Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(7): 154
https://doi.org/10.31083/j.ceog4907154

Editorial

In Search of Shedding More Light on Differences of Sex Development

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Academic Editor: Michael H. Dahan
Submitted: 29 January 2022 Revised: 28 February 2022 Accepted: 2 March 2022 Published: 7 July 2022

Differences/disorders of sex development (DSD) represent a heterogeneous group of rare conditions associated with atypical sex determination or differentiation [1,2]. Currently, the DSD classification is based on karyotype including sex chromosomal DSD, 46, XY DSD, and 46, XX DSD [1]. However, irrespective of these fundamental genetic characteristics, the clinical picture of DSD conditions might encompass a broad spectrum of clinical symptoms with different severity and prognosis [3,4]. In the last 15 years, the research on the topic has increased rapidly because of multicenter collaborative studies and the creation of international registers [2]. These scientific efforts have resulted in up-to-date recommendations for diagnosing and treating individuals with DSD, especially in childhood [3,4]. Evidence-based guidelines have also been published for Turner syndrome [5] and congenital adrenal hyperplasia (CAH) [6]; however, specific recommendations are lacking for most other DSD conditions. Additionally, current DSD guidelines are focused mainly on childhood, adolescence, and early adulthood, while recommendations for older adults are practically lacking [1–4]. The knowledge gap could only be filled with more long-term studies in middle-aged and elderly DSD individuals.

The optimal DSD management during lifespan should involve a multidisciplinary approach ensured by different specialists [2,3]. DSD individuals have complex medical needs including but not limited to evaluation of gonadal cancer risk and subsequent procedures, long-term hormone-replacement therapy, surgical corrections of the external genitalia, treatment of concomitant diseases, and psychological support [1–4]. However, the access to health services, specialists familiar with DSD, and expensive genital reconstructive surgery is very different in distinct countries [2,3]. In addition, socio-economic obstacles could preclude the implementation of current guideline recommendations in actual clinical practice, thus affecting long-term DSD morbidity and mortality. Therefore, it is essential to have more studies provided in different countries to have a clear picture of DSD care worldwide.

Infertility is a common issue in DSD individuals, depending on the specific diagnosis. Patients with TS have about a 5% chance for spontaneous pregnancy, usually in the case of mosaicism, which resembles the rate of spontaneous pregnancies in women with premature ovarian failure (POF) [7,8]. Oocyte or ovarian tissue cryopreservation, egg donation or adoption are the main possibilities to overcome infertility in patients with depleted ovarian reserve [5]. Nevertheless, current assisted reproductive techniques could not considerably improve the pregnancy rate with autologous oocytes in TS and genetic POF. Moreover, spontaneous miscarriages and cardiologic complications during pregnancy are significantly increased in TS patients [5,7]. On the opposite, testicular sperm extraction and intra-cytoplasmic sperm injection have led to a remarkable increase in live births reaching 16% in patients with Klinefelter syndrome (KS), without increased risk of miscarriages [9]. However, most reported studies include a low number of KS patients; thus, further studies are necessary. Additionally, the role of assisted reproductive technologies in different 46, XY DSD conditions has not been clarified yet.

Some DSD conditions such as CAH are not associated with diminished follicular reserve, but the affected individuals have fewer pregnancies and live births than the general population [6,10]. Prenatal hormonal variations and the genital surgery outcomes might influence the interest of some DSD individuals to become parents [10].

This special issue aims to gather original research and case series-based reviews focused on different DSD conditions, including but not limited to Turner syndrome, congenital adrenal hyperplasia, gonadal dysgenesis, disorders of androgen synthesis, genetic variants of premature ovarian failure, and many others. The additional information about hormone replacement therapy, reproduction, and perimenopausal transition in DSD individuals with different ethnic backgrounds and socio-economic characteristics would help to expand current clinical recommendations. Further development of assisted reproductive techniques could increase the pregnancy rate in the DSD groups. Novel findings, new ideas, and different opinions might help to shed more light on these rare conditions.

Author Contributions

RR wrote the manuscript and approved the final version.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest.

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