

Evaluation of Prenatally Diagnosed Structural Congenital Anomalies

This committee opinion was prepared by the Genetics Committee and approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

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guideline. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The evidence obtained was reviewed by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC). Recommendations were quantified using the evaluation of evidence guidelines developed by the Canadian Task Force on Preventive Health Care.

Benefits, Harms, and Costs: Findings of isolated or multiple fetal anomalies on prenatal ultrasound examination always lead to stressful times for women and families. Although a proportion of such anomalies can be explained by chromosomal abnormalities (aneuploidy, unbalanced translocation, deletions, or duplications), others may represent recognizable syndromes with another genetic basis (microdeletion or autosomal dominant, recessive, or X-linked inheritance). Providing accurate information and relevant reproductive genetic counselling to these women and families will allow them to make informed decisions. This is not easily accomplished because of the limited information available prenatally. This document does not provide an extensive description of every syndrome but rather a framework of reference. No cost-benefit analysis is provided.

Recommendations

1. When a fetal structural anomaly is identified, the pregnant woman should be offered a timely consultation with a trained genetic counsellor and with a maternal-fetal medicine specialist and/or a medical geneticist. The counselling should be unbiased and respectful of the patient's choice, culture, religion, and beliefs. (III-A)
2. Patients should be informed that prenatal ultrasound at 18 to 20 weeks can detect major structural anomalies in approximately 60% of such cases. (II-2A)
3. When a fetal structural anomaly is suspected or identified, a referral to a tertiary ultrasound unit should be made as soon as possible to optimize therapeutic options. (II-2A)
4. In ongoing pregnancies with fetal structural anomalies, ultrasound examination should be repeated (at a frequency depending on the anomaly) to assess the evolution of the anomaly and attempt to detect other anomalies not previously identified, as this may influence the counselling as well as the obstetrical or perinatal management. (II-2B)
5. Once a fetal structural anomaly is identified by 2-D ultrasound, other imaging techniques such as fetal echocardiography, 3-D obstetrical ultrasound, ultrafast fetal MRI, and, occasionally, fetal X-ray and fetal CT scan (using a low-dose protocol) may be helpful in specific cases. (II-2A)

Abstract

Objective: To provide information to genetic counsellors, midwives, nurses, and physicians who are involved in the prenatal care of women dealing with prenatally diagnosed isolated or multiple structural congenital anomalies.

Outcomes: To provide better counselling for women and families who are dealing with the diagnosis of a fetal structural anomaly.

Evidence: Published literature was retrieved through searches of PubMed or Medline, CINAHL, and the Cochrane Library for relevant articles using appropriate controlled vocabulary (e.g., structural congenital anomalies, prenatal ultrasound diagnosis of congenital anomalies, invasive testing results, and diagnosis of genetic syndromes; soft markers of aneuploidy were not included in this search) and key words. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and material from between 1985 and 2008 incorporated in the

Key Words: Fetal anomalies, congenital anomalies, syndromes, obstetrical ultrasound

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Table 1. 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
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	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.³⁷

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.³⁷

6. Parental imaging should be considered in specific cases, depending on the fetal anomaly identified (e.g., potential dominant inheritance). (III-A)
7. Parental blood testing and invasive prenatal testing may also be required to clarify the diagnosis for a fetus with isolated or multiple structural anomalies. (II-2A)
8. Women should receive information regarding the abnormal ultrasound findings in a clear, sympathetic, and timely fashion, and in a supportive environment that ensures privacy. Referral to the appropriate pediatric or surgical subspecialist(s) should be considered to provide the most accurate information possible concerning the anomaly or anomalies and the associated prognosis. (II-2 B)
9. Parents should be informed that major or minor fetal structural anomalies, whether isolated or multiple, may be part of a genetic syndrome, sequence, or association, despite a normal fetal karyotype. (III-A)
10. If early or urgent postnatal management may be required, delivery at a centre that can provide the appropriate neonatal care should be considered. (III-A)
11. When any congenital structural anomaly has been identified prenatally, a comprehensive newborn assessment is essential for diagnosis and counselling on the etiology, prognosis, and recurrence risk for future pregnancies, especially when the etiology has not been clearly identified prenatally. (III-A)
12. In cases of termination of pregnancy, stillbirth, or neonatal death, the health professional should encourage the performance of a complete autopsy by a perinatal or pediatric pathologist to provide maximum information on the diagnosis and etiology of the structural fetal anomaly or anomalies. When a complete autopsy is refused, the health professional should encourage the performance of at least a partial or external autopsy (including X-rays and photographs). (III-A)

Validation: This committee opinion has been prepared by the Genetics Committee of the SOGC and approved by the Executive of the SOGC.

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INTRODUCTION

Prenatal ultrasound has become a standard part of prenatal care in Canada.^{1–3} Although the vast majority of the ultrasound examinations performed provide reassurance to patients and care providers, around 1% of these scans will reveal a fetal structural anomaly.⁴ As women often feel unprepared for adverse findings on obstetrical ultrasound,⁵ such a situation typically leads to high psychological stress levels for the patient, and pressure is placed on the caregivers to provide accurate information about the findings as quickly as possible. Since many fetal anomalies are associated with an increased risk of chromosomal anomalies, many practitioners will offer karyotype analysis as the primary and initial investigation of the anomaly or anomalies. An anomaly or anomalies with a documented normal karyotype require classification as isolated or as part of a defined syndrome, sequence, or association (see glossary). With over 4000 syndromes listed in the Winter-Baraitser Dysmorphology Database,⁶ health professionals can easily be overwhelmed in refining the diagnosis. This document provides a framework for managing fetal anomalies prenatally. Recommendations were quantified using the evaluation of evidence guidelines developed by the Canadian Task Force on Preventive Health Care (Table 1). Although some syndromes are used to illustrate the discussion, the provision of detailed information on any given syndrome is beyond the scope of this document.

HISTORY, PHYSICAL EXAMINATION, AND CONSULTATIONS

Once a fetal structural anomaly is identified, a thorough and targeted pregnancy and family history and a maternal physical examination (and paternal examination if indicated) should follow.⁷ A detailed medical history of both parents should be obtained, keeping in mind the possibility of unidentified autosomal dominant traits such as tuberous sclerosis, myotonic dystrophy, or velocardiofacial syndrome (22q11.2 microdeletion) that can be mild and variably expressed and remain unidentified well into adulthood. The obstetric history should be reviewed, and attention paid specifically to exposure to teratogens such as medication, infection, radiation, illicit drugs, and other factors related to lifestyle.⁸ Finally, a detailed family history (a 3-generation pedigree) should be obtained from both parents, and particular attention should be paid to children born with congenital anomalies, to early deaths, and to the possibility of consanguinity between the parents.

A physical examination should focus on identifying evidence of the detected fetal anomaly in the parents to rule out an autosomal dominant or chromosomal trait. For example, a fetus with a cardiac conotruncal anomaly may unveil a familial 22q11.2 deletion, and one of the parents may present with the typical facial features associated with the syndrome, such as micrognathia and high-arched palate.⁹

In view of the complexity of the issues surrounding fetal structural anomalies, such as causes, associated syndromes, and prognosis, timely consultation with a maternal-fetal medicine specialist and/or a medical geneticist should be initiated.

Recommendation

1. When a fetal structural anomaly is identified, the pregnant woman should be offered a timely consultation with a trained genetic counsellor and with a maternal-fetal medicine specialist and/or a medical geneticist. The counseling should be unbiased and respectful of the patient's choice, culture, religion, and beliefs. (III-A)

IMAGING

The published background risk of major or minor structural congenital anomalies is estimated at 2% to 3.5%.^{4,10,11} The following three studies emphasize that not all anomalies are detected prenatally.

Lemyre et al. reported their experience in a Canadian tertiary level unit. They demonstrated a residual risk of 2.9% (95% CI 2.3 to 3.7) for any congenital anomaly at birth after a second trimester level II ultrasound examination with or without amniocentesis in a population considered to be at

increased risk for fetal anomaly on the basis of personal or familial history.¹² The overall rate of congenital anomalies in their population was not provided, and sensitivity of the ultrasound could therefore not be determined.

The RADIUS study provides insight on the detection of fetal anomalies using prenatal ultrasound. The overall incidence of major anomalies present at birth was 2.3%. The overall anomaly detection rate in the screened population was 35% (65/187), including almost one half of those deemed detectable by ultrasound. The detection rate of anomalies before 24 weeks' gestation was significantly higher in tertiary units (35%) than in non-tertiary units (13%) (relative detection rate 2.7; 95% CI 1.3 to 5.8), although only one half of the anomalies detected were detected before 24 weeks.⁴ Although its detection rate was lower than rates in some contemporary studies that reported detection rates as high as 61%,¹³ the RADIUS study highlights the potential benefits of a tertiary unit in identifying the majority of major structural anomalies present in a fetus. It is therefore suggested that all suspected fetal anomalies be re-evaluated in a tertiary unit in an attempt to provide the most detailed ultrasonographic assessment possible.

In two separate studies, false positive rates were determined to be 0.1% to 0.5% of all prenatal ultrasound examinations, the most frequently unconfirmed anomalies being ventriculomegaly, hydronephrosis, short limbs, and cysts (renal, pulmonary, abdominal, or cerebral).^{14,15} These may be true false positive results, or they may be spontaneous resolution of the condition.

The use of 3-D ultrasound has been increasing consistently over the last two decades, although its contribution to prenatal diagnosis has been controversial. While assessing fetuses with congenital anomalies in the early 1990s, Merz and colleagues found that 3-D ultrasound provided additional information in 62% of cases, provided the same information in 36% of cases, and provided less information in 2% of cases.¹⁶ In review articles published in 2005 and 2007, 3-D ultrasound was listed as particularly useful in assessing facial structures, limbs, and skeletal anomalies.^{17,18}

The newest fetal imaging modality is ultrafast magnetic resonance imaging. Significant costs and difficulty of access limit the use of this modality to specific diagnoses or concerns. It appears most useful in the assessment of brain and lung anomalies, in the presence of complex multiple anomalies, when oligohydramnios is present, or when planning complex and high-risk in utero interventions.¹⁹⁻²¹

Fetal X-ray was the first in utero imaging modality in obstetrics and was used before the advent of ultrasound for diagnostic purposes (number of fetuses, size, and position). Currently, fetal X-rays and CT scans are reserved for the

investigation of skeletal dysplasia when other non-ionizing radiation imaging techniques fail to provide an answer.²⁰

Parental imaging should be considered when the fetal anomaly or anomalies identified could represent an autosomal dominant condition (e.g., enlarged echogenic fetal kidneys and autosomal dominant polycystic kidney disease or fetal cardiac rhabdomyomas and tuberous sclerosis). In such circumstances, making a diagnosis in one parent allows a specific diagnosis to be made in the fetus.

Many educational and clinical tools have been developed to facilitate targeted imaging and investigations: paper-based,^{22–25} computerized,^{6,26} or Internet-based instruments.^{27–30} The efficacy of these tools in improving prenatal patient care has not been evaluated prospectively.

Recommendations

2. Patients should be informed that prenatal ultrasound at 18 to 20 weeks can detect major structural anomalies in approximately 60% of such cases. (II-2A)
3. When a fetal structural anomaly is suspected or identified, a referral to a tertiary ultrasound unit should be made as soon as possible to optimize therapeutic options. (II-2A)
4. In ongoing pregnancies with fetal structural anomalies, ultrasound examination should be repeated (at a frequency depending on the anomaly) to assess the evolution of the anomaly and attempt to detect other anomalies not previously identified, as this may influence the counselling as well as the obstetrical or perinatal management. (II-2B)
5. Once a fetal structural anomaly is identified by 2-D ultrasound, other imaging techniques such as fetal echocardiography, 3-D obstetrical ultrasound, ultrafast fetal MRI, and, occasionally, fetal X-ray and fetal CT scan (using a low-dose protocol) may be helpful in specific cases. (II-2A)
6. Parental imaging should be considered in specific cases, depending on the fetal anomaly identified (e.g., potential dominant inheritance). (III-A)

ADDITIONAL TESTING

Non-invasive Testing

Parental blood testing can be a valuable source of information in identifying a specific etiology for the prenatally diagnosed fetal structural anomaly or anomalies. Parental genetic testing for specific autosomal dominant or recessive or X-linked disorders can be useful when such a diagnosis is suspected in the fetus. For example, the finding of sonographic signs of meconium peritonitis (sign of a bowel perforation in utero) raises the potential diagnosis of fetal cystic fibrosis, an autosomal recessive disorder for which

mutation testing identifies approximately 90% of carriers. Testing a parent with physical signs of a microdeletion (e.g., 22q11.2) for that disorder may facilitate pregnancy management. A history of infectious exposure (occupational, travel history, contact with children) or a constellation of ultrasound findings suggestive of a congenital infection⁸ should encourage maternal serology testing for evidence of recent exposure to that infectious agent.

Invasive Testing

Invasive testing is well-known as a direct method to assess the fetal karyotype, via chorionic villus sampling or placental biopsy, amniocentesis, or fetal blood sampling (cordocentesis). It will typically be indicated when the risk of aneuploidy is estimated to be greater than a certain cut-off, usually 1 in 200 or 1 in 300 (0.3–0.5%). The precision provided by these chromosomal analyses is reliable for the detection of aneuploidy, deletions, duplications, and translocations visible by G-banding with a resolution of 450 to 500 bands. This analysis will not provide information about microdeletions or microduplications, which need to be assessed using techniques such as fluorescence in situ hybridization, using a probe for the specific chromosomal region where the deletion/duplication is suspected.¹⁰

Amniotic fluid may also be used to test for biochemical disorders caused by enzymatic deficiencies (such as 17-hydroxyprogesterone when the diagnosis of congenital adrenal hyperplasia is entertained while investigating ambiguous fetal genitalia), for infectious agents (polymerase chain reaction for viral DNA) when a congenital infection is a possibility, or for other components (such as alpha-fetoprotein and acetylcholinesterase to determine if a neural tube defect is open or closed).

Recommendation

7. Parental blood testing and invasive prenatal testing may also be required to clarify the diagnosis for a fetus with isolated or multiple structural anomalies. (II-2A)

COUNSELLING

Counselling starts as soon as a health care provider tells the pregnant woman about a fetal structural anomaly. In a survey of 76 Canadian women who had received the news of an abnormal prenatal ultrasound in their most recent pregnancy, Alkazaleh et al. found that women valued most “immediate, clear information with different options explained, enough time to ask questions, information regarding follow-up care, privacy and the sympathy of the person giving the bad news.”³¹ Women also valued accurate information and “the presence of a support person, but to a lesser degree.”³¹ Consequently, prenatal counselling by maternal-fetal, genetics and/or pediatric, and surgical

Table 2. Frequency of non-chromosomal syndromes diagnosed prenatally and postnatally*

System affected (in isolation or in association with other anomalies)	Number of cases with a fetal anomaly (isolated or in association with another anomaly)†	Non-chromosomal syndromes detected prenatally n (%)	Non-chromosomal syndromes detected postnatally n (%)
Cardiac	2454	51 (2)	53 (2)
Renal	1130	53 (4.7)	11 (1)
Limbs	250	12 (4.8)	26 (10)
Abdominal wall	243	19 (3.7)	2 (1)
Congenital diaphragmatic hernia	187	6 (3.2)	0 (0)
Intestinal	349	13 (3.7)	19 (5)
Cleft lip and /or cleft palate	751	26 (3.5)	23 (3)
Open neural tube defect	489	34 (7)	1 (0.2)

*Table adapted from Witt DR and Hall JG³² and Stoll C, et al.³³

†Note that multiple anomalies are more likely to have a syndromic etiology compared to isolated anomalies.

subspecialists is required to provide women and families with the information they need to make appropriate decisions about pregnancy management.

Despite advances in prenatal diagnosis and knowledge of etiologies of known genetic syndromes, uncertainty may remain regarding the final diagnosis (Table 2) until delivery, when the newborn is assessed by a pediatrician, a neonatologist, or a geneticist. Early management of many congenital anomalies may require additional consultants such as pediatric cardiologists and pediatric surgeons in order to optimize neonatal outcome.

When any congenital structural anomaly has been identified prenatally, a comprehensive newborn assessment is essential for diagnosis and counselling on the etiology, prognosis, and recurrence risk for future pregnancies, especially in cases where the etiology has not been clearly identified prenatally. Witt and Hall proposed an approach to the investigation of a newborn with multiple congenital anomalies.³² Dysmorphism assessment (including facial dysmorphic features) is a significant part of such investigation. As this is often unsuccessful prior to delivery, and given the limitation of prenatal ultrasound (shown in Table 2), a significant proportion of non-chromosomal syndromes, depending on the system or systems affected, remain undiagnosed until the postnatal period.^{33,34} Parents should be made aware of this possibility, especially when multiple anomalies have been identified prenatally. As many syndromes have a recurrence risk (25% if autosomal recessive, 50% if autosomal dominant and if one of the parents is affected), it has been suggested that a comprehensive newborn assessment is essential to provide counselling about future pregnancy and familial implications. The assessment should be performed postnatally, or, in cases of pregnancy

termination, stillbirth, or neonatal death, a limited or complete autopsy should be performed by a perinatal or pediatric pathologist.^{35,36}

Recommendations

8. Women should receive information regarding the abnormal ultrasound findings in a clear, sympathetic, and timely fashion, and in a supportive environment that ensures privacy. Referral to the appropriate pediatric or surgical subspecialist(s) should be considered to provide the most accurate information possible concerning the anomaly or anomalies and the associated prognosis. (II-2 B)
9. Parents should be informed that major or minor fetal structural anomalies, whether isolated or multiple, may be part of a genetic syndrome, sequence, or association, despite a normal fetal karyotype. (III-A)
10. If early or urgent postnatal management may be required, delivery at a centre that can provide the appropriate neonatal care should be considered. (III-A)
11. When any congenital structural anomaly has been identified prenatally, a comprehensive newborn assessment is essential for diagnosis and counselling on the etiology, prognosis, and recurrence risk for future pregnancies, especially when the etiology has not been clearly identified prenatally. (III-A)
12. In cases of termination of pregnancy, stillbirth, or neonatal death, the health professional should encourage the performance of a complete autopsy by a perinatal or pediatric pathologist to provide maximum information on the diagnosis and etiology of the structural fetal anomaly or anomalies. When a complete autopsy is refused, the health professional should encourage the

performance of at least a partial or external autopsy (including X-rays and photographs). (III-A)

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APPENDIX*

Syndrome: A recognizable pattern of structural defects, often with a predictable natural history.

Sequence: A pattern of multiple anomalies that results from a single abnormal developmental process.

Association: Pattern of anomalies more frequently seen together without a common cause identified.

Autosomal dominant: Inherited disorder that is manifested fully when only one copy of the gene (located on chromosome 1 to 22) is abnormal.

Autosomal recessive: Inherited disorder that is manifested fully only when both copies of the gene (located on chromosome 1 to 22) are abnormal.

X-linked dominant: Inherited disorder that is manifested fully even if one copy of the normal gene (located on chromosome X) is present.

X-linked recessive: Inherited disorder that is manifested fully in males when no copy of the normal gene (located on chromosome X) is present.

Dysmorphism: Term used to describe a body part that has not followed a normal pattern of growth or formation.

*Appendix adapted in part from Alkazaleh F, et al.³¹