that may lead to social, occupational, psychological, or physical problems.

Late onset sepsis (>72 hours after birth) confirmed by blood or CSF culture. Any evidence of infection requiring antibiotic therapy which is confirmed on culture.

Major cerebral anomaly. Including evidence of parenchymal haemorrhage as determined by ultrasound, ventricular dilatation (defined as >97th centile for gestational age) or the presence of porencephalic cysts or cystic leukomalacia.

Maternal seizure
Convulsions due to eclampsia or other causes, e.g. epilepsy

Meconium aspiration syndrome. The presence of meconium stained liquor at birth and severe respiratory distress within 1 hour of birth and compatible X-ray changes.

Necrotising enterocolitis. Infants with abdominal distension, gastric aspirate and/or blood in stools together with abdominal X-ray showing bowel oedema, pneumatosis or pneumoperitoneum, i.e. Bell's staging 2 or 3.

Passive Cooling
Therapeutic hypothermia commenced by discontinuing active warming of the baby i.e. turning off the incubator, removing blankets etc.

Placental abruption
Separation of a normally situated placenta after 28th week of pregnancy

Placenta Praevia
Placenta partially or wholly covering the internal cervical os.

Pre-eclampsia
Hypertension greater than 140/90 mmHg, during pregnancy.

Pregnancy complications. This can include: pre-eclampsia, maternal seizure, thyroid disorder, diabetes, placenta praevia, known illicit drug use etc.

Prolapsed cord
Cord presentation following rupture of membranes.

Pulmonary airleak. Any radiologically confirmed airleak serious enough to affect management (including pneumothorax, pulmonary interstitial emphysema, pneumopericardium, pneumoperitoneum and pneumomediastinum).

Pulmonary haemorrhage. Copious bloody secretions with clinical deterioration requiring change(s) in ventilatory management.

Pulmonary hypertension. Severe hypoxaemia disproportionate to the severity of lung disease and evidence of a right to left shunt.

Respiratory support
Use of mechanical ventilation, CPAP or supplementary oxygen

Ruptured uterus
Spontaneous full-thickness tear in the uterine wall due to existing scar, obstructed labour, etc

Seizures
Clinical or subclinical, identified on CFM /EEG.

Sepsis
Any evidence of infection requiring antibiotic therapy which is confirmed on culture.

Shoulder dystocia
Failure of the shoulders to rotate into the anteroposterior diameter of the pelvis following delivery of the head, resulting in a substantial delay in delivery.

Maternal Thyroid disorder
Thyroid dysfunction requiring treatment during pregnancy

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