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Preconceptual Folic Acid Use and Recurrence Risk Counseling for Congenital Heart Disease

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Abstract

Objective—Recurrence risk of congenital heart disease (CHD) in families with an affected first-degree relative is increased as compared to the general population. Advances in genetic testing and evidence that preconceptual folic acid supplementation may decrease risk of CHD, warrants preventative counseling for at-risk families. Our goal was to document patterns of preconceptual folic acid supplementation and recurrence risk counseling in at-risk families in order to identify opportunities for improved preventative care.

Design—Mothers referred for a fetal echocardiogram were prospectively enrolled. Cases were defined as mothers deemed to be at higher risk of having an affected fetus with CHD given an affected parent or affected previous pregnancy with CHD. Controls were defined as mothers with no prenatal risk factors. Mothers completed a validated questionnaire assessing use of folic acid supplementation and receipt of recurrence risk counseling. Chi-square analyses were performed to analyze questionnaire responses and demographic data.

Results—314 subjects participated (controls= 216, cases= 98). Cases took preconceptual folic acid supplementation more often than controls ($p<0.001$), but only 55% started preconceptually. Maternal advanced education and counseling ($p<0.001$) were associated with preconceptual supplementation, whereas complexity of CHD in the relative was not. While 70% of cases

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received some recurrence risk counseling, those with advanced education and complex CHD in the affected relative were more likely to receive counseling. Few at-risk cases interacted with genetic services (19%).

Conclusions—At- risk mothers with lower education are less likely to take preconceptual folic acid supplementation or receive recurrence risk counseling. Healthcare providers should proactively provide this information to all at-risk patients and develop collaborations with genetic services.

Keywords

Congenital heart disease; recurrence risk; risk factors; folic acid supplementation

Introduction

Congenital heart disease (CHD) is a common birth defect occurring in 4-8 per 1000 live births (1,2). The etiology of CHD is heterogeneous with multiple genetic and environmental influences (3,4). Many environmental risk factors have been implicated in the development of CHD including maternal diabetes, maternal medication use and various maternal illnesses (5). In particular, studies suggest that preconceptual folic acid supplementation decreases the risk of CHD similar to its effects on neural tube defects (6-10).

Although some families with CHD exhibit a Mendelian pattern of inheritance (11,12), most cases of CHD are sporadic or exhibit non-Mendelian patterns of inheritance. Multiple studies have demonstrated an increased recurrence risk of CHD in families with an affected first degree relative as compared to the general population, such that offspring of affected parents and siblings of affected children define an at-risk group (13-17). Some organizations have recommended providing at-risk families with genetic services to provide thorough information on genetic risk factors and testing (18). Others, such as the March of Dimes, recommend that all mothers of childbearing age should take preconceptual folic acid supplelemntation to decrease the risk of neural tube defects and other congenital anomalies such as CHD (19). Identifying and communicating potential genetic and environmental risk factors to at-risk families may allow them to engage in preventative practices, such as preconceptual folic acid supplementation, that may modify outcome. Most of these families have regular contact with the medical community by way of pediatricians, and pediatric and adult congenital cardiologists, thus providing an opportunity to convey this information to patients and make appropriate referrals to genetic services, for example.

We sought to determine whether healthcare providers successfully convey information about preventative strategies (i.e. preconceptual folic acid supplementation) and recurrence risk. Our aims were to determine: 1) the patterns of preconceptual folic acid supplementation in the at-risk group of mothers as compared to a group of mothers with no obvious prenatal risk factors, 2) patterns of perceived recurrence risk counseling in the at-risk group, and 3) factors that influence preconceptual folic acid supplementation use and the receipt of recurrence risk counseling.

Methods

Patients

From October 2011 to October 2012, pregnant mothers referred for a fetal echocardiogram at the Fetal Heart Program of The Children's Hospital of Philadelphia were consecutively invited to complete a questionnaire. Consenting mothers were asked whether they used preconceptual folic acid supplementation and, if applicable, whether they received recurrence risk counseling from a healthcare provider prior to their current pregnancy. Subjects with maternal diabetes, maternal medication use or family history of CHD in a distant family member (i.e. not the mother, father or sibling of the fetus) were excluded. Participating subjects were assigned into two groups (cases and controls) based on the reason for referral for a fetal echocardiogram. The cases consisted of mothers deemed to be at higher risk of carrying an affected fetus with CHD given an affected parent or affected previous pregnancy with CHD as the referral reason. The controls consisted of mothers with no obvious prenatal risk factors that were referred for: 1) suspected CHD, 2) other congenital anomalies (those with cardiac or neural tube defects were excluded), and 3) abnormal maternal screen (e.g. first trimester maternal blood screening test). This study was approved by the Institutional Review Board for the Protection of Human Subjects at The Children's Hospital of Philadelphia.

Questionnaire

A multiple-choice questionnaire was designed to address three major areas as they pertained to the current pregnancy: 1) use of preconceptual folic acid supplementation, 2) receipt of counseling on preconceptual folic acid supplementation from a healthcare provider, and 3) receipt of counseling on recurrence risk of CHD from a healthcare provider if applicable to the subject. The questionnaire was validated via a modified Delphi method (20). As such, a version of the questionnaire was dispersed to twelve clinical experts in fetal cardiology, cardiovascular genetics, and epidemiology outside of our institution. The experts were asked to rate the clarity and content of each question. Based on the expert response, a new version of the questionnaire was created and piloted for four weeks. Subsequently the questionnaire was administered to each consenting subject (online supplement).

Demographic information was obtained from the subject's medical record including age, educational status and race. For cases, the cardiac diagnosis of the sibling or parent was also obtained from the medical record. The cardiac diagnosis was categorized into simple, moderate or severe based on the 2008 ACC/AHA guidelines on the Care of the Adult with Congenital Heart Disease (18).

Statistical Analysis

Demographic information was analyzed by descriptive statistics for all cases and controls separately. Student T tests and chi square analyses were used to compare demographic variables between the cases and controls. Counts and frequencies were tabulated for questionnaire responses. Questions with no response were excluded from all analyses. A chi-square test of association compared the timing of folic acid supplementation in the cases and controls. Subjects were categorized into two groups: (1) those starting folic acid

supplementation prior to conception (as recommended), and 2) those who either did not use it at all or started folic acid supplementation anytime during pregnancy. For both groups, the chi-square test of association was used to assess the association between timing of folic acid supplementation and: 1) maternal educational status, 2) receipt of counseling on folic acid supplementation, and for the cases, 3) complexity of CHD in the affected sibling or parent of the fetus (subjects that reported "unknown" for type of CHD were excluded). Similarly, the chi-square test of association was used to assess the association between cases receiving recurrence risk counseling and: 1) maternal educational status, and 2) complexity of CHD in the affected sibling or parent of the fetus. Cases that reported receiving recurrence risk counseling were asked to select which healthcare practitioner(s) provided that information from a list, which included obstetrician/gynecologist, pediatric cardiologist, genetic counselor/geneticist, pediatrician, family member or other. All analyses were conducted using SAS version 9.2.

Results

A total of 585 pregnant mothers were approached, of which 314 (54%) agreed to participate and provided consent (controls= 216 (69%), cases= 98 (31%)). Demographic descriptors were similar for each group: mean maternal age was approximately 31 years; the majority of subjects were white; and the educational status was evenly divided between high school, college and advanced degrees (Table 1).

Preconceptual use of folic acid

Cases started folic acid supplementation before pregnancy more often than controls ($p<0.001$), but only 55% of cases started folic acid supplementation prior to conception. There was no obvious difference in counseling on folic acid supplementation between the control subjects (n= 112, 53%) and case subjects (n= 55, 60%). Advanced education ($p<0.0001$) and reported counseling on folic acid supplementation ($p<0.0001$) were both associated with preconceptual folic acid supplementation in both groups (Table 2). After accounting for age, the association between educational status and preconceptual folic acid supplementation held true (data not shown). In contrast, the complexity of CHD in the affected sibling or parent of the fetus was not associated with timing of folic acid supplementation among the cases ($p=0.28$). A significant association between educational status and reported counseling on preconceptual folic acid supplementation was also observed ($p=0.008$).

Reported recurrence risk counseling

The majority (70%, n=58) of cases reported receiving recurrence risk counseling. Subjects with a higher educational status were more likely to report that they received recurrence risk counseling ($p=0.045$), as were those with more complex types of CHD in the sibling or parent of the fetus ($p=0.041$) (Table 3). Most subjects with an affected prior child reported receiving this information from a pediatric cardiologist (44%) and/or an obstetrician (39%), whereas affected parents received this information from an obstetrician (43%) and less frequently from a pediatric cardiologist (23%). Very few subjects reported receiving this information from a geneticist or genetic counselor (prior child 10%, affected parent 14%)

(Table 4). Finally, 73% of cases reported receiving counseling on both recurrence risk and preconceptual folic acid supplementation, with a significant association between the two types of counseling noted (p= 0.012)

Discussion

Our results demonstrate that the at-risk patient appears more likely to use folic acid supplementation at the appropriate time as compared to patients with no obvious prenatal risk factors; however, a large percentage of at-risk patients continue to take folic acid supplementation later than recommended (after conception) or not at all. In addition, although many of the at-risk patients appear to be informed about the potential for recurrence risk of CHD, very few report interacting with genetic services.

Multiple studies in the 1990s demonstrated that the use of folic acid supplementation in the preconceptual period decreased the risk of neural tube defects in offspring (21,22). The association of folic acid supplementation with neural tube defects led to studies on the association of folic acid supplementation with other congenital malformations such as CHD. Studies suggest that maternal preconceptual folic acid supplementation decreases the risk of CHD (6-10). Based on these studies, organizations have stated the importance of preconceptual folic acid supplementation to try to decrease the risk for CHD and neural tube defects (19). Although not proven, maternal preconceptual folic acid supplementation may be of particular benefit when one parent or a previous child has CHD.

Population based studies from various countries have investigated the general use of folic acid supplementation among childbearing women. Most studies discovered that although many women take folic acid supplementation during pregnancy, a smaller percentage initiate folic acid supplementation during the critical preconceptual time period (23-25). In one recent population based-study, education, race/ethnicity and age were the most distinguishing factors that described folic acid supplementation use (26). We observed similar patterns in both our cases and controls. In our study, 45% of at-risk mothers reported starting folic acid supplementation during or after the first trimester. Of the mothers that reported preconceptual folic acid supplementation, most had engaged in higher education (college or beyond) and most received counseling on folic acid use from a healthcare provider, suggesting that patients with more advanced education are more likely to receive and recall counseling on folic acid and thus take folic acid supplementation at the appropriate time. It is unclear from our study whether patients with more advanced education receive such counseling because they or their practitioners initiate such conversations. These data suggest that mothers with a lower educational status are either: 1) not adequately informed of the potential benefits of preconceptual folic acid supplementation and therefore do not engage optimally in this preventative practice, 2) receive counseling but do not understand or recall the recommendations, or 3) have fewer resources to engage in this preventative practice.

In general, sibling recurrence risk is estimated to be 3-4%, whereas recurrence risk in offspring of affected parents is estimated to be 4-10% depending upon the specific cardiac lesion in the proband (4,13,15). Each family may have unique genetic and environmental

risk factors that may influence the development of CHD in future offspring (3,5). Multiple organizations have recommended the engagement of at-risk families with genetic services to have a clear understanding of their individual risks as well as the benefit of genetic screening (18,27-29). In our study, although many at-risk subjects were aware of the potential for recurrence risk of CHD in subsequent pregnancies, very few reported interacting with genetic services. In addition, similar to our findings on folic acid use, most subjects that received recurrence risk counseling reported higher levels of education. In fact, there was a significant association between receiving recurrence risk counseling and counseling on folic acid supplementation suggesting that when patients receive counseling, it is fairly comprehensive. A recent study investigating adults with CHD demonstrated that the majority of subjects lacked knowledge on the inheritance and recurrence risk of CHD and did not engage with genetic services (30). In addition, subjects that had higher levels of knowledge on recurrence risk had received higher levels of education, similar to our findings. Our data further supports the need for healthcare providers, particularly pediatricians, and pediatric and adult congenital cardiologists, to provide this information proactively and perhaps repeatedly to all at-risk patients, in collaboration with genetic services.

Limitations

Patients recruited for this study were referred to and sought care from a highly specialized tertiary care center for a fetal echocardiogram, and thus do not necessarily represent the general population of at-risk patients. These subjects may be more informed as compared to the general population of at-risk patients having been referred to a specialty service and likely represent the best-case scenario. The number of cases as compared to controls was small and overall participation rates were moderate; however, an adequate number of subjects were recruited to perform our analysis. In addition, there is the possibility of recall bias on the questionnaire responses. However, by asking about the subject's current pregnancy, recall time was minimized. Furthermore, the questionnaire asked whether the subject received counseling on folic acid supplementation and recurrence risk but did not assess: 1) whether counseling occurred that was not reported by the subject, 2) the detail and complexity of counseling provided, and 3) whether the patient or one of their practitioners initiated a conversation about recurrence risk and preventative measures.

Conclusions

At-risk families with an affected parent or child should be educated about potential preventative measures and recurrence risk of CHD in future offspring. Although this information is reaching many families who have engaged in higher education, there continues to be a substantial number of at-risk families who do not practice such preventative measures and are seemingly unaware of these issues. Given their close contact with at-risk families, healthcare providers, particularly pediatricians, pediatric cardiologists and adult congenital cardiologists, should proactively provide information to these families to allow for educated decision-making on reproduction. Close collaborations should be developed with genetic services to provide thorough and accurate information on the genetic basis of each individual's CHD, and thus accurate assessment of recurrence risk of CHD for each individual family. Referral to genetic services and new joint cardiovascular genetic

clinics may facilitate the dissemination of this information and application of genetic testing. A formalized educational program or written material may be helpful but should be tested for efficacy and optimal timing in future large-scale studies.

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Table 1

Subject Demographics

	Control N= 216	Case N= 98	P value
Maternal Age Mean (SD)	30.9 (6.6)	31.1 (5.5)	0.78[1]
Maternal Race- N (%)			
White	125 (58)	62 (64)	0.54[2]
Black or African American	26 (12)	12 (12)	
Asian	8 (4)	2 (2)	
Pacific Islander/Hawaiian	1 (<1)	0	
Other	36 (17)	10 (10)	
Not Specified	20 (9)	12 (12)	
Maternal Education- N (%)			
High School	51 (24)	26 (26)	0.94[2]
College	67 (31)	30 (31)	
Advanced	62 (29)	27 (28)	
Not Specified	36 (16)	15 (15)	

[1] Student T test

[2] Chi-square test

Table 2

Factors influencing the timing of folic acid supplementation

	Timing of folic acid supplementation					
	Control[1]			Case[1]		
Educational status	Prior to pregnancy n (%)	1st trimester or later n (%)	P value[2]	Prior to pregnancy n (%)	1st trimester or later n (%)	P value[2]
High school	6 (9.4%)	45 (39.5%)	<0.0001	3 (7.1%)	21 (53.8%)	<0.0001
College	25 (39.1%)	41 (36.0%)		19 (45.2%)	11 (28.3%)	
Advanced degree	33 (51.5%)	28 (24.5%)		20 (47.7%)	7 (17.9%)	
Total	64	114		42	39	
Counseling[3]						
Yes	56 (80%)	56 (40%)	<0.0001	41 (80.4%)	14 (33.3%)	<0.0001
No	14 (20%)	84 (60%)		10 (19.6%)	28 (66.7%)	
Total	70	140		51	42	

[1] Subjects that did not answer questions about educational status [n= 38 (18%) controls and n=17 (17%) cases] or whether counseling was received [n=6 (3%) controls and n=5 (5%) cases] were excluded from the analysis.

[2] Chi-square test of association

[3] Counseling= subject reported receiving counseling on folic acid supplementation

Table 3

Factors associated with reported recurrence risk counseling among cases

	Recurrence risk counseling[3]		
	Yes- n(%)	No- n(%)	P value[1]
Educational status[3]			
High school	11 (21.2%)	10 (52.6%)	0.045
College	21 (40.4%)	4 (21.1%)	
Advanced degree	20 (38.4%)	5 (26.3%)	
Total	52	19	
Complexity of CHD[2]			
Simple	14 (25.9%)	11 (57.9%)	0.041
Moderate	24 (44.4%)	5 (26.3%)	
Severe	16 (29.7%)	3 (15.8%)	
Total	54	19	

CHD= congenital heart disease

[1] Chi-square test of association

[2] Complexity of CHD= in the affected parent or sibling of fetus (current pregnancy)

[3] Subjects that did not answer questions about educational status [n= 27 (27%)], or the complexity of CHD in the family member [n= 25 (25%)] were excluded from the analysis

Table 4

Distribution of healthcare practitioners providing recurrence risk counseling among cases

	Study group	
Healthcare provider[1]	**Parent with CHD (N= 22)**	**Prior child with CHD (N= 36)**
Obstetrician/gynecologist	15 (42.8%)	23 (38.9%)
Pediatric cardiologist	8 (22.8%)	26 (44.1%)
Genetic Counselor/Geneticist	5 (14.3%)	6 (10.2%)
Pediatrician	0	2 (3.4%)
Family member	3 (8.6%)	0
Other	4 (11.4%)	2 (3.4%)

[1] Subjects that reported receiving recurrence risk counseling (parent with CHD= 22/31; prior child with CHD= 36/52) were asked to select which healthcare professional provided the counseling. Multiple providers were selected in some cases.