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Epidemiology of Major Congenital Malformations with Specific Focus on Teratogens

Sonia Chaabane[*,1,2] and Anick Bérard[*,1,2]

[1]*Research Center, CHU Ste-Justine, Montreal, Qc, Canada*

[2]*Faculty of Pharmacy, University of Montreal, Montreal, Qc, Canada*

Abstract: *Background*: Major congenital malformations (MCMs) are a significant cause of infant morbidity and mortality and constitute an important societal and economic burden.

Methods: We conducted a literature review to synthesize current evidence on MCMs. Specific objectives were to: 1) summarize internationally reported prevalence of MCMs based on registries and surveillance systems; 2) describe the epidemiology of different MCM types including critical periods and causative factors; 3) to identify the role played by principal known teratogens on the increase in the risk of MCMs; and 4) determine challenges associated with the epidemiologic assessment of potential risk factors for MCMs as well as potential preventive measures.

Results: It is estimated that 7.9 million infants worldwide are born every year with a MCM, yet there is considerable variation in reported rates across countries. This may be attributable to varying definitions arising from heterogeneity among different classes with respect to critical periods for embryogenesis and organogenesis. There is also substantial etiologic heterogeneity among MCMs classes that potentially contribute to challenges in epidemiologic studies. Modifiable factors such as pharmacologic exposures have received considerable attention and a number of drugs have been shown to be teratogenic including folic acid antagonists, angiotensin converting enzyme inhibitors, antidepressants, anticonvulsants, coumarin derivatives and retinoids including isotretinoin.

Conclusion: The majority of MCMs are due to unexplained causes. Other contributing factors include genetics, environmental factors, multifactorial inheritance, maternal-related conditions, and maternal drug or chemical exposure. However, there remains a need to better understand the epidemiology of MCMs when studying drug effect during gestation.

Keywords: Congenital malformation, teratogen, drug use, risk factor, prevalence, critical period in pregnancy, epidemiology, and review.

INTRODUCTION

A congenital malformation is defined as an abnormality of structure, function or body metabolism that is present at birth and results in physical or mental disability, or is fatal [1]. It results from the failure of specific organ systems or structures to form and develop normally [2]. Major congenital malformations are significant causes of infant morbidity and mortality [1-3]. In addition, major congenital malformations cause diverse grades of disability and are an important social and economic burden for families and society. Major congenital malformations constitute a group of rare outcomes with specific characteristics, which generate high interest and heightened attention by the public and health care community.

The etiologic heterogeneity, among major congenital malformations classes, may contribute to challenges in epidemiologic studies designed to identify major congenital malformation risk factors. Isolated congenital malformations have been shown to be epidemiologically and most likely etiologically distinct from malformations associated with additional malformations [4]. For example, a protective effect of periconceptional multivitamin use, observed for isolated conotruncal heart defects, is not founded for those associated with other noncardiac defects or with a recognized syndrome [5]. Consequently, Syndromic cases with multiple congenital malformations are always excluded or studied separately [6].

Different classes of major congenital malformations have a specific critical period (period of high susceptibility to teratogens) during the embryogenesis and the organogenesis in human development [3, 7].

It is estimated that 7.9 million infants worldwide are born every year with a major congenital malformation of genetic or partially genetic origin [7]. According to Zarocostas 2006 [7], about 60% of babies with serious birth defects were born in poor countries, 34% in middle income countries, and 6% in rich countries. There is a considerable difference in the reported prevalences of major congenital malformations according to country. Depending on surveillance systems, we note a variation in case classification reported (certain types of major congenital malformations were not reported or collected), the maximum age at diagnosis and the inclusion of pregnancy issues.

*Address correspondence to these authors at the Sainte-Justine Hospital, Research Center, 3175, Chemin de la Côte-Ste-Catherine, Montreal (Quebec) H3T 1C5, Canada; Tel: (514) 345-4931, Ext. 4272;
Fax: (514) 345-4801;
E-mails: sonia.chaabane@umontreal.ca, anick.berard@umontreal.ca

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The reduction of prevalence of major congenital malformations is an international goal. Considering that 50-60% of major congenital malformations have unexplained causes [3], it is difficult to orient their prevention based only on surveillance systems data. The environmental exposures involve multiple agents and other confounding elements, creating difficulty in identifying the underlying causes. Moreover, results from animal models are not necessary applicable to humans. The lack of human clinical trials including pregnant women gives to epidemiologic studies a crucial role to play in evaluating preventive measures and in providing an evidence-base for maternal health program and policy development.

An American study reported that for 64% of all deliveries, a drug other than a vitamin or mineral supplement was dispensed during pregnancy [8]. The same study reported that 37.8% of pregnant women used a drug for which the risk to foetus cannot be ruled out because human studies are lacking, 4.8% of them used a drug with a positive evidence of risk to foetus and 4.6% of them used a drug contraindicated in pregnancy (category C, category D, and category X of the United States Food and Drug Administration (FDA) risk classification system respectively)[8]. The prevalence of prescribed drugs, during pregnancy, range between 44 and 79% in European countries [9-11]. A number of drugs, such as thalidomide and isotretinoin [12], have clearly been shown to be major teratogens and cause specific congenital malformations in 30-40% of cases [13]. In the last decade, some drugs were identified as low or moderate risk teratogens and for some others, the teratogenic effect still unclear. Given that approximately half of the pregnancies were unintended [14], numerous women are likely to be exposed to different environmental agents before they know they are pregnant. Choosing between stopping a treatment, reducing dosage or switching to another treatment represents a challenge for physicians treating pregnant women. It also highlights the importance and the need of understanding the effects of these medications on congenital development of the foetus.

In order to better understand the epidemiology of major congenital malformations and inform clinicians, researchers and policy development in health programs, the primary aim of this review was to summarize the international reported prevalence of major congenital malformations based on registries and surveillance systems. The second aim was to describe the epidemiology of different major congenital malformations classes including critical periods and causative factors. The third aim was to identify the role played by principal teratogenic drugs and their contribution along with other known causes and maternal or environmental risk factors for major congenital malformations. Finally, the fourth aim was to determine challenges associated with the epidemiologic assessment of potential risk factors for major congenital malformations as well as potential preventive measures.

MATERIALS AND METHODS

This is a narrative review that aims to describe the prevalence and etiology of major congenital malformations and summarize the role of teratogens reported in recent literature. It differs from a systematic review by involving general discussion of the subject and having no stated hypothesis. An extensive search of the reported literature from 1975 to June 2012 was conducted using the Pubmed database. The search strategy used the following key words concomitantly: major congenital malformation, birth defect, prevalence, risk factors and teratogens. The citation lists from the included references were subsequently examined in an attempt to identify additional reports.

RESULTS

International Comparisons of the Prevalences of Major Congenital Malformations

About 3-5% of infants are born with a major congenital malformation worldwide [15-17]. The prevalence of major congenital malformations varies greatly from one country to another. In 2007 in Canada, the most prevalent anomalies are those affecting genital organs (undescended testis and hypospadias respectively 33.2 and 26.8 per 10 000 all births) and Down syndrome (trisomy 21) with a prevalence of 13.6 per 10 000 all births [18]. In the United States, Down syndrome was the most common condition with a prevalence of 13.6 per 10 000 live births [15]. Common truncus, a type of heart defect, was the least common birth defect in the United States according to the last update of the Centers for Diseases Control and Prevention (CDC) [15]. The estimated national prevalence of common truncus was 0.72 per 10 000 live births [15]. According to the European surveillance of congenital anomalies (EUROCAT), congenital heart diseases (CHD) are the most common congenital malformation in Europe with a prevalence of 60.5 per 10 000 all births and terminations of pregnancy [19, 20]. The trend of major congenital malformations differs between European countries. Down syndrome represents the most common congenital malformation in Finland (30.8 per 10 000 all births and terminations of pregnancy) [18]. Similarly as in Canada, Sweden reported that undescended testis and Down syndrome were the most common congenital malformations. The highest prevalence of undescended testis is observed in New Zealand (63.5 per 10 000 live births [18]). According to the results of the annual report 2010 of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), in India the most common anomalies are those affecting the nervous system (anencephaly and spina bifida 13.4 and 15.5 per 10 000 live all births and terminations of pregnancy) in 2008. According to the Chinese Birth Defects Monitoring Network, cleft lip with or without cleft palate and polydactyly preaxial, a hand malformation, are the most frequent major congenital malformation in China with a prevalence of 13.0 and 13.9 per 10 000 all births, respectively in 2006 [21]. In Turkey, the most common congenital anomalies between 2000 and 2004 are, respectively, nervous system anomalies and cleft palate and cleft lip [17]. According to the ICBDSR, in Iran, limb reduction defects and oesophageal atresia/stenosis with or without fistula are the most common major congenital malformations, in 2008, with a prevalence of 21.7 and 14,8 per 10, 000 live births, respectively. In Japan, cleft lip with or without cleft palate was the most common major congenital malformation with a prevalence of 22.8 per 10 000 all births, in 2008 [18]. The prevalence of Down syndrome in Iran and in Japan was similar to those observed

Table 1. Summary Table of International Prevalences of Major Congenital Malformations (MCM)

Country	The Most Prevalent MCM	Prevalence	Year
Canada [18]	Undescended testis Hypospadias Down syndrome	33.2 per 10, 000 TB 26.8 per 10, 000 TB 13.6 per 10, 000 TB	2007
United States [15]	Down syndrome Common truncus	13.6 per 10,000 LB 0.72 per 10,000 LB	2006
Finland [18]	Down syndrome Hypospadias	30.8 per 10, 000 TB and ToP 19.3 per 10, 000 TB and ToP	2008
India[6] [18]	Anencephaly Spina bifida	13.4 per 10,000 TB and ToP 15.5 per 10,000 TB and ToP	2008
Sweden [18]	Undescended testis Down syndrome	21.6 per 10, 000 TB and ToP 29.8 per 10, 000 TB and ToP	2008
New Zeland [18]	Undescended testis Hypospadias	63.5 per 10,000 LB 23.6 per 10,000 LB	2008
China [21]	Cleft lip with or without cleft palate Polydactyly preaxial	13.0 per 10, 000 TB 13.9 per 10, 000 TB	2006
Europe [19, 20]	Congenital heart disease Anomalies of urinary system	60.5 per 10, 000 TB and ToP 31.7 per 10, 000 TB and ToP	1999-2008
Turkey [8]	Nervous system anomalies Cleft palate and cleft lip	31.1% among all MCM 18.6% among all MCM	2000-2004
Iran [18]	Limb reduction defects Oesophageal atresia/stenosis with or without fistula	21.7 per 10,000 LB 14,8 per 10,000 LB	2008
Japan [18]	Cleft lip with or without cleft palate Down syndrome	22.8 per 10, 000 TB 12.8 per 10, 000 TB	2008

*SB: Stillbirths, LB: live births, ToP: terminations of pregnancy, TB: Total births= SB+LB.

in the other countries [18]. Table **1** summarizes the most prevalent major congenital malformations in some countries.

Several factors can explain the variations in the measure of the prevalence of major congenital malformations between countries. Some of these factors concern the monitoring program and health system. The number of cases of major congenital malformation among stillbirths and/or the terminations of pregnancies is not reported in the Canadian Congenital Anomalies Surveillance Network, the Chinese Birth defects Monitoring Network or the Turkish monitoring program. According to EUROCAT, in Europe 53% of cases of major congenital malformations were live births and 43% of them were terminations of pregnancy [20]. Moreover, major congenital malformations are the first cause of infant's mortality and spontaneous abortion [1, 2]. The prevalence of congenital malformations in surveillance systems including only live births, underestimate the prevalence of certain congenital malformations. The impact of the inclusion or the exclusion of stillbirths and terminations of pregnancy on prevalence's estimation, of a given type of congenital malformation, depends how much this congenital malformation is associated with stillbirths or terminations of pregnancy. The updated national birth prevalence estimates, in the United States, show that the addition of pregnancy outcomes, other than live births, contribute to an increase in the estimated prevalence from 80% to 4 ½ - fold depending on the specific type of major congenital malformation [15]. It seems that anencephaly was the most impacted major congenital malformation with the inclusion of pregnancy outcome compared to Down syndrome and spina bifida which showed the least amount of change with added pregnancy outcomes [15]. The amount of change can also be impacted by the accessibility to amniocentesis and ultrasound during the first trimester of pregnancy.

The skill and intensity of the examination can also have an impact on the apparent birth prevalence for a specific defect [22]. Overall, major congenital malformations are observed in approximately 3% of infants at birth and among another 3% later [3, 22].

The maximum age at diagnosis of congenital malformations and the criteria defining stillbirth differ according to monitoring programs; it varies between 3 days and 18 years and from 20 to 28 weeks or 400 to 500 grams respectively [18]. Classification systems used for the definition of a major congenital malformation and data source (administrative databases, perinatal databases, foetal anomaly databases, registers or surveys and multiple information sources) can also play a crucial role in the accuracy and effectiveness of the assessment of specific types of major congenital malformation. Changes in the surveillance methodology, in prenatal diagnostic practices and congenital malformations coding modifications between collection periods could have accounted for some of the variability in the prevalence of major congenital

malformation between countries. A European study showed that changes in case ascertainment, in definition and inclusion criteria or in diagnostic methods account for 63% of the increasing trends observed [19]. Some of these variations may also be explained by social, racial, ecological, and economical influences [17].

Overall, in Europe, the statistics show a decreasing trend for several types of major congenital malformations especially neural tube defects (NTD) and CHD [19]. However, a consistent evidence of increasing trend was observed for gastroschisis and hypospadias [19]. In the United States, a significant decrease in the prevalence of anencephaly and transposition of great arteries, a CHD, and an increase in the prevalence of gastroschisis were observed between 1999-2001 and 2004-2006 respectively [15]. According to the last report of the ICBDSR [18], a trend in decreasing prevalence of anencephaly, spina bifida, and omphalocele was observed in Canada. The same trend was observed in India where in addition, we observed a trend in decreasing prevalence of other congenital anomalies of nervous system, cleft palate/cleft lip and congenital anomalies of urinary system during the past ten years [18].

The decrease in the prevalence of NTD in several countries was attributable, largely, to food fortification with folic acid and promotion of the importance of folic acid intake before and during the first trimester of pregnancy [19, 23, 24]. The negative trend in the prevalence of certain major congenital malformations can be attributable to detection rates and measures taken following the diagnosis. According to EUROCAT, in Europe, overall prenatal detection rate of major congenital malformations was 64% (range 25-88% between regions) and the proportion of terminations of pregnancy varied from 15-59% of all cases of major congenital malformations [20]. The number of elective terminations of pregnancy depends on the accessibility to prenatal diagnosis (chorion villus sampling, amniocentesis and cordocentesis) and differences in advice and abortion legislation. The evidence, regarding factors affecting positive or negative temporal trends of the prevalence of other types of major congenital malformations, is less known. In the rest of this review we will focus on the synthesis of recent knowledge of causes of major congenital malformations and on the update of known teratogen and risk factors.

THE EPIDEMIOLOGY OF DIFFERENT MAJOR CONGENITAL MALFORMATIONS

Causative Factors

The factors behind different major congenital malformations can be categorized into three major causes: 1) genetic; 2) environmental and 3) interaction between genetic and environmental.

Genetic Factors

Genetic factors are considered as the most important cause of congenital malformations. They cause approximately one third of all birth defects and about 85% of anomalies with known causes [3]. We estimate that 6 to 7% of zygotes present chromosomal aberrations [3]. Many of the embryos with chromosomal aberrations will never become blastocysts. During gametogenesis (formation of germ cells), the number of chromosomes is reduced and multiplied during a complex division process called meiosis and mitosis. This process involves the chromosomes and cytoplasm of human gametes and may sometimes malfunction. These abnormalities may affect the sex chromosomes, the autosomes (all the chromosomes other than the sex chromosomes) or both [3, 25]. Chromosomal complements can be affected by numerical and structural modifications during gametogenesis. Numerical aberrations usually have a prezygotic origin but can arise from postzygotic errors [26].

In human females, the inactivation of one of the two X chromosomes during embryogenesis or implantation process, leads to cells with mutant genes causing disease [3]. Turner syndrome is the most frequent sex chromosome aneuploidy (1/2500) [26]. Half of newborn females affected by Turner syndrome have 45X chromosomes in embryo's cells caused by a reduction in the chromosome number and approximately 99% of them abort spontaneously. The other half is caused by other abnormalities affecting the sex chromosomes [3]. The monosomy X, missing a chromosome, is caused by non disjunction, an error in the disjointing of the chromosome pair or two chromatids during the gametogenesis [3]. The monosomy X account for about 18% of all abortions caused by chromosomal abnormalities [3]. Hyperdiploidy is another numerical aberration of chromosomes resulting in the presence of three chromosomes instead of a usual pair. This abnormality is known as trisomy [3]. There are three types of trisomy; trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) are the most severe cases rarely survive beyond 6 months of age [3]. Trisomy 21 (Down syndrome) is the most common form of trisomy of autosomes with an incidence at birth of about 1 in 800 [3, 26]. In 95% of cases, Trisomy 21 is secondary to a maternal meiotic non disjunction of homologous chromosomes 21 [26]. The incidence of trisomy increases with maternal age [1, 20]. Between 3% and 4% of persons with Down syndrome have translocation trisomies, where the extra chromosome 21 is attached to another chromosome [3].

Gene defects cause 7 to 8% of congenital anomalies [3]. The mutation rate can be increased by a number of environmental factors as doses of chemicals or radiation. Most mutations are deleterious and some of them are lethal [3]. A mutation in any of the genes encoding enzymes, implicated in the detoxification of certain environmental chemicals or drug and in DNA reparations, can lead to increase the susceptibility to diseases and cancers [25].

The concept of epigenetic refers to process leading to diversification of the expression of genetic material, without involving changes in nucleotide sequences involved [27]. The DNA methylation is the most critical modification involved in the maintenance of chromosomal stability and the inactivation of the chromosome X during the embryo development. This process is controlled by a family of enzymes called DNA methyltranferase (DNA MTase) [27]. A study, in mouse, demonstrated that the inactivation of DNA MTase induce lethal anomalies [28]. DNA methylation have also a crucial role in the maintenance of gene expression profile of tissue-specific and in the development

and operating of the placenta which has a central role in the regulation of foetal growth and development [29]. Any deregulation in DNA methylation process will potentially lead to deceleration of subsequent developmental stages. Traditionally, dysregulation of multiple imprinted genes is related to human syndromes, such as Prader-Willi (PWS), Beckwith-Wiedemann (BWS), Angelman (AS) and Silver-Russell (SRS) [27, 29]. Many factors are known to disturb DNA methylation. In humans, the global DNA methylation decrease with age [30]. The genome is constantly accumulating changes in DNA methylation and chromatin modifications as a result of environmental factors such as diet, smoking, alcohol, sun exposure and other toxicants [31, 32].

Environmental Factors

Environmental factors, such as drugs, infections and radiations, cause 7% to 10% of congenital anomalies [3]. Such factors such as radiations and certain chemicals can cause mutations. X-rays and nuclear fallout emit ionising radiation that can break the bonds between the double stranded DNA and alter the bases within the strands. Ionising radiation has the capacity to penetrate deep into the tissues, reach the gonads and potentially causing somatic and germ-line mutations [25, 33]. They also can cause chromosome breakage [25]. This breakage can be followed by an abnormal reconstitution. The broken pieces of the chromosome can be transferred to a nonhomologous chromosome (translocation) or lost (deletion) [3]. Translocations and inversion are the only structural chromosomal aberrations that are likely to be transmitted from parents to child [3]. The quantity of exposure and the intensity of the effects are cumulative and determine the degree of genetic damage [25].

The mutagenic effect of commonly used substances, such as alcohol and caffeine, is controversial in experimental animals and not well studied in humans [25, 34]. In fact, chromosome breakage may be also induced by such factors as viruses, chemicals, and drugs [3] but may not necessarily cause mutations [26]. If the induced mutations affect germ cells, it will have a deleterious effect on the embryo and is usually lethal [25].

Substances introduced in human body, such as smoking, alcohol or illicit drugs, may cross placenta, reach the foetus and be dangerous for his development [26]. The clinical effects of environmental factors depend on individual, placental metabolism, dosage and timing of exposure during pregnancy [26].

The cascade of molecular signals period and embryonic induction precede the stage of morphologic differentiation visible [3]. This period is sensitive to teratogens action and can cause the death of the embryo. The exact mechanisms by which environmental factors lead to congenital anomalies are unclear. However, several researches increase attention to molecular mechanisms. A summary of potential known mechanism is described later.

Smoking, Alcohol, Illicit Drugs, Multivitamins Use, and Caffeine Consumption

Several studies consider maternal or parental smoking during the first trimester of pregnancy as a risk factor of some major congenital malformations [35-39]. A recent meta-analysis shows a non significantly increased risk of anorectal malformations (ARM) following any maternal cigarette consumption (OR, 1.03; 95% confidence interval (CI), 0.83-1.29) [40]. However, in the same meta-analysis [40] an association was found for any parental cigarette consumption and ARM (OR, 1.53; 95% CI, 1.04-2.26). The overall odds ratio obtained from another meta-analysis [39] was 1.29 [95% CI, 1.18 to 1.42] for cleft lip with or without cleft palate (CL/P) and 1.32 (95% CI: 1.10 to 1.62) for cleft palate (CP), indicating a small increase risk of having a child with either a CL/P or a CP for mothers who smoke during the first trimester of the pregnancy. A study from the National Birth Defect Prevention Study identified that periconceptional smoking exposure as a potential risk factor for isolated Bochdalek congenital diaphragmatic hernia [41]. A recent population-based study suggested an interaction between maternal overweight and smoking that contributes significantly to the occurrence of all cardiac subgroup anomalies except right ventricular outflow tract obstructive anomalies [42].

In the last 20 years, alcohol consumption in women of childbearing age is estimated around 55% worldwide, including approximately 11% of pregnant women who reported consuming alcohol in the previous month [43]. It was reported that 30% of women admitted consuming alcohol at some point during pregnancy, and 8% report having more than four drinks on one occasion [43]. It is increasingly clear that alcohol crosses the placental barrier and affects functional brain development. A heavy consumption of alcohol (daily use) beyond 24 weeks of pregnancy is associated with developmental disabilities [35]. In the United States, it is estimated that 3-5% of pregnant women drink heavy throughout pregnancy [44]. Several studies demonstrated that heavy maternal alcohol use during periconceptional period was associated with an increased risk of isolated simple ventricular septal defect [37, 38]. Mateja [45] suggested that multiple episodes of maternal binge alcohol drinking in early pregnancy might increase the odds of congenital cardiac defects, and found that this relationship was more dramatic when combined with maternal smoking. Results from an Australian cohort study showed a fourfold increased risk of birth defects, classified as alcohol-related birth defects, observed after heavy prenatal alcohol exposure in the first trimester [46]. Results of meta-analysis suggested an absence of association between maternal alcohol consumption and ARM [36]. One of the most severe birth defects can be caused by prenatal alcohol exposure is Fetal Alcohol Syndrome (FAS). FAS is an enduring and irreversible condition marked by a set of distinctive facial traits as well as growth retardation and central nervous system dysfunction. Approximately 1 - 3 per 1000 viable infants are born with FAS. These rates increase to 10 - 15 per 1 000 in at-risk groups such as the foster care population [43]. The term Fetal Alcohol Spectrum Disorders (FASDs) has been introduced in recent years to include a larger range of deficits associated with prenatal alcohol exposure. During childhood, these deficits are characterized by an increased reactivity, irritability and activity level, and struggle with deficits in attention [43]. The prevalence of FASDs in the general population is estimated at 9.1 per 1000 live births [43]. The frequency of congenital malformations

and functional abnormalities among infants born from heavy drinking mothers was twice that of infants born to abstinent or moderate drinking mothers [47]. Moreover, effects of alcohol prenatal exposure on children and families represent a significant financial burden for governments and communities. For instance, the lifetime cost for the care of one child with FAS is estimated at $2 million in special medical, health and educational resources [43].

According to the 2010 National Survey on Drug Use and Health (NSDUH) conducted by the United States Substance Abuse and Mental Health Services Administration, among pregnant women aged 15 to 44, 4.4 % were current illicit drug users between 2009 and 2010 [48]. Some illicit drugs, such as cocaine, are rapidly transferred across the placenta to the foetus by a simple diffusion and may cause marked vasoconstriction of foetal blood vessels [49]. In fact, maternal vasoconstriction can affect the foetal effects of cocaine and decreased uteroplacental blood flow may lead to uteroplacental insufficiency, acidosis, and foetal hypoxia [49]. The exact mechanisms by which illicit drugs, as methamphetamine, cocaine and marijuana, lead to congenital malformations are currently unknown [49]. It is increasingly clear that these substances are associated with a variety of specific congenital anomalies affecting different organ systems which suggests an influence of common factors involved in embryonic development [50]. A limited number of population-based studies examine the risk of major congenital malformations associated with illicit drug use during pregnancy. Illicit drug use is reported by the mother then it can be imprecise. It is also socially frowned upon, especially during pregnancy, which complicates data collection. Studying the impact of maternal illicit drug use on the child is faced to certain limitations. Some of this limitations concern the small number of exposed mothers and the assessment of illicit drug use. Illicit drug consumption is underreported by mothers and persons who consume one illicit drug usually use other illicit drugs and have unhealthy lifestyles and fewer adherences to prenatal care. These weaknesses limit the ability to identify statistically significant difference and lead to large confident intervals. However, several studies consider maternal illicit drug use during the first trimester of pregnancy as a risk factor of various major congenital malformations [50]. The study of Abe reported that mothers of infants with renal anomalies were more likely to report cocaine use [35]. The study of Forrester found an increased rate for methamphetamine, cocaine and marijuana occurred predominantly among birth defects affecting the central nervous system, cardiovascular system, and oral clefts and limbs [50]. Despite the fact that these three illicit drugs have different mechanism of action and different clinical effects, according to authors, these results suggested that the three illicit drugs had similar effects on embryonic and foetal development [50]. Some studies suggested an absence of association between maternal illicit drug use and neural-tube defect [36], cardiovascular defect [51], intestinal atresia/stenosis or gastroschisis [50], craniosynostosis [52] and oral clefts [53]. Other studies suggested an association between maternal illicit drug use and limb reduction deformities [50], gastroschisis [54], cardiovascular defect [37, 55-57] and musculoskeletal defect [57]. These findings suggested that illicit drug use is not a risk factor of all major congenital malformations. Maternal use of these substances must be taken into account when assessing the risk of a particular congenital malformation as cardiovascular defects. Duration of exposure, dosage, timing of exposure during the first trimester of pregnancy and type of illicit drugs used can play an important role in the likelihood of occurrence of the congenital defect.

According to the results of a recent review [58], on the whole, associations of prenatal caffeine consumption with congenital malformations are not routinely observed and most of recent studies have not suggested an increased risk of congenital malformations with greater caffeine consumption. However, it is not clear if there is an evidence of an increased risk of specific type of major congenital malformations or for an exposure to certain quantity of caffeine. Because caffeine consumption is not accurate and is reported by the mother, the reports of modest associations between coffee intake (use equivalent to 3 cups of coffee per day) and cryptorchidism [59] and all categories of caffeine intake and anorectal atresia [60] could not rule out potential sources of bias such as selection bias due to missing data, exposure misclassification due to changes in caffeine intake during pregnancy and in certain cases confounding [58].

A meta-analysis [61] showed that the use of multivitamin supplements provided consistent protection against neural tube defects, cardiovascular defects, and limb defects. These results are supported by several other studies [62-66]. No effects were shown in preventing Down syndrome, pyloric stenosis, undescended testis, or hypospadias [61].

Folic acid is involved in early growth and cellular proliferation of the embryo [50]. It also plays a role in nucleic acid synthesis and cell division [23]. It is more and more evident that periconceptional folic acid or folic acid containing multivitamin supplementation has resulted in a breakthrough in the primary prevention of neural tube defects but there are very limited data concerning a similar preventive effect of folic acid alone for the other congenital malformations [64, 67, 68].

The North American guidelines recommend periconceptual supplementation of folic acid or folic acid containing multivitamin supplementation at least two to three months before conception and during the first trimester of pregnancy to reduce the occurrence of NTD [24, 69]. The recommended dosage depends on personal health risks (women with no personal health risks: a daily supplementation of 0.4-1.0 mg folic acid; women with intermediate to high health risks or who had risky lifestyles and possible teratogenic substance use or with a previous child or foetus with a NTD or another congenital anomaly: a higher daily supplementation (4-5 mg of folic acid) [24].

These results demonstrate the importance of taking into account, in human studies, the periconceptual folic acid intake when assessing the risk of NTD and probably other major congenital malformations. In epidemiologic studies, folic acid supplementation is reported by the mother and can be a concern of recall bias. Moreover, it is unlikely that the dosage and the timing are evaluated with accuracy. Factors related to health care access and drugs plan (access to physician before their pregnancy, drug cost, and information

system) can also have an impact on adherence to the recommendations.

Although most women reduce their consumption of alcohol, tobacco, caffeine and illicit drugs once they find out they are pregnant, many of them do not know about the pregnancy before the fourth or sixth week of gestation and continue their consumption of caffeine, alcohol, and illicit drug during that sensitive period [43].

Critical Periods for Major Congenital Malformations

To better understand the potential teratogenic effect of some environmental factors, it is helpful to review some principles of embryogenesis in order to establish critical periods of development for each class of major congenital malformations.

During periconceptual period, 2 weeks following fertilization, the zygote begins implantation in the uterus and undergoes rapid cell division. Environmental exposure, during this period, usually leads to embryo loss rather than damage [2, 70]. From day 11 or 12 after conception, the zygote is in contact with maternal blood [70].

Growth and development of the majority of major organs begin during embryonic period (3 to 7 or 8 weeks following fertilization) and continue through the remainder of pregnancy for certain systems such as brain, teeth and skeletal system [2, 3]. During this period, all essential internal and external structures are formed [3].

The foetal period starts from the 9th week after conception and continue through the remainder of pregnancy. It is characterized by body growth and organ differentiation and maturation [3].

Development of the embryo is more susceptible to disruption when organs and tissues are forming. This period of high susceptibility for major congenital malformations cover the embryonic period and the first part of the foetal period [3]. This period varies by organ system and covers approximately the first trimester of pregnancy therefore the period between 3-16 weeks after conception (Table **2**). Disruption of the development during this period can result in a major or minor congenital malformation [3]. The type of congenital malformation depends on which parts, tissues and organs are most susceptible at the time the teratogen is introduced [3]. Table **2** presents critical periods of development according to the type of major congenital malformations. It is noted that these critical periods are approximative and cannot be used to determine the day of congenital malformation's occurrence.

Teratogen Update

A teratogen is an environmental agent that can produce or increase the incidence of congenital malformations [3]. In a recent survey of safety information for 172 drugs approved by the FDA, between 2000 and 2010, 97.7% had an ''undetermined'' teratogenic risk in human pregnancy, and 73.3% had no data available regarding safety in pregnancy [73].

To determine whether an agent, such as a drug, chemical or virus, is a teratogen, three important factors are important to consider: stage of development/critical period of development, dose of the agent and genotype (genetic constitution) of the embryo [2, 3]. In addition to these principal factors, Jim Wilson, reported other factors that impact the susceptibility to teratogens. These factors are mainly related to nature of the agent itself, route and rate of

Table 2. Periods of Structural Development and Critical Periods of Development During Pregnancy According to Organ System and Specific Types of Congenital Malformations

Organ System	Period of Structural Development (Weeks After Conception)	Major Congenital Malformation	Period of High Susceptibility to Teratogens (Weeks After Conception)
Central nervous system anomalies (CNS)	3-40 weeks	Neural Tube defect Mental retardation	3-4 weeks 3-16 weeks
Heart	3-8 weeks	Truncus arteriosus, Atrial septal defect, Ventricular septal defect	3-6 week
Respiratory system	4-40 weeks	Laryngeal atresia A tracheoesophageal fistula (TEF)	4-10 weeks 4-16 weeks
Limbs	4-8 weeks	Amelia/Meromelia	4-5 weeks or 24-36 days
Lip	5-10 weeks	Cleft lip Cleft palate	5-6 weeks 6-9 weeks
Ears	4-20 weeks	Low-set malformed ears and deafness	4-9 weeks
Eyes	4-40 weeks	Microphthalmia, cataracts, glaucoma	4-8 weeks
Teeth	6-40+ weeks	Enamel hypoplasia and staining	7-8 weeks
Genital system	7-40+ weeks	Masculinization of female genitalia	7-9 weeks
Kidneys	4-40 weeks	N/A	N/A

Source [2, 3, 71, 72].
N/A: not available.

placental transfer as well as systemic absorption. These characteristics define the way in which the teratogen will act on developing cells and tissues leading to specific sequences of abnormal developmental events (functional defect, malformation, growth retardation and death) [74].

As mentioned above the most critical period for major congenital malformations is the organogenetic period, from 3 to 16 weeks after conception, when cell differentiation and morphogenesis are at their peak. Examples of mechanisms by which some drug induce major congenital malformations will be discussed later. Usually congenital anomalies will occur following exposure to more than one teratogen during the critical period for congenital malformation [3]. The teratogenic risk, in human pregnancy, still undetermined for more than 90% of drug treatments approved in the United States between 1980 and 2000 [75]. Table **3** shows an updated list of potential human teratogens that can be used during pregnancy. In addition to the literature review, the list of teratogens was compared with information available on Motherisk website (http://www.motherisk.org/women/drugs.jsp), the IMAGe center (Info-Médicaments en Allaitement et Grossesse) and The Teratogen Information System, TERIS (http://depts.washington.edu/terisweb/teris/index.html) accessed through MICROMEDEX and REPROTEXT.

The interaction of these environmental agents with genes account for 25-50% of all developmental defects [76].

Potential Mechanisms

Several mechanisms are proposed in the literature. Some drugs, such as carbamazepine, cholestyramine, cyclosporine, lamotrigine, metformin, methotrexate, nicotinic acid, phenobarbital, phenytoin, primidone, pyrimethamine, sulfasalazine, triamterene, trimethoprim, valproic acid, may have teratogenic effect by disturbing the folate metabolism or impairment and the vitamin B_{12} absorption [106]. Folate requirements increase during pregnancy and folate-dependent reactions are essential for foetal growth and development [106]. These drugs act as folate antagonist and increase the risk of folate sensitivity-birth defects as neural tube defect, orofacial clefts [107, 108] and limb defects [65, 66]. The prevention of neural tube defects with periconceptional folic acid supplementation was demonstrated and supported by several studies and accepted by the scientific community [62, 68]. Moreover, some studies suggest a reduction of the risk of cardiovascular and limb defects with periconceptional folic acid-containing multivitamin supplementation [61, 66, 109, 110]. These finding suggested a causative role of folate deficiency in the aetiology of these defects. Because of the polymorphism of genes associated with folate metabolism, such as methylenetetrahydrofolate reductase and methionine synthase reductase polymorphism, the susceptibility of the embryo to folate antagonists can lead to different responses [106].

During neurulation, the neural crest cell, a pluripotent cell, migrate into the embryo to give rise to numerous structures. The induction, migration, proliferation and differentiation of neural crest cells are strictly regulated. Different molecular signals and receptors are involved in the development process of neural crest cells. Drug, such as bosentan used for the treatment of pulmonary artery hypertension, interferes with these molecular pathways and can induce neural crest-related malformations, as aortic anomalies [111], conotruncal defects [111], craniofacial malformations [112], esophageal atresia [113] and abnormalities of the pharyngeal glands [114]. Drugs indicated for the treatment of dermatologic conditions and that can inhibit embryonic retinal dehydrogenases and CYP26 [115], as tretinoin, isotretinoin and etretinate, may be involved in disturbances of retinoid homeostasis necessary for foetal normal development [106].

A number of drugs that interfere with the action of the sex hormones, such as diethylstilbestrol, oral contraceptives, hormones used in fertility treatments or endocrine disrupting chemicals (EDCs), such as bisphenol A and phthalates, may interfere with physiologic functions of endogenous hormones by affecting their release, binding or metabolism [106]. The mechanism by which these synthetic hormones and EDCs can disturb normal cell development seems to be complex. In male animal model, prenatal exposure to EDCs has been shown to cause hypospadias and cryptorchidism [116, 117]. A study noted that preparations containing phthalate may affect human male reproductive development due to their anti-androgenic proprieties [118]. The susceptibility of an individual to the adverse effects of EDCs varies according to genetic predisposition [119].

Because testosterone is responsible for most of the development of the male reproductive tract and external genitalia, the use of drugs that can disturb testosterone production may result in hypospadias [106]. A potential role of oestrogen exposure is raised [106]. However there is no strong epidemiological evidence to indicate that prenatal exposure to estrogen are linked to an increased risk of hypospadias or cryptorchidism [120, 121].

Thalidomide is a major teratogen for which many mechanisms were proposed. The loss of immature blood vessels thalidomide-induced was presented us the primary cause of teratogenic effect of this drug [122]. Another teratogenic mechanism was proposed and concerns the increasing of free radicals production and the induction of oxidative stress [123]. This last mechanism is common to other drugs such as phenytoin [124], valproic acid [125], class III antiarrhythmic drugs [126], iron supplements among mothers did not have iron deficiency [127] and various chemotherapeutic drugs [128]. In early stages of organogenesis, weak embryo's antioxidant defence makes the developing embryo more susceptible to oxidative stress [129] involved in the pathogenesis of skeletal malformations [130, 131], limb defects [122, 132], neural tube defects [133] and cardiovascular defects [134].

Several epidemiological studies reported an association between structural birth defects and prenatal exposure to vasoactive therapeutic drugs as aspirin [135, 136], ergotamine [137] and pseudoephedrine [136, 138]. These drugs induce a vascular disruption, disturbances in the blood circulation in the uterine or foetal placental unit or in the foetus itself, resulting in abnormal differentiation, distortion tissues and incomplete development of structures within embryonic development field [106]. The vascular disruption can also be caused by acute or chronic decreases in uterine blood flow, vascular infections or an abnormal anatomy in

Table 3. Update on Known Human Teratogens Used During Pregnancy

Type of Teratogen	Known Teratogens
Medications	Amiodarone [77] Angiotensin-converting enzyme inhibitorsduring 2nd and 3rd trimester § [35, 78-80] Androgens/high doses of progesterones (progestins, ethisterone, norethisterone, oral contraceptive [3, 35]) Antiepileptic drugs (Trimethadione [3, 26, 35], **Valproic acid/ Divalproex** [3, 26, 35], Phenobarbital [81], Phenytoin (Dilantin) [3, 35], Carbamazepine [13, 35]) Benzodiazepine § [3, 82] Bosentan (Reprotext) Carbimazole/methimazole [35] Corticosteroids (prednisone in systemic use) [83] **Diethylstilbestrol** [2, 35] Etretinate [35] Fluconazole (>400 mg/day)[84] Gadolium-based contrast agents (Motherisk) **Isotretinoin (Acutane)** [3, 13, 35, 85], Tretinoin (Reprotext)/Vitamin A (10,000 Unit /day) [86, 87] Lamotrigine † [88] Lithium [3, 35] Misoprostol [84, 89] Methimazole [84, 87] Mycophenolate mofetil [85, 89, 90] Non-steroidal anti-inflammatory drugs [91, 92] (Ibuprofen [93], Aspirin [94]) during the 3rd trimester. Penicillamine [35, 89] Quinine (dose dependent) [84] Selective serotonin-reuptake inhibitor (SSRI) § [80, 95-99] **Tetracycline (streptomycin)** (2nd and 3rd trimester) [3, 35, 89] **Thalidomide [3, 35]** Thiouracil [35] **Tumor-inhibiting chemicals** (**Methotrexate** [3, 35], Aminopterin [35]) Trimethoprim [84, 89] **Warfarin** [3, 35, 84, 89]
Maternal infections	**Cytomegalovirus infection** [2, 3, 26, 85] Herpes simplex virus [3] Human immunodeficiency virus [3] Human parvovirus B19 [3] Rubella infection [3, 26, 100] Syphilis [85] Toxoplasmosis [2, 3, 26, 85] Treptonema pallidum [3, 26] Varicella-Zoster virus [3, 26]
Maternal lifestyle	Alcohol, smoking and illicit drug use [2, 3, 26, 36-38, 53]
Maternal illness	Diabetes mellitus [26, 85] Hyperthermia [76] Phenylketonuria [85] Uterine constriction [85]
Chemicals/metals agents	Glycol ethers [101] **Methylmercury [2, 35]** **Organic solvents [35, 102, 103]** Pesticides [104, 105] Polychlorobiphenyls [3, 35] **Radiation [2, 3, 76, 85]** **X-ray [25, 76]**

*Major known teratogens are in bold. Some of the other teratogens are considered dose-dependent-teratogens or gestational-age teratogens.
§ Controversial.
† Few data.

the uterine-placental unit. Factors, other than drugs, such as placental insufficiency, umbilical cord obstruction, disruption of newly formed vessels and embolic events may also lead to vascular disruption [139]. Congenital malformations related to vascular disruption include Poland anomaly [140], hydranencephaly/porencephaly [141], small intestinal atresia [142], gastroschisis [143] and terminal limb reductions [144].

Epidemiological studies on the association of antihypertensive drugs, such as angiotensin-converting enzyme (ACE), exposure during the first trimester of pregnancy and the risk of major congenital malformations are controversial [35, 78-80]. It is demonstrated that angiotensin receptors AT1 and AT2 are expressed very early in development (24 days of gestation), suggesting a role for angiotensin II in organogenesis [145]. Based on the expression pattern of these receptors, angiotensin II likely plays a role in the growth and differentiation of the kidney, adrenal gland, heart, liver, and all organs that are of major importance for the regulation of blood pressure later in life [145]. The potential teratogenic effect of these drugs can be produced by foetal hypotension, vascular disruption or decrease of the renal vascular tone depending on the stage of development affected by the exposure to these drugs [106, 146].

The teratogenic mechanism of known teratogen drugs can be associated with one or more mechanisms described above. A teratogenic mechanism can be common to different drugs. Consequently, usually potential teratogen drugs will increase the risk of one class of congenital malformations and thus several specific types of congenital malformations. Most of these mechanisms are deduced from animal models and case reports and cannot always be applicable to human models and foetal mechanisms specifically. Human experimental and observational studies cannot be used to identify these mechanisms because of ethical reasons and methodological or data collection challenges. Discontinuing medication during pregnancy can be associated with a higher risk of complications in the baby. The type and the risk of major congenital malformations depend on the timing of exposure during gestation, dosage, severity of damage and the response of the foetus to the potential teratogen. A balanced ratio benefice/risk should be considered when treating mothers with potential teratogens.

CONCLUSION

The definition and classification of major congenital malformations, used by surveillance systems, differ between countries and change across the time. Developed countries are characterised by a high prevalence of Down syndrome and anomalies affecting genital organs. Despite that, the causes of the majority of major congenital malformations still unknown, great progress regarding genetic factors and molecular mechanisms were noted. To decide if an agent is a teratogen, a minimum of requirements, as dosage and timing during gestation, should be verified. In general, the problem is that the proof of teratogenicity is not completed to draw a conclusion about the safety of taking a certain dosage of a drug during a specific moment of pregnancy. Moreover, the majority of data is based on animal studies, with uncertain ability to transfer preclinical results to human foetuses. Randomized clinical trials, including pregnant women, are not possible for the majority of medications because of clinical issues and ethical concerns. There are multiple sources, based on epidemiologic studies, available to provide information on a large range of medications that can be used during pregnancy. However, inclusion and exclusion criteria used for the definition of a teratogen are not necessary the same for all teratology communities which have established different lists of medications that should be avoided during pregnancy. There are also some uncertainties about teratogenic exposures effect that are related to weakness of some epidemiologic study designs such as bias, confounding and limited statistical power.

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CONFLICT OF INTEREST

Anick Bérard and Sonia Chaabane have no potential conflicts of interest to disclose.

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