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An expanded view of infertility: The challenge of the changing profiling of major birth defects in China

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SUMMARY Over the past two decades, China has experienced a significant decline in birth rates, accompanied by a decrease in fertility and changes in major congenital defects. The development of assisted reproductive technology (ART) has brought hope to individuals facing infertility. However, some issues related to reproductive health and congenital defects have arisen. The reasons for the changing profiling of birth defects and the relationship between the decline in fertility and ART need to be further investigated. Lifestyle factors such as nutritional supplementation need to be altered to protect reproductive capacity. Birth defects, such as congenital heart defects and hypospadias, may serve as a signal for understanding the decline in fertility. To improve fertility, the factors contributing to it need to be identified, vital genetic and medical technologies need to be introduced, and environmental interventions, such as nutritional changes, need to be implemented.

Keywords assisted reproductive technology (ART), infertility, birth defect, hypospadias, congenital heart defects

Over the past two decades, China has undergone significant changes in the structure of its population, with a decline in birth rates from 14‰ to 6.8‰ (Figure 1A) and an acceleration of aging. At the same time, there has been a notable decrease in the incidence of severe birth defects during the perinatal period, such as neural tube defects (NTDs) (Figure 1B). However, the fact that the prevalence of infertility among couples of childbearing age in China has increased to 25% is concerning (*1*). Advances in assisted reproductive technology (ART) have led to a significant demand for surrogacy, resulting in the emergence of a substantial underground market driven by infertile individuals seeking to fulfill their desire for parenthood (*2*). The fact that factors such as age, environmental exposure, lifestyle, and pathophysiological factors contribute to infertility is evident (*3*), but it is the obligation to be aware of several critical aspects of reproductive health related to birth defects.

First, the prevalence of major birth defects has changed, accompanied by a decline in fertility. In 2020, the ten most prevalent birth defects during the perinatal period were congenital heart disease (CHD), polydactyly, syndactyly, hypospadias, clubfoot, total cleft lip, cleft palate, rectal anal atresia or stenosis, hydrocephalus, and microtia (Figure 1B). The prevalence of NTDs and limb shortening has significantly declined, and the two no longer rank among the ten most prevalent birth defects. CHD ranked as the most prevalent birth defect, while polydactyly has consistently been the second most prevalent since 2000. Syndactyly and hypospadias, in contrast, have respectively risen from the ninth and eighth most prevalent birth defect in 2010 to the third and fourth most prevalent in 2020. The prevalence of CHD, polydactyly, syndactyly, hypospadias, and clubfoot in 2020 was significantly higher than in year 2000, with the prevalence CHD increasing 15.2-fold, that of polydactyly increasing 1.9-fold, that of syndactyly increasing 2.0-fold, that of hypospadias increasing 1.6-fold, and that of clubfoot increasing 1.1-fold. In a recent retrospective cohort study involving 507,390 singleton or twin pregnancies, the prevalence of CHD was found to be higher in pregnancies assisted by reproductive technology compared to non-assisted pregnancies (adjusted odds ratio: 1.70, 95% confidence interval: 1.48-1.95) (*4*). The etiology of CHD is multifactorial (*5*), indicating the involvement of multiple genetic and environmental factors that interact

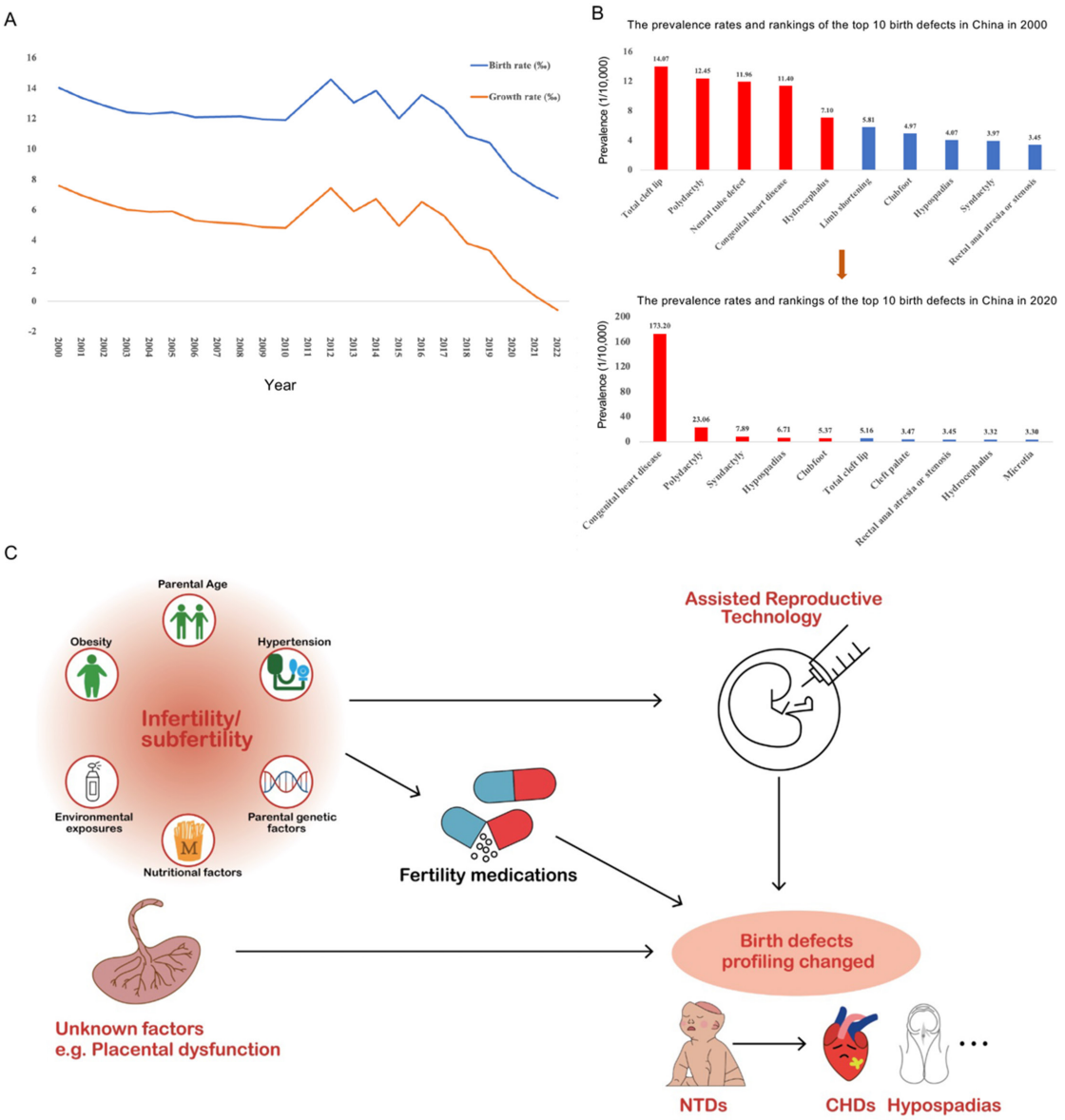

Figure 1. The changing trends in birth defects in China and the potential causes of an increase in specific birth defects. (A) Changes in the birth rate and growth rate, from 2000 to 2022 in China. **(B)** The changing prevalence and rankings of the top 10 birth defects in China in 2000 and 2020. **(C)** The potential multifactorial etiology of an increase in the specific birth defects associated with infertility and assisted reproductive technology.

with each other. Confounding factors, such as maternal age, fertility medications, and placental dysfunction, appear to play a crucial role in determining the increased risk of CHD. However, further evidence is necessary for a precise assessment of the actual risk. Men with hypospadias have a reduced likelihood of fathering biological children due to impaired fertility, leading to an increased reliance on ART and a higher risk of being diagnosed with male infertility (*6*). Overall, the changing prevalence of major birth defects and the association between ART and impaired fertility in men with hypospadias highlight the complex dynamic relationship between reproductive health and birth outcomes and the need for comprehensive research and interventions in this field.

Second, nutritional supplementation plays a role in influencing the types of major birth defects. Findings from years of animal and human studies have revealed that the vast majority of birth defects have multifactorial origins, with contributions from environmental exposure and inherited genetic factors. Environmental exposure refers to kinds of non-genetic factors that disrupt the normal developmental process during intrauterine life. These factors encompass exogenous elements (such as metallic elements, air pollutants, and pesticides), substances consumed during early pregnancy (alcohol, drugs, smoking, *etc.*) and maternal nutritional status (folic acid (FA), inositol, choline, Vitamin B12, *etc.*). Despite the reduction in the prevalence of NTDs due to the introduction of FA supplementation during pregnancy by

the Chinese Government (*7,8*), the changing landscape of birth defect types presents new challenges. A decrease in fertility is mainly dependent on the low quality of female and male gametes. Metabolic levels of the nutrient inositol were reported to ensure the proper functioning of male and female reproductive cells, and impaired or abnormal levels in follicular fluid (FF) or semen are frequently associated with pathological features and reduced fertility (*9,10*). Encouraging proper nutrition and supplementation, with supplements such as inositol, that positively impact the reproductive system can improve fertility rates to ensure safe embryo formation and fetal development.

Further elucidation is needed to understand the genetic causes and underlying mechanisms that contribute to infertility associated with CHD and hypospadias. A recent large prospective cohort study involving 38,528 postmenopausal women found that infertility is associated with an increased risk of overall heart failure in the future (*11*). ART offers hope to infertile patients, but the transmission of infertility-associated variants to future generations is a concern. The analysis of genetic factors influencing infertility holds significant promise in providing valuable insights into the development of targeted treatments for patients and unraveling the causes of idiopathic infertility. The multifactorial inheritance of CHD and hypospadias suggests a significant genetic component contributing to the risk of these birth defects (*5*). The association between 37 transcription factor (TF) genes and CHD and hypospadias suggests their critical role in these conditions, where a stable equilibrium network governed by TF expression contributes to robustness (*5*). Emerging sequencing technologies that offer a global perspective on genetic analysis have the potential to advance our understanding of the etiology of infertility by genetically profiling CHD and hypospadias associated with infertility. Over half of the genes responsible for CHD that have been identified through whole-exome sequencing (WES) are associated with ciliopathies in mouse models (*12*). Moreover, damaging variants of ciliary genes were found to be enriched in patients with transposition of the great arteries (TGA) (*13*), a complex congenital heart defect. Chen *et al*. reported that knock-out of the *Dnah8* gene causing hypospadias resulted in decreased testosterone levels in male mice and failure to produce offspring (*14*). These results further substantiate the established link between ciliary function and CHD, hypospadias, and infertility. In addition, rare diseases affecting the endocrine and reproductive systems, such as disorders of sex development (DSD), androgen insensitivity syndrome (AIS) (*15*) and urogenital sinus malformation (*16*), can also have implications for fertility and warrant attention.

The changing trends in birth defects in China and the prevalence of infertility pose a significant medical concern, and yet the mechanisms underlying infertility are still poorly understood. The rising prevalence of infertility has driven an increased demand for ART. Birth defects, including CHD and hypospadias, may serve as an early warning signal for reproductive health issues in the broader population. Preimplantation genetic diagnosis and appropriate nutritional supplementation are crucial, particularly for individuals with a family history of infertility. To improve fertility, factors contributing to it need to be identified, vital genetic and medical technologies need to be introduced, and environmental interventions, such as nutritional changes, need to be implemented in the future.

Data availability: The birth rate and growth rate data (from 2000 to 2022 in China) are available from the National Bureau of Statistics of the People's Republic of China (*http://www.stats.gov.cn/sj/*) (in Chinese). The prevalence and rankings of the top 10 birth defects in China in 2000 and 2020 are available from the Maternal and Child Health Surveillance of China (*https://www.mchscn.cn*) (in Chinese).

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