Linking Family History in Obstetric and Pediatric Care: Assessing Risk for Genetic Disease and Birth Defects

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ABSTRACT

Family history captures the collective influence of shared genetic susceptibility, shared environmental factors, and common behaviors within families. Throughout the reproductive continuum, pediatricians, obstetricians, family practitioners, genetic counselors, and other clinicians can work with families to elicit relevant family history information and factor it into risk-assessment calculations and, when appropriate, decision-making. Current screening tools have focused on understanding the risk for single-gene disorders, chromosomal conditions, and teratogen exposures during the preconception, prenatal, and interconception periods. More research and data are needed to understand how family history influences risk for a wide variety of complex birth outcomes such as preterm birth, stillbirth, and many birth defects. With a better understanding of the impact of family history on many adverse birth outcomes, tools for the collection of a broader set of pertinent family history information must be developed.

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Key Words
family history, preconception, prenatal, interconception, pregnancy, genetics

Abbreviations
NTD—neural tube defect
CF—cystic fibrosis
CMA—chromosomal microarray analysis

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When seeing a child for pediatric care, a pediatrician will compile a family history that includes not only the complete medical history of the child but also that of first-degree relatives (ie, siblings and parents), as well as more distant relatives such as aunts, uncles, and grandparents. Although a family history of birth defects or genetic conditions is of obvious particular relevance, more subtle medical conditions such as premature ovarian failure or multiple miscarriages can also be risk factors. Linking pediatric information with family medical history during the preconception (before pregnancy) or interconception (between pregnancies) period will provide the most comprehensive assessment of risk and provides a valuable supplement to information that is gathered routinely by obstetricians during prenatal visits.

The importance of preconception care has been emphasized for women by their health care clinicians. Pediatricians serve an important role in identifying family history information that is relevant to future pregnancies and making families aware of the need to discuss that information with the mother’s clinician during the interconception period to enhance continuity of care. Because pediatricians see children and their families frequently during the first year of a child’s life, they are likely to detect abnormalities that become important aspects of the family history for the mother in the preconception period should she choose to have a subsequent pregnancy. In addition, the father’s family history is important and may be captured in a pediatric visit.

Family history includes shared genetic susceptibility, shared environmental factors, and common behaviors within families. Although for most traditionally defined genetic conditions the prenatal influence of environmental factors and behaviors on infant outcome is largely unknown, these risks are increasingly being defined for a number of birth defects such as neural tube defects (NTDs) and orofacial clefts. Identifying family history of a condition during the preconception or interconception period provides the physician with a unique opportunity to raise familial awareness of increased risk and motivate behavior modification and decision-making to reduce risk and improve obstetric and subsequent pediatric outcome. Family history can also lead to early diagnosis during pregnancy, which allows for secondary interventions in decision-making during pregnancy, including location and mode of delivery and tertiary interventions in medical care during the newborn period and childhood.

An emerging challenge is the collection, translation, and transfer of family history information among the many health care professionals who will assist the family in using the information during these times of potentially unique opportunities for intervention. Electronic medical records may provide improved mechanisms to link information between family members, while still respecting their privacy. To enhance communication and continuity of care, pediatricians play a key role in conveying information about a child to his or her family and emphasizing the importance of sharing such information with the appropriate family members and clinicians to assist in health care and reproductive planning.

Advances in genetics and genomics are broadening the scope of conditions that can be screened or tested for during the preconception, prenatal, interconception, and early childhood periods. Here we examine several pediatric conditions for which a family history might warrant a number of screening and testing options.

**ROLE OF THE PEDIATRICIAN IN TRANSLATING FAMILY HISTORY**

Family medical history belongs to the entire family and should reflect as broad a picture of the nuclear and extended families as is feasible. Genetic conditions and birth defects may have implications for the parents’ own health as well as their reproductive planning. Pediatricians serve a critical role in interpreting for the parents the clinical findings that pertain to a child’s health and the implications for the parents’ own health and that of their subsequent pregnancies.

An autosomal recessive condition diagnosed in a child will often reveal for the first time that parents are asymptomatic carriers of the condition. Parents with a child who tragically dies of sudden infant death syndrome and whose workup reveals medium-chain acylcoenzyme A dehydrogenase deficiency should receive counseling about the possible implications for their older children, who might also have the condition. This could include anticipatory guidance regarding the importance of intervening early in the event of infection or febrile illness. In addition, reproductive planning for future children might include identifying the parents’ mutations to facilitate prenatal diagnosis.

Because pediatricians often see women more frequently than their obstetricians do between pregnancies, pediatricians can be important purveyors of family history information and counseling during the interconception period and can bridge the gap between a family’s pediatric and obstetric care. However, mechanisms to transfer family history information between pediatricians and obstetricians are not well established and often rely on the family with the potential inherent problems of miscommunication and inaccuracy. By linking a family’s health care, all of a family’s health clinicians can help facilitate the transfer of accurate and reliable information and thereby enhance continuity of care.

**TOOLS FOR SCREENING**

The role of family history as a marker for shared genetic susceptibility is growing as more is known about the genetic basis of many pediatric conditions. Several tools are commonly used during the prenatal period that can also be used during the preconception and interconcep-
tion periods to screen for increased risk on the basis of family medical history. One example is First Page, a screening tool developed by the Foundation for Blood Research. The simple 1-page tool inquires about personal or family history of many single-gene and chromosomal conditions as well as structural birth defects, teratogen exposures, and recurrent miscarriages. The First Page tool assesses risk for single-gene disorders that affect children, such as sickle cell disease and cystic fibrosis (CF), and provides detailed algorithms for appropriate counseling and testing. It also screens for complex pediatric conditions such as developmental delay, for which varying genetic and environmental causes exist.

The American College of Obstetricians and Gynecologists dedicates one section of its antepartum record to genetic screening and teratology counseling. The tool can be used to screen the patient, the infant’s father, or anyone in either family for increased risk for thalassemia (of Italian, Greek, Mediterranean, or Asian ancestry or with a mean corpuscular volume of <80), NTDs, congenital heart defects, Down syndrome, Tay-Sachs disease, Canavan disease, familial dysautonomia, sickle cell disease or trait, hemophilia or other blood disorders, muscular dystrophy, CF, Huntington’s disease, mental retardation/autism (specifically fragile X syndrome), other inherited genetic or chromosomal disorders, and maternal metabolic disorders (specifically type 1 diabetes or phenylketonuria) and find out about a previous child with a birth defect, recurrent pregnancy loss or stillbirth, and medications (including supplements, vitamins, herbs, over-the-counter drugs, illicit or recreational drugs, and alcohol). The American College of Obstetricians and Gynecologists also provides an obstetric medical history form, which the patient fills out by answering questions about personal health history, exposures affecting health, gynecologic health history, family history and genetic screening, and psychosocial screening. In the family history and genetic screening section, the patient is asked to identify her ethnicity and the ethnicity of the father. Subsequent questions ask whether she or the father has ever had a child born with a birth defect or whether they have birth defects themselves. The patient is then asked to describe any abnormalities that have occurred in children within her family or the father’s family, including mental retardation, birth defects, early infant death, deformities, or inherited diseases such as hemophilia, muscular dystrophy, or CF. A history of pregnancy losses (miscarriages or stillbirths) is then asked with follow-up information regarding previous genetic or chromosomal testing for the losses. The form also asks the patient whether she or the father is of an ethnic group that is associated with increased carrier risk for several autosomal recessive conditions. The patient is asked whether she desires a Down syndrome risk assessment and if she has any additional concerns about birth defects or inherited disorders. The final question asks whether the father will be ≥50 years old at the time of delivery, which reinforces the importance of including paternal information in risk assessment. As evidenced by the issues presented above, this screening is currently focused mainly on single-gene and chromosomal disorders, with the exception of NTDs and congenital heart disease. Future research might identify other complex birth outcomes in which family history indicates increased risk.

**FAMILY HISTORY OF SINGLE-GENE DISORDERS**

Traditionally, family history has revealed increased risk for single-gene disorders such as sickle cell disease and CF. These conditions follow autosomal recessive-inheritance patterns, and a positive family history suggests that unaffected, at-risk family members should undergo carrier testing. In the case of CF, a child born with meconium ileus might be tested for CF; if the child were affected, the test would reveal that both parents are obligate carriers. Prenatal testing would be recommended in any subsequent pregnancies and could be performed after identifying the specific mutations that the parents carry. Whereas family history was previously the sole indicator for carrier screening, population-based screening programs such as newborn screening are, in many states, now identifying newborns affected with CF well before they exhibit symptoms. In addition, preconception, prenatal, and interconception carrier-screening recommendations are broadening the scope of carrier testing, thereby providing more information to families whose members are CF carriers.

Families of certain ethnicities are encouraged to undergo carrier testing on the basis of increased carrier frequency among their ethnic group. For instance, all women with an Ashkenazi Jewish family background should be offered carrier screening during the preconception or prenatal period for Tay-Sachs disease, Canavan disease, CF, familial dysautonomia, mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher’s disease. Likewise, patients of Southeast Asian or Mediterranean background should be screened for abnormal hemoglobin variants, because thalassemias are more common in these regions. Individuals of African ancestry are offered screening for hemoglobinopathies, as well, because of the increased risk for being carriers of sickle cell disease or α-thalassemia.

**FAMILY HISTORY OF BIRTH DEFECTS: NTDs**

The prevention of NTDs has been quite successful with the implementation of public health messages encouraging folic acid supplementation and fortification of the food supply with folic acid. Family history serves a role in preventing NTDs during the preconception and interconception periods by providing a targeted recommendation for women at increased risk for NTD on the basis...
of their personal or family histories. The general recommendation for all women of childbearing age is to take a multivitamin containing 400 μg of folic acid daily in addition to eating a healthy, well-balanced diet. The targeted recommendation is that women who have a personal history of an NTD or who have had a pregnancy or child affected by an NTD take 4 mg of folic acid starting 1 month before conception and continuing through the first 3 months of pregnancy. Screening for a family history of NTDs can have direct implications on preconception and interconception care by invoking targeted recommendations for prevention.

**FAMILY HISTORY OF DEVELOPMENTAL DELAY**

**Fragile X Syndrome**

Global developmental delay is a challenging pediatric diagnosis with a complex etiology that includes genetic and environmental factors and gene-environment interactions. One example of a single-gene condition that presents as a global developmental delay is fragile X syndrome, which is passed on through a triplet repeat expansion in a premutation state with ramifications for the entire family. For instance, a 32-year-old woman found out about the fragile X syndrome diagnosis in her 2-year-old child of the then–32-year-old mother who presents for preconception care or other health care concerns with a family history that includes a 42-year-old sister with premature ovarian failure and a father with late-onset tremor/ataxia would warrant fragile X carrier testing during the preconception period to screen for the fragile X premutation. Within the same family, the 2-year-old child of the then–32-year-old mother might present with developmental delay and normal karyotype. This child would need fragile X testing. If this finding occurred before the mother desired a subsequent pregnancy, testing to determine premutation carrier status of the mother would be indicated during the interconception period. The prenatal implications are clear: a child affected with fragile X syndrome is likely to have a premutation carrier mother; thus, prenatal testing for fragile X syndrome during any subsequent pregnancy would be warranted.

In the scenarios presented here, establishing the diagnosis in one member of a family has implications for the entire family. Furthermore, the conditions that can affect premutation carriers provide expanded opportunities for screening. Whereas screening for a family history of developmental delay or autism currently occurs during preconception and prenatal care, screening for a sister with premature ovarian failure or a father with ataxia does not. Screening tools for use during the preconception and prenatal periods could be expanded to include other aspects of family history that can identify a family at risk. This would offer increased opportunities for a family to understand its risk earlier, which is generally desirable. A 2003 study showed that 55.5% of families with at least 1 child diagnosed with fragile X syndrome reported having another child before they found out about the fragile X syndrome diagnosis in their first child.

**Chromosomal and Genomic Etiologies**

Global developmental delay can also result from chromosomal abnormalities, including an unbalanced translocation (exchange of material between 2 chromosomes). For example, Down syndrome can result from an unbalanced translocation involving chromosome 21. A parent with a balanced translocation and, thus, a full complement of chromosomes can pass on an unbalanced translocation to his or her child, which leads to developmental delay and other abnormalities. The family history might reveal a history of recurrent miscarriages in the individual carrying the balanced translocation. If a known balanced translocation carrier becomes pregnant, prenatal testing should be undertaken via chorionic villus sampling during the first trimester or by amniocentesis during the second trimester to determine the chromosomal complement of the fetus. Thus, a family history of Down syndrome, developmental delay, or multiple miscarriages could indicate the need for karyotype analysis of the mother to test for a balanced translocation.

**Technology** is moving forward rapidly and expanding our ability to test for more conditions. Array-based comparative genomic hybridization, also known as chromosomal microarray analysis (CMA), offers simultaneous testing for an increase or loss of genetic material on all 23 pairs of chromosomes. The role of family history as an indicator for such testing remains an interesting future research subject. When a child with developmental delay or congenital anomalies is tested in childhood and found to have a chromosomal abnormality, the finding becomes part of the family history. With this family history, prenatal testing during subsequent pregnancies could then be undertaken via CMA. Furthermore, perhaps a woman in a family with a deceased member with unexplained mental retardation or developmental delay would consider undergoing CMA testing during her pregnancy. Whether testing is warranted remains unclear, and research is needed to understand the performance and role of CMA testing.

**COMPLEX CONDITIONS: ADVERSE BIRTH OUTCOMES**

Family history might also be relevant to the assessment of risk for complex conditions and adverse birth outcomes such as placental abruption or preeclampsia. The factor V Leiden mutation imparts an increased risk for clotting abnormalities, which can lead to miscarriage during the first trimester or increase the risk for placental abruption and subsequent poor birth outcomes during the second and third trimesters. A woman with a sister or mother who had a deep venous thrombosis at a young age while taking oral contraceptives, a history that is consistent with factor V Leiden heterozygosity,
might consider factor V Leiden mutation testing when anticipating pregnancy. The factor V Leiden carriage rate is ~5.3% among white Americans, 2.2% among Hispanic Americans, 1.3% among Native Americans, 1.2% among black Americans, and ~0.5% among Asian Americans.20 Women in whom the factor V Leiden mutation is detected can be managed with aspirin or low molecular weight heparin during the preconception, prenatal, and interconception periods with improved birth outcomes. Because clotting abnormalities are implicated in outcomes such as abruptio that lead to preterm birth with potentially lifelong sequelae, such screening and testing for complex birth outcomes represents the future direction of preconception and interconception screening.

CONCLUSIONS

Although risk reduction through the elimination of environmental risk factors remains an important aspect of preconception, prenatal, and interconception care, research in the genomic era is in the process of translating the vast information found in the genome sequence into information that will improve health. Family history helps to capture the information that is contained within each individual child’s genome and currently holds much promise to raise awareness of individual risk and motivate interventions and behavior change to minimize that risk.

Current screening tools have focused on understanding the risk for single-gene disorders, chromosomal conditions, and teratogen exposures during the preconception, prenatal, and interconception periods. More research and data are needed to understand how family history influences risk for a wide variety of complex birth outcomes such as preterm birth, stillbirth, and many birth defects. With a better understanding of the impact of family history on many adverse birth outcomes, tools for the collection of a broader set of pertinent family history information must be developed.

Pediatricians can facilitate the linking of pediatric, preconception, and interconception care by working with families and their obstetricians, family practitioners, and other health care clinicians to enhance communication and knowledge about risk as well as provide guidance on how to minimize that risk and improve pregnancy outcomes.

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