Original Article

The Influence Of Various Methods Of Treatment Of Juvenile Dysmenorrhea On The State Of Reproductive Health In Uzbek Women With Genetic Determination Of Connective Tissue Dysplasia

Yakubova O.A., Isakova D.B., Suleymanova N.A., Ismailova S.S., Rizakova D.P., Ergashbaeva D.A.

Andijan Medical Institute, Uzbekistan
DOI: 10.47750/pnr.2022.13.S08.87

Abstract

A clinical and genetic examination of 118 girls with painful menstruation, with signs of CTD - 64 and without it - 54, was carried out, the control group consisted of 68 healthy girls with normal menstruation with an assessment of the state of reproductive health after 8 years. It was found that the single nucleotide variant COL1A1 G2046T plays a role in the pathogenesis of the development of JD accompanied by CTD, which is indirectly confirmed by the indicators of hydroxyproline, the increase in the level of which was significant both in comparison with practically healthy individuals and in comparison with a group of patients with JD without signs of CTD. Carrying out a differentiated approach to the treatment of JD, taking into account the presence of phenotypic manifestations of connective tissue dysplasia, allows you to correct menstrual function, prevents further disruption of connective tissue metabolism with normalization of the hypothalamic-pituitary-ovarian activity and the implementation of the function of the reproductive system.

Keywords: primary dysmenorrhea, juvenile dysmenorrhea, connective tissue dysplasia, estrogen receptor alpha (ESR1), COL1A1 G2046T genes.

Introduction

All over the world, one of the factors that worsen the quality of life of girls and adolescent girls is the pain syndrome that accompanies the physiological process - menstruation [13,22,21]. According to WHO, the prevalence of menstrual pain syndrome in the structure of adolescent gynecological pathology is extremely high, while about 15% of them characterize menstrual pain as excruciating [1,2,21,]. Juvenile dysmenorrhea (JD) - painful menstruation in girls under 18 years of age in the absence of pelvic pathology is a common and often debilitating gynecological suffering, regardless of age or nationality [15,19,25]. Despite its high prevalence, primary dysmenorrhea in girls is often misdiagnosed and even ignored by healthcare professionals and by the girls themselves and their mothers, who may accept painful periods as a normal part of the menstrual cycle [7,18,20]. Juvenile dysmenorrhea (JD) is a signal of disorders that have developed in the systems that provide and control the process of endometrial rejection [4]. When a pathological situation arises in the body of a growing female body, the formation of pathological conditions of organs and tissues occurs in the form of undifferentiated connective tissue dysplasia n(CTD) [6,12]. The main component of the connective tissue is collagen fibers, and hydroxyproline is a biochemical marker of its breakdown [5]. Connective tissue is continuously renewed and rebuilt in response to stress and damage. The intensity of collagen biosynthesis by fibroblasts depends on many factors: hereditary, hormonal, and metabolic [9]. When studying CTD, the question arises about the possible cause of changes in connective tissue based on genetic predisposition. As you know, the manifestation of a particular disease is often due to a combination in the genotype of a growing organism of certain allelic variants of genes, polymorphisms that form a certain hereditary background, which can be realized

through the interaction of a pathological genotype with environmental factors. In a number of studies, some hypotheses were found, which are listed below, which are still relevant to this day. These studies revealed morphological changes characteristic of CTD and changes in genes encoding the synthesis and spatial organization of collagen, as well as gene defects in enzymes, cofactors, and steroid hormones, leading to changes in connective tissue architectonics. In this case, the influence of the environment plays the role of triggering factors [10,16].

Collagen is known to be one of the most abundant proteins in the extracellular matrix and in the connective tissue. Collagens differ in their position in the tissue and in the function they perform. There are four main types of collagen (I-IV), which include the following genes: collagen I (genes COL1A1, COL1A2) - the main component of bone, which is also present in scars, tendons and cartilage; collagen II (COL2A1 gene) is the main component of cartilage; collagen III (COL3A1 gene) forms reticular fibers that hold together the extracellular matrix; Collagen IV (genes COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6) forms the basal lamina that supports the epithelium. [11,24]. It was found that in women with systemic connective tissue insufficiency, there is a partial decrease in type I collagen in the interstitial substance, which is probably the result of a violation of collagen secretion with its intact synthesis [17]. Some studies have shown that in all patients with CTD, regardless of the severity, collagen types I and III had an atypical spatial structure without the formation of pronounced fiber bundles, and then there was a replacement in the ligamentous apparatus of collagen types I and III with type IV collagen, which led to deep violations of mechanical characteristics and functional insufficiency of the design of the ligament-supporting tissues of the small pelvis [8].

There is an opinion that in the presence of a genetic predisposition in the future, especially with the adverse effects of external factors, one or another clinical form of the disease is observed. In order to detect this genetic predisposition, a number of scientists investigated the polymorphism of the type I collagen receptor gene (COL1A1). The α1 collagen type I chain gene (COL1A1) is located on chromosome 17q21.3–22. The G2046T polymorphism is a point substitution of G for T at position 2046, localized in the non-coding region of the gene, affecting the binding site of the transcription factor of the alpha-1 gene of the collagen type 1 chain. Considering CTD as the result of a defect in collagen genes, much attention in the literature is paid to the components responsible for the metabolism of the latter: fibrillogenesis proteins, cross-links responsible for the ordered distribution of collagen chains and its remodeling (degradation and proteolysis) [3]. To date, morphological changes characteristic of CTD and changes in the genes encoding the synthesis and spatial organization of collagen, as well as gene defects in enzymes, cofactors, and steroid hormones, leading to changes in the architectonics of the connective tissue, have been identified [8,11,24].

The purpose of the study:

was to study the effect of various methods of treatment of juvenile dysmenorrhea on the state of reproductive health in Uzbek women with genetic determination of connective tissue dysplasia

Material and research methods:

Conducted clinical and genetic examination of 118 girls aged 13 to 18 years, with signs of CTD - 64 and without it - 54, the control group consisted of 68 healthy girls with normal menstruation. The genetic study was carried out by polymerase chain reaction (PCR) using specific primers (NPF Litekh, Russia) in an automatic cycler "Rotor Geene 6000". The determination of free and bound hydroxyproline in urine was carried out according to the method of P. N. Sharaev [4]. The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2012 software package.

The results obtained and their discussion:

The basis for the diagnosis of dysmenorrhea was a complaint of painful menstruation. Patients to exclude organic pathology i.e. secondary dysmenorrhea, a health examination was carried out (ultrasound of the pelvic organs, a smear for flora, examination by a vertebrologist).

As shown in Table 1, an analysis of the distribution of allelic variants of the COL1A1 G2046T gene showed that in the group of patients with JD accompanied by CTD, there was only a trend towards the significance of alleles, but they did not reach true significance.

Table 1 Distribution of allele and genotype frequencies of the COL1A1 G2046T gene in girls with JD with CTD compared with the control group of apparently healthy individuals

Genotype	**JD + CTD**		Control		OR	$\chi 2$	P
	n=64	%	n=68	%			

G	97	75,78	114	83,82	0,60	2,658	0,1
T	31	24,22	22	16,18	1,66	2,658	0,1
GG	41	64,06	48	70,59	0,74	0,639	0,4
GT	15	23,44	18	26,47	0,85	0,162	0,6
TT	8	12,50	2	2,94	4,71	4,302	0,03

Whereas a significant increase in the homozygous TT genotype was noted in the group of girls with JD and CTD compared with the control group ($\chi 2$= 4.302, p < 0.03, OR≥4.71). Further, when studying the distribution of allelic variants of the COL1A1 G2046T gene in the group of patients with JD accompanied by CTD compared with the group of girls with JD without CTD, it was found that there were no significant differences in allele frequencies in these groups (Table 2). At the next stage, it was decided to analyze the distribution of the frequencies of occurrence of allelic variants and genotypes of COL1A1 G2046T in the group of girls with JD without CTD compared with practically healthy individuals in the population control.

Table 2 Distribution of allele and genotype frequencies of the COL1A1 G2046T gene in girls with JD with CTD compared with the control group with YD without CTD

Genotype	**JD + CTD**		**YD without CTD**		OR	$\chi 2$	P
	n=64	%	n=54	%			
G	97	75,78	88	81,48	0,71	1,124	0,2
T	31	24,22	20	18,52	1,41	1,124	0,2
GG	41	64,06	37	68,52	0,82	0,26	0,6
GT	15	23,44	14	25,93	0,87	0,09	0,7
TT	8	12,50	3	5,56	2,43	1,671	0,2

As can be seen from Table 3, during the analysis of these groups, no significant difference was found either for allelic variants or for genotypes.

Table 3 Distribution of allele and genotype frequencies of the COL1A1 G2046T gene in girls with JD without CTD compared with the control group of apparently healthy individuals

Genotype	**YD without CTD**		Control		OR	$\chi 2$	P
	n=54	%	n=68	%			
G	88	66,67	114	83,82	0,85	0,23	0,6
T	20	18,52	22	16,18	1,18		
GG	37	68,52	48	70,59	0,91	0,06	0,8
GT	14	25,93	18	26,47	0,97	0,005	1
TT	3	5,56	2	2,94	1,94	0,523	0,4

Thus, when studying the association of the COL1A1 G2046T genotype, a significant increase in the TT mutant genotype was revealed in the group of girls with JD with CTD, compared with practically healthy individuals.

Table 4 The level of hydroxyproline in daily urine (μmol/day) in girls with JD depending on the presence of CTD criteria, M±m

Groups	The content of hydroxyproline, μmol/day		
	free	Peptide-bound	protein-bound
Practically healthy, n=25	18,4±1,34	155,7±13,6	8,4±0,63
YD without CTD			
easy, n=10	18,81±0,30	156,63±0,16	8,33±0,26
average, n=31	18,42±0,27	155,81±0,24	8,32±0,23
severe, n=15	17,82±0,35	156,33±0,37	8,11±0,35
JD with CTD			
easy, n=10	26,02±0,96[a,б]	163,64±0,97 [a,б]	8,45±0,55
average, n=31	34,54±1,07 [a,б]	167,33±0,92 [a,б]	8,20±0,63
severe, n=15	57,83±0,88 [a,б]	171,06±0,97 [a,б]	8,82±1,51

Note: a - differences relative to the data of the group of healthy girls are significant, b - differences relative to the data of the group of girls with JD without CTD are significant (P<0.05).

This may indicate that the single nucleotide variant COL1A1 G2046T plays a role in the pathogenesis of JD accompanied by TSD. This is indirectly confirmed by the indicators of hydroxyproline (Table 4), but taking into account the fact that the increase in the level of this indicator was significant both in comparison with practically healthy individuals and in comparison with the group of patients with JD without signs of CTD, allows us to assume that this polymorphism is only one of the polymorphisms involved in the pathogenesis of the pathology under study. Long-term use by girls of various symptomatic, pathogenetically unreasonable therapy leads to a more severe course of dysmenorrhea and persistent psychological discomfort, which can be traced not only during menstruation, but throughout the entire menstrual cycle of girls with juvenile dysmenorrhea.

For a comparative assessment of the effectiveness of the therapy, groups were formed:

1. Non-steroidal anti-inflammatory drugs (NSAIDs)
2. NSAIDs + magnesium preparation
3. NSAIDs + duphaston
4. NSAIDs + magnesium preparation + vegetocorrector + duphaston
5. NSAIDs + microdosed Combined oral contraceptives (ethynyl estradiol 20 mcg and gestodene 75 mcg)
6. NSAIDs + magnesium preparation + vegetocorrector + microdosed Combined oral contraceptives (ethinyl estradiol 20 mcg and gestodene 75 mcg)

To improve the diagnosis of JD and to exclude secondary dysmenorrhea, all examined by us underwent an antiprostaglandin test with NSAID s, which was used 1 powder 2 times a day after meals 3 days before the expected menstruation and for 3 days during menstruation. The disappearance of pain during the next menstruation, with the exclusion of secondary dysmenorrhea, testified to idiopathic dysmenorrhea, in which the use of NSAID s pursued a therapeutic goal. Based on modern principles of therapy, avoiding polypharmacy, taking into account the pathogenetic mechanisms of the development of painful menstruation and the results we obtained, complex therapy was carried out differentially depending on the severity of dysmenorrhea.

21 girls with mild dysmenorrhea without CTD, hormonally related to the group with a normal ratio of progesterone and estradiol, treatment was limited to the use of NSAIDs 1 powder 2 times a day after meals 3 days before the expected menstruation and for 3 days during menstruation in for 3-4 cycles.

19 girls with moderate JD without CTD, whose steroid profile had a normal estrogen content and low progesterone, in addition to NSAIDs for the purpose of correcting the hormonal state, the progesterone drug duphaston was added to the treatment, which was used in the II phase of the menstrual cycle, 1 tablet 2 times per day for 3 months.

16 girls with severe judiciary without CTD hormonal state, which is characterized by hypoestrogenism and hypoprogesteronemia, were treated with NSAIDs with the addition of microdose COCs, starting from the 1st day of the cycle, 1 table. 1 per day.

17 girls with mild dysmenorrhea, who had manifestations of CTD, and according to the hormonal type they belonged to the group with a normal ratio of progesterone and estradiol, were treated with NSAIDs, 1 powder 2 times a day after meals 3 days before the expected menstruation and during 3 days during menstruation and a magnesium preparation in combination with pyridoxine as a collagen stimulator, 1 tablet 3 times a day for 3-4 cycles.

With moderate dysmenorrhea in 32 girls who had manifestations of CTD, in whose steroid profile normal estrogen levels and low progesterone were determined, in addition to NSAIDs to correct the condition of the connective tissue, a magnesium preparation was added to the treatment in combination with pyridoxine 100 mg, which was used in during the menstrual cycle, 1 tablet 3 times a day for 2 weeks, and then 48 mg, 1 tablet 3 times a day for 5-6 months, and progesterone-duphaston, 10 mg 2 times a day, in the II phase of the menstrual cycle, and also vegetocorrector sulpiride 50 mg in the morning 1 time per day.

In severe dysmenorrhea and the presence of CTD criteria in 31 girls, the hormonal state, which is characterized by hypoestrogenism and low progesterone, was used NSAIDs, a magnesium preparation in combination with pyridoxine 100 mg 3 times a day with meals in a saturating dose for 2 weeks, and then 48 mg 3 times a day with meals, continuing treatment for 3-6 months. with the addition of a microdosed monophasic COC in the composition of ethinylestradiol 20 mcg and gestodene 75 mcg, starting from the 1st day of the cycle, 1 tab for 3 months, as well as the vegetocorrector sulpiride 100 mg in the morning 1 time per day.

It should be said that the main biochemical manifestation of CTD is hydroxyprolinuria, reflecting the breakdown of connective tissue. In this regard, it was of interest to evaluate the effectiveness of the proposed treatment for JUD on the content of hydroxyproline and its fractions in the daily urine of girls. The results of the study of the content of hydroxyproline in morning urine after various types of treatment for JUD with the presence of CTD manifestations are shown in tables 5-7

Table 5 The content of hydroxyproline and its fractions in the urine of girls with mild primary dysmenorrhea with signs of CTD during treatment, M±m

Groups	Oxyproline, µmol/day	
	Free	peptide-bound
Control	18,4±1,34	155,7±13,6
Before treatment	26,02±0,96[a]	163,64±0,97 [a]
After standard therapy	21,76±0,82 [a,б]	161,42±0,81
After the proposed therapy	20,63±0,92 [б]	156,33±1,09

Note: a - the differences are significant relative to the data of the group of healthy girls, b - the differences are significant relative to the data before treatment, c - the differences are significant relative to the values of the comparison group after treatment (P<0.05).

As can be seen from Table 5, the content of free hydroxyproline in the urine of girls with mild primary dysmenorrhea against the background of CTD with standard treatment significantly decreases by 1.2 (P<0.05) times relative to the initial parameters, while the level of free and peptide-bound hydroxyproline only had a downward trend.

It should be noted that these values differed from the normative values. With the proposed therapy with the inclusion of NSAIDs and a magnesium preparation, the excretion of hydroxyproline and its fractions decreased and approached the standard values.

In the group of girls with moderate JUD and signs of CTD who received standard treatment, the content of free and peptide-bound hydroxyproline in the urine significantly decreased by 1.2; 1.18 and 1.22 times relative to the initial parameters, but still significantly exceeded the values of practically healthy girls by 1.52 (P<0.01); 1.42 (P<0.01) and 1.64 (P<0.01) times, respectively, to the above indicators (Table 6).

Table 6 The content of hydroxyproline and its fractions in the urine of girls with moderate UD with signs of CTD during treatment, M±m

Groups	Oxyproline, µmol/day	
	Free	Peptide-bound
Control	18,4±1,34	155,7±13,6
Before treatment	34,54±1,07 [а]	167,33±0,92 [а]
After standard therapy	28,78±0,9 [а,б]	164,63±0,77 [а,б]
After the proposed therapy	20,50±0,47 [б,в]	156,31±0,31 [б,в]

Note: a - the differences are significant relative to the data of the group of healthy girls, b - the differences are significant relative to the data before treatment, c - the differences are significant relative to the values of the comparison group after treatment (P<0.05).

The proposed therapy with the inclusion of NSAIDs and a magnesium preparation contributed to a more pronounced decrease in the studied parameters: the content of free hydroxyproline by 1.68 (P<0.001) and 1.4 (P<0.01) times, peptide-bound hydroxyproline - by 1.68 (P<0.001) and 1.42 (P<0.01) times compared with baseline and comparison group values. The excretion of all hydroxyproline fractions decreased significantly and approached the values of practically healthy individuals.

In the group of girls with severe YD and signs of CTD who received standard treatment, the content of free and peptide-bound hydroxyproline in the urine significantly decreased by 1.21 (P<0.05); 1.28 (P<0.05) and 1.14 times relative to baseline parameters (Table 7). Despite this decrease, all of the above parameters still significantly exceeded the values of practically healthy girls in 2.52 (P<0.001); 2.34 (P<0.001) and 2.72 (P<0.001) times, respectively, of the above indicators.

Table 7 The content of hydroxyproline and its fractions in the urine of girls with severe YD with signs of CTD during treatment, M±m

Groups	Oxyproline, µmol/day	
	Free	peptide-bound
Control	18,4±1,34	155,7±13,6
Before treatment	57,83±0,88 [а]	171,06±0,97 [а]
After standard therapy	47,63±0,76 [а,б]	169,21±4,12 [а,б]
After the proposed therapy	22,11±0,88 [а,б,в]	157,12±6,35 [а,б,в]

Note: a - the differences are significant relative to the data of the group of healthy girls, b - the differences are significant relative to the data before treatment, c - the differences are significant relative to the values of the comparison group after treatment (P<0.001).

The proposed therapy with the inclusion of NSAIDs + magnesium drug with pyridoxine + microdosed monophasic COC and vegetocorrector sulpiride contributed to a more pronounced decrease in the studied parameters: the content of free oxyproline - 2.62 (P<0.001) and 2.15 (P<0.001) times, peptide-bound hydroxyproline - 2.79 (P<0.001) and 2.18 (P<0.001) times compared to baseline and comparison group values. All studied indicators approached the values of practically healthy individuals.

In order to study the long-term results of the impact of our proposed treatment on reproductive function, an analysis of the obstetric and gynecological anamnesis of girls who were 14-17 years old in 2011 after 8 years (22-25 years) of the state of reproductive function was studied.

We have observed and analyzed the reproductive function of 122 girls who were hospitalized in the Andijan Regional Perinatal Center for the period from January to August 2019. Of these, 42 girls with CTD who received the treatment developed by us - the main group, 40 girls with CTD who did not receive treatment - the comparison group, 40 girls - the control group. The prevailing phenotypic manifestations of CTD in the girls we observed were: asthenic type of constitution, underweight in 27 (64.2%) girls of the main group and 31 (77.5%) in the comparison group, hyperelastic skin in 20 (47.6%) %) girls of the main group and 29 (72.5%) in the comparison group, thin skin and thin

hair in 22 (52.3%) girls of the main group and 18 (45%) in the comparison group, teething anomalies in 14 (33.3%) girls of the main group and 12 (30%) in the comparison group, flat feet in 17 (40.4%) girls of the main group and 16 (70%) in the comparison group.

In the main group of mild severity of JD with CTD, there were 12 girls: 2 of them had up to 9 points of CTD criteria, 5 to 14 points, in this regard, they received treatment according to the NSAID + magnesium preparation in the second phase of the menstrual cycle for 6 menstrual cycles.

There were 17 girls with moderately severe degree of JD with CTD: 6 of them had CTD criteria up to 9 points, 8 up to 14 points, 3 over 15 points, in connection with this they received treatment according to the NSAID + magnesium preparation + vegetocorrector + duphaston in the second phase of the menstrual cycle for 6 menstrual cycles.

There were 15 girls with severe JD with CTD: 4 of them had CTD criteria score up to 9 points, 5 up to 14 points and 6 girls had more than 15 points, in this regard, they received treatment according to the NSAID + magnesium preparation regimen from the beginning in the saturating, and then at a maintenance dose + vegetocorrector + microdose COC (ethinyl estradiol 20 mcg and gestodene 75 mcg) for 6 months. Indicators of the obstetric and gynecological history of the examined girls with JD are presented in Table. eight.

As can be seen from the table, in the comparison group, the gynecological history was complicated in every 3-4 women by abnormal uterine bleeding (27.5%) and infertility from 2 to 4 years, and in the main group only in 2 (7.1%). Miscarriage was observed in 15 (37.5%) in the comparison group, which is 3 times less than women in the main group. Toxicosis of the first half of pregnancy occurred in every second comparison group, while in the main and control groups it was observed only in 3 women. Childbirth was complicated by labor dystocia in 11 (27.5%) women and hypotonic bleeding in 9 (22.5%) women in the comparison group, while in the main group it was 3 times less. Varicose veins of the small pelvis were diagnosed during a caesarean section due to the ineffectiveness of labor stimulation after premature rupture of the membranes. Various forms of urinary disorders bothered 9 (22.5) women of the comparison group, which are most likely associated with the state of the pelvic floor and prolapse of the genital organs.

As the analysis of the observation of the outcomes of the implementation of the reproductive function of girls with JUD and CTD, who received the differentiated treatment of JUD with CTD manifestations developed by us, had fewer complications from the obstetric and gynecological anamnesis, and the implementation of their reproductive plans had fewer obstacles.

Table 8 Indicators of obstetric and gynecological history of examined girls with JD

Nosology	Main group n=42		Comparison group n=40		Control n=40	
	n	%	n	%	n	%
Abnormal uterine bleeding	3	7,1	11	27,5	-	-
Infertility from 2 to 4 years	2	4,7	9	22,5	2	5
Physiological childbirth	33	78,5	23	57,5	32	80
Miscarriage	5	11,9	15	37,5	3	7,5
Spontaneous miscarriages	2	4,7	14	35	1	2,5
Toxicosis of the first half of pregnancy	3	7,1	17	42,5	3	7,5
severe preeclampsia	1	2,3	5	12,5	1	2,5
mild preeclampsia	3	7,1	9	22,5	1	2,5
preterm birth	4	9,5	17	42,5	4	10
Premature detachment of a normally located placenta	1	2,3	6	15	-	-
placenta previa	-	-	3	7,5	-	-
Childbirth dystocia	2	4,7	11	27,5	2	5
hypotonic bleeding	3	7,1	9	22,5	-	-
Vaginal tears	4	9,5	13	32,5	3	7,5
Cervical ruptures	-	-	2	5	-	-
perineal tears	2	4,7	7	17,5	-	-
Inferiority of the scar after caesarean section	-	-	3	7,5	-	-
Varicose veins of the small pelvis	2	4,7	7	17,5	-	-
Genital prolapse	-	-	6	15	-	-

Various forms of urination disorders	2	4,7	9	22,5	-	-

Prevention of the consequences of untreated JUD consists in preventing the aggravation of menstrual dysfunction by the type of dysmenorrhea in the absence of pathological changes in the pelvic organs. When carrying out the proposed treatment of JUD in girls with CTD, our goal was to prevent violations of reproductive function and reproductive losses in the future.

Prevention of the development of disorders of connective tissue metabolism is carried out by using complex treatment, including a magnesium preparation, correcting the steroid profile by using duphaston for hypoprogesteronemia, and in the case of hypoestrogenism, by prescribing a low-dose hormonal drug. Carrying out a differentiated approach to the treatment of JUD, taking into account the presence of phenotypic manifestations of connective tissue dysplasia, allows you to correct menstrual function, prevents further disruption of connective tissue metabolism with normalization of the hypothalamic-pituitary-ovarian activity and the implementation of the function of the reproductive system.

Conclusions: 1) the detection of hydroxyprolinuria in girls with UCTD with juvenile dysmenorrhea indicates a violation of the state of collagen in the connective tissue that is part of the ligaments of the pelvic organs

2) juvenile dysmenorrhea in girls with uCTD is a genetically determined condition that manifests itself when exposed to risk factors

3) a differentiated approach to the treatment of JUD, taking into account the presence of phenotypic manifestations of connective tissue dysplasia, makes it possible to prevent further disruption of connective tissue metabolism with normalization of the hypothalamic-pituitary-ovarian activity and the implementation of the function of the reproductive system.

REFERENCES:

1. Gynecology. National leadership. GEOTAR Media. Association of Medical Societies for Quality. 2011.- pp. 428-437
2. Pediatric and adolescent gynecology. Uvarova E. V. - Moscow, 2009. - S. 301-318.
3. Gromova O.A. The multifaceted role of macro- and microelements in the construction of bone tissue / Gromova O.A., Torshin I.Yu., Limanova O.A. // Gynecology. - 2014. - T. 16. - No. 2. - S. 50-56.
4. Gynecological endocrinology and reproductive medicine. Michel von Wolff, Petra Stute per. with him. Under the general editorship of Doctor of Medical Sciences Prof. E.N. Andreeva Moscow MED press-inform.2018 P.96-101
5. Lukina T.S. Evaluation of the hydroxyproline marker and its significance in women with undifferentiated connective tissue dysplasia. Modern Medicine: Current Issues No. 6-7 (41). - 2015. - S. 27-31
6. National recommendations of the Russian Scientific Medical Society of Physicians for the diagnosis, treatment and rehabilitation of patients with connective tissue dysplasia, developed by a group of specialists from the section "Connective tissue dysplasia" of the Russian National Medical Society of Physicians, were approved at the X National Congress of Physicians on October 14-16, 2015. Medical Bulletin of the North Caucasus 2016. V.11 No. 1 - P. 247-248.
7. Ozhogina E. V., Mozes V. G. Quality of life in women with primary dysmenorrhea. // Issues of gynecology, obstetrics and perinatology. - 2016. - No. 1. - P. 42-44
   Optimization of the choice of the method of surgical treatment in patients with complicated forms of genital prolapse / S.N. Buyanova, N.A. Schukina, M.A. Chechneva [et al.] // Russian Bulletin of an obstetrician-gynecologist. - 2012. - No. 6. –c87-91.
8. Orlova V.S., Trushina O.V., Kalashnikova I.V. Connective tissue dysplasia is a factor that exacerbates menstrual pain in adolescence // Journal of Obstetrics and Women's Diseases. - 2018. - T.67. - No. 1. - S. 38-46.
9. Puzyrev, V.P. Pathological anatomy of the human genome / V.P. Puzyrev, V.A. Stepanov. - Novosibirsk: Science. Sib. Enterprise of the Russian Academy of Sciences, 1997. - P. 22. 10.
10. Systematic analysis of the molecular physiological effects of the synergistic effects of iron, manganese and copper on connective tissue /N.V. Kerimkulova, I.Yu. Torshin [et al.] // Reproductive endocrinology. - 2013. - No. 4 (12). – S. 101–110].
11. Trushina O.V., Orlova V.S., Kalashnikova I.V. et al. Physical development and somatic background of adolescent girls suffering from dysmenorrhea combined with connective tissue dysplasia. Series Medicine. Pharmacy. 2018. Volume 41. No. 1. P.36-45
12. Chaika G. V., Lomachuk B. O., Kucherenko O. M. Now look at the etiology of primary dysmenorrhea. (review of the literature) Actual nutrition of pediatrics, obstetrics and gynecology. Obstetrics and gynecology. - 2015. No. 2. - P. 183 - 188.Шараев П. Н. Биохимические методы анализа показателей обмена биополимеров. - Ижевск, 1990. - С. 4-5.
13. F.K. Akhmedov., M.N. Negmatullaeva. The significance of genetic factors and new aspects in predicting preeclampsia (overview)- Thematic journal of microbiology, 2021. 10.5281/zenodo.5081885
14. F.K. Akhmedov. The role of interleukin 10 in the development of preeclampsia: diagnosis and prognosis- British Medical Journal, 2022 Volume-2, No 410.5281/zenodo.6912557
15. Abu Helwa HA, Mitaeb AA, Al-Hamshri S, Sweileh WM. Prevalence of dysmenorrhea and predictors of its pain intensity among Palestinian female university students. BMC Womens Health. 18(1):18. DOI: 10.1186/S12905-018-0516-1. 2018 Jan 15.
16. Bajalan Z, Moafi F, MoradiBaglooei M, Alimoradi Z.Mental health and primary dysmenorrhea: a systematic review. J Psychosom Obstet Gynaecol. 2019 Sep; 40(3):185-194.
17. Yakubova O. A. Effectiveness of Magne V6 in adolescent girls with dysmenorrea. European Conference on Innovations in Technical and Natural Sciences, 12 th May 2014. Vienna, Austria, 2014.-.pp.2-95

18. Yakubova O. A. Stady of Polymorphism of COL1A1 G2046T in Girls with Juvenile Dysmenorrhe depending on the Presence of Connective Tissue Dysplasia in the Uzbek Population. International Journal of Science and Research (IJSR) 2019.-№7.-P.609-610 SJTF-7.426.
19. Yakubova O. A. Impact Of Connective Tissue Dysplasia On The Worsening Of Juvenile Dysmenorrha Flow. Medicine and Low. Impact Factor 5. ISSN:21394-634/ Vol-38-Issue-1-Year-2019.-P.212-220
20. Oltinoy Yakubova, Farida Ayupova, Zainitdin Kamalov, Khabibahon Negmatshaeva, Dilfuzahon Mamarasulova. Role of COL1A1 and G2046t Genes in Uzbeks With Juvenile Dysmenorrhea In The Presence Of Criteria For Undifferentiated Connective Tissue Dysplasia.Journal of Critical Reviews. ISSN- 2394-5125/ Vol 7, Issue 2, 2020.-P.391-394
21. Yakubova O. A. Relationship of connective tissue dysplasia and hypomagnemia in genesis of juvenile dysmenorrhea.//European Medical Health and Pharmaceutical Journal. 2012.- №3-pp.5-6 (14.00.00.№2)
22. Yakubova O. A. Juvenile dysmenorrhea associated with hypomagnezemia and connective tissue dysplasia.//Medical and Health Science Journal, 2012.- №11.- С.85-88(14.00.00.№3)

Якубова Олтиной Абдуганиевна-доктор медицинских наук, доцент, заведующая кафедрой акушерства и гинекологии, неонатологии и эндокринологии Андижанского медицинского института

Исакова Дилноза Бахтияровна - ассистент кафедры акушерства и гинекологии, неонатологии и эндокринологии Андижанского медицинского института

Сулейманова Насиба Адашевна – кандидат медицинских наук, доцент кафедры акушерства и гинекологии, неонатологии и эндокринологии Андижанского медицинского института

Исмаилова Савринисо Султановна - кандидат медицинских наук, ассистент кафедры акушерства и гинекологии, неонатологии и эндокринологии Андижанского медицинского института

Ризакова Дилором Пулатовна ассистент кафедры фармакологии, клинической фармакологии и медицинских биотехнологий Андижанского медицинского института

Эргашбаева Дилрабо Абдурасуловна - кандидат медицинских наук, доцент кафедры акушерства и гинекологии, неонатологии и эндокринологии Андижанского медицинского института