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Review

Urgent global opportunities to prevent birth defects

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SUMMARY

Birth defects are an urgent global health priority. They affect millions of births worldwide. But their prevalence and impact are largely under-ascertained, particularly in middle- and low-income countries. Fortunately, a large proportion of birth defects can be prevented. This review examines the global prevalence and primary prevention methods for major preventable birth defects: congenital rubella syndrome, folic acid-preventable spina bifida and anencephaly, fetal alcohol syndrome, Down syndrome, rhesus hemolytic disease of the fetus and the newborn; and those associated with maternal diabetes, and maternal exposure to valproic acid or iodine deficiency during pregnancy. Challenges to prevention efforts are reviewed. The aim of this review is to bring to the forefront the urgency of birth defects prevention, surveillance, and prenatal screening and counseling; and to help public health practitioners develop population-based birth defects surveillance and prevention programs, and policy-makers to develop and implement science-based public health policies.

1. Introduction

Birth defects are one of the leading causes of infant mortality in the world, contributing to more than 3 million deaths among children aged <5 years [1]. Their impact is immeasurable, having life-long health and economic implications for the affected individual, the family, and society. Middle- and low-income countries have twice the prevalence and mortality associated with birth defects compared with developed countries [1]. When addressing mortality among people aged <50 years, birth defects are among top contributors.

A recent report on the global burden of disease ranked birth defects as the 17th most common cause of disability-adjusted life-years (DALYs), amounting to 39 million DALYs. This came as an improvement since 1990, when birth defects ranked 13th among the leading causes of DALYs and contributed to a total of 54 million DALYs [2]. These statistics indicate that birth defects prevention efforts in the last two decades were beneficial, and there is a need to further intensify their surveillance and prevention. Only then can we achieve maximum reduction in birth defects-associated DALYs in a global context. Also, there is an increasing consensus on shifting focus to non-communicable diseases worldwide, which are now leading the burden of disease and rising in prevalence.

Lack of population-based surveillance and prenatal care programs contributes to gaps in our knowledge of birth defects in the developing world. Even though they appear to be rare, birth defects are a major public health priority at a population level. As with polio and smallpox, many birth defects are preventable and can be completely eliminated by timely primary prevention.

We have reviewed current literature on a group of major birth defects that are highly preventable. These birth defects include congenital rubella syndrome, folic acid-preventable spina bifida and anencephaly, fetal alcohol syndrome, Down syndrome, and rhesus hemolytic disease of the fetus and newborn. We have also reviewed birth defects associated with maternal diabetes, those with in-utero exposures to valproic acid, and maternal iodine deficiency. Our aim is to identify their prevalence in the populations and challenges to primary prevention strategies. We hope that this review will serve as a resource to address modifiable risk factors for preventable birth defects and provide an update on current research in the field. Public health practitioners and epidemiologists can use this review as an update on population-based birth defects surveillance and prevention programs. Our review may be helpful to policy-makers to implement science-based policies such as mandatory food fortification, and universal prenatal screenings and vaccinations.

2. Congenital rubella syndrome

Congenital rubella syndrome is a group of birth defects that result from maternal infection to rubella virus during pregnancy. Affected infants suffer with cataracts, hearing loss, congenital heart defects,

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and both physical and mental retardation. Severity of these defects depends on the time at which the fetus is exposed to the infection in utero, with the highest risk during the first trimester. Congenital rubella syndrome also poses a high risk of transmission from the affected infant during the first year after their birth, contributing to the spread of infection to those in their household or close contact. First identified in 1941, congenital rubella syndrome has been associated with a high infant mortality worldwide [3]. Introduction of rubella vaccination during the early 1970s and effective implementation of mass vaccination programs in several World Health Organization (WHO) member countries in recent years has led to about 80% reduction in rubella cases, and consequently congenital rubella syndrome [4]. However, its prevention has not been complete due to challenges associated with birth and transmission rates in different countries [5]. Congenital rubella syndrome has been completely eliminated in the USA as of December 2011 [6], and an ongoing surveillance monitors the success of this program [7], whereas middle- and low-income countries in Africa, the Western Pacific, and South East Asia, where the vaccination rates are below 70%, have significantly high rates of rubella infections among women of childbearing age [8]. Because of these gaps in primary prevention, about 120 000 rubella cases still occur each year in the world [4]. China, Bangladesh, Poland, Bosnia and Herzegovina, and Ukraine document the highest proportion of congenital rubella cases, with an estimated total of 100 000 births affected each year [9]. Some of the challenges to total prevention of congenital rubella syndrome are variability in vaccination coverage within and between countries. Countries with high birth rate require more than 80% vaccine coverage among women of childbearing age, thus requiring additional vaccination campaigns. Also, population isolation in low-income countries hinders vaccination programs [5]. The WHO has strongly urged countries that are lacking rubella immunization programs to accelerate their efforts to prevent rubella and congenital rubella syndrome [10]. Complementing current immunization programs with selective rubella vaccination among girls and young women is recommended [3].

3. Folic acid-preventable spina bifida and anencephaly

Folic acid-preventable spina bifida and anencephaly (FAPSBA) are common birth defects affecting the central nervous system. In spite of unequivocal evidence from controlled trials in 1991 confirming the effectiveness of folic acid in prevention of spina bifida and anencephaly [11], each year about 246 000 cases of FAPSBA occur globally [1]. Countries that have implemented mandatory folic acid fortification of food have seen a significant reduction in the prevalence of FAPSBA [12–14]. But not all countries implement mandatory fortification policies that promote adequate folic acid by women of reproductive age [15]. Bell and Oakley [16] have estimated the proportion of FAPSBA cases that can be prevented worldwide, suggesting that 75% of all neural tube defects can be prevented through folic acid fortification, and when there is a good coverage of population with access to the country-specific fortification program. Accordingly, less than one-quarter of total preventable cases of FAPSBA were prevented worldwide. The number of cases of FAPSBA prevented have increased from 9% in 2006 [16] to 15% in 2012 [17]; however, more needs to be done to prevent remaining cases, which amount to 200 000 cases each year globally. There is an urgent need for those countries with the majority of these cases, such as India [18] and China [19,20], to implement mandatory folic acid fortification policies and to promote consumption among women of reproductive age. Some countries opt to offer folic acid supplements to adolescent girls and women, instead of fortifying centrally processed food. Such a prevention strategy based on folic acid supplement intake is shown to be effective in only 50% of women who adhere to the program [21]. It has also been shown that supplement programs for high-risk women with a history of neural tube defect-affected pregnancy, even if successful, prevent only a small fraction (2–5%) of FAPSBA [21]. Thus, optimal prevention of FAPSBA is achievable only through mandatory fortification of centrally processed food. There are many challenges for mandatory fortification programs in low- and middle-income countries: fortification programs are known to be dynamic and influenced by industry and consumption patterns, lack of political will to implement mandatory fortification, resistance from the milling industry to purchase and disseminate folic acid premix in the flour, isolation and individual dietary practices of communities that limit intake of centrally processed flour, and concerns about safety, cost-effectiveness, and impact on consumer choice. In countries that implement fortification, compliance and uptake have to be monitored periodically. Overall, assessment of serum folate concentrations among women of reproductive age can serve as an easy and cost-effective way to identify risk for FAPSBA and implement primary prevention Figure 1.

4. Fetal alcohol syndrome

Fetal alcohol syndrome is a structural and neurodevelopmental group of disorders in individuals with prenatal exposure to alcohol. Those affected suffer lifelong disability, with no cure. There is a wide variation in the prevalence of fetal alcohol syndrome worldwide, and numbers of cases have steadily increased in the last decade [22]. In the USA, the estimated prevalence is 2–7 cases per 1000 live births [23]. Studies from Europe [24], Africa [25–27], Israel [28], Australia [29,30], and Russia [31] show a much higher prevalence. The highest prevalence to date has been reported from high-alcohol-consuming regions of South Africa (90 per 1000 births) [32]. The WHO has recently convened to study the burden of fetal alcohol syndrome in developing countries using in-school screeners. Worldwide, 5–10% of all pregnancies are at risk for alcohol-related birth defects [33,34]. Recent studies in the USA show that almost 50% of reproductive-aged women used alcohol, which included about 8% of pregnant women; while binge drinking is prevalent in 15% of non-pregnant women and 1.4% of pregnant women [35]. Drinking during pregnancy is also a major concern in low- and middle-income countries [36–38]. As maternal alcohol use during pregnancy is frequently under-ascertained during the prenatal period, this estimate may be much higher in reality [39]. Behavioral modification among reproductive-aged women should be the central theme in the prevention of fetal alcohol syndrome [40]. Some challenges to prevention of fetal alcohol syndrome include cultural and societal attitudes concerning alcohol use, women with high-risk behaviors entering prenatal care late in pregnancy, and lack of, or inaccessible, preventive and counseling services in several countries. Addressing barriers such as guilt and embarrassment among women regarding their alcohol use will also be an important challenge in assessing the burden [41]. It has been shown that a majority of health care providers fail to address the effects of alcohol abuse or to diagnose fetal alcohol syndrome due to lack of training and knowledge [42,43]. Assessment of maternal alcohol use during pregnancy should become a standard and routine measure to aid in risk assessment for the fetus and for counseling and treatment of alcohol use. Finally, an integrated approach should be developed to provide health, social, and referral services in a culturally adopted setting to those affected with alcohol-related birth defects.

5. Maternal age and Down syndrome

Down syndrome is the most common chromosomal abnormality in newborns. Affected individuals have high rates of intellectual disability and several birth defects. Down syndrome was first characterized in the mid-1800s, and advanced maternal age was determined as the most significant risk factor in the early 1930s [44]. Non-

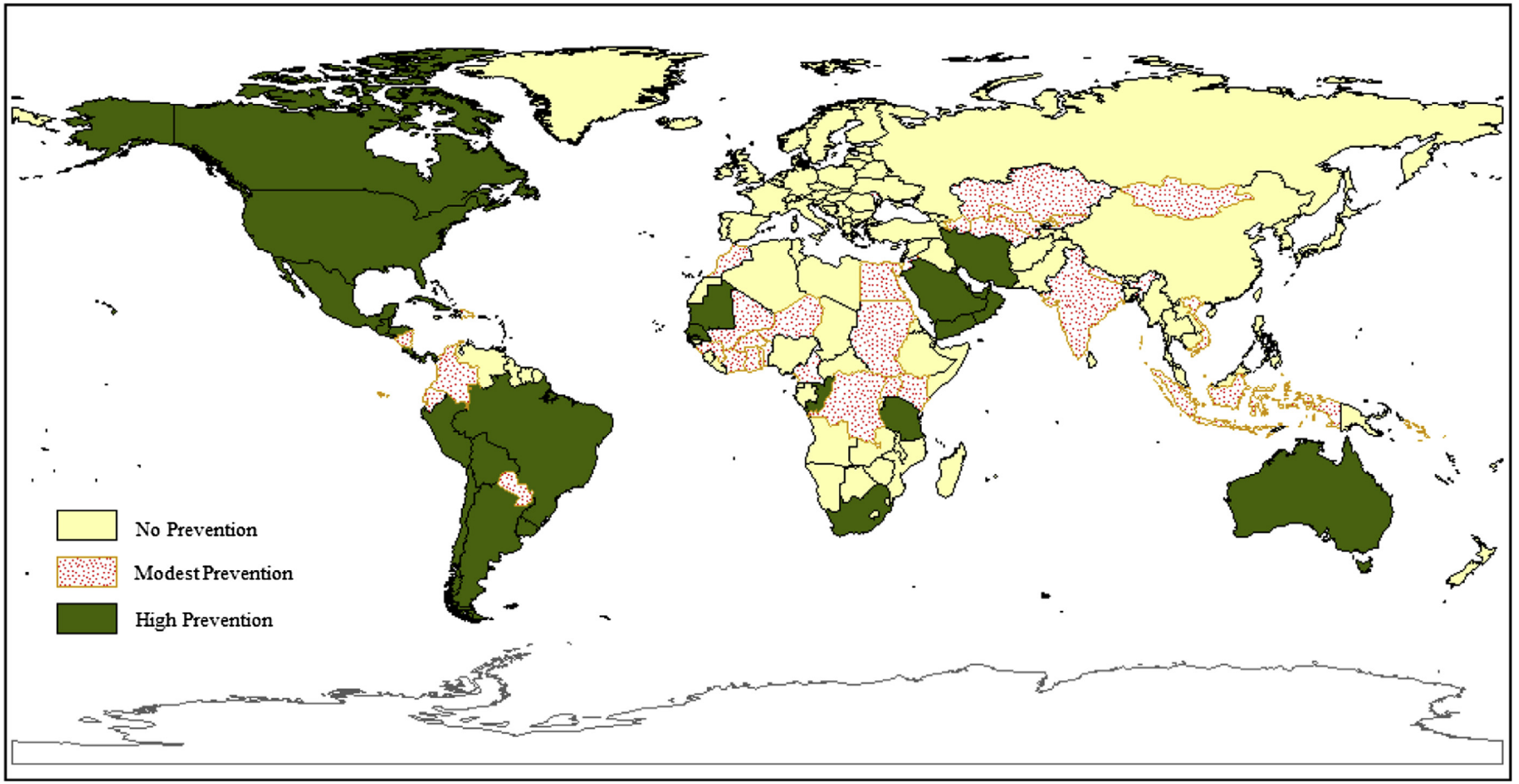

Figure 1. The status of global prevention of folic acid-preventable spina bifida and anencephaly, 2012 [17].

disjunction errors in chromosomes and/or biological aging of oocytes in mothers of advanced age are suggested as probable causes for Down syndrome [45]. Despite improved knowledge and screening, about 5400 births in the USA are affected with Down syndrome each year [45]. The prevalence of Down syndrome has increased in the last two decades, with an increasing trend in delaying childbirth globally [46]. Middle- and low-income countries record a large proportion of births to women of advanced age, while reporting twice as many cases of Down syndrome as developed countries [1,47]. On the contrary, countries where family planning is well-promoted show early and better-spaced pregnancies, and have lower births to women of advanced maternal age. European countries that have national screening policies for Down syndrome (within the first trimester) identify a large number of prenatally diagnosed Down syndrome cases, as compared to countries without such policies [48]. A large majority of prenatally diagnosed Down syndrome cases ($\sim$90%) are medically terminated. Socio-economic and technological disparities hinder the success of prenatal screening programs in both developed and developing countries. Both individual and societal changes that encourage lowering the age of conception among women will serve as the single most cost-efficient and effective intervention to prevent Down syndrome in future births. Implementation of universal screening and counseling (both pre and post conception) is urgently required in middle- and low-income countries. Improving organizational and cultural factors to reduce variation in prenatal screening will better contribute towards Down syndrome prevention in several countries [48].

6. Rhesus hemolytic disease of the fetus and newborn

Several red-cell antigens have been identified in association with the hemolytic disease of the fetus and the newborn (HDFN). Among these, antigen RhD is one of the most common. Incompatibility between RhD-negative mother and RhD-positive fetus during pregnancy will result in production of antibodies to the fetal RhD antigens (also termed as alloimmunization) [49]. Pregnancies complicated by alloimmunization have a high risk of fetal and neonatal morbidity and mortality in future pregnancies, and in the absence of timely prophylaxis can lead to fetal jaundice, hydrops (requiring intrauterine transfusions), fetal anemia, and stillbirths in about 2.4 per 1000 live births [50]. The mortality rate associated with HDFN in a developed country such as the UK is about 6 per 100 000 live births or 50 deaths per year [51], and is expected to be much higher among developing countries. The alloimmunization is completely treatable by early identification and administering anti-D immune globulin to the expectant mother. Anti-D immune globulin has been in use since the 1960s and has resulted in marked reduction in the alloimmunization to RhD antigen in pregnant women [52]. Lacking prophylaxis, it is estimated that at least one in every six RhD-negative women delivering an RhD-positive baby would be at risk [53]. To understand the racial distribution of this burden, $\sim$15% of Caucasians, 3–5% of African-Americans, 8% Asian-Indians, and $<$1% of Asians have RhD-negative blood groups [50,54,55]. The prevalence of RhD-negative blood group in Europeans is relatively high, and varies between 11% and 21%. For example, in western countries, as in England and Wales, it is estimated that $\sim$17% of the pregnant women are RhD-negative, and, among these, 59% are at risk for alloimmunization [56]. Non-invasive methods have gained prominence and have aided significantly in the reduction of the affected cases. However, several limitations exist. Improper screening for RhD-negative status, limited prenatal care facilities, and failure of identification and treatment with immune globulin among high-risk pregnancies has contributed to persistence of the problem around the world. Developed countries have implemented successful screening programs to identify RhD-negative women early in pregnancy and administer the immune globulins to prevent HDFN; however, there is a wide variation in both screening methods and clinical management policies among different countries [57]. On the other hand, most developing countries lack screening. According to the March of Dimes, 100% of cases with HDFN can be prevented by immune prophylaxis [1]. In sub-Saharan Africa the frequency of RhD-negative women is: Nigeria 4.4%, Guinea 4.1%, Kenya 3.9%, western Uganda 3.6%, and Cameroon 2.4%; yet there is limited prophylaxis available due to several challenges including poor research, limited access, affordability of anti-D immune globulin, high prevalence of illegal abortions, and poor documentation of medical histories on previous pregnancies, all of which are associated with high rates of HDFN-related morbidity and mortality in the region [58–63]. In order to achieve reduction in the deaths associated with HDFN, there is an urgent need for prenatal screening for RhD antigens, universal access of immune prophylaxis to all women who test RhD negative, better documentation of reproductive histories, and promotion of post-partum prophylaxis to mothers at risk.

7. Maternal diabetes associated birth defects

Maternal insulin-dependent diabetes and adverse glycemic control in pregnancy has been consistently associated with a high risk of birth defects in the offspring both in developed and developing countries [1]. A three-fold increased risk has been noted for major cardiovascular, renal, and gastrointestinal defects in infants born to diabetic mothers compared with their counterparts [64–66]. Overweight and obesity are significant predisposing factors that lead to diabetes, and both children and adults are at risk worldwide [67]. Despite advances in medical management, birth defects associated with maternal diabetes are a common occurrence. In the USA $\sim$100 000 babies are born to diabetic mothers. The prevalence estimates for diabetes-associated birth defects range between 2 and 6 per 1000 births in high-income countries, and are expected to be several times greater in low- and middle-income countries [1]. Pregnant mothers with higher levels of HbA1c at conception have a greater risk of delivering a baby with birth defects as compared to pregnant mothers with normal levels. Better glycemic control before pregnancy is shown to reduce the risk significantly [68]. Unfortunately, more than one-third of women of reproductive age with diabetes are unaware of their condition [69]; this proportion may be incrementally more in developing countries [70]. However, prevention of diabetes-associated birth defects is possible [71]. Selectively monitoring women with juvenile diabetes can be part of the solution. Also, screening women for high Gamma-hydroxybutyrate (GHb) concentration will help identify high-risk pregnancies, and prevention efforts can be focused accordingly [72]. Both public- and patient-oriented approaches in lifestyle modification are needed. Awareness of diabetes and its pregnancy-related risk must be improved among women of reproductive age worldwide. Population-based screening for women with undiagnosed diabetes is also an urgent need. Challenges exist in terms of feasibility and funding for universal screening. Africa and South East Asia, which face the highest burden of diabetes, have a dearth of primary health centers that can provide oral hypoglycemic agents to pregnant diabetic women [73]. Other challenges include failure to adhere to, or respond to, treatment among those who are on diabetes medications [74]. A multi-pronged approach with increased awareness among health care professionals, periodic screening, and management, has been shown to have a positive impact on prevention [75,76]. As a primordial prevention, governments should devise health policies that promote both education and healthy lifestyles. Political will, advocacy by health care professionals, and involvement from the community are important next steps to boost prevention of diabetes-associated birth defects [74].

8. Valproic acid

A positive association between valproic acid (an anti-epileptic drug) taken in early pregnancy and having offspring with spina bifida was first shown in the year 1982. This association was highly significant, with a 20-fold increase in risk of spina bifida to babies born to mothers who were exposed to valproic acid in the first trimester compared with those born to mothers who were unexposed [77]. Several subsequent studies further confirmed this association, along with new findings of valproic acid teratogenicity in association with other major birth defects, including cardiac, urinary, and oro-facial defects in the fetus [77–84]. Following these studies, many countries have revised their prescription guidelines for women with epilepsy and have recommended judicious use of valproic acid during pregnancy for epilepsy disorders, advising less teratogenic forms of anti-epileptic drugs to women of childbearing age [85–88]. However, other uses of valproic acid, such as for pain, migraine, and bipolar disorder make them highly likely to stay in the market, and be prescribed to women of childbearing age without an epilepsy indication [89]. There is a high risk of off-label use of this drug in developing countries. The US Food and Drug Administration has made valproic acid a class X drug for migraines, where the risks involved in using valproic acid in pregnant women clearly outweigh potential benefits. Within the USA, it was estimated that ~40 cases of spina bifida have occurred due to valproic acid use [90], and about 4 per 1000 prescriptions are still written for valproic acid for non-epilepsy conditions [89]. The March of Dimes *Global report on birth defects* (2006) indicated that the risk of such exposure is even higher in developing countries where valproic acid use may be uncontrolled and more common compared with more expensive and less teratogenic anticonvulsive drugs [1,91]. Thus, it becomes an urgent necessity to educate not only neurologists, but psychiatrists and other practitioners to eliminate valproic acid prescriptions among women of childbearing age, and that its use is seldom justified, for both epilepsy and non-epilepsy indications. Additionally, awareness needs to be brought both among the medical community and among the population about the teratogenic effects of this drug, so women in developing countries are not exposed to valproic acid.

9. Iodine deficiency

Iodine deficiency affects ~2 billion people globally and is a large concern for women of childbearing age. Each year, about 50 million children are born to iodine-deficient mothers, and about 40% of these children suffer significant intellectual disability [92]. In 2007, the WHO reported a high prevalence of iodine deficiency in both developed and developing regions of the world, and not just confined to remote and mountainous regions, as previously thought [93]. National nutritional surveys from the USA estimate that ~35% of pregnant women have at least mild iodine deficiency [94]. To address this problem, the American Thyroid Association recommends 150 μg per day of iodine intake for pregnant and lactating women, starting early at preconception [95,96]. Pregnancy confers an increased need for iodine, [97] and its insufficiency has been associated with cretinism, intellectual delays, birth defects, and other suboptimal outcomes in the infant [95,98]. Iodine deficiency is also the most important cause of preventable intellectual disability in infants worldwide [96]. Dietary intake is the only source of iodine; however, prenatal vitamins and supplements also contain iodine and should be recommended to women of childbearing age. Use of iodized salt has been implemented in several countries to reduce iodine deficiency. But only 70% of households worldwide have access to iodized salt, and there is a need to promote it extensively to achieve optimal intake [99]. Known challenges to successful iodization include use of cheaper non-iodized salt, limitation in quality control during salt production, compliance failures, personal preferences, lack of awareness by households about benefits of iodized salt, market fluctuations, and poor enforcement of regulations mandating iodization [92]. Political commitment and salt iodization legislation are also important to move ahead. There is a need to identify optimal indicators for iodine deficiency, improved screening of women of childbearing age, and monitoring iodine content in salt. As most people are limiting their salt intake to reduce their risk of hypertension, other vehicles have to be explored to deliver needed iodine to populations worldwide [92]. Taking these timely steps, we may be able to prevent a majority of babies from the ill outcomes associated with iodine deficiency.

10. Other opportunities for prevention

A recent review summarized a list of preventable birth defects (Box 1) [100]. This prevention can be achieved by screening for chromosome abnormalities and genetic disease, vaccinations, screening for teratogenic infectious diseases such as human immunodeficiency virus and gonorrhea, and limiting or eliminating the use of all known teratogenic drugs (e.g. anticoagulants, retinoids, and thalidomide). We should also be vigilant of new teratogens. Parents should be informed of preconception diagnostic choices including amniocentesis, chorionic villous sampling, maternal serum monitoring, and ultrasound monitoring to diagnose identifiable genetic diseases and serious birth defects.

Box 1
Prevention of congenital malformation and reproductive effect [100].

1. Rubella vaccination.
2. Folic acid and vitamin B_{12} supplementation: 400 μg and 6 μg per day.
3. Supplementation of iodide to deficient patients and populations.
4. Meticulous diabetic control.
5. Competent diagnosis and management of maternal hypothyroidism.
6. Screening for chromosome abnormalities and genetic disease.
7. Hepatitis B vaccination for at-risk women.
8. Human immunodeficiency virus screening and treatment.
9. Screening for *Neisseria gonorrhoea*, *Chlamydia trachomatis*, group B streptococcus.
10. Vaccination of patients with group B streptococcus.
11. Maternal phenylalanine management for maternal phenylketonurics.
12. Management or discontinuation of oral use of anticoagulants, anticonvulsants, retinoids, thalidomide and all known teratogens.
13. Recognize that new teratogens can be represented in the next new drug or chemical exposure: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mycophenolate, tumor necrosis factor blockers.
14. Amniocentesis, chorionic villus sampling, maternal serum monitoring, ultrasound monitoring to diagnose identifiable genetic diseases and serious birth defects in order for the parents to be informed about their options.
15. Maternal smoking and alcohol cessation.
16. Obesity control in itself reduces the risk of birth defects and decreases the risk of developing diabetes.
17. Immunization against known teratogenic infections. Botulina toxin vaccine for the pregnant mother to prevent infant botulism.
18. Malaria vaccine to prevent malaria in pregnancy which increases the risk of miscarriage.

Timely counseling on high-risk behavioral and lifestyle choices such as maternal smoking, alcohol, caffeine, recreational drugs, and obesity and overweight is needed in relation to their adverse effects on pregnancy. While there are many prevention strategies to reduce the incidence of birth defects worldwide, there is not enough space allotted in this article for such extensive review.

11. Conclusion

Opportunities to prevent birth defects are abundant, but there are also many challenges in the process. Pediatricians, researchers, and public health practitioners in the field of birth defects should intensify prevention efforts, and undertake comprehensive and integrated efforts to accelerate the pace of prevention at a global scale for preventable birth defects. Help and commitment from governmental and non-governmental organizations, in a complementary manner, is crucial to developing affordable and feasible prevention programs. Only then can we achieve our goal of bringing current rates of major preventable birth defects close to nil.

We have witnessed the global eradication of polio, which is almost of the same magnitude as the current number of cases of folic acid-preventable spina bifida. Similarly, an integrated approach from the government and non-governmental agencies has resulted in global eradication of smallpox. Lessons from successful programs can be shared. Birth defects prevention is achievable by combating socio-economic inequities and disparities in health care for women of reproductive age. Need-driven and impact-oriented approaches with improved education, prophylaxis, and prenatal care are needed. There exists an urgent need to translate research findings to policy.

Now that developed countries are on their path towards success, priority should now be placed on middle- and low-income countries. Funding for birth defects surveillance is urgently required to plan and develop a functional primary prevention infrastructure for future births. Over time, the health and economic returns, both at micro and macro levels, would be significant. Political will and commitment by communities are an absolute necessity to initiate and sustain birth defects prevention on a global scale.

Practice points

- Global programs to prevent birth defects are an urgent global health priority.
- Congenital rubella syndrome and folic acid-preventable spina bifida and anencephaly could be eliminated from all countries by implementing prevention programs already shown to eliminate these birth defects in a few countries.
- Effective intervention programs must be developed and implemented to prevent the three-fold increase in major malformations among women with insulin-dependent diabetes mellitus, as well as birth defects and developmental disorders from in-utero exposure to alcohol.
- Valproic acid should be limited to persons with epilepsy who have been shown not to have control with at least one other anticonvulsant, and should never be the first-line treatment for epilepsy for women of reproductive age.
- Active, effective intervention programs promoting optimal maternal birth age are needed to reduce the current Down syndrome epidemic in developed countries and to prevent the epidemic in countries that have yet to experience it.
- There is a need to further intensify birth defects surveillance and prevention programs in developing countries.
- Political will and commitment by communities are integral for birth defects prevention on a global scale.

Conflict of interest statement

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