Management of gonads in DSD

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(a note from dsdfamilies: further information on the ‘Management of gonads in DSD’, differentiating between low-risk conditions such as AIS, and high-risk conditions, and from the same team of authors, will be available from later summer 2011)

MALIGNANT TUMOR RISK IN DSD

Individuals with DSD who have a specific part of the Y chromosome in their karyotype, possibly mosaic (implying girls and boys with 46,XY DSD and 45,X/46,XY DSD, or variants thereof) are at increased risk for developing a malignant germ cell tumor (cancer) of the gonads. It has been shown that some germ cells in a DSD gonad may gain malignant characteristics already before birth and/or in the first years of life. However, they remain in a silent stage for many years, and can only be recognized with specific techniques, currently only after a biopsy or gonadectomy (surgical removal of one or both gonads), under the microscope at this stage. Gradually, these pre-malignant cells begin to develop an in situ neoplasia, meaning a tumor with malignant potential but which has not (yet) the capacity to spread beyond the initial localization. If the gonad is removed at this stage (or eventually irradiated), no additional treatment is necessary to prevent development of a cancer. However, without interference, upon time (sometimes only after many years), these cancer cells will become invasive and can spread through the body. When this happens, the patient can only be cured after gonadectomy, irradiation and/or chemotherapy.

In principle, there are two forms of in situ neoplasia, called carcinoma in situ, and gonadoblastoma. They can only be discriminated from each other under the microscope and they both give rise to the same type of invasive tumors, called seminoma (of the testis) or dysgerminoma (of the ovary and dysgenetic gonad) and non-seminoma. At present, it is unknown what triggers the transformation from an in situ neoplasia to an invasive cancer but, it is highly likely that hormones (e.g. during puberty) are one of the involved factors.
To avoid formation of invasive cancer, and because premalignant cells or an *in situ* neoplasia cannot be detected with imaging techniques (ultrasound, MRI), it used to be common to perform bilateral gonadectomy at a young age in all patients with a supposed increased risk. However, recent research has shown that the risk to develop gonadal cancer can be very different between various DSD subtypes, and ranges from approximately 1% in CAIS to over 30% in some other forms of DSD.

**WHAT ARE FACTORS THAT DETERMINE CANCER RISK?**

- A specific part of the *Y chromosome* (called GBY) has been identified which is likely to be involved in promoting tumor development in DSD patients. This means that individuals with 46,XX DSD (without *Y* chromosome material) have no increased risk.

- In DSD, the process of gonadal maturation (the evolution from the bipotential, undifferentiated gonad early in fetal life towards a (mature) testis or ovary) is more or less disturbed. Cancer risk is much higher in gonads that are highly abnormal (or immature), compared to gonads that look like “normal” testes or ovaries. Generally spoken, one can say that in gonadal dysgenesis (46,XY gonadal dysgenesis and 45,X/46,XY gonadal dysgenesis), tumor risk is higher than in disorders of androgen synthesis (e.g. 17β-HSD deficiency) or action (e.g. AIS) for this reason. Evidently, within the various forms of gonadal dysgenesis, there is wide variability, as some gonads remain very immature, and other gonads differentiate almost normally. Unfortunately, with our actual knowledge, this cannot be fully predicted from the underlying genetic defect (if this is known) or from someone’s body features. In many situations, the only way to gain more information on cancer risk is with a biopsy of the gonad.

- In boys, tumor risk is lowest when the testes are naturally in the scrotum. When they are in the *inguinal or abdominal position*, it is advised to bring them in scrotal position with an operative procedure, called orchidopexy, preferably before the age of 1 year. During this procedure, a biopsy can be taken to assess the degree of testicular development and to predict cancer risk.

**HOW HIGH IS THE RISK FOR CANCER DEVELOPMENT IN THE DIFFERENT FORMS OF DSD?**

As stated above, it was only recently fully appreciated that cancer risk is very different in the various groups of DSD. Actually, we have an idea of this risk in some forms of DSD, but not in all. The numbers given below are only estimations, mostly based on small numbers of cases and thus should be interpreted with caution.
CAIS: Around 1%.

PAIS: The risk is probably high (10-15%) when gonads are in the inguinal or abdominal region and much lower (but unknown) when testes are in the scrotum at birth or when orchidopexy is performed early in life.

17β-HSD deficiency, SF-1 mutations: Unknown. Theoretically, a similar incidence as in PAIS is expected.

5-α reductase deficiency, Leydig cell hypoplasia: Unknown, but probably low risk.

46,XY girls with gonadal dysgenesis: High risk, maybe more than 30%

46,XY boys with gonadal dysgenesis and gonads in the abdominal or inguinal position: High risk, maybe more than 30%. Boys with a severe degree of undervirilization (e.g. born with ambiguous genitalia) probably have a higher risk than boys with only mild undervirilization at birth. Orchidopexy early in life will probably reduce the risk, especially in those with mild undervirilization at birth.

46,XY boys with gonadal dysgenesis and gonads in the scrotum at birth: Unknown, but probably lower risk.

45,X/46,XY girls who have no enlarged clitoris: Low risk, estimated at 1-5%.

45,X/46,XY girls who have an enlarged clitoris, and 45,X/46,XY boys with ambiguous genitalia or undescended testes: High risk, maybe more than 30%.

45,X/46,XY boys with a (nearly) normal aspect of the genitalia at birth, and testes in the scrotum: Unknown, but probably low risk.

**IN WHICH CASES CAN GONADECTOMY BE AVOIDED OR POSTPONED?**

If cancer risk is estimated to be low, and especially when there is an expected benefit of leaving the gonads in place, the medical team, together with the parents can decide to postpone the decision with regard to gonadectomy until after puberty. Postponing gonadectomy has the advantage that the decision can be taken by the patient himself or herself, and not (only) by the parents, and that it often allows a natural progression through puberty. This may increase self-confidence in many adolescents.

In girls with CAIS, the chance that invasive cancer will occur before the end of puberty is extremely low. Therefore postponing gonadectomy until mid- or end-puberty seems justified. This approach will allow spontaneous breast development.

In girls with PAIS, SF-1 mutation, or other forms of DSD (Danys-Drash, Frasier etc.), gonads have to be removed before puberty because of the high cancer risk as well as to prevent virilisation due to the production of male hormones.
In boys with DSD, the testes are left in place if possible, because they often produce sufficient amounts of male hormones to allow spontaneous puberty. However, if testes are not in a scrotal position, it is very important to perform orchidopexy early in life, and to assess testicular development and cancer risk by means of a biopsy. If testes appear to be underdeveloped, or cannot be brought in a stable scrotal position, they should be removed.

HOW CAN WE MONITOR GONADS?

Boys with DSD and scrotal testes are advised to perform self-examination by palpation of their testes once a month from pubertal age onwards. In case of any abnormal finding an ultrasound is the next step.

Non-scrotal testes that surgically cannot be brought into the scrotum are either removed or placed in an inguinal position. When an inguinal position is accepted an additional biopsy is taken to assess the cancer risk. Testes that are located in the inguinal region might be difficult to palpate; in these cases a yearly ultrasound might be justified, especially when the result of the biopsy showed a high cancer risk.

Remember that at this moment ultrasound as well as MRI are insufficient diagnostic tools to monitor abdominally located gonads at risk. Tumor markers, that can be measured from a blood sample, can only detect some forms of gonadal malignancies, but not the malignancies in the still silent stage.

PRACTICALITIES OF THE GONADECTOMY AND GONADAL BIOPSY PROCEDURES

Gonadal structures can be located either in the abdominal cavity or they can be descended and be found outside the abdominal cavity from the groin area to the labioscrotal fold. Descended gonads have always at least partial testicular differentiation.

The position determines the way a biopsy or gonadectomy is done. If the gonad is in the abdominal cavity a laparoscopic approach will be done. In this minimal invasive approach instruments are introduced in the abdomen through very small openings (< 1 cm), one in the umbilicus and most often two in the lateral side of the lower abdomen. With this instruments observed through a camera a small part of the gonad can be taken. The capsule of the gonad is incised and a small part of the gonadal tissue is excised and sent to the laboratory for further examination. The capsule of the gonad can be repaired with a suture and the gonad is left in the abdomen. The result of the biopsy will determine what will happen with the gonad in the future. If a gonadectomy needs to be done, this can be done with the same laparoscopic procedure. The blood vessels of the gonad are identified and clipped and the gonad can then be removed. Most often the small opening for the
instruments is large enough to allow removal of the gonad. If the gonad is too big, the largest of these openings can be enlarged. Laparoscopic procedures are most often performed in day clinic. If the gonad is outside the abdominal cavity, the biopsy and gonadectomy are performed through a groin incision. The procedures are similar to the laparoscopic procedures. If the gonad will be preserved most often it will be descended to a full scrotal position in the same procedure. The groin incision can be small (2 cm) and most of these procedures are also done as day cases. The risks are the typical risks associated with general anesthesia which in otherwise healthy children are extremely low. In experienced hands the surgical risks are minimal.