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Ovarian Reserve of the Female Adolescents with Amenorrhea and the Factors Reducing it

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Abstract: The study presents the ovarian reserve criteria in 93 girls with secondary amenorrhea. The ovarian reserve was evaluated by the hormone level: FSH, LH, E2, AMH, Inhibin B and ultrasonic markers ovarian volume and the number of antral follicles in the section. In 9.7% of cases the low ovarian reserve was detected. The factors that resulted in reduction in the ovarian reserve were specified and the predictive indices were estimated.

Key words: Secondary amenorrhea, female adolescents, ovarian reserve, disturbing factors, predictive factor

INTRODUCTION

The issue of the reproductive potential of a female population remains rather acute. The state of adolescent health determined the reproductive health of the population in the future (Zakharova *et al*., 2002). In case of feto-maternal diseases, the embryogenesis processes are impaired which forms the intrauterine gonadal inferiority expressed in increased number of the tertiary and large primary follicles, fibrous tissue hypertrophy, reduced number of primordial follicles and acceleration of the atresia process (Zhakhur, 2011). At the prepubertal and puberty age different functional disorders may also impair the reproductive system (Bogdanova, 2000).

MATERIALS AND METHODS

The objective of this research was the study of the Ovarian Reserve (OR) status in female adolescents with secondary amenorrhea and statement of the predictive value of the main disturbing factors. The study involved 123 female teens at the age from 13-18 years. The main group included 93 female teens with secondary amenorrhea the average age of which made 15.9±0.2 years, the control group consisted of 30 female teens without clinical-laboratory deviations with symmetrical menstrual period. The inclusion criteria were: female teens up to 18 years with absence of spontaneous menstruations for 6 and more months with the burdened history of the somatic, gynecological and endocrine health. The exclusion criteria: congenital pathology of ovarian genesis gonadal dysgenesis. The OR status was evaluated with the use of the passive method by analyzing the level of sex hormones: FSH, LH, Estradiol (E2), Anti-Mullerian Hormone (AMH) and inhibin B with the use of the enzyme-immunoassay and set of the test-systems (ELISA). The ultrasonic OR parameters were evaluated including the ovarian volume and counting the antral follicles in the section using the "Aloka 630" device (Japan) with the use of the transabdominal and transvaginal probe. In order to find out the disturbing factors the medico-social audit was performed by means of interviewing, questioning and review of medical records (prenatal record Form No. 111/U).

Statical data analysis was performed with the use of electronic spreadsheets Microsoft Excel 2010 and application software package «Statistica for Windows v. 6.1, StatSoft Inc. (USA). For evaluation of correlation between the factors being studied and effective features the probabilistic method of Odd Ratio (OR) computation was used: using statistics software package MedCalc 12.1.4.0 the predictive factor (R) was estimated.

RESULTS AND DISCUSSION

On the basis of results of studying the OR status in the main group of female adolescents with secondary amenorrhea the two subgroups were allocated. The first subgroup included 9 female teens (9.7%) that demonstrated reduction in all the OR criteria, the average age of which was almost the same (16.1±0.2 years). The second subgroup was made of 84 (90.3%) remaining female teens with secondary amenorrhea the hormonal panel figures of which did not demonstrate any deviations from the reference values, the average age made 16.9±0.4 years. In female adolescents from the first subgroup the Anti-Mullerian Hormone (AMH) was by 16.3 times lower as compared to the teens with amenorrhea the genesis of

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Table 1: Hormone rates in the female adolescents in the subgroup compared

Hormones	Main group of female adolescents with amenorrhea (n = 93) (M±m)		Control group (n = 30) (M±m)	$P_{1,2}$	$P_{1,3}$	$P_{2,3}$
	1st subgroup (n = 9)	2nd subgroup (n = 84)				
AMG (ngm L^{-1})	0.4±0.1	6.5±0.6	5.5±0.7	0.000007	0.000001	0.923102
Inhibin B (pgm L^{-1})	6.8±2.7	65.9±4.3	73±5	0.000007	0.000010	0.194739
FSH (IUL^{-1})	47.6±19	7.2±0.7	5.9±0.5	0.001728	0.002027	0.055974
LH (IU L^{-1})	19.3±3.2	9.7±0.7	7.2±1.5	0.000410	0.002517	0.009592
Estradiol (pmole L^{-1})	40.2±9.2	88±9.7	94.5±9.8	0.002044	0.013306	0.046060

Table 2: Ultrasonic parameters of the ovarian reserve in the female adolescents in the groups being compared

Ultrasonic parameters	Female teens from the main group with amenorrhea n = 93 (M±m)					
	I subgroup n = 9		II subgroup n = 84		Control group n = 30 (M±m)	
	RO	LO	RO	LO	RO	LO
Ovarian volume (cm^3)	4.6±0.5*◇	3.9±0.4*◇	6.8±0.3	6.4±0.4	9.2±0.4	8.5±0.9
	Number of antral follicles					
	I subgroup n = 9		II subgroup n = 84		Control group n = 30	
Parameters	abs.	(%)	abs.	(%)	abs.	(%)
<5 follicles	7*	77.8	4	4.7	0	0
5-10 follicles	2*	22.2	51	60.7	20	66.7
10-5 follicles	0	0	29	34.5	10	33.3

which was determined by dysfunction of the central regulating mechanisms. The inhibin B rate as the OR criterion appeared to be a less sensitive diagnostic indicator of ovarian insufficiency in the teens of the first subgroup it was by 9.7 times lower as compared to the teens from the second subgroup (Table 1).

In the female adolescents with the low OR the mean FSH values were by 6.6 times higher (476. IU L^{-1}) against the teens from the second subgroup (7.2 IU L^{-1}). Also, the LG rate in the teens of the first subgroup was more statistically significant, almost twice as much as that of the teens from the second subgroup (19,3 IU L^{-1} and 9, 7 IUL^{-1}, respectively), however, these differences were less pronounced as compared to the FSH estimates in the same subgroups.

The estradiol rate in the female teens of the first subgroup was statistically lower (40.2±9.2 pmole L^{-1}) than in the teens with undisturbed period and teens with amenorrhea of central origin.

According to the ultrasonic investigation data the ovarian volume in female teens with the reduced OR was by 2.1 lesser (4.53 cm^3) as compared to the teens with amenorrhea of central origin (9.8 cm^3) and by 2.6 times lesser (11.82 cm^3) as compared to the control group of female teens with undisturbed menstrual period (Table 2). The ovarian volume and counting of the follicle number are the important OR criteria it has been found out that the ovarian volume <3 cm^2 may be indicative of the increased concentration of FSH (Syrop *et al*., 1999). According to the findings of ultrasonic examination of the female teens from the first subgroup the number of antral follicles in the section (Table 2) characterizing the OR was less statistically significant (5.6±0.8) as compared to the teens with amenorrhea of central origin (12.3±0.3) and as compared to the girls from the control group with the undisturbed menstrual period (15.4±0.2).

Reduction of OR in the female teens must have been present since the "intrauterine childhood". All mothers of the girls demonstrating the reduced OR had complications during the pregnancy (Table 3).

At the early gestation stage, the threatening of miscarriage during the intrauterine childhood period was observed which allows considering the lasting threatening of miscarriage in the early stages of pregnancy as the predictive factor of the reduced OR (R = 8.4). The female teens during the Intrauterine childhood also in the early stages of pregnancy had infectious diseases that were accompanied by hyperthermia and could affect the laying of the follicl pool, the high predictive factor as for the reduction of OR has been derived (R = 10). Placental Insufficiency (PI) also presented high risk of reduction of the ovarian reserve with the high predictive factor (R = 8.3). The pathogenic mechanisms of the OR reduction by PI are described disturbance of the vascular tone results in the reduced blood filling of gonads during the intrauterine period and ischemia which may cause the fetal hypoxia and sharp reduction of OR (Howel and Shalet, 1998). Preeclampsia was more frequently observed during the intrauterine childhood period of the girls from the first subgroup, the risk of the impairment of the follicular apparatus was assessed R = 6.7. Parents' alcoholism was acknowledged

Table 3: Comparative analysis of factors reducing the ovarian reserve during the intrauterine period

	Female teens from the main group with amenorrhea (n-93)				Control group (n = 30)				
	1 subgroup (n = 9)		2 subgroup (n = 84)						
Perinatal period	abs	%	abs	%	abs	%	$P^{1,2}$	$P_{1,3}$	$P_{2,3}$
Threatening miscarriage in the early stages of pregnancy	9	100	16	19	3	10	0.0001	0.0001	0.3
Abuse of alcohol by parents	3	33.3	1	1.2	--	--	0.003	<0.05	
Previous infectious diseases	3	33.3	5	6	1	3.3	0.003	0.03	1
Placental insufficiency	6	66.7	14	16.7	3	10	0.002	0.001	0.5
Preeclampsia	6	66.7	14	16.7	3	10	0.002	0.001	0.5
Small-for-date fetus	3	33.3	1	1.2	1	3.3	0.003	0.03	0.5
Premature delivery	5	55.5	2	2.4	1	3.3	0.00001	0.0001	0.6
Acute fetal asphyxia during delivery	2	22.2	--	--	--	--	<0.05		

p = Statistical significance between the groups being compared, $p<0.05$

Table 4:Comparative analysis of factors reducing the ovarian reserve at the puberty age

	Female teens from the main group with amenorrhea (n-93)				Control group (n = 30)				
	1 subgroup (n = 9)		2 subgroup (n = 84)						
Diseases	abs	%	abs	%	abs	%	$P^{1,2}$	$P_{1,3}$	$P_{2,3}$
Rubella	6	66.7	9	10.7	3	10	0.0001	0.002	1
Parotitis	3	33.3	1	1.2	1	3.3	0.003	0.03	0.5
Frequently and chronically ill children	6	66.7	11	13.1	3	10	0.0005	0.002	0.7
Hypothyroid	3	33.3	6	7.1	1	3.3	0.04	0.03	0.7
Diabetes mellitus	1	11.1	--	--	--	--	<0.05		
Smoking	4	44.5	11	13.1	3	10	0.03	0.04	0.8
Subfertility disorders in the girls' mothers	4	44.5	7	8.3	1	3.3	0.001	0.002	0.7
Operative treatment of ovaries	4	44.5	2	2.4	1	3.3	0.001	0.007	1

$p_{1,2}$: Statistical significance between the first and the second subgroup. $p<0.05$; $P_{1,3}$ Statistical significance between the first subgroup and the control group ($p<0.05$); $p_{2,3}$: Statistical significance between the second subgroup and the control group ($p<0.05$)

to be a damaging factor during the intrauterine childhood which was by 28 times more frequently observed in mothers of girls from the first subgroup ($p<0.05$). Nearly each fourth girl with the reduced OR (22.2%) was exposed during the intrauterine childhood period to the fetal hypotrophy and acute asphyxia during delivery ($p<0.05$), every second one of them (55.5%) was delivered prematurely ($p<0.05$). In her researches Medvedeva (2007) notes that by the severe forms of preeclampsia, PI, infectious processes in the genital tract as well as presence of bad habits in a mother during pregnancy the inhibition of maturation of the fetal gonads along with the progress of hypoplastic ovaries and reduced follicle number was observed (Medvedeva, 2007).

At the prepubertal and puberty age in the girls of the main group with the reduced OR the most significant predictive factor was the previous rubella (R = 6.7), every fourth one has had epidemic parotitis ($p<005$) (Table 4).

There is an assumption that girls that suffered rubella, epidemic parotitis might have parallel suffered from silent diffuse ovaritis as the result of which due to the acceleration of apoptosis in an ovary the premature loss of follicular structures with the fibrosis outcome took place (Marchenko *et al*., 2006). Another viral and bacterial infection was relevant as the OR-reducing factor. Thus, a great number (66.7%) of girls with the reduced OR frequently suffered the Acute Respiratory Viral Infection (ARVI) and were included in the dispensary group of the "frequently and chronically children" which was relevant at the prepubertal and puberty age as the predictive factor was rather high (R = 6.7). Alone in the group of girls with reduced OR meningococcosis, adenovirus infection and diabetes mellitus were diagnosed which may be considered as predictive factors indicating the risk of reduction of the ovarian reserve. Hypothyroid (R = 2.2) and chronic tonsillitis (R = 1.7) were less significant as predictive factors in this subgroup. However, the most aggressive factor reducing the OR were the operative interventions to ovaries present in the history of 44.4% of girls from the first subgroup where the risk factor was the highest (R = 13.3). All these girls underwent operative intervention in the right ovary: in 22.2% cases cystectomy was performed and in 22.2% cases girls underwent resection of the right ovary. According to the data available the right ovary features higher functional performance and the loss of it is more significant (Kurilo, 1980). Today up to 15% of girls are subjected to unjustified operative interventions, ovariectomy or

resection of ovaries (Kutusheva and Umancheeva, 2001). The studies by other researchers show that not only operative interventions in the ovaries reduce their functional-morphologic reserve but also the surgical energy used for maintenance of hemostasis. Coagulation performed for maintenance of hemostasis causes damage of the health ovarian tissue with appearance of the additional center of damage in the form of the pronounced inflammatory response in the perifocal exposure areas (Bukharina, 2003). Among the factors having a negative effect on the ovaries of female adolescents there were the bad habits, abuse of alcohol and cigarettes. In the group of girls with the reduced OR in 37.5% the teens misused (2-3 times a week) alcohol (beer) and cigarettes (daily) combined.

SUMMARY

It was found for the first time that the female adolescents with secondary amenorrhea having different damaging factors since the intrauterine childhood in 9.7% cases the premature OR reduction is observed. During the intrauterine period the following probable predictive criteria of genesis of gonadal inferiority shall be considered: prolonged threatening miscarriage and infections at the early stages of pregnancy, placental insufficiency, preeclampsia, fetal hypoxia, hypotrophy and immaturity, continuous effect of alcohol. At the prepubertal and puberty age the reduced OR may be predicted in the girls that suffered from rubella, epidemic parotitis, ARVI, operative interventions in ovaries, endocrine disorders (hypothyroid, diabetes mellitus). This pathology aggravates the risks of the intrauterine childhood and represents the multiple damages causing the OR reduction. Smoking and use of alcohol at the puberty age may also impair the gonads. Detection of the damaging factors along with the forecast of functional inferiority of ovaries allows distinguishing the risk groups at early stages and planning the reproductive behavior, taking rehabilitation measures on reduction of burden of the damaging factors as well as performing the preventive and treatment measures aimed at maintenance of the reproductive potential. Analyses of the OR in girls from the risk groups allows forecasting the ovarian response and calculate the likelihood of pregnancy upon achievement of sexual maturity or store the genetic material for the delayed maternity.

CONCLUSION

Based on the foregoing the conclusion may be drawn that knowledge of the probable factors reducing the OR in the female adolescents allow forming the risk groups at the preclinical stage.

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