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Air pollution and congenital anomalies

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Congenital anomalies, a leading cause of fetal loss, contribute significantly to preterm birth and childhood and adult morbidity. Serious structural defects are present in 3%–8% of newborns worldwide and, while some can readily be attributed to chromosomal or syndromic disorders or known teratogenic or fetotoxic agents, a recent commentary maintained that the causes for most anomalies remain a mystery.¹ Maternal smoking during pregnancy has long been associated with birth defects² and numerous biological pathways have been identified whereby particulate air pollutants might impact on the placenta and fetus (reviewed in Kannan *et al*³) providing biological rationale for the assessment of air pollution's influence on fetal development. Although quantitatively lower than exposure from maternal smoking, exposure to ambient air pollutants affects large populations and, importantly, is not modifiable by the individual and is thus of great public health and policy relevance.

The study by Dolk *et al*⁴ in this issue (*see page 223*) is the latest in the small set of publications investigating air pollution's impact on birth defects,^{5–10} a subset of the larger body of literature focussing on air pollution's effect on the more common adverse birth outcomes (ie, preterm birth and low birth weight) which are considered more general indicators of abnormal fetal development.

The California⁵ and Texas⁶ studies reported positive associations between some specific cardiac defects and several but different pollutants measured at the air monitoring station closest to the mother's home during weeks 3–8 of gestation. These studies found little evidence for an increased risk of oral clefts or other types of birth defects. The Taiwanese study,⁷ however, linked oral clefts to ozone exposure during months 1 and 2 of pregnancy, but not to other air pollutants as estimated using 72 countrywide monitoring stations.

Earlier this year Strickland *et al*⁸ in Atlanta, Georgia, found a small risk increase for one of 12 specific cardiac defects evaluated against particulate exposure, but used only one central monitoring station to assess exposures in weeks 3–7 of pregnancy, thus relying solely on temporal while ignoring spatial differences in air pollution. A much smaller study from Brisbane, Australia⁹ used the closest monitor approach to average exposures for weeks 3–8 of pregnancy and suggested associations between ozone and SO₂ exposure with two different subgroups of cardiac defects as well as with clefts.

Using 1980's data from the Northern England region, Rankin *et al*¹⁰ estimated average first trimester pollutant exposure based on measurements at all monitors within 10 km of the mother's residence. The investigators reported a significantly negative association between black smoke (particulate exposures) and SO₂ and all cardiac defects as well as patent ductus arteriosus, a small increase in risk for nervous system defects and black smoke, and no

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associations with clefting. The recent, larger study by Dolk *et al*⁴ modelled exposures for three combustion-related air pollutants (SO₂, NO₂, PM₁₀) using 1996 annual background measurements and emissions data, thus relying solely on spatial contrasts to assess the influence on all defects registered in four major regions in England in the 1990s. They concluded that only the positive association for all pollutants with tetralogy of Fallot would merit further attention.

Thus, while studies linking different birth defects to routinely measured air pollutants have been accumulating internationally, results thus far, even for cardiac defects, are equivocal at best. Results should be cautiously compared across studies since each employed a somewhat different set of rules to identify and classify both pollutant exposures and subgroups of defects. Birth defects research will always be limited by difficulties in detection: a number of defects (including some heart malformations) go undetected at birth, while other severe malformations may be detected in prenatal screening and followed with induced abortions; birth defect registration may or may not take this into account. Birth defects research is also limited by the data available in the registries: is there sufficient information to allow investigators to distinguish between isolated, multiple, syndromic and chromosomal defects? Are the assigned anatomical subcategories confirmed by autopsy or surgical reports, catheterisation or echocardiogram?

Exposure assessment is similarly challenging. The density of air pollution monitoring networks varies by region and country, as is observed in the seven studies discussed. Furthermore, the composition of ambient air pollution is dependent on the contributing sources. Some pollutants vary strongly by geographical area over a relatively short distance, while others are influenced more by temporal patterns. Pollutants may also co-vary, creating multi-collinearity when estimating effects for individual exposures assessed from the same sources. Finally, the most relevant pollutant may depend on the specific birth defect of interest and/or the main sources of pollution, and there are limited well-established animal models to inform such specific hypothesis construction.

The relatively short 8-week period early in gestation during which most organs rapidly develop in the fetus, provides a unique opportunity to study exposures acting on a narrow susceptibility window. Thus, one might be as much concerned about temporal as spatial fluctuations in air pollution. The assumption of spatial homogeneity is more accurate for some (ozone, PM₁₀) than for other air pollutants (CO, NO₂). While it is difficult to rule out residual confounding in studies relying solely on spatial gradients since risk behaviours related to socioeconomic status might be differentially distributed between communities, studies relying on temporal contrasts would also need to assess potential seasonal covariates such as flu epidemics or indoor exposures. Furthermore, population based studies, relying on data from registries to ensure a large sample size and avoid recall bias, are restricted to a minimal set of potential covariates, limiting their ability to control for confounding.

Since excessive toxin exposure during pregnancy may lead to competing outcomes such as spontaneous early abortions, the selective survival of more viable fetuses may translate to non-linearity in dose effects for agents causing birth defects. Additionally, certain sub-populations of women and fetuses may be especially susceptible to air pollutants, for example those with social disadvantages that translate into increased exposure to toxins, adverse behaviours (poorer diet, alcohol use, smoking) and/or lack of access to prenatal care. Finally, a recent study suggesting a possible gene–environment interaction increasing congenital heart defects risk in carriers of an endothelial nitric oxide synthase variant also exposed to maternal smoking during pregnancy,¹¹ highlights the importance of research in gene–environment interactions affecting early embryogenesis.

There are many opportunities for missteps in fetal development resulting in specific but rare malformations. While one can envision a toxin causing defects in multiple organ systems, it is unlikely that any specific agent would cause an overall increase in all types of anomalies. The distinction between relevant subgroups is quite challenging since even specific defects are likely to be of multifactorial aetiology. The rarer the defect, the larger the data source needed, in other words, adequate and reliable exposure and outcome data for not just thousands but hundreds of thousands of pregnant women. In Western nations these studies have become possible because of extensive and coordinated efforts in population-level monitoring of both birth defects and air pollution. While the limitations of previous studies make it difficult to compare results, future studies present an opportunity to re-assess these earlier associations with higher quality outcome and exposure assessment.

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