

PROBLEMS OF PEDIATRICS

Analysis of Menstrual Dysfunction in Girls Suffering from Juvenile Idiopathic Arthritis

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Abstract

Juvenile Idiopathic Arthritis (JIA) is the commonest and most debilitating rheumatic disease occurring among children.

Objective: To identify the frequency and nature of the menstrual disorders observed in girls affected with JIA.

Material and Methods: The study included 147 patients of the Rheumatology department of St. Petersburg State Pediatric Medical University's clinic, 58 of who were afflicted with JIA. We used anamnestic, clinical and laboratory methods as well as analysis of the medical records to diagnose this disease.

Results: We examined 58 patients with JIA. Menstrual function was present in 40 girls in the age range of 12 to 17 years among the 58 patients with JIA selected for this study. The average age of menarche was 12.4 ± 2.5 years. Menstrual irregularities were observed in 27 cases (67.5%). Excessive menstruation with regular cycle was observed in 44.4% of the cases; primary oligomenorrhoea and secondary amenorrhoea were detected in 29.6% of the girls and primary dysmenorrhoea in 29.6%.

Conclusions:

- The frequency of the menstrual disorders in girls with JIA is 67.5%. The form associated with excessive menstruation with regular cycle occurs most often.
- The most frequent menstrual disorders were observed in the polyarticular and systemic course of JIA.
- The age at onset, disease duration and use of glucocorticoid therapy affected the nature of the menstrual disorders
- Menstruating girls suffering from JIA require gynecological control to determine the status of menstrual function with the purpose of prevention of reproductive disorders.

Keywords: adolescents; menstrual dysfunction; juvenile idiopathic arthritis.

Introduction

Over the recent years, the health of pregnant women has deteriorated. Thus, 79.8% of pregnant women have medical or obstetric pathology and any one of three children today is born ill [1-3]. An increase in the number of frequently long-term ill children and children with chronic illnesses has been registered [4].

However, according to a survey including 495 adolescents conducted by the Department of Pediatric Gynecology and Women's Reproductive of St. Petersburg State Pediatric Medical University in 2011, 95.9% teenagers rated their health as good or satisfactory [5]. Most often,

it is the children who reflect public opinion on a particular issue. Teachers (n=104) too indicated a similar assessment of the health of their pupils and 82.1% of them believed their pupils were either healthy or relatively healthy [6]. The data collected in this study demonstrate the improper assessment of children's health in the community.

Based on the clinical examination of children and adolescents in the Russian Federation in 2010, only 20% qualified for inclusion in the First Group of health among 13.5 million children learning in schools [7]. In 2012, according to the data released by the Health Committee of the St. Petersburg Government, 56,365 diseases were revealed during the in-depth medical examination conducted among 26,864 fourteen-year-olds. Thus, newly diagnosed diseases were identified in 34.7% of the adolescents examined. Only 5.23% of the children were healthy (Health Group I), 59.59% (Health Group II) had functional abnormalities, and 35.18% (Health Groups III-IV-V) had chronic diseases [7].

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The increase in the number of diseases of the circulatory system, genitourinary system, musculoskeletal system and connective tissue including JIA was marked in the Russian adolescents over the past decade [7].

In light of these findings, the question that obviously rises is what will be the reproductive potential of these prior somatic debilitated women in the future? A conscious rejection of pregnancy, even in a benign disease course, is possible [8].

Juvenile Idiopathic Arthritis (JIA) is the most common type of arthritis affecting children. JIA, an autoimmune disease, is defined by the presence of arthritis for at least six weeks in a child below 16 years of age. The causes of JIA are not well understood. The development of the signs and symptoms of JIA have been attributed to both environmental and genetic influences. The disease is characterized by systemic lesions, recurring pattern, progression of joint destruction and dysfunction syndrome [9-11].

Currently, according to the classification of the International League of Associations for Rheumatology (ILAR), the following types of JIA are highlighted: oligoarticular, polyarticular and systemic onset.

It should be noted that both boys and girls suffer from systemic JIA in equal frequency. An oligoarticular JIA subtype with early onset develops between the ages of 1 and 5 and occurs predominantly in girls (in 85% of the cases). The subtype of the late-onset develops mainly in boys (in 90% of cases) between the ages of 8 and 15 years. The polyarticular variant depending on the presence or absence of the rheumatoid factor is distinguishable as two subtypes, viz., seropositive (developed in the age range of 8-15 years, and again more common in girls (in 80% of the cases)) and seronegative (onset between 1 and 15 years of age, once again developing more frequently in girls (in 90% of the cases)).

JIA is the commonest and most debilitating rheumatic disease occurring among children. The prevalence of JIA among the children in the Russian Federation is 62.3 per 100,000, the primary morbidity being 16.2 per 100,000 individuals. In adolescents, the prevalence of JIA is 116.4 per 100,000 and in children below 14 years of age it is 45.8 per 100,000 [9,10].

The aim of this study was to identify the frequency and nature of the menstrual disorders observed in girls affected with JIA.

Material and Methods

Between 2011 and 2012, the pediatric and adolescent gynecologist of the St. Petersburg State Pediatric Medical University's clinic examined 1225 patients, among who 147 girls were treated in the Rheumatology department.

Menstrual dysfunction occupies the first place in the structure of gynecological morbidity in the patients examined in the Rheumatology department.

Girls suffering from JIA (n=58, 39.5%) required treatment by the children's gynecologist most often.

Menstrual function was present in 40 of the 58 girls in the age group of 12-17 years suffering from juvenile idiopathic arthritis. Menstrual irregularities were observed in 27 cases

(67.5%). It is these patients who constitute the main group in this study (n=27).

According to the medical history, most of these girls had experienced childhood infections, frequent viral respiratory infections (19/70.4%), upper respiratory tract pathology (20/74.1%) and gastrointestinal disorders (13/48.1%). In perinatal history, pregnancy complications (the threat of pregnancy termination, early toxemia) were revealed in 66.7% of the cases and birth complications (preterm labor, fast and breech delivery, premature amniorrhea, cord entanglement) in 63% of the cases.

The average age of menarche was 12.4±2.5 years. Significantly, 48.1% of these patients had visited a gynecologist due to painful menstruation and 25.9% of the patients had excessive menstruation while 40.7% of the patients experienced rare and scanty menstruation.

The diagnosis of JIA was performed by the pediatric rheumatologist according to the ILAR criteria. Information from the patients and parents, data collection and analysis were conducted in accordance with the Russian National Guidelines.

In our main group of patients, polyarticular JIA was visible in 66.7% of the cases, oligoarticular JIA in 25.9% of the cases and systemic JIA in 7.4% of the cases. Eye disorders were observed in 14.8% of the cases. The first or second degree of disease activity was noted in 37% of the cases. In addition 7.4% of the children were seropositive on rheumatoid factor and 11.1% on HLA-B27 antigen.

Stage I was detected on the x-ray in 51.9% of the cases, stage II in 29.6%, stage II-III in 11.1% and stage III in 3.7% of cases. Class I of functional status was identified in 37.0% of the cases while Class I-II was found in 25.9% of the cases, Class II in 18.5% of the cases, and Class O in 18.5% of the cases.

Results were statistically processed using the software package Statistica 6.0. The mean (M) and standard error of the mean (SEM) were calculated. For data with normal distribution, inter-group comparisons were performed using Student's t-test. The Mann-Whitney (U Test) was used to compare the differences between the two independent groups (for non-parametric data). A value of $P < 0.05$ was considered statistically significant. Group comparisons with respect to categorical variables are performed using chi-square tests.

Results

Thus, menstrual irregularities were identified in 67.5% of the cases among the 40 JIA patients with menstrual function. Among the main group of patients, excessive menstruation with regular cycle was more common and was observed in 40.7% of the cases. During the investigation, four of these patients were afflicted with pubertal uterine bleeding.

A combination of dysmenorrhea, excessive menstruation, and oligomenorrhea was registered in two patients. No features of gynecological status were observed in all the patients examined. Discrepancy of the endometrium to the day of the menstrual cycle was identified in 37% of the patients by ultrasound investigation of the pelvic organs. Ovarian changes

characterizing the phase of the cycle were not detected in 29.6% of the cases. Hypoplasia of the uterus or violation of its development was noted in 25.9% of the cases. Hypoestrogenic status was identified in 29.6% of the patients.

During the study, we analyzed the relationship between the characteristics of the arthritis (age at onset, disease duration, JIA variants, disease activity, the presence of anatomical and functional disorders, treatment administered) and menstrual cycle dysfunction.

The average age at onset of JIA in girls with primary dysmenorrhoea was 6.7 ± 6.3 years, with excessive menstruation - 8.6 ± 6.5 years and with oligomenorrhoea - 3.3 ± 5.2 years (Table 1).

Table 1

The average age at onset of JIA and menstrual cycle dysfunction

Age	Painful menstruation	Excessive menstruation	Rare menstruation
	(n=8)	(n=11)	(n=8)
Neutral period including	4 (50%)*	3 (27.3%)	5 (62.5%)*
10-13 years	2	2	3
6-8 years before menarche	2	1	2
Prepubertal period including	1 (12.5%)	5 (45.5%)*	2 (25%)
5 years	-	1	-
3 years	-	1	-
2 years	1	2	2
1 years before menarche	-	1	-
Pubertal period including menarche's period	1 (12.5%)	6 (54.5%)*	1 (12.5%)
1 year	2	2	1
2 years after menarche	1	4	-
Mean age	6.7 ± 6.3	8.6 ± 6.5	3.3 ± 5.2

* - $p < 0.05$

Taking in account the period of sexual maturity, we identified certain patterns. The age at onset of JIA in girls with excessive menstruation concurred with the prepubertal and pubertal periods. Painful and rare menstruation was observed in girls with onset of disease during a neutral period.

Analyzing the possible association of menstrual cycle irregularity with JIA duration, we discovered that the debut of the disease occurred at the age of 9-10 months or at the end of the first year of life in 14.8% of the cases. In fact, 22.2% of patients became ill between the ages of 2 and 4 years, 14.8% of the patients – at the age of 5 to 6 years (neutral period), 22.2% – between 10 and 11 years (prepubertal period) and 25.9% at the age of 12-15 years of age (pubertal period). In this connection, all the patients were categorized into the following groups in accordance with the duration of the disease: 2-6 years, 7-11 years and 13-16 years. We analyzed the features of the menstrual dysfunction in each group (Table 2).

When the disease duration ranged from 2 to 6 years, excessive menstruation with regular cycle was the most frequent occurrence. Thereafter, puberty-related uterine bleeding was identified in two patients during the first observation and in one of case against a background of polymenorrhoea.

Table 2

The features of the menstrual dysfunction on the duration of JIA

Menstrual disorders	Duration of JIA		
	2-6 years (n=12)	7-11 years (n=8)	13-16 years (n=7)
Painful menstruation age at onset – 7.7 ± 6.3 (yr)	4 (33.3%)	2 (25%)	2 (28.6%)
Excessive menstruation age at onset – 8.6 ± 6.5 (yr)	7 (58.3%)*	2 (25%)	2 (28.6%)
Rare menstruation age at onset – 3.3 ± 5.2 (yr)	1 (8.3%)	4 (50%)*	3 (42.9%)*

* - $p < 0.05$

After 7-11 years of the disease, painful and heavy menstruation was identified equally in 25% of the cases. Primary dysmenorrhoea combined with the primary oligomenorrhoea was revealed in one case. Notably, rare menstruation was the most frequent occurrence in this group. These menstrual dysfunctions were expressed as forms of primary oligomenorrhoea and secondary amenorrhoea.

When the duration of the disease was 13-16 years, painful and excessive menstruation was identified with the same frequency and primary oligomenorrhoea was observed in 42.9% of the cases.

The associations between menstrual dysfunctions and JIA characteristics are presented in Table 3.

Table 3

The associations between menstrual dysfunctions and JIA characteristics

Characteristic	Painful menstruation (n=8)	Excessive menstruation (n=11)	Rare menstruation (n=8)
Clinical course of JIA			
Polyarticular	5 (62.5%)*	7 (63.6%)*	6 (75%)*
Oligoarticular	3 (37.5%)	2 (18.2%)	2 (25%)
Systemic	-	2 (18.2%)	-
Degree of disease activity			
0	2 (25%)	1	2 (25%)
0-I	1	1	-
I	3 (37.5%)	3 (27.4%)	4 (50%)*
II	2 (25%)	6 (54.5%)*	2 (25%)
Rheumatoid factor			
(+)	1 (12.5%)	-	1 (12.5%)
(-)	7 (87.5%)*	11 (100%)*	7 (87.5%)*
HLA-B27 (+)	2 (25%)	-	1 (12.5%)
Stage of x-ray changes			
0	1		
I	4 (50%)*	6 (54.5%)*	4 (50%)*
II	3 (37.5%)	3 (27.4%)	2 (25%)
II-III	-	2 (18.2%)	1
III	-	-	1
Class of functional disorders			
0	2 (25%)	2	1
I	4 (50%)*	3 (27.4%)	3 (37.5%)
I-II	-	5 (45.5%)*	2 (25%)
II	2 (25%)	1	2 (25%)

* - $p < 0.05$

Most violations of the menstrual function were associated with activities 1 and 2 of the polyarticular type of JIA. Here, the excessive menstruations with regular

menstrual cycle were dominant, primary oligomenorrhoea ranked second, whereas painful menstruation was in third place. When the oligoarticular form was observed, primary dysmenorrhoea ranked first, excessive menstruation was in the second place and primary oligomenorrhoea was in the third place. In the systemic type of JIA, only the form of excessive menstruation with the regular menstrual cycle was observed. However, significant differences between the different forms of the menstrual dysfunction were not found (it was probably connected with a few number of patients), which prevents us from drawing more detailed conclusions and requires further observation.

The following agents were used in the treatment of JIA viz., methotrexate, glucocorticoids, immunosuppressive agents, basic anti-rheumatic drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and the preparations for anti-tumour necrosis factor therapy. No significant differences in the treatment received by the patients in the different groups of menstrual dysfunction were observed. We analyzed the nature of the menstrual dysfunction in accordance with the therapy. According to anamnesis, during primary dysmenorrhoea, specific therapy (methotrexate, glucocorticoids or immunobiotherapeutic agents) was started equally during the prepubertal and pubertal periods. Methotrexate was used only during the prepubertal period (the average duration of the treatment was 3.2 ± 3.0 years). The reduction in the painful menstrual syndrome in the non-steroidal anti-inflammatory drug course (particularly as the monotherapy of the NSAIDs) confirmed the diagnosis of primary dysmenorrhoea. In the case of excessive menstruation, methotrexate therapy was conducted in the prepubertal period in 18.2% of the patients. The greatest impact of the drug therapy (Methotrexate (average duration of therapy - 3.4 ± 3.0 years), corticosteroids, immunobiotherapy) was found for the pubertal form. It should be noted that the two cases of pubertal uterine bleeding occurred exactly during the time of the glucocorticoid treatment. In the cases of rare menstruations, in 50% of the cases, methotrexate therapy was performed in the prepubertal period. In the current time, half of these patients continued the therapy with methotrexate, Sandimmune and immunobiotherapy agents (average duration of therapy - 2.7 ± 2.3 years). Only these patients were prescribed the glucocorticoid therapy in the prepubertal period (pulse therapy, prednisolone at continuous mode, Diprosan).

Discussion

In the structure of the gynecological pathology diagnosed in patients being treated in a multidisciplinary clinic of St. Petersburg State Pediatric Medical University menstrual disorders included 44% of all disorders, with inflammatory diseases constituting 37.9%, and non-inflammatory diseases 14.2%, besides others (12.7%) (Table 4). Many of the girls examined had several gynecological diseases.

Evaluation of the menstrual disorders in girls with chronic extragenital pathology requires special attention. We noted the difference in the characteristics of menstrual disorders in various somatic diseases. Therefore, long and heavy menstrual bleeding were most often detected in girls

Table 4

The structure of gynecological pathology among patients of the St. Petersburg State Pediatric Medical University's clinic

Variable	Nephrology department	Endocrinology department	Gastroenterology department	Rheumatology department
Inflammatory diseases	46.4-59%	32.2-44.4%	27.8-41.1%	29.2-48.5%
Menstrual dysfunction	30.8-34.5%	46.2-75.9%	38.3-53.2%	56.9-63.3%
Non-inflammatory diseases	16.4-23.9%	4.7-7.7%	8.9-13.7%	10.8-16.3%

suffering from connective tissue disease, long and painful menstruation in girls with diseases of the gastrointestinal tract, painful menstruation in diseases of the urinary system; however, rare and scanty menstruation was associated with an endocrine pathology.

The results of our study revealed the association of JIA with reproductive disorders in the form of menstrual dysfunction in 62.5% of the cases. Herewith, excessive menstruation with regular menstrual cycles occurred more frequently and was observed in 40.9% of the patients. The average age at JIA onset in girls with excessive menstruation was seen in the prepubertal period (8.6 ± 6.5 years). However, the most excessive menstruation was associated with disease duration up to six years (in 58.3% of the cases). Most violations of menstrual function including the excessive menstruations with regular menstrual cycle were associated with activities 1 and 2 of the polyarticular type of JIA. Primary oligomenorrhoea and secondary amenorrhoea were associated with the debut of the disease onset during a neutral period (average age at onset of JIA - 3.3 ± 5.2 years) and the duration of the disease over a seven-year-period (in 46.7% of the cases). A clarification of the dependence of menstrual disorders on the age of onset, duration and characteristics of JIA warrants further observation.

No effects of the JIA's therapy were seen on the nature of menstrual dysfunction, although it should be noted that the two cases (18.2%) of puberty uterine bleeding occurred during the course of glucocorticoid therapy. The occurrence of rare menstruation was observed in the group of patients treated with glucocorticoids during the prepubertal period (3/37.5%).

Despite the fact that the menstrual irregularities were described in information to any glucocorticoid drugs, the correlation between the type of dysfunction with age at onset and the duration of therapy also requires further observation.

The study conducted enables us to draw the following **conclusions**:

- The frequency of the menstrual disorders in girls with JIA is 67.5%. The form associated with excessive menstruation with regular cycle occurs most often.
- The most frequent menstrual disorders were observed in the polyarticular and systemic course of JIA.
- The age at onset, disease duration and use of glucocorticoid therapy affected the nature of the menstrual disorders.
- Menstruating girls suffering from JIA require gynecological control to determine the status of menstrual function with the purpose of prevention of reproductive disorders.

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