**Gonadotropin surge during the early postnatal activation period in 46,XX testicular/ovesticular disorder of sex development (DSD) patients**

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**Introduction**

The postnatal surge of gonadotropins and sex steroids is a sexually dimorphic physiological phenomenon that occurs during the first months of postnatal life. Gonadotropin levels increase significantly after the first week of life and peak between 1-3 months. During this period serum FSH levels are higher in girls and LH levels predominate in boys.

The mechanism of this sex difference is not completely understood. It has been proposed that it is a direct consequence of the different prenatal hormonal milieu.

Animal studies suggested that fetal or perinatal exposure to androgenic steroids exert organisational actions on the GnRH neuronal network and the control of LH secretion.

In humans postnatal Hypothalamic-Pituitary-Gonadal (HPG) axis activation has been studied in several disorders of sexual development. Data from infants affected with Congenital Adrenal Hyperplasia and Androgen Insensitivity Syndrome provided insight into the potential role of i-uterine androgen exposure in the regulation of the gonadotropin secretion in humans. 46,XX DSD patients with disorders of gonadal development (testicular/ovesticular DSD) represent another unique model for the assessment of postnatal HPG axis activation as a function of i-uterine androgen exposure. To our knowledge there are no data available in these patients.

**AIM**

To study the possible influence of high levels of androgens on serum gonadal gonadotropins in a cohort of nine 46,XX testicular/ovesticular DSD patients during the early postnatal activation period.

**MATERIAL AND METHODS**

Medical records of all patients evaluated at the endocrinology department because of 46,XX disorders of gonadal development (testicular/ovesticular DSD) such as 1) physical examination, 2) hormonal determinations, 3) abdominal and pelvic ultrasound, 4) laparoscopic surgery; 5) gonadal histology, 6) molecular studies, were collected.

Methods: Cyto genetic study was performed on peripheral blood lymphocytes using the G banding technique, in at least 30 metaphases. Genomic DNA was isolated from mononuclear cells of affected subjects according to standard procedures.

Detection of the SRY gene in peripheral genomic DNA was evaluated by FISH technique using SRY-specific DNA probe and 9Y centromere region probes on interphase nuclei and/or PCR amplification in DNA obtained from blood leukocytes and/or paraffin embedded gonadal tissue. PCR amplification of other Y sequences (Amy or PABY) were investigated in gonadal tissue.

The coding sequence and flanking intronic regions of NR0B1, RSPO1 and WNT4 were PCR amplified and automated sequenced. The copy number variations of SRY, SORRY, NR0B1, NR3C1 and WNT4 were assayed by MLPA.

The only molecular study performed in peripheral genomic DNA from patients 4 and 9 was the search of SRY gene. Samples of gonadal tissue from patients 1,3,4 and 7 were available.

Molecular studies retrieve negative results in all cases.

**RESULTS**

**Discussion**

Gonadotropins and sex steroid surge during the postnatal activation of the HPG axis showed a masculinised profile in our cohort of nine 46,XX DSD patients with evidence of functional testicular tissue. The presence of mildly increased FSH levels in three patients could be related to gonadal dysgenesis, since one of them also presented low AMH levels, and FSH/LH ratio pertains within the males normal range. The results of this study reinforce the concept that prenatal androgen exposure might be involved in programming of the HPG axis independently of chromosomal sex.

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