Genetic Considerations for a Woman’s Pre-conception Evaluation

Abstract

Objective: To give health care providers information about the genetic information that can be used as part of health surveillance for women undergoing a pre-conception evaluation for genetic risk assessment and possible genetic screening or testing.

Options: This genetic information can be used for patient education and possible prenatal testing.

Outcomes: The use of this genetic information may allow improved risk-benefit assessment for pre-conception counselling for individual patients and their families.

Evidence: PubMed or Medline and the Cochrane Database were searched in November 2009, using appropriate key words (pre-conception, genetic disease, maternal, family history, genetic health risk, genetic health surveillance, prenatal screening, prenatal diagnosis, birth defects, and teratogen). Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, and national and international medical specialty societies.

Benefits, harms, and costs: The benefits for the patient and her family include understanding of possible genetic risk and enhanced pregnancy outcomes. The harm includes increased anxiety or psychological stress associated with the possibility of identifying genetic risks.

Validation: The evidence obtained was reviewed by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada.

Recommendations and Summary Statements

A review of the current literature does not provide enough information for this committee opinion to present evidence-based recommendations.

INTRODUCTION

This committee opinion offers the health care provider an overview of the genetic conditions that should be considered as part of a pre-conception evaluation for women. With the advances made in the area of genetic testing, screening and predictive testing can be undertaken...
following non-directive counselling and consent, so that couples planning a pregnancy can consider risk-prevention strategies.

Two broad areas of pre-conception care are addressed in this committee opinion.

1. Genetic risk and risk screening (family history, history of childhood cancer, history of recurrent pregnancy loss, history of primary amenorrhea, advanced maternal and paternal age, and premature ovarian failure).
2. Prevention and teratogens (e.g., medical conditions and medications, obesity, multivitamin and folic acid supplementation, drugs, chemicals, infections, and immunization status).

SUPPORT FOR THE PRE-CONCEPTION COUNSELLING CARE MODEL

A number of medical and government agencies have put forward summaries and statements regarding pre-conception care.2–10 It is important to emphasize that this committee opinion deals with only the genetic aspects of pre-conception care, but with no intent to minimize the other important determinants of health.

Health Canada emphasizes that parental health before pregnancy is vital to the health of the baby.3 However, because most women in their reproductive years cannot be certain when (or if) they will become pregnant, there is no agreed upon definition of the pre-conception period.

Table 1, adapted from the Family Centered Maternity and Newborn Care National Guidelines,3 provides a guide that may be useful for clinicians conducting health assessments for women prior to conception.

Additional reports8 on maternal and child health in Canada emphasize 10 effective interventions to improve maternal, infant, and child health. Three of these 10 interventions deal with pre-conception and prenatal care:
1. Screening and counselling of women who smoke during pregnancy
2. Screening and counselling of women who drink alcohol during pregnancy
3. The use of vitamin supplements containing folic acid prior to pregnancy and during the first trimester to prevent birth defects (Table 2)

As outlined in the Canadian Perinatal Health Report 2008,11 fetal and infant mortality rates in Canada have declined steadily over the last 15 years, with birth cohort-based crude infant mortality rates of 5 per 1000 live births, and infant mortality rates among live births > 1000 g estimated at 3 per 1000 live births. Congenital anomalies as a cause of infant death fell by 43%, from 2.31 per 1000 live births in 1985–1988 to 1.32 per 1000 live births in 1996–1999. Prenatal diagnosis of congenital anomalies followed by selective termination is responsible for dramatic declines in late fetal and infant death rates. Maternal mortality ratios have declined from 6.1 maternal deaths per 100 000 live births in 1979–1981 to 2.5 per 100 000 in 1997–1999.

The American College of Obstetricians and Gynecologists7 reinforces the importance of pre-conception care, provides resources for clinicians, and proposes that every woman capable of reproduction create a reproductive health plan. Core pre-conception care considerations include the following factors: undiagnosed, untreated, or poorly controlled medical conditions; immunization history; medical and radiation exposure in early pregnancy; nutritional issues; family history and genetic risk; tobacco and substance abuse and other high-risk behaviours; occupational and environmental exposures; social issues; and maternal mental health issues. ACOG emphasizes the importance of asking the question, “Are you considering pregnancy or could you possibly become pregnant?” This can initiate several pre-conception care interventions including the following.

1. Dialogue about the patient’s readiness for pregnancy
2. An evaluation of the patient’s overall health and opportunities for improving her health
3. Patient education about the significant effect of social, environmental, occupational, behavioural, and genetic factors in pregnancy
4. Identification of women at high risk for an adverse pregnancy outcome

Pre-conception and inter-pregnancy care are components of a larger health care plan whose goal is to optimize the health of every woman. Reproductive capacity spans almost 4 decades for most women, and optimizing woman’s health before and between pregnancies is an ongoing process that requires access to and the full participation of all segments of the health care system.

Recent recommendations to improve pre-conception health and health care in the United States were published by the Department of Health and Human Services Centers for Disease Control and Prevention.5 They define pre-conception care as follows:
### Table 1. Taking a pre-conception history for assessment and counselling

**GENETIC HISTORY**
A thorough pre-conception history identifies couples who are genetically at risk. When women and their partners are informed of the risks of having a baby with birth defects or a genetic disorder prior to pregnancy, they are then able to determine their options regarding a pregnancy (including contraception, artificial insemination, adoption, prenatal invasive testing, or chance).

**Family History**
- Construct three-generation pedigree.
- Include assessment of genetic diseases, including muscular dystrophy, hemophilia, cystic fibrosis, fragile X syndrome, congenital heart disease, phenylketonuria, dwarfism, sickle cell anemia, and Tay-Sachs disease.
- Include assessment of multifactorial congenital malformations, such as spina bifida, anencephaly, cleft palate and lip, hypospadias, and congenital heart disease.
- Include assessment of familial diseases with a major genetic component, such as developmental disability, premature atherosclerosis, diabetes mellitus, psychosis, epileptic disorders, hypertension, rheumatoid arthritis, deafness, and severe refractive disorders of the eye.

**Ethnic History**
Establish risk for specific conditions related to ethnic origin, such as sickle cell anemia, Tay-Sachs disease, neural tube defects, beta-thalassemia, and alpha-thalassemia.

**Age**
Establish risks associated with age (e.g., women under age 15 or over age 35 may carry increased biological risks).

**HEALTH HISTORY**

**Chronic Conditions**
- Assess the presence of chronic conditions that can affect a woman’s ability to conceive, as well as the use of medications in treatment of chronic disease and their potential effect on pregnancy.
- The following specific conditions should be considered: diabetes mellitus, anemias, thyroid disorders, gynaecological disorders, hyperphenylalaninemia, asthma, sexually transmitted infections, heart disease, hypertension, deep venous thrombosis, kidney disease, systemic lupus erythematosus, epilepsy, hemoglobinopathies, cancer, seizure disorders, tuberculosis, rheumatoid arthritis, and mental health/psychiatric disorders.

**Infectious Conditions**
- Identify women who are rubella or varicella susceptible. If they are not actively attempting pregnancy, offer a vaccination.
- Identify and counsel women at risk for hepatitis B. Routine pre-conception testing of all women with hepatitis B is not currently recommended.
- Counsel women to avoid exposure to cat feces and raw and undercooked meats. Routine serologic testing for toxoplasmosis in the pre-conception period is not recommended.
- Evaluate the woman and her partner for exposure are to sexually transmitted disease (e.g., Chlamydia, HIV, gonorrhea, syphilis).

**Reproductive History**
- Collect information about menstrual, contraceptive, and sexual histories; infertility; abnormal Pap smears; and in utero exposure to diethylstilbestrol.
- Discuss past obstetric history, including early miscarriages; number of pregnancies; type of birth; length of labour; and specific complications, such as premature labour or delivery, gestational diabetes, pregnancy-induced hypertension, and postpartum depression.
- Discuss menstrual difficulties, specifically excessive cyclic bleeding, amenorrhea, and oligomenorrhea.
- Discuss gynaecological disease, such as endometriosis and pelvic inflammatory disease.

**Lifestyle Assessment**
Assess lifestyle issues, including nutrition; physical activity; prescription and over-the-counter drug use; other substance use; and environmental exposures, current and past.

Preconception care is a set of interventions that aim to identify and modify biomedical, behavioural and social risks to a woman’s health or pregnancy outcome through prevention and management. Improving preconception health and pregnancy outcomes will require more than effective clinical care for women. Changes in the knowledge, attitudes and behaviors related to reproductive health among both men and women need to be made to improve preconception health. Despite several health promotion campaigns aimed at reducing smoking, misuse of alcohol, intimate partner violence, obesity, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), reduction of vaccine-preventable diseases and exposure to occupational hazards, the majority of U.S. adults are not aware of how these and other health and lifestyle factors influence reproductive health and childbearing.

### GENETIC RISK AND RISK SCREENING

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have grouped the main components of pre-conception care into 4 categories of intervention: physical assessment, risk screening, vaccination, and counselling. The following are the 8 areas of risk screening.

1. Reproductive awareness
2. Environmental toxins and teratogens
3. Nutrition and folic acid
4. Genetics
5. Substance abuse including tobacco and alcohol
6. Medical conditions and medications
7. Infectious diseases and vaccination
8. Psychosocial concerns (depression or violence)

A 3-generation pedigree can identify familial genetic risks, as can a genetic screening questionnaire that the patient can be asked to complete before her appointment or as she waits for her consultation. When a strong or recurrent family history or diagnosis of possible genetic conditions is identified, the patient should be offered medical genetic counselling. Common familial genetic or increased risk conditions include X-linked disorders, which affect only males who inherit the faulty X gene, and autosomal recessive disorders, which affect both males and females who inherit the faulty gene. These disorders (thalassemia, alpha and beta, other hemoglobinopathies, cystic fibrosis, deafness, Tay-Sachs disease, spinal muscular atrophy) predominate in certain ethnic populations, in the Ashkenazi Jewish population, and in the case of consanguinity.

### Female Exposure to Cancer Treatment

Edgar and Wallace reviewed the pregnancy outcomes of women who had had cancer in childhood.

The majority of female cancer survivors will have normal reproductive function and would be expected to have a successful pregnancy. Female survivors of childhood cancer who were able to become pregnant carry an excess risk of preterm delivery and low birth weight infants. This restricted fetal growth and inability of the uterus to carry the fetus to term is associated with radiation-induced damage to the uterus. Chemotherapy does not appear to be associated with adverse pregnancy outcomes. However, prospective follow-up of cohorts of patients treated with contemporary therapies, frequently involving more intensive therapies, are required to determine the risk.

The risk of genetic abnormalities in the offspring of cancer survivors was found to be the same as in the offspring of controls, which provides reassurance that cancer therapies do not confer a greater risk of inherited genetic disease in the offspring. Edgar and Wallace found that after excluding known cancer predisposition syndromes, there was a minimal increase or no increase in the risk of cancer development in the offspring. This would indicate that
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“following potentially gonadotoxic chemotherapy and radiotherapy, if the surviving oocyte pool is sufficient for the woman to conceive, there does not appear to be an increased risk of germline mutations in the surviving oocytes.” Survivors of childhood cancers appear to have a significantly increased risk of premature menopause. “The majority of female survivors of childhood cancer will have regular menstrual cycles. However, for a minority of women, loss of ovarian function may occur unexpectedly resulting in premature menopause and infertility.” Survivors of cancer are 13 times more likely than controls to develop non-surgically induced menopause, with a cumulative incidence of 8% by the age of 40 years. Clinicians who provide pre-conception health care should ensure that female cancer survivors are aware of these issues.

Infertility and Amenorrhea
The 4 most common causes of primary amenorrhea are gonadal dysgenesis (48.5%), congenital absence of the uterus and vagina (16.2%), gonadotrophin-releasing hormone deficiency (8.3%), and constitutional delay of puberty (6.0%). Genetic diagnoses to consider are Turner syndrome (45, X or variant), congenital adrenal hyperplasia (autosomal recessive), congenital absence of uterus and vagina (most cases are 46, XX, normal female development and isolated Müllerian aplasia), complete androgen insensitivity syndrome (X-linked androgen mutation in 46, XY female phenotype), gonadal agenesis/dysgenesis (females or 46, XY females 80% unknown etiology; 15% to 20% SRY chromosomal mutations or deletions), hypogonadotropic hypogonadism, and Kallmann syndrome (variable etiology dominant, recessive, X-linked).

Advanced Parental Age
The risk of fetal aneuploidy associated with advanced maternal age and the appropriate prenatal screening process were reviewed in 2009 SOGC guideline. The key recommendations are summarized below.

1. All pregnant women in Canada, regardless of age, should be offered, through an informed consent process, a prenatal screening test for the common clinically significant fetal aneuploidies in addition to a second trimester ultrasound for dating, growth, and anomalies.

2. Maternal age is a poor minimum standard for prenatal screening for aneuploidy and should be removed as an indicator for invasive diagnosis testing. Amniocentesis and chorionic villus sampling should not be provided without multiple marker screening results except for women over the age of 40. Women should be counselled that the risk of fetal aneuploidy increases with maternal age; the risk of having a live born neonate with Down syndrome (trisomy 21) at age 20 is 1:1450, at 30 is 1:950, and at 40 is, 1:85.

Advanced paternal age is associated with an increased risk of new dominant mutations. There is no clearly accepted definition of advanced paternal age, but a frequently used risk criterion is any male aged 40 years or over at the time of conception. Some studies have suggested that the risk of genetic defects, specifically new dominant single gene mutations, is 4 to 5 times greater for fathers aged 45 than for their 20- or 25-year-old counterparts (achondroplasia has an estimated birth prevalence of 1 per 27 000). The increased risk for new genetic mutations for autosomal dominant conditions in the offspring is related to advanced age of the father. Family histories will not provide clues, because these types of mutations are new events in the family. Autosomal dominant conditions associated with advanced paternal age include achondroplasia, neurofibromatosis, Marfan syndrome, Treacher Collins syndrome, Waardenburg syndrome, thanatophoric dysplasia, osteogenesis imperfecta, and Apert syndrome. X-linked conditions associated with increased maternal grandfather’s age include hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency), Duchenne muscular dystrophy, Hunter syndrome, X-linked agammaglobulinemia, and retinitis pigmentosa. No specific testing is available to screen for these conditions when there is no known family history, and the risk remains low. However, patients should be informed of these paternal age-related conditions when it is appropriate because of the age of the partner.

The median age of menopause in Western populations is approximately 51 years. About 5% of women experience early menopause at 40 to 45 years of age. Premature ovarian failure (POF), which occurs in

<table>
<thead>
<tr>
<th>Birth defect</th>
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<td>Spina bifida</td>
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<td>Heart defects</td>
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<tr>
<td>Anorectal atresia</td>
<td>1.46</td>
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<td>Hypospadius</td>
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<td>Limb reduction defects</td>
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<td>1.42</td>
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<tr>
<td>Omphalocele</td>
<td>1.63</td>
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Table 3. Adjusted odds ratios for the 7 birth defects positively associated with maternal obesity (after excluding case–control mothers with gestational diabetes)
1% of women in the general population, is defined as cessation of menses due to hypergonadatrophic amenorrhea before the age of 40. The probability that the cause will be genetic or autoimmune depends on the patient’s age at diagnosis, and at least 25% to 33% of cases remain idiopathic. Among women with idiopathic sporadic POF, approximately 2% will carry a pre-mutation for the fragile X syndrome. Among women with familial premature ovarian failure, 14% carry fragile X pre-mutation. A 2007 publication also identified an oocyte-specific homeobox that may represent a candidate gene for non-syndromic ovarian failure. Other genes identified as being associated with premature ovarian failure (FSH receptor, POF1B, FOXL2, BMP15) are summarized in this review. Other genetic conditions to be considered in the evaluation of the patient with POF are chromosomal disorders such as Turner syndrome (45,X); mosaic Turner syndrome; X chromosome rearrangements involving the critical chromosomal region for normal ovarian function at Xq26.2-q28; galactosemia; and two rare genetic syndromes, blepharophimosis-ptosis-epicanthus inversus syndrome and autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy.

**Prevention and Teratogens**

A significant proportion of women of childbearing age suffer from various chronic conditions and are exposed to or consume substances that can adversely affect pregnancy outcomes, leading to pregnancy loss, infant death, birth defects, or other complications for mothers and infants. In 2002, approximately 6% of adult women aged 18 to 44 had asthma, 50% were overweight or obese, 9% had diabetes mellitus, 3% had cardiac disease, 3% were hypertensive, and 1% had thyroid disorder. More than 80% of women aged 20 to 39 had dental caries or other oral diseases, which are associated with pregnancy complications for women and infants. High-risk behaviours included smoking and drinking alcohol during pregnancy (11% and 10% of women, respectively); 55% of women at risk of getting pregnant consumed alcohol.

There is evidence that pre-conception care is effective in reducing the adverse outcomes of isoretinoids, alcohol misuse, antiepileptic drugs, diabetes (pre-conception), folic acid deficiency, hepatitis B, HIV/AIDS, hypothyroidism, maternal phenylketonuria, rubella seronegativity, obesity, oral anticoagulant, sexually transmitted infections (e.g., Chlamydia and gonorrhea), and smoking. These risk factors and evidence for evaluation at pre-conception care were recently reviewed. Each of these reviews of medications, drugs, and viral infections emphasized the teratogenic exposures that may occur in embryonic and fetal life with adverse outcomes.

Waller et al. emphasized pre-pregnancy obesity (BMI > 30 kg/m²) as a risk factor for structural defects. The obese women had up to a 2-fold greater likelihood of giving birth to an infant with 1 of 7 structural defects than non-obese women. The 7 defects were spina bifida, heart defects, anorectal atresia, hypospadius, limb reduction (missing toes, fingers, or limbs), diaphragmatic hernia, and omphalocele (Table 3).

Animal and human studies provide evidence that alterations in glycemic control are responsible for a wide range of structural birth defects among women who have diabetes prior to becoming pregnant. A similar mechanism may occur in some rare X-linked dominant disorders such as incontinentia pigmenti, Goltz syndrome, and oral-facial-digital syndrome, but it is a rare presenting feature and represents only a very small portion of recurrent miscarriages. Consultation with someone who has training in medical genetics could be considered if the other factors, such as exposure to toxins or drugs, pelvic infections, endocrine or metabolic dysfunction, immunological disorders, and uterine abnormalities have been evaluated and ruled out.
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thus be responsible for the effects observed in this study. Women with a confirmed diagnosis of gestational diabetes were excluded, but women with undiagnosed diabetes were likely included. Obesity is associated with an increased risk of stillbirth (OR 2.07; 95% CI 1.59 to 2.74), although the mechanism is unclear. Weight management guidelines are available.

In 2007, The Society of Obstetricians and Gynaecologists of Canada published clinical practice guidelines that reviewed teratogenicity associated with pre-existing and gestational diabetes, and drug, chemical, and infectious exposures in pregnancy. Prospective and retrospective cohort studies have demonstrated an increased risk of congenital anomalies (4% to 10%) in both pre-existing and gestational diabetes (including probable unrecognized type 2 diabetes). Women with diabetes should be offered pre-conception counselling, ideally with a multidisciplinary team, to optimize general health and glycemic control and to review the risks of congenital anomalies. For women who have pre-existing type 1 or type 2 diabetes or who are at an increased risk of having type 2 diabetes identified for the first time in pregnancy, optimal glycemic control may reduce the risk of congenital anomalies. The most common anomalies are those involving the cardiovascular system, the central nervous system, and the face and extremities.

In the case of exposure to drugs, chemicals, and infections, the congenital anomaly risks depend on the specific agent and dose, gestational age, and genetic susceptibility.

Pre-conception care counselling should include a discussion of multivitamin and folic acid supplementation for the prevention of birth defects. A 2007 SOGC-Motherisk guideline recommended folic acid and multivitamin supplementation, beginning at least 2 to 3 months before conception and continuing through the first trimester of pregnancy. The optimal dose can be decided once a review of the woman's medical and family history has determined her risk of having a child with a birth defect. Congenital anomalies that can be reduced in incidence and recurrence by this nutritional protocol include neural tube defects (e.g., anencephaly, myelomeningocele, meningocele), oral facial clefts, congenital heart disease, urinary tract anomalies, and limb defects.

Because of the known teratogenic risks of certain viruses during pregnancy, immunization status should be reviewed with the patient at a pre-conception visit. Travel exposures are now more common, and they increase the importance of this immunization review. Immunization in pregnancy was reviewed in a 2009 SOGC clinical practice guideline and in a 2003 ACOG committee opinion. The SOGC guideline recommends the following:

1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization.
2. Health care providers should obtain an immunization history from all women accessing prenatal (or pre-conception) care.
3. In general, live and/or live-attenuated virus vaccines are contraindicated during pregnancy, as there is a, largely theoretical, risk to the fetus.
4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk.
5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks.
6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy.

The guideline also provides a summary of available vaccines and indications for use.

SUMMARY

Pre-conception planning is important but may not always be possible because some pregnancies are unintended. The reproductive risks must be considered at all patient interactions because personal situations change, and new discoveries can affect family histories. Primary prevention of genetic and congenital anomalies is the goal in reducing perinatal morbidity and mortality and enhancing healthy families. Health care providers should always ask patients of reproductive age “Are you considering a pregnancy or could you possibly become pregnant?”

REFERENCES


