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Review Article

Birth defects: Risk factors and consequences

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Abstract. Birth defects (BDs) or congenital anomalies include all structural and functional alterations in embryonic or fetal development resulting from genetic, environmental or unknown causes, which result in physical and/or mental impairment. BDs occur in about 3% of newborn babies and in most cases of pregnancy loss. BDs are a very complex and heterogeneous group of single or multiple changes that, in most cases, are of unknown etiology. Among the risk factors are advanced maternal and paternal ages, parental consanguinity, teratogenic agents such as infectious agents and drugs, and poor nutrition, in particular folic acid deficiency. One of the consequences of these defects is the high death rate within the first year of life. Information on BDs is becoming increasingly more important throughout the world so that preventive measures can be taken. Knowledge of BDs enables the development of therapeutic and preventive strategies besides adequate genetic counseling.

Keywords: Congenital anomalies, congenital malformation, chromosomal abnormalities

1. Classification and etiology

Congenital anomalies or birth defects (BDs) include all functional and structural alterations in embryonic or fetal development resulting from genetic, environmental or unknown causes that originate during pregnancy, are present at birth and that cause physical or mental impairment [1].

BDs are a very complex and heterogeneous group of single or multiple changes that, in most cases, are of unknown etiology. The genetic etiology of BDs is relatively well known and includes monogenic causes (about 20% of cases), chromosomal alterations (approximately 25%), which may be numerical or structural and multifactorial causes (about 50% of cases). The etiology of environmental factors responsible for disruptive effects exists in approximately 5% of cases and these cases are the most difficult to investigate. Aneuploidy is the cause of BDs in more than 30% of all cases; most are monosomy of chromosome X and trisomies of chromosomes 16, 21 and 22, and are responsible for about 60% of gestational losses. Although trisomies of chromosomes 13, 18 and 21 are responsible for many pregnancy losses, they also have an impact at birth, as they are present in approximately 0.3% of all births together with trisomy of chromosome X [2–4].

Thus, genetic factors are among the most common causes of BDs and are one of the main causes of infant mortality. BDs are observed in about 3% of newborns and are the cause of 50% of spontaneous neonatal deaths [5–8].

Stillbirths occur in between 1 in 1000 and 1 in 160 pregnancies and are related to maternal, fetal, and placental causes; in half of the cases, no cause can be determined. BDs occur in 14% of these cases with genetic diseases being a common cause [9,10]. Stillbirths can

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typically be defined according to gestational age at birth: early stillbirths (20–28 wk gestation) and late stillbirths (>28 wk). However, there is no standard international classification system that takes into account cause of death, nor is there agreement about the lower limits of birth weight or gestational age to define stillbirth, making comparisons of causes, and rates over time or between sites problematic [11]. Many systems include both stillbirths and neonatal deaths. These variations in the lower gestational age limit the ability to compare findings between different studies [12].

According to Reece [8], an estimated 185,000 children are born with BDs in the United States annually and about 8 million worldwide. Studies in underdeveloped and developing countries are sparse and are usually hospital-based and not population-based. In Brazil, for example, between 1.7% and 5% of newborns have BDs; this variation is probably a reflection of differences in the methodologies used to classify BDs [13–16].

As classification into subgroups is complex, the most commonly used methods are based on severity and categorize BDs into major and minor disorders. According to the classification of Opitz, anomalies that result in the impairment of health, those that require medical or surgical treatment, or have aesthetic and social impact, such as anencephaly, cleft lip or palate, hydrocephalus and heart defects are considered major. These disorders are responsible for high morbidity and mortality rates and physical and intellectual disabilities [17]. Minor birth defect, such as polythelia (supernumerary nipples), micrognathia and clinodactyly, do not require medical intervention although they may, in some individuals, be aesthetically important. These minor symptoms serve as indicators of more serious problems such as the occurrence of three or more minor anomalies can signify the presence of malformation syndromes [18]. Another classification, proposed by Czeizel et al. [19] divides BDs in three groups: lethal, when the defect causes stillbirth or infant death in more than 50% of cases; severe if, without medical intervention, the defect causes handicap or death; mild if the defect requires medical intervention but life expectancy is good. Lethal and severe defects together constitute major congenital abnormalities. It is clear that the use of different methods can affect the percentage of cases.

The individual may present with single or multiple defects that occur as components of syndromes, sequences or associations (complex) [19]. With rare exceptions, the clinical diagnosis of malformation patterns cannot be conducted based on a single defect. Even if it is a rare event, it may be characteristic of several different syndromes. The specific diagnosis usually depends on the recognition of the global pattern of the defect and detection of minor defects can be as useful as major malformations [17].

2. Risk factors

There are a number of risk factors related to the appearance of BDs in progeny. Advanced maternal and paternal age (more than 35 and 40 yr, respectively) constitutes the most studied risk factors. A progressively greater number of women are postponing motherhood, resulting in a gradual increase in the annual percentage of live births to mothers aged 35 yr or more [20].

Advanced maternal age is related to the risk of numerical chromosomal disorders in offspring, with the most prevalent being trisomy 21 (Down syndrome). At birth, the incidence of this syndrome in newborns of women with ages between 25–30 yr is about 1:1000; among those with 35 yr it is 1:385 and for over 45-year-old women it is 1:25 [21,22]. One of the false beliefs in the general population is that the babies of these women are only at risk for Down syndrome; other aneuploidies are not considered nor are other types of birth defects. The results of a study developed by Miller et al. [21] demonstrated a significant association for maternal age of 35 yr or older with cardiac abnormalities and with other BDs. However although many biological factors involved in increased age and predisposition to BDs are suggested, they have not yet been truly elucidated [22].

Advanced paternal age has been associated with an increased risk for spontaneous congenital disorders and common complex diseases (such as some cancers, schizophrenia, and autism), but the mechanisms that mediate these changes are poorly understood. A small group of other disorders including Apert syndrome (caused by *FGFR2* mutations), achondroplasia, and thanatophoric dysplasia (*FGFR3* mutations), and Costello syndrome (HRAS), which are collectively termed "paternal age-effect" disorders, provide a good model to study the biological and molecular basis of this phenomenon. All are caused by a small number of dominantly acting point mutations in key developmental regulators, which cluster within the growth factor receptor-signaling pathway; moreover, causative point mutations originate almost exclusively from

unaffected fathers, indicating that the original mutational events take place during spermatogenesis (de novo mutation). Among the biological phenomena to explain the higher mutagenic risk in older man are reduced activity of anti oxidative enzymes in seminal fluid and spermatozoa, decreased ability to respond to mutagens with apoptosis to avoid genetically altered spermatozoa, the reduced ability of the deoxyribonucleic acid repair system in late spermatids and spermatozoa and the hypermethylation of ribosomal deoxyribonucleic acid in spermatozoa [23–27].

Another risk factor for BDs is parental consanguinity. The influence of parental consanguinity on BDs has been known from ancient times. The rate of consanguineous marriages varies depending on the country and involves several factors, such as ethnicity, type of population, geographical location, cultural factors, religious beliefs, etc. Consanguineous marriages that are rare in developed countries are still a challenge in some populations with around 1.1 billion people currently living in countries where consanguineous marriages are customary [28,29]. In the offspring of consanguineous couples, BDs arise as a result of the homozygosity of deleterious recessive genes that both parents (heterozygous) have in common [30].

Exposure during pregnancy to some environmental toxic agents (physical, chemical and biological) can also confer an increased risk of BDs to the offspring. These disruptive teratogenic agents are able to interfere in the originally normal embryo/fetal development, resulting in secondary malformations that do not compromise the genotype. Among these agents are ionizing radiation, alcohol, and certain medications such as anticonvulsants, anticoagulants and chemotherapeutic drugs, viruses such as rubella and maternal diseases such as diabetes [31–34].

Some infectious agents are especially harmful to fetal organogenesis. Rubella is cited as it is the gestational infection that has the most severe teratogenic action. It almost invariably affects embryonic and/or fetal development and can result in central nervous system lesions, deafness, blindness and heart defects. The literature also reports the negative action of herpes simplex, cytomegalovirus, Treponema pallidum and Toxoplasma gondii [35,36].

In respect to alcohol, the consumption of which is becoming ever more common in women of reproductive age, prenatal exposure can lead to a wide range of adverse effects that are related to the length of exposure and the amount ingested. This can result in miscarriages (prenatal death), low birth weight and stature, microcephaly, palpebral fissure ptosis, orofacial fissures, overall development delay, intellectual disabilities, and behavior changes, among others. As there is no estimate as to the safe dose to which the developing child can be exposed, women should be advised to abstain from alcohol consumption from conception [37,38].

Diabetes during pregnancy has well-documented teratogenic effects and significantly increases the risk for major BDs. Congenital malformations are up to 10-fold more frequent with preexisting type I, type II, or gestational diabetes. Diabetic embryopathy can affect many organ systems, but the most common malformations affect the heart and the neural tube. Teratogenesis may directly result from hyperglycemia, aberrant glycosylation, elevated metabolites or changes in the gene expression profile of the fetus involving epigenetic factors. Thus, the control of blood sugar levels during pregnancy is a major preventive strategy for BDs [39–43].

Maternal hyperthermia is another risk factor for a wide range of structural and functional BDs. The central nervous system is most at risk probably because it cannot compensate for the loss of prospective neurons by additional divisions by the surviving neuroblasts; it remains at risk at stages throughout pre and postnatal life. The most common defects also included neural tube, microphthalmia, cataracts, and micrencephaly, with associated functional and behavioral problems. Defects of craniofacial development involving clefts, the axial and appendicular skeleton, the body wall, teeth, and heart have also been described [44].

Epilepsy, which affects one in every 300 women of childbearing age, is also considered a maternal disease that can interfere with originally normal child development. This is because anticonvulsants have proven teratogenic effect and represent an additional risk factor in these cases causing predisposition of orofacial clefts, distal phalanx hypoplasia and neural tube defects [45].

There are also suggestions that an inadequate diet, with insufficient nutrients during the gestational period can increase the risk of BDs. A diet deficient in folate, for example, increases the risk of neural tube closure defects in genetically predisposed fetuses [46]. With 400 mcg of folic acid daily in the periconceptional period, at least one month prior to conception and in the early days of pregnancy, 50 to 70% of neural tube defects may be prevented with a decreased risk of heart and extremity defects [47].

Infant mortality is one of the most important situations to be considered with congenital anomalies because it is

indicative of the health of a community or country as it is directly associated with factors such as maternal health, quality of and access to health services, socioeconomic conditions and public health practices. After the causes of infant mortality were stratified, decreases in the total mortality rate, in particular deaths due to infection, were observed in several regions of the world. As a result, the proportion of deaths attributable to BDs is increasing [48,49].

3. Consequences

In fact, BDs play an important role in the morbidity and mortality of children [50]. Several studies have reported that more than 20% of newborn deaths result from BDs [3,51]. In the United States about seven deaths occur for every 1000 live births. Congenital anomalies, leading to the death of about 6000 babies per year, are the main cause of infant mortality in this country [2].

As an example of the reality of a developing country, perinatal causes in Brazil in 1980 were responsible for about 38% of deaths in under 1-year-old children and congenital anomalies for only 5%. In 1990, this situation began to change and in 2000, infectious and respiratory diseases were the cause of less than 10% of deaths and congenital anomalies for 13%. Thus, between 1980 and 2000, BDs passed from the 5th to the 2nd highest cause of death in under 1-year-old children [1,52].

In addition to death, another factor related to congenital anomalies is the chronicity, which imposes high costs of treatment. BDs are among the leading causes of loss of potential years of life. It is estimated that children with these defects represent up to 30% of all pediatric hospitalizations [53]. However, knowledge about the economic impact of these defects on society, including the direct and indirect costs over the lifetime of the affected, remains scarce in Brazil. The estimated mean cost-life per child should take into account, among other things, the need for early stimulation (usually physiotherapy, speech therapy and occupational therapy), special or inclusive education needs, and loss of productivity due to disability or death and decreased family income of the guardian of the child [54]. The psychosocial costs, such as psychological trauma in the family and the difficulties of adapting to 'normal' society with great risk of the family breaking up, should also be added to this calculation [50].

The prevalence of BDs is often high due to the lack of understanding of preventive measures. This difficulty is summed to an absence of effective public health policies including reductions in fertility, immunization against maternal infectious diseases that affect the fetus, family planning, preconception care, vitamin supplementation and antenatal diagnosis [55]. Information about congenital defects is becoming increasingly relevant worldwide because this is an important public health problem [56]. Hence, identification of the prevalence, risk factors and consequences of BDs are essential to plan preventive measures and effective treatment.

The elucidation of specific risk factors may offer opportunities for prevention. Women who have optimum health prior to conception and are aware of the risks and possible preventive strategies can reduce the risk of babies with defects. The study of Czeizel [57] showed an example of preconception prevention that significantly reduced the rate of congenital malformations (2.9% versus 4.0%), in particular neural tube defects and cardiovascular malformations, due to multiple-vitamin periconceptional supplementation, a reduction in mothers smoking, the identification of high risk couples and better access to specialists. In summary, experience has demonstrated the feasibility and usefulness of preconception care in preventing BDs.

The precise diagnosis of this kind of defect is also a prerequisite for the prognosis and decisions on the conduct to treat affected infants [58]. When there is no etiological diagnosis, not only are therapeutic and preventive strategies impaired, but genetic counseling will be less effective because it will not be possible to explain to the family about the source of the problem and the risk of recurrence. These are sufficient reasons to encourage epidemiological studies on BDs throughout the world.

Further research should evaluate the health policies and preventive measures related to BDs and their potential benefits. It is very important to train clinicians to diagnose BDs and to offer genetic counseling services to this population because of the complexity of the information to be conveyed in the context of a dynamic and emotional process of adaptation to the diagnosis and prognosis.

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