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Review Article

Down syndrome from Epidemiologic Point of View

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Abstract

Down syndrome (DS) is the most frequent chromosomal disorders in the world. It occurs in all countries, all races, and both sexes. There are many factors affecting the occurrence of DS as it is multi-factorial and includes both genetic and environmental factors. These factors include the maternal age distribution in the population, efficiency and completeness of ascertainment, the degree of accuracy of diagnosis, the degree of acceptance of selective prenatal termination of affected pregnancies in the community, as well as different unrecognized genetic and environmental factors. Incidence of DS is found to be high in the developing countries, probably related to the higher morbidity due to the comorbidities associated with DS. Improving survival of infants with DS due to the improved provided health care affects the prevalence rather than the incidence of DS. The global predictable incidence of DS according to World Health Organization is expected to be between 1-10/ 1000 live births all over the world. This article will discuss the difference in prevalence among different populations and countries and the potential risk factors affecting occurrence of DS in the community.

Keywords: *Africa; America; Arab world; Asia; Chemical Toxins; Children; Chromosome aberrations; Consanguinity; Cytogenetic; Down syndrome; Environmental factors; Europe; Genetic Factors; Gonadal trisomy mosaicism; Incidence; Ionizing radiation; Maternal age; Paternal age; Prevalence; Smoking; Socioeconomic Status*

Introduction

Down syndrome (DS) is the commonest chromosomal disorder all over the world. It occurs in all countries, all races, and both sexes. In the modern medicine, it was described for the first time by Jean Etienne Dominique Esquirol (1772-1840) followed by Édouard Séguin who described some clinical features of DS after 6 years in 1844. However, John Langdon Down was the first one who did a complete description of clinical features of the syndrome in 1866. In 1909, Shuttleworth was the first physician who observed the association between the increased maternal age and the increased risk of DS [1]. However; trisomic aberration of chromosome 21 as reason for development of DS was first described by a French human geneticist Jérôme Jean Louis Marie Lejeune (1926-1994) in 1959. After that, a flow of researches was done to uncover the role of the extra chromosome 21 in relation to the phenotype of DS [2].

Many epidemiological studies interested with the prevalence of DS have been conducted over the last 100 years, describing the multifactorial nature of the syndrome and studying both the genetic and the environmental factors. These studies were also interested in the temporal, racial, geographical, and environmental differences in rates. The prevalence of DS differs from a country to another and sometimes from a district to another within the same country. However; the global predictable incidence is generally between 1 to 10/1000 live births all over the world according to World Health Organization [3]. The aim of this review article is to shed some light about the factors that could increase the risk of having a child with Down syndrome as well as the prevalence of this condition in the different parts of the world.

Factors affecting the Risk of Down syndrome

Occurrence of DS is multi-factorial and includes both genetic and environmental factors. Down syndrome results from chromosomal imbalance due to the genomic content of an extra chromosome 21 and with altered expression of these genes due to presence of a third copy which usually generally result from non-disjunction during the stage of meiosis of either in the ovum or the sperm. In less frequent occasions, it results from either translocations or mosaicism (one normal cell line and one trisomic cell line) [2]. These factors that could affect the prevalence of the syndrome include; the maternal age distribution in the population, efficiency and completeness of ascertainment, the degree of accuracy of diagnosis, the degree of acceptance of selective prenatal termination of affected pregnancies in the community, as well as different unrecognized genetic and environmental factors [4]. These factors can be categorized into physiological and acquired factors as shown in table 1.

Physiological factors	Acuired Factors
1- Maternal age at the time of conception	1- Availability of antenatal diagnostic tests
2- Increasing father age	2- Socioeconomic status and parents education
3- Increasing maternal grandmother age	3- Rate of acceptance of pregnancy termination in the community.
4- Altered recombination pattern along chromosome 21	4- Exposure to environmental chemicals, toxins, drugs, cigarette smoking, and ionizing radiation
5- Short interval between pregnancies	5- Maternal diseases: e.g. maternal autoimmune diseases including gestational diabetes and thyroid autoimmunity
6- Multiple Versus singleton pregnancies.	6- Nutritional deficiency: e.g. Folate deficiency
7- Previous child with DS	7- Maternal use of hormonal contraception and vaginal spermicides
8- Unrecognized genetic factors	8- Unrecognized environmental factors

Table 1: *Factors affecting the Risk of Down syndrome.*

Physiological Factors

The maternal age at the time of pregnancy is considered as the most important risk factor to have a child with DS. Many studies documented that the average maternal age at the time of pregnancy of a fetus with DS is significantly higher than that of mothers with normal euploid fetus in different populations and races [5,6]. The risk of getting a baby with DS is less than 1 in 1,400 for a mother below the age 25 years, which increases to 1 in 1,000 for a mother less than 30 years. The risk further increases to 1 in 350 for mothers who become pregnant at age 35 and continues to increase as the woman get elder, so that by age 42, and by age 49, the chance is 1 in 60 and 1 in 12 correspondingly [7]. However, some studies reported that nearly 80% of children with DS are born to young mothers less than 30 years [8].

The increased maternal age increases the risk of aneuploid oocyte formation probably due to increased susceptibility of the eggs to the aging effects more than the sperms which when associated with damaging changes and toxic environmental effects accumulated over time increases the likelihood of aneuploid oocyte formation [9]. Maternal aging can also impair the chiasmatic chromosome segregation especially after the age of 35 years. Lack of chiasma, defective configurations of chiasma and decline in chiasma frequency can induce non-dysjunction of chromosome 21 and subsequent DS birth. This impaired chiasma segregation is due to delayed regulation of human proteins concerned with segregation of non-exchange chromosome with increasing ovarian age [10].

Advanced maternal age is associated with natural aging of the ovary which is distinguished by a decrease in the entire oocyte pool, a decrease in the number of antral follicles maturing/cycle and sex hormonal changes. Decreased oocyte pole may predispose the released oocyte to chromosome malsegregation and hence chromosome non-disjunction. Ovarian aging is also associated with inadequate level of hormonal signal and higher rate of meiotic errors [11]. The effect of advanced maternal age as a risk factor for having a child with DS

is limited to non-disjunction errors that occur in the ovum and not implicated in occurrence of DS due to paternal non-disjunction error in spermatogenesis, post-zygotic mitotic error, or translocation either inherited or de novo [12]. Maternal age does not only affect the prevalence of occurrence of DS, but also affect the prevalence of associated anomalies e.g. there is decrease in rate of associated congenital heart diseases in mother older than 32 years of age [13].

Altered recombination pattern along chromosome 21 is another important risk factor for occurrence of DS. Genetic recombination means exchange of genetic information between two DNA molecules with production of a new combination of alleles. Impaired, reduced or abnormal recombination along chromosome 21 is associated with a proportion of maternal non-disjunction errors [14]. Increasing mother age induces suboptimal exchange patterns and in turn increases the susceptibility to non-disjunction which increases with time and raises the proportion of non-disjunction due to normal exchange configurations [15].

Advancing maternal age is not the only risk factor for pregnancies with DS. Increasing father and maternal grandmother ages are other risk factors to have DS child. Increasing maternal grandmother age may disturb her daughter meiosis when the grandmother conceived. With advancing age, the grandmother's gonads may not succeed to make the necessary proteins like spindle associated proteins, factors responsible for resting of oocyte, chiasma-binding proteins, DNA repair enzymes, etc. which are required for proper meiotic segregation in her daughter germ cells and gives rise to non-disjunction of chromosome 21 in the daughter oocyte [16]. However, Kovaleva., et al. failed to support the suggestion that advanced age of the DS grandmother is responsible for meiotic disturbance in the daughter [17]. About 10% of trisomy 21 is due to non-disjunction of paternal origin [18]. Advanced father age (> 49 years) has been associated with increased risk of DS births due to production of more sperms with aneuploidy. However, this risk is considerably low with the appropriate adjustment for maternal age and many studies failed to confirm these effects and relate that risk to the associated advanced maternal age [19].

Short interval between pregnancies might increase the risk of subsequently bearing a child with DS due to increased vulnerability to maternal meiotic non-disjunction during the transitional period between an ovulation and the establishment of regular ovulation after childbirth [20]. The risk of DS per fetus/baby is lower in multiple than singleton pregnancies. These approximations can be used for genetic counseling and antenatal screening [21]. This was in contrast to the earlier studies which reported higher frequency of twinning among newborns with DS [22].

Having a previous child with DS increases the constant absolute excess risk above their maternal age-related risk of having a subsequent affected pregnancy. This absolute excess risk is determined by the age at which the affected pregnancy occurred and is higher for younger than for older women. For example; after a DS pregnancy at age 20, this excess is 0.62% at early second trimester, and, after pregnancy with a baby with DS at age 40, the risk is about 0.04%" [23]. Women, who have had a previous trisomic pregnancy, particularly those less than 35 years of age at the time, appear to be at an increased risk of future pregnancies being trisomic [24]. The higher recurrence risk for trisomy 21 among younger mothers can be explained if Gonadal trisomy mosaicism accounts for a larger proportion of recurrences in women whose maternal age–related risk is low. In these cases; DNA marker analysis does not provide a valuable tool for patient counseling in case of recurrent trisomy 21 [25].

Environmental Factors

Incidence of DS is expected to be significantly high in the developing countries, probably due to the limited use of DS antenatal diagnosis. The rate of using these diagnostic tests depends on many factors. The most important factor is the availability of the antenatal diagnostic tests (including chorionic villus sampling, ultrasonographic screening and maternal serum screening) to the community which successively led to the identification of trisomy 21 fetuses mainly in mothers aged less than 35 years. Antenatal diagnosis of DS helps the women to make an informed decision to terminate pregnancy when they have sufficient knowledge about DS. The decision will depend on the social standards, ethnic factors, economic status and religious factors. In countries where abortion is allowed to terminate pregnancies with DS such as France and many European countries; the birth prevalence of DS is significantly reduced. However, the situation is not the same among women of other races and from countries that do not allow abortion [26, 27].

Poor maternal socioeconomic status such as poor nutrition or environmental toxin exposures; increases the risk of congenital malformations and DS due to inadequate antenatal care and poor medical knowledge in the early stages of pregnancy, prevalence of nutritional deficiency, and other environmental factors that could share in the increased frequency of malformations. Educational status of the parents especially of the mother can affect the use of the health services for antenatal diagnosis; improve the parents' knowledge regarding pregnancy care and the health of their progeny as well as the selective impact of antenatal diagnosis, elective termination, and acceptance of prenatal diagnostic measures among population [28].

Exposure to environmental chemicals, toxins and drugs may potentially induce chromosomal non-disjunction including DS. Psychological diseases and frequent use of medications in the year before pregnancy is considered as a risk factor to have a baby with DS [29]. Maternal autoimmune diseases including gestational diabetes and thyroid autoimmunity are also considered as a risk factor for DS [30]. Mothers with abnormal folate metabolism and mutation in the methylene tetrahydrofolate reductase (MTHFR) gene or other genes concerned with folate metabolism were reported to have higher incidence of DS children. However, there is no evidence supporting that folic acid supplementation may reduce the incidence of DS. However, folic acid deficiency may affect the frequency and types of the anomalies associated with DS including congenital heart diseases [31, 32].

Maternal use of hormonal contraception may increase the frequency of DS as well as increasing the frequency of giving birth to more female children with DS than the usual predominance of DS among the male children. This observation is particularly noted in mothers older than 35 years and with irregular dose of oral contraceptive which exacerbate the adverse effects of natural aging-related hormonal imbalance in the ovary and lead to an increased anomaly in follicles [33]. The use of vaginal spermicides was also linked to the occurrence of DS among offspring born to women who used these contraceptive agents during the ten months before conception. However, studies failed to provide substantial precision in estimating the magnitude of the association between reported spermicide use and DS [34].

Some studies showed that cigarette smoking may increase incidence of DS but this effect is restricted to women younger than 35 years of age due to induction of meiosis II non-disjunction and disturbances of molecular components common to meiosis I and meiosis II stages among these women [33, 35]. However; Ghosh., *et al*.; denied this effect [36]. Despite ionizing radiation is able to induce non-disjunction in experimental animals but most studies failed to prove the link between ionizing radiation exposure and the increase incidence of giving birth to DS. Laziuk., *et al*.; found that it impossible to establish a causal relationship between these clusters of DS and exposure to the Chernobyl fallout, at a geographical level [37]. However, Sperling., *et al*.; reported increased incidence of DS births in low-dose irradiation exposed regions in Europe after the Chernobyl reactor accident [38].

Prevalence of Down syndrome

The incidence of DS may differ from a country to another according to the social and environmental factors predominate in such countries. For example; the incidence of DS may be significantly lower in developed countries than that observed in the developing countries due to the better application and uptake of antenatal diagnostic services and the permission of pregnancy termination among the discovered cases in the developed countries. However, the prevalence of DS which is based on the real population may be higher in the developed countries due to the improving survival of infants with DS observed due to the better care especially of cardiovascular malformations which affects the prevalence rather than the incidence of DS [39]. According to WHO; the estimated incidence of DS is between 1 to 10/1000 live births worldwide. The difference in prevalence among populations; countries or in the same population over time will depend on the potential risk factors in common for that community.

Africa	Australia: 0.6-0.9/1000
1- West Nigeria: 1.15/1000 (Year 1982) 2- South Africa: 2/1000 (1974-1993)	**Europe:** 1-3/1000 1- Belgium: 0.62/1000 2- Croatia: 1.4/1000 3- Czech Republic: 1.07/1000 4- Denmark: 1.14/1000 (in 1979) increased to 3.2/1000 (in 1994) 5- England and Wales: 1.08/1000 6- Ireland (EUROCAT): 1.83/1000 7- Scotland: 1.29/1000 8- Estonia: 1.17/1000 9- France: 2.17/1000 10- Hungary: 1.5/1000 11- Netherlands: 1.46/1000 12- Norway: 2/1000 13- Russia: was 0.93-2.2/1000 14- Spain: 1.3-2.91/1000
Arab world: 1- Emeritus: 3.12/1000 2- Oman: 2/1000 3- Libya: 1.94/1000 4- Qatar: 1.83/1000 5- Arabs in Israel: 1.83/1000 6- Saudi Arabia: 1.8/1000 7- Kuwait: 1.72/1000 8- Egypt: 1.42/1000	**North America:** 1- Canada: 1.24-1.7/1000 2- Mexico: 1.53/1000 3- USA: 0.9-1.18/1000
Asia China: 2/1000 Taiwan: 0.8/1000 India: 0.83/1000 Timor Leste: 1.24/1000 Indonesia:1.24/1000 Laos: 1.25/1000 Malaysia: 1.25/1000 Philippine: 1.25/1000 Singapore: 1.25/1000 Thailand: 1.25/1000 Vietnam: 1.25/1000 Japan: 2.55/1000 Pakistan: 0.9-1.24/1000 Iran: 1.22/1000 Turkey: 0. 9-0.99/1000	**South America:** 1- Brazil: 1.25/1000 2- Chile: 2.47/1000 3- Colombia: 1.25/1000 4- Paraguay: 1.25/1000 5- Peru: 1.25/1000 6- Venezuela: 1.25/1000

NB: the prevalence may differs from a region to another inside the same country.

Table 2: *Prevalence of Down syndrome in some parts of the world.*

Africa

The prevalence of DS in the African populations is not precisely estimated because of inaccuracy of most of the studies concerned with the incidence and prevalence of DS in sub Saharan Africa due to ignoring the influence of important factors such as socioeconomic, cultural, educational, genetic, racial and environmental characteristics of the different African populations on the prevalence of the condition, thus affecting the reliability of the data. The incidence in South Western Nigeria was 1 in 865 live births in 1982 [40] while was 1 in 500 live births in South Africa over 20 years periods between 1974 and 1993. There is also higher prevalence (1.88) among the white population compared with the prevalence in colored (1.54) and blacks because the prenatal screened and diagnosis of the condition and the relative distribution of the number of terminations following prenatal diagnosis, being higher among whites (18.3%), intermediate in colored (5.8%) and lowest in blacks (1.4%) [41].

Arab Worlds

The Arab world had rich history, diverse ethnic, cultural and religious makeup. The incidence of DS in the Arab world is generally higher than international figures. For example, DS incidence rates were 1:319 live births in Dubai, 1:500 in Oman, 1 in 516 in Libya, 1:546 in Qatar, 1:547 in Arabs in Israel, 1:554 in Saudi Arabia, 1:581 in Kuwait, and 1 in 700 in Egypt [42]. This high rate of DS among the Arabs is due to their characteristic socioeconomic and religious beliefs and views including common practice of consanguineous

marriages, increased maternal age and multiparity. Complete or partial lack of antenatal screening tests and strategies able to detect DS which could help the parent decision making to terminate pregnancies with DS fetuses as early as possible is another important confounding factor [43].

Asia

Asia is the largest continent in the world and is the most populous with very wide variation in demographics and ethnicity groups with subsequent variation in the incidence and prevalence of DS among the different countries and nations. In China with the integrated screening for DS in a Chinese population; the overall incidence of DS was 2/1000 in 2012 [44]. On the other hand; the overall incidence of DS in Hong Kong was 0.3 per 1000 population in 2010 which was much lower than the rest of China [45]. In Taiwan; with the widespread use of first-trimester screening augmented with the second-trimester quadruple test implemented after 2001; there was marked reduction in DS live birth rate among Taiwanese population to reach 0.8/1000 in 2010 [46].

Due to the wide diversity in demographics and ethnic characters of the Indians; there are different prevalence rates for DS from area to area inside India. In a relatively recent study done in Mumbai, the prevalence rate was 0.83/1000 with high frequency of DS in younger couples of first cousin marriages [47]. In the rest of Southeast Asia, the estimated number of people with DS in 2013 were 1,274 cases (out of 1,019,252 people) in Timor Leste, 298,066 (out of 238,452,952 people) in Indonesia, 7,585 (out of 6,068,117 people) in Laos, 29,403 (out of 23,522,482 people) Malaysia, 107,802 (out of 86,241,697 people) in Philippine, 5,442 (out of 4,353,893 people) in Singapore, 81,081 (out of 64,865,523 people) in Thailand and 103,328 (out of 82,662,800 people) in Vietnam. In Japan, the prevalence of DS failed to decrease despite the use of antenatal screening tests most likely due to the associated increase rate of pregnancy in mothers with elder age; to reach its peak in 2008 with an incidence of 1/392 of live birth; then started to decline and remained stationary between 2009 and 2012 [48].

In Pakistan, the 6th most populous country in the world; the incidence of DS is about 0.9-1.24/1000 of population [49] while in Iran, the incidence of DS is about 1.22/1000 of population live births [50]. In Turkey; a sixteen years of survey done between 1994 and 2010 showed that the prevalence rates of DS were 0. 9/1000 live births before 2000 and became 0.99/1000 live births after 2000. The relatively non-changing prevalence during these 16 years is related to the young population in Turkey, high fertility rate in women under 35 years old and the extensive application of prenatal screening programs [51].

Australia

The prevalence rate of DS in Australia is much lower than the worldwide rate of around 1 in 700 due to the high termination rates in Australia. In 2010; the overall population rate of people with DS is approximately 1:1,700 [52].

Europe

Europe is the third ranking populated continent with a population of 733-739 million and over 7000 new pregnancies affected with DS reported in European Union every year due to the increased mean of maternal age at the time of conception. However; the effect of increasing maternal age is partially counteracted by the widespread practice of prenatal screening and termination of pregnancy in most parts of Europe. However, the prevalence rate of DS may differ from a part to another inside Europe due to the large difference in screening policies, regulatory and cultural factors between countries in Europe [53]. The antenatal detection rate of DS ranges between 0-95 percent with a mean of 68%. About 88% of these affected pregnancies ended by termination. This resulted in a total prevalence (including terminations of pregnancy) of DS varied from 1-3/1000 births. The highest rate of antenatal detection of DS was observed in countries with a first-trimester screening policy while the lowest rate was observed in countries with no official national DS screening or structural anomaly scan policy [54].

North America

In United States of America, the birth prevalence of DS rose by 24.2% from 0.9 to 1.18 /1000 live births in 10 representative US regions from 1979 through 2003. There were about 6,000 diagnoses of DS each year in the USA with 1/691 babies is born with DS which is higher than the previously reported statistic of 1/733. The increased total birth prevalence of DS was largely due to the raised

number of women conceiving after the age of 35; portends an ever-growing population of people with DS who may be prone to pathogenic aging and improved longevity in people with DS due to the improved medical care especially for treatment of congenital heart diseases [55]. The prevalence at birth also varied significantly according to the region, age of the mother, race/ethnicity, infant gender, and presence or absence of CHDs. The lowest prevalence was in Arkansas (0.97/1000) and the highest prevalence was in Iowa (01.27/1000) and Utah (1.37/1000) and was significantly higher among males than among females [56].

In Canada; DS remains the most frequently occurring chromosome anomaly. The birth prevalence of DS was relatively constant during the period for 1998–2007 with average 1.41/1000 total births (1.24 and 1.7/1000 for live birth and stillbirth DS respectively). Advanced maternal age is a key risk factor for DS in Canada, though the chromosomal anomaly can also occur in babies born to younger mothers. Despite the rising rates of advanced maternal age at delivery, the national Canadian birth prevalence rates have remained stable over the 1998–2007 time periods. This is most likely due to increased access and utilization of prenatal screening and testing and subsequent termination of pregnancies affected with aneuploidy [57]. In Mexico, the incidence of DS is 1/650 newborns. It is higher than that of USA because of poor health care available for most people in Mexico, including prenatal care thus preventing a correct diagnosis. This factor is also augmented by the low rate of pregnancy termination for religious reasons [58].

South America

According to the Latin American Study of Congenital Malformations (ECLAMC) which was conducted between 1995 and 2008; Chile had the highest rate of DS (2.47/1000 live birth) while Uruguay, had the lowest rate (1.36/1000 live birth). Chile had the highest percentage of women aged 35 years or more giving birth (14%), followed by Uruguay (13%). Despite being the second country with the highest rate in women over 34 years; Uruguay has the lowest rate of DS in Latin America. This could signify the importance of the maternal age as a risk factor for this condition, but it seems not to be the only factor. Other factors should be considered such as ethnicity, for example. It has been reported that mothers of Hispanic origin are at increased risk of having children with DS. The ethnic composition of Chile is mainly of Hispanic and Indian American, while Uruguay has European and African components [59].

Conclusion

Down syndrome is the most frequent chromosomal disorder known in the human being. The prevalence and incidence of this disorder showed marked heterogeneity all over the world depending on many factors which are different from one part of the world to another according to local circumstances in these countries. The rate of the disorder is in continuous dynamic changes related to the modifications of the cofactors, with higher rates in countries where antenatal screening is not available in an acceptable level. Application of antenatal screening, termination of the affected pregnancy and the maternal age are among the most important factors affecting both the incidence and the prevalence of the disorder.

Conflict of interest

Non

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