

## **Abstracts**

### **Session 1 – Setting The Scene**

#### **“Stuck in the middle”**

Eric Vilain MD PhD

For families, the birth of a child with a Disorder/Difference of Sex Development (DSD), and uncertainty about the child's gender and future psychosocial development, is believed to be very stressful. Potential stressors include the parents' need to gather medical information, make decisions about gender assignment and surgical interventions, cope with medical treatments and the possibility of multiple operations, and handle familial strains related to the perceived stigma of DSD. These stressors are amplified by a large number of uncertainties in the management of DSD. I will review the current uncertainties in the world of DSD (naming, diagnosis, gender, genital surgery, disclosure, fertility, outcomes) and discuss how I have attempted to navigate the waters –often troubled- flowing between the different stakeholders involved with DSD.

### **Session 2 – International Collaborations & Moving Forward**

#### **The needs of people with conditions affecting sex development**

Joanne Hall (CLIMB CAH Group)

Joanne is a mother of two daughters with salt wasting Congenital Adrenal Hyperplasia and is a member of the UK based CAH support group. Joanne represents the support group at European COST Action meetings and through this recently co-ordinated a European based patient/parent workshop, primarily to engage with professionals and discuss what has worked and has not worked with patient care from childhood through to adulthood. Using learning from this workshop, along with her personal and professional experience of working with families and facilitating groups, Joanne hopes to provide information and practical guidance for professionals to engage with parents and patients, in order to find out what the needs are for people affected by conditions of sexual development within the professional's own local clinical setting.

#### **Harmonisation of diagnostic pathways**

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Disorders of sex development (DSD) are a wide range of conditions with diverse features and pathophysiology. Ambiguous genitalia in newborns with a 46,XX karyotype most frequently result from congenital adrenal hyperplasia. Newborn screening programs, 17OH-progesterone determination and electrolyte measurements most usually lead to the aetiological diagnosis. In rarer cases, ovotesticular or testicular DSD, aromatase deficiency, androgenic tumours or exposure to androgenic drugs may be the underlying cause. In 46,XY newborns, possible aetiologies include gonadal dysgenesis (affecting both Leydig and Sertoli cell function), isolated hypoandrogenism (due to defective Leydig cell development or function), or end-organ effects due to defective DHT synthesis or androgen insensitivity. Determinations of serum androgens and AMH can be evocative of the underlying aetiology, provided

normative reference ranges are available for patient's age. In patients with sex chromosome aberrations, dysgenetic DSD (including ovotesticular or testicular DSD) is the rule. Finally, the condition may not be endocrine-related, e.g. when defective development of the genital anlagen occur in early embryogenesis. The enhancement of laboratory and imaging techniques has allowed an increase of aetiological diagnosis efficacy. Particularly, the advent of massive sequencing techniques has increased diagnostic efficacy particularly in 46,XY DSD up to 40-60% of the cases. However, difficulties persist in: a) patients with overlapping clinical and biochemical phenotypes, b) sensitive measurement of steroids and normative reference ranges in the newborns, c) patients with isolated hypospadias, and d) assessment of the existence of ovarian tissue in the newborns with suspected ovotesticular DSD.

### **Standardisation of clinical assessment**

Martine Cools

on behalf of COST Action BM1303 "DSDNet" Working Group 1

Sharing expertise among healthcare workers and international collaboration in prospective studies is essential to gain insight in health-related outcome of individuals affected by a rare condition. Working group 1 of the COST Action "DSDNet" aimed to develop guidance for healthcare workers on data that should be collected routinely and longitudinally, and which could be incorporated into a detailed registry, such as the I-DSD registry. Through round-table discussions and literature review within a multidisciplinary expert group, consensus was reached on optimal long-term follow-up of individuals with atypical sex development and on standardized collection of outcome data, reflecting phenotypical aspects, associated morbidities, mental health and gender contentedness across ages. The age (ranges) of 1 month after birth, 4 and 8 years, prepuberty, at end of puberty and between ages 18-25, 25-40, 40-60 and 60-75 were identified as critical milestones for clinical assessment. Per age category, a core dataset was developed, with pre-specified outcomes and an option to include limited free text for each variable. Emphasis was placed on a non-binary and holistic approach of DSD conditions, covering a broad range of physical (e.g. external genitalia, cardiovascular health, bone strength) as well as psychological (e.g. gender development, received psychosocial support) determinants of health and well-being that could be quickly captured objectively as part of routine clinical practice.

This will provide clinical guidance for new multidisciplinary teams and enable standardised and routine collection of outcome data at all developmental ages, facilitating large-scale multicenter studies.

### **The I-DSD & I-CAH registries & future direction**

S. Faisal Ahmed

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Given their rarity and the need for input from a range of clinical disciplines, the management of the child with a rare condition such as DSD or CAH may be quite complicated, and the situation is worsened by a lack of evidence for many diagnostic and interventional procedures that are undertaken. It is, therefore, not surprising that there will be variation in the management as well as the outcome of people with these conditions. By working as a network of clinical and research centres it is possible that these variations can themselves be better managed and studied. Disease registries form the cornerstone of such networks and the advent of the DSD registry in 2007, initially as the ESPE DSD Registry, followed by the EuroDSD Registry and currently as the I-DSD Registry is a clear example of how registries can also be used to address a number of important issues ranging from understanding fundamental mechanisms to understanding clinical practice and health care outcomes. Given that there may be over 8,000 rare conditions and only a proportion of conditions are covered in registries of variable quality, there is a

need to explore how greater coverage can be provided without compromising the quality and sustainability of registries.

### **European Reference Networks for DSD & related conditions**

Olaf Hiort

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Rare Diseases and Conditions encompass approximately 8.000 different entities affecting several million people in the European Union. Because of their scarcity the diagnosis is often delayed and management difficult since experts are scattered and in many countries not every rare condition can be cared for entirely. Therefore the EU has recently launched 24 European Reference Networks for Rare Diseases (ERN), which will define expert centres within the EU member states and join them to enhance transparency and quality of care. Furthermore, these networks are meant to enforce the possibility of cross-border health care in rare conditions in order to diminish inequalities in patient diagnostics and management. The aim is not to have the patient travel, but rather foster expertise through the expert centres and exchange biomaterials or technical information.

The conditions comprising Differences of Sex Development (DSD) are a good example of accomplishments through networking activities. The national networks in several EU countries and the EU-related networks EuroDSD, DSDLife, and ongoing, the DSDnet have led to transparency of clinical centres as well as research activities with recommendations regarding care and diagnostics (1-3). In a process accompanied by the European Endocrine Societies ESE and ESPE, an extensive ERN for rare endocrine conditions called Endo-ERN has been constructed, which encompasses eight main thematic areas, among them also the group defined as “Conditions affecting sex development and maturation”. With this approach, the COST Action DSDnet has been joined by the COST Action network GnRHnet, to address common approached in diagnostics, management and research. Consequently we aim for an integrative ERN to manage all complex endocrine conditions with a gain in medical and scientific excellence.

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## Oral Communications 1

### Effects of the prenatal androgen exposure in psychosexual parameters in a large cohort of 46, XY DSD patients

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**Introduction:** Psychosexual alterations can be common in 46,XY DSD individuals. It is caused by many factors as androgen prenatal exposure, the presence of alterations in external genitalia and the pubertal delay.

**Objective:** To evaluate psychosexual parameters including gender role, gender identity and sexual orientation in a large cohort of individuals with 46, XY DSD from different etiologies and to correlate these parameters with prenatal androgen exposure.

**Methods:** 141 patients with 46, XY DSD were evaluated. The psychological parameters were evaluated through a structured questionnaire and by the application of a projective psychological test (HTP: Human Tree Person). To determine the effect of prenatal androgen exposure, the whole cohort was divided into 3 groups, according by the prenatal androgen exposure: Group A: no androgen exposure (CAIS and complete gonadal dysgenesis), n = 34; Group B: intermediate exposure - (PAIS, partial gonadal dysgenesis and defects of testosterone synthesis), n = 76; and Group C: with normal exposure - (5 $\alpha$  Reductase deficiency type 2), n = 31.

**Results:** A total of 114 patients were raised in the female social sex (81%). Ambiguous gender identity was identified in the HTP test in 29%. Ambiguous Identity was more frequently in individuals raised as female (24.5 vs 4.9%, p <.001). The incongruence between gender identity and sex of assignment was 51%. Sex change from female to male was 23% and male to female in 11%, and 60% happened at adulthood ( $\geq$ 16 years). Regarding testosterone exposure, in group A (without exposition), there was concordance between gender identity and social sex in 100% of the cases and there was not sex change. In group B, there was a disagreement between gender identity and sex assignment in 38% of cases and sex change in 13% (p = 0.02). In group C (normal exposure to T) there was a 62% of disagreement between gender identity and social sex, and 50% of sex change (all cases from female to male) - p <.01. The heterosexuality rate was 96% according by the final social sex. Regarding sexual life, when we compared individuals in the female with male social sex, we observed differences in the orgasm frequency (p = 0.015), masturbation (0.02) and satisfactory sexual intercourse (<0.01), all of them were better in males. Comparing males who kept the social sex with males who changed it, there were not differences in the sexual parameters.

**Conclusion:** Prenatal exposure to testosterone influenced the psychosexual differentiation of individuals with 46, XY DSD. In general, 46,XY individuals have a good psychosexual adaptation, but some psychosexual parameters are better in the male social sex. In the male 46,XY patients, there were not differences between who kept with who changed the social sex.

**Androgen insensitivity due to increased methylation in the androgen receptor promoter**

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**Background:** Androgen insensitivity syndrome (AIS) is a common cause of 46,XY differences in sex development. Although classically defined as the inability of the androgen receptor (AR) to respond to androgens only 40% of clinically diagnosed AIS cases reveal a partial or complete loss of function mutation in the AR-gene. This leaves a considerable amount of AIS patients without a clear diagnosis and underlines the need of factors outside the AR for proper androgen action.

**Objective:** To investigate, if changes in AR-transcription can explain AIS in the absence of an AR-gene mutation.

**Methods:** Analysis of AR function (APOD-assay) and AR mRNA levels in AR-gene mutation negative cultured genital skin fibroblasts (GF) from individuals with the clinical diagnosis AIS as well as bisulfite-sequencing of the AR-promoter in these GF. In order to define AIS on a functional basis we previously established an assay measuring the transcriptional activity of the AR to induce its target gene Apolipoprotein D (APOD) in GF. The APOD-assay clearly distinguishes AR-activity in GF of male controls from GF of individuals with a mutation in the AR gene ( $p < 0.0001$ ).

**Results:** Applying this assay to GF from clinically diagnosed AIS individuals but no mutation in the AR gene we saw a reduced AR function in about one-third of the cases ( $n=23$ ). This subgroup can be defined as functional AIS in the absence of an AR-gene mutation (AIS type II). Analyzing AR mRNA levels in these 23 GF revealed a reduced AR mRNA expression in 8 cases compared to age and tissue matched controls. Methylation analysis of the AR-promoter in these cases showed a significantly increased methylation at specific, so far not described sites in 5 cases.

**Conclusion:** Using the APOD-assay we were previously able to validate the clinical diagnosis AIS on functional grounds (AIS type II). In search for co-regulators of androgen action in AIS type II we identified a region in the AR promoter necessary for proper AR expression. We postulate that high methylation of this promoter region leads to a reduced AR-transcription and thereby androgen insensitivity in the absence of a mutation in the AR gene.

**Psychosocial screening in DSD: Psychometric evaluation of the Psychosocial Assessment Tool**

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**Objective:** The DSD-TRN – a clinical research network sponsored by the U.S. National Institutes of Health – was created in 2011 to advance discovery of the genetic causes of differences/disorders of sex development (DSD), standardize the diagnostic process, and systematically evaluate the relationships between treatment strategies and health and quality of life outcomes of patients and families by prospectively and longitudinally capturing diagnostic and intervention data elements in its patient registry. DSD-TRN participating sites administer a battery of psychosocial measures to identify patients/families in need of psychosocial support and to guide intervention. While information from these questionnaires is clinically useful, there is an organizational burden associated with the administration and scoring of multiple psychosocial measures, and some centers delivering DSD care may not have the resources or clinical expertise to implement comprehensive psychosocial screening. The Psychosocial Assessment Tool (PAT) – currently administered as part of the DSD-TRN battery – has been validated for use in other chronic pediatric conditions as a means of efficiently triaging psychosocial services. Utilization of a single screening measure to detect patients and families at elevated psychosocial risk, rather than an entire battery of measures, would potentially improve care delivery by DSD teams with limited psychosocial resources. This study evaluated the psychometric properties of the PAT as a screener for family psychosocial risk.

**Methods:** Study sites were health care institutions comprising the DSD-TRN. Caregivers of patients with DSD (n = 197) completed the PAT as part of routine care during clinic visits. The PAT is comprised of 7 subscales and provides a total score estimating overall level of family risk. Subsets of caregivers also completed a brief screening measure of adult depression/anxiety (PHQ-4) and a psychometrically robust measure of child emotional-behavioral issues (Child Behavior Checklist, CBCL) which yields scores reflecting internalizing problems (i.e., anxiety, depression and somatic symptoms), externalizing problems (e.g., rule-breaking and aggressive behavior) and overall total problems.

**Results:** The mean PAT Total score for the entire sample was  $0.89 \pm 0.66$  (i.e., low risk). A total of 65% of caregivers scored in the low risk category, 29% in the medium risk, and 6% scored in the high risk range. Internal consistency for the PAT Total score was high ( $\alpha=0.86$ ), with 6 of the 7 subscales having  $\alpha > 0.60$ . The PAT Family Problems subscale and the PAT Total score were correlated with the caregiver PHQ-4 score ( $r=0.47$ ,  $p<0.001$  and  $r=0.43$ ,  $p<0.001$ , respectively). The PAT Child Problems subscale and the PAT Total score were correlated with CBCL scores (PAT Child Problems and Internalizing score  $r=0.69$ , Externalizing score  $r=0.69$ , Total problems score  $r=0.80$ , all  $ps<0.001$ ; PAT Total score and Internalizing score  $r=0.55$ , Externalizing score  $r=0.62$ , Total problems score  $r=0.62$ , all  $ps<0.001$ ).

**Conclusions:** The PAT demonstrated both internal consistency and convergent validity in this DSD sample: PAT scale scores correlated as expected with both caregiver psychosocial distress and with child emotional-behavioral problems. Notably, a third of caregivers reported concerns placing the family in one of the 2 at-risk categories, highlighting the importance of providing psychosocial support and resources to families managing a DSD condition. Children with DSD and their families may face a range of challenges including complex treatment decision-making, medication/hormone management, coping with medical exams/procedures, gender concerns, and fears of stigmatization. DSD care guidelines emphasize the importance of providing routine psychosocial assessment and intervention for patients and families, yet lack of psychosocial resources may compromise implementation. Use of a validated psychosocial screener such as the PAT has the potential to effectively identify at-risk families so that care teams can provide targeted psychosocial care.



### **Current surgical practice in DSD: results of the COST/DSDnet surgery survey**

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**Objectives:** Differences in Sex Development (DSD) describe a heterogeneous group of conditions with unusual sex development, often with effect on the appearance of the genitalia and function of the reproductive system. Surgical treatment of these conditions is not standardized and controversial. The purpose of the survey was to delineate current surgical practice in DSD within the dedicated surgical community.

**Methods:** A surveymonkey® survey consisting of 49 items was developed by a working group of COST BM1303/DSDNet and spread among the surgical DSD community using an email invitation to subspecialty organisations, personal contacts, and social media. There were 124 responders: 76%/24% male/female; >80% pediatric surgeons and pediatric urologists; from all regions of the world (Europe 56%).

**Results:** 90% of the participants work in a multidisciplinary DSD team (67% always with endocrinologists, 35% always with psychologists). In only 20% the surgeon is clinical lead of the team. In 19% of participants surgical options cannot be discussed in the team. However, in 15% support groups are involved in the decision making process. There is no standardized tool how DSD surgical activity is recorded. More than 70% of the DSD centers do not take part audit or quality improvement exercises. Case load in diagnostic procedures as well as feminizing surgery was around 2-4 cases per doctor per year. In contrast to optimal sexual functioning and fertility issues, cosmesis was regarded as least important outcome parameter. Stratification according to geopolitical criteria, sex, subspecialty or year of graduation showed no significant differences except for timing of feminizing surgery which was postponed significantly more often (29%) to adolescence or adulthood by surgeons from Western countries ( $p < 0.05$ ). Almost all respondents preferred surgery for hypospadias during the first 24 months of life.

**Conclusions:** This survey shows that there is considerable variation in the surgical treatment of DSD. Multidisciplinary management, audit and prospective patient registries still have to be developed.

### **Transcriptome analysis of Klinefelter testis from fetal life to adulthood**

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Men with Klinefelter syndrome (KS, 47,XXY) are azoospermic due to degeneration of the seminiferous tubules. Degeneration accelerates during puberty, and even though gene dosage effects of X-chromosomal genes escaping inactivation are likely to be involved, the molecular mechanisms remain unknown.

Here, we report preliminary results of transcriptome analysis by RNAseq of archived paraffin-embedded testicular tissue samples from 9 fetuses (4 KS, 5 controls), 8 pre-pubertal boys (4 KS, 4 controls) and 11 adult men (6 KS, 5 controls with similar histology but normal karyotype).

Due to fixation and ageing of the tissue, data quality was compromised leaving on average only 1.2M reads per sample. Nevertheless, using an unadjusted p-value of 0.01, we identified several differentially expressed genes in the KS testis at each developmental stage. *XIST* was upregulated at all stages, and only one gene, *OR6B1*, was upregulated at fetal and adult stages. No genes were downregulated at more than one stage. Focused analysis of X-chromosomal genes showed that majority of the differentially expressed genes was previously reported to undergo X-inactivation (e.g. *GAB3*, *STARD8* and *PGRMC1*). For the first time, we describe the transcriptome of KS testis samples throughout development and our preliminary results indicate that different genes are implicated at different developmental stages.

### **Living with clitoromegaly day to day: early findings from a qualitative study**

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Surgical interventions for children born with atypical genitalia is highly controversial, particularly management of clitoromegaly. Parents are often invited to consider differing levels of surgical intervention for their child, either in infancy or at a later stage. Parents' questions centre around what will be the impact of different options on the child but information regarding contemporary psychosocial outcomes for children and parents is needed

In this qualitative study, parents of 30 families of girls with CAH and cliteromeagly diagnosed in the neonatal period at two specialist UK, discussed the impact of differing management strategies of clitoromegaly. Parents described aspects of the day to day life that are commonly raised as concerns by new parents of girls with CAH. The participants are parents of girls whom have undergone interventions including clitoral reduction, labiaplasty or no surgery.

The study also considers parents' views on children's participation in research about clitoromegaly. This informs whether it is viable to progress to the stage of the study that involves direct conversations with children.

This critical psychology study contextualises personal accounts to inform on-going debate.

### **“Extended androgen profile”: determination of androstenediol, androsterone, dihydrotestosterone, androstenedione, testosterone, 17-hydroxyprogesterone by LC-MS/MS and its application in a cohort of 21-hydroxylase deficiency patients**

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The “backdoor” pathway for biosynthesis of dihydrotestosterone (DHT) is known to exist in Tammar wallabies and suggested to exist in humans as well. Recently published molecular analyses identified pathologic mutations of genes involved in the backdoor pathway leading to undermasculinization in affected patients. In addition, urine steroid profiles of patients with 21-hydroxylase deficiency (21-OHD)



demonstrated that the backdoor pathway is active postnatally. Our aim was to develop an LC-MS/MS based method to determine hormones from both pathways, the classical - and the backdoor pathway to DHT.

We developed a LC-MS/MS method for the determination of androstenediol (adiol), androsterone (asterone), DHT, androstenedione (delta4), testosterone (T), 17-hydroxyprogesterone (17OHP) for plasma and serum. We compared the steroid profiles of 16 molecular proven 21OHD patients (10 females, 6 males, aged 0-7 years) and 16 matched control subjects. In a second step we compared 21-OHD patients under treatment with matched controls (12 females, 32 males, aged 0-17 years).

The assay was linear from 0.01 nmol/L up to 200 nmol/L and requires a sample volume of 0.1 mL plasma or serum. The lowest limit of quantification was 0.01 nmol/L.

Untreated 21-OHD patients had significantly higher concentrations for 17OHP and delta4 compared with controls ( $p < 0.0001$ , respectively). We found also higher concentrations for T and DHT ( $p < 0.0001$ ,  $p = 0.0001$ , respectively). Moreover, we found higher concentrations for asterone ( $p = 0.003$ ) being part of the backdoor pathway. When categorizing these patients by the severity of the disease as predicted by CYP21A2 genotype, we found a strong correlation to asterone and T ( $r = 0.75$ ,  $p = 0.0005$ ,  $r = 0.73$ ,  $p = 0.005$ , respectively).

21-OHD patients under treatment had significant higher concentrations of adiol and DHT ( $p = 0.005$ ,  $p = 0.003$ , respectively) compared to controls.

In essence, we developed a reliable assay for an “extended androgen profile”. Determination of these six androgens allows a snapshot of an extended androgen pathway as well as for each of the measured single steroids. In our cohort we could demonstrate that steroids playing roles in the backdoor pathway are present in 21OHD patients.

### Cognitive abilities in women with CAIS and gonadal dysgenesis

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**Background:** Sex differences in cognitive abilities exist for spatial and verbal abilities, memory functions on average in groups of men and women. Theories concerning the origin of sex differences in cognitive functions involve both hormonal influences, mainly androgen exposure for masculinisation or defeminisation and social and cultural structures of the society that influences the individual to conform to gender stereotypes. Recently, evidence for factors associated with sex chromosomes influencing brain masculinisation has also been acknowledged.

**Aim:** To investigate cognitive sex differences in a group of individuals with variations in sex development to further the understanding of the sexual differentiation of the brain and cognitive functions.

**Method:** This study was performed at Karolinska University Hospital, Stockholm in connection with a follow up of somatic, psychiatric and gynaecological wellbeing. Cognitive tests that previously showed sex differences 3D mental rotation, line judgement, verbal fluency, typing, episodic memory/face recognition and emotion recognition were administered to a group of women with Complete Androgen

Insensitivity Syndrome (CAIS) (n18), 46XY Gonadal Dysgenesis (46 XY GD) (n 6) and 46XX Gonadal Dysgenesis (46 XX GD) (n 7) compared with age matched male and female control groups recruited from the population registry.

**Results:** All the tests showed the expected sex differences between control women and control men. Women with CAIS performed intermediary between male and female control groups with no significant differences on a group level. The trend was for women with CAIS and XY GD to perform as the female control group except on the typing test and the test for emotional recognition. Women with XX GD outperformed both control men and women on tests that usually show a female advantage.

**Conclusion:** Androgen exposure seems to be the most influential factor for brain masculinisation important for spatial abilities. Factors related to sex chromosomes might play a role in the development of social cognition.

### **Ethical considerations of fertility preservation for youth with DSD**

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**Background and Objective:** Oncofertility emerged as a field to preserve fertility in cancer patients undergoing life-saving treatments that could render them infertile. Advances made in fertility preservation (FP) techniques have inspired expansion to other patient populations facing infertility, including individuals undergoing stem cell transplant for non-oncologic conditions and transgender individuals pursuing gender-affirming treatments which may compromise fertility. FP could also be expanded to individuals with differences (disorders) of sex development (DSD), a group of diverse conditions resulting from variation in an individual's chromosomal, gonadal or phenotypic sex development.

**Methods:** Ethical issues related to FP for individuals affected by DSD were identified and reviewed by a multi-disciplinary team. The analysis was focused on pediatric patients with DSD because they often face early gonadal failure and/or fertility-altering medical treatments before reaching the age of majority such that the likelihood of preserving fertility may be maximized when pursued at younger ages. Expertise represented on the team included: ethics, psychology, community advocate, urology, and endocrinology. Key ethical issues related to FP for individuals with DSD were summarized by sub-topic.

**Results:** While some ethical considerations are consistent across patient populations considering FP, others are unique to the DSD population. FP in DSD differs from other patient populations because individuals with DSD often have inherent subfertility due to their medical condition. For example, abnormal (i.e., dysgenetic) gonads carry risk for germ cell neoplasia from birth and progressive gonadal failure in adolescence. Additionally, fertility potential for many specific DSD conditions is unknown and requires further investigation to clarify which individuals are candidates for FP. Key ethical issues raised by FP for individuals affected by DSD include: (1) Ethics of gonadectomy, (2) Consent/assent, (3) Parental proxy decision-making, (4) Experimental nature of treatment (5) False hope, (6) Cost and insurance coverage, (7) Transmitting genetic condition to offspring, and (8) Gender identity and gender dysphoria.

**Conclusions:** Fertility preservation for youth with DSD is a new frontier that requires careful consideration of multiple complex and evolving ethical issues in order to establish best practices.

### Gonadal function in adult male patients with congenital adrenal hyperplasia

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**Introduction:** Reported fertility problems in men with congenital adrenal hyperplasia (CAH) range from normal to severely impaired. Previous studies are most often based on data from a single center. Mechanisms for fertility impairment include primary, secondary and tertiary gonadal dysfunction or psychosexual problems. Primary gonadal dysfunction may be due to benign testicular adrenal rest tumors (TART). In addition, central gonadal dysfunction may be caused by the suppressive effects of elevated adrenal androgens or their metabolites on the HPG axis. Aim of the study is to determine gonadal function in male CAH patients in the European DSD life cohort.

**Methods:** The DSD LIFE database contains data of 1161 patients with different forms of disorders of sex development (DSD) including 121 male CAH patients from 14 European centers. Indirect markers of gonadal function were collected including hormone concentrations, serum analysis (n=43-90) and ultrasound testes (n=67). Patient characteristics, biochemical parameters and treatment in patients with and without gonadal dysfunction were evaluated.

**Results:** In 118 patients, median age 28 (range 15-68) years, gonadal function could be evaluated, as 3 patients were excluded due to longstanding testosterone treatment. Two patients had 11 $\beta$ -hydroxylase deficiency, while 116 patients suffered from 21-hydroxylase deficiency (genotype O=23 pts, A=36 pts, B=32 pts, C=3 pts, no mutation=22 pts). Low testosterone concentrations (c.q. lower than reference range) were reported in 19/97 (19.6%), low LH in 12/90 (13.3%), low FSH in 9/90 (10%), and low inhibin B in 8/43 (18.6%) patients. Pathologic semen parameters (according to WHO 2010) were observed, considering low sperm count (15/39 patients), decreased motility (13/37 patients), and abnormal morphology (4/28 patients). TARTs were present in 27 of 67 patients (in 2 patients unilaterally). 26 patients had fathered a total of 43 children.

**Conclusions:** Gonadal function in male CAH patients can be compromised with a high prevalence of TART. Further analyses are necessary to compare TART and non TART patients and to determine other contributing pathogenetic factors.

### Exome sequencing identifies known and new genes involved in DSD

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Disorders of sex development (DSD) are a group of rare complex orphan disorders of anomalies of gonadal development and hormone synthesis or action. This includes the rare disorders of sex-determination – a lack of testis-determination (46,XY gonadal dysgenesis) or testis formation on a 46,XX background (46,XX testicular or ovotesticular DSD). 40% of all cases of 46,XY gonadal dysgenesis can be explained by mutations involving *SRY*, *NR5A1* or *MAP3K1*. Rare cases are caused by mutations involving *GATA4* or its partner *FOG2/ZFPM2*. Most non-syndromic 46,XX DSD patients carry the *SRY* gene or have rearrangements involving different *SOX* gene loci. However, the majority of *SRY*-negative 46,XX DSD cases and 46,XY gonadal dysgenesis cases do not have a molecular diagnosis. Unbiased genomic approaches, such as exome sequencing should reveal new gene mutations causing DSD. Since 2009, we have performed whole exome sequencing on 260 cases of DSD that have a normal ploidy by high resolution arrayCGH. This includes 180 individuals with either 46,XY gonadal dysgenesis or 46,XX-*SRY* negative (ovo)testicular DSD. This also included 20 familial cases of DSD and 37 syndromic forms of DSD. Analysis of datasets revealed novel mutations in genes known to be associated with syndromic and non-syndromic forms of DSD including the genes *RSP01*, *WT1*, *ARX*, *SRY*, *GATA4*, *FOG2*, *DMRT1*, *WNT4*, *MAP3K1*, *MAMLD1*, *LHCGR*, *HHAT*, *DHH*, *FGFR1*, *IER3IP1*, *CHD7*, *FANCA*, *FANCM* and *NR5A1*. In addition, novel and likely pathogenic mutations were identified in genes that have not previously been associated with DSD. This includes missense mutations in *SOX* genes that are related to and co-expressed with *SOX9*, extra-cellular matrix proteins, and genes involved in the WNT signalling pathway that are expressed in the developing gonad. Overall, exome sequencing is a powerful, cost-effective and rapid approach to identify known causes of DSD as well as offering the possibility to identify new genetic factors involved in human urogenital development. However, overall around 60% of all cases still remain unexplained, particularly those individuals with 46,XX DSD. Whole genome sequencing is underway to understand the aetiology of these cases.

### The Scottish Audit of Atypical Genitalia

Martina Rodie, Naser Alenazi, Faisal Ahmed

On behalf of the Scottish DSD Network and the Scottish Paediatric Endocrine Group

**Introduction:** The early management of atypical genitalia has been highlighted as being of critical importance by the UK-DSD Guidance in 2011 and more recently in 2016.

**Objectives:** To estimate the incidence of atypical genitalia requiring early specialist input in neonates and its clinical presentation and management.

**Method:** Prospective audit through the Scottish DSD network and the Scottish Paediatric Endocrine Group, between June 2013 and December 2016. Monthly emails were sent to clinician members to notify newborns  $\geq 37$  wks gestation with atypical genitalia requiring specialist input in the previous month and aged  $< 4$  wks at presentation. Notified newborns were followed up to 3 months age.

**Results:** 64 newborns were reported, of whom 40 were true positives. In addition, 16 cases were identified through cytogenetic laboratories. Amongst the 24 false positives, 8 were born at gestation <37wks. The incidence of atypical genitalia requiring specialist input within the first month of birth, in term newborns in Scotland was 1 in 3,480. Of the cases who completed follow up, 37(65%) presented within 24hrs. Age at sex assignment ranged from birth to 6 days and 70% had sex assignment at birth. All continued to have same sex at 3 months. Parental questionnaire enquiring of their experience were sent to parents of 30 infants. Of the 11(36%) of parental questionnaires returned from three regions of Scotland, 83% reported a good explanation of their child's clinical condition, health professionals who listened and answered questions well with good communication across health care teams.

**Conclusions:** Atypical genitalia requiring specialist input and investigations within the first month of life is a rare occurrence affecting one term newborn in every 3,480 born in Scotland. To avoid selection bias, patient/parent reported experiences need to become a routine part of clinical care.

### Session 3 – Guest Lecture

#### DSD as an extreme variant of testicular dysgenesis

Niels E. Skakkebaek (Copenhagen)

Niels E. Skakkebaek, Ewa Rajpert-De Meyts, Katharina Main, Niels Jørgensen, Anna-Maria Andersson, Tina Kold Jensen, Jorma Toppari and Anders Juul, Dept. of Growth and Reproduction and EDMaRC, Rigshospitalet and University of Copenhagen, Denmark.

Although the phenotypes of DSD individuals with 46, XY and other karyotypes with Y chromosome material in their karyotype vary enormously, they seem to have one thing in common: they carry an increased risk of developing germ cell neoplasia, including gonadoblastoma, seminoma or non-seminoma. Similarly, patients with cryptorchidism, hypospadias and infertility also are at increased risk of developing germ cell tumor, even without any signs of mutations. A common factor in the pathogenesis seems to be testicular dysgenesis which has a broad spectrum from very severe, e.g. due to *SRY* mutations and sex reversal, to mild as seen in some phenotypically normal men with poor semen quality. Common features in gonadal histology are dysgenetic tubules, microliths and sometimes germ cell neoplasia in situ or gonadoblastoma. The crucial factor behind the risk of germ cell neoplasia seems to be a delay in differentiation of the primordial germ cells from embryonic gonocytes into spermatogonia due to dysgenesis and abnormal function of Leydig- and Sertoli cells.

In experimental animals, and in wild-life, endocrine disrupting chemicals, e.g. phthalates given perinatally seem capable of inducing testicular dysgenesis syndrome (TDS), including severe DSD-like phenotypes. It has been hypothesized that an increasing number of symptoms of TDS in human populations, including poor semen quality, testicular cancer and cryptorchidism may be due to environmental exposures from modern life-style factors, including endocrine disrupting chemicals during fetal period. The fetal hypothesis has lent some support from recent longitudinal studies, although extensive clinical studies on larger mother-child cohorts remain to be carried out.

Unfortunately, information on incidence trends in DSD seems lacking.

Further reading:

Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM, Toppari J, Andersson AM, Eisenberg ML, Jensen TK, Jørgensen N, Swan SH, Sapra KJ, Ziebe S, Priskorn L, and Juul A. Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility. *Physiol Rev* 96: 55-97, 2016.



## **Session 4A – Gonadal & Adrenal Development**

### **Novel conditions affecting adrenal and gonadal function: molecular insights and translational impact**

John C Achermann (London)

UCL GOS Institute of Child Health, UCL, London, UK

The adrenal glands and gonads have a shared developmental origin and common biological processes, such as steroidogenesis. Consequently, several distinct clinical conditions can affect both adrenal and gonadal function. Making the correct diagnosis and understanding the potential short-and long-term impacts can be important for personalised management. This presentation will focus on several recent developments in our knowledge, novel conditions, and variations of established diagnoses. The main areas highlighted will include:

- 1) the role of steroidogenic factor-1 (SF-1, NR5A1) in DSD and adrenal dysfunction; 2) the impact of the cell growth regulators CDKN1C in IMAGE syndrome and the rapidly emerging role of SAMD9-associated phenotypes in MIRAGE syndrome, where dynamic somatic “rescue” mechanisms can modify phenotype; 3) SGPL1 as a new cause of adrenal dysfunction with renal and possible gonadal effects; and 4) the clinical consequences of non-classic STAR and non-classic CYP11A1 deficiencies.

The translational impact of next-generation sequencing studies of large cohorts of children with undiagnosed adrenal insufficiency will also be discussed. Finally, data from a recently published Atlas of Human Adrenal and Gonad Development will be presented, which has identified potential novel core components of adrenal and gonad development and steroidogenesis, and which may provide insight into novel candidate genes in humans.

### **Novel genes and insights in ovarian development and maintenance**

David Zangen (Jerusalem)

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### **Essential points:**

- Throughout this review we elucidate on the recently characterized genes involved in ovarian development and maintenance which reflect a major change in the concept and understanding of ovarian development; from being a default pathway to a carefully regulated specific developmental cascade.
- This ovarian developmental cascade is suggested here to be divided into three subgroups by the developmental stage and character (see table 1): (i) transcription or early differentiation factors - involved in the primary gonadal differentiation and development of stromal and gonadal specific supporting cells; (ii) hormonal signaling genes - involved in subsequential ovarian development and maintenance; and (iii) recently characterized genes involved in germ cell differentiation and maintenance. These 3 interdependent parallel developmental cascades result in the differentiation of 3

major cell types in the ovary: the somatic supporting cells, the hormone producing cells and the germ cells.

- New findings elucidating the genetic etiology for ovarian dysgenesis in several human families created a new postulate that aberration in differentiation of germ cells due to abnormal meiosis (aberrant double-strand breaks (DSB) repair, chromosome synapsis and sister chromatid cohesion) could account for complete ovarian (but not testicular) dysgenesis
- The Nucleoporin gene, NUP107, mediating the nuclear-cytoplasmic transport found very recently to be specifically involved in ovarian development through a probable role in meiosis and in the ovarian somatic cells differentiation is described and discussed too.
- Significant clinical implications are derived from these recent findings and are elaborated and discussed in the last part of the talk.

### Testis development

Anu Bashamboo (Pasteur Institute, Paris)

Gonad development in mammals is a fate choice made by the bipotential somatic cell to commit to Sertoli (male) or granulosa (female) cells. In the XY gonad, pre-Sertoli cells express SRY. Implementing both cell-autonomous and non-cell-autonomous mechanisms, *Sry* expression ensures the differentiation of sufficient Sertoli cells required for initiation of testicular development. Our understanding of human sex-determination is largely due to the genomic analysis of individuals with 46,XY gonadal dysgenesis or (ovo)testicular DSD. This includes the SRY and SOX9 genes, which initiate Sertoli cell differentiation. Once formed, Sertoli cells induce the development of foetal Leydig cells, via a hedgehog signaling pathway leading to testosterone production. In mice, the synergistic interaction of *Sry* and *Nr5a1* activates *Sox9* expression via a testis-specific enhancer termed *Tesco*. Other cofactors in this system such as *GATA4* or *FOG2* form a part of the signaling network active during formation of the gonad and mutations in these genes are associated with 46,XY gonadal dysgenesis. *Sry* also initiates a positive feedback loop between *Sox9* and *Fgf9*, which results in the up-regulation of *Fgf9* and the repression of the pro-ovarian gene *Wnt4* in the testis. SOX9 also represses the genetic pathways (*WNT4/FOXL2*) involved in ovarian development.

In contrast to the testis, ovarian somatic sex-determination appears relatively labile with a potential to switch to a testis state. Our understanding of how a testis is formed is also beginning to emerge from the genomic analysis of individuals with (ovo) testicular DSD. This includes other members of the SOX family and recurrent mutations in a growing number of genes that may be required to repress testis development. This highlights that the development and maintenance of the mammalian gonad is an unusual biological process that is regulated by a double repressive system, where an equilibrium of mutually antagonistic pathways must be attained for normal development of either the testis or ovaries.

## Session 4B – Results from the European study dsd-LIFE

### **dsd-LIFE: Concept of the study and cohort description.**

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**Background:** dsd-LIFE is a comprehensive cross-sectional clinical outcome study of individuals with differences/disorders of sex development (DSD). This study focuses on various rare genetic conditions characterized by impaired gonadal or adrenal functionality and aims to assess quality of life (QoL), psychosocial adaptation, psychological wellbeing, therapies and support, health status, satisfaction with care, psychosexual issues, participants' views on health care and ethical considerations.

**Results:** The study collected self-reported data (using standardized instruments and self-constructed questionnaires with condition-specific questions) and current and previous clinical data on medical treatment and health status. 1040 participants with different DSD conditions were recruited by 14 study centres in 6 European countries (France, Germany, Great Britain, Poland, Sweden, and the Netherlands) from February 2014 until September 2015. The conditions included were: Turner syndrome (n=301); 45,X0/46,XY conditions (n=45); Klinefelter syndrome (n=218); 47,XYY (n=1); 46,XY gonadal dysgenesis/ovotestes (n=63); complete androgen insensitivity (CAIS) (n=71); partial androgen insensitivity PAIS) (n=35) and androgen synthesis disorders (n=20); severe hypospadias (n=25); other or non- classified 46,XY DSD (n=7); 46,XX congenital adrenal hyperplasia (CAH) (n=226); 46,XX gonadal dysgenesis/ovotestis (n=21); and 46,XX in males (n=6). Additionally, 121 46,XY male-assigned individuals with CAH due to 21-hydroxylase deficiency were recruited. The participants' mean age was 32.4 yrs (range 16 to 75 yrs). Participation was high in conditions not commonly described as DSD, such as Turner and Klinefelter syndromes or CAH. Recruitment of individuals with XY DSD conditions proved to be more difficult. The data collection of patient-reported outcomes (PROs) resulted in high data quality. Within medical and physical examination data, more missings and/or inaccurate data were found than expected. Overall, the sample of the study covers individual experiences of adolescents and adults with various DSD conditions, including a broad range of diagnostic methods, therapies as well as social and cultural backgrounds.

**Conclusions:** The European dsd-LIFE study recruited and evaluated the largest cross- sectional sample of individuals with different conditions classified under the term DSD. The data from this large sample will provide a sufficient basis for evidence-based recommendations for improvement of clinical care of individuals affected by a DSD condition.

**Proxy- and self-reported outcome after surgery in people with DSD.**

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**Introduction:** Outcome studies of genital surgery in disorders/differences of sex development (DSD) often lack the patient's perspective. We describe observer's and patient's satisfaction with the anatomical and functional result after genital surgery in a large European cohort.

**Patients and Methods:** 1040 adolescents (>15 yrs.) and adults with DSD took part in a cross-sectional multicentre clinical evaluation study in six European countries in 2014/15. Diagnosis were Turner syndrome (n=301), 45,X/46,XY (n=45), Klinefelter syndrome (n=218), XYY (n=1), 46,XY DSD (n=222) and 46,XX DSD (n=253). Study protocol included a clinical report file; optional genital examination, and patient reported outcomes including satisfaction with anatomical and functional outcome.

**Results:** Five hundred participants had been subjected to genital or breast surgery, with the highest rate in 46,XY DSD and the lowest in Turner syndrome. Altogether, 240 participants had feminising and 112 masculinising surgery, and 217 underwent gonadectomy. Physicians evaluated anatomical appearance at genital examination as poor in less than 10%. Participants reported they were (very) dissatisfied with anatomical appearance in 22%, and with function in 20%. Clitoridectomy had a very negative effect on participant's life. Gonadectomy was experienced negatively by one third while other surgeries appeared to have a more positive effect on life.

**Conclusion:** Gonadectomy was performed frequently in DSD. Physicians should be aware of its possible long-lasting negative effect on patient's life and its irreversibility. Patient reported outcome should be evaluated to understand the influence of genital surgery on life situations.

**Voice deviations in people with DSD (dsd-Life)**

Ulrika NYGREN, Maria SÖDERSTEN, Claire BOUVATTIER, Peggy COHEN-KETTENIS, Birgit KÖHLER, Anna NORDENSTRÖM, Robert RÖHLE, Ute THYEN, Agneta NORDENSKJÖLD on behalf of dsd-LIFE

**Introduction:** Voice characteristics are strong markers for gender. In patients with disorders/differences of sex development (DSD) there is a risk that the voice does not sound in congruence with the patient's gender identity. We have earlier described virilisation of the voice in a Swedish cohort of women with CAH. The aim was to study whether voice deviations also exist in other kinds of DSD in a large (European) cohort.

**Patients and Methods:** 1040 adults and adolescents (>15 yrs) with DSD took part in a cross-sectional multicentre clinical evaluation study in six European countries in 2014/15. Diagnoses were Turner syndrome (n=301), 45,X/46,XY (n=45), Klinefelter syndrome (n=218), XYY (n=1), 46,XY DSD (n=222) and 46,XX DSD (n=253). The study protocol included patient reported outcomes (on satisfaction with voice) and whether the participants had been mistaken for the wrong gender due to the voice when answering the phone and if so, if that bothered them.

**Results:** In total, only 27 rated that they were very satisfied with the voice and 73 satisfied based on the ratings of the statement "I am satisfied with my voice" and that between 66 and 82% in the different groups of participants were "(very) dissatisfied" with their voices. Altogether 147 participants declared that their gender had been mistaken on the phone, but 45 were not bothered because of that. Among the 102 who were bothered (9.8%), it was most commonly described by patients with XY, DSD (n=50/222, 41%) in both males and females.

**Conclusion:** Almost 10% of patients with DSD have experienced that their gender have been mistaken on the phone and were bothered by that, with a highest prevalence among persons with XY, DSD of both sexes. This problem should be more taken into account in clinical care of persons with DSD. A vast majority of participants with DSD declare that they are not satisfied with their voices. The reasons for the overall dissatisfaction with the voice have to be further explored.

**Body Image and Self-Esteem in Disorders/Differences of Sex Development. The Effect of Diagnosis, Medical Treatments and Psychological Characteristics.**

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Body image and self-esteem are known mediators of psychological wellbeing and sexual satisfaction. Although studies point out suboptimal levels of body image and self-esteem in specific disorders/differences of sex development (DSD) diagnoses, little comparative and explanatory studies have been performed. Therefore, the aim of this study was to assess subjects across the DSD spectrum and to study the impact of diagnosis and mediating characteristics. Data collection was part of dsd-LIFE, a multicenter cross-sectional European study on wellbeing and healthcare evaluation of adults diagnosed with DSD. Participants were recruited through expert clinics and support groups. Main



outcome measures in the present analyses were the Body Image Scale (BIS) and Rosenberg Self-Esteem Scale (RSES). Data from charts and surveys was obtained on medical treatments, openness and body embarrassment, sexual satisfaction, anxiety, and depression. The participating sample (n = 1040) included 226 classified as Congenital Adrenal Hyperplasia, 225 as Klinefelter Syndrome/XX males, 322 as Turner Syndrome/XX gonadal dysgenesis, and 267 as a condition with 46,XY karyotype. In general, participants reported poorer body image and self-esteem than control values, and condition-specific areas of concerns were observed. Positive body image was predicted by lower BMI, no hormone use, openness about one's condition, and lower scores on body embarrassment, anxiety and depression. The latter three predicted self-esteem as well. In conclusion, although some participants have a positive body image and self-esteem, mean group levels are lower than controls. Clinical care should be attentive to these subjects to improve psychosocial and sexual wellbeing. Especially openness and body embarrassment could be target of psychological support.

### **Sexuality in adults with differences/disorders of sex development (DSD):**

#### **findings from the dsd-LIFE study**

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Patients with differences/disorders of sex development (DSD) may have genital variations or ambiguous genitals. Some of these patients receive genital surgery. Genital surgery in patients with DSD is mostly aiming at making coital contact possible in adulthood. However, such interventions may affect sensitivity of genital tissue and have problematic long term consequences on sexuality. In addition, many patients with DSD receive hormonal treatment. Sex hormones are known to have an effect on sexual desire and arousal and patients often complain about the impact of hormone treatment on their sexual life. The aim of this part of the study was to describe relationship status, sexual activity, satisfaction with sex life in general, satisfaction with genital function and sexual problems in people with different DSD conditions.

From 14 centers in Europe, 1040 participants were recruited. We will present data on satisfaction with sex life in general, satisfaction with genital function and sexual problems in people with different DSD entities (Congenital Adrenal Hyperplasia, Klinefelter Syndrome, Turner Syndrome, conditions with 46,XY karyotype). We will pay attention to commonalities in sexual functioning across the various conditions, but also to the differences between the conditions in satisfaction with sex life and sexual problems.

### **Psychological support for individuals with differences/disorders of sex development (DSD): results from the dsd-LIFE study**

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Congenital conditions with atypical development of chromosomal, gonadal, or anatomic sex are medically labelled as differences/disorders of sex development (DSD). DSD can have different effects on

the individual's body, health and well-being depending on the impact of androgens, the functional impairment of the gonads and the reproductive system. Since the early 1990s clinical management of individuals with DSD has evolved towards holistic patient-centred care which should be offered by multidisciplinary specialist teams. At present, the need for psychological services can be identified in most key clinical recommendations related to DSD. It is recommended, that psychosocial support (PsySupp) is provided to children, adolescents, adults with DSD and their family as soon as the diagnosis is made. This study is part of the European research project "dsd-LIFE". The aim of the study is to describe the experiences and needs of the 1040 dsd-LIFE participants with PsySupp. Moreover, participants' opinions about inclusion of PsySupp in DSD care will be addressed. Results of PsySupp of the participants according the different diagnoses included in "dsd-LIFE" (congenital adrenal hyperplasia (CAH), Klinefelter syndrome, Turner syndrome and other rare XY and XX DSD conditions) will be shown and discussed.

## Oral Communications 2

### **Morbidity, mortality, and socioeconomic status in females with 46,XY disorders of sex development**

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**Background:** Phenotypic females with 46,XY disorders of sex development (XY females) occur with a prevalence of approximately six per 100,000 newborn girls. This study aimed to elaborate the trajectory of health and socioeconomic status in XY females compared to the background population.

**Study design:** A nationwide registry study where morbidity, mortality, and socioeconomic status were identified in the Danish registries. The socioeconomic status included education, income, retirement, partnerships, and motherhood.

**Patients and controls:** A national cohort of 124 XY females (AIS: n=78, GD: n=25, and “other” XY females: n=21) born during 1908-2015 and 12,400 randomly selected age-matched female controls. Follow-up started at birth, at relevant age, or at start of registration and ended in 2015. XY females had a median age of 29.3 (range: 0.4-97.0) years at the end of follow-up.

**Results:** Morbidity was increased in XY females compared to controls (HR=2.0, 95% CI: 1.6-2.4), also before the DSD diagnosis (HR=1.6, 95% CI: 1.2-2.0), with XY females having the first hospital admission at a median age of 6.9 (range: 0-67) years compared to a median age of 15.9 (range: 0-93) years in controls (P=0.003). No difference in overall morbidity was observed between AIS and GD (P=0.6). Morbidity was significantly increased for endocrine and gastrointestinal diseases and for congenital malformations. Excluding endocrine and congenital diseases from the analyses the overall morbidity remained significantly increased in XY females (HR=1.8, 95% CI: 1.5-2.2) compared to controls.

Death was observed in five XY females (unknown etiology: n=4; GD: n=1). Overall mortality was not significantly different from controls (HR=0.7, 95% CI: 0.3-1.7).

The incidence of cohabitating with a partner was significantly decreased in XY females compared to controls (HR=0.43, CI: 0.33-0.58) and likewise was the incidence of motherhood (HR=0.10, CI: 0.05-0.18). The incidence of achieving an education and the incidence of retirement was the same in XY females and controls (HR=0.91, CI: 0.61-1.36 and HR=0.76, CI: 0.38-1.53, respectively). XY females had a higher income than the median income among controls in the higher age groups (50-59 years) and a lower income in the younger age groups (20-29 years)

**Conclusion:** Morbidity, but not mortality, was increased in XY females compared to controls. A divergent socioeconomic profile was apparent with a reduced proportion of XY females finding a partner and becoming mothers. XY females were educated similar to controls.

**Sex-Specific Effects of Testosterone on the Sexually Dimorphic Transcriptome and Epigenome of Embryonic Neural Stem Cells: A Model for Early Hormonal Brain Organization.**

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The mechanisms by which sex differences in the mammalian brain arise are poorly understood, but are influenced by a combination of underlying genetic differences and gonadal hormone exposure. Using a mouse embryonic neural stem cell (eNSC) model to understand early events contributing to sexually dimorphic brain development, we identified novel interactions between chromosomal sex and hormonal exposure that are instrumental to early brain sex differences. RNA-sequencing identified 103 transcripts that were differentially expressed between XX and XY eNSCs at baseline (FDR = 0.10). Treatment with testosterone-propionate (TP) reveals sex-specific gene expression changes, causing 2854 and 792 transcripts to become differentially expressed on XX and XY genetic backgrounds respectively. Within the TP responsive transcripts, there was enrichment for genes which function as epigenetic regulators that affect both histone modifications and DNA methylation patterning. We observed that TP caused a global decrease in 5-methylcytosine abundance in both sexes, a transmissible effect that was maintained in cellular progeny. Additionally, we determined the transcriptional and epigenetic effects of TP were modulated in part by direct androgen signaling via androgen receptor. These findings highlight an unknown component of androgen action on cells within the developmental CNS, and contribute to a novel mechanism of action by which early hormonal organization is initiated and maintained. These findings reveal unique interactions between genetic background and androgen exposure, which has the potential to better explain some of the variations in cognitive outcomes and behavioral differences observed in individuals with congenital adrenal hyperplasia (CAH).

**Understanding the clinical and professional needs of professionals who provide psychosocial care for children and adults with DSD**

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**Background:** To investigate the facilities for psychosocial care that is provided to children, adolescents and adults with DSD and their parents in centres of specialist care an international survey was conducted among 93 providers of psychosocial care, identified through clinicians of DSDnet, I-DSD Registry, PPN and EuroPsi, performed in the last quarter of 2015.

**Results:** Forty-six respondents (49%) from 22 different countries completed the survey. Respondents were trained in different disciplines, from psychiatry to religious workers. All respondents had obtained at least a bachelor's degree and 76% of them had attended a specific course on DSD. Almost all respondents (87%) were collaborating with a team of professionals specialized in DSD care, most of them were based in hospital-based expert teams (78%). Most referrals for psychosocial counseling came from paediatric endocrinologists (76%), gynaecologists (39%) and paediatric urologists (37%); psychological counseling was most frequently provided to parents (74%), followed by children (39%), adolescents (37%) and adults (11%) and was most frequently focused on education (52%), coping and acceptance of DSD (54%) the atypical body (39%) and genitalia (41%), decisions on genital surgery (33%), problems in making love and sexual intercourse (29%), disclosure (28%) and coping and acceptance of infertility (11%). Respondents most frequently observed DSD related confusion about gender (54%), acceptance of cross gender behavior (50%), anxiety (43%), sadness and depression (38%).

**Conclusion:** Most DSD related psychosocial care is provided to parents. Parental support is important, as comprehension and acceptance is conditional to become affectionate caretakers. Although it may be more difficult for youngsters to communicate about their condition and treatment, children and adolescents should be stimulated to bring up the issues that are important for them. Clinicians and parents should be aware that parental and patients' interests may not correspond completely. Psychosocial management should also include transition and adult care.

### Human and mouse *FGF9* missense mutations resulting in XY gonadal dysgenesis

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Patient screening of twenty-nine 46,XY GD patients with a 1032-gene DSD sequencing panel<sup>1</sup> identified the missense variant in *FGF9*, D195N and *in silico* analysis predicted the D195N variant to be deleterious for *FGF9* protein function. The D195 residue lies at the homodimerisation interface.

Wildtype and mutant *FGF9* was produced in *E. coli* and purified. *FGF* homodimerisation is facilitated by heparin however *FGF9*-D195N protein shows reduced binding to its co-receptor, heparin and a reduced proliferative response in a gonadal cell line. In addition, a mouse *FGF9* 'knockin' mutation *FGF9*-N143T with highly similar biochemical deficiencies to D195N (in heparin binding and homodimerisation) shows partial XY gonadal sex reversal with a truncated coelomic blood vessel and partial sex reversal.

Essential for testis development is the known role of *FGF9* signalling to repress the pro-ovarian *RSPO1*-*WNT4* pathway. Recently using a *FGFR2c*<sup>-/-</sup>;*Foxl2*<sup>-/-</sup> knockout mouse, we have identified that testis



development also relies on FGF9 signalling to repress the separate, but complimentary, FOXL2 pro-ovarian pathway. Notably, XY *Fgf9*<sup>N143T/N143T</sup> gonads show ectopic activation of FOXL2 expression but not WNT4 expression. Therefore a key role of FGF9 signalling for testis development is the repression of the expression of the ovarian factor FOXL2.

Together, these results suggest that FGF9 homodimerisation and heparin binding are required for FGF9 anti-ovarian function in testes determination. In addition, human FGF9 mutations may be the cause of a subset of hitherto undiagnosed human DSD patients.

<sup>1</sup>Eggers et al., (2016) Disorders of sex development: insights from targeted gene sequencing of a large international patient cohort. *Genome Biol.* 2016 Nov 29;17(1):243

### **Surgery on DSD children - necessary intervention or human rights violation?: medical, parental, and affected individual perspectives in the United States**

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Issues of informed consent and medical necessity in healthcare practices for children with DSD have sparked major controversy in recent years, and have attracted increasing publicity and attention from human rights bodies and policymakers. Human Rights Watch, an international independent research and advocacy organization that works in more than 90 countries, and InterACT, a US-based advocacy organization, partnered to conduct in-depth qualitative research on informed consent and medical necessity in care of children with DSD in the United States. Researchers, including Human Rights Watch staff and a consulting physician hired for this project, conducted semi-structured interviews with 15 healthcare providers, 22 parents of children with DSD, two children with DSD, and 35 adults with DSD to gather data on: their experiences of receiving and providing care; how information about care options, including surgeries, is presented in clinical settings; the impact of various care pathways, including surgeries, on individuals' and families' lives; perspectives on if and where thresholds of medical necessity can and should be established; and reactions to the growing number of international human rights bodies, including the United Nations Committee Against Torture and the World Health Organization, that oppose medically unnecessary non-consensual surgeries on children with DSD. The sample included a range of opinions in all three categories of interviewees. For example, parents who opted to have surgery conducted on their children and parents who did not; physicians who routinely conduct surgeries and those who advise parents not to; and adults with DSD who experienced trauma and other negative outcomes from their surgeries as well as adults who express positive outcomes and gratitude for having had surgery conducted on them. All participants were guaranteed anonymity to protect their privacy, and researchers undertook Human Rights Watch's internal ethical research vetting as well as the Ethical Research Board approval process at Physicians for Human Rights. The full report will be published in July 2017 with a series of policy recommendations.

### **Impact of Klinefelter syndrome on social life and career in Europe**

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**Background:** Klinefelter syndrome (KS), one of the most common chromosomal conditions in men, is associated with an increased risk for a variety of psychopathology and comorbidities. Men with KS often suffer from learning disability and social challenges, which have a huge psychological impact. The objective of this study was to investigate socio-economic outcomes and various determining factors of men with KS, compared to the general European male population.

**Material and Methods:** The DSD-life data base contains data of 1161 patients with different forms of disorders of sex development (DSD). The study contains self-reported data (using standardized instruments and self-constructed questionnaires with condition-specific questions) and current and previous clinical data on medical treatment and health status. For this multicenter study, two hundred eighteen men with KS were recruited by 14 study centres in 6 European countries (France, Germany, Great Britain, Poland, Sweden, and the Netherlands) from February 2014 until September 2015. For comparison with the general European population, normative data from males from the participating countries were used from the ESS surveys on sociodemographic and economic factors.

**Results:** Less men with KS achieved a high level of education compared to the general population (34% vs 52%). There was no notable difference in having a paid job (55% vs 56%), but the percentage of men being permanently sick or disabled was higher amongst men with KS (10% vs 4%). Furthermore, the satisfaction with current household's income was lower (32% vs 41%). Men with KS reported less engagement in social activities compared to others of the same age (35% vs 50%). The number of people with whom intimate and personal matters can be discussed was also lower for men with KS (0-2: 49% vs 31%; >2: 51% vs 69%). There was no difference in discrimination between the European population and men with KS (6% vs 8%). A univariate analysis on the highest level of education achieved did not show any association with hormonal substitution with testosterone, higher scores for coping, subjective general health, age of diagnosis of KS, presence of a physical or mental health problem.

**Discussion:** The lower levels of education achieved by men with KS might be due to higher levels of psychopathology and comorbidities including learning problems, as reported in several earlier studies. Lower satisfaction with current income compared to the general population is in accordance with previous studies. Achievements in education and career might be hampered by reduced engagement in social activities. Therefore, early support in childhood and puberty may be very important for men with KS to increase social engagement, to help them to achieve higher levels of education and subsequently a higher socioeconomic status.

**Conclusion:** Men with KS achieve lower levels of education, and report less satisfaction with income and reduced engagement in social activities compared to the general European population. Early support might help them to achieve higher levels of education, a higher socioeconomic status and therefore a better quality of life.

### **The Prevalence Of Adults With DSD Conditions At Risk Of Hypogonadism In The International Disorders of Sex Development Registry**

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**Introduction:** Disorders of Sex Development (DSD) can be associated with impaired sex hormone synthesis or action. To date however knowledge regarding the prevalence and outcomes of affected adults is unclear.

**Methods:** The I-DSD Registry was interrogated for anonymised information regarding the diagnosis, karyotype and sex of rearing of all individuals of any karyotype who were over the age of 16 years at the time of search and who had one of the following disorders that may lead to long-term hypogonadism: androgen action, androgen synthesis; gonadal dysgenesis; Leydig cell hypoplasia; persistent Müllerian duct syndrome or a non-specific disorder of undermasculinisation.

**Results:** At the time of search in January 2017, of a total of 2,141 cases were accessible on the I-DSD Registry. A total of 1,068 (50%) of these cases were currently over the age of 16 years (median 27 (range 16, 90) years). Of these, 614 (57%) had one of the conditions described in the methods. The frequency of conditions reported is summarised in the table. The cases were registered from 34 different centres in 21 different countries, over 4 continents. 207 (34%) (median age 25 years, range 17-75 years) of these individuals were currently registered male. 407 (66%) individuals were currently registered as females (median age 28 years, range 16-90 years). Gonadectomy had been reported on the Registry in 145 cases (24% of total); 16 men (8% of total men) and 77 women (19% of total women). The cases of gonadectomy included CAIS (23, 16%), complete gonadal dysgenesis (21, 14%), partial gonadal dysgenesis (14, 10%) PAIS (11, 8%) non-specific disorders of undermasculinisation (8, 6%), 5 alpha reductase deficiency (4, 3%), 17b-HSD deficiency (3, 2%), Leydig cell hypoplasia (2, 3%) and other (5, 3%).

Condition	Male	Female
Complete androgen insensitivity syndrome	N/A	167 (41%)
Non specific disorder of undermasculinisation	53 (26%)	6 (1%)
Partial gonadal dysgenesis	56 (27%)	28 (7%)
Partial androgen insensitivity syndrome	48 (23%)	28 (7%)
Complete gonadal dysgenesis	10 (5%)	84 (21%)
17 beta HSD deficiency	1 (0.4%)	35 (9%)
5 alpha reductase deficiency	7 (3%)	15 (4%)
Persistent Müllerian duct syndrome	6 (3%)	N/A
Leydig cell hypoplasia	4 (2%)	7 (2%)
Other	21 (10%)	33 (8%)

**Conclusions:** The I-DSD Registry contains a large number of young adults who are at risk of hypogonadism and provides an opportunity to study the effectiveness of current therapeutic interventions and explore novel methods of treating hypogonadism.

#### **Management of fludrocortisone and salt therapy over the first 3 years of life in children with congenital adrenal hyperplasia (CAH) – preliminary analysis**

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**Objectives/Background:** Congenital adrenal hyperplasia (CAH) is one of the most common inherited autosomal recessive disorders. In most European countries, children are now detected by newborn screening program. Therefore salt wasting crisis can be mostly prevented due to early treatment.

However, there are no evidence based guidelines how to treat young infants especially with respect to salt and mineralocorticoid treatment. Aim of our study is to evaluate the current medical treatment in CAH-children <3 years of age due to 21 hydroxylase deficiency according the therapy with glucocorticoid (GC) medication, fludrocortisone (FC) and salt supplementation.

**Design:** Retrospective study using the new developed longitudinal module of the I-CAH registry. Dose of GC, FC and salt supplementation was collected. Height, weight, blood pressure and use of medication were collected anonymously after written informed consent at the age of 3, 6, 9, 12, 18, 24, 30 and 36 months in genetically confirmed CAH patients. Here we present preliminary data from two participating centres from Berlin (1), Germany and Nijmegen (2), Netherlands.

**Results:** 58 patients with CAH due to 21 hydroxylase deficiency from Berlin (n=25) and Nijmegen (n=33) born between 2001 and 2015 were included. All patients started with hydrocortisone (HC) within the first week of life. There was no information about salt supplementation in 3 patients from Nijmegen. All patients from Nijmegen (30/58) were treated with salt supplementation within the first year of life, while patients from Berlin (25/58) were not treated. In 52/58 patients therapy with FC was started at the first visit; no information was given in 6 patients. At 3 years of age, 41/52 patients were still treated with FC, 4 patients were not treated and there was no information on 5 patients. Initial FC dosage is lower in the salt treated patients from Nijmegen (1: 344,4±111,7 mcg/sqm, 2: 556,9±181,9 mcg/sqm, p<0,001) and showed no significant differences in the remaining first year of life, whereas hydrocortisone dosage/m<sup>2</sup> is significantly lower in patients from Nijmegen until the age of 1.5 years (0 month - 1: 33,2±5,1 mg/sqm, 2: 14,4±3,8 mg/sqm, 18 month - 1: 10,4±2,6 mg/sqm, 2: 8,4±1,8 mg/sqm, p<0,05 at time points 0, 3, 6, 9, 12, 18 month). To compare growth, weight gain and blood pressure during the first 3 years of life further analysis will be done.

**Conclusion:** The I-CAH registry offers the opportunity to compare treatment regimens and outcome of patients with CAH from different centres. Salt supplementation is primarily dependent on treatment centre. Salt treated patients had lower doses of fludrocortisone at the beginning while hydrocortisone dose remained higher in the non-salt treated group until 18 month of age. To evaluate different treatment regimens in different international centres and the influence of FC and HC dose in childhood and salt supplementation in early infancy on growth and blood pressure in the first 3 years inclusion of other international centres is necessary.

### **Whole-Exome Analysis of 46,XY Heterozygous *NR5A1* Patients Suggests an Oligogenic Origin of their Broad Disorder of Sex Development Phenotypes**

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**Introduction:** Steroidogenic factor 1 (SF1/*NR5A1*) is a transcriptional key regulator of adrenal and gonadal development and function. *NR5A1* mutations cause a disorder of sex development (DSD) and adrenal failure; however, the majority of affected individuals show a broad DSD/reproductive phenotype only. Functional *in vitro* studies show pathogenic effects of *NR5A1* variants, but no dominant negative effect for heterozygous mutations. Subjects harboring an identical heterozygous *NR5A1* mutation may present with different phenotypes. Thus, genotype-phenotype correlation for *NR5A1* variants remains an unsolved question. We postulate that this may be due to oligogenic inheritance.



**Objective:** We performed whole exome sequencing (WES) in heterozygous *NR5A1* 46,XY DSD patients to screen for additional genetic factors, which might modify their DSD phenotype.

**Patients and Methods:** Four 46,XY DSD patients carrying a heterozygous *NR5A1* mutation and one 46,XY related healthy carrier were whole-exome sequenced. WES-revealed variants were filtered by a newly developed algorithm based on project-specific DSD- and SF1-related gene lists. Variants were also filtered by their consequences and frequencies in a control population. We rejected synonymous and intronic variants, and variants present in the healthy carrier. Variants were also tested by *in silico* tools and further interpreted according to their reported significance in literature, databases and webtools.

**Results:** We identified 21 disease causing heterozygous variants in 20 genes in 4 subjects with a 46,XY DSD phenotype. One variant was found in patient 1, 7 in patient 2, 8 in patient 3 and 5 in patient 4. Nine variants originated from the DSD list and 12 variants came from the SF1-related gene list. With these data, we then constructed a scheme of the oligogenic hits identified in the SF1 patients against the genetic landscape of currently known gene interactions involved in male sex determination and differentiation.

**Conclusions:** WES analysis reveals that the broad phenotype in heterozygous *NR5A1* 46,XY DSD subjects may be explained by an oligogenic mode of inheritance. Finding a hit in one (known) DSD gene in an affected individual may not exclude additional disease-causing variants.

#### **45, X/46, XY Mosaicism: Report on 15 patients from a Single Center in China and Review of the Literatures**

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**Objective:** The aim of this study was to review the management and outcome of patients with 45, X/46, XY mosaicism presenting to a single centre in China.

**Methods:** Retrospectively records review and follow-up of 45, X/46, XY mosaicism seen in our hospital from August 2005 to September 2016. The main outcome measures were their genital phenotypes and follow-up data on growth, gonadal function, gonadal position, histologic results and immunohistochemistry studies are reported. Also we review the literature.

**Results:** Fifteen consecutive patients with 45, X/46, XY mosaicism and variants were included in the study. The age of first visit ranged from 8 days to 14.3 years. Six subjects were assigned to the female and nine to the male gender. Twelve patients had ambiguous genitalia, 2 had short stature and 1 had lack of breast development. Height standard deviation score (SDS) was normal in 4 patients who were measured at age < 2 years, 0.7 (-1.6 to 2.1) [median (range)]. Eight patients, measured at age > 2 years at first visit showed short stature with height SDS, -2.2 (-6.2 to 0.6) [median(range)]. The most severe short stature was -6.2SD. In the patients raised as male, 3 had partial gonadal dysgenesis (PGD), and 4 patients had mixed gonadal dysgenesis (MGD). In the patients raised as female, 4 had complete gonadal dysgenesis (CGD), 1 patient had MGD, 1 patient had ovotesticular. Histological examination of the four gonads in one female patient and two male patients showed positive reaction for octamer binding transcription factor3/4(OCT3/4). The locations of the gonads were in the scrotal fold (1/4), intra-abdominal (1/4) and inguinal fold (2/4) respectively. Two boys underwent bilateral gonadectomy. Two boys underwent unilateral gonadectomy. Two boys underwent gonadal biopsy. Three girls underwent bilateral gonadectomy. Two girls underwent unilateral gonadectomy and genitoplasty. After detailed assessment by the Multidisciplinary team, thirteen patients were reared in the previously assigned gender, and two patients underwent change of gender from male to female.

**Conclusions:** Patients with 45, X/46, XY DSD may have various presentations. After the age of two years there is a pattern of early growth failure. The gonadoblastoma risk was high, even in gonads located in the scrotal or inguinal regions. Evaluating each patient with parents and the multidisciplinary team is the important step in the clinical management.

**Creating a viable alternative to early elective genital surgery in DSD: Exploration of a psychosocial option**

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**Background:** Elective surgery has been a commonly practiced procedure for infants born with genital differences. However, some healthcare stakeholders have questioned the benefits of early genital surgery and drawn attention to the reports of poor appearance and functional long-term outcomes<sup>1</sup> and the unjustifiable risks of neurotoxicity associated with prolonged general anesthesia in children younger than 3 years<sup>2</sup>. In contrast, other stakeholders have claimed superior surgical outcomes and psychological benefits of early genital surgery, although support for such claims are largely anecdotal<sup>3</sup>. In general, research is inconsistent and opinion divided. Even though parents of children born with genital differences have the option of deferring decisions regarding genitoplasty to the older child, they may perceive this as “doing nothing” and leaving their child and family unprotected from stigmatization. Differences/Disorders of Sex Development (DSD) teams can support patients and their families by providing an alternative care pathway that is active, comprehensive, and supports parents in managing some of the drivers underpinning decisions in favor of early surgery, such as expectations of negative psychosocial and psychosexual outcomes without surgery. Informed decision making is predicated on the decision-maker's perception that more than one option exists and that the various options have the potential for positive outcomes.

**Objective:** This presentation will propose a care pathway – translated from its effective application in other areas – that provides clinicians and parents with an alternative to elective genital surgery in the young child that addresses the belief that unaltered genital differences necessarily serve as a barrier to healthy psychological development.

**Methods/Results:** Psychosocial research regarding parenting within the context of a chronic medical condition (including DSD), patient-provider communication and the role of support groups in moderating decisions and outcomes will be reviewed and summarized to inform a care model that supports families from initial diagnosis through early childhood.

**Conclusions:** There is sufficient evidence from within the area of DSD and related fields to offer comprehensive care plans that enable patients and families to mitigate psychosocial concerns associated with genital differences without surgery. Given the existing gaps in outcome studies of early genital surgery and reports of long-term harm, it is incumbent on DSD healthcare teams to develop and offer a non-surgical alternative based on sound science.

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**SF1 transactivation of the *AMH* gene through binding to a specific site of the *AMH* proximal promoter is essential for Müllerian duct regression in humans**

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Regression of Müllerian ducts, the anlagen of the uterus and Fallopian tubes, in the male fetus depends on the action of anti-Müllerian hormone (AMH) during a short developmental window, after which Müllerian ducts become insensitive to AMH. Therefore, AMH expression needs to be tightly regulated. Failure of AMH action during the specific window in the 46,XY fetus underlies the Persistent Müllerian Duct Syndrome (PMDS), characterised by the presence of uterus and Fallopian tubes in a newborn with normally virilized external genitalia. SOX9, SF1, GATA4, WT1 and DAX1 are major modulators of AMH expression in early fetal life in the mouse. However, their relevance in humans is less clear owing to species differences. For instance, SF1 knockout in mice results in a complete lack of testis development and feminisation of the XY fetus, whereas in humans SF1 mutations lead to variable phenotypes.

Two SF1 consensus sites are present in the human *AMH* proximal promoter: one 228-222 bp and one 102-96 bp upstream of the *AMH* transcription start site. *In vitro* studies using luciferase reporter assays showed that when the -228 or the -102 SF1 elements was modified by site-directed mutagenesis, the transcriptional activity of a 0.4-kb *AMH* promoter was significantly impaired ( $0.66 \pm 0.05$  RLU for the -228 mutation and  $0.41 \pm 0.17$  RLU for the -102 mutations, as compared to  $1.03 \pm 0.07$  RLU for the wild-type (WT) promoter, ANOVA + Bonferroni test,  $n=9$ ). However, in a longer *AMH* promoter context (3 kb), only the mutation of the -228 site significantly impaired the promoter activity ( $0.35 \pm 0.06$  RLU for -228,  $0.84 \pm 0.06$  for -102, and  $1.02 \pm 0.07$  for WT, ANOVA + Bonferroni test,  $n=9$ ). These results indicate that in experimental *in vitro* conditions, the SF1 element at -228 of the human *AMH* promoter is relevant for AMH expression.

Recently, the diagnosis of PMDS due to AMH deficiency was made in a non-dysmorphic newborn who presented with a normal sized penis and non-palpable gonads. Laboratory work-up showed normal serum testosterone (358 ng/dl), extremely low serum AMH (7.8 pmol/l) and a 46,XY karyotype. A sonogram and MRI showed a uterus measuring 5 x 1.4 x 1.9 cm; VCUG showed a normal male urethra without a urogenital sinus. Unexpectedly, DNA sequencing detected no mutations in the *AMH* gene coding sequences. However, a homozygous single-base deletion (c.-225delA) was identified, coinciding with one of the putative SF1 response elements of the *AMH* promoter.

The c.-225delA variant was experimentally created by site-directed mutagenesis, and analysed in luciferase assays, showing a decrease to a similar extent ( $0.54 \pm 0.08$  RLU in the 0.4-kb promoter and  $0.59 \pm 0.04$  in the 3-kb promoter context) of what was observed when the -228 SF1 site was completely disrupted, as shown above. Electro-mobility shift assays (EMSA) showed that the interaction between

SF1 and its -228 binding site was lost when the oligonucleotide carried c.-225delA or the fully disrupted -228 site.

In conclusion, the single base deletion c.-225delA within the SF1 site of the AMH gene promoter impaired SF1 binding to and transactivation of the AMH promoter, resulting in extremely decreased AMH production, leading to PMDS in this patient. This is the first description of an AMH promoter mutation leading to PMDS.

## **Session 5: Androgen Deficiency & Excess**

### **Molecular Basis to AIS**

Prof. Dr. Paul-Martin Holterhus

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Virilization in males requires normal androgen biosynthesis in the testes and normal androgen action via the androgen receptor (AR) which is a ligand activated transcription factor of androgen regulated genes. Androgen insensitivity syndrome (AIS) is characterized by decreased or even absent function of cellular androgen signaling in the genital target tissues (Quigley et al. 1995, Endoc Rev). Accordingly, this results in either partial AIS with a variable undervirilization or in complete AIS (CAIS) characterized by female external genitalia in 46,XY individuals (46,XY DSD). Since the first cloning of the AR gene in 1988 (Lubahn DB, Science; Trapmann et al. 1988, Biochem Biophys Res Commun) it became evident that inactivating AR mutations are the classical molecular basis of AIS. Also since then, there was a tremendous increase of functional understanding of the AR (Jenster et al. 1992, Biochem J). Various mechanisms of impaired AR function had been uncovered, e.g., inhibited ligand binding, inhibited DNA-binding, inhibited transcriptional activation, inhibited NC-terminal interaction. Unfortunately, there is only a limited genotype-phenotype correlation which hampers clinical management in some cases. Underlying molecular causes explaining this phenomenon may be differences in 5 $\alpha$  reductase type 2 expression (Boehmer et al. 2001, JCEM), somatic mosaicism in de novo AR mutations (Holterhus et al. 1997, JCEM), and variable degrees of AR function in response to different androgen concentrations (Holterhus et al. 2000, JCEM). While in about 90% of CAIS AR mutations can be found this is only the case in about 2/3 of PAIS cases (Deeb et al. 2005, Clin Endocrinol). Measuring the transcriptional response to androgen by apolipoprotein D (APOD)- induction in response to DHT in cultured genital fibroblasts ("APOD-assay"), we could recently identify an AR-mutation-negative but functionally androgen insensitive subgroup of clinical AIS which we called "AIS type 2" (Hornig et al. 2016, JCEM). The underlying molecular mechanisms are not uncovered to date. Coactivators might play a role therein as has been reported in one single case many years ago (Adachi et al. 2000, NEJM). In 2 cases, we could detect for the first time a 5'UTR mutation far outside the coding region creating an aberrant start coding impairing AR protein translation (Hornig et al. 2016, PLoS One). Some unpublished data will be presented (see also N. Hornig et al. at this conference) suggesting that impaired AR mRNA transcription can be found in quite a number of individuals pointing to a crucial role of epigenetic control of the AR promoter. Large scale transcriptomics in AIS versus male controls has uncovered long-term AR-linked programming of the transcriptomes of cultured genital fibroblasts (Holterhus et al. 2003, Genome Biol) and blood mononuclear cells (Holterhus et al. 2009, BMC Genomics) - a phenomenon which can similarly be found at the epigenome level by methylation arrays (Ammerpohl et al. 2013, PLoS One). Therefore, long-term and large-scale aberrations from regular androgen programming are also part of the molecular basis of AIS.



## **Outcomes of Testosterone Replacement Therapy in Hypogonadal Men**

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Testosterone replacement therapy is indicated in hypogonadal men, who have signs and symptoms of androgen deficiency and consistently low testosterone levels, to induce and maintain secondary sex characteristics, and to improve sexual function, wellbeing, muscle mass and bone mineral density. There are only a few randomized placebo-controlled efficacy trials of testosterone therapy in young hypogonadal men. These trials indicate that testosterone replacement of hypogonadal men improves sexual desire, erectile function, satisfaction with erections and overall sexual activity, but does not improve orgasmic or ejaculatory function. Testosterone improves areal as well as volumetric bone density and bone strength more consistently in the spine than in the hip. Testosterone's effects on mood and energy are less clear in randomized trials. Testosterone increases muscle mass and strength and reduces fat mass; it promotes the differentiation of mesenchymal progenitor cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage through an androgen receptor-mediated mechanism by promoting the association of liganded AR with beta-catenin, activation of Wnt signaling pathway, and upregulation of follistatin. Testosterone stimulates erythropoiesis by increasing iron availability and iron incorporation into the erythropoietic cells through its inhibitory effects on hepcidin transcription, and by stimulating erythropoietin secretion and action.

There are no randomized clinical trial data on the long term cardiovascular and prostate safety of testosterone therapy, but the frequency of adverse events in short term trials of testosterone replacement in young hypogonadal men is low. Erythrocytosis is the most frequent adverse event associated with testosterone therapy in hypogonadal men. Testosterone does not worsen lower urinary tract symptoms in men who do not have severe lower urinary tract symptoms at baseline.

Testosterone therapy should be accompanied by standardized monitoring at 1 to 6 months, 12 months and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects, and to monitor compliance. There is enormous variability in on-treatment testosterone levels, especially with transdermal gels, due to variation in transdermal absorption and differences in testosterone clearance. Therefore, dose titration based on on-treatment testosterone concentrations is needed to optimize testosterone therapy and reduce the risk of supraphysiologic levels.

## **Management of Androgen Excess in Congenital Adrenal Hyperplasia**

**Nils P Krone**

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Congenital adrenal hyperplasia (CAH) represents a group of autosomal recessive disorders encompassing enzyme deficiencies in the adrenal steroidogenesis pathway leading to impaired cortisol biosynthesis. Steroid 21-hydroxylase deficiency accounts for 95% of all CAH cases and is associated with deficient glucocorticoid and mineralocorticoid biosynthesis as well as sex steroid excess. The aim of

treatment is the replacement of mineralocorticoids and glucocorticoids and the normalisation of elevated androgen concentrations. The classic treatment approach to reduce the ACTH-driven androgen excess has been the supraphysiological treatment with glucocorticoids. However, meeting the correct balance between glucocorticoid overtreatment and control of sex hormone excess remains the key challenge in the treatment of CAH. Long-term complications include abnormal growth and development, adverse effects on bone and the cardiovascular system as well as infertility. In recent years, novel treatments have been developed, which are aiming to reduce glucocorticoid exposure and to improve androgen excess, as well as mimicking physiological hormone patterns. This presentation will provide an overview on strategies towards optimising glucocorticoid treatment, potential add-on therapies and novel promising approaches to improve androgen excess and medical treatment of individuals with CAH.

## Session 6: Assisted Reproduction

### **Optimising the management of hypogonadotrophic hypogonadism.**

Marco Bonomi

University of Milan

Hypogonadotropic hypogonadism (HH), independently of its etiology, represents one of the treatable form of male infertility. Indeed, HH can benefit from medical treatments to induce spermatogenesis, together with androgenization, by long term GnRH or gonadotropin replacement therapies. Pulsatile GnRH therapy is surely the more physiological treatment approach, but requires a conserved pituitary gonadotropic cell functioning. This therapy is demonstrated to allow a full testicular function, either in term of spermatogenesis or steroidogenesis. Nevertheless, GnRH pulsatile therapy is usually not routinely used since it does not present any advantage compared to the gonadotropin therapy, while it requires the wearing of an infusion pump, which is not practical nor well tolerated by the patients. Thus, the use of subcutaneous gonadotropin injections (2-3 times per week) is more commonly used in the clinical practice. Indeed, hCG treatment is effective in stimulating steroidogenesis and it may be sufficient in inducing spermatogenesis in some patients, while co-administration of FSH is required in those patients that not respond to hCG alone. Spermatogenesis is achieved in around 75% of HH patients during gonadotropin treatment. Nonetheless, more effective results are reported in those patients that present a pure pituitary HH form and a post-pubertal onset of the disorder. Thus, gonadotropin therapy, either with urinary derivatives, is an efficient and appropriate choice in inducing/reestablishing fertility in HH patients.

### **Preserving fertility in girls and adult females with gonadal disorder and at risk of ovarian insufficiency.**

Kutluk Oktay, MD, PhD; Professor of OB/GYN and Reproductive Sciences

Fertility preservation has extended beyond cancer patients and adult patients. Now this service is increasingly commonly used for a variety of indications. These include those at risk for premature ovarian failure such as the girls with Turner Syndrome and other conditions that puts them at risk for POF. For sexually immature girls, ovarian tissue freezing may be the only option which can also be combined with in vitro maturation. Livebirth rates from ovarian transplantation have approached 40%. With the advent of new techniques such as the robotic surgery and the use of extracellular matrix scaffolds as we described recently, these rates may even be higher. As a result, ovarian cryopreservation and transplantation may soon be considered a non-experimental technique. For sexually mature children generally older than 13 years, ovarian stimulation and oocyte freezing may be considered. Though oocyte freezing is now considered an established FP technique for adults, more data are needed for success rates with oocytes frozen from children especially with Turner Syndrome and other chromosomal conditions.

### **Male fertility preservation-prospects for generating male gametes *in vitro*.**

Jan Bernd Stukenborg (Stockholm)

Late side effects affecting future fertility in children undergoing gonadotoxic treatments do still exist. So far, no treatment can be offered to rescue fertility in those patients. In the past, major efforts have been put into optimizing *in vivo* and *in vitro* methods for maturation of immature germ cells, but these

techniques still remain experimental. For the *in vivo* methods the immature testicular tissue or spermatogonial stem cells (SSCs) could be transplanted back to the patient after cancer treatment, however in such case there is a potential risk of introducing cancer cells back to the patient. Transplanting the tissue or the isolated SSCs to other animal species for maturation is also an option but then there is a potential risk of introducing the germ cells to xenogenic tissue hosting unknown viruses such as retroviruses. Therefore, such methodology would presently not be considered acceptable for clinical practice.

For *in vitro* methods, the SSCs could be differentiated in a monolayer on supporting feeder layer or on extracellular matrixes. Also it has been reported that pre-meiotic germ cells from mice can be differentiated in soft agar culture system (SACS) where the cells have 3D support. In addition to those 3D culture approaches, in 2011, Japanese researchers demonstrated for the first time viable offspring from *in vitro* generated murine sperm using an organ culture. This experiment demonstrates a big step towards the establishment of clinical tools to use *in vitro* differentiated gametes as potential fertility preservation for young cancer patients. More studies are required to meet efficiency/safety concerns and translate results to the situation in humans.

### **Uterus transplantation and live births**

Lotta Wassen MD, PhD

Sahlgrenska University Hospital, Gothenburg, Sweden

The last frontier to conquer in female infertility has been absolute uterine factor infertility caused by uterine aplasia, hysterectomy at young age (cervical/uterine malignancy, emergency postpartum hysterectomy), Asherman's syndrome or major uterine malformation. A translational research program on uterus transplantation (UTx) was initiated in 1999, which initially was conducted in the mouse followed by uterus transplantation in the rat, pig, sheep and baboon. The first clinical trial on UTx was launched in 2013. The first trial included nine human live donor UTx procedures. Extensive medical and psychological screening of donors, recipients and partners were done. All recipients went through 2-3 IVF cycles prior to UTx in order to cryopreserve embryos for use after UTx. Five of the donors were mothers and in the other cases they were aunt on mother's side, sister, mother-in-law and close family friend. Five of the donors were postmenopausal at the time of surgery, and these donors were prescribed cyclic HRT for some months before surgery. Two out of the nine patients lost the graft during the initial months after UTx, due to intrauterine infection (1) and and uterine vessel thrombosis (2). Seven patients showed regular menstruations from 1-2 months after UTx. Embryo transfers were initiated 12-16 months after transplantation. So far six healthy babies have been born from these seven transplanted women and there are three ongoing pregnancies. All babies have been delivered by c-section and have been of normal weight for gestational age.

### **The ethics of assisted reproduction**

Daniela Cutas (Gothenburg)

When determining access to fertility preservation or fertility treatment, a distinction is often drawn between medical and social justifications - with the implication that medical reasons are more, or exclusively, worthy of medical treatment or financial support, and of motivating research efforts. The distinction between social and medical justifications for access to fertility preservation aims at separating legitimate reasons (e.g. of a child facing loss of fertility due to a genetic condition or impending medical treatment), from more diffuse reasons that it is acceptable or even morally necessary

to question or even reject outright (e.g. of healthy women aiming to preserve their capacity to reproduce).

However, the definitions of infertility currently in use when determining access to fertility treatments do not necessarily overlap with any medical condition. For example, according to the World Health Organisation, infertility is “a disease of the reproductive system defined by failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” (Zegers-Hochschild et al 2009: 1522). Such a definition will exclude a woman without ovaries or an azoospermic man who did not have “12 months or more of regular unprotected sexual intercourse”. It presupposes sexual intercourse, presumably between individuals of different sex, of reproductive age, etc. – and in some legislatures, all these conditions are made explicit, and accompanied by supplementary requirements, such as that the couple be married or cohabiting. What is offered as a conceptual, clinical, definition here is in fact a normative one that describes the circumstances in which a baby *should* be born.

I will show that the distinction currently drawn between medical and social reasons is misleading. It serves to discriminate between individuals who fit certain expectations of close personal relationships and desirable prospective parenting, and those who do not. By applying definitions such as the one cited above, policy makers medicalise the wish to become a parent of individuals who fulfil a number or non-clinical requirements, and leave out those who do not but are unable to reproduce; they reward certain circumstances and chastise others. However, for an ethical argument and for a legal provision to hold, they have to rely on considered judgment and they have to be fair. Reproduction and parenting are highly cherished values for many individuals, whose denial can have a great impact on the wellbeing of the person to whom they are denied – and the justifiability of privileges or denial of access is therefore a matter of social justice.



## **Session 7: Defining Outcome In DSD**

### **Changes in management of DSD over time**

#### ***What did we learn from outcome studies?***

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The term outcome has been defined as a conclusion reached through a process of logical thinking. The Chicago Consensus meeting in 2005 has given an immense boost in basic science and clinical research but also in rethinking of principles of management of DSD. The findings of Money in the sixties that prenatal androgen exposure is associated with masculinization of postnatal gender-related behaviour has been confirmed in outcome studies indicating a dose-dependent effect of prenatal androgens on gender role behaviour. Over the years many studies have been conducted focussing on Quality of Life and psychosocial well-being. Recent studies report no significant impairments in overall health related quality of life, good psychosocial well-being; and coping with DSD compared to reference groups. However, when looking into more detail several issues of relevance need mentioning. Almost universally the response rate of patients participating in outcome studies is about 50%. Studies on psychosocial aspects are hampered by lack of standardized instruments for DSD; Disease-specific instruments for young children are being developed but cross-cultural applicability will be challenging. Possibly hormonally related some women experienced increased fatigue. Patients/parents reported posttraumatic stress disorder (PTSD) more often if they felt that they did not understand information that was provided to them. Some participants described themselves as a gender other than male or female but rated their quality of life and psychological distress as similar to the rest of the cohort. The management practice has greatly improved with protocols and ethical guidelines at national and international level proclaiming open communication and full disclosure tailored to the individual's need and developmental level with access to psychological counselling for reinforcement of coping. We have learned that undergoing clinical photography causes unnecessary distress and suffering and standards for good practice in obtaining medical images have been formulated. There is an important role for further development of teaching and instruction among (young) doctors in the various health care settings. It should be recognized that the management practice in resource limited countries differs greatly as compared to in Western countries. Poverty makes health-care facilities not only less available but, if available, also less accessible for poor patients. Cultural background and social context influence the patients', as well as health-care professionals' cognition about DSD and their decisions in dealing with it. E-learning can be instrumental to provide a certain standard of state of the art knowledge and attitudes towards patient care and management for target groups of students, residents fellows/postdocs but also can reach out to "educationally underprivileged" areas in the world, bypassing traditional geographic boundaries by using the internet. Age adjusted E-information for families and patients of all ages has become widely accessible online, with focus on DSD biology, medical care, and psychological and social support.

### **Norms and attitudes**

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In this talk, I offer *norms* and *attitudes* as two conceptual resources to clinicians and scientists in the i-DSD network to allow greater engagement with the psychosocial, humanities and legal scholarship on intersex. Social scientists describe *norms* as implicit assumptions that go without saying in language which nonetheless have powerful social effects. Norms often conflate beliefs about *what is* with prescriptions about what *ought to be*. Drawing on 23 interview, I describe how clinicians in specialist DSD teams think about the boundary between medically essential and cosmetic interventions. These data allow us to see norms at work and to understand how well-intentioned clinicians may form attitudes and recommendations about interventions that allow them to become vulnerable to the charge that they have misused medicine to *normalize* intersex bodies. Next, I contrast medical opinion about what the terms 'intersex' and 'disorders of sex development' do, drawing on SENS data with young people with diverse sex development, their parents, and unaffected focus group participants accounts of those terms. These data and others informs my conclusion that neither term, nor their conjunction fully addresses the needs that arise in everyday situations that young people and their parents encounter. Finally, social scientists define *attitudes* as evaluations of social groups, practices, policies or other matters. Attitudes are often explicit and people can report them more directly than they can report on implicit norms. I report a new survey describing social variation in attitudes about the medical management of DSD and its alternatives, and an experiment that shows how engaging the public about DSD and intersex via *YouTube* affects attitudes about the harms and benefits of medicalizing intersex/DSD.

### **The relevance of core outcome sets and the COMET Initiative to DSD research and clinical practice**

Professor Paula Williamson, University of Liverpool

A core outcome set (COS) is an agreed standardised collection of outcomes to be measured and reported, as a minimum, in research or practice setting(s) for a specific clinical area. The credibility of a COS depends on the use of sound methodology in its development, and, transparent reporting of the processes adopted. To influence policy and practice, the outcomes need to be relevant and important to key stakeholders. This session will address issues related to how researchers, patients, trialists, systematic reviewers, guideline developers, HTA organisations and other policy-makers can develop, appraise and make use of COS and the COMET database.