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Maternal Cigarette Smoking and Congenital Heart Defects

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Congenital heart defects (CHDs) are of public health concern because they affect approximately 1% of newborns,[1-3] are a leading cause of infant mortality,[4] and often result in increased use and costs of health services among affected children, adolescents, and adults.[5] In recent decades, epidemiologic research has made notable progress in the identification of modifiable risk factors for some CHDs (eg, congenital rubella infection, use of certain medications, and pregestational diabetes).[6] For most CHDs, however, the causes remain unknown. In this issue of The Journal, Sullivan et al[7] describe results of a population-based study in which they assessed the possible association of maternal periconceptional cigarette smoking and the occurrence of CHDs among live births by linking self-reports of cigarette smoking on birth certificates with records of children with CHD (ie, cases) identified from birth certificates and a statewide hospital discharge registry. The authors examined 19 specific CHD phenotypes and observed associations between maternal cigarette smoking during the first trimester of pregnancy and 3 phenotypes: pulmonary valve anomalies, pulmonary artery anomalies, and isolated secundum type of atrial septal defects. They also observed a suggestion of a doseresponse relationship between maternal cigarette smoking and the risk of CHDs examined as a group. These findings are of interest because they highlight: (1) methodologic issues common to studies of associations of maternal cigarette smoking, a prevalent and modifiable exposure, with specific CHD phenotypes in the offspring; (2) challenges in interpreting the nature of observed associations between maternal cigarette smoking and CHDs; and (3) opportunities for prevention and smoking cessation efforts among women of childbearing age.

Methodologic Issues in Studies of Associations between Maternal Cigarette Smoking and CHD

There are a number of methodologic issues in epidemiologic studies of cigarette smoking and CHDs that careful design and execution can help address. CHDs encompass a wide range of phenotypes with varying severity and potentially different etiologies. These can involve a single cardiac lesion or multiple cooccurring cardiac lesions. Additional defects

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also may be present in other organ systems. These additional defects may or may not be part of known genetic disorders. The different phenotypes of CHDs also can vary in risk factors and in the proportion that result in spontaneous fetal death or elective termination of pregnancy after prenatal diagnosis. The effect of inclusion or exclusion of these birth outcomes on the estimated prevalence may vary for different CHD phenotypes. Therefore, population-based studies of CHDs generally should aim to include all CHD cases among live births, stillbirths, and pregnancy terminations, whenever possible, to minimize the potential for selection bias and use a system of classification of CHD phenotypes into relatively homogeneous subgroups with respect to the presence of known underlying etiologies and the potential risk factors under study to maximize the potential for meaningful analysis.[8]

Classification of CHDs, however, into specific phenotypes requires expertise that often is not readily available, and, when available, can pose a dilemma for analysis. Although classification of specific CHD phenotypes may offer a better potential for identifying risk factors specific for such phenotypes, individual CHD phenotypes tend to be rare. The sample size obtained for a given phenotype in a given study may be inadequate for reliable analysis. A case-control study design often is used to examine multiple risk factors for various specific CHD phenotypes because this type of design generally is less costly and more efficient than cohort studies designed to examine one specific exposure in relation to the risk for various specific CHD phenotypes. However, case-control studies of prenatal exposures often rely on maternal self-reports (ie, subject to recall errors) that may result in misclassification of exposure status and possible biases in the relative risk estimates. Because of these and other methodologic issues (eg, accuracy of CHD phenotype classification based on International Classification of Diseases, 9th Revision, Clinical Modification codes, multiple comparisons of exposures and phenotypes), epidemiologic studies of cigarette smoking and CHDs clearly are challenging to conduct. Nonetheless, such studies are needed and valuable because they help to add to the body of literature on a possible risk factor for CHDs that is prevalent and potentially modifiable.[6,9-11]

Challenges in Interpreting the Causal Nature of the Association between Cigarette Smoking and CHDs

Interpreting associations between maternal cigarette smoking and CHDs is further complicated by the fact that different CHD phenotypes are multifactorial in origin, involving complex interplays between genetic and environmental factors, so that infants with the same CHD phenotype (eg, hypoplastic left heart syndrome) may exhibit different risk factor profiles. Therefore, in interpreting whether observed associations between one type of exposure such as cigarette smoking and specific CHDs are likely to be causal, it is useful to consider the quality of the evidence with respect to guidelines for establishing causality for a given exposure (ie, temporality, strength of association, biological or dose-response gradient, consistency across studies, plausibility/coherence, experimental evidence, and specificity).[12] Maternal cigarette smoking can be considered causally related to oral clefts because there is moderate-to-strong evidence for 5 of the 7 guidelines for causality.[9,13] In contrast, the evidence for causality for the association between maternal cigarette smoking

and right-sided obstructive heart lesions and secundum type of atrial septal defects is more limited: there is moderate-to-strong evidence for only 3 of the guidelines (temporality, strength of association, and specificity) and weak-to-moderate evidence for a fourth and fifth (consistency across studies and dose-response).[9,11] However, there is little to no evidence for coherence/biologic plausibility and no experimental evidence in support of the associations between maternal cigarette smoking early in pregnancy and CHDs.

Thus, at present, the level of evidence regarding a causal relationship between maternal cigarette smoking and right obstructive heart defects and secundum atrial septal defects probably could be considered suggestive at best. Worth noting is that because most studies of CHDs and maternal cigarette smoking have involved multiple comparisons of various groupings of CHDs, there is always the concern that some of the observed associations in analyses of multiple exposures and/or phenotypes could reflect chance (ie, type I error). Further studies are needed to rule out chance and bias inherent to observational studies as possible explanations for the observed associations between maternal cigarette smoking and CHDs.[9,11,14,15]

In this issue of *The Journal*, Sullivan et al[7] report on a population-based, case-control study in which they examined possible associations of CHDs with maternal cigarette smoking. They found frequencies of CHDs and of maternal cigarette smoking comparable with those reported in other recent population-based studies.[14-16] In addition, they reported aORs for maternal cigarette smoking that were weakly to modestly associated with pulmonary valve anomalies (aOR 1.48, 95% CI 1.15-1.90); pulmonary artery anomalies (aOR 1.71, 95% CI 1.40-2.09); and isolated secundum type of atrial septal defects (aOR 1.22, 95% CI 1.08-1.38). These findings are consistent with findings from 2 population-based case-control studies that also examined maternal cigarette smoking and CHDs (Table).[14,15] Furthermore, Sullivan et al[7] reported a dose-response relationship between maternal cigarette smoking and the risk for all CHDs as a group, particularly among offspring of mothers 35 years of age and older. Because these dose-response data were presented only for all CHDs combined, and different studies differ in inclusion and exclusion criteria and classification systems for specific CHD phenotypes, direct comparison with previous studies is not possible.

Smoking Prevention and Cessation among Pregnant Women

Although the evidence for a causal relationship between cigarette smoking and CHDs is still open to question, the other known adverse effects of smoking for pregnancy outcomes[9] and the current 10%-15% prevalence of smoking among women of childbearing age[16] make it imperative to continue to support smoking prevention and cessation efforts in this population. A variety of measures could be adopted to prevent women from initiating smoking and to encourage those who currently smoke to quit. These include increasing the price of tobacco products, implementing and enforcing comprehensive smoke-free laws, and increasing access to help quitting.[17-19] Increasing awareness of the consequences of smoking during pregnancy among women is also important. A recent study conducted among a sample of US women who smoke found that they were aware there were general health risks of smoking during pregnancy, such as an increase in premature delivery or

having an infant with low birth weight; however, many were not aware of other specific consequences, such as birth defects.[20] Providing more information to women about the risks of smoking during pregnancy could motivate many of them to quit. Studies suggest that pregnant women are often motivated to change or adopt new behaviors because they want their unborn babies to be healthy.[21,22] Health education efforts also could include antismoking media campaigns such as Centers for Disease Control and Prevention *Tips from Former Smokers* campaign,[23] which features a story about the dangers of smoking during pregnancy.

Women who wish to quit smoking during pregnancy have options such as brief tobacco counseling (eg, the 5As: ask, advise, assess, assist, arrange[24]) in settings in which women of child-bearing age encounter medical professionals and calling a quitline. The ideal time to reach women with prevention messages and cessation assistance, however, is during the preconception period. By the time a woman finds out about her pregnancy and begins prenatal care, it may be too late to prevent some adverse outcomes, such as oral clefts, CHDs, and other birth defects, that occur early in pregnancy.[25] Additionally, women who decide to quit smoking before pregnancy have more treatment options available for doing so. Cessation medication is not recommended as first-line treatment for pregnant women, and the safety and efficacy of nicotine-replacement therapy during pregnancy has not been established.[10,26,27]

The study by Sullivan et al[7] adds to the body of literature on possible associations between maternal cigarette smoking early in pregnancy and 3 of 19 specific CHD phenotypes examined in the offspring. Although further studies are war-

ranted to corroborate the observed associations, the current evidence on adverse effects of maternal cigarette smoking on pregnancy outcomes suggests that the wisest course of action is to continue to promote smoking prevention and cessation efforts among women of childbearing age.

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Table

ORs from published studies of associations between maternal cigarette smoking, atrial septal defects, and right ventricular outflow tract obstruction defects

		Light smoking*,†		Moderate smoking*,†		Heavy smoking*,†	
Study, location	**Types of CHDs**	**No. of case/ control infants**	**OR (95% CI)**	**No. of case/ control infants**	**OR (95% CI)**	**No. of case/ control infants**	**OR (95% CI)**
Malik, et al,[15] US	Atrial septal defects‡	69/458	2.02 (1.47-2.77)	22/190	1.78 (1.05-3.01)	6/45	2.35 (0.92-6.00)
	Right ventricular outflow tract obstruction defects	79/522	1.25 (0.95-1.65)	23/204	0.93 (0.59-1.49)	13/47	2.35 (1.21-4.53)
	Pulmonary valve stenosis	58/458	1.24 (0.90-1.70)	17/190	0.91 (0.53-1.55)	10/45	2.31 (1.11-4.83)
Alverson, et al,[14]	Atrial septal defects ‡	37/539	1.41 (0.95-2.11)	22/314	1.59 (0.98-2.58)	7/107	1.64 (0.74-3.62)
Maryland, Washington, DC, northern Virginia	Right ventricular outflow tract obstruction defects	49/539	1.20 (0.88-1.69)	27/314	1.25 (0.81-1.91)	12/107	1.71 (0.92-3.18)
	Pulmonary valve stenosis	45/539	1.53 (1.06-2.19)	18/314	1.15 (0.69-1.92)	9/107	1.79 (0.88-3.54)
	Pulmonary atresia with intact ventricular septum	4/539	0.73 (0.25-2.14)	8/314	2.43 (1.06-5.53)	1/107	0.88 (0.12-6.62)

*The study by Malik et al[15] included maternal smoking from 1 month before conception through the end of the first trimester; smoking levels were defined as light, 1-14 cigarettes per day; medium, 15-24 cigarettes per day; heavy, ≥25 cigarettes per day.

†The study by Alverson et al[14] included maternal smoking during the first trimester; smoking levels were defined as light, 1-10 cigarettes per day; medium, 11-20 cigarettes per day; heavy, ≥21 cigarettes per day.

‡This category refers to secundum type of atrial septal defects.