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Environmental Exposures and Development

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Structured Abstract

Purpose of Review—Summarize recent studies exploring the relationship between paternal and maternal environmental exposures to chemicals before, at the time of and after conception to adverse developmental outcomes including; preterm birth, death, structural and functional abnormalities and growth restriction.

Recent Findings—Recent studies have demonstrated that human pregnancy and development is vulnerable to environmental exposures of the father and mother to chemical, biological and physical agents. Exposures associated with adverse developmental outcomes include; air and water pollution, chemicals in foods, occupational exposures, agricultural chemicals, metals, persistent and volatile organics. Developmental endpoints which are linked with these exposures include; growth restriction, functional abnormalities, structural abnormalities, preterm delivery and death. Despite this general understanding we still have incomplete knowledge concerning most exposures and the biological interactions responsible for impaired development and preterm delivery.

Summary—While single genes and individual chemical exposures are responsible for some instances of adverse pregnancy outcome or developmental disease, gene-environment interactions are responsible for the majority. These gene-environment interactions may occur in the father, mother, placenta or fetus suggesting that critical attention be given to maternal and paternal exposures and gene expression as they relate to the mode of action of the putative developmental toxicant both prior to and during pregnancy.

Keywords

Birth defects; developmental disability; fetal death; neonatal death; functional disability; growth impairment; occupational exposure; environmental exposure; chemical; biological; physical agents; gene-environment; development; life-course; maternal; paternal; air pollution; water pollution

Introduction

Developmental diseases (fetal and neonatal death, structural alterations (birth defects), functional alterations, growth restriction and preterm delivery (1-3)) account for more than 25% of infant mortality and morbidity (2,4,5). The etiology of many developmental disorders is poorly understood, consequently, it is thought that infections, maternal or paternal health

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and genetic factors, drugs, over the counter medications, abused substances, environmental or occupational exposures are responsible (6-10).

This increases concern about maternal and paternal environmental exposures (5,11,12), and natural or terrorist inflicted disasters on pregnancy outcome and developmental health (13-17). Adding to these concerns have been publications evaluating the capabilities of surveillance systems in the United States to identify emerging developmental diseases (18, 19), and information on human body burdens of an enlarging list of chemicals, many suspect as developmental hazards (20)

Given these concerns it is important to understand the methods by which environmental exposures, genetic factors and adverse developmental outcomes have been assessed. This review summarizes recent selected publications from 2000 through 2009 concerning environmental chemical exposures and impact on human developmental outcomes.

The Etiology of Developmental Diseases

Estimates of the etiology of developmental diseases (1,21) have evolved as our understanding of developmental processes and environmental exposures has progressed (Table 1).

It is clear that definitions used and duration of follow-up has substantial impact on infants identified as having a developmental disorder (24,25). Initial work in experimental embryology and developmental biology used single agents to disrupt developmental processes, demonstrating vulnerability to a range of exposures (10). As our understanding of developmental biology and toxicology improved it was recognized that interactions between exposures and maternal/paternal health or fetal/placental genetic constitution could play a role (23,26). While much still remains to be understood, current data suggests that developmental abnormalities are predominantly the result of biological-environmental interactions (27,28). However, maternal or paternal genetic factors (23) as well as maternal or paternal (29,30) exposures to developmental toxicants will still contribute to developmental disease (28,31, 32)

Many surveys of developmental disease focus on assessment at birth, with attention to structural abnormalities and little attention to functional characteristics which can only be evaluated over time (33-36). Unfortunately, developmental disease characterized at birth only identifies ~1/3 of those with a structural abnormality (37-39), even those with life-threatening cardiovascular malformation (40) and will miss most functional abnormalities. Additionally, focusing on assessments at birth does not represent the impact of developmental disease over the life-course (24,25,41,42).

Exposure Characterization

A significant challenge in describing associations between environmental exposures and developmental outcomes is characterizing exposures as they relate to relevant developmental windows (43-47). For persistent chemicals such as dioxin, lead and organochlorine pesticides, fetal exposure can result from parental exposures prior to conception. Paternal exposures may contribute to fetal risk through mutagenic and epigenetic mechanisms involving the sperm, and the chemical can also be carried in semen (11,30,48).

Exposure characterization can be derived from questionnaire data, environmental monitoring, personal monitoring or measurement of exposures or metabolites in blood, hair, urine, or expired air. Improvements in exposure characterization is critical (49,50) It is also essential to characterize biological factors in the pathways that influence disposition of, and response to the environmental pollutants.

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Over the past decade there has been interest in personal monitoring, biomarkers and physiologically based models to refine exposure characterization. An example of use of a biomarker for monitoring PAH exposure during pregnancy is urinary 1-hydroxypyrine (51). Recently a detailed comparative analysis of physiologically based models has been conducted, and example utilized for characterizing drug exposure (52,53).

Methods for defining prenatal exposure to flame retardants found in fabrics as well as other exposures, the class of chemicals called polybrominated diphenyl ethers (PBDEs) have been developed and the exposures during pregnancy and childhood summarized (54) This class of chemical is a concern because of diverse routes for exposures including indoor air, because body burdens of these lipid-soluble chemicals are greater in the North America than other regions of the world, and because of neurodevelopmental toxicity (55).

Exposures to polychlorinated biphenyls (PCB) are a concern for neurodevelopmental toxicity including; cognitive, motor and behavioral (56). One approach to define potential risk is analysis of body burdens of the PCBs among women of reproductive age (56) (20). Analysis of CDC data demonstrates the decrease in body burdens and suggests specific PCB congeners to follow with respect to prenatal exposure and potential developmental consequence.

Abnormal Developmental Outcomes

Five health outcomes comprise the spectrum of developmental disorders: death, structural abnormalities, functional abnormalities, alteration of growth and preterm birth (1,9,57-59). (Table 2)

Gestation length is included because rates of prematurity are increasing, there is evidence gestational length is altered by environmental exposures (3,81-86), gestation length and developmental disease appear to have common causal pathways and it is a significant public health problem (82,83).

The recognition that exposures early in life may influence expression of disease across the life course, including the prenatal origin of diseases has drawn attention to these various developmental disorders and focused attention on the relationships beyond birth (87-89). This review will focus on methods to determine if developmental disease which emerges across pregnancy, after birth and early in childhood is linked with environmental exposure.

Paternal Exposures and Abnormal Development

Analysis of environmental impacts on development tend to focus on maternal exposures; however animal and human evidence suggests that is inadequate (11,29,30,90,91). Currently it is clear that offspring are vulnerable to all endpoints of developmental toxicity following paternal exposures (92-95), however much work remains to be done to fully understand this relationship (30).

Developmental Health Endpoints

One challenge of studying environmental impacts on developmental health is that outcomes vary with definition and duration of follow-up (Table 3).

One early assessment of prenatal influences on health and development was the British Perinatal Mortality Survey, conducted in 1958 (96). A similar birth-cohort study in the US, the Collaborative Perinatal Project (CPP), enrolled ~50,000 women from about the first trimester, through birth and followed their infants through 7 years of age (38,98,100,101). Both studies demonstrated increased diagnosis of developmental disease with longer follow. Recently a

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dataset has been created and analyzed using a composite index of adverse developmental outcome (2).

Recently the CPP has explored relationships between; PCBs and hypospadias and cryptorchidism (102) (none observed); PBCs and gestation length (103) (none observed); PCBs and growth restriction (103) (weak association); theobromine and preeclampsia (104) (none observed), heptachlor epoxide, hexachlorobenzene and hexachlorocyclohexane and cryptorchidism (105) (none observed), DDE and prenatal (85) or postnatal growth (106) (inverse relationship observed), as well as body size in adolescent males (107) (no relationship observed); DDE and gestation length (85) (inverse association observed). Additional contributions have come from use of the data for biostatistical methods development; impact of previous reproductive history (108,109), structural defects, polymorphisms in metabolizing enzymes and exposures (110) (association observed for some enzymes).

Growth

Environmental exposures associated with abnormal growth include; indoor air pollution from biomass fuel combustion (111) (questionnaire data); benzene (112). Exposure to particulates (PM2.5) and NO2 is associated with increased risk for growth restriction (113) (linked birth certificates with LMP and environmental monitoring data).

A survey of air pollutants (SO2, NO2, O3, CO and PM2.5) and impact on fetal growth was explored in three Canadian cities (Calgary, Edmonton, and Montreal) (114). Exposure was determined from air monitoring stations and birth data from vital statistics. The data suggested an inverse relationship between exposure to NO2, CO and PM2.5 and fetal growth. A similar study in Brisbane, Australia (115) measuring fetal growth and NO2, PM10 and O3 did not observe an inverse relationship between these pollutants and proxy measures for fetal growth (head circumference, crown-heel length, and small for gestational age). Differences in air pollutant composition may account for this as NO2 concentrations were higher in Canada and O3 concentrations higher in Brisbane.

Several studies have demonstrated ethnic differences in response to PAH and fetal growth (63), with growth and gestational length is inversely related to PAH exposure among African-Americans but not Dominicans in New York City. Studies with personal monitoring demonstrated an association with PAH and perinatal growth restriction (116,117). While a study in S. Korea supports effects from exposures early in the pregnancy, a study in China finds a relationship only from exposures during the third trimester (118). Results from North America, where levels of pollution are lower, typically find an association between reduced birth weight and PM, but the findings are variable. Studies in California have found some association with PM, though in southern California not when adjusting for gaseous pollutants (119-121). There was no association between PM and low birth weight in a study in the northeastern United States (122), and a study in Canada found a small, but insignificant association with low levels of PM (123).

Collaborators in New York and Poland have contributed much to our understanding of air pollution and developmental disease. Recently they explored the role of prenatal particulate exposure (PM2.5) during pregnancy and growth (124) using personal exposure monitors. Previous work demonstrated that prenatal exposure to air pollutants is associated with growth impairment at birth (length, weight and head circumference), this work explored sex differences in response to prenatal exposure and growth. As PM2.5 levels increased fetal growth was impaired more in male than female fetus, other studies have suggested that the female was more sensitive to the effect of air pollution on birth weight, while males were more sensitive to effect of air pollution on preterm birth (125).

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A study by Hansen explored ultrasound characterization of fetal growth in relationship to air pollution (126); femur length, abdominal circumference, head circumference and biparietal diameter. Air pollution exposures were monthly averages of PM10, SO2, NO2 and O3. This study demonstrates that as distance from the air monitoring station increases, adverse effect on fetal growth diminishes, reinforcing the benefit of personal monitoring and biomarkers of exposure.

Paternal exposures before pregnancy and maternal exposures before and during pregnancy to welding and metal fumes and dusts were associated with adverse pregnancy outcome. Paternal exposures may be associated with premature delivery and maternal exposures with impaired growth and prematurity (60) (exposures defined by questionnaire data and health outcomes by pregnancy records).

The Danish National Birth Cohort Study (DNBC) has evaluated maternal fatty fish consumption (127) exposure to PCBs, and fetal and placental growth (128). They observed that greater ingestion of fatty fish was associated with greater concentrations of PCBs and greater concentrations of PCBs was associated with impaired fetal and placental growth. The DNBC has also explored the association between the persistent organic pollutants perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) on fetal and placental growth (129) demonstrating an inverse association between PFOA and fetal growth.

Drinking water may contain diverse array of pollutants including products resulting from disinfection treatment. Studies using infrequent ecological exposure assessment have suggested adverse developmental consequences. A study collected water samples every week from the distribution system utilized by the subjects, and was unable to discern a relationship between drinking water exposures and developmental outcomes (130).

Functional Abnormality

Over the past three decades, beginning with the research on lead and neurodevelopmental abnormalities greater attention has been given to functional abnormalities (74). Blood lead levels during pregnancy are associated with increased risks for pregnancy associated hypertension (131)), and ongoing research suggests that there is no threshold for fetal neurodevelopmental impacts (132) both cognitive and behavioral.

While it is clear that postnatal exposure to air pollution can alter pulmonary function, it is not know if similar exposures during pregnancy can alter pulmonary development and/or function in children later in life. A study by Latzin et al (133) explored this question using a birth cohort in Bern Switzerland and Swiss air pollution monitoring data, with lung function assessed at 5 weeks of age, demonstrating that PM10 exposure was associated with higher minute ventilation and tidal flows postnatally.

Airborne exposures to PAH are found in smoking and urbanized environments (134), and associated with reduced growth (63,65,135,136) and shortened gestation (46). Analysis by Perera and colleagues extends the impact on functional deficits demonstrating an inverse relationship between PAH and IQ (134). Exposure to increased PAH concentrations following the World Trade Center terrorist incident altered neurocognitive development (137).

Prenatal mercury exposure (organic mercury, methyl mercury) has been known to be a developmental toxicant (producing cognitive, attention, behavior and motor alterations) for humans since the exposures in Minamata Japan in the 1950's as documented by the photographer W. Eugene Smith (138,139). Prenatal mercury exposure is a concern because a common route is via fish, which also provides health benefits and it appears that there is no threshold for neurodevelopmental toxicity (140). However, the consequences of exposure to

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organic mercury may be modified by other environmental factors, including; diet, social factors, genetic constitution, exposure to other chemicals and lifestyle (141). An environmental chemical thought to interact with organic mercury in altering developmental consequences are the PCBs, themselves known to be developmental toxicants (55). In designing future studies it will be necessary to include these complex interactions as they will both buffer and exacerbate the adverse effects of many different chemical exposures on developmental endpoints.

Exposure to triazine and other herbicides, common contaminants of rural drinking water sources, may also lead to decreased fetal growth. An investigation of women living in a region of Iowa with raised levels of triazine, metolachlor, and cyanazine herbicides in the drinking water found that their offspring were more likely to suffer from growth restriction than infants born to women in other parts of the state (142). A Polish study similarly found that exposure to triazine herbicides in combination with other pesticides resulted in increased low birth weight rates, even when controlling for length of pregnancy (143). French researchers found that atrazine levels in municipal drinking water throughout pregnancy were not associated with increased risk of small-for-gestational age birth, but that the risk of SGA birth increased when the third trimester occurred in whole or in part during the period of May through September, when atrazine levels typically peak (84).

Structural Abnormality

Structural abnormalities have traditionally been a focus of attention for abnormal pregnancy outcomes research, the idea that they may be related to gene-environmental interactions has become increasingly apparent, and adds to the complexity of experimental design (144,145). In addition, the weight of evidence that air pollutants add to this burden of developmental disease is increasing (144,146), although it is not always consistent (147). Maternal smoking has also been associated with clubfoot (148), tracheoesophageal-fistula (149,150), renal agenesis (151). One especially interesting area has been the analysis of polymorphisms, smoking and structural malformations (152)

Analysis of prenatal exposure to SO2 and PM suggested relationships between PM and nervous system anomalies (146). Interestingly, structural abnormalities may increase following disasters (17). Paternal exposures during recent wars has been a concern with respect to birth defects, recent analysis suggests no impact on structural anomalies or pregnancy loss (153).

Cardiovascular defects are a common endpoint for environmental exposure studies (154-158). Occupational exposures of male electronics workers prior to conception has been associated with increased risk for cardiovascular defects (78). Maternal occupational exposure to nickel did not increase risk of defects but occupational exposure to copper did (159). Other maternal occupations which do not appear to increase risk for abnormal pregnancy outcome based on the DNBC studies include hairdressers (160), laboratory work (with the exception of those exposed to radioisotopes) (161), and gardening and farming (162). Other investigators have however suggested associations between maternal laboratory work and malformations (163).

Cardiovascular defects have been associated with air pollution (158,164). Some studies have linked cardiovascular defects with maternal proximity to hazardous waste sites, but not all have observed that association (165), nor did proximity to municipal waste incinerators appear to be a risk factor for birth defects (166). Data from the Texas Birth Defects Registry found no association between hazardous waste sites and neural tube defects, but did observe an association between industrial sites and neural tube defects (167). Studies of trichloroethylene, a common water pollutant because of use as an industrial cleaning/degreasing agent suggests no relationship between exposure and cardiac defects (168).

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There is conflicting evidence concerning preconception or pregnancy exposures to agricultural chemicals and birth defects; studies in Ontario suggest an association between preconception exposure to cyanazine or dicamba and defects in male offspring (169). Agricultural chemicals are found in surface water with seasonal variation, providing an opportunity for evaluation of the ecological relationship between surface water concentrations and developmental disease including birth defects (170). Studies exploring proximity to specific crops (corn, soybeans) have observed an increased risk of limb defects in proximity to cornfields, with no increased risk associated with proximity to soybean fields (171). Analysis of urban versus rural residence suggests atrial septal defects more common in rural areas (172), with other studies suggesting ventricular septal defects more common in rural areas (173).

Human exposures to environmental chemicals which interact with the endocrine systems (endocrine disrupting chemicals) prior to or during pregnancy are of concern because of the role these systems play in development. Paternal exposures to polychlorinated and phenolic compounds and maternal exposures to heavy metals and phthalates (174) alter the developing human reproductive systems. One concern is development of the reproductive system, including hypospadias (175), which may represent an interesting malformation for assessment of gene-environment interactions, and appears to be increasing (176).

Death

Early studies described a relationship between PM10 (particles less than or equal to 10um in size) or PM2.5 and postneonatal mortality (177) and prenatal growth restriction (117,178). Exposure to PM in the North of England during the period 1962-1992 was not associated with the risk of stillbirth (179) (vital statistics and routine air monitoring data). PM10 was associated with increased postneonatal mortality and both PM sizes were associated with prenatal growth restriction; however chemical composition and individual exposures were not defined in these early studies.

Gestation Length

Exposure to pesticides has been correlated with preterm birth and reduced fetal growth (8). A study of agricultural organophosphate pesticides found a significant positive association between maternal exposure and growth retardation (180). This finding is supported by studies of inner city and minority populations exposed to indoor pesticides; exposure to chlorpyrifos was inversely associated with birth weight (181), the inverse association between chlorpyrifos and birth weight was highly significant when limited to those born before the EPA banned residential use of this pesticide. Those born later had much lower exposure (182).

Studies of organophosphate metabolite levels and fetal growth have been less conclusive; a study of multiethnic mothers living in New York City found no relation (183), and a study of Latina women living in an agricultural area did not find (180). The latter study did find an association between exposure and preterm birth, most clearly related to increasing exposure levels in the later part of pregnancy (184).

Airborne exposures to PAH are found in smoking and urbanized environments (134), and associated with reduced growth (63,65,135,136) and shortened gestation (46). Studies of preterm birth have found associations between preterm birth and PM in the Czech Republic (80), China (86), southern California, (119), Pennsylvania, (185), and California (186). The associations tend to be relatively small, though typically statistically significant (8).

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Conclusions

Maternal and paternal environmental exposures can produce human developmental disease including; preterm birth, growth restriction, functional or structural abnormalities or death. Our understanding of developmental diseases is changing; we recognize that environmental exposures during development can be expressed across the life of the individual, into adulthood (187). In addition, we now know that paternal exposures can result in developmental disease in their offspring (11,29). Of greatest concern, however, is the growing recognition that functional impacts of environmental exposures may not have thresholds (132). This means that the only reasonable approach is to keep environmental exposures for all individuals as low as possible.

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Highlighted references

188. Reference 2** presents an innovative approach to combining human vital statistics data to develop an integrated assessment of developmental disease)

189. Reference 8* a thoughtful, comprehensive review of the literature on environmental chemicals and reproductive and developmental health.

190. (Reference 11* review of our current understanding of paternal exposures and developmental diseases)

191. (Reference 12** analysis of methodological issues which need attention to improve our ability to assess reproductive and developmental impacts of environmental exposures)

192. (Reference 20** a frequently updated compilation of the concentrations of environmental chemicals found in humans in the US).

193. (Reference 31* provides a current review of genetic factors in preterm birth).

194. (Reference 40* provides a current review of cardiovascular defects with attention to recognition at birth and later in life, including postmortem diagnosis).

195. (Reference 50* provides a summary of issues in exposure characterization, methodological issues, health endpoint assessment and mode of action useful for thinking about design of epidemiological studies).

196. Reference 53* (good resource for literature and methodological approaches

197. Reference 56* (good resource for literature and methodological approaches

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198. Reference 81** (the issue of race in developmental disease has a long and complicated history, the approach and analysis by Kramer and Hogue provides a superb analysis of our current understanding and limitations in understanding

199. Reference 82** (while it has been observed for some time that a relationship exists between preterm birth and developmental disease this analysis represents a good resource for literature and methodological approaches

200. Reference 112(** personnel monitoring, this paper is an excellent example of contemporary monitoring needed for careful assessment of individual exposure)

201. Reference 113(* provides a good description of an approach to evaluate trimester of exposure on growth)

202. Reference 124(* demonstration of benefit of personal monitoring rather than ecological exposure estimation)

203. Reference 128 Reference ** demonstrating benefit of biomarker exposure characterization and ongoing utility of birth cohort studies with tissue samples available for measure of genetic and exposure biomarkers).

204. (Reference 130 ** provides the framework for a well designed exposure assessment in a drinking water pollution and fetal growth study)

205. Reference 131** (represents an excellent example of the utility of a birth cohort to explore an innovative question, maternal blood lead and pregnancy associated hypertension, and open a new area for scientific inquiry)

206. Reference 133 * an innovative question and methods exploring prenatal exposures and postnatal lung function

207. Reference 170* ecological analysis of atrazine, nitrates and other pesticides in surface water provides a fascinating starting point for more detailed analysis of agricultural chemical exposures to broad human populations and birth defects.

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Table 1

Estimates of the proportion of developmental disease by etiology.

Table legend: Year – approximate year or decade in which the estimate was made and during which the estimate was considered authoritative, Genetic or Chromosomal – proportion of developmental disease at the time of evaluation thought to be the result of genetic or chromosomal factors, Developmental toxicant – proportion of developmental disease at the time of evaluation thought to be due to a teratogen (chemical, biological or physical exposure or maternal health condition, eg age, diabetes or fever), Gene Environment – proportion of developmental disease at the time of evaluation thought to be the result of interaction between a teratogen and genetic factors, Unknown – proportion of developmental disease at the time of evaluation that could not be categorized with respect to etiology, NE – no estimate given.

Year	Genetic or Chromosomal	Developmental Toxicant	Gene Environment	Unknown	Comments
~1970	25%	10%	NE	65%	Early estimates by Wilson based on assessment of hospital and animal data (10,22)
~1990	17%	3%	37%	43%	Estimates by Nelson and Holmes based on ~70,000 deliveries (23)
~2007	10 – 30%	4–13%	20-49%	34 – 70%	Published literature and reference texts (1)
Anticipated	~15%	~5%	~80%		These figures represent the authors' assessment of causation of developmental abnormality.

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Table 2

Developmental endpoints vulnerable to environmental disruption

Category	Description and comment
Growth	Growth in all its manifestations (body size, birth weight and rate of growth) is sensitive to environmental insults (60, 61). While growth is sensitive, it is not specific to environmental exposures, because many factors influence growth, including; genetic, nutrition, maternal disease, tobacco smoke, alcohol, maternal education and socioeconomic status. In characterizing fetal and neonatal growth special attention needs to be given to gestational and postnatal age (62-67).
Functional abnormality	Functional abnormalities, typically identified after birth, may be a consequence of environmental exposure prior to or during pregnancy. Neurodevelopmental impairment resulting from prenatal lead exposures represents an example (33,68-73). Either paternal or maternal lead exposure increases the risk of spontaneous abortion and impairs fetal growth and postnatal neurodevelopment. Because maternal bone lead is mobilized during pregnancy, exposures producing abnormal fetal development may have occurred many years prior to the pregnancy (73). Other functional abnormalities are included in the emerging literature on developmental origins of health and disease (41,44,74,75).
Structural abnormality	Traditional concern about exposures in pregnancy has focused on birth defects or structural abnormalities. There are ~50 chemicals, ~15 infectious agents and several physical agents known to produce human structural malformations (1,7,9,76,77).
Death	A common developmental consequence of a chromosomal or genetic abnormality is embryonic, fetal or neonatal death (10). There are data suggesting an association between certain paternal occupations and increased risk of mortality (11,78). Additionally, there are data linking a variety of environmental exposures with embryonic, fetal and neonatal mortality (8,79).
Gestational length	Prematurity has not been a traditional developmental endpoint, however, given the increasing evidence that it is susceptible to environmental exposures (3), the life-long consequences of prematurity, and the persistence of prematurity as a public health problem it will also be considered as an endpoint of abnormal development in this review (80,81).

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Table 3

Developmental endpoints in pregnancy cohort studies and population surveys

Table legend: Data at birth represent all analysis beginning at ~5 lunar months of pregnancy, Growth abnormalities are those born <2500 grams, Functional abnormalities represent those with an abnormal neurological exam at 1 year of age, Structural abnormalities are those identifiable by an examination of the infant over the first 4 years of life, Death includes those born at 5 or more lunar months (includes stillbirth, perinatal deaths and those who were “fresh stillbirths”), Neonatal deaths are those born alive who died in the first 30 days of life, Premature are those born less than 37 completed weeks of pregnancy.

Pregnancy Cohort or Population Studied	Growth	Structure	Function	Death	Premature
British Perinatal Mortality Survey (1958) ~17,000 births (96,97)					
Developmental Endpoints at birth in singleton pregnancies	6.7%	2.4%		3.6%	9.4%
Not walking by 18 months			4.3%		
Not talking by 2 years			6%		
Developmental endpoints at 7 years		3.7%		5.2%	
USA Collaborative Perinatal Project (1959 – 1965) ~50,000 births (38,98,99)					
Developmental Endpoints at Birth in singleton pregnancies	10.4%	4.5%	1.7%	8.7%	17.7%
Developmental endpoints at 1 year		15.6%		9.5%	
Developmental endpoints at 7 years		20.2%		10.0%	
Developmental Endpoints at Birth, Florida linked datasets (1997 – 1998) (2)					
Developmental endpoints at birth in singleton pregnancies	8%	2.4%			
Abnormal condition			6.7%		
Developmental delay or disability			2.1%		