Chapter 3
Effects of Environmental Chemical Exposure on Birth Defects (Except Cryptorchidism and Hypospadias)

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Abstract Currently, the causes of birth defects remain unknown in approximately 80% of the cases. Here, the etiologies are likely multifactorial and may involve the genetic background, exposure to drugs, environmental chemical exposure, infections, maternal factors, and intrauterine mechanical factors. In this review, we discuss the effects of environmental chemical exposure on the incidence of birth defects by summarizing the previous epidemiological studies. Notably, chemical exposure was most frequently associated with elevated risks of central nervous system and congenital heart defects and oral clefts than with other types of birth defects. Although exposure to air pollutants, persistent organic pollutants, polycyclic aromatic hydrocarbons, and perfluorinated compounds were associated with increased risks, no substance-specific birth defects were identified. Many case–control studies had the limitation due to poor exposure assessment. In terms of the risk assessment, it is difficult that epidemiological study indicates the hazard identification including the dose-response relationship. We conclude that descriptions of the disease prevalence and individual chemical exposure levels are important roles of reproductive epidemiological study.

Keywords Birth defects · Air pollutants · Persistent organic pollutants · Polycyclic aromatic hydrocarbons · Perfluorinated compounds

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3.1 Introduction

Experimental evidence has demonstrated the complexity and multilayered nature of fetal development, as even a single defective mechanism will result in birth defects. The twenty-first century marks the era of elucidation of the mechanisms underlying fetal development at a molecular level. Soon, it may be possible to use an in vitro molecular disruption in this process to screen comprehensively for the risk of birth defects caused by exposure to environmental chemicals. However, many previous epidemiological studies of the relationship between exposure to environmental chemicals and birth defects have been limited by small sample sizes or weak exposure assessments.

This review summarizes current trends in the prevalence of birth defects, the possible mechanisms underlying birth defects associated with environmental chemical exposure, and previous epidemiological findings regarding this topic. This paper also discusses the goals and expectations of future epidemiological studies that aim to investigate the causative agents of birth defects.

3.2 Trends in the Prevalence of Birth Defects

Table 3.1 summarizes data from populations in Japan and Texas, USA that were obtained from the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) [1, 2]. In this table, the Japanese data are hospital-based, the US data are population-based, and both datasets use the total number of live births and stillbirths as the denominator. In this table, all diseases have been classified according to the method described by St. Louis et al. [3]. In this comparison, Japan reported a relatively higher incidence of congenital heart defects, oral cleft, gastrointestinal defects, and chromosomal anomalies but a lower incidence of genitourinary

Table 3.1 Prevalence rates of birth defects in Japan and Texas as reported by the ICBDSR

	Japan		Texas, USA	
Birth year	2005	2012	2004	2011
Live births and stillbirths	71,765	108,087	380,905	377,336
Central nervous system	7.2	6.4	7.3	8.1
Ear defects	1.3	2.0	3.3	3.6
Congenital heart defects	19.1	22.7	13.4	17.2
Oral cleft	24.7	28.6	16.6	17.2
Gastrointestinal defects	22.2	17.5	7.6	13.5
Genitourinary defects	4.6	5.7	16.3	17.4
Musculoskeletal defects	22.2	19.3	17.1	21.5
Chromosomal anomalies	21.9	29.3	16.4	18.7

Rates are presented as numbers per 10,000 live births and stillbirths
Diseases are classified according to the method described by St. Louis et al. [3]

defects (hypospadias). However, these datasets cannot be compared directly because of the differences in the maximum age at diagnosis and the criteria used to define stillbirth.

The analysis reveals an increasing incidence of oral clefts and chromosomal anomalies over time in Japan, but not in Texas. This difference appears to be based on an environmental difference, which includes factors related to maternal exposure, rather than racial differences between these two populations. This observation highlights the need to conduct a focused study of disease in which the incidence changes over time and among regions.

3.3 Causes of Birth Defects

Figure 3.1 presents the causes of birth defects according to Feldkamp et al. [4]. The causes are unknown in approximately 80% of cases, whereas birth defects caused by obvious teratogens account for only 0.8%. Additionally, chromosomal abnormalities and birth defects of unknown etiology are likely attributable to multifactorial causal factors, which include the genetic background, drugs, environmental chemical exposure, infection, maternal factors, and intrauterine mechanical factors. However, each factor likely makes a small individual contribution; and therefore, it is difficult to assess the risks associated with environmental chemical exposure in the context of an epidemiological study. Many researchers believe that although the majority of teratogenic factors have a threshold below which no malformations are induced (i.e., the "no-effect" level), a sufficiently high dose of xenobiotics will affect a developing embryo [5]. Therefore, it is important to determine whether daily exposure to a particular environmental chemical will have an effect on fetal development.

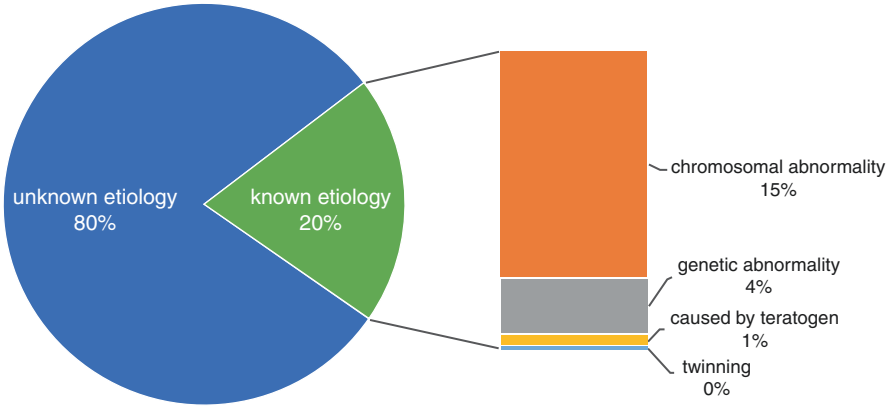

Fig. 3.1 Etiology of birth defects [4]

3.4 Mechanisms Associated with Birth Defects

The complex intracellular signal transduction mechanisms associated with normal development and embryonic induction have largely been elucidated. Specifically, the roles of factors such as intercellular communication factors, morphogens, receptor tyrosine kinases, the Notch-Delta pathway, various transcription factors, and epigenetic factors have been identified [6]. Exposure to an environmental chemical can disrupt these complex molecular pathways within the cell, and exposure beyond the "no-effect" threshold can lead to irreversible disruption and birth defects.

According to Levi, the initiating mechanisms of birth defects include mutations, chromosomal abnormalities, interference with mitosis and/or nucleic acid function, nutritional deficiencies, changes or deficiency in the energy supply, changes in osmolarity, changes in the cell membrane, and enzyme inhibition [5]. Exposure to a causative substance can trigger these mechanisms, which alters molecular signaling pathways within the cell and thus causes birth defects.

Epigenetic alterations of the germ cells can lead to inherited phenotypes. Although researchers have concluded that the malformations caused by thalidomide are not inherited [7], recent studies have demonstrated the heritability of cleft palate [8]. This latter finding suggests that cleft palate may be attributable to an epigenetic change. Table 3.2 presents the chemicals and pollutants that are known to induce methylation [9]. DNA methylation is a known epigenetic factor. In some cases, exposure to these substances may induce an epigenetic alteration that leads to a birth defect.

In addition to genotoxic and endocrine-disrupting effects, chemicals such as tetrachlorodibenzo-p-dioxin (TCDD) and halogenated aromatic hydrocarbons can directly affect molecular signaling within the cell. These chemicals activate the aryl hydrocarbon receptor (AHR) and trigger downstream cell signaling pathways associated with extracellular matrix synthesis and repair. Additionally, AHR activation is known to affect the regulation of processes essential for development, including cell cycle progression, proliferation, differentiation, apoptosis, and cell migration [10–14]. Studies have shown that intrauterine exposure to TCDD and

Table 3.2 Chemicals and pollutants known to induce methylation [9]

Tobacco smoke
Particulate air pollution
Asbestos
Bisphenol A (BPA)
Diethylstilbestrol (DES)
Metal ions (such as chromium, cadmium, nickel, arsenic, and methylmercury)
Vinclozolin
Methoxychlor
Silica
Benzene
Di- and trichloroacetic acid, trichloroethylene

halogenated aromatic hydrocarbons induces isolated clefts of the secondary palate and hydronephrosis even at doses that do not cause other toxicities in adult women during pregnancy or breastfeeding. Accordingly, the effects of low-level exposure to these chemicals cannot be ignored [15–17].

3.5 Exposure to High Levels of Environmental Chemicals and Birth Defects

Several historical incidents have demonstrated the causal association between exposure to high levels of environmental chemicals and birth defects. For example, the epidemic of Minamata disease in the Kumamoto prefecture of Japan in the 1950s is a famous example. This central nervous system disorder is caused by exposure to organic mercury via polluted water. In this case, the children of exposed mothers developed congenital Minamata disease, which manifested as microcephaly in 60% of cases [18]. In another example, a fivefold increase in the incidence of hydrocephalus was observed among the children of Vietnam War veterans who had been exposed to Agent Orange (odds ratio [OR] 5.1, 95% confidence interval [CI] 1.1–23.1) [19]. Notably, these cases may not be suitable as references for risk evaluations because they involved exposure to high doses of xenobiotic chemicals, which are always likely to affect embryonic or fetal development.

3.6 Exposure to Low Levels of Environmental Chemicals and Birth Defects

3.6.1 Dioxins, Dioxin-Like Compounds, and Pesticides

A nested case–control study conducted in the USA reported a high incidence of L-transposition of the great arteries (OR 13.4, 95% CI 4.7–37.8) in the Baltimore–Washington region, which was attributed to exposure to industrial pollution and hazardous waste [20]. In an Italian cohort study, the levels of exposure to dioxins were estimated based on the distance between the participants' dwellings and incinerators, as well as the atmospheric concentration of dioxins. However, that study did not identify an increased risk of birth defects [21]. Similarly, a Japanese cross-sectional study did not identify a significant correlation between the distance from an incinerator and the risk of birth defects [22]. In France, a population-based case–control study estimated the dioxin exposure level based on the distance between the participants' dwellings and waste processing plants. Interestingly, that study reported an increased risk of urinary tract birth defects in the offspring of women exposed to dioxin levels at or above the median atmospheric level during early pregnancy (OR 2.0, 95% CI 1.2–3.4 for atmospheric dioxins) [23].

Finally, a case–control study in the USA observed no significantly elevated risk of spina bifida upon pesticide exposure, which was estimated on the basis of occupational history. However, the effects of specific agricultural chemicals were unknown [24].

3.6.2 Perfluorinated Compounds

Animal studies have reported an association between fetal exposure to perfluorinated compounds (PFASs) and an increased risk of left ventricular hypertrophy [25]. The C8 Health Project, a cohort study in the USA, observed a significant increase in the risk of brain defects with each interquartile increase in the estimated serum perfluorooctanoate (PFOA) exposure of pregnant women in regions where the drinking water was contaminated with high concentrations of PFOA [26]. However, another cross-sectional study in the USA found no correlation between the residential area, as classified by public water supply category, and the risk of birth defects [27]. Similarly, a nested case–control study of 215 male infants in Denmark and Finland found no correlation between the level of PFASs in cord blood and cryptorchidism [28].

3.6.3 Organic Solvents

In Canada, a prospective study that compared 125 pregnant women with occupational exposure to organic solvents and a group of pregnant women without such exposure identified an increased risk of major malformations in the former group (risk ratio (RR) 13.0, 95% CI 1.8–99.5) [29]. By contrast, a register-based prospective study conducted in Russia between 1973 and 2005 did not observe statistically significant increases in the risks of multiple, circulatory system, genital organ, or musculoskeletal system anomalies in female employees at nickel-refining plants who were exposed occupationally to organic solvents [30]. As exposure assessments of in occupational populations are relatively accurate, further studies are expected.

3.6.4 Air Pollutants

A meta-analysis of 10 epidemiological studies conducted in the USA, UK, Australia, Korea, Taiwan, and other countries found that prenatal exposure to nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) was associated with an increased risk of tetralogy of

Fallot (NO_2: OR 1.2, 95% CI 1.02–1.4 and SO_2: OR 1.03, 95% CI 1.01–1.1), while exposure to fine particulate matter (PM10) was associated with an increased risk of atrial septal defect (OR 1.1, 95% CI 1.01–1.3). However, no correlations were identified between air pollutants and other birth defects [31]. In Italy, a case–control study observed a correlation between SO_2 exposure and congenital heart disease (OR 3.2, 95% CI 1.4–7.3) [32], while a population-based case–control study identified a borderline dose-response relationship between PM10 exposure and musculoskeletal and chromosomal abnormalities but not cardiovascular defects [33]. In summary, many previous studies have observed associations between air pollutants and birth defects. However, these studies have been limited by the difficulties inherent to individual exposure assessments.

3.6.5 Nitro Compounds

Several studies have suggested a relationship between exposure to nitro compounds in drinking water and birth defects such as neural tube defects (NTDs) [34–36], general central nervous system defects [37], oral cleft defects, musculoskeletal defects [36], and congenital heart defects [38]. A case–control study conducted by the US National Birth Defects Prevention Study estimated the intake of nitrates from drinking water and found that prenatal exposure to this factor correlated with an increased risk of limb deficiency (OR 1.8, 95% CI 1.1–3.1), cleft palate (OR 1.9, 95% CI 1.2–3.1), and cleft lip (OR 1.8, 95% CI 1.1–3.1) [34]. In future studies, exposure assessments will likely be based on the internal doses.

3.6.6 Summary of Previous Epidemiological Studies

Table 3.3 summarizes the statistically significant associations identified in previous epidemiological studies. Although not all of these studies focused solely on birth defects, the risks of central nervous system and congenital heart defects and oral clefts in response to chemical exposure were reported more frequently than were other types of birth defects. Exposure to air pollutants, persistent organic pollutants, polycyclic aromatic hydrocarbons, and PFOA led to increased risks. Interestingly, no substance-specific birth defects were identified, suggesting that different substances affect the same developmental mechanisms and/or the same substances affect different developmental mechanisms. Notably, the gestational age of 6 weeks is considered the most sensitive period for the development of all three organ types; and therefore, study outcomes may be affected by the accurate assessment of exposure during that period (Fig. 3.2).

Table 3.3 Previously reported significant relationships of birth defects with environmental chemical exposure

Birth defects	Environmental chemicals	Study design	Individual exposure assessment	References
Central nervous system	CO	Case–control		[40]
	NO	Case–control		[40]
	NO_2	Case–control		[40]
	Amide, benzimidazole, methyl carbamate, organophosphorus pesticides	Case–control		[41]
	Avermectin, petroleum derivative, bromoynil	Case–control		[42]
	PCBs and PBDEs	Case–control	Available	[43]
	PAHs, *o*,*p*-DDT, *c*-HCH, and *a*-Endosulfun	Case–control	Available	[44]
	PAH	Case–control		[45]
		Case–control	Available	[46]
	PFOA	Case–control	Available	[26]
Congenital heart defects	CO	Case–control		[47]
		Case–control		[48]
	NO_2	Case–control		[49]
	O_3	Case–control		[50]
		Case–control		[47]
	SO_2	Case–control		[48]
		Case–control		[32]
	PM <10 μm	Case–control		[51]
		Case–control		[48]
		Case–control		[51]
		Case–control		[52]
	PM <2.5 μm	Case–control		[49]
		Case–control		[51]
	Chlorophenoxy herbicide	Case–control		[53]
Oral cleft	O3	Case–control		[54]
		Case–control		[55]
	SO_2	Case–control		[50]
	PM <2.5 μm	Case–control		[55]
	Atrazine	Birth cohort		[56]
	2,6-dinitroanaline, dithiocarbamate MITC, 2,6-dinitroanaline, dithiocarbamate MITC	Case–control		[42]
	Herbicides, rodenticides	Cross-sectional		[57]

Table 3.3 (continued)

Birth defects	Environmental chemicals	Study design	Individual exposure assessment	References
Gastrointestinal defects	PM <10 μm	Case–control		[58]
	Pesticides except for atrazine	Birth cohort		[56]
	Atrazine	Case–control		[59]
	Herbicides, insecticides	Case–control		[60]
Musculoskeletal defects	Atrazine and nitrate	Observational		[61]
	Atrazine	Birth cohort		[56]
	Pesticides except for atrazine	Birth cohort		[56]
	Herbicides, rodenticides	Cross-sectional		[57]
Chromosomal anomalies	Atrazine	Birth cohort		[56]

Previous studies in which the specific diseases or chemicals were unknown are not included in this table

3.7 Future Epidemiological Studies

The importance of surveillance is unquestionable. However, current large-scale, multicenter surveillance methods are prone to errors and limitations [39]. The interpretation of changes in exposure over time and the utilization of these data in epidemiological studies should be addressed in future studies, which may require a narrowed focus on diseases with an increased incidence.

Currently, there are two possible approaches to the use of genetic polymorphism data in future epidemiological studies. One approach involves the consideration of gene-environment interactions if genetic information involving developmental processes (e.g., AhR polymorphisms) is available. The other approach involves the consideration of polymorphisms in phase I and phase II metabolic enzymes when evaluating the accumulation of lipophilic chemicals in the body.

Finally, an accurate risk assessment depends on an accurate exposure assessment. Therefore, descriptive studies of the individual exposure level are important. The effects of socioeconomic factors on the incidence of birth defects related to chemical exposure can only be clarified through an epidemiological analysis.

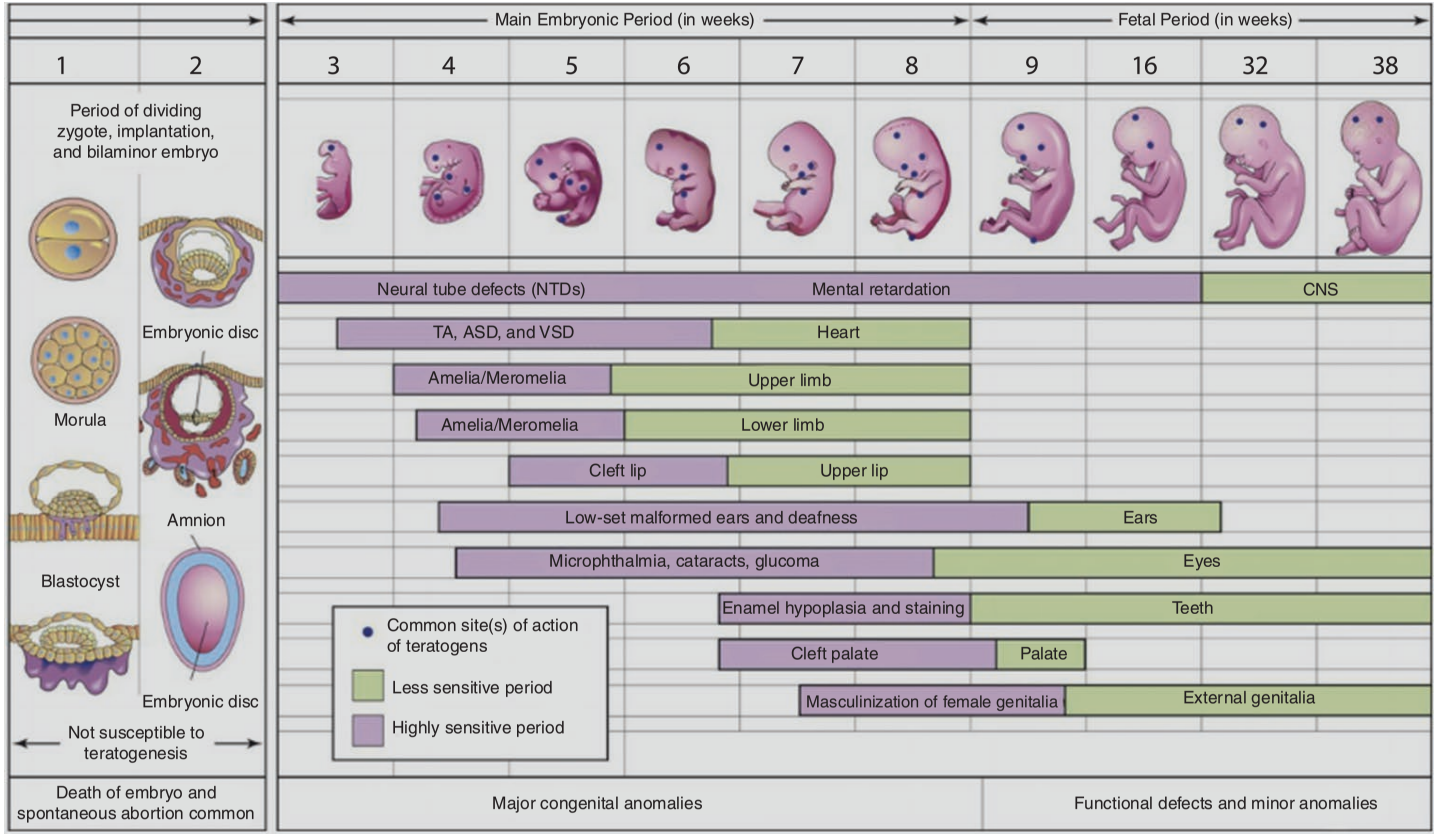

Fig. 3.2 Critical periods in human prenatal development [6]

3.8 Conclusions

We review previous epidemiological studies concerning environmental chemical exposure and birth defects. Many case–control studies had the limitation due to poor exposure assessment. Even previous large-scale prospective studies, i.e., the Norwegian cohort study, showed ambiguous results due to small sample sizes. In terms of the risk assessment, it is difficult that epidemiological study indicates the hazard identification including the dose-response relationship. Descriptions of the disease prevalence and individual chemical exposure levels are important roles of reproductive epidemiological study.

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