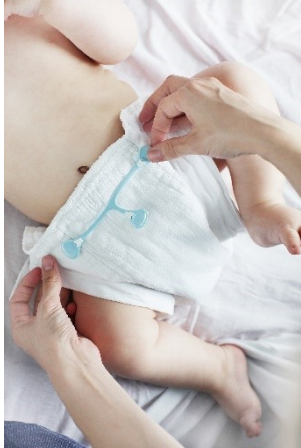


Briefing **22** — Differences in sex development: what is the current medical practice? — June 2020
no.

What can biomedical research tell us?



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Summary

- Differences in sex development include conditions that are similar from a morphological point of view, but whose underlying mechanisms are very different. Care needs to be provided on a case-by-case, collegial and multidisciplinary basis.
- Reducing surgery to its aesthetic advantages neglects the medical, societal and psychological aspects of the atypicality; nevertheless, abstaining from treatment until adolescence is desirable in very many cases.
- Research in this field suffers from a lack of patient follow-up. Epidemiological data could be collected through a national register.

Mr Jean-François Eliaou, Member of the National Assembly

If determination of gender at birth is obvious for most newborns, the external genital organs can in certain cases take on a wide variety of appearances, somewhere between typically female and male features. Previously known as "sexual ambiguity", these differences in sex development cover a range of diverse situations, which, although they appear similar from a phenotypical point of view (i.e. what can be observed), are due to different biological processes.

For several decades now, the medical treatment and "pathologisation" of these differences have been challenged by certain associations. They are asking that surgery to normalise the appearance of the external genital organs be delayed until the child can give their consent, in the name of self-determination over one's own body and respect for fundamental human rights. This demand has been supported among others by the Parliamentary Assembly of the Council of Europe.¹

Although sensitive to the ethical arguments and aware of the pitfalls of the old practices, the medical world insists on the need not to prevent these interventions, that it would be wrong to reduce them to their aesthetic role, as has also been emphasised by the Council of State (*Conseil d'État*).²

By presenting the current state of knowledge about differences in sex development and the current medical practice, this briefing aims to highlight the main legislative issues as part of the examination of the bioethics bill.

■ Genital development

In humans, the development of the urogenital system is partly governed by the sex chromosomes – X and Y – and by hormones. In the embryo, certain organ primordia are bipotential – they can differentiate into female or male organs. Others only exist in one of the two sexes and regress in the other.

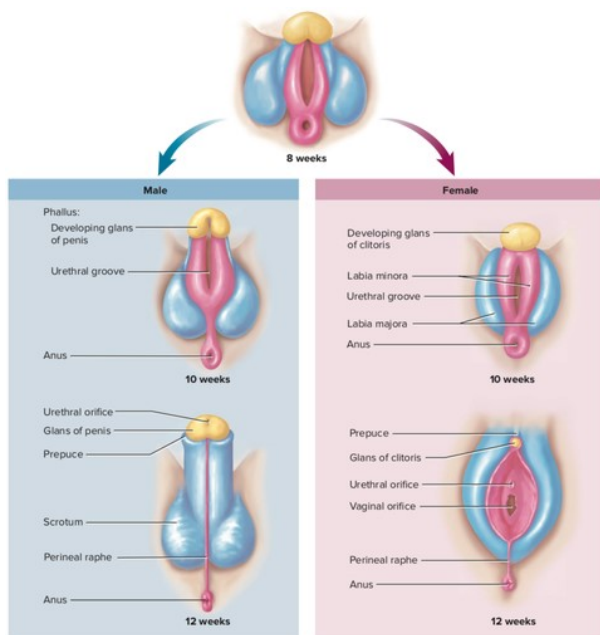
● Gonadal differentiation

The first structures to form are the gonads, which become testicles or ovaries. These glands contain the germ cells, which produce spermatozoa and oocytes from puberty onwards. Gonadal differentiation is an active process in both sexes requiring the involvement of the genes carried by the sex chromosomes, which induce specific regulation pathways.

● Their influence on the development of the other structures

The gonads themselves then produce the hormones that participate in the differentiation of the other structures. Thus, in the presence of anti-Müllerian hormone produced by the testis, the Müllerian ducts regress in boys, whilst they are maintained in girls to form the Fallopian tubes and the uterus. Conversely, the Wolffian ducts regress in girls, but become the vas deferens in boys.

Male and female external genital organs (EGO) derive from bipotential embryonic structures. It is the effect of the androgens derived from hormones produced by the Leydig cells in the testicles that induces the differentiation into male EGOs. Without these androgens, they evolve into female structures.



Evolution of male and female EGOs at 10 and 12 weeks gestation. The same embryonic tissues (identified by colour) produce quite different structures.

- **Sex at birth**

Differentiation into the external genital organs of one sex or the other occurs in the 9th week of pregnancy and continues until full term. At birth, only the external genitalia are visible and it is based on observation of them that the child's sex is assigned.³

■ Differences in sex development (DSD)

DSDs constitute a very varied set of conditions that have in common the fact that they manifest with a phenotype that is not typically male or female, or a phenotype that is different to the chromosomal or gonadal sex. Knowledge of DSDs has progressed considerably thanks to molecular biology and imaging techniques. In 2005, a scientific and medical consensus conference introduced the term "*difference of sex development (DSD)*" to qualify any variation in sex or genital development.⁴

- **Very diverse origins**

The origin of DSDs can be genetic – a mutant gene is transmitted from one generation to another – or congenital, appearing during pregnancy. Different biological mechanisms can be the cause:

Sex chromosome abnormalities, occurring when the gametes are produced or in the first embryonic cell divisions, are the cause of DSDs. The genes involved in determining sex and differentiating the urogenital system are carried by the sex chromosomes.

These abnormalities can concern **entire chromosomes**: instead of being XX or XY, the karyotype can be X or XXY, either totally or with mosaicism.⁵ XY/X mosaicism – the coexistence of XY cells and X cells – leads to a gonadal differentiation defect called mixed gonadal dysgenesis, which induces undervirilisation of the EGOs.

Rearrangements can also occur, leading to exchanges of fragments of chromosomes between each other. Thus, the translocation of a Y chromosome fragment carrying sex-determining genes onto an X chromosome is one of the causes of the development of gonads with the characteristics of both ovaries and testes (*ovotestis*), and the androgens produced by the gland virilise the EGOs.

Mutations can occur affecting genes that play a determining role in gonadal differentiation. If it does not differentiate completely into a testis, the gonad produces fewer androgens, which leads to the development of atypical EGOs.

Alteration of other genes can also give rise to DSDs: those involved in the **hormone synthesis, hormone-receptor interaction** or **degradation** of the **hormones** necessary to the differentiation of the EGOs. Androgen receptor mutations are thus responsible for insensitivity to these hormones in XY children. In this case, although the gonad produces androgens, the embryonic primordia of the EGOs are not sensitive to them and therefore evolve into female structures.

In XX children, the most common DSD is congenital adrenal hyperplasia, caused by a mutation in a gene that codes for an enzyme involved in the synthesis of steroid hormones in the adrenal gland. This enzyme deficiency leads to an overproduction of adrenal androgens and the development of atypical EGOs.

- **Consequences varying in severity**

Congenital adrenal hyperplasia is the only condition associated with a DSD that can be life threatening, due to the adrenal hormone imbalance.⁶

In the long term, poorly differentiated gonads are qualified as dysgenetic and have an increased risk of carcinogenesis.⁷

In the EGOs, the different DSDs can give rise to slight differences compared to the typical structures of one or other of the sexes. More pronounced differences may be observed and are associated with functional disorders.⁸

- **Disorders varying in frequency**

There is no national register that records the incidence of DSDs in the population. An attempt at quantification based on administrative medical data from the Social Security system has been proposed, but doctors are agreed that the method would be imprecise, due to the heterogeneity of coding practices in hospitals.⁹

Estimates can be given, backed by incidence data obtained abroad. Whereas hypospadias and cryptorchidism of all anatomical types are common and are said to affect one birth in 300 and one in 100¹⁰ respectively, congenital adrenal hyperplasia is rarer: one birth in 14,000. Mixed gonadal dysgenesis is thought to concern one birth in 10,000, and

ovotesticular disorder, one in 100,000.¹¹

- **The semantic issue and the societal debate**

The semantic issue reflects the societal debate: the medical profession prefers to talk of "disorders" of sex development as better reflecting the underlying congenital genital malformation. According to doctors, the notion of "difference" corresponds to non-pathological differences that fall within the inter-individual variability found in the general population. Whenever there is an abnormality in the embryology and/or physiology of genital development and it is a source of functional disorders and potentially a disability and psycho-emotional disorders, there is justification for remaining in the medical register, given that the purpose of medical practice is to "reduce suffering and increase personal fulfilment".

A part of those involved in the relevant associations consider that referring to "differences" carries less stigma. This corresponds to a wish to see a "de-pathologised" response to the care of these conditions excluding any medical intervention on children in the absence of any threat to life and better acceptance of the body through better inclusion in society. However, the rest of those involved in the associations prefer to use the disorder register to talk about these differences and wish EGOs to be rendered normal in appearance.

A small section of the medical profession has adopted a proactive approach of appeasing and listening to the associations and prioritises the term "difference", which has also been recommended by the ombudsman (*Défenseur des droits*).¹²

■ **Current status of biomedical research on DSDs**

Clinical and fundamental research on DSDs is focused on a number of aspects:

- **The biological mechanisms at work**

Studying the genome of persons with DSDs has enabled new genes to be identified that are involved in determining sex and in the mechanisms of infertility. A great deal of inter-individual variability has been found in the presentation of one gene mutation: mutations of the NR5A1 gene are found in men without DSDs but with infertility, in XY women and XX men.¹³ This poor correlation between genotype and phenotype, as yet unexplained, is probably the consequence of the multigenic,¹⁴ even multifactorial character of genital development.

- **Environmental origins of DSDs**

The possibility of an environmental origin has been advanced following an increase in DSDs over the last few decades. Indeed, in animals, the endocrine disruptor dethylstilbestrol does have harmful effects on genital development and leads to an increase in the incidence of hypospadias.¹⁵ In humans, the incidence of hypospadias is higher in the children of women exposed to the molecule *in utero*, suggesting

an epigenetic effect.¹⁶ The incidence also appears to be higher in children liable to be more exposed to chemicals due to a parent's occupation.¹⁷

Other studies favour the hypotheses of a link to older mothers¹⁸ or to higher body mass index.¹⁹

- **Psychological disorders associated with DSDs and long-term quality of life**

Clinical research is also investigating the quality of life of people with DSDs, as they are more susceptible to psychological disorders such as anxiety, depression and social anxiety disorder.²⁰ The main determinants are the type of DSD, the atypical nature of the EGOs, the feeling of being different and dissatisfaction with one's body.²¹ Surgical interventions, sometimes iterative, and their possible consequences can also be a source of ill-being.²²

Research is particularly limited by the low incidence of severe DSDs and by the lack of follow-up of the more benign forms. The setting up of a **national register**, in cooperation with an international register,²³ would allow cohorts to be tracked.

■ **Medical care**

- **Medical interventions**

Depending on the presentation of the DSD, medical interventions may be more or less invasive, and generally aim to restore functionality and²⁴ reduce atypicality. This may involve surgery to reconstruct posterior hypospadias accompanied by serious functional disorders or a risk of infection, to reduce the size of the clitoris or to bring the vagina down to the perineum. Doctors stress the improvement in practices over several decades and the improvement in knowledge of the tissues, but these are still major surgical procedures with a high risk of complications.²⁵

Hormone therapy is used to replace adrenal hormones, to block or amplify the virilisation of the EGOs or to allow the feminisation of secondary sexual characteristics in puberty.

- **Deciding whether to intervene**

When a DSD is diagnosed at birth or at the latest in childhood, the different possibilities for treatment are proposed to the parents. It is the parents who take such decisions, in agreement with the medical team, as long as the child is too young (although this will vary between individuals) to take an informed decision. The decision must be enlightened by an understanding of the abnormality and the risk of complications involved and by the psychological support given to the child and the parents.

With the exception of DSDs that have a high risk of developing into cancer, serious functional abnormalities (e.g.: reconstruction of hypospadias which is associated with more complications if done belatedly)²⁶ or recurring infections, there is not

enough evidence from clinical studies to decide whether or not to operate, or the best time to do so.

Concerning non-intervention, a part of the medical profession is worried about the lack of hindsight on society's capacity to be inclusive and allow persons with DSDs to live fulfilling lives, but also on the ability of parents to support their child. Indeed, some parents are distraught to find that their newborn has atypical EGOs, whereas parental dedication to their child is "the best defence against the development of psycho-emotional consequences". In France, experiments with non-intervention are beginning, at the initiative of doctors/researchers, in order to get a better appreciation of its advantages. This approach is encouraged in Germany and Switzerland.

For these reasons, the medical profession considers that there should not be an age limit on medical interventions in children with DSDs. Insofar as the functional disorders associated with DSDs appears partly with the sex life, it nevertheless seems reasonable to wait until adolescents ask, so that the interventions are desired and not imposed.

- **Psychological care**

As DSDs are associated with a higher risk of psycho-emotional disorders, the provision of psychological support for parents and children is essential, whether there is medical intervention or not. The child must be monitored over the long term as the feeling of satisfaction with one's body changes over the course of one's life, in particular in relation to one's sex life.

- **The organisation of care**

In France, several university hospitals treating DSDs have organised themselves into a reference network, as part of the rare diseases plan.²⁷ Their multidisciplinary teams meet regularly to study cases in a collegial way.²⁸

Although a systematic method of care based on criteria established by a health authority can hardly be envisaged, given the heterogeneity of the presentation of DSDs and of family situations, an ethical framework can be laid down. This is the purpose of Article 21 *bis* of the Bioethics bill, which enshrines in the law the obligation for medical professionals to inform parents and to refer children to reference centres for their care. This measure is intended to avoid decisions being taken unilaterally and to prioritise care by practitioners specialised in the field.

In the rare cases where it is difficult to assign a sex (25 to 50 children per year), the child must be examined

by a multi-disciplinary team as soon as possible, as the child's sex must be declared to the registry of births within five days of birth. There is also strong demand from families at the birth of their child.

Errors in determining sex at birth, particularly in cases of congenital adrenal hyperplasia, still occur every year.²⁹ For the well-being of the persons concerned, it would be important to facilitate the rectification procedure and that this would (?) not be mentioned on the certificate.

Conclusions

The great diversity of biological mechanisms causing differences in sex development and the poor correlation between genotype and phenotype do not allow rules to be laid down to systematise the response and justify **not imposing constraints medical practice** such as the introduction of an age limit or the need to obtain the child's consent. The **adaptation of care on a case-by-case basis** is also justified by the diversity of family situations.

Nonetheless, fixing an **ethical framework** with an obligation of **information, shared or "collegial" decision-making on treatment**³⁰ and **systematic referral** of children with DSDs to a **reference centre**, will usefully reduce the risk of unilateral or uninformed decisions being made.

The reference centres must be given the resources to ensure that each child and their family can benefit from **psychological support**, whether an intervention has been decided upon or not.

The diversity of biological mechanisms, the rarity of severe cases and the difficulty of tracking the most benign cases over the long term all hamper research, whereas *evidence-based* medical care recommendations are required, to guide the decision on whether to intervene or not. The setting up of a **national register** and the provision of qualified **personnel** for the **clinical research** in the reference centres are necessary so that research can move forward and provide answers.

In the absence of any consensus on the nature of the medical conditions that should be dealt with by a reference centre, the latter, in conjunction with the competent health authorities, should define the spectrum of DSDs that must be examined in a collegial manner.

OPECST websites:

<http://www.assemblee-nationale.fr/commissions/opicst-index.asp>
<http://www.senat.fr/opicst/>

Persons consulted*

- A representative of the Amihe association (Association maison intersexualité et hermaphrodisme Europe).
- Ms Anu Bashamboo, researcher at the Institut Pasteur, editor-in-chief of the Sexual Development scientific journal
- Mr Rémi Besson, professor of paediatric surgery, paediatric urological surgeon at the Lille Reference Centre for Rare Genital Development Disorders.
- Ms Claire Bouvattier, paediatric endocrinologist and coordinator of the Paris-Bicêtre Reference Centre for Rare Genital Development Disorders.
- Ms Laurence Brunet, legal expert specialising in family law, author of a book chapter entitled "La mention du sexe à l'acte de l'état civil : enjeux et chausse-trappes" (on specifying sex in civil status certificates) and project coordinator at the Paris-Bicêtre Reference Centre for Rare Genital Development Disorders.
- Two representatives of the Collectif intersexes et allié-e-s association.
- A representative of the GSSIA association (Groupe de soutien du syndrome de l'insensibilité aux androgènes et assimilé (androgen insensitivity syndrome support group)).
- Mr Nicolas Kalfa, professor of urology, paediatric surgeon and coordinator of the Montpellier Reference Centre for Rare Genital Development Disorders, President of the French Society for Paediatric Urology.
- Mr Kenneth McElreavey, researcher at the Institut Pasteur, editor of the pathology section of the Sexual Development journal
- Mr François Medjkane, child psychiatrist at the Lille Reference Centre for Rare Genital Development Disorders.
- Mr Benjamin Moron-Puech, associate professor of private law at Université Paris II Panthéon-Assas, specialist in minority rights.
- Mr Pierre Mouriquand, professor of paediatric surgery, paediatric urological surgeon and coordinator of the Lyon Reference Centre for Rare Genital Development Disorders.
- Two representatives of Surrénales, an association of patients suffering from conditions related to the adrenal glands.

* NB: The persons consulted in some cases expressed divergent opinions on one or more points in this briefing.

Scientific coordination by Ms Mathilde Lecompte, scientific advisor

References

Information report compiled by Senators Maryvonne Blondin and Corinne Bouchoux on behalf of the Delegation on women's rights and equal opportunities between men and women on differences in sex development: lift a taboo, fight stigma and exclusion. February 2017.

¹ "Promoting the human rights of and eliminating discrimination against intersex people", Council of Europe, Resolution 2191 of 12/10/2017; <http://assembly.coe.int/nw/xml/XRef/Xref-XML2HTML-fr.asp?fileid=24232&lang=fr>.

² French Council of State Study requested by the Prime Minister, adopted on 28 June 2018 "Révision de la loi de bioéthique : quelles options pour demain ?" (Revision of the Bioethics Law: what are the options for the future?); <https://www.conseil-etat.fr/ressources/etudes-publications/rapports-etudes/etudes/revision-de-la-loi-de-bioethique-queelles-options-pour-demain>.

³ Visual observation is completed by palpation of the scrotum to check that the testes are present.

⁴ The conference adopted a classification listing the different phenotypic possibilities of each chromosomal sex, linked to the underlying biological phenomena. There are 5 main groups which are very different to each other:

[NB: 46 indicates that there are 46 chromosomes present in the karyotype; 45 means that one chromosome is missing; 47 that there is a supernumerary chromosome]

- 46, XX DSD essentially represented by congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency;
- 46, XY DSDs, which are much more heterogeneous, covering a number of very different subgroups:
 - steroidogenesis defects (17 β -HSD);
 - gonadal dysplasia/dysgenesis with dysfunction of the Leydig cells (testosterone) and Sertoli cells (AMH) ;
 - target tissue abnormalities: 5-alpha reductase deficiency; partial or complete androgen insensitivity syndrome due to androgen receptor deficiencies;
 - central hormonal control deficiency (gonadotropins);
 - unlabelled hypospadias and micropenis;

-
- mosaicism, mainly by 45X/46, XY mosaicism, which is probably the group of situations most difficult to resolve;
 - ovotesticular DSD, where male and female structures are both present and the karyotype is most often 46, XX or mosaic;
 - "non-hormonal/non-chromosomal" DSDs, which mainly include exstrophy, certain caudal abnormalities, aphallia and certain very severe types of micropenis.

Bouvattier, C. and P. Mouriquand. "Prise en charge des anomalies du développement génital pour les nuls". *Annales d'Endocrinologie*, 33rd SFE congress, 77, no. 4 (1 September 2016): 248. <https://doi.org/10.1016/j.ando.2016.07.045>.

⁵ The presence of only one sex chromosome (X) is described in Turner syndrome. This syndrome is associated with incomplete development of the female urogenital system (<https://www.orpha.net/data/patho/Pub/fr/Turner-FRfrPub44v01.pdf>). An XXY karyotype is known as Klinefelter syndrome and is characterised by underdeveloped testicles, leading to sterility, and, in some cases, breast enlargement (<https://www.orpha.net/data/patho/Pub/fr/Klinefelter-FRfrPub362.pdf>). Mosaicism is when not all the cells in the body have the same number of chromosomes. This phenomenon is the result of errors in the segregation of chromosomes during the first embryonic cell divisions.

⁶ Salt-wasting congenital adrenal hyperplasia is the only condition that can be life threatening. For this reason, congenital adrenal hyperplasia, in its main form due to 21-hydroxylase deficiency, is systematically screened for at birth in France using a test to measure its product, 17-hydroxyprogesterone. This condition is nonetheless well understood and can be stabilised with corticosteroids.

⁷ Mouriquand, et al. "Surgery in Disorders of Sex Development (DSD) with a Gender Issue: If (Why), When, and How?" *Journal of Pediatric Urology* 12, no. 3 (June 2009): 139-49. <https://doi.org/10.1016/j.jpuro.2016.04.001>.

⁸ Cryptorchidism (undescended testicles) and anterior hypospadias (urinary meatus on the underside of the penis) when the phenotype is male, or hypertrophied clitoris when the phenotype is female, are benign differences. Anterior hypospadias is distinguished from posterior hypospadias by a position of the meatus very close to the base of the penis. Posterior hypospadias is associated with more serious functional deficits than anterior hypospadias. More pronounced differences may be observed, for example in the more advanced stages of virilisation in XX children suffering from congenital adrenal hyperplasia, where the upper part of the vagina does not reach the perineum but joins the urethra.

⁹ When he appeared before the Senate Special Bioethics Committee on 12 December 2019, legal expert Benjamin Moron-Puech, described the results of his research work aimed at establishing the number of operations performed in France to repair disorders of sex development. According to his research, a total of almost 5,000 operations were performed in 2017, according to the Sniiram register of the CNAM (National health insurance fund). The doctors questioned by the Office warned against misinterpreting these data, due to the fact that the procedures involved are not coded in the same way from one hospital to another.

¹⁰ These data concern hypospadias and cryptorchidism of all anatomical types (anterior and posterior hypospadias; true cryptorchidism - abdominal, inguinal and suprascrotal – and ectopic cryptorchidism – femoral, prescrotal, etc.), occurring either as an isolated event or in association with other phenotypes.

¹¹ These conditions are, however, very rare and may be underdiagnosed, meaning that it is difficult to know the exact prevalence; https://www.orpha.net/consor4.01/www/cgi-bin/Disease_Search.php?lng=EN&data_id=2037.

¹² Opinion of the Défenseur des droits no. 17-04, 20 February 2017; https://juridique.defenseurdesdroits.fr/doc_num.php?explnum_id=18576.

¹³ Bashamboo, et al. "Human Male Infertility Associated with Mutations in NR5A1 Encoding Steroidogenic Factor 1". *American Journal of Human Genetics* 87, no. 4 (8 October 2010): 505-12. <https://doi.org/10.1016/j.ajhg.2010.09.009>.

¹⁴ The expression of a gene may depend on many other genes; this is referred to as the "genetic background".

¹⁵ Stewart, et al. "In Utero Exposure to Both High- and Low-Dose Diethylstilbestrol Disrupts Mouse Genital Tubercle Development". *Biology of Reproduction* 99, no. 6 (1 December 2018): 1184-93. <https://doi.org/10.1093/biolre/ioy142>.

¹⁶ Kalfa, et al. "Prevalence of Hypospadias in Grandsons of Women Exposed to Diethylstilbestrol during Pregnancy: A Multigenerational National Cohort Study". *Fertility and Sterility* 95, no. 8 (30 June 2011): 2574-77. <https://doi.org/10.1016/j.fertnstert.2011.02.047>.

¹⁷ Kalfa, et al. "Is Hypospadias Associated with Prenatal Exposure to Endocrine Disruptors? A French Collaborative Controlled Study of a Cohort of 300 Consecutive Children Without Genetic Defect". *European Urology* 68, no. 6 (December 2015): 1023-30. <https://doi.org/10.1016/j.eururo.2015.05.008>.

¹⁸ Carlson, et al. "Maternal and Fetal Risk Factors Associated with Severity of Hypospadias: A Comparison of Mild and Severe Cases". *Journal of Pediatric Urology* 5, no. 4 (1 August 2009): 283-86. <https://doi.org/10.1016/j.jpuro.2008.12.005>.

¹⁹ However, this hypothesis has been validated by some studies (Akre et al. "Maternal and Gestational Risk Factors for Hypospadias". *Environmental Health Perspectives* 116, no. 8 (1 August 2008): 1071-76. <https://doi.org/10.1289/ehp.10791>) and invalidated by others (Adams, et al. "No Association between Maternal Pre-Pregnancy Obesity and Risk of Hypospadias or

Cryptorchidism in Male Newborns". *Birth Defects Research Part A: Clinical and Molecular Teratology* 91, no. 4 (2011): 241-48. <https://doi.org/10.1002/bdra.20805>.

²⁰ The studies conducted suggest that they suffer from psycho-emotional disorders in a similar way (in terms of intensity) to persons with a chronic disease. Vries, et al. "Mental Health of a Large Group of Adults With Disorders of Sex Development in Six European Countries". *Psychosomatic Medicine* 81, no. 7 (2019): 629-40. <https://doi.org/10.1097/PSY.0000000000000718>.

²¹ Bohet, et al. "Mental Health Status of Individuals with Sexual Development Disorders: A Review". *Journal of Pediatric Urology* 15, no. 4 (1 August 2009): 356-66. <https://doi.org/10.1016/j.jpuro.2019.04.010>.

²² Roen, Katrina. "Intersex or Diverse Sex Development: Critical Review of Psychosocial Health Care Research and Indications for Practice". *The Journal of Sex Research* 56, no. 4-5 (13 June 2019): 511-28. <https://doi.org/10.1080/00224499.2019.1578331>.

²³ For example, with the I-DSD international register; <https://home.i-dsd.org/>.

²⁴ The functions involved are urinary and sexual and fertility-related.

²⁵ It is estimated that the rate of complications (whether benign or severe) for a hypospadias reconstruction is 50%.

²⁶ Garnier, et al. "Late Surgical Correction of Hypospadias Increases the Risk of Complications: A Series of 501 Consecutive Patients". *BJU International* 119, no. 6 (2017): 942-47. <https://doi.org/10.1111/bju.13771>.

²⁷ In particular the Reference Centre for Rare Gynaecological Disorders (<http://www.maladiesrares-necker.aphp.fr/pgr/>), the Reference Centre for Endocrine Growth and Development Disorders (<http://crmerc.aphp.fr/>) and the Reference Centre for Rare Genital Development Disorders (<https://www.developpement-genital.org/>).

²⁸ These are national multidisciplinary meetings (MDMs) organised on a monthly basis and involving the four centres. External participants are also invited to present cases.

²⁹ Indeed, as the phenotype of a girl with congenital adrenal hyperplasia can be the same as that of a boy presenting with hypospadias and cryptorchidism. Mouriquand, et al. "Surgery in Disorders of Sex Development (DSD) with a Gender Issue: If (Why), When, and How?" *Journal of Pediatric Urology* 12, no. 3 (June 2009): 139-49. <https://doi.org/10.1016/j.jpuro.2016.04.001>.

³⁰ Collegiality, or shared decision-making is one of the measures recommended in 2005 by the consensus conference. It involves the presence of specialists from several disciplines: paediatrics, neonatology, surgery, urology, psychiatry, medical genetics.