Gonadotropin surge during the early postnatal activation period in 46,XX testicular/ovotesticular 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[1-2].

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[3-4].

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 *in-utero* androgen exposure in the regulation of the gonadotropin secretion in humans[5-6].

46,XX DSD patients with disorders of gonadal development (testicular/ovotesticular DSD) represent another unique model for the assessment of postnatal HPG axis activation as a function of *in-utero* 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 postnatal gonadotropins in a cohort of nine 46,XX testicular/ovotesticular DSD patients during the early postnatal activation period

CLINICAL MATERIAL AND METHODS

Medical records of all patients evaluated at the endocrinology department because of 46,XX disorders of gonadal development (testicular/ovotesticular 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: Cytogenetic 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 XY centromeric 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 *NROB1, RSPO1* and *WNT4* were PCR amplified and automated sequenced. The copy number variations of *SRY, SOX9, NROB1, NR5A1* 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

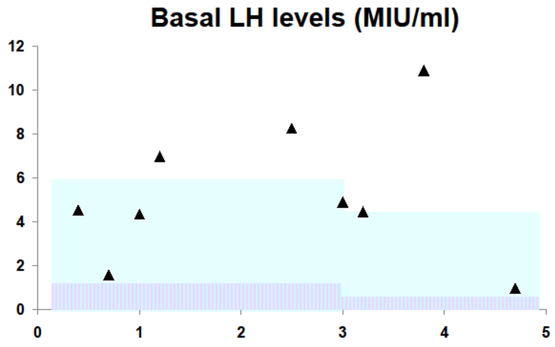
P	CA (months)	EMS	Sex of rearing	Gonadal histology	LH MIU/ml Basal	LH MIU/ml Peak	FSH MIU/ml Basal	FSH MIU/ml Peak	FSH/LH	BasalTestosterone ng/ml (nmol/l)	AMH pmol/l	Inhibin B pg/ml
1	2.5	8.5	M	Bilateral biopsy : left ovotestis, right dysgenetic teste (CA 3 months)	8.3	16.3	2.1	3.4	0.25	4.12 (14.3)	>140	395
2	3.8	8.5	F	Bilateral gonadectomy: ovotestis (CA 3 ys)	10.9	ND	6.1	ND	0.56	0.26 (0.9)	ND	ND
3	4.7	4	F	Bilateral gonadectomy : ovotestis with gonadoblastoma (CA 1.2 ys)	1.0	ND	3.8	ND	3.83	0.66 (2.3)	ND	ND
4	3.0	4.5	F	Gonadectomy left dysgenetic teste, biopsy right ovary (CA 5 months)	4.9	ND	4.3	ND	0.87	1.26 (4.4)	ND	ND
5	0.7	8	M	Bilateral biopsy: right dysgenetic teste, left ovary (CA 2 months)	1.6	21.8	1.3	6.9	0.81	1.24 (4.3)	677	136
6	0.4	7	F	Bilateral gonadetomy: ovotestis (CA 2 months)	4.6	20.2	1.8	3.8	0.39	1.76 (6.1)	82.1	127.8
7	3.2	4	M	Bilateral biopsy: dysgenetic testes (CA 3 months)	4.5	29.4	5.9	19.7	1.34	0.51 (1.8)	164	122
8	1.2	8	M	Bilateral biopsy: dysgenetic testes (CA 4 months)	6.9	ND	5.2	ND	0.75	4.27 (14.8)	ND	ND
9	1.0	9.5	M	Bilateral biopsy pending (normal testicular appearence on US)	4.4	30.2	1.9	4.6	0.44	1.60 (5.5)	632	148.2

P: patient CA: Chronologycal age EMS: external masculinization score (0-6)
M: male F: female ND: not done US: ultrasound
Numbers in red represent values outside the reference range for male infants
Cells in pink represent values outside the reference range for male infants and within the female reference range

Normal reference values	MALE LH MIU/ml	MALE FSH MIU/ml	MALE Testosterone ng/ml	MALE AMH pmol /l	MALE Inhibin B pg/ml	MALE FSH/LH	FEMALE LH MIU/ml	FEMALE FSH MIU/ml	FEMALE Testosterone ng/ml	FEMALE AMH pmol/l	FEMALE Inhibin B pg/ml	FEMALE FSH/LH
0-3 months	2.52±1.74	2.40±1.67	0.05-1.77	578-2022	25-250	0.42-5.51	0.47±0.38	5.39±3.38	<0.05	6.2-95.6	0-33	1.47 – 44.7
3-5 months	1.21±1.65	1.35±0.81				0.25-12.5	0.21±0.18	6.57±5.23				5.19-116.1

RESULTS

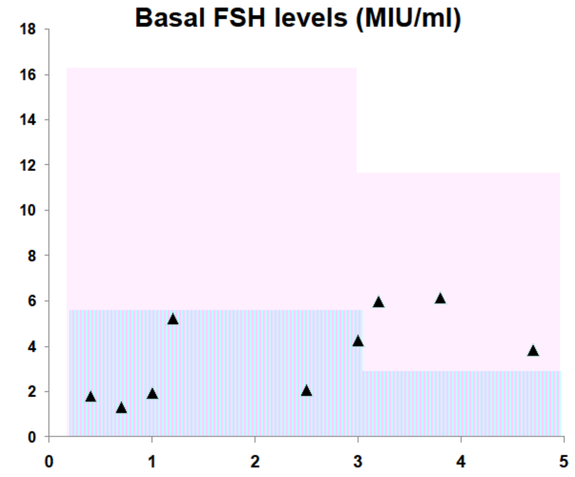
Basal LH levels (MIU/ml)



In all patients, serum basal LH levels (mean ± SD: 5.23 ± 3.11, range 1-10.9 U/L) were significantly higher than in normal female ($p<0.05$), and in 3 were even higher than reference values (RV) for male

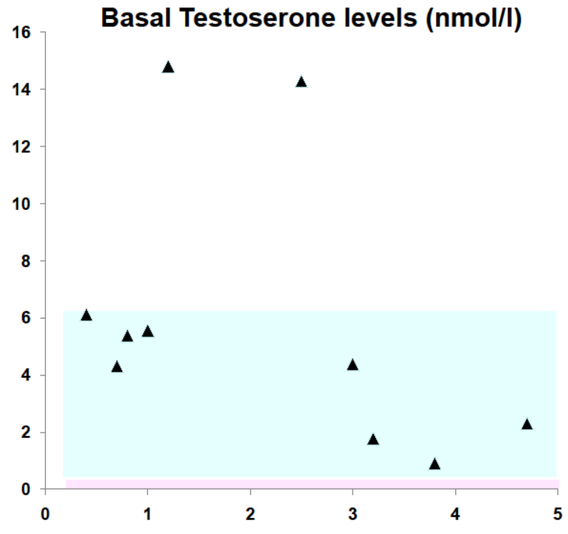
Normal reference ranges presented as colored shadow
Male reference range
Female reference range
Overlaping female and male reference range

Basal FSH levels (MIU/ml)



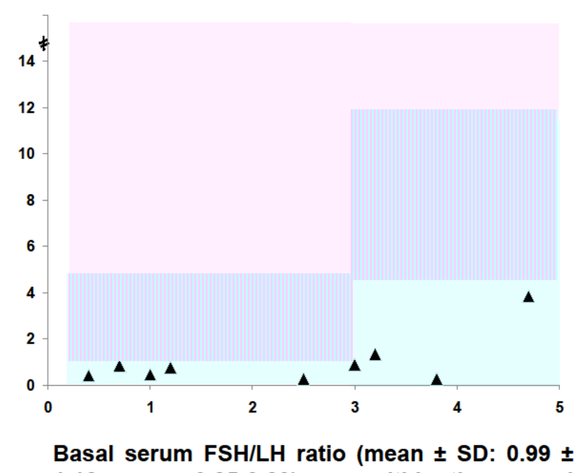
Serum basal FSH levels (mean ± SD: 3.61 ± 1.89UI/l, range 1.3 - 6.13UI/l) were in all patients within female RV and in 6 within male RV

Basal Testoserone levels (nmol/l)



Testosterone levels were consistent with male mini puberty

FSH/LH ratio



Basal serum FSH/LH ratio (mean ± SD: 0.99 ± 1.12, range 0,25-3.83) was within the normal range for the male sex and below the normal range for the female sex

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 ration persists within the normal males reference 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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