MYELOMENINGOCELE
PRENATAL EXAMINATION AND MANAGEMENT, INCLUDING FOETAL SURGERY

Modern medical treatment of individuals with a myelomeningocele has improved survival and reduced morbidity. Foetal surgery has been added to the range of treatment options in recent years, although it still cannot be regarded as standard treatment. Within habilitation, the focus is on people with a functional impairment resulting from a myelomeningocele in order to help them achieve the highest possible level of involvement and functioning in their day-to-day lives and in the community generally.

The aim of these recommendations is to ensure that when a pregnant woman and her partner receive a prenatal diagnosis of a foetal myelomeningocele, they also receive correct information and management. This document has been prepared by a multidisciplinary working group comprising foetal medicine experts, paediatric neurologists and neurosurgeons from different regions in Sweden, see Annex 5.

RECOMMENDATIONS

- ***All women who are carrying a foetus with a suspected myelomeningocele ought to be referred for a prenatal examination at a regional foetal medicine unit, and be informed about the diagnosis, prognosis and treatment options. The information should be objective and be provided by a foetal medicine expert together with a paediatric neurologist and preferably a neurosurgeon. Ideally, the information should be both verbal and in writing, and it should be adapted to the woman/couple and the pregnancy in question.***
- ***Treatment options in the case of a myelomeningocele are 1. Termination of the pregnancy; 2. Continuation of the pregnancy with postnatal surgical treatment; 3. Prenatal surgery (in selected cases).***

- ***All women who choose to continue with the pregnancy, regardless of whether they undergo foetal surgery or not, should have a plan in place for follow-up during pregnancy, for the birth, and for examination and follow-up of the child.***
- ***A foetal autopsy should be recommended to those women who choose to terminate pregnancy in order to confirm the prenatal diagnosis.***
- ***All women should be informed about the importance of prophylactic folic acid supplementation, and receive a prescription for folic acid, 4-5 mg daily, from at least two months before future pregnancies and for at least up to and including pregnancy week 12.***
- ***If the woman wishes, an investigation should be carried out to assess whether the criteria for foetal surgery have been met. If that is the case, current information should be provided about the procedure, as well as expected benefits, risks and possible social implications for the family prior to their decision, and the woman should be referred to a foetal surgery centre.***

Terminology

Neural tube defects/myelomeningocele (spinal dysraphism) cover a spectrum of malformations with highly varying symptoms and functional impairments. Certain individuals could be entirely symptom-free. Classification and terminology vary, and new proposals for a classification have been published, partly due to improved MR technology (1). *Neural tube defect* ought to be used as an overall term instead of *spina bifida* for example, which is misleading.

Neural tube defects not covered by a layer of skin – myelomeningocele and myeloschisis – are the most difficult forms, often combined with Chiari malformation and hydrocephalus. Skin-covered defects could have a similar neurogenic effect on the bladder, intestine and lower extremities. Hydrocephalus, however, is extremely uncommon.

Prenatal examination and treatment in conjunction with a myelomeningocele in the foetus

An open myelomeningocele can be identified with the aid of an anatomic ultrasound during the first trimester. However, the level of detection is low, approximately 15% (2). With the aid of a systematic assessment of the posterior cranial fossa (3, 4), up to 50% of cases of a myelomeningocele not covered by skin can be identified as early as the first trimester. If an

abnormality in the posterior cranial fossa is detected in conjunction with the first trimester ultrasound, a myelomeningocele ought to be suspected and the ultrasound ought to be repeated to assess the intracranial anatomy and spinal column. This ought to be done during pregnancy week 16 and be performed vaginally if necessary.

In the case of all routine ultrasounds during the second trimester, the intracranial anatomy ought to be assessed (shape of the skull, centre line, cavum septum pellucidum, biparietal diameter, lateral ventricles, cerebellum, cisterna magna) as well as the spinal column as a whole on at least two levels (sagittally and axially and preferably also coronarily).

The skin on the back should be assessed to determine whether it is intact or not. An open myelomeningocele is found in most cases due to intracranial abnormalities. A foetus with a skin-covered myelomeningocele often reveals normal intracranial findings, and detection prenatally is more seldom.

<u>In the case of a suspected myelomeningocele during the second trimester or late in the pregnancy</u>

1. Case history: family case history, maternal case history, obstetric case history.
2. Detailed anatomic ultrasound to discover any other malformations. Are they isolated or not? Consider foetal echocardiography for a good structural assessment of the foetal heart.
3. Level diagnosis (the uppermost affected vertebra) and spread of the defect with the aid of 2D and 3D ultrasound.
4. Assess the type of malformation: foetal echocardiography, myelomeningocele, myeloschisis, open/closed defect (see Figure 1).
5. Assess vertebral malpositioning: kyphosis, scoliosis, other vertebral defects.
6. Assess the level where the conus ends. Tethered (attached) cord? The conus should not end further down than L3.
7. Assess the lower extremities: movement in the hips, knees and feet.
8. Assess the intracranial anatomy: Head shape, head circumference, BPD (often < 5th percentile), cerebellum, cisterna magna, occurrence of Chiari malformations (vermis, brainstem and the fourth ventricle herniate down into the cervical canal), degree of

hydrocephalus, ventricle size (anterior and atrium). Exclude other intracranial malformations. MR ought to be carried out to complement the ultrasound and for a more detailed assessment of the intracranial anatomy.

9. Amniocentesis: QF-PCR and aCGH. Analysis of AFP in the amniotic fluid can be considered, although with modern imaging diagnostics and an experienced examiner it is in most cases not necessary in order to distinguish an open defect from a closed defect (AFP amniotic fluid > 2.5 MoM).

In the event of continued pregnancy, an ultrasound is recommended covering growth, amniotic fluid volume and intracranial anatomy every third week through to birth. Following possible foetal surgery, a specific follow-up programme issued by the surgical centre is conducted.

Birth

Should be at a regional hospital with adequate expertise and experience of a myelomeningocele (foetal medical expert, neonatologist, paediatric neurologist, neurosurgeon, paediatric urologist, paediatric orthopaedic surgeon). A planned caesarean section at full term is usually recommended. There is insufficient scientific evidence to show that a caesarean section reduces the risk of further neurological damage, even if this has been reported (5). The time of birth is planned via consultation within the team, in particular in order to plan the primary neurosurgical procedure. A set time for birth would benefit the family's planning arrangements, as the parents need to be involved during their child's first weeks of life at the hospital, and often during the first weeks spent at home. A caesarean section is also justified in many cases as these foetuses are normally in a breech position. If open foetal intrauterine surgery is carried out, vaginal delivery is contraindicated in the current pregnancy and in all subsequent pregnancies. Planning of the birth in terms of time and place should thus take place in consultation with the foetal surgery centre.

Legal abortion

If the woman chooses to terminate the pregnancy, a foetal autopsy should always be recommended, and a genetic examination should be conducted, either prenatally with amniocentesis, or using placenta tissue or other foetal tissue following the termination. Information about prophylactic folic acid supplementation and prescription of folic acid for the

woman, 4-5 mg daily, commencing at least two months before the next pregnancy and at least up to and including pregnancy week 12, should be provided.

Foetal surgery in conjunction with a myelomeningocele

A foetus with a myelomeningocele is often affected by progressive functional deterioration during the second half of the pregnancy in the form of motor disruption in the lower extremities, development of hydrocephalus, Chiari malformation, and secondary brain malformations. These are probably the result of a mechanical injury to the spinal cord as a result of rubbing against the uterine wall, the toxic influence of the amniotic fluid, and leakage of chyme from the rupture. By closing the myelomeningocele during the second trimester, this progressive damage could possibly be avoided, and functional loss could thus be reduced. Cerebellar herniation in the lower cranial fossa can recede if the defect is ended prenatally and hydrocephalus development could possibly be avoided (6). Foetal surgery for open neural tube defects (myelomeningocele and myeloschisis) is nowadays an established form of treatment at several centres throughout the world.

Foetal surgery is not a cure for a myelomeningocele but could bring about certain functional improvements. It increases the probability of improved walking ability and avoidance of a Chiari malformation and hydrocephalus that would require a shunt. In a prospective randomised NIH study (MOMS; Management Of Myelomeningocele Study) the results of foetal closure were compared with traditional postnatal surgery (7). An interim analysis following the inclusion of 183 patients showed that prenatal surgery offered significant benefits and the study was thus concluded prematurely.

The MOMS study showed a halving of the need for a ventricular shunt in children who had undergone surgery prenatally. Twice as many children who were operated on prenatally walked unaided at follow-up compared with the control group (7-10). The effect on cognitive functions, miction, defaecation and sexual function has still not been evaluated in a long-term follow-up although this is expected to materialise within a few years. A reduction in the need for an alternative form of surgery as a result of secondary complications, such as tethered cord, has not been demonstrated. MOMS II monitors the original study subjects up to the age of 10.

Prenatal surgery for a myelomeningocele takes place between pregnancy weeks 19+0 and 25+6. An expanded laparotomy and hysterectomy are performed during the operation. The back of the foetus is exposed, and the myelomeningocele is then closed by a neurosurgeon. Serious complications, such as perinatal death in close conjunction with the operation, occurred in 3% of the cases in the MOMS study. Premature birth before 30 weeks occurred in 13%, which is a marked increase in risk. The average length of pregnancy at birth following the procedure is just over 34 weeks. A premature rupture of the amniotic sac occurred in 30-45% of cases. It is still unclear if the benefits of foetal surgery outweigh the risks for the child in the long term due to morbidity, mainly resulting from premature birth. See Annex 3 for exclusion and inclusion criteria for prenatal surgery.

The maternal risks in conjunction with open intrauterine surgery are significant and are summarised in Annex 4. An increased risk of serious complications exists both during the current pregnancy and in future pregnancies, secondary to damage to the uterine walls, and careful monitoring of the woman is necessary (11). There are thus ethical considerations when exposing a pregnant woman to the risks involved in this type of surgery for the purpose of reducing morbidity for the expected child (12).

If prenatal surgery is required, contact should be made as soon as possible with one of the established centres in Europe, see Annex 3. A person who is entitled to Swedish social insurance is also entitled to free care or reimbursement of care costs within the EU/EEA or Switzerland. In the event of a planned operation abroad, an application for specialist care should be made by the care provider, and should be signed by the Medical Director. In the case of care within the EU, an S2 form (preliminary consent) should be requested from the Social Insurance Agency. Patients who are granted specialist care abroad are also entitled to receive compensation for food and travel costs incurred in conjunction with the care that has been granted. See Annex 6 ‘Checklist regarding an application for public/private specialist care abroad’. Regional differences can arise and contact with the regional Social Insurance Agency ought to be made as soon as possible. In certain county council areas, consent is also required from the county council healthcare administration.

There are centres in Europe that carry out minimally invasive prenatal foetoscopic surgery for a myelomeningocele, although this technique has not yet been standardised or evaluated in prospective, randomised studies, and for the time being it cannot be recommended.

National follow-up programme, MMCUP

In Sweden, there is a structured follow-up programme and quality register for a myelomeningocele and hydrocephalus in which every individual born with a myelomeningocele is offered the opportunity to participate – see website www.mmcup.se. Children who have undergone prenatal surgery should also be examined and monitored in accordance with Swedish national guidelines. It is particularly important that children are monitored according to the neurogenic disruption of bladder function guidelines, under which plain intermittent catheterisation (RIK) is generally commenced during the neonatal period to minimise the risk of renal damage.

Annexes

1. **Patient information**
2. **MOMS study**
3. **Inclusion and exclusion criteria for foetal surgery in conjunction with a myelomeningocele, plus contact details for European surgical centres.**
4. **Maternal aspects and follow-up following foetal surgery for a myelomeningocele.**
5. **Contact details, person with regional responsibility, MMC**
6. **Checklist, Social Insurance Agency**

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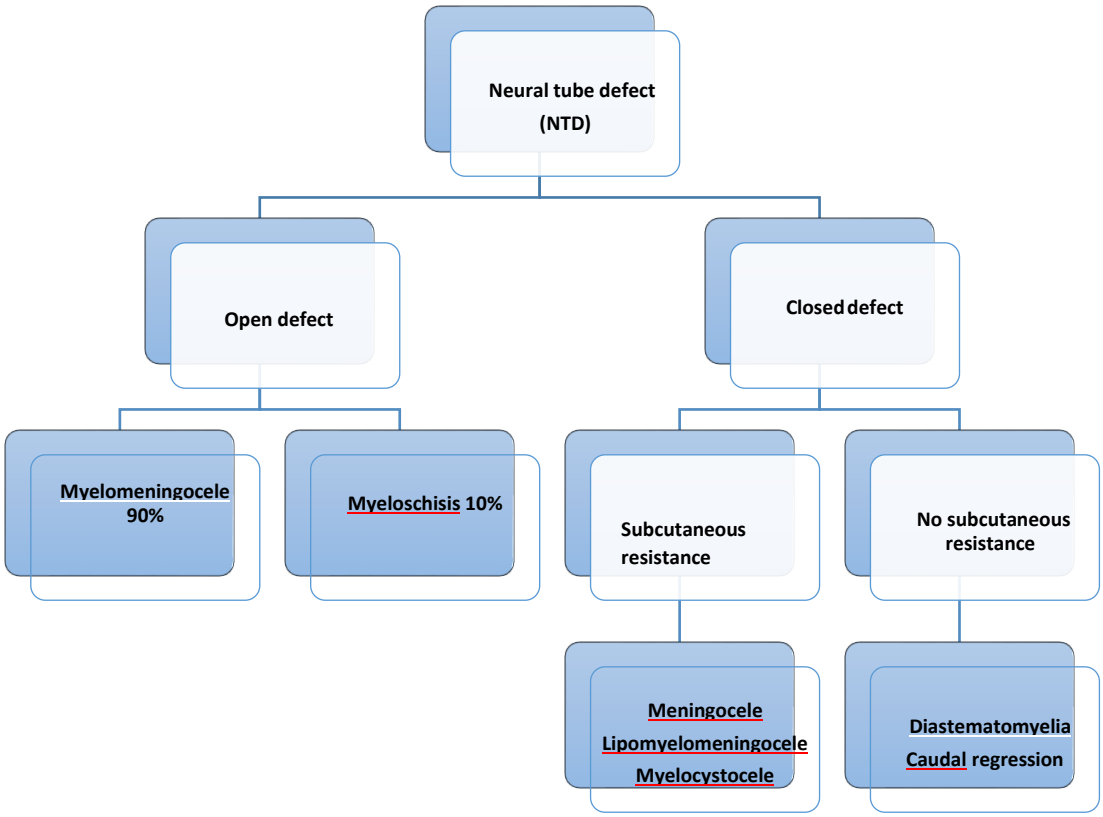
Figure 1. Different types of neural tube defects that can be diagnosed prenatally. The prognosis differs markedly for open and closed defects.



Annex 3. Inclusion and exclusion criteria for foetal surgery in conjunction with myelomeningocele.

MATERNAL	FOETAL
> 18 years	Single birth
BMI < 40	No other congenital malformations
Non-insulin-dependent diabetes mellitus or serious maternal disease	Normal genetic examination
No history or increased risk of premature birth	Myelomeningocele not above Th1 or at the beginning below S1
Normal cervical length	Length of pregnancy according to ultrasound 19+0 – 25+6 weeks
No placenta previa	Arnold-Chiari II malformation with cerebellar herniation
No uterine malformations	Kyphosis < 30 degrees
No previous neurosurgery (normal caesarean section with an incision in the isthmus is not counted)	Movement in the legs
No blood infection (HIV, HBV, HCV)	Ventriculomegaly ≤ 15 mm*
Adequate social support and psychosocial situation	

* In the case of ventriculomegaly > 15 mm, the risk of a postnatal need for a shunt is increased significantly (10).

Centres in Europe that perform open foetal surgery for a myelomeningocele

Leuven, Belgium

UZ Leuven

Professor Jan Deprest: jan.deprest@uzleuven.be

Zürich, Switzerland

Zürich Center for Fetal Surgery, Diagnosis and Therapy, www.swissfetus.ch

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Katowice, Poland (reference 14)

Medical University of Silesia

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Annex 4. Maternal aspects of foetal surgery for a myelomeningocele.

Open foetal surgery entails both foetal and maternal risk factors.
Prior to referral for a planned surgical procedure, the parents are informed in detail.
It is the duty of the referrer (regional hospital) to discuss the risks involved with surgery, and to highlight the consequences with regard to possible future pregnancies and delivery methods.

Maternal risks/complications

1) Bleeding requiring a transfusion (4–9%)
2) Pulmonary embolism or pulmonary oedema (2–6%)
3) Ablatio placentae (placental abruption) < 5%)
4) Premature rupture of the amniotic sac (30–45%)
5) Premature pain

Maternal risks/complications in future pregnancies

1) Thin or fenestrated uterine wall (20–25%)
2) Uterine rupture
3) Placenta accreta/increta (placental growth into/through the uterine wall) in conjunction with subsequent pregnancies (5–10%)
4) Premature birth (20%)

Following open foetal surgery, the patient gives birth with a planned caesarean section at the institute that carried out the procedure or at the regional hospital that referred the patient for the procedure. Following the caesarean section, a return appointment is planned for 6-8 weeks later at the specialist maternity clinic at the regional hospital. The regional hospital that referred the patient for foetal surgery is responsible for ensuring correct follow-up prenatally and postpartum.

During the visit, the importance of commencing contraception at an early stage is discussed (contraceptives should ideally be prescribed during the visit) and the patient is strongly recommended not to become pregnant again within 24 months due to the increased risk of placental and uterine complications during a subsequent pregnancy.

Folic acid supplementation, 4-5 mg daily, is recommended at least two months before the next planned pregnancy and up to and including the third month of pregnancy. The prescription is issued during the visit.

In the case of a possible new pregnancy, the patient is urged to contact the specialist maternity clinic at an early stage, both at their local hospital and at the regional hospital (in the event of a positive pregnancy test) in order to plan the monitoring of the new pregnancy. An early ultrasound to determine myotomy thickness and subsequent placenta examinations are recommended. There is a considerable risk of a uterine rupture and placenta accreta, and an increased risk of premature birth in a subsequent pregnancy. If complications are expected, delivery should take place with a planned caesarean section at a regional hospital.

Annex 5. Contact details of persons responsible for MMC in each region

Southern Healthcare Region – Skåne University Hospital (Lund)

Foetal medicine: Jana Brodszki*, jana.brodszki@med.lu.se, 0707-125379

Paediatric neurologist: Lena Westbom*, lena.westbom@med.lu.se, 046-178081. If Lena is not available, contact should be made in the second instance with Anna Börjesson, paediatric surgeon: anna.borjesson@skane.se, 046178300.

Neurosurgery:

In the first instance Nils Ståhl 046/ 171248 (switched to a mobile), nils.stahl@skane.se

In the second instance David Cederberg 070 2060344 david.cederberg@skane.se

In the third instance Peter Siesjö 0705655778 peter.siesjo@skane.se

Western Healthcare Region – Sahlgrenska University Hospital (Gothenburg)

Foetal medicine: Ylva Carlsson*, ylva.carlsson@vgregion.se, 0703-641240

Paediatric neurologist: Lisa Bondjers, lisa.bondjers@vgregion.se. Ingrid Olsson Lindberg has played an active part in this work.

Neurological surgeon: Magnus Tisell*, magnus.tisell@vgregion.se. Daniel Nilsson, daniel.nilsson@vgregion.se

South East Healthcare Region – Linköping University Hospital

Foetal medicine: Kristina Kernell, kristina.kernell@regionostergotland.se, 070-207 88 05

Paediatric neurologist: Peter Wide, peter.wide@regionostergotland.se, Helene Sundelin, helene.sundelin@regionostergotland.se

Neurological surgeon: Rafael Turczynski Holmgren*, rafael.turczynski.holmgren@regionostergotland.se, 070-8857669

Stockholm Healthcare Region – Karolinska University Hospital

Foetal medicine: Eleonor Tiblad*, eleonor.tiblad@sll.se, 0709-821752 and Peter Conner, peter.conner@sll.se, 0707-952519

Paediatric neurologist: Åsa Eriksson, asa.g.eriksson@karolinska.se,
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Uppsala-Örebro Healthcare Region – University Hospital, Uppsala

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Northern Healthcare Region (Norrland University Hospital, Umeå)

Foetal medicine:

Paediatric neurologist: Eva Vikberg Martinez, eva.vikberg.martinez@vll.se

Neurological surgeon: Saeed Shahidi, saeed.shahidi@neuro.umu.se

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The final version of this document is dated March 8, 2018. If you have any questions regarding updates or change proposals, please contact eleonor.tiblad@sll.se.