Environmental Factors in the Etiology of Esophageal Atresia

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The etiology of esophageal atresia (EA) is mainly unknown. Data from twin and family studies do, however, show that the occurrence of more than 1 child with EA in a family is low, on the order of 1%, and the twin concordance rate is likewise low, around 2.5% (1). This suggests that hereditary factors do not play a major role in the etiology of EA. Thus, the majority of EA cases are sporadic, and environmental risk factors seem to play an essential part in the etiology of EA. It is reasonable to assume that risk exposures of the pregnant mother during early fetal development, when the esophagus and the trachea are separating, are particularly critical. Only a few environmental exposures of the pregnant mother have been investigated in relation to the risk of EA in the infant. This is a summary of the current knowledge of environmental exposures in the etiology of EA.

ENVIRONMENTAL RISK EXPOSURES

Parity

Several studies have shown that low maternal parity increases the risk of EA in offspring (2). It has been suggested that an increased risk of EA with low parity may be linked with fertility problems (3).

Maternal Age

Partly contradictory results have been reported regarding the association of maternal age to the risk of EA in the child. It has been hypothesized that a link between EA and increasing maternal age may be due to confounding by chromosomal abnormalities, because older mothers are at increased risk of having a child with chromosomal abnormalities and such abnormalities are overrepresented among infants with EA (1). Our group has conducted a large, population-based study providing support for an increased risk of EA with older maternal age. The association remained when the analysis was restricted to cases without chromosomal abnormalities (2).

Paternal Age

Recently, 2 studies exploring the effect of paternal age on birth defects have been published that suggest an increased risk of EA in the infant with increasing paternal age (4,5). Maternal and paternal age and maternal parity may be indicators of a role for endocrine or other biological mechanisms in the etiology of EA.

Ethnicity

There seems to be an increased risk among white women, compared with other ethnic groups, of having an infant with EA (2). This may reflect differences in environmental risk exposures and differences in genetic predispositions, triggered by environmental risk factors.

Drugs

Few studies have assessed the role of drugs in the etiology of EA. A relation between maternal use of exogenous sex hormones during early pregnancy and risk of EA in the infant has been suggested (6). A potential link between maternal exposure to the hyperthyreosis medication methimazole and EA has also been reported (7), but except for 1 smaller cohort study (8), this potential association is mainly addressed in case reports. Further studies and with more valid study designs must be undertaken to investigate these potential associations.

Herbicides or Insecticides

One study has shown an association of borderline significance between contact with herbicides or insecticides during pregnancy and risk of EA in the infant (9). This is, however, a hypothesis-generating study, with more than 100 different possible risk exposures studied, opening a substantial risk of chance findings, and the results must be confirmed in other studies.

Tobacco Smoking and Alcohol

Three case-control studies have addressed the role of maternal tobacco smoking during pregnancy in relation to the risk of EA in the infant. No increased risk of EA with maternal smoking was found overall (9–11). In 1 of the studies, a statistically significantly increased risk of EA with associated anomalies was found in a subgroup of smokers (10). Combined exposure to maternal tobacco smoking and alcohol further elevated some of the odds ratios in the study (10).

Obesity

Several studies have shown an increased risk of a range of birth defects with maternal obesity. A recently published systematic review and meta-analysis did, however, not find any support for an association between obesity during pregnancy and the risk of EA in the infant, based on 222 cases with EA (12). During the same time period, our research group conducted a population-based study, including 722 cases, supporting the lack of any association between maternal obesity and risk of EA (11).

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Socioeconomic Status

The literature on socioeconomic status inequalities with respect to EA has been sparse and hampered by limited statistical power. Our research group conducted a study, using educational level as a marker of socioeconomic status, that contradicts an increased risk of EA in women of low socioeconomic status (11).

Diabetes

Associations between diabetes and gastrointestinal malformations have been seen in some studies, but not in all (13). Results of a recent, larger, case-control study suggested that women with preexisting diabetes had an increased risk of delivering a child with EA associated with other malformations, but not isolated EA (14). We have conducted a population-based case-control study including 780 infants with EA in which there was a 70% higher risk of EA in infants of women with any type of diabetes (preexisting or gestational) during pregnancy compared with those of women without diabetes (15).

Future Perspectives

Epidemiological studies of exposures during pregnancy and the risk of EA or other malformations in the infant often reveal weak to moderate associations (16). The etiology of EA is generally considered to be multifactorial (17), and the weak associations found between different risk exposures and EA may reflect biological interactions (16). Much remains to be learned about environmental risk exposures affecting the risk of EA in the infant; the list presented in this summary is short. A first step may be to identify more exposures that increase the risk of giving birth to an infant with EA and to subsequently identify other factors that explain why only some of those exposed are affected. Biological interactions may be interactions between different environmental exposures and between environmental exposures and different genotypes, either of the mother or of the infant, that gives a susceptibility to certain environmental risk factors. Gene–environment interaction studies for birth defects are evolving. Collaboration between geneticists and epidemiologists with an interest in environmental risk factors could be the progress in our knowledge in the etiology of EA.

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