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Prenatal Screening, Diagnosis, and Pregnancy Management of Fetal Neural Tube Defects

This clinical practice guideline has been prepared by the Genetics Committee, reviewed by Family Physician Advisory and Diagnostic Imaging Committees, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide obstetrical and genetic health care practitioners with guidelines and recommendations for prenatal screening, diagnosis, and obstetrical management of fetal open and closed neural tube defects (OCNTD).

Options: This review includes prenatal screening and diagnostic techniques currently being used for the detection of OCNTD including maternal serum alpha fetoprotein screening, ultrasound, fetal magnetic resonance imaging, and amniocentesis.

Outcomes: To improve prenatal screening, diagnosis, and obstetrical management of OCNTD while taking into consideration patient care, efficacy, cost, and care procedures.

Evidence: Published literature was retrieved through searches of PubMed or MEDLINE, CINAHL, and The Cochrane Library in November, 2013, using appropriate controlled vocabulary and key words (e.g., prenatal screening, congenital anomalies, neural tube defects, alpha fetoprotein, ultrasound scan, magnetic resonance imaging). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English from 1977 to 2012. Searches were updated on a regular basis and incorporated in the guideline to November 30, 2013. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies. An online survey of health care practitioners was also reviewed.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table).

Benefits, harms, and costs: This review will provide health care practitioners with a better understanding of the available prenatal screening methods for OCNTD and the benefits and risks associated with each technique to allow evidenced-based decisions on OCNTD screening, diagnosis, and obstetrical management.

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Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[109]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[109]

RECOMMENDATIONS

Screening Evaluation

1. The primary screening test for the detection of fetal structural abnormalities including open/closed neural tube defects (anencephaly, encephalocele, spina bifida) is a second trimester anatomical ultrasound with detailed fetal intracranial and spinal imaging and assessment. (II-2A)
2. The primary use of maternal serum alpha fetoprotein for open/closed neural tube defects screening should be discontinued with the limited clinical exceptions of pregnant women with a pre-pregnant body mass index ≥ 35 kg/m^2 or when geographical or clinical access factors limit timely and good quality ultrasound screening at 18 to 22 weeks' gestation. (II-2A)
3. When used as a component in maternal serum genetic aneuploidy screening, maternal serum alpha fetoprotein can be used as a secondary screening tool in the second trimester. (II-2A)
4. Positive screening results for open/closed neural tube defect (ultrasound ± maternal serum alpha fetoprotein) require timely referral to appropriate experienced providers for genetic review, diagnosis, and counselling. (II-2A)

Diagnostic Evaluation

5. If the second trimester screening fetal ultrasound indicates a probable diagnosis of neural tube defects, the women should be referred to a tertiary or regional centre with ultrasound expertise for a more detailed ultrasound examination looking for the features associated with a neural tube defect sequence. (II-2A)
6. Prenatal magnetic resonance imaging can be considered as an additional fetal imaging technique if further detailed fetal central nervous system assessment is required for diagnostic or management counselling. (II-2A)

Invasive Prenatal Diagnostic Methods

7. The amniotic fluid specimen from a diagnostic amniocentesis (following the ultrasound detection of fetal anomalies including confirmed or suspected open/closed neural tube defect), should be evaluated for a fetal karyotype (and, if indicated and available, a chromosomal microarray), amniotic fluid alpha fetoprotein, and amniotic fluid acetylcholinesterase. These test results will allow comprehensive evaluation of the etiology, estimated risk of recurrence, and prediction of long-term neonatal and childhood outcomes of open/closed neural tube defect for family counselling. (II-2A)
8. When a routine diagnostic amniocentesis indicates only a *risk* of aneuploidy, and no identified fetal anomalies, it is not necessary to take an amniotic fluid specimen or to order amniotic fluid alpha-fetoprotein and acetylcholinesterase testing to screen for open neural tube defects. (II-2E)
9. The diagnostic identification of a pregnancy with an open/closed neural tube defect (isolated or in a more complex multiple-anomaly grouping) requires referral for comprehensive genetic, maternal–fetal medicine, and pediatric neurosurgical counselling for complete patient-focused care. (II-2A)

Pregnancy Management

10. Following the detection of an isolated open/closed neural tube defect, families should be offered a choice of 3 obstetrical care management options after diagnostic and genetic testing results are available. Options should include information about *prenatal* myelomeningocele repair and prognosis (if there are no maternal or fetal contraindications for prenatal repair at 20–26 weeks' gestation), *postnatal* myelomeningocele surgical repair and prognosis, and *pregnancy termination* with autopsy. Because anencephaly is a lethal condition, pregnancy with anencephaly may be interrupted at any gestational age on the woman's request. For an encephalocele, individualized counselling is recommended because of the possibly unique circumstances of the anomaly. (II-2A)
11. Caesarean section is the most common method of delivery for a fetus with a myelomeningocele (MCC) in either vertex or breech presentation, but is it mandatory for breech presentation. Vaginal delivery with intrapartum fetal heart rate monitoring can be considered in selected MMC vertex presentation cases that have no macrocephaly related to gestational age and a small or no MMC sac. (II-2A)

12. Delivery management for a fetus with complex multiple anomalies including a neural tube defect will need to be individually determined by the multidisciplinary health care providers at the anticipated delivery centre based on the differential diagnosis, congenital anomalies identified, prenatal testing results, prenatal care requirements, anticipated neonatal morbidity or mortality, and family consultation and requests. (III-A)
13. Autopsy is recommended for all cases of prenatal and postnatal open/closed neural tube defect (isolated or complex) following either termination of pregnancy or prenatal/postnatal death. Induction of labour may be the preferred method for pregnancy termination, allowing for a more complete autopsy evaluation of the fetal central nervous system. If autopsy is declined, fetal magnetic resonance imaging should be considered to better evaluate fetal abnormalities either in utero or after postnatal death. If genetic studies have not been completed prior to the termination, at the minimum, chromosomal karyotyping and/or chromosomal microarray should be considered or encouraged, even if a full autopsy is not performed. This procedure will maximize information for postnatal review and counselling. (II-2A)

Pregnancy Follow-up

14. Follow-up consultation is recommended when postnatal genetic and pathologic studies are complete, to provide the woman with information related to the etiology, risk of recurrence, recurrence prevention, and the possible impact on other family members of the congenital isolated or complex anomaly. (II-2A)
15. When a previous pregnancy history is complicated by a presumed folic acid-sensitive open/closed neural tube defect (i.e., no karyotype, chromosomal microarray, or identified single gene disorder etiology) for either member of the couple, or if either member of the couple planning the pregnancy is personally affected with an isolated neural tube disorder, oral folic acid supplementation of 5 mg within a multivitamin preparation should be recommended to the female partner, starting at least 3 months prior to pregnancy conception and through the first trimester of the pregnancy. (I-A)

ABBREVIATIONS

AChE	acetyl cholinesterase
AFAChE	amniotic fluid acetyl cholinesterase
AFAFP	amniotic fluid alpha fetoprotein
AFP	alpha fetoprotein
CNS	central nervous system
CSF	cerebrospinal fluid
FPR	false positive rate
LMP	last menstrual period
MC	meningocele
MMC	myelomeningocele
MRI	magnetic resonance imaging
MSAFP	maternal serum alpha fetoprotein
NICU	neonatal intensive care unit
NTD	neural tube defect
OCNTD	open/closed neural tube defect
OEIS	omphalocele, extrophy, imperforate anus, spinal syndrome
ONTD	open neural tube defect
OR	odds ratio
QoL	quality of life
RCT	randomized controlled trial
SNP	single nucleotide polymorphisms

INTRODUCTION

OCNTDs are congenital abnormalities or malformations of the neuraxis. Structural developmental malformations can affect the thoracic, lumbar, or sacral spine (spina bifida) and the cranium (anencephaly or encephalocele). Secondary co-anomalies (disruption or deformation) can involve the lower limb, bowel, bladder, cerebellum, and cerebral cortex or cerebral ventricles (for myelomeningocele).[1–3] The human neural tube normally closes during the 3rd and 4th weeks of embryonic development (correlating with 5–6 weeks' gestation from LMP).

The primary method of preventing the majority of OCNTDs is with increased red blood cell folate by maternal food folic acid fortification and oral folic acid supplementation, but this increased maternal folate strategy must occur before conception and continue through the first trimester to produce and maintain new cell production during rapid cell division.[4–6] This biological folic acid factor is important because embryogenesis has certain folic acid-sensitive anomalies or malformations that could be prevented during first trimester development. With the introduction of folic acid food fortification (1997–1998) and maternal folic acid supplementation (1991–1992), there has been a significant reduction in the occurrence and recurrence of OCNTDs in Canada. This reduction and new clinical prenatal surgical outcomes for OCNTD highlighted the need for new clinical care protocols and recommendations to be developed for prenatal screening, diagnosis, and management of OCNTDs.

Since the introduction of ONTD screening methods in the 1970s, the total number of reported cases has increased, most likely because of advances in prenatal screening and early detection.[2,7–14] A decrease in birth prevalence is the result of both primary prevention, in the form of folic acid fortification and supplementation, and secondary prevention methods (prenatal screening and termination of an affected pregnancy).[4,6,13,14]

OCNTD screening and diagnosis are carried out by MSAFP measurement, fetal imaging techniques (ultrasound imaging and MRI), and amniocentesis. It is recommended that prenatal screening be offered and undertaken in the second trimester between 15 and 22 weeks' gestation to

maximize testing accuracy, achieve a low FPR, and allow optimal management of affected pregnancies.[4,10,15–27] Factors that have been reported to affect the accuracy and interpretation of OCNTD screening results include type of NTD malformation, gestational age, maternal weight, maternal insulin-dependent diabetes, multiple gestations, ethnicity, environmental factors (prescription and non-prescription medications), and concurrent fetal anomalies.[1,9,13,17,22]

Early prenatal screening for ONTD gives parents and health care practitioners the ability to evaluate the anomaly and the overall health of the fetus during the second trimester. This guideline focuses on NTD screening, diagnosis, and post-diagnostic pregnancy management.

GENETICS OF NTD

In humans, the neural tube closes between 21 to 28 days of embryonic development, and abnormal closure is characterized by the improper fusion of the neural tube in the developing embryo.[1,2,7] NTD prevalence ranges from 1 in 300 to 1 in 1000 pregnancies and is affected by ethnic, genetic, and dietary factors, with the highest NTD rates in the United Kingdom and the United States and the lowest rates in Japan.[9,10,28–31]

Certain chronic maternal medical conditions will increase the risk of NTDs, including poorly controlled maternal insulin-dependent diabetes (OR 11.5), antiepileptic medications (valproic acid, carbamazepin), therapy with folic acid antagonists, and maternal obesity (OR 3.5).[28–31]

NTDs are described by their anatomical location and neural content type as follows:

1. spina bifida (closure failure of rostral NT folds) 50%: 93% ONTDs (neural placode at the base of the NTD) and 7% CNTDs (MC = dural sac only; MMC = neural elements attached to the dural sac);
2. anencephaly (closure failure of caudal NT folds causing failure of brain development) 40%;
3. encephalocele (outpouching of the brain through a bony skull defect; occipital is most common, with anterior and lateral locations) 8.5%; and
4. inencephaly/craniorachischisis (abnormal skull and upper spine development) 1.5%.[32]

Seventy percent of NTDs related to genetic abnormalities are isolated, non-syndromic anomalies or malformations, and with current genetic knowledge, are considered to have a multi-factorial inheritance. Chromosomal abnormalities associated with an "apparently isolated" NTD have a 2.4% to 16.3% incidence.[33–37] Syndromes or sequences associated with NTDs include amniotic band syndrome, cloacal extrophy, limb body wall complex, OEIS (omphalocele, extrophy, imperforate anus, spinal) syndrome, cerebrocostomandibular syndrome, and caudal regression.[38] Other syndromic OCNTDs are associated with single gene disorders such as mutations in the VANGL1 (caudal regression) and VANGL2 (cranial ONTD and holoprosencephaly) genes. Other single gene disorders reported include Waardenburg syndrome and Curarino syndrome.[38]

There are reports of gene mutations or alterations of gene expression leading to ONTDs, such as polymorphisms or SNPs in genes responsible for folate transport, the methionine/homocysteine metabolic cycle, methylation, and nucleotide biosynthesis. Rare mechanisms contributing to ONTDs include epigenetic modifications, maternal autoantibodies to the folate receptors, and infertility or assisted reproductive technology therapy.[39–42]

NON-INVASIVE NTD SCREENING TECHNIQUES

Ultrasound Screening

Ultrasound is the non-invasive screening modality of choice for the detection of fetal anomalies including NTDs because of its safety, cost efficiency, and detection sensitivity.[4,21,22,43,44] The current generation of ultrasound machines allow for highly detailed fetal imaging. National screening policy documents cite detection rates of approximately 68% to 94% for NTDs,[9,22,45–47] with EUROCAT reporting a 68% detection rate for spina bifida (2003–2007),[48] and British Columbia an 86% detection rate (1997–1999).[4]

A second trimester screening ultrasound should be offered to all pregnant women, as recommended in a number of SOGC guidelines[43,49,50] for the detection of congenital anomalies from 18 to 22 weeks' gestation, avoiding the need for a second trimester MSAFP screening test.[15,43,45,47,48] Ultrasound is recommended routinely in all second trimester pregnancies and is a more effective screen for OCNTD (improved sensitivity with lower FPR although more expensive) than MSAFP screening, and diagnostically it is safer than amniocentesis which carries the risk of infection or spontaneous abortion.[9,11,45,47,51–53] In addition, ultrasound has the major advantage of screening for multiple congenital anomalies at a single ultrasound imaging visit. The factors that may affect ultrasound screening for NTDs include gestational age, amniotic fluid volume, position and number of fetuses, and maternal BMI. Other factors to consider are parental ethnicity, "at risk" maternal medication use, maternal diabetic status, and personal, pregnancy, and family histories.[1,15,43,54–61] In a fetus with an OCNTD, features visible by ultrasound in the second trimester include anencephaly

(with the absence of the cranial vault and significant facial dysmorphology), open spinal anomalies (abnormal skull shape [lemon sign], abnormal appearance and possible increased width of the cerebral ventricles, abnormal appearance of the posterior fossa/cerebellum [banana sign], and abnormal or incomplete appearance of the posterior vertebral arches in thoracic, lumbar, or sacral locations), and closed spinal anomalies (with the possible absence of the lemon and banana signs and a thick appearing MMC sac protruding from the posterior vertebral opening). Abnormal lower limb movement and positioning of the foot or feet may also be present.[43,49,50] Preliminary research has been reported for first trimester ultrasound screening for NTD at 11 to 13 weeks' gestation, assessing structural developmental variation, such as the absence of intracranial translucency, decreased frontomaxillary facial angle, partial or complete cisterna magna obliteration (brainstem diameter and brainstem to occipital bone diameter), and (significant) decreased intracranial CSF volume.[61–65] This first trimester NTD imaging should be conducted under a research protocol at the present time.

The experience of the sonographer and up-to-date and well-maintained equipment are important in screening evaluation.[7,15] The importance of these factors is highlighted in the recent publication from the rural areas of China,[7] where researchers found that ultrasound did not meet its full potential as a method of secondary screening of NTDs; ultrasound was a satisfactory screening method, but NTD detection rate was low. This study did not report that ultrasound was a poor method for screening, but rather that the ultrasound screening skills of the user were not optimal for the detection of NTD anomalies.[7]

Fetal MRI

Obstetric application of MRI began approximately 20 years ago, 10 years after its discovery and initial use.[66,67] The main use of fetal MRI is as an adjunct to the primary ultrasound when sonographic findings are abnormal and further MRI detail could be obtained for management planning and counselling.[68–70] Fetal MRIs are usually conducted between the late second and early third trimesters, between 23 and 32 weeks' gestation.[21,59,70] This gestational age allows for optimal imaging of the entire fetal brain and subarachnoid space[15,21,67,71]; however, late gestation MRI can delay decisions regarding pregnancy management, including termination of pregnancy.

The use of fetal MRI, primarily known for its superior brain imaging capabilities, has now been expanded to detect non-CNS abnormalities.[22,27,67,70] Although there have been many advances in MRI technology such as the use of T2-weighted sequences, which allow for better contrast and spatial resolution, and single-shot rapid acquisition with relaxation enhancements for decreasing fetal movement effects,[22,69–71] there is no established standard imaging reference because MRI is not used as a screening modality.[22,67,70,72] Visualization of the fetal brain by MRI emphasizes the importance of correct imaging methods and radiologic interpretation. Many new techniques under development are already commonly used in the neonatal period, when anatomical structures are very different; the techniques must be modified in order to use them safely during pregnancy.[66–70] Operator interpretation of the MRI requires a thorough knowledge of normal and abnormal fetal anatomy. As the option of fetal NTD surgery becomes available in perinatal medicine, the use of MRI could significantly enhance CNS evaluation.[70,73,74]

MRI is considered safe for the fetus, but there are hypothetical concerns about teratogenesis and acoustic damage.[67,70] While additional fetal MRI research with neonatal follow-up is needed, an SOGC Diagnostic Imaging Committee Guideline[75] reports that fetal MRI is safe at 1.5 tesla magnet exposure during the second and third trimesters.

Ultrasound has the advantage over MRI of easier patient access to imaging services; it is not hampered by fetal movement, it is less expensive than MRI, and it provides good spatial resolution. MRI, however, is not limited by field of view restrictions, provides very good soft tissue contrast, and performs well regardless of oligohydramnios, maternal obesity, or fetal lie.[22,27,70,73,74]

MRI has the potential to confirm the results of an equivocal ultrasound finding and can possibly identify additional anomalies,[76] but its expense, lack of a standard of reference for imaging, and limited availability are factors that continue to favour ultrasound as the imaging choice for the detection of OCNTDs.[77,78]

Maternal serum AFP

MSAFP screening was once considered the gold standard of prenatal ONTD screening, but with advances in technology, research, and knowledge, MSAFP screening now has limited value when reliable second trimester ultrasound (screening and diagnostic) is available. Since the mid-1970s, non-invasive MSAFP has been used for the detection of ONTDs.[10,11,19,27,51,79] MSAFP levels rise early in the pregnancy, and ONTD screening was optimized to discern normal from abnormal MSAFP results in the second trimester between 15 and 18 weeks' gestation.[14,15,18,45] MSAFP levels are measured in multiples of the median, using unaffected pregnancies of the same gestational age as

the control value.[11,14,18] To interpret results, it is important to correctly identify the gestational age, number of fetuses, maternal ethnicity, and maternal weight. Furthermore, such factors as a personal or family history of OCNTD, any maternal "at risk for NTD" medications (epilepsy control [valproic acid, carbamazepine] or folate antagonists), or certain chronic medical conditions, such as diabetes, must be taken into consideration.[14,18] First trimester MSAFP (11 to 13 gestational weeks) levels in normal pregnancies are affected by maternal race, weight, smoking status, and method of contraception (oral birth control).[46]

Second trimester MSAFP detects 71% to 90% of NTDs, with an FPR of 1% to 3% percent.[11,14,18] Elevated levels of MSAFP can be associated with other conditions, such as fetal skin disorders, abdominal wall defects, fetal demise, fetal nephrosis, and pregnancies at an increased risk for placenta-related adverse events.[14,17,19] First trimester MSAFP NTD screening has a 50% detection rate at a fixed FPR of 10%,[55] and it is not recommended of NTD screening.

A detailed fetal structural ultrasound at 18 to 22 gestational weeks and amniocentesis (AFAFP, AFAChE, and chromosome karyotype analysis) is recommended as a diagnostic follow-up with an elevated second trimester MSAFP level (screen-positive result).

A second trimester detailed ultrasound (at 18 to 22 gestational weeks) is recommended as the standard of care for all pregnancies to determine the approximate gestational age, confirm fetal viability, identify multiples, detect closed NTDs (not usually detected by MSAFP screening), or screen for other congenital anomalies.[43,49,50] Earlier ultrasound imaging for dating or evaluating the pregnancy may be required, based on clinical care factors as determined by the primary obstetrical provider. First trimester dating by crown–rump length has a ± 3 to 5 day standard deviations for estimating the gestational age, compared to the ± 7 day standard deviations for the 18 to 22 gestational weeks' ultrasound.

Many recent retrospective studies have shown that with present screening approaches and new technology measuring MSAFP is no longer practical for the detection of NTDs, especially in the first trimester, but it is useful for selecting women for diagnostic testing, such as ultrasound or amniocentesis.[14,16,19,20,51,79]

MSAFP screening for ONTDs is less costly than ultrasound or amniocentesis,[11,52] but its cost advantage must be weighed against its decreased sensitivity and specificity, its inability to detect closed NTDs, and the requirement of further testing that includes detailed second trimester ultrasound when second trimester screening MSAFP levels are elevated.

Recommendations

Screening Evaluation

1. The primary screening test for the detection of fetal structural abnormalities including open/closed neural tube defects (anencephaly, encephalocele, spina bifida) is a second trimester anatomical ultrasound with detailed fetal intracranial and spinal imaging and assessment. (II-2A)
2. The primary use of maternal serum alpha fetoprotein for open/closed neural tube defects screening should be discontinued with the limited clinical exceptions of pregnant women with a pre-pregnant body mass index ≥ 35 kg/m^2 or when geographical or clinical access factors limit timely and good quality ultrasound screening at 18 to 22 weeks' gestation. (II-2A)
3. When used as a component in maternal serum genetic aneuploidy screening, maternal serum alpha fetoprotein can be used as a secondary screening tool in the second trimester. (II-2A)
4. Positive screening results for open/closed neural tube defect (ultrasound ± maternal serum alpha fetoprotein) require timely referral to appropriate experienced providers for genetic review, diagnosis, and counselling. (II-2A)

Diagnostic Evaluation

5. If the second trimester screening fetal ultrasound indicates a probable diagnosis of neural tube defects, the women should be referred to a tertiary or regional centre with ultrasound expertise for a more detailed ultrasound examination looking for the features associated with a neural tube defect sequence. (II-2A)
6. Prenatal magnetic resonance imaging can be considered as an additional fetal imaging technique if further detailed fetal central nervous system assessment is required for diagnostic or management counselling. (II-2A)

INVASIVE PRENATAL DIAGNOSTIC METHODS (NTD SCREENING/TESTING)

Amniocentesis

AFP from the fetal yolk sac initially and subsequently the fetal liver and AChE specifically from fetal neural tissue are not normally found in amniotic fluid, however, only AFP is present in maternal blood.[5,14,17,80] Elevated levels of AFAFP and AFAChE are present is fetuses with ONTD and can be easily identified in amniotic fluid.[14,18,80]

An amniocentesis is most often performed for the detection of chromosomal aneuploidy or genetic mutations, but the amniotic fluid can also be used for the detection of NTDs.[18,23,74,81–84] The procedure is usually conducted between the 15th and 20th gestational weeks.[6,17,45,85–88] Amniotic fluid can be analyzed for fetal karyotype, chromosomal microarray, and AFAFP and AFAChE levels. When amniocentesis is performed with a suspicion of OCNTD, the information from the karyotype, chromosomal microarray, AFAFP, and the AFAChE levels will assist with the specific type of NTD diagnosis and with counselling regarding prognosis.

If amniocentesis is being performed for aneuploidy diagnosis only (i.e., there is no identified fetal NTD or malformation), amniotic fluid analysis for AFAFP and AChE is not routinely required.

Women who undergo first trimester CVS testing for fetal aneuploidy still require a routine second trimester screening ultrasound for fetal congenital anomalies, including NTD screening if a complete ultrasound anatomic assessment is not possible in the first trimester.

Risks associated with amniocentesis include spontaneous abortion (estimated procedural risk of 0.5% to 1.0% added to the no-procedure background spontaneous risk of pregnancy loss), post-procedure spotting, infections, rupture of membranes, and fetal damage or loss.[48,86–88]

Amniocentesis for genetic testing is especially important when considering prenatal or postnatal repair of congenital anomalies including OCNTDs. Identification of additional fetal genetic factors is important as these factors may interfere with the neonatal outcome.[73,74,81–83]

Although an amniocentesis is an important diagnostic option for high-risk pregnancies in the detection of chromosomal abnormalities and ONTDs, amniocentesis should not be used as a method for laboratory NTD (AFAFP, AFAChE) screening because of the risks and cost associated with the test.

Recommendations

Invasive Prenatal Diagnostic Methods

7. The amniotic fluid specimen from a diagnostic amniocentesis (following the ultrasound detection of fetal anomalies including confirmed or suspected open/closed neural tube defect), should be evaluated for a fetal karyotype (and, if indicated and available, a chromosomal microarray), amniotic fluid alpha fetoprotein, and amniotic fluid acetylcholinesterase. These test results will allow comprehensive evaluation of the etiology, estimated risk of recurrence, and prediction of long-term neonatal and childhood outcomes of open/closed neural tube defect for family counselling. (II-2A)
8. When a routine diagnostic amniocentesis indicates only a *risk* of aneuploidy, and no identified fetal anomalies, it is not necessary to take an amniotic fluid specimen or to order amniotic fluid alpha-fetoprotein and acetylcholinesterase testing to screen for open neural tube defects. (II-2E)
9. The diagnostic identification of a pregnancy with an open/closed neural tube defect (isolated or in a more complex multiple-anomaly grouping) requires referral for comprehensive genetic, maternal–fetal medicine, and pediatric neurosurgical counselling for complete patient-focused care. (II-2A)

PREGNANCY MANAGEMENT

Counselling Information for Continuing Pregnancies

Counselling should be based on the recognition of the personal impact that a physical or mental disability could have on a child and its family.

One of the major questions a family asks when their fetus is given an isolated, non-syndromic, non-chromosomal myelomeningocele diagnosis is "What will the quality of life be for my child?" Król et al. reported a follow-up study of 33 children (19 female; 14 male) with a myelomeningocele at ages 5 to 20 years. They were evaluated in 2 age groups: 5 to 12 (n = 17) and 13 to 20 (n = 16) using the Health-Related Quality of Life in Spina Bifida questionnaire as a quantitative tool. The study reported good, very good, and average QoL in 64%, 30%, and 6% of participants respectively. None of the participants felt their QoL was poor. Issues of visual perception in the younger group and ambulation in the older group were related to lower QoL scores. The vast majority of children had a history of good specialist care. The most common medical issues were related to hydrocephalus and neurogenic bladder.[89]

In a larger study of 119 patients with hydrocephalus and MMC, Barf et al. reported a near equal overall QoL in the study group (76%) as in an age-matched peer group (72%), with greater satisfaction in the areas of finance and family life, but less satisfaction with their sex lives and abilities to care for themselves. An important feature identified was that the severity of disease and the level of the lesion had little bearing on self-reported QoL.[90]

In a retrospective cohort study Hunt and Oakeshott reported on 117 open MMC patients. The cohort had had 54%

mortality and, at evaluation, had an average age of 35 years. Among the survivors, 40% were independent in activities of daily living, meeting medical needs, transportation, and continence care.[91]

Bowman et al. reported a 25-year follow-up of 118 MMC patients in which 75% lived to early adult age, 85% had high school or college education, 80% were able to maintain social bladder continence with catheterization, 90% reported acceptable levels of bowel continence, and 86% of long-term survivors were shunt-dependent. In this group, the most significant cause of death in childhood or early adulthood was an unrecognized shunt malfunction.[92]

For more complete counselling knowledge, the health care provider could consider an economic assessment of the cost of continuing care for the MMC patient. Yi et al. reviewed 14 cost-of-illness studies, with consistent findings reported across all.[93] The lifetime direct medical costs for MMC patients is significant, with the majority of the cost being for inpatient care, treatment at initial diagnosis in childhood, and co-morbidities in adult life. The caregiver time cost was also significant for the cohort.

Continuing Pregnancy Surveillance and Method of Delivery

Pregnancy surveillance and delivery recommendations for fetuses with OCNTDs are controversial because increased pregnancy termination has limited the study of the MMC delivery model for more than 2 decades. The ACOG Practice Bulletin[94] reports that most pregnancies complicated by MMC will deliver with appropriate lung maturity at term, and there is no evidence that antenatal fetal heart rate testing for an MMC indication improves outcome. It is recognized that anomalous fetuses frequently have abnormal fetal heart rate tracings that are difficult to interpret.[95]

Serial ultrasounds for fetal growth, head size, and ventricular size may be helpful in continued prognosis counselling and delivery planning. The fetus should be delivered at a centre with a level III NICU and pediatric neurosurgery services.[90] A latex-free delivery and surgical repair plan should be considered because individuals with MMC are at an increased risk of developing a severe and life-threatening allergy to latex.[96]

The mode of delivery for an MMC-affected fetus with a vertex presentation remains controversial. There are no RCTs, but at least 5 studies representing a total of 400 patients suggested vaginal delivery does not adversely affect neonatal outcome, and one large study of 200 patients suggested Caesarean sections as a safer method of delivery for the MMC-affected fetus.[97–102] Breech presentation is common in the MMC-affected fetus as a result of decreased lower limb neurologic function and megacephaly, and hence requires delivery by Caesarean section.

Prenatal in Utero Repair of MMC

The Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele[74] showed that prenatal fetal surgery for MMC reduced the need for ventricular peritoneal shunting (40% vs. 82%) and showed improved lower limb motor outcomes at 30 months of age. However, the surgery was associated with maternal and fetal risks. Additional improvement in the child composite score for mental development and motor function at 30 months of age was identified in the prenatal study group (primary outcome score: prenatal surgery [n = 64] 148.6 ± 57.5; postnatal surgery [n = 70] 122.6 ± 57.2; $P = 0.007$). Improved hindbrain herniation at 12 months and ambulation at 30 months was also reported. This landmark study provides an important treatment option for parents because it clearly identifies neonatal and childhood benefits of prenatal fetal surgery, albeit at the cost of increased maternal risks for the index and subsequent pregnancies.[74] An accompanying editorial counselled caution regarding the initiation of this new prenatal treatment in multiple fetal therapy/treatment centres and emphasized that most women who expressed an interest in the experimental trial were either ineligible or declined to participate, with only 15% of screened women participating in the study.[103] A legal and ethical opinion that drew attention to prioritizing the fetus stated that:

> unlike a born child, a fetus is not a patient in the real sense, but only a metaphor. However, it would be unethical if a care provider, without the woman's informed consent, promoted the interests of the fetus over those of the woman.[104]

When considering the consent to fetal surgery

> the parents have clear legal responsibilities to provide or consent to their born children's necessary medical care but the maternal duties to fetuses in utero are not generally recognized."[104]

Regarding whether this study was research or a therapeutic innovation they stated that:

> the research component of the study was not in the prenatal surgical and postnatal management of each child but in the systematic control of each case according to the research protocol and the retrospective comparative review for all the outcome data.[104]

Their conclusion was that "women, diagnosed with a fetal MMC and where open fetal surgery is available, will have to be informed of this treatment option."[104] This prenatal repair option needs therefore to be presented to families in Canada as part of the informed consent process because although it is not available here, it is available in the United States.[104]

Postnatal Repair of MMC

The decision to perform postnatal repair is the most likely clinical scenario in Canada for the MMC fetus or neonate because only mothers who have travelled to in utero MMC treatment centres in the United States will have received in utero MMC repair.

The postnatal group in the Randomized Trial of Prenatal Versus Postnatal Repair of Myelomeningocele[74] is used as the clinical outcome for comparison because the RCT study was done in selected Children's Hospital facilities with organized and comprehensively controlled pediatric neurosurgery services. The placement of a shunt within the first 12 months was significantly higher in the postnatal repair group (82%, compared to prenatal group 40%; $P = 0.001$). Other abnormal cranial and brain features were higher in the postnatal group than in the prenatal repair group (degree of hindbrain herniation, $P = 0.001$; brainstem kinking, $P = 0.001$; abnormal location of the 4th ventricle, $P = 0.002$).

The combined primary outcome at 30 months was significantly lower with postnatal repair than with prenatal repair, but this was mainly due to differences in motor function between the spinal anatomical levels of the defects ($P = 0.001$); the Bayley Mental Development Index was not significantly different ($P = 0.53$). This primary outcome difference was reflected in the clinical findings of 42% for the ability to walk independently with prenatal repair and 21% with postnatal repair (relative risk 2.01 ([95% CI 1.16–3.48]; $P = 0.01$). Children who had had postnatal repair also had significantly lower WeeFIM scores for self-care ($P = 0.02$) and mobility ($P = 0.003$), but not for cognitive ability ($P = 0.67$).

Immediate postnatal care for MMC is required whether the birth was by Caesarean section or vaginal delivery. Neonatology specialists should attend in the labour room for MMC protection and care, probable neonatal prematurity (less than 37 weeks' gestation), and planning and performing subsequent primary neurosurgical MMC closure within 24 hours of delivery, especially if the MMC is open or the MMC sac was ruptured at delivery

Termination of Pregnancy

Over the last 3 decades an estimated 70% to 80% of women and couples with a fetus affected by OCNTD have chosen termination of the pregnancy.[4,105,106]

For families choosing to terminate a pregnancy because of an MMC, anencephaly, or encephalocele, the health care provider should discuss fetal autopsy and chromosomal analysis and microarray because the autopsy findings may provide important information about the etiology for the NTD and the recurrence risk.[107] Measures to prevent recurrence, including maternal supplementation with 5 mg of preconception folic, are recommended in subsequent pregnancies because folic acid supplementation has been shown in an RCT to reduce the isolated recurrence risk of NTD by 72%, with a resulting reduction of the non-supplementation prevalence rate of 3% to a post supplementation recurrence rate of 1%.[5,108]

Recommendations

Pregnancy Management

10. Following the detection of an isolated open/closed neural tube defect, families should be offered a choice of 3 obstetrical care management options after diagnostic and genetic testing results are available. Options should include information about *prenatal* myelomeningocele repair and prognosis (if there are no maternal or fetal contraindications for prenatal repair at 20–26 weeks' gestation), *postnatal* myelomeningocele surgical repair and prognosis, and *pregnancy termination* with autopsy. Because anencephaly is a lethal condition, pregnancy with anencephaly may be interrupted at any gestational age on the woman's request. For an encephalocele, individualized counselling is recommended because of the possibly unique circumstances of the anomaly. (II-2A)
11. Caesarean section is the most common method of delivery for a fetus with a myelomeningocele (MCC) in either vertex or breech presentation, but is it mandatory for breech presentation. Vaginal delivery with intrapartum fetal heart rate monitoring can be considered in selected MMC vertex presentation cases that have no macrocephaly related to gestational age and a small or no MMC sac. (II-2A)
12. Delivery management for a fetus with complex multiple anomalies including a neural tube defect will need to be individually determined by the multidisciplinary health care providers at the anticipated delivery centre based on the differential diagnosis, congenital anomalies identified, prenatal testing results, prenatal care requirements, anticipated neonatal morbidity or mortality, and family consultation and requests. (III-A)
13. Autopsy is recommended for all cases of prenatal and postnatal open/closed neural tube defect (isolated or complex) following either termination

of pregnancy or prenatal/postnatal death. Induction of labour may be the preferred method for pregnancy termination, allowing for a more complete autopsy evaluation of the fetal central nervous system. If autopsy is declined, fetal magnetic resonance imaging should be considered to better evaluate fetal abnormalities either in utero or after postnatal death. If genetic studies have not been completed prior to the termination, at the minimum, chromosomal karyotyping and/or chromosomal microarray should be considered or encouraged, even if a full autopsy is not performed. This procedure will maximize information for postnatal review and counselling. (II-2A)

Pregnancy Follow-up

14. Follow-up consultation is recommended when postnatal genetic and pathologic studies are complete, to provide the woman with information related to the etiology, risk of recurrence, recurrence prevention, and the possible impact on other family members of the congenital isolated or complex anomaly. (II-2A)
15. When a previous pregnancy history is complicated by a presumed folic acid-sensitive open/closed neural tube defect (i.e., no karyotype, chromosomal microarray, or identified single gene disorder etiology) for either member of the couple, or if either member of the couple planning the pregnancy is personally affected with an isolated neural tube disorder, oral folic acid supplementation of 5 mg within a multivitamin preparation should be recommended to the female partner, starting at least 3 months prior to pregnancy conception and through the first trimester of the pregnancy. (I-A)

SUMMARY

NTDs occur early in embryologic development, secondary to failure of fusion of the neural groove and formation of the neural tube. NTDs include malformations or disruptions in the lower spine and upper cranium and occur in approximately 1 in 1000 live births. There are 2 methods of prevention: primary prevention with folic acid (food fortification and oral supplementation) and secondary prevention with prenatal screening and pregnancy interruption.

Ultrasound is presently the best screening method for prenatal detection of fetal anomalies including NTDs because of its safety, availability, accuracy, and cost-effectiveness. MSAFP screening should be used in limited clinical scenarios as an additional screening method. Although it may be cost effective, the MSAFP screen can detect only open NTDs; it has poor sensitivity and specificity for detecting closed NTDs. Fetal MRI should be used as an adjunct to ultrasound when more detail of the CNS is required or when fetal therapy is being considered. MRI is more expensive and is not as readily available as ultrasound; further research is necessary to ensure its reported safety and to allow the creation of reference standards.

Amniocentesis is an invasive diagnostic procedure that is accurate in the detection of ONTDs and in analyses for chromosomal or genetic abnormalities. With the use of ultrasound for guidance, amniocentesis performed by experienced hands, can greatly reduce the risks of miscarriage, infection, and harm to the fetus. However, although amniocentesis has a greater than 99% detection rate for ONTD, it is neither cost effective nor necessary for the detection of ONTD unless performed for the indication of abnormalities in fetal ultrasound findings.

Improved prenatal screening and diagnosis will enable mothers or couples to obtain precise information about detected anomalies so they can make informed decisions about whether to continue or interrupt the pregnancy and what their options are for fetal or postnatal repair.

Our current knowledge and experience indicates that pregnant woman should be offered 2 prenatal screening approaches:

1. risk screening for fetal aneuploidy and fetal anomalies, using a combination of non-invasive techniques that includes ultrasound (fetal anatomic and structural detail) and
2. maternal serum testing for placental biochemical analytes and values (presently used for first and second trimester screening approaches) or for placental cell-free fetal DNA (for future direct fetal molecular DNA screening or diagnostic testing).

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