



Mini puberty and its interpretation

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Abstract

Gonadotropins which are high in the middle of the fetal life are measured to be considerably low in the cord blood and estrogen is found to be high in the cord blood. Gonadotropins are suppressed by estrogen. After delivery, the hypothalamo-pituitary-gonadal axis is activated when estrogen is eliminated and a hormone profile which reaches pubertal levels is established. These changes are called mini puberty. In boys, long-term testicular functions and sperm production are regulated with mini puberty and mini puberty contributes to masculinization of the brain. The role of mini puberty in female newborns is not known. Central hypogonadism, Turner syndrome and ovarian hyperstimulation in preterm babies may be diagnosed with evaluation of mini puberty. In this article, mini puberty and related problems were reviewed and the importance of this issue was emphasized. (Türk Ped Arş 2014; 49: 186-91)

Key words: Mini puberty, newborn, interpretation

Gonadotropins which are at high levels in the middle of the fetal life are considerably low in the cord blood and estrogen is measured to be high. The reason for this is the inhibitory effect of increased estrogen levels in the circulation arising from the placenta on gonadotropin releasing hormone (GnRH) pulse generator and pituitary gonadotropins (1, 2). In male fetuses, testosterone levels probably contribute additionally to inhibition (3). Gonadotropin inhibition discontinues with placental separation, the hypothalamo-pituitary-gonadal axis is activated and the hormonal changes which occur are identified as mini puberty (2, 4). The activation of the hypothalamo-pituitary-gonadal axis reach a peak level approximately in the 6-8th week after delivery. In this period, the levels of sex steroids are similar to early-middle pubertal levels, but their peripheral effects are not realized (4).

In boys, the level of luteinizing hormone (LH) increases approximately 10-fold in the minutes following delivery and the level of testosterone increases. This state lasts approximately for 12 hours (5, 6). The increase in follicle stimulating hormone (FSH) and LH continues in the second week after delivery, reaches a peak in the 4-10th week, decreases in the 6th month to the prepubertal levels. The level of testosterone increased by release of luteinizing hormone reaches a peak at around the third month and decreases to the prepubertal levels in the 6-9th months (1, 7, 8). Similarly, the levels of 17-hydroxyprogesterone and androstenedione which are increased with testosterone decrease with reduction of the level of LH (2). After delivery, an increase in the number of Leydig cells starts. This increase reaches a peak in the third month. Afterwards, reduction and apoptosis occur in fetal and infantile Leydig cells (9-11). Inhibin-B is a glycoprotein belonging to the family of transforming growth factor beta (TGF- β) and is released from Sertoli cells in the prepubertal period. It is considered an indicator of sertoli cell function in prepubertal male children, but it does not reflect the number and function of germ cells. Inhibin-B acts as a regulator of release of FSH (1). Inhibin-B can be measured in the cord blood, it increases after delivery, reaches a peak in the 4-12th month (exceeds the male adult level). It is at a considerably low level at the age of 3-9 years and increases again with the initiation of the puberty (3, 7). Serum inhibin-B levels are low in cases of hypogonadotropic hypogonadism (1, 12).

Anti-Müllerian hormone (AMH) is a glycoprotein released from the sertoli cells starting from the fetal period. It is found in the cord blood and its level increases in the first 30 months after delivery. It reaches a peak in the 6th month, starts to decrease

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in the childhood and decreases to considerably low levels in the pubertal period (13, 14). The level of AMH decreases in parallel to increased testosterone in the puberty.

In boys, both inhibin-B and AMH levels give an idea about the presence and function of Sertoli cells in the months following delivery and in the prepubertal period (1). In cases of bilateral cryptorchidism, human chorionic gonadotropin hormone stimulation test can be performed to determine the presence and function of the testicles. However, it should be kept in mind that inhibin-B level may be normal and AMH may be low in "persistent Mullerian duct" syndrome, if there is AMH receptor unresponsiveness (1).

Conclusively, the testicular volume increases with elongation of the seminiferous tubules (6-fold until the age of one) with mini puberty which starts in the neonatal period and continues until the middle infancy (11, 15). It has been found that the mass of the Sertoli cells increases to constitute 85-95% of the seminiferous tubules (16). It is thought that transient scrotal hairing which can be observed in the first year of life in boys is related with the physiological testosterone level which increases in the process of mini puberty (Figure 1) (17-19). The increase in the number and proliferation of Sertoli cells is determinative for spermatogenic functions (20). The total number of germ cells increases approximately up to 100 days (50-150) (21). This increased mitotic activity allows the genocytes (non-primary reproductive cells) to transform into adult spermatogoniae which are considered stem cells for spermatogenesis between the 30th and 80th days in boys with increased gonadotropins and testosterone level (2, 20, 22). After the 6th month after delivery, the spermatogonia decrease in number in parallel to decreased gonadotropins. Activity in the GnRH pulse generator which lasts from the neonatal period to the middle infancy (mini puberty) is important for cryptorchidism and the spermatogenic function and fertility in advanced years (20, 23-27). In addition, it is thought that increased level of testosterone provides masculinization of

the brain and determines cognitive functions, sexual behavior and sexual orientation in relation (4, 28). In this period, the testicles increase from 0.5 mL to 1.5 mL, while penile growth is more insignificant. Lack of contribution to the penile growth and absence of other peripheral effects are explained by relative androgen insensitivity in the neonatal period and the first months of life (4). Similarly, acceleration in the bone age starts after the 6th month after delivery in cases of congenital adrenal hyperplasia (29). In contrast to some views, it has been proposed that increased testosterone after delivery has no effect on masculine type of psychosexual development based on the information that subjects with Kallman syndrome can be masculinized by administration of pubertal testosterone (2). One of the interesting points is the fact that no increase in LH and testosterone is observed after delivery in cases of complete androgen insensitivity in contrast to partial androgen insensitivity (3, 30).

The FSH level in the circulation in girls is high in the middle period of pregnancy, decreases at delivery and increases again with activation of the hypothalamic-pituitary-gonadal axis. Production of AMH is limited in fetal ovaries. In female babies, transformation to estradiol increases with production of LH and androstenedione which increases moderately after delivery and with increased FSH afterwards. The level of FSH is higher in girls. The hormones excluding follicle stimulating hormone decrease from the 6th month after delivery (31). Increased FSH in girls continues until the age of 2-4 years. In girls, the level of estradiol is high in the 2-4th months after delivery (the levels may fluctuate) (31). Inhibin-B reaches a peak in the first four months and is maintained at the prepubertal level until the age of 2 years. In premature babies, increased FSH in the postnatal period is more exaggerated. Folliculogenesis and increase in AMH starts with increased FSH. However, this is observed later in preterm and near term babies compared to term babies (32). This explains increased FSH levels. In contrast to boys, it is not exactly known which superiorities mini puberty provides for girls. In a study conducted with girls aged approximately three months, inhibin-B was found to be 82 pg/mL, FSH was found to be 3.8 IU/L, LH was found to be 0.07 IU/L, estradiol was found to be 31 pM and SHBG was found to be 137 nM (32). FSH was found to be higher than 4.5 IU/L in 38% of the girls. In preterm babies, estradiol and inhibin-B were found to be higher. In addition, estradiol was higher in babies with intra-uterine growth retardation. Anti-Mullerian hormone and inhibin-B are high in the follicular phase and interpreted as ovarian function with counting of the antral follicles by ultrasonography.

Evaluation of mini puberty

The external genitalia are examined carefully after delivery. In male newborns, the penile length and testicular volume are measured with Prader orchimeter and US and hypospadias, cryptorchidism, transverse testicular ectopy and inguinal her-



Figure 1. Scrotal hair growth

(from the archive of Erciyes University Medical Faculty, Department of Neonology)

nia are noted. In girls and in babies whose external appearances are compatible with female gender, the labia majora, minora, hymen and urethra are examined. Gonad palpation is performed inside the labia or inguinal channel. Pigmentation in the genital region and nipples and other malformations are explored in both genders. Approximately after two months when mini puberty appears, FSH, LH, testosterone, estradiol, MAH, inhibin-B are measured and uterus-ovarian US is performed (Table 1, 2) (33). In term male babies, the level of testosterone increases to 60-400 ng/dL between the 20th and 60th days and decreases to the prepubertal level after the 7th month (<3-10 ng/dL). In girls, the level of estradiol is high at delivery and decreases in the first week. It increases to 5-50 pg/mL between the 30th and 60th days. Afterwards, it decreases to the prepubertal level (below 15 pg/mL) (34). The uterus and ovaries are evaluated ultrasonographically in female babies. The dimensions of the uterus are increased due to the hormones crossing from the mother through the placenta (35, 36). The body of the uterus is more prominent compared to the cervix, the height of the uterus is 35 mm and the highest width is approximately 14 mm. The endometrium is apperent and echogenic. A small amount of fluid is found in the endometrial space in approximately 25% of the babies. The dimensions of the ovary in female newborns are larger compared to the childhood (approximately 1 mL). The size of the ovary is measured to be 1 mL until the age of one and 0.67 mL in the second year (37). In 84% of the babies, follicles the diameters of which do not exceed 1 cm are found from the neonatal pe-

riod to the age of 2 years. The same finding is observed with a rate of 68% in girls aged between 2 and 6 years (38).

Problems related with mini puberty

- 1) If there is hypogonadotropic hypogonadism in boys, decreased FSH, testosterone and inhibin-B is found in addition to micropenis (stretched penis <2.5 cm) and cryptorchidism; LH may be immeasurably low or may show low amplitude pulses. A blunted response is obtained in the gonadotropin releasing hormone test. Hypogonadotropism may be found solely in the spectrum of Kallmann syndrome, DAX-1 mutation, multiple pituitary hormone deficiency. With this objective, pituitary and cranial magnetic resonance imaging, pituitary hormone tests and genetic tests may be performed. A picture of hypergonadotropism is observed in cases of gonadal agenesis (2). Gonadotropin treatment starting from the newborn period and allowance of testicular function by mini puberty created are recommended in cases of congenital hypogonadotropic hypogonadism (39).
- 2) The most important cause of the picture of hypogonadism is Turner syndrome. In babies with Turner syndrome, low birth weight, edema on hands and feet, weblike neck, inverted and hyperteloric nipples and pigmented nevi are noted (Figure 2). Aort coarctation and horseshoe kidney may be found. The uterus is hypoplastic and streak ovaries are observed on ultrasonography. A level of FSH

Table 1. Gonadotropin levels in female newborn babies (RAI)

Days	LH (mIU/L)			FSH (mIU/L)		
	Mean	SD	Median	Mean	SD	Median
1-5	0.48	0.66	0.20	2	1.37	1.80
06-10	0.45	0.33	0.30	2.44	2.52	1.40
11-15	1.8	1.28	1.60	8.16	4.27	8.95
16-20	1.03	1.39	0.35	1.62	1.05	1.90
21-25	0.46	0.25	0.50	7.07	5.92	3.90
26-28	2.75	2.39	2.80	9.74	9.89	6.15

LH: luteinizing hormone; FSH: follicle stimulating hormone; SD: standard deviation

Table 2. Gonadotropin levels in male newborn babies (RAI)

Days	LH (mIU/L)			FSH (mIU/L)		
	Mean	SD	Median	Mean	SD	Median
1-5	0.39	0.48	0.20	0.96	0.60	0.85
06-10	2.31	2.29	1.50	2.91	4.38	1.40
11-15	3.55	2.84	2.90	3.71	2.69	3
16-20	4.13	2.76	3.65	2.63	1.45	2.15
21-25	2.86	1.51	2.70	2.50	1.5	2.10
26-28	2.22	2.37	1.40	2.25	0.81	2.40

LH: luteinizing hormone; FSH: follicle stimulating hormone; SD: standard deviation



Figure 2. Karyotype 45 x=, edema in the dorsal part of the feet, hypoplastic uterus, ovaries could not be visualized, FSH 49.47, LH 4.43 mIU/mL
(from the archive of Erciyes University Medical Faculty, Department of Neonology)

below 40 is diagnostic, but it may not always be increased (40). Luteinizing hormone is normal and estradiol is low.

- 3) Excessive ovarian stimulation syndrome in preterm babies: This syndrome was reported by Sedin et al. (41) in 1985 for the first time in four preterm babies with a gestational age of 24-28 weeks. Edema in the vulva, hypogastric area and thigh was noted in the postconceptional 36-39th weeks (Figure 3). The investigations performed revealed high gonadotropin levels in addition to multiple cysts in the ovaries on ultrasonography. Afterwards, nine cases were published by Starzyk et al. (42). In addition to the same laboratory and clinical findings, solitary or multiple ovarian cysts with a mean diameter of 21 mm were found. Increase in gonadotropins was observed with GnRH test in a portion of the cases. Breast growth may be added to the picture in some cases (43). Solitary or monthly vaginal bleeding may occur in cases with a severe clinical course (44, 45). The pathophysiology of this picture which is observed in preterm babies is not known fully. It is thought that lack of maturation of the hypothalamo-pituitary-gonadal axis and lack of complete development of negative feedback mechanisms with discontinuation of placental steroids are involved (42, 46). It has been proposed that edema observed in the subjects is related with vascular endothelial growth factor released from the theca and granulosa cells (43, 47). It has been reported that fetal ovarian hyperstimulation may occur rarely (47). In a fetus with a gestational age of 35 weeks, macrosomy, placental thickening, polyhydramnios, large ovaries (right 17.8, left 16.3 mL), 2 ovarian cysts with large septae and abdominal distention were observed and the clinical picture was associated with the increased level of beta-hCG found in the mother.

In the diagnosis, increased FSH, LH, estradiol, increased dimensions of the ovaries and uterus and presence of ovarian cysts are directive in addition to the clinical picture.



Figure 3. Severe edema in the vulva, upper thigh and lower abdomen in a case of overstimulation of the ovaries
(from the archive of Erciyes University Medical Faculty, Department of Neonology)

The subjects should be followed up with clinical picture, FSH, LH, estradiol levels and ovarian ultrasonography. Ovarian cysts should be expected to become smaller gradually. Hence, reduction in the cysts are observed in the first month in 50% of the cases and at the end of the second month in 25% of the cases. The cysts may persist for longer than three months in 10% of the cases (42). Drainage by aspiration may be necessary because of the risk of torsion in solitary or multiple cysts with a diameter larger than 4-5 cm which do not get smaller (41). In severe cases where clinical regression is not observed, intracranial medroxyprogesterone acetate may be administered at a dose of 150 mg/m² with the aim of decreasing the synthesis of ovarian estradiol (42).

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