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Noncytotoxic-Related Primary Ovarian Insufficiency in Adolescents: Multicenter Case Series and Review

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Abstract

Study Objective: Primary ovarian insufficiency (POI) in adolescents not due to cytotoxic therapy has not been well studied. Causes of POI have been described in adults, but adolescents might represent a unique subset necessitating a targeted approach to diagnosis, workup, and treatment. We sought to better characterize adolescent POI through a descriptive multicenter study.

Design: Case series of patients with POI.

Setting: Six tertiary care institutions.

Participants: Patients presenting from 2007 to 2014 aged 13-21 years diagnosed with noncytotoxic POI, with exclusions for those who received gonadotoxic therapy, with 46XY gonadal dysgenesis, or lack of evidence of hypergonadotropic hypogonadism on chart review.

Interventions: Review and data extraction of records identified according to International Classification of Diseases Ninth or Tenth Revision codes.

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Main Outcome Measures: Data were analyzed for signs and symptoms, workup, and treatments. Complete workup was on the basis of American College of Obstetricians and Gynecologists guidelines. Characteristics of patients with POI who presented with delayed puberty/primary amenorrhea vs secondary amenorrhea were compared.

Results: One hundred thirty-five records were identified. Those who had received cytotoxic therapy (n = 52), 46XY gonadal dysgenesis (n = 7), or on review did not have POI (n = 19) were excluded. Of 57 remaining cases, 16 were 45X, 2 had galactosemia, and 4 had X-chromosome abnormalities. Most did not undergo full etiologic evaluation. Girls diagnosed after primary amenorrhea/delayed puberty were less symptomatic and more likely to receive an estrogen patch than those diagnosed after secondary amenorrhea.

Conclusion: Noncytotoxic POI in adolescents is an uncommon condition with, to our knowledge, only 64 cases in 6 institutions over 7 years. These patients might not undergo complete etiological workup. Aside from 45X, the most common etiologies were X-chromosome abnormalities or galactosemia.

Keywords

Primary ovarian insufficiency; Amenorrhea; Hormone replacement therapy; Adolescents; Noncytotoxic

Introduction

Primary ovarian insufficiency (POI) is the depletion or dysfunction of ovarian follicles with cessation of menses before age 40 years per American College of Obstetricians and Gynecologists (ACOG) guidelines.¹ The prevalence of POI ranges from 1 in 100 to 1 in 10,000 for women aged younger than 40 years with increasing prevalence at each decade of life and is specifically uncommon in adolescents.^{2–6} Causes of POI in previously reported series include Fragile X-associated disorders, autoimmune oophoritis, enzyme deficiencies, genetic syndromes, and chromosomal anomalies, galactosemia, and gonadotoxic treatments, along with a large cohort due to idiopathic etiology.⁷ It is unclear whether the etiologies of POI in adolescents are similar to those in adult women.⁸

The most common cause of POI in adolescents is gonadotoxic therapy.^{9,10} There are few studies that have examined the noncytotoxic agent (NCA)-related causes of POI in adolescents.^{3,6,8} The workup for adolescent patients with POI has been described but has been inconsistently applied.¹¹ The treatment for adolescents with POI is also heterogeneous.^{12,13} Improved understanding of the unique subset of adolescents with NCA-related POI might not only reduce delays in diagnosis and treatment but also improve patient and family counseling. The present is a multicenter descriptive study of adolescents with noncytotoxic-related POI. Our primary aim was to describe the evaluation, underlying diagnosis, and management of POI in adolescents. Our overall hypothesis was that noncytotoxic diagnosis, causes, and management of POI in adolescents might differ from that of adult POI. A secondary hypothesis included that patients with NCA POI represent a unique subset even among the adolescent POI population that often is incompletely recognized by providers. Because of the variation in practice guidelines as we began data collection, our tertiary

hypothesis was developed that standards of diagnosis and care for these patients was lacking so increased provider awareness of the diagnosis might be needed to elucidate etiologies before treatment.

Materials and Methods

Subjects

We defined POI according to the ACOG definition of either primary amenorrhea/delayed puberty without menses or secondary amenorrhea in adolescents for 3 consecutive months with 2 follicle-stimulating hormone (FSH) levels greater than 40 mIU/mL repeated randomly twice at least 1 month apart.^{1,8} For this analysis, if a patient had at least 1 FSH level greater than 40 mIU/mL and an International Classification of Diseases Ninth Revision (ICD-9) or Tenth Revision (ICD-10) diagnosis, they were included in the analyses. Inclusion criteria were all female subjects age 13-21 years with POI identified using ICD-9 (256.39, 259.31) and ICD-10 codes for POI (E28.39, E28.0, E28.3, E28.31, E28.310, E28.319) at 6 institutions across the United States. These subjects presented to Texas Children's Hospital in Houston, Texas, American Family Children's Hospital and/or University of Wisconsin Health Center System in Madison, Wisconsin, Children's Mercy Hospital in Kansas City, Missouri, and Children's National Health System and/or MedStar Washington Hospitals Center in Washington, DC between 2007 and 2014. Exclusion criteria were history of gonadotoxic treatment, 46XY gonadal dysgenesis, or lack of POI on record review. Institutional Review Board approval was granted by each individual institution with Texas Children's Hospital as the primary site.

One hundred thirty-five patients were identified with the included ICD-9 and ICD-10 codes. Nineteen were excluded for incomplete documentation and 7 were excluded for 46XY gonadal dysgenesis. Fifty-seven patients met inclusion criteria for diagnosis of NCA POI (Fig. 1). Forty-five without Turner syndrome were included in a subgroup analysis related to differences between primary amenorrhea/delayed puberty without menses vs secondary amenorrhea. A separate subgroup analysis included 41 who presented without X chromosome abnormalities.

Study Design

This was a case series with data obtained from each institutions' electronic medical record. Diagnostic characteristics and patient evaluations were recorded in REDCAP database for all patients with documented NCA POI, as shown in Figure 1. Presenting signs and symptoms, POI etiologies, workup, and treatment were assessed in all patients (Tables 1 and 2). Accounting for nonuniformity of available data, all researchers extracted information according to evaluation criteria on the basis of ACOG recommendations for initial workup and expanded to assess for other conditions.¹

Statistical Analyses

Descriptive statistics were used to evaluate age at diagnosis, FSH value, and Tanner stage at start of treatment according to group. Results were presented as mean $\pm$ SD. POI workup and treatment modalities were analyzed. Subgroup analyses included: (1) evaluation of

primary amenorrhea/delayed puberty without menses and secondary amenorrhea presentations and treatment; and (2) workup and treatments of those presenting without X chromosome abnormalities. Patients with Turner syndrome who were diagnosed with POI prepubertally were excluded from these analyses. A value of $P < .05$ was considered to be statistically significant.

Results

The mean age at diagnosis was 16.2 years for all diagnosed with NCA POI and 14.7 years for girls who presented with primary amenorrhea/delayed puberty without menses. Most patients did not receive full evaluation. Specifically, 22% (9 of 41) of patients did not undergo a second FSH analysis. Additionally, there was limited endocrinology workup, including autoantibodies or anti-mullerian hormone (AMH), in this population. Of note, both of the 2 patients with abnormal galactose tests had previously diagnosed galactosemia so no new diagnoses of galactosemia as the etiology of POI were made in this patient population. The next most commonly performed aspect of workup after FSH and estradiol was the dual-energy x-ray absorptiometry (DXA) scan, which only 36.6% (13 of 41) obtained. Incidence of each aspect of POI workup, including lab work, imaging, and Tanner staging are shown in Table 2. Progression of Tanner staging from initiation of estrogen therapy to 1 year of treatment is shown in Figure 2.

Those who presented with primary amenorrhea/delayed puberty without menses described no symptoms whereas of those who presented with secondary amenorrhea 20% (7 of 33) had hot flushes, 20% (7 of 33) described mood changes, and 2.9% (1 of 33) complained of vulvovaginal atrophy before diagnosis.

Those who presented with primary amenorrhea/delayed puberty without menses at the time of POI diagnosis presented with average breast Tanner stage of 2.25 and pubic hair Tanner stage of 2.5, which progressed after 1 year of estrogen treatment to breast Tanner stage of 3.6 and pubic hair Tanner stage to 2.67. Of the 6 patients who presented with primary amenorrhea/delayed puberty without menses, all 6 patients received treatment with an estrogen patch but then 2 of 6 were given combined oral contraceptive pill, 2 of 6 received estrogen vaginal cream, 2 of 6 received medroxyprogesterone acetate, and 1 of 6 were also given conjugated estrogen tablets (Fig. 3).

Of those who presented with secondary amenorrhea at the time of POI diagnosis, the patients presented with average breast Tanner stage of 2.95 and pubic hair Tanner stage of 3.46, which progressed after 1 year of estrogen treatment to breast Tanner stage of 3.75 and pubic hair Tanner stage of 3.75. Of the 33 patients who presented with secondary amenorrhea and no known X chromosome abnormality many received multiple forms of hormonal treatment, including 22 of 33 treated with oral combination pills, 3 of 33 who received estrogen vaginal cream, 4 of 33 who received medroxyprogesterone acetate, and 22 of 33 (53.7%) who received conjugated estrogen via patch (14 of 33) or tablets (4 of 33; Fig. 3). Additionally, 2 of 33 patients who presented with secondary amenorrhea and POI did not receive hormonal treatment.

For the hormonal treatments for those with primary amenorrhea/delayed puberty without menses and secondary amenorrhea, the doses varied on the basis of formulation, provider preference, and included estrogen patches prescribed for in hormone replacement alone and or contraception formulations. The use of estrogen patches was significantly higher for those who presented with primary amenorrhea/delayed puberty without menses ($P = .014$) compared with those with secondary amenorrhea.

In the subgroup analysis of patients who presented without X-chromosome abnormalities, it was found that only 36.6% (15 of 41) had a DXA scan at diagnosis and 17.1% (7 of 41) had a follow-up DXA scan 1 year after initiation of hormonal treatment. There was no significant change in z-scores (total body z-score improved from a mean of -1.27 to -0.74 , lumbar spine z-score improvement from -1.77 to -1.3 , and stable hip z-score of -0.71 to -0.74).

Discussion

In this study, we present, to our knowledge, the largest multisite case series of adolescent noncytotoxic POI to date. Although this study began with an aim to compare the differences between adolescent and adult POI, the more salient findings were ultimately that there was great variability in workup and care within the adolescent population. Thus, although cytotoxic-related etiologies have been characterized in adolescents, NCA-related causes have been poorly described. The main findings of this study include incomplete workups limiting determination of etiology of NCA POI. This finding is consistent with previous work on this subject.^{2,11} Compared with etiologies of noncytotoxic exposure-mediated POI in adults, the most common etiologies for POI in this study were genetic or idiopathic diagnoses, although with a complete workup potentially other etiologies would be elucidated. Chief genetic etiologies found in our study population were X-chromosome abnormalities. This finding is consistent with previous research on POI in adolescents.^{2,8,11,14,15} Gonadal dysgenesis, including Turner syndrome, is an important cause of amenorrhea and POI. In fact, up to 50% of adolescents who present with amenorrhea and POI are found to have an abnormal karyotype.⁸ Adult studies have also identified autoimmunity and fragile X mental retardation 1 (FMR1) premutations as common etiologies for POI. Our data suggest a low frequency of testing for these conditions in adolescents and a low prevalence in this group. Nonetheless, our study is consistent with the review by Gordon et al, who concluded that chromosomal abnormalities appear to be associated with POI starting at an early age (ie, in adolescence).¹¹

As stated, one of the most significant findings in this study was the notable variability in diagnostic workup for POI in almost all of our subjects. The ACOG committee opinion for POI in adolescents and young women was released in 2014¹ and might facilitate more uniform workups in the future so that the findings in this study of incomplete workups might decrease. However, POI is a heterogeneous disease requiring physician awareness to presentation variability especially in adolescents.¹ Although the uniform committee opinion was not published during the time that the patients in this study presented, the recommendations for POI workup were available throughout the literature. Our study showed that up to one-third of patients did not have an evaluation for the basic diagnostic

criteria for POI. Adult studies and the ACOG guidelines recommend performing a complete workup to guide management.^{1,5,7,12,16} Although oligomenorrhea and abnormal uterine bleeding can be a normal presentation in the first 3 years post menarche until the hypothalamic-pituitary-gonadal axis matures, amenorrhea longer than 90 days is the 95% percentile for cycle length even within the first year after menarche.² Therefore, investigating the cause in adolescent girls who experience 90 days of amenorrhea or more is recommended.^{2,11}

Variability in diagnostic workup in adolescent POI might also delay diagnosis and treatment. Girls with POI are existing in a hypoeurogenic state that increases their risk for osteopenia at an age when bone mineralization should be at a peak.^{1,7,17,18} This risk has been documented in previous studies and can be minimized by early introduction of estrogen replacement.^{11,13,19,20} Additionally, dependent on the etiology of the POI, fertility preservation options might be available with early referral and should be discussed.²¹

As reflected by the lack of consensus on hormone treatment modalities and regimens for girls and adolescents with POI,^{13,19} the subjects in our study were treated with a wide variety of hormonal therapy combinations. The most common treatment was with combined oral contraceptives (61.5%) or estrogen patch (51.3%). Subjects with primary amenorrhea/delayed puberty without menses received estrogen patches significantly more often than those diagnosed with POI in association with secondary amenorrhea.^{1,12,13} This finding is consistent with recommendations to initiate low-dose transdermal estrogen and titrate to estrogen levels physiologic for age (26-165 pg/mL) and on the basis of phenotypic, clinical signs of estrogenization, slowly to aid in optimal bone mineralization and gradual development of secondary sexual characteristics.^{1,2,13,20,22} In light of recent studies that have suggested superiority of transdermal estrogen for bone mineralization, differential treatment in patients who present with primary amenorrhea/delayed puberty without menses vs secondary amenorrhea might have long-term effects on bone health.^{7,11,19} In the current study, only 15 subjects (36.6%) had at least 1 DXA scan performed. Although clear consensus for timing and frequency of bone mineral density measurement is still debated, closer monitoring of bone density is warranted in adolescents with POI.¹⁷⁻²⁰ The variation in hormone treatments and workup might affect patient health outcomes long-term, which we would recommend as a topic for future study.

There are multiple strengths and limitations to this study. This study comprised patient visits from 6 different institutions around the United States. This multicentered approach provides a more complete picture of national trends in adolescent POI presentation, workup, and management. We also used many redundant ICD-9 and ICD-10 codes to account for variability in clinician assessment, diagnosis, and coding. This approach allowed for assessment of rare conditions accounting for POI. However, it is possible that physicians used less specific codes, such as for amenorrhea, other ovarian dysfunction, or unspecified ovarian dysfunction, and therefore would have been missed in our analysis. Limitations to the multicenter and retrospective approach include institutional and regional referral patterns, nonuniformity of workup protocols, and recordkeeping with multiple data extraction personnel. We specifically do not have data available as to the clinical thought process for why certain tests, such as a second FSH level or autoimmune antibodies, were

excluded from each patient's evaluation nor the dosage of the estrogen patches nor the reasoning behind hormone therapy choice for those who were given oral contraceptive pills vs patches or conjugated estrogens vs not offered hormone replacement therapy. To aid in uniformity of data extraction with consideration for potential variation in available results and data, all researchers used the same specific question prompts in the REDCAP database. The researchers documented any results noted in each subject's chart to maximize information on workup and treatment available.

Nonetheless, these data represent, to our knowledge, the largest to date multiregional descriptive study on POI in an adolescent population. The findings of our study suggest inconsistencies with regard to diagnostic evaluation of this population (specifically, lack of concurrent genetic and autoimmune testing) as well as inconsistent treatment and follow-up. Therefore, we would like to use this study as a call to action to standardize clinical evaluation in an effort to improve patient outcomes. This is especially pertinent in rare conditions such as noncytotoxic POI to allow for quality improvement purposes and facilitate future prospective research. We would recommend that all practitioners working up adolescents with suspected POI meet the minimum ACOG recommendations for determination of the diagnosis including 3 months of amenorrhea, 2 levels of FSH and estradiol drawn at least 1 month apart, prolactin, and thyroid function tests plus karyotype, fragile X mental retardation 1 (FMR1) premutations, adrenal antibodies, and pelvic ultrasound if the initial lab tests confirmed POI.¹ Additionally, our findings support the notion that adolescent POI is very rare and represents a unique subset of women with ovarian insufficiency, with the most common etiology being genetic disorder. As with other rare conditions, future prospective registries might allow us to better characterize this condition. More rigorous prospective and genomic studies are warranted to further evaluate etiologies and optimal treatment modalities.

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Fig. 1.
Primary ovarian insufficiency (POI) etiology distribution among patients identified across 6 institutions. FSH, follicle-stimulating hormone.

Fig. 2.

Tanner stages of breast (A) and (C) and pubic hair (B) and (D) for patients with primary amenorrhea/delayed puberty without menses (A) and (B) and secondary amenorrhea) and (D) and primary ovarian insufficiency at initiation and 1 year into hormone replacement therapy. Before starting estrogen therapy, 50% of those with primary amenorrhea/delayed puberty without menses and 45% of those with secondary amenorrhea did not have breast Tanner staging. After 1 year of treatment, 83% of those with primary amenorrhea/delayed

puberty without menses did have a breast Tanner stage recorded but 75% of those with secondary amenorrhea did not have a breast Tanner stage reported.

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Fig. 3.

Treatment modalities for patients with idiopathic primary ovarian insufficiency who presented after primary amenorrhea/delayed puberty without menses vs secondary amenorrhea. Use of an estrogen patch was the only significant difference in treatments. OCP, oral contraceptive pill.

Table 1

Demographic Characteristics Including Karyotype Results of All Patients with ICD-9 and ICD-10 Codes for Noncytotoxic POI

Characteristic	Value
Age at diagnosis, years	16.19 (range, 13-21)
Karyotype, n (%)	
46 XX	31 (48.4)
46XX with mutations *	4 (6.3)
45X or 45X,46XX mosaic Turner's Syndrome	16 (25)
45X,46XY mosaic gonadal dysgenesis	7 (10.9)
Not obtained	7 (10.9)

ICD, International Classification of Diseases; POI, primary ovarian insufficiency. Patients with 45X,46XY mosaic gonadal dysgenesis were later excluded from further evaluation.

* One patient each with 45X [17],/46,X, del (x)(p11.1)(13); 46XX/46XX, dup (x)(q13); and 46XXDERX, 6XP 11.1 q21.1 diagnosed postpubertally. One patient with 46X, t(X;1)(q21.3;q23) diagnosed prepubertally.

Table 2

Prevalence and Results of POI Workup Components Performed in Patients Who Presented without Known X-chromosome Abnormalities (N = 41)

Variable	n, (%)	Mean $\pm$ SD
Laboratory Findings		
Initial FSH, IU/L	38 (92.7)	80.65 $\pm$ 39.50
Second FSH value at 3 months, IU/L	32 (78)	76.08 $\pm$ 39.00
Initial estradiol, pg/mL	26 (63.4)	26.03 $\pm$ 28.85
Second estradiol at 3 months, pg/mL	30 (73.2)	23.01 $\pm$ 32.18
FMR1 copy mutation, repeats	18 (43.9)	All normal
AMH level, ng/mL	12 (29.3)	0.70 $\pm$ 1.13
Galactose level, U/g Hb	4 (9.8)	50% in abnormal range—both with previously diagnosed galactosemia
17-OH progesterone	11 (26.8)	100% Normal range
Adrenal antibodies	22 (53.6)	100% Negative
Ovarian antibody	10 (24.4)	100% Negative
Inhibin B level, pg/mL	5 (12.2)	Median, 10 (range, 2-30)
Imaging findings		
Bone age		
Obtained at diagnosis	9 (22)	
Not obtained	32 (78)	
Total body Z-score		
Initial DEXA	12 (29.3)	
DEXA at 1 year	5 (12.2)	
Lumbar spine Z-score		
Initial DEXA	15 (36.6)	
DEXA at 1 year	7 (17)	
Hip Z-score		
Initial DEXA	8 (19.5)	
DEXA at 1 year	4 (9.8)	
Femur Z-score		
Initial DEXA	6 (14.6)	
DEXA at 1 year	3 (7.3)	
Pelvic ultrasound		
Initial volume	26 (63.4)	
Follow-up volume	2 (4.9)	
Tanner staging at diagnosis		
Breasts		
Initial staging performed	23 (56.1)	2.74 $\pm$ 1.03
Repeat 1 year post diagnosis	18 (43.9)	3.17 $\pm$ 1.07
Average change at 1 year		0.53 $\pm$ 1.04
Pubic Hair		
Initial staging performed	15 (36.6)	3.6 $\pm$ 0.8

Variable	n, (%)	Mean $\pm$ SD
Repeat 1 year post diagnosis	13 (31.7)	3.58 $\pm$ 0.86
Average change at 1 year		0.18 $\pm$ 0.94

AMH, anti-mullerian hormone; DEXA, dual-energy x-ray absorptiometry; FMR1, fragile X mental retardation 1; FSH, follicle-stimulating hormone; Hb, hemoglobin; 17-OH, 17-hydroxyprogesterone; POI, primary ovarian insufficiency.