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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-