AHA Scientific Statement

Noninherited Risk Factors and Congenital Cardiovascular Defects: Current Knowledge

A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young

Endorsed by the American Academy of Pediatrics

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***Abstract*—**Prevention of congenital cardiovascular defects has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. Over the past decade, there have been major breakthroughs in the understanding of inherited causes of congenital heart disease, including the identification of specific genetic abnormalities for some types of malformations. Although relatively less information has been available on noninherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic. This statement summarizes the currently available literature on potential fetal exposures that might alter risk for cardiovascular defects. Information is summarized for periconceptional multivitamin or folic acid intake, which may reduce the risk of cardiac disease in the fetus, and for additional types of potential exposures that may increase the risk, including maternal illnesses, maternal therapeutic and nontherapeutic drug exposures, environmental exposures, and paternal exposures. Information is highlighted regarding definitive risk factors such as maternal rubella; phenylketonuria; pregestational diabetes; exposure to thalidomide, vitamin A cogeners, or retinoids; and indomethacin tocolysis. Caveats regarding interpretation of possible exposure-outcome relationships from case-control studies are given because this type of study has provided most of the available information. Guidelines for prospective parents that could reduce the likelihood that their child will have a major cardiac malformation are given. Issues related to pregnancy monitoring are discussed. Knowledge gaps and future sources of new information on risk factors are described. **(*Circulation*. 2007;115:2995-3014.)**

Key Words: AHA Scientific Statements ■ heart defects, congenital ■ heart disease ■ risk factors

Congenital cardiovascular defects (CCVDs) represent some of the more prevalent malformations among live births[1] and remain the leading cause of death from congenital malformations.[2] Disease prevention has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. Over the past decade, there have been major breakthroughs in the understanding of inherited causes of CCVDs, including the identification of specific genetic abnormalities for some types of malformations.[3] Although relatively less information has been available on noninherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic. The proportion of cases of CCVDs that are potentially preventable through changes in the fetal environment is currently unknown. One study suggests that the fraction of cases attributable to identifiable and potentially modifiable factors may be as high as 30% for some types of defects.[4] The lack of reliable information on modifiable risk factors has made it difficult to create population-based strategies to reduce the burden of

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illness from CCVDs and for couples to make lifestyle choices to reduce the likelihood of having a child with a major cardiac malformation.

The purpose of this article is to review the current state of knowledge regarding noninherited risk factors for structural cardiac anomalies, to provide guidance to potential parents that could reduce the likelihood that their child will have a major cardiovascular malformation, and to provide guidance for pregnancy monitoring after known exposures. The current state of knowledge of inheritable causes of CCVDs is reviewed separately and is not included.[3] Similarly, because this statement focuses on factors that influence cardiac development during weeks 2 to 7 of gestation,[5] this review is limited to parental exposures during the first trimester of pregnancy and the 3 months before pregnancy (ie, periconceptional period) that could result in structural abnormalities; exposures that may cause other types of cardiac injury (eg, congenital heart block, myocardial damage) are not considered.

Methods

This statement summarizes the currently available literature, as of May 2006, on prenatal parental conditions and exposures and risk for CCVDs in offspring. English-language publications in scientific journals reporting data on risks of CCVDs in offspring after maternal or paternal diseases, conditions, or exposures were identified through Medline searches, bibliographies of individual articles, and reviews of scientific journals. The information about maternal drug exposure also includes information from the Teratogen Information System (http://depts.washington.edu/terisweb/teris/) and the online version of *Shepard's Catalog of Teratogenic Agents*. Publications were assessed to determine the quality of information available (eg, consistency of findings and study design, including the ability to estimate magnitude of risk and exclude chance and bias as possible explanations) regarding a specific type of parental condition or exposure during pregnancy and the risk of having an infant with a major CCVD. Conditions or exposures for which only limited information was available such as a single published epidemiological study were included but generally considered insufficient for discussion. Exceptions were maternal conditions about which there has been some concern (ie, systemic lupus erythematosus and HIV-1 infection). Case reports and case series were not considered to be sufficiently reliable for discussion, unless confirmed by epidemiological studies. From the review of published epidemiological studies, parental conditions and exposures were classified into one of the following categories: factors possibly associated with a decreased risk of CCVDs, factors associated with an increased risk of CCVDs, factors not associated with risk of CCVDs, and factors that have been studied but for which the information about risk of CCVDs is inconclusive. Although some exposures may be risk factors for specific types of CCVDs and not others, quantified measures of overall relative risk such as relative risk (RR) or odds ratios (ORs) are given, if known, to attempt to quantify the increased risk of having a child with any CCVDs, as well as with a specific CCVD, after a specific exposure. Presentation of results for specific types of malformations is, of course, often limited by the different methods used to identify and group malformations in different reports. Confidence limits for the RR or ORs are given if available; confidence limits that contain the value 1.0 indicate that the RR or OR estimate does not differ statistically from the null value (ie, 1.0).

To date, there are no published reports of large prospective cohort studies examining environmental or other exposures associated with CCVDs. The best available information comes from large population-based case-control studies specifically designed to investigate possible risk factors for CCVDs. Two such studies deserve specific mention. The Baltimore-Washington Infant Study (BWIS) was prospectively conducted in the Baltimore, Washington, and northern Virginia area between 1981 and 1989 with a random sample of infants without CCVDs ascertained from the same birth cohort.[6] The National Public Health Institute in Helsinki retrospectively conducted a study in Finland of cases and controls born during 1982 to 1984.[7] In both of these case-control studies, information on potential exposures early in pregnancy was obtained by interview of the parents after the child was born. There were no available reliability or validation studies of the parental reports.

Results

The findings from this review are summarized in the tables. Table 1 summarizes the literature regarding 1 factor that may be associated with a decreased risk of CCVDs, specifically supplementation with a multivitamin containing folic acid. Table 2 summarizes the literature on factors that may increase the risk of a pregnancy resulting in an infant with any CCVDs and with a specific CCVD. Table 3 shows the same information, organized by CCVD phenotype rather than type of exposure. Table 4 shows factors that have been studied but for which no associations have been found thus far. Table 5 shows factors that have been studied but for which too little information is available to make a determination about risk.

Multivitamins and Folic Acid

One of the most important recent discoveries is the possibility that periconceptional intake of multivitamin supplements containing folic acid may reduce the risk of CCVDs in offspring, similar to the known risk reduction for neural tube defects seen with folic acid. This finding was first identified

TABLE 1. Maternal Multivitamin/Folic Acid Supplements and Decreased Risk of Offspring With Congenital Cardiovascular Defects

Vitamin/Supplement	Defect	OR	Reference(s)
Multivitamin supplements (including folic acid)	Any	0.5–0.8	8–10
	VSD	0.2–1.2	9, 10, 12
	Conotruncal defects	0.5–1.0	10–12
Multivitamin supplements (including folic acid) in women with febrile illness	Any	*	15
Folate antagonist only	Any	2.1	13, 14

*OR not applicable.

after analysis of data from a Hungarian randomized trial on birth defects[8,9] (Table 1). Findings from subsequent case-control studies have been generally supportive but not conclusive.[8,10–12]

Two of the studies examined a broad range of heart defects rather than any specific type.[9,10] Use of multivitamins containing folic acid was associated with an ≈60% overall reduction in risk for congenital heart defects in the Hungarian randomized trial (RR, 0.42; 95% confidence interval [CI], 0.19 to 0.98)[8,9] and an ≈25% reduction in risk in a population-based case-control study done in Atlanta (OR, 0.76; 95% CI, 0.60 to 0.97).[10] These and other studies also examined specific types of CCVDs. Multivitamin use was associated with a reduced risk for conotruncal defects in 2 population-based case-control studies (54% and 30%, respectively).[10,11] The Hungarian trial also provides suggestive data (no case of conotruncal defects in the supplemented group, 2 cases in the nonsupplemented), but the trial was too small to provide definitive results. A third study showed possible risk reduction for 1 but not all types of conotruncal heart defects.[6] A fourth, a hospital-based case-control study,[12] showed no evidence of reduction.

For ventricular septal defects (VSDs), 2 studies, a population-based case-control study and the Hungarian randomized trial, were consistent with a reduction in risk (40% and 85% reduction, respectively).[9,10] The hospital-based case-control study again found no risk reduction.[12]

In addition to these studies directly testing the association between multivitamin use and risk for heart defects, other studies among high-risk groups present ancillary evidence supporting a protective effect of folic acid–containing multivitamin supplements. For example, 2 studies have shown that women who used medications that are folic acid antagonists had an increased risk of having babies with heart defects but that this risk was reduced for women who also took multivitamin supplements containing folic acid.[13,14]

In a third study,[15] an increased risk for heart defects associated with maternal febrile illness (see below) appeared to be reduced among women using multivitamin supplements around the time of conception and during early pregnancy. Similar findings have been reported for other birth defects.[16]

The findings of a possible protective effect for CCVDs from folic acid–containing multivitamin supplements are encouraging but inconclusive given the limited number of studies and mixed results. Additional studies are warranted to determine whether the association of specific phenotypes with multivitamins can be corroborated in large population-based studies in which multivitamin intake can be validated, potential confounders such as maternal age and diabetes can be taken into account, and the components of the multivitamin supplements responsible for the association can be identified.

Maternal Illnesses and Conditions

Phenylketonuria

Untreated maternal phenylketonuria is associated with a >6-fold-increased risk of heart defects.[17–20] The most frequent defects are tetralogy of Fallot, VSDs, patent ductus arteriosus (PDA), and single ventricle. Fortunately, with strict diet control before conception and during pregnancy, this excess risk can be reduced.[18–22]

Maternal Diabetes

CCVDs have been associated with maternal pregestational and, less consistently, with gestational diabetes.[6,23–34] The associations with gestational diabetes are hypothesized to be due to inclusion of a group of women with previously undetected type 2 diabetes among women classified as having gestational diabetes.[27–29] Specific types of cardiovascular malformations associated with maternal pregestational diabetes include laterality and looping defects,[6] transposition of the great vessels,[6,33] nonchromosomal atrioventricular septal defects,[6] VSDs,[6,33,35] hypoplastic left heart syndrome,[6] conotruncal defects,[36] outflow tract defects,[33,35] cardiomyopathy,[6] and PDA.[33] Diabetes appears to induce malformation before the seventh week of gestation.[37]

Studies have shown a clear link between glycemic control during organogenesis and fetal malformations.[38,39] Although strict glycemic control before conception and during pregnancy has been shown to reduce risk levels comparable to those of the general population,[40] achieving and maintaining euglycemia early in pregnancy remains a challenge because many women with diabetes neither plan their pregnancies nor achieve adequate glycemic control before conception.[39,41] Given the increasing prevalence of risk factors for diabetes,[42–44] it is important to gain a better understanding of the current impact of both preexisting and gestational diabetes on CCVDs.

Although congenital anomalies associated with maternal diabetes are presumed to be related to abnormalities in maternal metabolic fuels essential for embryogenesis,[45] precise pathogenic mechanisms remain unclear. One hypothesis is that abnormal glucose levels characteristic of diabetes mellitus disrupt expression of a regulatory gene in the embryo, leading to embryotoxic apoptotic cellular changes.[46] The prevention of diabetic embryopathy by antioxidants in animal studies suggests that oxidative stress resulting from metabolic abnormalities and generation of free radicals is another possible mechanism.[47–52] The increasing prevalence of type 2 diabetes among women of childbearing age in recent decades[42–44,53,54] makes identifying and implementing effective prevention strategies a high priority.

Rubella, Febrile Illnesses, and Influenza

The potential association between maternal infections and birth defects was first suggested by the observation of the relation between maternal rubella infection early in gestation and the congenital rubella syndrome in offspring.[55–57] It is now well known that maternal rubella infection during pregnancy can result in offspring with PDA, pulmonary valve abnormalities, peripheral pulmonary stenosis, and VSDs[58–60] and that the risk of rubella embryopathy can be virtually eliminated by ensuring that women of childbearing age are immunized against rubella.[61] More recent studies suggest that other maternal febrile illnesses during the first trimester of pregnancy also may be associated with an increased risk for certain heart defects.[6,15,62,63] Mothers reporting any febrile illnesses during the first trimester of pregnancy have a 2-fold-higher risk of offspring with any heart defect in these

TABLE 2. Exposures Associated With Definite or Possible Risk of Offspring With CCVD*

	Defect	RR	Reference(s)
Maternal illness			
PKU	Any defects	>6	17–20
Pregestational diabetes	Any defects	3.1–18	6, 23, 33, 34
	Conotruncal defects	5.55	36
	Laterality and looping	8.3	6
	d-TGA	3.8–27.2	6, 33
	AVSD	10.6	6
	Septal defects	2.9–20.2	6, 33, 35
	HLHS	3.9	6
	Outflow tract defects	3.7–17.9	33, 35
	PDA (BTW >2500 g only)	56.9	33
Febrile illness	Any defects	1.8–2.9	6, 16, 62, 63
	Conotruncal defects	1.55	36
	Any right-sided obstructive defects	2.2–2.9	6, 15
	Tricuspid atresia	5.1–5.2	6, 15
	All left-sided obstructive defects	2.7	15
	Aortic coarctation	2.7	15
	VSD	1.8	15
Influenza	Any defects	2.1	10, 63
	Conotruncal defects	1.74	36
	d-TGA	2.1	10
	All right-sided obstructive defects	2.5	10
	All left-sided obstructive defects	2.9	10
	Aortic coarctation	3.8	10
	VSD	2.0	10
	d-TGA with intact ventricular septum	2.2	6
	Tricuspid atresia	4.3	6
Maternal rubella	Any defects	†	55–57
	VSD	†	58, 59, 196
	PDA	†	58, 59, 196
	Pulmonary valve abnormalities	†	58, 59, 196
	Peripheral pulmonic stenosis	†	58, 59, 196
Epilepsy	Any defects	†	82
Maternal nontherapeutic drug exposure			
Maternal vitamin A	Outflow tract defects	0.0–9.2	169, 170
	Cranial neural crest defects (cardiac and noncardiac)	0.7–4.8	168, 171, 172
	Pulmonic stenosis and other noncardiac defects	0.5	173
Maternal therapeutic drug exposure			
Anticonvulsants	Any defects	4.2	105–107
Indomethacin tocolysis	PDA	†	123, 124
NSAIDs			
Ibuprofen	Any defects	1.86	122
	d-TGA	2.5	4
	AVSD (Down syndrome)	2.4	4
	VSD	1.9	4
	Bicuspid aortic valve	4.1	4
Sulfasalazine‡	Any defects	3.4	13
Thalidomide	Any defects	†	84
Trimethoprim-sulfonamide‡	Any defects	2.1–4.8	13, 14

TABLE 2. Continued

	Defect	RR	Reference(s)
Vitamin A congeners/retinoids	Any defects	†	85, 86
Maternal nontherapeutic drug exposure			
Marijuana	VSD	1.9	160
	Ebstein's	2.4	6
Environmental (maternal)			
Organic solvents	Conotruncal defects	2.3–3.9	150, 175
	HLHS	3.4	6
	Aortic coarctation	3.2	6, 176
	Pulmonic stenosis	5.0	6
	d-TGA with intact ventricular septum	3.4	6
	Tetralogy of Fallot	2.7	6
	TAPVR	2.0	6, 214
	AVSD, nonchromosomal	5.6	6
	Ebstein's anomaly	3.6	6, 215
	VSD		119

PKU indicates phenylketonuria; d-TGA, dextro-looped transposition of the great arteries; AVSD, atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; BTW, birth weight; NSAIDs, nonsteroidal antiinflammatory drugs; and TAPVR, total anomalous pulmonary venous return.

*Consider fetal echocardiogram or neonatal echocardiogram if any of these exposures are present based on the level and type of exposure and the timing of the exposure in gestation.

†OR not available.

‡Risk reduced if mother took folic acid simultaneously.

§If both parents smoked.

studies.[6,15] Specific groups of defects that have been shown to be associated with maternal febrile illness include pulmonic stenosis,[6] all right-sided obstructive defects,[15] tricuspid atresia,[6,15] coarctation of the aorta,[15] all left-sided obstructive defects,[15] conotruncal defects, and VSDs.[15] A case-control study in California found an association of maternal fever with conotruncal defects among offspring born to mothers who did not use multivitamins.[64] In some of these studies, the febrile illness often was characterized as flu-associated fever or influenza; thus flu-associated fever also was a risk factor for any cardiac defect and for some specific malformations.[10,63] The mechanism by which maternal febrile illnesses may result in malformations is unclear. One possibility is altered apoptosis. Apoptosis is known to be involved in cardiac morphogenesis, for example, in the development of the cardiac outflow tract,[65] and can be altered by both fever and infection.[66–69] Another possibility is a direct effect of the underlying infection, as with maternal rubella infection. Most studies to date have been unable to distinguish between independent and joint effects associated with maternal fever, maternal infection, and use of certain medications to control the fever or infection.

Obesity

A number of studies have examined the association between maternal prepregnancy obesity and CCVDs, although findings have been inconsistent. A study by Waller et al[70] reported an association between maternal obesity, defined as a body mass index of >26 kg/m^2, and a grouped category of defects of the great vessels. Two additional studies found no statistically significant increased risks for any heart defect[6,71] or conotruncal heart defects in relation to maternal obesity.[72] A recent study reported a 6.5-fold risk elevation for aggregate cardiac defects among obese black women,[73] and Watkins et al[71] reported a 2-fold increase in risk of aggregate cardiac defects in relation to maternal obesity. Obesity is a complex condition that has to be studied carefully to minimize underreporting of body weight, especially in case-control studies, and the possibility of confounding by other factors associated with nutrition, such as the intake of micronutrients or use of multivitamin supplements, or with obesity, such as type 2 diabetes.

HIV Infection

Maternal infection with HIV can transmit the infection vertically to offspring. Children infected with HIV-1 in utero have an increased risk of dilated cardiomyopathy and inappropriate left ventricular hypertrophy.[74–76] Such children also are more likely to have low left ventricular fractional shortening.[76] Maternal HIV has not been associated with an increased risk of structural congenital cardiovascular malformations thus far.

Systemic Lupus Erythematosus

Although a high proportion of infants with congenital complete heart block are born to women with systemic lupus erythematosus,[77–79] no published reports show an association between maternal connective tissue disease and an increased risk of structural congenital cardiovascular malformations.

Epilepsy

Offspring of women with epilepsy are at an increased risk for congenital malformations,[80,81] including congenital heart de-

TABLE 3. Exposures With Reported Risk for Specific CCVDs

Lesion	Exposures That May Increase Risk
All left-sided obstructive defects	Febrile illness
	Influenza
All right-sided obstructive defects	Febrile illness
	Influenza
	Organic solvents
Aortic coarctation	Febrile illness
	Influenza
	Organic solvents
	Pregestational diabetes
AVSD	Pregestational diabetes
AVSD (Down syndrome)	Ibuprofen
AVSD (nonchromosomal)	Organic solvents
Bicuspid aortic valve	Ibuprofen
	Vitamin A cogeners/retinoids
Conotruncal defects	Organic solvents
Cranial neural crest defects (cardiac and noncardiac)	Maternal vitamin A
d-TGA	Pregestational diabetes
	Influenza
	Ibuprofen
d-TGA with intact ventricular septum	Influenza
	Organic solvents
Ebstein's anomaly	Organic solvents
	Marijuana
HLHS	Organic solvents
	Pregestational diabetes
Laterality and looping	Pregestational diabetes
Membranous VSD	Vitamin A cogeners/retinoids
Outflow tract defects	Pregestational diabetes
	Maternal vitamin A
PDA (BTW >2500 g only)	Pregestational diabetes
	Maternal rubella
	Indomethacin tocolysis
Peripheral pulmonic stenosis	Maternal rubella
Pulmonic stenosis	Organic solvents
	Maternal vitamin A
Pulmonary valve abnormalities	Maternal rubella
Septal defects	Pregestational diabetes
	Febrile illness
	Influenza
	Marijuana
	Organic solvents
	Ibuprofen
	Rubella
TAPVR	Organic solvents
Tetralogy of Fallot	Organic solvents
Transposition of the great arteries	Pregestational diabetes
	Influenza
	Organic solvents
Tricuspid atresia	Febrile illness
	Influenza
VSD	Febrile illness
	Influenza
	Maternal rubella
	Marijuana
	Ibuprofen
	Organic solvents

Abbreviations and references as in Table 2.

fects.[82] Because several therapy-related factors could account for this increased risk, including direct teratogenic effects of anticonvulsant drug therapy and an indirect effect of the drugs by interfering with folate metabolism, it has been difficult to determine whether maternal seizures are independently associated with an increased risk of heart defects.

Maternal Therapeutic Drug Exposure

The US Food and Drug Administration (FDA) has classified a number of medications according to risk for birth defects if ingested during pregnancy. Although this classification relates to birth defects in general and not specifically to congenital cardiac defects, when available, the FDA description of risk as defined in Table 6 is included in each of the therapeutic drug discussions that follow.[83]

Thalidomide

Thalidomide is known to be a cardiac teratogen and therefore contraindicated during pregnancy and among women planning a pregnancy. Thalidomide embryopathy includes cardiovascular malformations ranging from ventricular and atrial septal defects (ASDs) to complex conotruncal defects.[84] No safe dose of thalidomide treatment during the critical period of gestation has been established, and cases of thalidomide embryopathy have been described after maternal ingestion of as little as one 50-mg capsule during this time (FDA category X).

Vitamin A Cogeners/Retinoids

Maternal intake of isotretinoin has been shown to cause congenital cardiac defects in addition to other malformations. Characteristic features of isotretinoin embryopathy include central nervous system malformations, micrognathia, cleft palate, thymic and eye anomalies, and cardiac and great vessel defects. The frequency of congenital anomalies does not appear to be increased among children of women who discontinue therapy before conception.[85] These medications are contraindicated during pregnancy and among women planning a pregnancy (FDA category X).

Etretinate persists in the body for an extremely long time after administration, and the length of time that teratogenic effects may occur is currently not known. In case reports, congenital abnormalities possibly related to prior etretinate therapy have been seen as long as 45 months after therapy was stopped.[86] No large studies examining the association of acitretin have been performed. Because acitretin can be

TABLE 4. Reported Exposures With No Evidence of an Association With Risk for CCVDs

Maternal Illnesses/Conditions	Reference(s)
HIV	74–76
Maternal therapeutic drug exposure	
Ampicillin	87–90
Corticosteroids	120, 121
Diazepam	87–89, 91, 118, 119
Oral contraceptives	138
Penicillin	91–95
Vaginal metronidazole	96–98
Maternal nontherapeutic drug exposure	
Caffeine	6, 91, 147–150

converted to etretinate in the body, the length of time that acitretin may cause teratogenic effects may be longer than its half-life (50 to 60 hours).

Topical therapy with tretinoin in usual doses during pregnancy is unlikely to pose a substantial teratogenic risk, but data are insufficient to state that there is no risk.

Antibiotics

Rothman et al[87] observed an association with maternal ampicillin (FDA category B) treatment "about the time pregnancy began" in a case-control study of 390 infants with congenital heart disease, specifically transposition of the great arteries. Their follow-up study of similar design did not confirm these findings.[88] Additionally, a separate case-control study failed to show an association between ampicillin use and congenital heart disease.[89] Finally, in a large population-based (Hungarian) case-control study of maternal ampicillin use in the second or third month of pregnancy, no association was found among 4468 cases with cardiovascular malformations.[90]

Multiple large studies have shown no association between the use of penicillin (FDA category B) and an increased risk of congenital anomalies in general.[91–94] One Danish population-based record linkage study that examined the frequency of congenital heart defects in mothers given penicillin during the first trimester showed it to be no higher than expected.[95]

The epidemiological data regarding maternal vaginal metronidazole (FDA category B) use early in pregnancy were summarized in 2 meta-analyses.[96,97] In both instances, the risk of congenital anomalies in offspring was not increased. One of the studies included in these analyses specifically examined a large group (984) of infants with cardiovascular defects.[98] In the BWIS, maternal use of metronidazole during pregnancy was found to be associated with an increased risk of outflow tract anomalies with normally related great arteries (OR, 6.0; 95% CI, 1.8 to 20.7) and an increased risk of membranous VSDs (OR, 12.2; 95% CI, 3.0 to 50.2).[6]

An association was found with maternal trimethoprim-sulfonamide (FDA category C) treatment during the second or third month of gestation in a case-control study among 3870 infants with cardiovascular defects (OR, 4.8; 95% CI, 1.5 to 16.1).[13] Similar findings were reported from the Hungarian case-control surveillance of congenital abnormalities (OR, 2.1; 95% CI, 1.4 to 3.3).[14] The risks were reduced if the mother also took folic acid supplementation.

Antiviral/Antiretroviral Agents

An association was observed between major congenital anomalies, including congenital cardiovascular malformations, and a maternal prescription for zidovudine (FDA category C) during pregnancy in a Medicaid record linkage study.[99] When the exposures were broken down by trimester of pregnancy, the significant association was seen among women who received the prescription in the third trimester, not in the first or second, a finding inconsistent with a teratogenic mechanism. The Antiretroviral Pregnancy Registry has been established and to date has not shown an increase in congenital defects in women receiving therapy in the second or third trimester.

Antifungal Therapies

In a UK cohort study and a Danish record linkage study, the frequency of congenital anomalies was not increased in infants of women who received prescriptions for a single oral dose of fluconazole (FDA category C) in the first trimester of pregnancy.[100,101] Similarly, in a prospective study, the frequency of congenital anomalies was not increased in women receiving fluconazole with median doses of 200 mg. It should be noted that 4 children have been described with a similar and unusual pattern of congenital anomalies (including congenital heart disease) in offspring whose mothers were treated during most or all of the first trimester with a high dose (400 to 800 mg/d) of fluconazole for coccidioidomycosis meningitis.[102–104] These observations suggest the need for further study of fluconazole treatment with consideration of possible threshold effects.

Anticonvulsants

Although many large epidemiological studies of the offspring of epileptic women have been published, currently available data are incapable of resolving the controversy as to whether the malformations are due to the epilepsy or the anticonvulsant therapy. Additionally, the studies examining congenital malformations in infants of women who took anticonvulsant therapies are difficult to interpret because accurate assessment of the effects of the anticonvulsant treatment may be confounded by multiple other factors.[105–107] Specifically, many women with seizures are treated with multiple therapies either serially or simultaneously, and most women with seizures are treated with an anticonvulsant drug (leaving no control group). There are characteristic anomalies associated with some of the anticonvulsants (eg, fetal hydantoin syndrome), which may involve cardiac abnormalities (phenytoin, FDA category D; valproic acid, FDA category D).

Lithium

An association has been observed between maternal treatment with lithium carbonate during pregnancy and the occurrence of Ebstein's anomaly.[108–113] In a voluntary reporting registry, serious congenital cardiovascular anomalies were observed in 8% of 225 infants born to mothers who had taken lithium during the first trimester of pregnancy.[114] One third of these infants had Ebstein's anomaly. Contradicting these

TABLE 5. Exposures Studied but Insufficient Data to Determine Risk for CCVDs

Exposure	Reference(s)
Maternal illnesses/conditions	
Gestational diabetes	6, 23–34
Obesity	6, 44, 70–73, 118
Systemic lupus erythematosus	77–79
Nausea	146
Life event stress	36, 197
Maternal therapeutic drug exposure	
Angiotensin-converting enzyme inhibitors	144
Amobarbital	6
Antihistamines	6
Antihypertensives	6
Aspirin	216
Barbiturates (except amobarbital)	6
Bendectin	88, 145
Clomiphene	5, 36
Dactinomycin	143
Deoxyrubicin	143
Fluconazole	100–104
Ibuprofen	6
Lithium	108–117
Metronidazole	6
Oral contraceptives	6
Narcotics	6
Parasympatholytics	6
Phenothiazines	6
Phenylephrine	87, 88, 91
Topical tretinoin	85, 86
Xanthenes	6
Ziduvudin	99
Maternal nontherapeutic drug exposure	
Alcohol	6, 36, 119, 151–154
Cigarette smoking	6, 64, 217
Cocaine	6, 155–159
Maternal environmental factors	
Air quality	178, 179
Herbicides/pesticides/rodenticides	175, 177, 214, 218
Proximity to hazardous waste site	187–189
Trichloroethylene in groundwater	180
Water chlorination byproducts	182–186
Maternal sociodemographic characteristics	
Age	6, 191
Race/ethnicity	36, 192–196, 211
Socioeconomic status	192
Paternal factors/exposure	
Age	198, 202–204
Cigarette smoking	6, 217
Cocaine	6, 204
Alcohol exposure (father)	
Frequency	6
Greatest number of drinks on any occasion	6
Housing characteristics	
Type of home (individual, townhouse, apartment)	6
Gas heating	6
Electric heating	6
Oil heater	6
Gas stove	6
Electric stove	6
Cooking with kerosene, coal, or wood	6
Medical exposures	
Maternal dental x-rays	6
Maternal chest x-rays	6
Maternal skeletal x-rays	6
Maternal abdominal x-rays	6
Paternal dental x-rays	6
Paternal chest x-rays	6
Paternal skeletal x-rays	6
Paternal abdominal x-rays	6
Maternal home and occupational exposures	
Anesthetic gas (occupational)	6
Arsenic	6
Art dyes	6
Arts and crafts painting	6
Cadmium	6
Carpentry	6
Cold, extreme (occupational)	6
Drug manufacturing	6
Dry-cleaning solvents	6
Heavy metals	6
Home tap water	181
Housekeeping cleaners	175
Jewelry making	6
Laboratory chemicals	6
Laboratory viruses	6
Lead score	6
Mercury	6
Pesticides, insecticides, rodenticides	175, 177
Plastics manufacturing	175
Propellants	6
Pyrolysis/combustion products	175
Stained glass crafts	6
Textile dyes	6
Welding	6
Paternal home and occupational exposures	
Anesthetic gas (occupational)	6
Arsenic	6
Art dyes	6
Arts and crafts painting	6
Auto body repair work	6

TABLE 5. Continued

Exposure	Reference(s)
Cadmium	6
Carpentry	6
Drug manufacturing	6
Dry-cleaning solvents	6
Extreme cold (occupational)	6
Hair dyes	6
Hypothermia	6
Ionizing radiation	6
Laboratory chemicals	6
Lead score	6
Marijuana	6
Mercury	6
Pesticides	6
Plastics manufacturing	6
Solvents	6
Stained glass crafts	6
Textile dyes	6
Varnishes	6

reports, no association was seen in a case-control study of 10 698 children with congenital anomalies, but the number of exposures in the case and control groups was small.[115] More recent retrospective, prospective, and meta-analysis studies suggest that lithium appears not to be a cardiac teratogen (FDA category D).[116,117]

Benzodiazepines/Barbiturates (Sedatives/Hypnotics)/Tranquilizers

An association with the maternal use of diazepam (FDA category D) or related drugs during the first trimester of pregnancy was observed in 2 case-control studies of almost 400 children each.[87,118] Bracken[89] reanalyzed these data and failed to find a significant association, and Zierler and Rothman[88] found no association in a follow up-study. No association with maternal use of diazepam during the first trimester of pregnancy was seen in case-control studies of 150 children with VSDs.[91,119]

The frequencies of congenital anomalies were not significantly increased among infants of women occasionally treated with amobarbital (FDA category D) as a hypnotic. However, the frequency of cardiac malformations was increased (RR, 2.6; 95% CI, 1.0 to 5.2).[91] The risk for chronic or high-dose maternal use is unknown.

Sympathomimetics

A case-control study by Rothman et al[87] observed a slightly higher rate of exposure to phenylephrine (FDA category C) early in pregnancy in mothers of infants with congenital heart disease than in controls. This observation was not confirmed in a later and more rigorous study by the same authors.[88] No association was seen between the first-trimester use of phenylephrine and congenital heart disease in a large cohort study.[91]

Corticosteroids

A possible association between maternal corticosteroid use and congenital cardiac malformations was identified in the BWIS by univariate analysis (OR, 1.71; 95% CI, 1.01 to 2.88). This finding was no longer significant after other variables were taken into account.[120] Using data derived from a population based case-control study that included 207 cases of conotruncal heart defects, Carmichael and Shaw[121] showed no association between maternal corticosteroid use and congenital cardiovascular malformations.

Folate Antagonists

Associations with maternal treatment with sulfasalazine (FDA category B) or another dihydrofolate reductase inhibitor during the second or third month of pregnancy were observed in a case-control study of 3870 infants with cardiovascular defects (OR, 3.4; 95% CI, 1.1 to 6.1). These associations were not seen among the subset of mothers who took supplemental folic acid. As mentioned, maternal use of trimethoprim-sulfonamide also has resulted in congenital heart defects in offspring,[13,14] with risk reduction if mothers also took folic acid supplementation (see the Antibiotics section).

Nonsteroidal Antiinflammatory Drugs

Ericson and Kallen[122] examined use of nonsteroidal antiinflammatory drugs in early pregnancy in a large registry study (n=2557) and found that the adjusted OR for any congenital malformation was 1.04 (95% CI, 0.84 to 1.29), but for cardiac defects, the OR was 1.86 (95% CI, 1.32 to 2.62). There was no drug specificity for cardiac defects.

Associations with maternal use of ibuprofen (FDA category B) during pregnancy have been reported in evaluations of infants with dextro-looped transposition of the great arteries (OR, 2.5; 95% CI, 1.2 to 4.9), membranous VSDs (OR, 1.9; 95% CI, 1.0 to 3.5), atrioventricular septal defects, Down syndrome (OR, 2.4; 95% CI, 1.1 to 4.2), and bicuspid aortic valve (OR, 4.1; 95% CI, 1.8 to 9.3).[4] No association

TABLE 6. FDA Categories of Risk for Birth Defects

Category	Description of Risk
A	No fetal risk shown in controlled human studies.
B	No human data available. Animal studies show no fetal risk or animal studies show a risk but not a fetal risk.
C	No controlled studies on fetal risk available for human beings or animals, or fetal risk shown in controlled animal studies but no human data available (benefit of drug use must clearly justify potential fetal risk in this category).
D	Studies show fetal risk in human beings (use of drug may be acceptable even with risks, such as in life-threatening illnesses or where safer drugs are ineffective).
X	Risk to fetus clearly outweighs any benefit from these drugs.

was seen in infants with atrioventricular septal defect without Down syndrome.

Two studies by Souter et al[123] and Hammerman et al[124] document the association between indomethacin tocolysis and persistent PDA. The magnitude of these effects appears to be greatest when indomethacin is administered within 48 hours of delivery. Additionally, there have been case reports of persistent pulmonary hypertension and premature closure of the ductus arteriosus in infants whose mothers took other forms of nonsteroidal antiinflammatory drugs, including naproxen,[125,126] diclofenac,[127,128] ketoprofen,[129,130] indomethacin,[131–134] and sulindac.[133,135,136]

Female Hormones

A potential risk for congenital cardiac defects in offspring from maternal use of oral contraceptives was identified in 2 case-control studies.[137,138] Wiseman and Dodds-Smith[139] evaluated the case histories included in Heinonen et al[138] study and found that only half were exposed during the critical period of cardiogenesis. Oral contraceptive use was no longer significantly associated with congenital heart disease in an analysis restricted to early exposure. Ferencz et al[140] studied mothers of 110 children with heart disease and found no association with maternal hormone therapy. Additionally, a recent meta-analysis failed to document any associations between oral contraceptive use and CCVD[141]; in general, the data are now thought to support their safety.

An association with maternal use of clomiphene was observed in a case-control study of 126 children with coarctation of the aorta (OR, 4.5; 99% CI, 1.0 to 19.9).[6] No association with maternal use of clomiphene was seen in a case-control study involving 83 infants with conotruncal cardiac defects.[36] In the BWIS, maternal use of clomiphene was found to be associated with an increased risk of tetralogy of Fallot (OR, 3.2; 95% CI, 1.6 to 6.3).[6]

Narcotics

Two case-control studies,[87,88] each involving 300 to 400 children with congenital heart disease, reported an association with maternal codeine (FDA category C) use during the first trimester of pregnancy, but methodological limitations raise doubt as to their validity. No association was observed in 2 other studies.[142]

Chemotherapy

There have been no published studies examining the effect of chemotherapy treatment during pregnancy. The literature has been limited to studies of patients who have been treated with chemotherapeutic agents before becoming pregnant. A large case-control study investigating congenital anomalies in children of patients who received chemotherapy for cancer in childhood and adolescence identified structural congenital cardiac defects in 10.0% (2 of 20) of the offspring of women who had been treated in the past with dactinomycin compared with 0.6% (24 of 144) among the children in a multicenter survey of fetal anomalies ($P=0.01$).[143] Of note, studies examining the use of doxorubicin showed no fetal effects in human or animal experiments[143] (antineoplastics, FDA category D).

Angiotensin-Converting Enzyme Inhibitors

A recent cohort of 29 507 infants from a large database of Tennessee Medicaid patients was linked with vital records and hospitalization claims during the first year of life to study the risk of congenital malformations after maternal exposure to angiotensin-converting enzyme used to treat maternal hypertension.[144] This study identified a prevalence of use of angiotensin-converting enzyme inhibitors in the first trimester of 0.7% and a higher risk of major congenital malformations, including malformations of the heart (OR, 3.72; 95% CI, 1.89 to 7.30), in offspring of mothers exposed to angiotensin-converting enzyme inhibitors in the first trimester of pregnancy. The prevalence of major malformations identified in the reference group (2.6%) was lower than expected in the general population (3.0% to 3.5%), raising questions about possible differences in ascertainment and classification of major malformations by exposure group. There is a need for further studies of this issue using standard methods of case ascertainment and classification and accounting for potential risk factors.

Composite Drugs

Bendectin, a combination of doxylamine and pyridoxine, is no longer available in the United States. Extensive studies provide no evidence that maternal use alters the risk of congenital anomalies in offspring. Specifically, case-control studies provide no consistent indication that maternal use of Bendectin during the first trimester of pregnancy increases the risk of congenital heart disease.[36,80,145,146]

Maternal Nontherapeutic Drug Exposure

Caffeine

Caffeine is known to cross the placenta, and concern that caffeine may cause birth defects prompted the FDA to caution pregnant women to limit their caffeine intake. As illustrated below, there is no clear association between caffeine ingestion during human pregnancy and congenital heart disease.

A case-control study of 2030 malformed infants, including 277 with cardiac defects, evaluated risk associated with caffeine ingestion, including consumption of tea, coffee, and cola. No risk was identified for consumption of any of the 3 beverage types. Risk also was assessed in relation to amount of total daily caffeine ingestion in the categories of any ingestion per day, >200 mg/d, and >400 mg/d. Again, no risk was identified in doses equivalent to 4 cups of coffee per day. Too few mothers consumed as much as 1000 mg/d caffeine to assess the risk of very high consumption.[147]

In a population-based cohort study of 850 mothers who drank ≥8 cups of coffee per day, the frequency of all congenital malformations, including heart disease, was not increased from expected.[148] In another well-controlled cohort study, 595 women who drank ≥4 cups of coffee daily also did not produce offspring with congenital anomalies any more frequently than expected.[149] In addition, in a study of 12 696 women who took caffeine-containing medications in the first 4 months of pregnancy, the frequency of congenital anomalies, including heart disease, was no greater than expected.[91] Caffeine also was evaluated as a potential risk

factor in the BWIS.[6] Again, no association was observed between cardiac defects and caffeine consumption or caffeine dose. Other studies also have failed to identify an association.[150]

Alcohol

Ever since the first description of the fetal alcohol syndrome by Jones and Smith in 1973, several studies have documented a wide range of teratogenic effects of alcohol consumption during pregnancy, including cardiac defects.[151] It has been suggested that ethanol may produce fetal tissue edema and affect the turgor of the primitive cardiac loop. Studies of this topic are especially difficult because of the notorious problem of obtaining reliable estimates of alcohol consumption during pregnancy in addition to other forms of recall bias. In a prospective study that collected information on maternal alcohol consumption during the first trimester of pregnancy, investigators noted no increased risk of major malformations among offspring of women who consumed 1 to 2 drinks per day compared with offspring of nondrinkers.[152] In a case-control study of 90 patients with conotruncal abnormalities and 150 with VSDs born in Finland between 1982 and 1983, the effect of maternal alcohol use was compared with 756 controls.[119] Although more mothers of infants with conotruncal malformations consumed any alcohol, consumed alcohol regularly every week, and consumed >1 drink per occasion, these results did not reach statistical significance. Maternal alcohol consumption during the first trimester of pregnancy was more common among the mothers of infants with VSDs (47%) than among those of controls (38%; $P<0.05$).[119] A case-control study of conotruncal defects in Atlanta showed no association with maternal reports of alcohol consumption (OR, 0.72; 95% CI, 0.49 to 1.06) or "binge" drinking (OR, 0.44; 95% CI, 0.13 to 1.46).[36] A more recent case-control study that examined the risk of congenital anomalies with different sporadic and daily doses of alcohol consumption in Spain reported an increased risk of congenital heart defects as a group only with the highest level of maternal consumption of alcohol per day (ie, >92 g/d).[153]

In the BWIS, the only association between alcohol and cardiovascular malformations was limited to increased risk for small muscular VSDs with heavy consumption (5 drinks on a single occasion) during the period defined by the last menstrual period ±3 months. There was no evidence of a trend in the risk of any cardiac defect with increased exposure.[6] A similar study from Finland also reported that maternal alcohol consumption during the first trimester appeared to double the risk of ASDs (OR 1.9; 95% CI, 1.0 to 3.4) but that the dose-response trends in risk were inconsistent with causal association.[154]

Cocaine and Marijuana

A case report by Shepard et al[155] suggested that single ventricle may result from maternal cocaine ingestion by inducing coronary occlusion in the developing fetal heart. Martin and Khoury[156] used data from a case-control study, the Atlanta Birth Defects Case-Control Study, to investigate the role of maternal cocaine ingestion in the induction of single ventricles. None of the 27 case infants were reportedly exposed to cocaine during early pregnancy, and only 7 of the control infants (0.43%) were exposed during early pregnancy. These data suggest that in this population the use of cocaine was rare or underreported.

An increased frequency of cardiovascular malformations was observed among 214 infants with neonatal toxicology screens showing the prevalence of cocaine in 1 study, with peripheral pulmonic stenosis as the leading diagnosis and in far greater numbers than in the general population.[157] A meta-analysis of 6 other epidemiological studies revealed no significant association between maternal cocaine use in pregnancy and fetal cardiovascular malformations.[158] Subsequent case-control studies have reported an association of maternal reports of cocaine use with an increased risk of any cardiac defects (adjusted OR, 11.6; 95% CI, 0.89 to 151.5),[159] heterotaxy (OR, 3.7; 95% CI, 1.3 to 10.7),[160] and membranous VSDs (adjusted OR, 2.4; 95% CI, 1.3 to 4.4).[6] The imprecise results in 2 of these studies are due to small numbers of cases with maternal reports and could reflect rare exposures, underreporting, or sampling variability.

In the Atlanta Birth Defects Case-Control Study, a 2-fold increase in risk of isolated simple VSDs was identified for maternal self- and paternal proxy-reported marijuana use. Risk of isolated simple VSDs increased with regular (≥3 d/wk) marijuana use for both maternal self- and paternal proxy report, although the association was significant only for maternal self-report.[161] Maternal use of marijuana was evaluated in the BWIS and was found to be associated with a slight increase in risk for Ebstein's anomaly.[6] Adams et al[36] used a case-control design with sufficient power to identify a 2-fold increase in risk for conotruncal defects and did not find an association (FDA category C).

Cigarette Smoking

A number of studies have investigated maternal cigarette smoking and congenital heart disease. A meta-analysis of studies published between 1971 and 1999 (12 analyses of all heart defects combined and 7 analyses of heart defect groups or specific phenotypes separately) found no association for all heart defects combined (OR, 1.07; 95% CI, 0.98 to 1.17) and mixed results for analyses of specific groups or phenotypes.[162] The latter probably reflects differences in methods, including case ascertainment, classification, control of confounding, and case group sample size, between the different studies. Some recent studies have reported associations of maternal smoking with heart defects combined (OR, 2.1; 95% CI, 1.2 to 3.5 in the Torf and Christianson[163] study; OR, 1.56; 95% CI, 1.12 to 1.82 in the Woods and Raju[164] study), but others such as the BWIS[6] and a Swedish study[165] have not. Some studies have reported associations between maternal smoking and heart defect groups, including ASDs (OR, 2.2; 95% CI, 1.1 to 4.3), atrioventricular septal defects (OR, 2.3; 95% CI, 1.2 to 4.5), and tetralogy of Fallot (OR, 4.6; 95% CI, 1.2 to 17.0).[163] However, these associations were not corroborated by larger studies such as the BWIS[6] and a study conducted in Sweden.[162] Recent exploratory analyses of small case groups based on the BWIS data have identified associations of maternal smoking with single ventricle and L-transposition of the great arteries.[160,166] Further research is needed to determine whether there is a relationship between

maternal smoking and risk of heart defects based on large population-based studies using more standardized case ascertainment and classification methods.

Vitamin A

A number of studies have examined the association between high vitamin A in the diet and/or supplements and neural crest cell defects (ie, cardiac and noncardiac defects) or outflow tract defects. Some studies suggest that a high intake of vitamin A is associated with an increased risk of CCVDs,[167–169] whereas others suggest no increased risk.[170–173] One possible reason for the inconsistency of the findings may relate to the differences in methods of assessing high exposure to vitamin A intake. Worth noting are 2 studies reporting an increased risk of CCVDs with an intake of >10 000 IU retinol in the form of supplements[168,169] and animal studies reporting the occurrence of defects of the cardiac outflow tract and other neural crest–derived structures[174] (FDA category X at dosages >18 000 to 25 000 IU/d).

Maternal Environmental Exposures

Organic Solvents

Studies of this topic can be difficult because organic solvents often comprise a mixture of chemicals, because the composition varies between different commercial preparations, and because of limitations in the way that exposure was defined in retrospective case-control studies. A few have reported associations of cardiac defects with reported maternal exposure to solvents and paints. Reports of exposure to degreasing or other solvents have been associated with an increased risk of hypoplastic left heart syndrome, coarctation of the aorta, pulmonic stenosis, transposition of the great arteries with intact ventricular septum, tetralogy of Fallot, total anomalous pulmonary venous return, nonchromosomal atrioventricular septal defects, and Ebstein's anomaly.[6] Maternal reports of occupational exposure to organic solvents have been associated with an increased risk of VSDs[119,175]; dyes, lacquers, and paints with conotruncal malformations[150]; and mineral oil products with coarctation of the aorta.[176]

Herbicides, Pesticides, and Rodenticides

A study suggesting an association of maternal employment in the agricultural industry with an increased risk of conotruncal defects[36] suggested a possible association with chemicals used in agriculture. In the BWIS, maternal reports of potential exposure to herbicides and rodenticides were associated with an increased risk of transposition of the great arteries and of potential exposure to pesticides with total anomalous pulmonary venous return and membranous VSDs.[6] A case-control study of various potential sources and numerous measures of maternal exposure to pesticides and congenital anomalies found mixed results for conotruncal defects.[177] A more recent case-control study of various end-product uses reported an increased risk of conotruncal defects with maternal reports of exposure to insecticides.[175]

Air Quality

Two recent studies have examined possible associations of ambient air pollutants with CCVDs. One study conducted in southern California reported possible increased risks of any heart defects and of VSDs with increased ambient levels of carbon monoxide, of aortic artery and valve anomalies with increased levels of ambient air levels of ozone during the second month of pregnancy,[178] and possible decreased risks of these defects with increased air levels of these pollutants during the third month of pregnancy. Another study conducted in 7 Texas counties evaluating potential exposures during weeks 3 to 8 of pregnancy reported possible increased risks of tetralogy of Fallot with carbon monoxide, isolated ASDs with particulate matter <10 μm in aerodynamic diameter, and isolated VSDs with similar dioxide, as well as a possible risk of isolated ASD with carbon monoxide and isolated VSD with ozone.[179] These findings underscore the need for further studies using standard heart defect classification systems to elucidate whether the associations are real or are due to chance or bias.

Groundwater Contamination

The risk of congenital cardiac defects was reported to be greater among children of parents who had contact with areas that had groundwater contaminated with trichloroethylene than among children of parents who had no such contact.[180] This study did not evaluate the relation between maternal water consumption and risk of cardiac defects. Another study that did evaluate maternal consumption of home tap water during the first trimester of pregnancy found an increased risk of cardiac anomalies.[181]

Water Chlorination Byproducts

A possible association between maternal exposure to chlorination byproducts that result from the interaction of residual chlorine and organic matter in tap water and cardiac defects in offspring has been the subject of several investigations.[182–186] These studies evaluated information on the type of chlorination treatment at the water plant or on levels of trihalomethanes measured at sampling points in the water distribution but not on actual levels of contaminants in water consumed or used for showering. These studies found no associations with cardiac defects.

Other Environmental Concerns

Evaluations of possible associations of heart defects with maternal exposure to ionizing radiation have been limited. The BWIS examined possible associations of heart defects with maternal reports of exposure to ionizing radiation in occupational settings or as part of medical or dental evaluations and found few reports of such exposures and no evidence of any associations.[6] Concerns have been raised about the risk of birth defects in communities situated near hazardous waste sites or other sources of environmental pollution. Large population-based studies have evaluated this issue with mixed results. One study found an increased risk of all heart defects as a group,[187] but the results were imprecise because of the small number of exposed cases (n=3). Two studies found no associations with cardiac defects.[188,189] Surveillance data from population-based congenital anomaly registers in 16 regions of Europe (mainly Western Europe) were analyzed to evaluate the impact of the Chernobyl accident on the prevalence of selected congenital anomalies.[190] Chernobyl had no detectable impact on the prevalence of congenital anomalies in Western Europe.

Maternal Sociodemographic Characteristics

Age

In the BWIS, maternal age was not associated with nongenetic CCVDs as a group.[6] Analysis by specific defects found that maternal age of ≥30 years was associated with an increased risk of transposition of the great arteries (OR, 1.7; 95% CI, 1.1 to 2.7) and Ebstein's anomaly (OR, 2.6; 95% CI, 1.4 to 4.8), that more advanced maternal age (>34 years) was associated with an increased risk of bicuspid aortic valve (OR, 2.5; 95% CI, 1.3 to 4.8) and ASDs (OR, 1.6; 95% CI, 1.0 to 2.5), and that young maternal age (<20 years) was associated with an increased risk of tricuspid atresia (OR, 2.8; 95% CI, 1.3 to 6.4).[6] An analysis of nonchromosomal birth defects of the Metropolitan Atlanta Congenital Defects Program from 1968 to 2000 found associations of advanced maternal age (35 to 40 years) with an increased risk of all heart defects (OR, 1.12; 95% CI, 1.03 to 1.22), tricuspid atresia (OR, 1.24; 95% CI, 1.02 to 1.50), and right ventricular outflow tract defects (OR, 1.28; 95% CI, 1.10 to 1.49).[191]

Race/Ethnicity

Racial/ethnic variations in risk of a specific CCVD have been noted by a number of reports. Compared with black infants, white infants have been found to have an increased prevalence of Ebstein's anomaly, aortic stenosis, atrioventricular septal defects, ASDs,[192] coarctation of the aorta,[36,192,193] truncus arteriosus, transposition of the great arteries, tetralogy of Fallot,[36,192] PDA,[192,194] pulmonary stenosis,[192,194] hypoplastic left heart syndrome,[194,195] and a decreased prevalence of pulmonary stenosis.[194] In a population-based study of variations in prevalence of birth defects in offspring of Hispanic and black women in California between 1987 and 1997, no variations in prevalence were noted compared with the prevalence in offspring of non-Hispanic white women.[196]

Reproductive History

A history of reproductive problems has been associated with an increased risk of tetralogy of Fallot (previous miscarriage: OR, 1.5; 95% CI, 1.0 to 2.2), nonchromosomal atrioventricular septal defects (previous stillbirth: OR, 5.61; 95% CI, 1.94 to 16.21), ASDs (previous preterm birth: OR, 2.1; 95% CI, 1.24 to 3.4), and Ebstein's anomaly (previous miscarriage: OR, 3.2; 95% CI, 1.7 to 5.9).[6] Whether a history of reproductive problems represents a proxy for teratogenic exposures (eg, diabetes) or for an inherent increased susceptibility for CCVDs is unclear.

Maternal Stress

Maternal stress as measured by maternal reports of job loss, divorce, separation, or death of a close relative or friend was found to be associated with an increased risk of conotruncal heart defects (OR, 2.4; 95% CI, 1.42 to 4.2) in a case-control study in Atlanta.[36] A more recent case-control study in California obtained a similar result (OR, 1.4; 95% CI, 1.0 to 2.1) with a stronger effect among offspring of mothers who had not completed high school (OR, 2.4; 95% CI, 1.3 to 4.8).[197]

Paternal Exposures

There is growing concern that paternal factors may play a role in the origin of congenital defects in general and of CCVDs in particular. New dominant mutations are more common in older fathers,[198] and paternal age has been shown to be associated with birth defects such as achondroplasia and Alpert syndrome[199] and in genetic conditions known to affect the cardiovascular system such as Marfan syndrome[200]; the average age of fathers of children with sporadic or new mutation forms of Marfan syndrome was greater (37 years versus 30) than the general population. Paternal factors also have been shown to be important in diseases thought to have a combined genetic and environmental origin such as diabetes mellitus; children of a type 1 diabetic father have a greater likelihood of developing type 1 diabetes mellitus[201] than children of a mother with diabetes. This section examines the evidence for various paternal factors.

Paternal Age

Several studies have focused on paternal age as a risk factor for congenital cardiac defects in offspring. Olshan et al[202] evaluated the effect of paternal age on the risk of congenital heart defects in 4110 cases of congenital heart defects from the British Columbia Health Surveillance registry; matched controls were obtained from the birth files of British Columbia. The association of paternal age with 8 cardiac defects was examined after controlling for maternal age and other risk factors. A general pattern of increasing risk with increasing paternal age was found for ASDs, VSDs, and PDA. Offspring of men <20 years of age were also at higher risk for VSDs (OR, 2.0; 95% CI, 1.1 to 3.6) and possibly ASDs (OR, 1.9; 95% CI, 0.9 to 4.3). A separate study by Lian et al,[198] using data from the Metropolitan Atlanta Congenital Defects Program, also found an increased risk for ASDs and VSDs with increasing paternal age after adjustment for maternal age and race. In contrast, a Chinese study found no relationship between advancing paternal age and congenital heart defects.[203] In fact, risk was higher for men <25 years of age compared with men ≥25 years of age at the time of the child's birth (OR, 2.27; 95% CI, 1.85 to 2.79).

Risk for men ≥25 years of age also was increased for VSDs, PDA, and tetralogy of Fallot. Similarly, an analysis of data from the BWIS[204] that focused on isolated membranous VSDs found no association with paternal age.

Other Paternal Exposures

Some studies have been conducted to evaluate the role of paternal exposures in the origin of congenital heart disease, but the number of studies is limited, and the results are inconclusive. The BWIS reported an association of paternal cocaine use with an increased risk of any CCVD in general and with VSDs and tricuspid atresia in particular.[6]

An analysis of data from the BWIS performed by Ewing et al[204] found that reports of paternal marijuana use (OR, 1.36; 95% CI, 1.30 to 11.86) and use of cocaine among older fathers (OR, 3.92; 95% CI, 1.30 to 11.86) were associated with the occurrence of an isolated membranous VSD in offspring. Other authors suggested that 5% of cases of isolated membranous VSDs may be attributed to older fathers who used cocaine.[205] The potential for recall bias associated with illicit drug use makes it difficult to interpret the conclusiveness of these findings.

Savitz et al[206] evaluated the influence of paternal factors on congenital cardiac anomalies using data from 1959 to 1966 Kaiser Health Plan members who participated in the Child Health and Development Study. The authors could not demonstrate any statistically significant relationships, although trends were identified for paternal cigarette smoking, alcohol intake, and older age.

Discussion

This statement provides a summary of well-known prenatal maternal conditions or exposures associated with an increased risk for cardiac defects (ie, definite risk factors) such as maternal rubella infection, phenylketonuria, diabetes, thalidomide, vitamin A congeners/retinoids, and indomethacin tocolysis. In addition, this article summarizes available information on several prenatal maternal and paternal factors that also may alter the risk for cardiac defects in the offspring (ie, possible risk factors). Particularly noteworthy is the suggestion that maternal use of multivitamin supplements containing folic acid during the periconceptional period may be associated with a reduced risk for some cardiac defects. This association and others reported in the literature warrant further evaluation because findings thus far are based on limited studies and/or tend to be mixed. This article also summarizes available information on a wide range of factors for which no associations have been noted or the evidence has been found to be insufficient to assess the risk for CCVDs.

Caveats

In interpreting findings on possible associations between nongenetic factors and CCVDs, we must remember that such associations from observational studies may be due to the exposures or factors of interest, but they may also be a result of chance, bias, or confounding. An observational study can yield an association as a result of sampling variation of the controls or multiple comparisons in an exploratory study. Recall bias is a potential concern because assessment of exposure to many factors (eg, first-trimester fever, medication use, consumption of vitamin supplements, solvents) often is based on parental recall after the birth of the child. Confounding is also of concern in that an apparent association between reported analgesic use and a heart defect might be due to confounding by the condition for which the analgesic was taken (eg, influenza or a febrile illness), and the apparent protective effect of multivitamin supplement use might be due not to the use itself but to the behavior of the user. Because some maternal illnesses can result in treatment with medications, uncertainty remains in some areas regarding independent effects of the disease or its treatment on fetal risk. A lack of an association between exposure and disease risk may be real, but it also may reflect effect dilution resulting from grouping of phenotypes with different inherent susceptibilities or errors in exposure assessment. In this review, most of the findings on risk factors come from case-control studies, and the best available information comes from 2 large population-based case-control studies specifically designed to investigate risk factors for congenital heart disease in an exploratory manner: the BWIS conducted in the Baltimore-Washington area between 1981 and 1989[6] and the study conducted in Finland by the National Public Heath Institute in Helsinki of cases and controls born during 1982 to 1984.[7] Although these larger, population-based studies used standardized methods for ascertaining and classifying cardiac defects, control selection, and methods to minimize potential biases and confounding, the above methodological issues may still be present. Therefore, the consistency of the findings from among multiple well-designed studies is particularly important.

TABLE 7. Recommendations to Prospective Parents Based on Evidence and the Precautionary Principle*

Mothers who wish to become pregnant should:
Take a multivitamin with folic acid daily
Obtain preconception and prenatal care with specific attention to detection and effective management of phenylketonuria and diabetes and vaccination for rubella
Discuss any medicine use with your doctor, even over-the-counter medications
Avoid contact with people with flu or other febrile illnesses
Avoid exposures to organic solvents

*These are recommendations based on evidence available in the medical literature to reduce risk of offspring with a congenital heart defect only. Prospective parents should discuss other important health behaviors with their healthcare provider and/or obstetrician.

Implications for Prevention

With these caveats in mind, the information presented here and the precautionary principle[207–209] yield some guidelines that could be useful to prospective parents who wish to minimize their chances of having a baby with a CCVD. These guidelines are listed in Table 7. It is important to note that these guidelines are aimed at minimizing potential prenatal exposure to risk factors for congenital heart defects only, not other adverse health outcomes. Prospective parents should discuss important health behaviors that may affect a pregnancy such as nutrition, physical activity, lifestyle, and occupation with their primary care provider or obstetrician. Women of childbearing age should take multivitamins containing folic acid on a daily basis in the periconceptional period and should avoid certain types of behaviors such as exposure to organic solvents. Women of childbearing age also should obtain prenatal care, including testing for diabetes and past rubella exposure; should discuss any medication use with their obstetrician; and should avoid contact with ill people, especially those with rubella or influenzalike illnesses.

Recommendations also are possible for screening for possible cardiac defects using fetal echocardiography during pregnancy when warranted by reports of prenatal maternal illnesses or exposures. The need for screening any individual should be made on an individual basis from the type, likelihood, and level of potential exposure, as well as the time of gestation during which it occurred. This decision typically will be made as a result of the obstetrical history.

Ultimately, the aim of epidemiological studies is to provide information necessary for development of prevention policies and interventions. Because congenital heart defects represent

some of the more prevalent birth defects, result in significant lifelong morbidity, and are an important cause of mortality attributed to birth defects, the development of effective prevention interventions is paramount from a public health perspective. However, the evidence base to support the development and implementation of effective prevention policies and interventions specifically directed at reducing the public health impact of congenital heart defects is somewhat limited.

Nevertheless, some strategies may be considered that may help to ameliorate risk for congenital heart defects on a population basis. In part, these must be based on concern regarding a broader set of risks for pregnancy outcomes other than heart defects alone. Preconception care and appropriate dietary management for women with phenylketonuria should be an important strategy. Detection and appropriate management of diabetes before and during pregnancy should be an important priority, given the increasing prevalence of type 2 diabetes and glucose intolerance in the general population. Guidelines for managing diabetes before and during pregnancy have been published by the American Diabetes Association.[210,211] Ensuring that women of childbearing age are immunized against rubella is also an important and practical strategy. Medications that are suspected of causing congenital defects, including congenital heart disease, should have warnings about that risk to allow mothers and physicians to make informed decisions about the risks and benefits of use of the medication during pregnancy. One strategy that has already been implemented is the recommendation for use of prenatal vitamins. Continuing to emphasize the importance of using prenatal vitamins containing folic acid is practical and important.

Implications for Further Research

Information available regarding several potential noninheritable risk factors for congenital heart defects is limited because of few studies, few exposures of mothers or fathers to yield highly reliable findings, or possible methodological issues. A recent example of this problem of limited available information involves the drug paroxetine. The FDA has recently changed the pregnancy category of this drug from C to D because of concerns related to possible increased risk of congenital cardiac malformations in the fetus raised by preliminary results from epidemiological studies. A warning has been placed in the prescribing information for the drug and on the FDA Web site (http://www.fda.gov/medwatch/safety/2005/safety05.htm#Paxil3). No evidence-based studies have been published in the scientific literature to date. Clearly, further research on many of the potential risk factors discussed in this statement is needed to expand the evidence base needed for the development of prevention strategies. The potential for expansion of the evidence base may be realized within the next few years, with the recent implementation of 2 large population-based studies in which standard methods for classification and grouping will be used. One of these is the National Birth Defect Prevention Study (NBDPS), a multicenter population-based case-control study of birth defects, which has been ascertaining and collecting clinical information on children with birth defects, including congenital heart defects, on an ongoing basis since 1997.[212] This is the largest case-control study of birth defects conducted in the United States and will include one of the largest collections of cases of heart defects from several regions of the country. The NBDPS will facilitate evaluation of a wide array of known and suspected risk factors for subgroups of the population and will enable investigators to evaluate the relation between various types of heart defects and candidate genes, environmental factors, and gene-environment interactions. A number of data analyses have already been initiated, and some results should become available within the next few years. Another potential future source of information is the National Children's Study (NCS).[213] This study will explore a broad range of environmental factors that influence health and well-being of children. Because this study plans to examine ≈100 000 children across the United States and follow them during prenatal development, through birth, in childhood, and into adulthood, it will provide opportunities to evaluate prospectively the impact of prenatal exposures on some of the more common heart defects, as well as the developmental outcomes, other comorbidities, transition to adulthood issues, and the survival experience of children with heart defects.

Conclusions

In conclusion, this statement summarizes the current state of knowledge of noninherited risk factors for both mothers and fathers that may increase or, in some cases, decrease the likelihood that a congenital cardiac defect may occur in offspring. Much of the recent evidence is preliminary and may not ultimately prove to be causal. Nevertheless, some reasonable recommendations are offered to prospective parents and healthcare professionals that may reduce the risk of having a child with a congenital cardiac defect based on the current state of knowledge for the prevention of other birth defects and the precautionary principle. Similarly, pregnancies with some types of maternal exposures may warrant prenatal screening with fetal echocardiography. To date, no public policies or interventions are specifically directed at reducing the public health impact of congenital heart disease. However, new studies such as the NBDPS or the NCS may yield evidence needed to support the development of such policies or interventions in the future.[214–218]

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