46,XX DSD: bilateral ovotestis with duplication in region upstream SOX9

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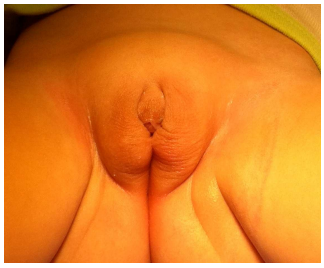
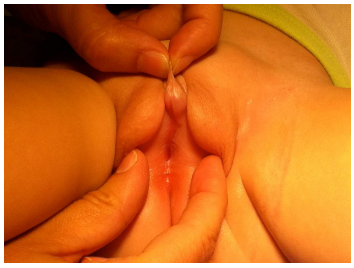
Background

Disorders of sex development (DSD) are congenital conditions in which chromosomal, gonadal or anatomical sex is atypical.

Objective and Hypotheses

We describe the case of a 46,XX newborn with ambiguous genitalia.





Differential diagnosis include disorders of gonadal development (ovotesticular DSD, testicular DSD, gonadal dysgenesis), androgen excess of fetal (mainly congenital adrenal hyperplasia due to 21-hydroxylase, 11-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiency), feto-placental (aromatase deficiency) or maternal (luteoma, virilizing tumors) origin and malformations.

Results

At birth (exams done at birth center)

- Kariotype: **46,XX**
- **SRY negative** (FISH)
- ACTH test: cortisol ↓, ACTH = → suspected adrenal insufficiency → started Hydrocortisone (HC)
- LH 5.9 U/l, FSH 5.1 U/l, **T 1.06 ng/ml**
- Pelvic ultrasound: two gonads at the external genitalia, no uterus (confirmed by abdominal RMN)
- **Female sex assigned**
- No definitive diagnosis

At 8 months:

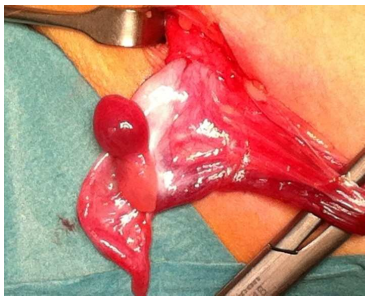
- LH < 0.1 mU/ml, FSH 0.8 mU/ml, T < 0.1 ng/ml
- Cortisol (in stop HC): 140 ng/ml → excluded adrenal insufficiency
- HCG test:

Hormones	Pre	Post
Testosterone (ng/ml)	< 0,1	0,76
DHT (pg/ml)	< 25	202,6
DHEAS (ng/ml)	< 150	< 150
Δ4- androstenedione (ng/ml)	< 0,30	< 0,30
Estradiol (pg/ml)	< 25	< 25

- Pelvic ultrasound (post HCG): suspected ovotestis

Gonadal Biopsy → **BILATERAL OVOTESTIS**

CGH array → **Duplication 17q24**, region upstream of **SOX9 gene** (also present in her father)



Conclusions

Ovotesticular DSD is a rare disorder defined by the presence of both ovarian and testicular tissue in the same individual. Structure of the ovary is usually normal, while testicular tissue is immature and histologically abnormal. Development of müllerian and wolffian derivatives is variable.
In 46,XX ovotesticular patients SRY gene is present in approximately 1/3 of cases.

In embryos XY SRY interacts with SOX9 in the differentiation of the testis. In subjects XX duplication of SOX9 has been described as a cause of 46,XX DSD.

Peter A. Lee et al. Consensus Statement on Management of Intersex Disorders. Pediatrics 2006;118;e488-e500.
Ono M, Harley VR. Disorders of sex development: new genes, new concepts. Nat Rev Endocrinol. 2013;9(2):79-91.