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COMMENTARY

Down syndrome and infertility: what support should we provide?

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Abstract

Down syndrome (DS) is the most common genetic disease at birth; on average, it affects 1 in 700 newborns. The syndrome features cognitive impairment, susceptibility to certain diseases, and (in some cases) congenital malformations. Improvements in medical care for people with DS have led to an increase in life expectancy. Furthermore, the systematic provision of specific support during childhood improves cognitive function and autonomy in adulthood. Consequently, patients and their families are now seeking the same rights as healthy people. Access to procreation is an emerging debate. The presumption of infertility in DS is based on a few old studies. Down syndrome appears to cause spermatogenesis defects in men and premature menopause in women. When assisted reproductive technology makes it possible to solve these problems, the question of fertility in DS must be addressed. Without entering into highly controversial ethical considerations related to parenthood for people with DS, we reviewed the literature on fertility in DS and tried to specify the associated genetic risk.

Keywords Down syndrome · Infertility · Genetic risk · Premature ovarian failure

Down syndrome

Etiology

Down syndrome (DS) is a genetic disease caused by the presence of an extra (third) chromosome 21. In most cases, the extra chromosome is free and present in all cells, but in a few cases, the extra chromosome is not free (i.e., it bears a Robertsonian translocation) and/or is not present in all cells (i.e., resulting in mosaicism). Although the cell possesses three copies of the 255 genes carried on chromosome 21, only overexpression of the genes located within the Down syndrome critical region [1] appears to be responsible for DS phenotype. Down syndrome is currently the most common genetic disease, since it affects 1 in 700 individuals at birth [2]. The frequency of DS in the child increases with maternal age because of the premature separation of sister chromatids during meiosis [3].

Since the mid-1970s, developed countries have set up prenatal screening programs so that the parents of affected fetuses can decide whether or not to terminate the pregnancy. Screening of free fetal DNA in maternal blood is now extremely efficient, with specificity and sensitivity values close to 99% [4].

Characteristics of the disease

Down syndrome is the only homogeneous autosomal trisomy (i.e., a trisomy that affects all cells) in which affected people survive after puberty. The three main clinical characteristics of DS (described for the first time by L. Down in 1866) are as follows: (i) highly specific and recognizable dysmorphisms; (ii) cognitive impairments, and (iii) frequent cardiac, endocrine, and ophthalmologic complications. Life expectancy is linked to survival of the first 5 years of childhood (congenital heart disease, digestive tract malformations, hypothyroidism, and susceptibility to infection are the main causes of death in childhood [5]) and premature aging in the forties (Alzheimer's disease [6], obesity, and cardiovascular diseases [7]). At

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present, the mean life expectancy in DS is around 55 y.o. and continues to increase.

Intellectual disability in DS is thought to be linked to a low in total volume brain (involving gray and white matter) at birth [8]. This feature might be related to abnormally low cell proliferation during neurogenesis, an imbalanced neuron/astrocyte ratio, and accentuated apoptosis [9].

The lack of gray and white matter is mainly due to the negative impact of four overexpressed genes: *DYRK1A*, *APP*, *SOD1*, and *RCAN1* [10]. This overexpression is associated with the activation of the p53, STAT3, and caspase signaling pathways, which leads to the apoptosis of neuronal cells [9], prevents the differentiation of neuroblasts into neurons, promotes the differentiation of neuroblasts into astrocytes [11], and thus ultimately alters the proliferation of neuronal precursor cells [10]. Although intellectual disability is always present in DS, the absolute magnitude of intellectual disability varies from one individual to another. The mean intellectual quotient (IQ) is around 60, i.e., 40 points below the average for "healthy" individuals.

As mentioned above, DS is caused by the overexpression of genes located on chromosome 21. In the brain, this overexpression is also responsible for early-onset Alzheimer's disease (i.e., at around the age of 40). Interestingly, amyloid precursor protein (APP, the major protein responsible for Alzheimer disease) is encoded by the *APP* gene on chromosome 21 and is therefore overexpressed in cases of DS [12].

Desire for integration and autonomy on behalf of patients

Five percent of people with DS have an IQ close to the normal threshold (80), and it has been found that early provision of cognitive and behavioral therapy tends to increase this proportion [13]. These patients can live independently and thus are now seeking to integrate into society [14]. According to various studies, the proportion of people with DS who can read, write, and live independently varies as a function of their education and their IQ [15]. Hence, these people are more integrated socially and, in some cases, wish to have children.

Fertility and parenthood

Difficulties caused by cognitive impairment in DS

In the past, sterilization of patients with intellectual disability was the rule; it was assumed that such people were not able to take care of or educate their children, and should not be allowed to risk transmitting their intellectual disability to offspring. Setting aside the mutilatory nature of this practice (which is supposed no longer practiced today), sterilization is unjustified for at least two reasons. Firstly, 5% of people with DS have an IQ similar to that of "healthy" individuals (i.e., between 80 and 120), who are allowed to reproduce. Secondly, many people with DS do not necessary wish to have a child. Although sterilization is no longer countenanced, one can legitimately question the educational impact on a child raised by parents with a significant developmental disability or cognitive impairment. This question has been addressed in several studies, and the results have varied markedly. In some studies, the educational process has been problem-free (for both the child and the parents), whereas other studies have found that parents fail to take responsibility for the child or under-stimulating the child [16]. These disparate results might prompt concerns about education, learning, and perhaps even neglect or abuse. It should be noted that 43% of children born to parents with mental retardation themselves are mentally retarded; in most cases, however, this is not due to somatic or psychological illnesses [16]. However, similar situations can be observed in families without intellectual disabilities or with previously unidentified intellectual disabilities. The true risks for children born to parents with intellectual disabilities have not really been established. Furthermore, there are no cognitive prerequisites for parenthood in the general population or among people seeking to access assisted reproductive technology (ART). Furthermore, studies have shown that more than half of people with DS do not exhibit behavioral problems [17]; hence, their children would not necessarily be exposed to a major risk. A similar analysis of patients with early-onset dementia would be of value.

Difficulties associated with DS

In addition to a low IQ, many other comorbidities are associated with DS (diabetes, depression, sleep apnea, hypothyroidism, etc.) and worsen the patient's medical condition [12]. As mentioned previously, DS is associated with early dementia (in the forties), which significantly impairs personal independence and parenting abilities.

Fertility in men with DS

Observation of partial gonadal dysfunction

Only three cases of spontaneous conception in men with DS have been described in the literature [18–20]. This low number may be due to the small percentage of sexually active patients or those wishing to have children. According to the literature data, this low number may also be due to partial gonadal dysfunction. Indeed, many studies have reported impaired spermatogenesis and Sertoli and Leydig cell dysfunction in men with DS. Men with DS appear to experience a normal puberty, which starts at the usual age. After puberty, however, the testicular volume falls, the production of gonadotropins rises, and the gonadal dysfunction worsens with age.

The increased production of luteinizing hormones and follicle-stimulating hormones [21] and decreased production of anti-Müllerian hormone [22] evidence the Sertoli and Leydig cell dysfunction [23]. Other studies have shown that the sperm count is abnormally low in men with DS; the resulting azoospermia or oligospermia may be associated with damaged spermatogenesis [24]. This impairment might be caused by (i) a sorting mechanism that eliminates aneuploid gametes produced during spermatogenesis, (ii) meiotic failure [25], or (iii) post meiotic failure [26]. Other hypotheses include the effect of *DYRK1A* overexpression on the maturation of primordial germ cells, which reduces the spermatogonial reserve [27].

Assisted reproductive technology and DS

As described above, people with DS wishing to have children may face a number of difficulties. Previously, only spontaneous pregnancies have been reported in literature—all fathered by men with DS and a normal sperm count. The most recently reported cases include men with DS who used ART (intracytoplasmic sperm injection, ICSI) [28] and, in some instances, pre-implantation genetic diagnosis (PGT-A) of the embryos. This strategy revealed that only 1 of the 13 tested embryos exhibited mosaic trisomy. Hence, spermatogenesis in men with DS does not appear to produce one in two spermatozoa with trisomy as one would expect; meiosis appears to sort the spermatozoa, which might explain infertility in men with DS. If ICSI + PGT-A might constitute a solution for men with DS to be confident regarding the aneuploidy status and especially for DS, this risk is probably dramatically lower compared with maternal age one.

Fertility in women with DS

Early menopause

As in men with DS, puberty appears to be normal in women with DS and starts at the same average age as in the healthy population. Women with DS are fertile, since many cases of maternity have been reported [29]. However, the literature data have highlighted early menopause in women with DS (relative to a healthy population) and a marked decrease in levels of anti-Müllerian hormone [30]. Hence, even though fertility does not seem to be directly impacted, premature menopause in women with DS will reduce their ability to conceive a child at the desired time. As with men with DS, this premature ovarian failure might be associated with a reduced ovarian reserve [31] due to oogenesis failure and/or lower levels of primordial cell maturation. Access to an oocyte donation program could be considered in this situation.

Intellectual disability/Alzheimer's disease and the menopausee

Given that early menopause leads to estrogen deficiencies known to be associated with an increased risk of dementia [32] and/or cognitive impairment [33], several studies have studied this association in DS—a disease that naturally predisposes to dementia [34]. In women with DS, an early estrogen deficiency is associated with the onset of Alzheimer's disease [35]. This raises the question on the impact of early parental dementia on a child's development.

The chromosomal risk

In addition to questions related to the impact of intellectual disability and early dementia on parenting, another significant risk for individuals with DS would be the transmission of the pathology to their offspring. According to the literature data, all the children fathered by a man with DS (with or without ART) have been healthy [28]. In contrast, one out of three children born to a woman with DS themselves have DS [29]. Hence, the risk of transmission of DS differs dramatically for men vs. women with DS.

There are two possible explanations for this difference. Firstly, spermatozoon sorting probably occurs during spermatogenesis—limiting the production of aneuploid spermatozoa and thus impairing male fertility. However, this hypothesis has not yet been proved, and the small number of cases of paternity prevents an accurate study of the likelihood of transmission. Furthermore, if meiotic arrest occurs during spermatogenesis, why would it not occur during oogenesis? In mouse models, defects in genes associated with sperm meiotic arrest and azoospermia (e.g., SYCE1) also induce premature ovarian failure [36, 37]. Secondly, considering that maternal ovarian age is likely to be associated with an elevated risk of DS, whatever the karyotype [38], we could hypothesize that the elevated frequency of children with DS born to women with DS is related to the elevated maternal ovarian age rather than extra chromosome. Oocyte donation might be an option in cases of premature ovarian deficiency and an elevated risk of aneuploidy.

Conclusion

The literature data suggests that fertility is impaired in people with DS. Nevertheless, some people with DS have become parents, and others are seeking to have children. A case-by-case evaluation appears to be necessary, in order to assess (i) the person's ability to care for and educate a child and (ii) the rationale for access to ART and/or oocyte donation programs. Such evaluation needs to be multidisciplinary including psychologist and clinics/practitioners willing to undertake these cases. Furthermore, the cost and access to treatment in

countries without insurance or that are government funded must be considered; DS may not be able to afford assisted reproduction.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Delabar JM, Theophile D, Rahmani Z, Chettouh Z, Blouin JL, Prieur M, et al. Molecular mapping of twenty-four features of Down syndrome on chromosome 21. Eur J Hum Genet. 1993;1:114–24.
2. Canfield MA, Honein MA, Yuskiv N, Xing J, Mai CT, Collins JS, et al. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999–2001. Birth Defects Res A Clin Mol Teratol. 2006;76:747–56.
3. Allen EG, Freeman SB, Druschel C, Hobbs CA, O'Leary LA, Romitti PA, et al. Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National down Syndrome Projects. Hum Genet. 2009;125:41–52.
4. Gil MM, Accurti V, Santacruz B, Plana MN, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2017 Sep;50(3):302–14. https://doi.org/10.1002/uog.17484.
5. Frid C., Drott P., Lundell B., Rasmussen F., Annerén G. Mortality in Down's syndrome in relation to congenital malformations. J Intellect Disabil Res. 1999 Jun;43 (Pt 3):234–41.
6. Zigman WB, Lott IT. Alzheimer's disease in Down syndrome: neurobiology and risk. MRDD Res Rev. 2007;13:237–46.
7. Esbensen AJ. Health conditions associated with aging and end of life of adults with down syndrome. Int Rev Res Ment Retard. 2010;39:107–26.
8. Koran ME, Hohman TJ, Edwards CM, Vega JN, Pryweller JR, Slosky LE, et al. Differences in age-related effects on brain volume in Down syndrome as compared to Williams syndrome and typical development. J Neurodev Disord. 2014;6:8.
9. Seidl R, Bidmon B, Bajo M, Yoo BC, Cairns N, LaCasse EC, et al. Evidence for apoptosis in the fetal Down syndrome brain. J Child Neurol. 2001;16:438–42.
10. Stagni F, Giacomini A, Emili M, Guidi S, Bartesaghi R. Neurogenesis impairment: an early developmental defect in Down syndrome. Free Radic Biol Med. 2018;114:15–32.
11. Wisniewski KE, et al. Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. Am J Med Genet. 1990;Suppl. 7:274–81.
12. Wiseman FK, Al-Janabi T, Hardy J, Karmiloff-Smith A, Nizetic D, Tybulewicz VL, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci. 2015;16:564–74.
13. Smith DS. Health care management of adults with down syndrome. Am Fam Physician. 2001;64(6):1031–8.
14. Skotko BG, Levine SP, Goldstein R. Self-perceptions from people with Down syndrome. Am J Med Genet A. 2011;155A(10):2360–9.
15. Sloper P, Cunningham C, Turner S, Knussen C. Factors related to the academic attainments of children with Down's syndrome. Br J Educ Psychol. 1990;60:284–98.
16. Morch W-T, Skar J, Andersgard AB. Mentally retarded persons as parents: prevalence and the situation of their children. Scand J Psychol. 1997;38:343–8.
17. Carfi A, Antocicco M, Brandi V, et al. Characteristics of adults with Down syndrome: prevalence of age-related conditions. Front Med (Lausanne). 2014;1:51.
18. Sheridan R, Llerena J Jr, Matkins S, Debenham P, Cawood A, Bobrow M. Fertility in a male with trisomy 21. J Med Genet. 1989;26:294–8.
19. Zuhlke C, et al. Down syndrome and male fertility: PCR derived fingerprinting, serological and andrological investigations. Clin Genet. 1994;46:324–6.
20. Pradhan M, Dalal A, Khan F, Agrawal S. Fertilty in men with Down syndrome: a case report. Fertil Steril. 2006;86:1765.e1–3.
21. Campbell WA, Lowther J, McKenzie I, Price WH. Serum gonadotrophins in Down's syndrome. J Med Genet. 1982;19:98–9.
22. Grinspon R, et al. Early onset of primary hypogonadism revealed by serum anti Mullerian hormone determination during infancy and childhood in trisomy 21. Int J Androl. 2011;34:e487–98 ISSN 0105Z6263.
23. Hsiang G. et al. Gonadal function in patients with Down syndrome. Am J Med Genet. 1987 Jun;27(2):449–58.
24. Stearns PE, Droulard KE, Sahhar FH. Studies bearing on fertility of male and female mongoloids. Am J Ment Defic. 1961;65:37–41.
25. Johannisson R, Gropp A, Winking H, Coerdt W, Rehder H, Schwinger E. Down's syndrome in the male. Reproductive pathology and meiotic studies. Hum Genet. 1983;63(2):132–8.
26. Kjessler B, de la Chapelle A. Meiosis and spermatogenesis in two post-pubertal males with Down's syndrome: 47,XY,G+. Clin Genet. 1971;2:50–7.
27. Liu Y, Lin Z, Liu M, Wang H, Sun H. Overexpression of *DYRK1A*, a Down syndrome candidate gene, impairs primordial germ cells maintenance and migration in zebrafish. Sci Rep. 2017;7:15313.
28. Aghajanova L, Popwell JM, Chetkowski RJ, Herndon CN. Birth of a healthy child after preimplantation genetic screening of embryos from sperm of a man with non-mosaic Down syndrome. J Assist Reprod Genet. 2015;32(9):1409–13.
29. Bovicelli L, Orsini LF, Rizzo N, Montacuti V, Bacchetta M. Reproduction in down syndrome. Obstet Gynecol. 1982;59(6 Suppl):13S–7S.
30. Schupf N, Zigman WB, Kapell D, Lee JH, Kline J, Levin B. Early menopause in women with Down's syndrome. J Intellect Disabil Res. 1997;41:264–7.
31. Hojager B, et al. Follicular development in ovaries of children with Down's syndrome. Acta Paediatr Scand. 1978;67(5):637–43.
32. Janicki SC, Schupf N. Hormonal influences on cognition and risk for Alzheimer's disease. Curr Neurol Neurosci Rep. 2010;10(5):359–66.
33. Patel BN, Seltzer GB, Wu HS, Schupf N. Effect of menopause on cognitive performance in women with Down syndrome. Neuroreport. 2001 Aug 28;12(12):2659–62.
34. Zigman WB, Devenny DA, Krinsky-McHale SJ, Jenkins EC, Urv TK, Wegiel J, et al. Alzheimer's disease in adults with Down syndrome. Int Rev Res Ment Retard. 2008;36:103–45. https://doi.org/10.1016/S0074-7750(08)00004-9.
35. Coppus AM, Evenhuis HM, Verberne FE, Elkelenboom P, Van Good WA, Janssens AC, et al. Early age at menopause is associated with increased risk of dementia and mortality in women with Down syndrome. J Alzheimers Dis. 2010;19(2):545–50.

36. Maor-Sagie E, Cinnamon Y, Yaacov B, Shaag A, Goldsmidt H, Zenvirt S, et al. Deleterious mutation in SYCE1 is associated with non-obstructive azoospermia. J Assist Reprod Genet. 2015;32:887–91.
37. Bartmann AK, Araujo FM, Iannetta O, Paneto JC, Martelli L, Ramos ES. Down syndrome and precocious menopause. J Assist Reprod Genet. 2005;22:129–31. https://doi.org/10.1007/s10815-005-4878-6.
38. Grande M, Borobio V, Bennasar M, Stergiotou I, Mercadé I, Masoller N, et al. Role of ovarian reserve markers, antimullerian hormone and antral follicle count, as aneuploidy markers in ongoing pregnancies and miscarriages. Fertil Steril. 2015;103(5):0015–282.