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Review Article

Risk of Congenital Malformations: A Systematic Review

Dr. Kishore Kumar Soni*[a] , Dr. Sushil Singh[a]

Department of Epidemiology, National Institute for Research in Environmental Health, Indian Council of Medical Research, Bhopal (M.P.), India

Corresponding author. Email address: k.soni2310@gmail.com (Kishore Kumar Soni)

Abstract: Congenital malformations (CM) are a public health issue, because they cause infant mortality, chronic disease and disability. The origin can be genetic, environmental or unknown causes. Among environmental contaminants, pesticides stand out. Many different causes of malformations have been established. The surveillance of a consecutive population of births, including stillbirths and elective terminations of pregnancy because of fetal anomalies, can identify each infant with malformations and determine the frequency of the apparent etiologies. CM abnormality of structure and, consequently, function of the human body arising during development. This large group of disorders affects almost 5 percent of infants and includes several major groups of conditions.

Keywords: Congenital Abnormalities, Chromosome Abnormalities, Ecology, Infections, Diseases, Drugs, Spontaneous Abortion

1. Introduction

A congenital malformation (CM) or birth defect is defined a s a s tructural o r chromosomal malformation with a significant i mpact o n the health and development of a child. [1] It contributes significantly to infant mortality and morbidity . Over the years, the proportion of infant mortality due to CM has increased significantly from 15.1% in the 1970s to 22.1% in the late 1990s, which makes it the leading cause of infant mortality. [2, 3] With regard to morbidity, congenital malformations account for 12% of all pediatric hospitalizations. This subset of patients with CMs has longer hospital stays and incurs higher hospitalization costs, compared to other patients. [4] In the United States population, an estimated 2.3% of cases of premature death and disability, as measured by disability-adjusted life years , occurs because of congenital abnormalities. [5] Based on these findings, i t i s apparent that CM is a major public health problem because of its significant contribution to mortality and morbidity. Studies published worldwide report a birth prevalence of CM that ranges 20–55 per 1000 live births with significant variation, depending on the demographics of the study population , the study design, and the method of case ascertainment. [1] [6–10] Most prevalence rates are estimates derived from clinical studies of small sample populations or population-based studies from a specific geographic location. In addition, there is a significant variation in the inclusion criteria or in the definition of CM in these different studies, which makes it difficult to compare data from these different studies. There has been a tremendous progress in the prenatal diagnosis of CM because of improvements in fetal ultrasound and prenatal genetic testing . This allows parents the choice of terminating the pregnancy. In the past 2 decades, there has also been a concordant increase in the rate of termination of pregnancy for fetal anomaly. [10, 11] Some studies have shown that Corresponding author. Email address: k.soni2310@gmail.com (Kishore Kumar Soni) prenatal folic acid and other multivitamin supplementation significantly decrease the birth prevalence of some CMs. [6–8] We hypothesized that these factors altered the birth prevalence of CM, which rendered estimates from older studies obsolete.

2. Epidermiology

Major congenital malformations are abnormalities that have medical, surgical, or cosmetic significance . They occur in approximately 2 to 4 percent of livebirths [12, 13] and are more common in stillborn spontaneous miscarriages. The overall prevalence of most major birth defects does not vary much across ethnic groups [14, 15]. However, the risk for different types of malformations is variable and may be related to genetic susceptibilities, as well as cultural and social differences that can influence exposures (eg, increased presence of neural tube defects in populations that have dietary deficiency of folic acid) [15–17] . The prevalence of most major birth defects has remained constant, although some have shown a significant increase such as gastroschisis [18] . Minor anomalies are seen more frequently than major malformations. Disruptions are vascular defects that result from destruction of or interference with normal development. The prevalence of disruptions (see 'Disruptions'below) is dependent upon the type of anomaly but can range from 0.5 to 4 per 10,000 [12, 13] . Deformations (see 'Deformations' below) are the result of modification of normal structures, are more common in the limbs and head, and are seen in approximately 3 percent of newborns [19] .

3. Causes of Congenital Malformations

The cause of congenital malformations can be divided into 3 categories: unknown, genetic, and environmental Figure 1. The cause of a majority of human malformations is unknown. A significant proportion of congenital malformations of unknown cause is likely to have an important genetic component. Malformations with an increased recurrent risk, such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases, pyloric stenosis, hypospadias, inguinal hernia, talipes equinovarus, and congenital dislocation of the hip, fit in the category of multifactorial disease as well as in the category of polygenic inherited disease. [20, 21] The multifactorial/threshold hypothesis postulates the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors. Spontaneous errors of development may account for some of the malformations that occur without apparent abnormalities of the genome or environmental influence. Spontaneous errors of development may indicate that we never achieve our goal of eliminating birth defects because a significant percentage of birth defects are attributable to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation. It is estimated that the majority of all conceptions are lost before term, many within the first 3 weeks of development. The World Health Organization estimated that 15% of all clinically recognizable pregnancies end in a spontaneous abortion, 50% to 60% of which are attributable to chromosomal abnormalities. [22, 23] Finally, 3T to 6% of offspring are malformed, which represents the background risk for human maldevelopment Table 1 .

Table 1: Background Reproductive Risks Per Million Pregnancies

Reproductive Risk	Frequency
Immunologically and clinically diagnosed spontaneous abortions per million conceptions	350 000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies	150 000
Genetic diseases per million births	110 000
Multifactorial or polygenic genetic environmental interactions) (eg, neural tube defects, cleft lip, hypospadius, hyperlipidemia, diabetes)	90 000
Dominantly inherited disease (eg, achondroplasia, Huntingtons chorea, neurofibromatosis)	10 000
Autosomal and sex-linked genetic disease (eg, cystic fibrosis, hemophilia, sickle-cell disease, thalassemia)	1200
Cytogenetic (chromosomal abnormalities) (eg, Down syndrome [Trisomy 21]; Trisomy 13, 18; Turner syndrome; 22q deletion)	5000
New mutations*	3000
Severe congenital malformations†(as a result of all causes of birth defects: genetic, unknown, environmental per million births)	30 000
Prematurity/million births	40 000
Fetal growth retardation/million births	30 000
Stillbirths (>20 wk)/million births	2000–20 900
Infertility	7% of couples

* The mutation rate for many genetic diseases can be calculated. This can be readily performed with dominantly inherited diseases when offspring are born with a dominant genetic disease and neither parent has the disease (reference).
†Congenital malformations have multiple causes, including a significant proportion that are genetic.

3.1 Genetic Disorders

3.1.1 Chromosomal Abnormalities

Almost every cell in our body contains 23 pairs of chromosomes, for a total of 46 chromosomes. Half of the chromosomes come from our mother, and the other half come from our father. The first 22 pairs are called autosomes. The 23rd pair consists of the sex chromosomes, X and Y. Females usually have two X chromosomes, and males usually have one X and one Y chromosome in each cell. All of the information that the body needs to grow and develop comes from the chromosomes. Each chromosome contains thousands of genes, which make proteins that direct the body's development, growth, and chemical reactions. Many types of chromosomal abnormalities exist, but they can be categorized as either numerical or structural. Numerical abnormalities are whole chromosomes either missing from or extra to the normal pair. Structural abnormalities are when part of an individual chromosome is missing, extra, switched to another chromosome, or turned upside down. Chromosomal abnormalities can occur as an accident when the egg or the sperm is formed or during the early developmental stages of the fetus. The age of the mother and certain environmental factors may play a role in the occurrence of genetic errors. Prenatal screening and testing can be performed to examine the chromosomes of the fetus and detect some, but not all,

types of chromosomal abnormalities. [24]

3.1.2. Single Gene Defects

These disorders are the result of a single mutant gene and follow the Mendelian rules, either as autosomal dominant, autosomal recessive or Xlinked traits. Many of the more than 8,000 disorders identified are rare and others may not show morphological defects [23] . Known single gene defects account for approximately 8% of congenital malformations at term. Autosomal dominant gene defects give rise to recognizable effects in heterozygous individuals, usually with an equal sex distribution in about 50% of the offspring. Some of these disorders, such as Huntington disease and some of the autosomal dominant cerebellar ataxias, do not produce recognizable disease before adult life, whereas others, such as achondroplasia and thanatophoric dysplasia, are recognizable at birth and may be detected prenatally by ultrasound examination.When an autosomal disorder occurs with unaffected parents, a new mutation is not likely to recur in siblings. Gonadal mosaicism, reduced penetrance and variable expression may represent a small but real recurrence rate. Small deletions, responsible for contiguous gene syndromes, may segregate as dominant mutations.

3.1.3. Mitochondrial DNA mutations

The known effects of mitochondrial DNA (mtDNA) mutations, transmitted by the mother, are mostly metabolic and apparently degenerative diseases. Since mitochondria are present in all cells with nuclei, every tissue or organ may be involved in mtDNA mutations. Most frequently, the brain, the heart and skeletal muscles are affected; therefore, these disorders are usually described as mitochondrial encephalomyopathies. A better term may be defects of oxidative phosphorylation (OXPHOS defects), since all tissues and organs may be affected.

3.1.4. Multifactorial Disorders

Common congenital malformations such as cleft lip with or without cleft palate and neural tube defects have a familial distribution consistent with multifactorial inheritance, suggesting that the disease is due to the interaction of different genes and environmental factors. Such disorders occur with increased frequency among family members of an affected individual in an inverse frequency to their relationship.

3.2. Environmental Causes

Teratogenic factors have an adverse, disruptive effect on an embryo or a fetus between fertilization and birth. The term teratogen is usually limited to environmental agents, such as drugs, radiation and viruses. The disruptive effects include congenital abnormalities, embryonic and fetal death, intrauterine growth retardation (IUGR) and mental dysfunction. The fetus is less sensitive to morphological alterations than the embryo, but changes in functional capacity, intellect, reproduction or renal function may occur. Mechanical effects may be due to vascular disruptions and the amnion disruption sequence.

3.3. Chemicals, Drugs, Hormones and Vitamins

Drugs with a known teratogenic effect are relatively few [25, 26] . Examples include alcohol, cocaine, thalidomide, lithium, retinoic acid, warfarin and anticonvulsant drugs **Table 2.**

Table 2: Some drugs and infectious agents with teratogenic effects

Drugs Alcohol	In- creased cell death	Fetal alcoholsyndrome: IUGR;CNS abnormalities; characteristic facialexpression	Ultrasound for growth, anomalies
Aminopterin andantifolates	Dis- rupted celldivi- sion	IUGR; skeletaldefects;malformations ofthe CNS, notably meroanencephaly	Ultrasound foranomalies
Cocaine	Vasocon- striction	IUGR; prematurity;microcephaly;cerebral infarction; neurobehavioural disorders	High-riskcare
Isotretinoin (13-cis-retinoic acid or Accutane)	Exces- sive celldeath	Retinoic acidsyndrome:craniofacialmalformations; NTDs;cardiovasculardefects	Ultrasound
Lithium carbonate		Right heart defects;increased incidenceof NTDs	Fetal echo- cardography
Methotrexate	In- creased celldeath	Multiple anomalies, especially skeletal (face, skull, limbs,vertebral column);hydocephalus; meningomyelocele; cleft palate	Ultrasound
Phenytoin (Dilantin)	In- creased celldeath	Fetal hydantoinsyndrome: IUGR; microcephaly; mental retardation;cleft lip/palate	Ultrasound
Thalidomide	Abnor- mal celldivi- sion	Abnormaldevelopment limbs(meromelia, amelia)	Ultrasound

Retinoic acid syndrome malformations first appeared after the introduction of Accutane (13-cis-retinoic acid), a drug used for the treatment of severe cystic acne [27] . Although the retinoids (the normal biologically active retinoic acid and related compounds such as vitamin A, the dietary precursor of retinoic acid) had been long known to be potent teratogens, and the drug Accutane was not to be taken during pregnancy,. Maternal chronic or excessive alcohol consumption, in particular during the first trimester of pregnancy, may lead to the fetal alcohol syndrome [26, 28]. The newborn baby is small and may show craniofacial anomalies. Brain anomalies are variable and unspecific, in contrast to the more common craniofacial anomalies. Hydrocephalus, agenesis of the corpus callosum, neural tube defects and porencephaly may be found [28] , and even holoprosencephaly has been noted [29] .

3.4. Maternal Conditions

A variety of maternal diseases, either genetic or acquired, and deficiency states may affect the developing embryo. In other disorders, such as epilepsy, the therapy is most likely damaging.

Maternal phenylketonuria (PKU) is the best documented example of a genetic disorder in the mother affecting her offspring when her serum phenylalanine level is elevated during pregnancy. Without a strict diet throughout pregnancy, the children of women with PKU have severe mental retardation, microcephaly and heart defects.

Maternal diabetes mellitus type 1 is a risk factor for all sorts of congenital anomalies. Good control can prevent birth defects, however. A high incidence of Down syndrome and caudal regression syndrome [30] have been noted. Maternal connective tissue disorders, such as osteogenesis imperfecta and Ehlers– Danlos syndrome, are risk factors for early amnion disruption sequence. **Radiation effects** on the developing brain were extensively studied after the atomic bombings of Hiroshima and Nagasaki .The most conspicuous effect on brain development is an increased occurrence of severe mental retardation, with or without microcephaly at specific gestational ages.

Hyperthermia during pregnancy can cause embryonic death, abortion, growth retardation and developmental defects [31] . Cell proliferation, migration, differentiation and apoptosis are all adversely affected by elevated maternal temperature, showing some similarity to the effects of ionizing radiation. The development of the CNS is especially vulnerable: a 2.5 ◦C elevation for 1 h during early neural tube closure in rats resulted in an increased incidence of craniofacial defects, whereas 2–2.5 ◦C elevation for 1 h during early neurogenesis in guinea pigs caused an increase in the incidence of microcephaly [31].

3.5. Infectious Agents

A number of infectious agents can affect the fetus, producing a range of effects from structural anomalies to mental retardation . Classically, the TORCH group of infections (toxoplasmosis, rubella virus, cytomegalovirus and herpes/varicella virus) are screened for in the case of permanent cerebral impairment in the neonate [32] . But also infections with human immunodeficiency virus (HIV) and other agents may lead to permanent fetal injury. Microcephaly, hydrocephalus, hydranencephaly and cerebral calcifications are the sequelae most often found in the TORCH group of infections , and lead to developmental delay, psychomotor retardation and seizures. Microphthalmia is also often noted in toxoplasmosis, rubella and HIV infection. Often the infection ultimately leads to destruction of cerebral tissue with the formation of cystic spaces in the brain.

4. Determining the cause of congenital malformations:

1. No teratogenic agent should be described qualitatively as a teratogen, because a teratogenic exposure includes not only the agent but also the dose and the time in pregnancy when the exposure has to occur.
2. Even agents that have been demonstrated to result in malformations cannot produce every type of malformation. Known teratogens may be presumptively implicated by the spectrum of malformations that they produce. It is easier to exclude an agent as a cause of birth defects than to conclude definitively that it was responsible for birth defects, because of the existence of genocopies of some teratogenic syndromes.
3. When evaluating the risk of exposures, the dose is a crucial component in determining the risk. Teratogenic agents follow a toxicologic dose-response curve. This means that each teratogen has a threshold dose below which there is no risk of teratogenesis, no matter when in pregnancy the exposure occurred.
4. The evaluation of a child with congenital malformations cannot be performed adequately unless it is approached with the same scholarship and intensity as the evaluation of any other complicated medical problem.
5. Each physician must recognize the consequences of providing erroneous reproductive risks to pregnant women who are exposed to drugs and chemicals during pregnancy or alleging that a child's malformations are attributable to an environmental agent without performing a complete and scholarly evaluation.
6. Unfortunately, clinical teratology and clinical genetics is not emphasized in medical school and residency education programs, but pediatricians have a multitude of educational aids to assist them in their evaluations, which includes consultations with clinical teratologists and geneticists, the medical literature, and the OMIM web site.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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