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The Clinical Content of Preconception Care: Genetics and Genomics

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Abstract

The prevalence of paternal and maternal genetic conditions that affect pregnancy varies according to many factors, including parental age, medical history, and family history. While some genetic conditions that affect pregnancy are easily identified early in life, others are not and may require additional diagnostic testing. A complete three-generation family medical history that includes ethnicity information about both sides of the family is arguably the single best genetic "test" applicable to preconception care. Assessment of genetic risk by an experienced professional has been shown to improve the detection rate of identifiable risk factors. Learning about possible genetic issues in the pre-conception period is ideal, as knowledge permits patients to make informed reproductive decisions. Options available to couples before conception include adoption, surrogacy, use of donor sperm, *in vitro* fertilization after pre-implantation genetic diagnosis, and avoidance of pregnancy. Future technological advances will increase the choices available to couples.

Keywords

Family history; genetics; preconception

Introduction

Applications of genetics (the scientific study of heredity) and genomics (the study of an organism's complete genetic makeup) are expanding into virtually every sphere of health care; preconception care is no exception. However, the evidence-based application of genetics and genomics to preconception care is a work in progress for several reasons. First, less research attention has been given to genetic and genomic interventions in the preconception setting than to those in the prenatal period. Second, conducting prospective randomized trials in either the prenatal or preconception period is ethically and legally problematic. Finally, genetic technologies are emerging at a mind-numbing pace, and time will be required to develop evidence supporting their utility.

Despite the rapid evolution of this field, individuals who provide medical care to any person who is considering pregnancy should be aware of recommendations for genetic care in the

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preconception and prenatal period.[1, 2] Some recommendations apply to all individuals. Other recommendations are more important for patients with specific risk factors. In many cases, these recommendations draw heavily on consensus and expert opinion. Additionally, the majority of prenatal care guidelines have been extrapolated to the preconception period. Logically this makes sense; however, formal studies demonstrating the validity of this extrapolation are lacking, and will likely never be completed. One final caveat is that the diversity and rarity of many genetic disorders that affect pregnancy ensures that any document containing recommendations, including this one, will be incomplete.

All Individuals

Obtaining a complete three-generation family medical history that includes ethnicity information about both sides of the family is arguably the single best genetic "test" applicable to preconception care. Additionally, a discussion of obstetrical and medical history and parental age at anticipated delivery are critical aspects of a preconception healthcare visit. Family history and other historical data provide an inexpensive and non-invasive assessment of conditions that might affect pregnancy. Learning about these risks in the preconception period is ideal. Improved knowledge about the heritability of a disorder can allow individuals to make informed reproductive decisions and can improve prenatal care during pregnancy. Options available to couples before conception include adoption, surrogacy, use of donor sperm, pre-implantation genetic diagnosis after in-vitro fertilization, with transfer of unaffected embryos, and avoidance of pregnancy. Future technological advances will likely further broaden the choices available to couples.[3, 4, 5, 6, 7]

Providers of preconception care should also urge women to take a multivitamin, with at least 400 micrograms of folate, daily beginning at least one month prior to conception. Folate has been shown to reduce the incidence of neural tube defects, and may also reduce the incidence of other malformations such as orofacial clefting, limb deficiencies, cardiac defects, urinary tract defects, and omphalocele. Women with a history of medical conditions such as epilepsy or diabetes mellitus, or a previous gestation with a neural tube defect, may require increased folate intake.[8, 9, 10]

Finally, in addition to the testing discussed in Table 1 (see section on Couples with Ethnicity-Based Genetic Risk Factors), all couples, regardless of ethnicity, should be made aware of the availability of cystic fibrosis carrier screening.[11]

Recommendation: All women considering pregnancy should have a screening history in the preconception visit. Providers should ask about risks to pregnancy based on maternal age, maternal and paternal medical conditions, obstetric history, and family history. Ideally, a three-generation family medical history should be obtained for both members of the couple with the goal of identifying known genetic disorders, congenital malformations, developmental delay/mental retardation, and ethnicity. If this screening history indicates the possibility of a genetic disease, specific counseling should be given, which may include referral to a genetic counselor or clinical geneticist. *Strength of recommendation:* B; *Quality of evidence*: III

Recommendation: All women should take a multivitamin with at least 400 micrograms of folate daily starting at least one month prior to conception. Women with specific risk factors may require higher daily dosages of folate. *Strength of recommendation:* A; *Quality of evidence:* II-2

Recommendation: All couples should be made aware of the availability of cystic fibrosis carrier screening. ***Strength of recommendation:*** **B;** ***Quality of evidence:*** **III**

Couples with Ethnicity-Based Genetic Risk Factors

Ancestry influences the probability of being a carrier of many disorders that affect pregnancy. Carriers will typically not themselves show any signs of a genetic disorder, and there is often no known family history of the condition. The guidelines for testing by ethnicity include conditions for which there is evidence that testing is effective or where there is strong expert opinion that testing should be performed. However, this is not meant to imply that these conditions do not occur or should be ignored in populations of other ethnicities. Individuals of mixed ancestry or ethnicity should consider carrier testing recommended for any component ethnicity. A formal referral could be considered if practitioners are unsure which disorders should be tested. See Table 1 for a summary of counseling/testing by ethnicity.[11,12,13,14,15,16,17,18]

Carrier testing can have important psychological consequences for an individual and should only occur after obtaining informed consent. Choosing the appropriate test and interpreting results of testing can be complex, and may vary between different ethnicities. For example, using the current recommended mutation panel, negative carrier testing for cystic fibrosis in an Ashkenazi Jewish couple would result in a different chance of having an affected child than negative testing in an African-American couple. Depending on the provider's proficiency in genetics, carrier testing may necessitate referral to genetic services.[19]

> *Recommendation:* Couples at risk for any ethnicity-based conditions should be offered preconception counseling about the risks of that condition to future pregnancies. Screening and/or testing should be offered based on couples' preferences. This may require referral to a genetic counselor or clinical geneticist. *Strength of recommendation:* B; *Quality of evidence:* II-3

Couples with Genetic Risk Factors Based on Specific Family History

If at least one member of a couple has a family history of developmental delay, congenital anomalies, or other known or suspected genetic conditions, they should be referred to a qualified healthcare provider for appropriate counseling and potential testing.[2, 4] If a disorder in the individual's family has been identified as having a genetic cause, it may be possible to test an individual to see if they are at risk for having an affected child. For example, a family history of known genetic conditions such as cystic fibrosis or Tay-Sachs should prompt offering of testing for at least the person with affected relatives. If the person is found to have inherited a gene that could cause the disorder in their children, their partner could be tested in order to quantify the overall risk. In the case of an X-linked disorder such as hemophilia, sex selection should be discussed.[2, 11, 12, 13, 14, 15, 16] See below for recommendations in the case of a family history of thrombophilia. See Table 2 for information about examples of family history findings that should prompt further counseling/testing.

> *Recommendation:* Individuals identified as having a family history of developmental delay, congenital anomalies, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy. *Strength of recommendation:* B; *Quality of evidence:* II-3

Couples with Genetic Risk Factors Based on Previous Pregnancies

A history of recurrent pregnancy loss (classically defined as more than 2 spontaneous abortions) should prompt testing of both parents for genetic conditions such as chromosomal anomalies and hereditary thrombophilia.[17] Testing for chromosomal anomalies can be performed by sending peripheral blood for chromosome analysis (karyotyping).[2] If a chromosomal anomaly such as a balanced translocation is found, providers should discuss the use of in vitro fertilization with pre-implantation genetic diagnosis in order to increase the

chance of an unaffected pregnancy.[18, 19, 20] Please see the article by Dunlop et al. in this issue for recommendations regarding thrombophilia.

> *Recommendation:* If at least one member of a couple is found to have a chromosomal anomaly, in vitro fertilization with pre-implantation genetic diagnosis should be discussed. *Strength of recommendation:* C; *Quality of evidence:* III

Individuals with Risk Factors due to Known Genetic Conditions

Individuals with known genetic conditions should be counseled regarding optimal control of their condition and the chances of having affected offspring, and should be aware of how the presence of a genetic disorder could affect both their health and the health of their fetus. For example, women with sickle cell disease (SCD) have an increased risk of preterm labor and premature rupture of membranes, and women with Marfan syndrome have an increased risk of aortic dissection during pregnancy.[21, 22]

In certain genetic disorders, there are specific recommendations for management in the preconception period. For example, women with SCD require increased amounts of folate, and women with phenylketonuria (PKU) should maintain low phenylalanine diets prior to conception, as infants born to women with PKU with phenylalanine levels over 20 mg/dl are more likely to have microcephaly, developmental delay, growth restriction, and heart defects.[**Error! Bookmark not defined.**, 23, 24]

> *Recommendation:* Suspected genetic disorders may require further work-up prior to conception. Known or discovered genetic conditions should be optimally managed before and after conception. *Strength of recommendation:* B; *Quality of evidence:* II-3

Conclusion

No provider is expected to be aware of every genetic condition that could possibly affect a pregnancy; however, it is important that all providers be able to do two things. First, providers should be able to ask the right questions in order to determine who might be at risk. This includes the ability to take a three-generation family history. Second, providers should know when to refer a patient, and to whom a patient should be referred. There is a wide array of excellent educational resources regarding genetic disorders and family history available on the web. See Table 3 for a list of resources. Finally, providers should keep in mind that this is a very rapidly expanding field. Researchers are unraveling the genetic etiologies of many conditions for which screening and testing may soon become available.[25]

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Table 1

Recommended Counseling/Testing by Ethnicity

Ethnicity (of at least one member of the couple)	Disorders with recommended counseling/testing	Type of test
Caucasian	Cystic fibrosis	DNA testing of *CFTR* gene[11]
European	Cystic fibrosis	DNA testing of *CFTR* gene[11]
Ashkenazi Jewish	Canavan disease, cystic fibrosis, familial dysautonomia, Tay-Sachs, Gaucher, Niemann-Pick Type A, Bloom syndrome Mucolipidosis IV, Fanconi syndrome	Canavan disease: DNA testing of *ASPA* gene[13,15,19] Cystic fibrosis: DNA testing of *CFTR* gene[11,13,19] Familial Dysautonomia DNA testing of *IKBKAP* gene[13,15,19] Tay-Sachs: Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[13,15,19] Gaucher: DNA testing of *GBA* gene Niemann-Pick Type A: DNA testing of *SMPD1* gene[13,15,19] Bloom syndrome: DNA testing of *BLM* gene[13,19] Mucolipidosis IV: DNA testing of *MCOLN1* gene[13,19] Fanconi syndrome: DNA testing of *FANCC* gene[13,19]
French-Canadian	Tay-Sachs	Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[12,14,19]
Cajun	Tay-Sachs	Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[12,14,19]
African	Sickle cell disease/trait, thalassemia	Complete blood count(CBC) with red blood cell indices (RBC), iron indices, hemoglobin electrophoresis[16,17,18]
Mediterannean	Thalassemia	CBC with RBC indices and iron indices; hemoglobin electrophoresis if anemia and normal iron indices[16,17,18]
Asian	Thalassemia	CBC with RBC indices and iron indices; hemoglobin electrophoresis if anemia and normal iron indices; DNA testing of alpha-globin genes for alpha thalassemia if Southeast Asian with low MCV anemia but normal iron studies[16,17,18]

Table 2

Details from personal or family history that should prompt further counseling.

Chromosomal disorders (e.g., Trisomy 21)
Clotting disorders
Deafness
Developmental delay/mental retardation (e.g., Fragile X syndrome)
Early infant death
Heart defects
Other known genetic disorders (e.g., phenylketonuria, Marfan syndrome)
Neural tube defects
Familial cancer syndromes (known or suspected)
Family history of other congenital malformations
Neural tube defects
Orofacial clefts
Recurrent miscarriages
Sickle cell disease or trait
Sudden infant death syndrome (SIDS)
Thalassemia
Thrombophilia

Table 3

Further Resources

Resources	Comments
American College of Medical Genetics (www.acgme.net)	Includes links to the latest standards and guidelines for clinical genetics laboratories, with disease/phenotype-specific standards and guidelines
CDC National Office of Public Health Genomics (cdc.gov/genomics)	Resources on how human genomic discoveries can be used to improve health and prevent disease
Gene Tests (genetests.org)	Reviews about specific conditions, laboratory and clinical directories, handouts for patients
Genetic Alliance (geneticalliance.org)	Information about specific disorders, advocacy, support and discussion groups
Genetic and Rare Diseases Information Center (rarediseases.info.nih.gov/html/resourc es/info_cntr.html)	Information about specific disorders, explanations for patients, financial assistance information, access to specialists.
National Society of Genetic Counselors (nsgc.org)	Directory of genetic counselors, guidelines for counseling specific conditions
Online Mendelian Inheritance in Man (ncbi.nlm.nih.gov/sites/entrez?db=omim)	Searchable database of genes and genetic disorders targeting health care professionals
PubMed (ncbi.nlm.nih.gov/PubMed)	Medical literature database
U.S. Surgeon General's Family History Initiative (hhs.gov/familyhistory)	Education about family health history through tools such as My Family Health Portrait