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Original article

# Primary Ovarian Insufficiency Nationwide Incidence Rate and Etiology Among Israeli Adolescents

Noah Gruber, M.D., M.Sc. [a,b,*], Shir Kugler, M.D. [a,b], Liat de Vries, M.D. [b,c], Avivit Brener, M.D. [b,c], Amnon Zung, M.D. [d,e], Ori Eyal, M.D. [b,f], Marianna Rachmiel, M.D. [b,g], Ilana Koren, M.D. [h], Yardena Tenenbaum-Rakover, M.D. [i,j], Eli Hershkovitz, M.D. [k], Zohar Landau, M.D. [b,l], Meirav Oren, M.D. [m], Alon Eliakim, M.D. [b,n], David Zangen, M.D. [e,o], Alina German, M.D. [p], Hussein Majdoub, M.D. [h], Kineret Mazor-Aronovitch, M.D. [a,b], Dalit Modan-Moses, M.D. [a,b], Yonatan Yeshayahu, M.D. [a,b], Larisa Naugolni, M.D. [g], Yael Levy-Shraga, M.D. [a,b], Michal Ben-Ami, M.D. [a,b], Gherta Brill, M.D. [q], Nehama Zuckerman-Levin, M.D. [j,r], Floris Levy-Khademi, M.D. [e,s], Carmit Avnon-Ziv, M.D. [e,s], Dov Tiosano, M.D. [j,m], Shira Harel, M.D. [t], Einat Kedem, M.D. [l], Anat Segev-Becker, M.D. [f], Yehuda Shoenfeld, M.D., Mc.A.C.R. [b,u], and Orit Pinhas-Hamiel, M.D. [a,b]

[a] *Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel*
[b] *Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel*
[c] *The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petach Tikva, Israel*
[d] *Pediatric Endocrinology Unit, Kaplan Medical Center, Rehovot, Israel*
[e] *The School of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[f] *Pediatric Endocrinology and Diabetes Unit, Dana-Dwek Children Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[g] *Pediatric Endocrinology Unit, Assaf Haroffeh Medical Center, Zerifin, Israel*
[h] *Pediatric Clinic, Armon Child Center, Clalit Health Services, Haifa, Israel*
[i] *Pediatric Endocrine Unit, Ha'Emek Medical Center, Affula, Israel*
[j] *The Rappaport Endocrinology Faculty of Medicine, Technion, Haifa, Israel*
[k] *Pediatric Endocrinology and Metabolic Unit, Soroka University Medical Center, Israel and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel*
[l] *Pediatric Endocrine and Diabetes Unit, E. Wolfson Medical Center, Holon, Israel*
[m] *Paediatric Endocrine Unit, Rambam Health Care Campus, Haifa, Israel*
[n] *Pediatric Department, Meir Medical Center, Kfar Saba, Israel*
[o] *Division of Pediatric Endocrinology, Hadassah Hebrew University Medical Center, Jerusalem, Israel*
[p] *Pediatric Department, Bnei Zion Medical Center, Haifa, Israel*
[q] *Migdal Hamea Health Services, Clalit Health Services, Tel Aviv, Israel*
[r] *Institute of Diabetes, Endocrinology and Metabolism, Rambam Medical Center, Haifa, Israel*
[s] *Division of Pediatric Endocrinology, Shaare Zedek Medical Center, Jerusalem, Israel*
[t] *Maccabi Health Services, Central District, Tel Aviv, Israel*
[u] *Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel*

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* Address correspondence to: Noah Gruber, M.D., M.Sc., Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan 5265601, Israel.

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*E-mail address:* noahgruber@gmail.com (N. Gruber).


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A B S T R A C T

**Purpose:** The aim of the study was to estimate the current incidence and the distribution of etiologies of primary ovarian insufficiency (POI) in a nationwide study. The prevalence of POI in young adult women has recently increased, but the data cited for adolescents are more than three decades old.

**Methods:** Data regarding females aged <21 years diagnosed with POI during the years 2000–2016 were collected from all the pediatric endocrinology units in Israel. POI was defined by at least 4 months of amenorrhea in association with menopausal levels of follicle-stimulating hormone. Iatrogenic cases were excluded.

**Results:** For the 130 females aged <21 years included in the study, the distribution of POI etiologies was Turner syndrome/mosaicism in 56 (43%), idiopathic in 35 (27%), and other (developmental, genetic, metabolic, adrenal, and autoimmune) in 39 (30%) females. During the years 2009–2016, compared with 2000–2008, the incidence rate of new POI diagnoses per 100,000 person-years doubled (4.5 vs. 2.0; $p$ value <.0001), and incidence rates of idiopathic and other etiologies increased by 2.6 ($p$ value = .008) and 3.0 ($p$ value = .002), respectively. In contrast, the incidence of Turner syndrome was constant ($p$ value = .2). In the age group of 15–21 years, the current incidence of non-Turner POI in adolescents is one per 100,000 person-years.

**Conclusions:** In this nationwide study, the incidence rate of POI in youth aged <21 years was one tenth of the rate that is commonly cited. A significant increase in the rate of POI in non-Turner females was observed over the last decade. Contributions of environmental and epigenetic factors should be studied.



**IMPLICATIONS AND CONTRIBUTION**

This study established a current incidence of primary ovarian insufficiency among adolescents, which is one tenth what is commonly cited. Findings show a significant increase of non-Turner primary ovarian insufficiency over the last decade. This worrisome increase warrants an investigation of environmental and epigenetic factors.

Primary ovarian insufficiency (POI) occurring in youth is a devastating condition. POI is commonly defined by at least 4 months of irregular menses in association with menopausal levels of follicle-stimulating hormone (FSH), on two occasions at least one month apart, in women aged <40 years [1–3]. According to historical data published more than 3 decades ago, non-iatrogenic POI affects about 1:100 females by age 40 years, 1:1,000 by age 30 years, and 1:10,000 by age 20 years [4]. However, the current incidence of POI in adolescents are scarce. A 1% prevalence of idiopathic POI was reported in a study of 34,000 Estonian women aged >18 years, during 2003–2013 [5]; this indicates a possible increased prevalence in young adult women. A similar trend for adolescents has been reported in several case series [6–12]. Factors that have been suggested as relevant to the increased incidence of POI in young adults are social stress, postponement of childbearing, prolonged survival after gonadotoxic treatments, and increased exposure to environmental pollutants [13]. The etiology of POI is mostly idiopathic in adult women [1,14] and iatrogenic (because of chemotherapy, radiation, or environmental endocrine-disrupting chemicals [EDCs] [15–17]) or related to chromosomal abnormalities in adolescents.

The only multicenter study that characterized POI in adolescents aged 13–21 years identified 57 cases over 7 years retrospectively [11]. More than half the individuals of that study were found to have a normal karyotype and lacked a profound workup to determine the etiology of their condition. In case series of POI that included individuals with Turner syndrome, this syndrome tended to be the predominant causative etiology, followed by unexplained ovarian insufficiency [7,9,12].

We conducted a multicenter nationwide study to assess the current incidence and distribution of POI etiologies among adolescents in Israel.

## Materials and Methods

This multicenter nationwide study comprised all the pediatric endocrine units in Israel, from 14 medical centers: Edmond and Lily Safra Children's Hospital in Sheba Medical Center, Schneider Children's Medical Center, Kaplan Medical Center, Tel Aviv Sourasky Medical Center, Assaf Harofeh Medical Center, Armon Child Center in Clalit Health Services, Ha'Emek Medical Center, Soroka University Medical Center, Wolfson Medical Center, Rambam Health Care Campus, Meir Medical Center, Hadassah Hebrew University Medical Center, Bnei Zion Medical Center, and Shaare Zedek Medical Center. Institutional review board approval was granted by each individual institution, with Sheba Medical Center as the primary site.

We accessed data of patients with POI from all the pediatric endocrinology units in the country, in collaboration with the Israeli Pediatric Endocrinology Society. Data were collected from the medical records of females aged <21 years diagnosed with POI during the years 2000–2016. POI was defined as irregular menses of at least 4 months and elevated FSH, above 20 IU/L. Historically, FSH levels above 40 IU/L were used to define POI [18]. However, in guidelines published by the European Society for Human Reproduction and Embryology (ESHRE) in 2014, POI was defined as FSH above 25 IU/L [2]. Moreover, in a committee opinion of the American Society for Reproductive Medicine published in 2015, POI was defined as FSH above 10–20 IU/L [19]. A case series published in France defined POI with FSH above 9 IU/L [8] and from the U.S. with FSH above 20 IU/L [20]. Notably, the Israeli Ministry of Health states that fertility preservation is indicated for women with POI who have FSH above 10 IU/L. However, once FSH is above 20 IU/L, the option for fertility preservation is reduced because the ovarian reserve is already diminished [21]. Considering the

above, we decided to choose the cutoff for POI as FSH above 20 IU/L. In cases without two measurements of FSH (n = 5) or with borderline FSH (18–20 IU/L; n = 3), the persistence of amenorrhea in long-term follow-up led to confirmation of POI diagnosis and determination of its etiology (genetic mutations that pose a high risk for POI (Turner syndrome [22] and Woodhouse–Sakati Syndrome [23])). In adolescents without a previous genetic diagnosis, primary amenorrhea was defined as the absence of menarche at age 15 years and secondary amenorrhea as the absence of menses for more than 4 months [1]. Exclusion criteria were a history of a gonadotoxic treatment (chemotherapy or radiation), 46XY gonadal dysgenesis, and hypogonadotropic hypogonadism. The cutoff age of 21 years was selected according to the definition of a pediatric population by the American Academy of Pediatrics [24].

Clinical, familial, laboratory, and imaging data were collected. To account for nonuniformity of available data, information was extracted according to criteria based on the American College of Obstetricians and Gynecologists (ACOG) [3] and the ESHRE [2]. Clinical data included age at diagnosis, anthropometric measurements, birth weight, and presentation (primary amenorrhea vs. secondary amenorrhea). The standard deviation scores (SDSs) of height, weight, and body mass index were calculated using the Boston Children's Hospital Growth Calculator software version 2.01. Familial data included midparental height, maternal menarche, consanguinity, and family history of POI in first-degree relatives. Midparental height was calculated as the average height of the parents after subtracting 13 cm from the paternal height [25]. Laboratory data comprised FSH and luteinizing hormone (LH) levels at diagnosis, anti-Mullerian hormone, estradiol, progesterone, thyroid function, prolactin, autoimmune antibodies, adrenal profile, vitamin 25OHD, and metabolic profile including glucose and lipid profile. The autoimmune antibodies assessed included antithyroid antibodies (anti-TPO and antithyroglobulin), antiadrenal, and antiovarian antibodies. Patients with positive antiadrenal or antiovarian antibodies were classified as autoimmune POI, but positive thyroid antibodies were not classified as such. The imaging data consisted of a pelvic transabdominal ultrasound and bone age at diagnosis. Pelvic ultrasound findings were defined as “normal” and “abnormal.” The criterion for an “abnormal” study was the presence of at least one of the following: unobservable uterus, infantile uterus, undetected ovaries, and ovaries smaller than expected for age. In addition to karyotype, the genetic evaluation included one or more of the following: *FMR1* genetic analysis, chromosomal microarray analysis, whole exome sequencing, and Sanger sequencing of the genes for the *FSH receptor, MCM8, NUP-107, and PSMC3IP* in individual cases. Of the 184 patients identified with POI, 54 did not meet the study eligibility criteria because of inappropriate age (n = 15), FSH of 20 IU/L or below (n = 27), inappropriate diagnosis year (n = 6), or Y chromosome component (n = 6). For analysis, the patients were categorized into three subgroups based on diagnosis: Turner syndrome (45X0 and mosaicism), “other known etiology” (including developmental/congenital, genetic, metabolic, adrenal, and autoimmune), and idiopathic when the etiology was unknown. Of note, the cohort includes a rather high proportion of patients with ataxia telangiectasia because of consanguinity in certain ethnicities in Israel [26]. Patients with autoimmune polyglandular syndrome type I were genetically diagnosed. The incidence rate of new POI diagnosis was calculated based on birthdate information from the Israeli Central Bureau of Statistics [27]. Incidence was calculated for each examined age group (0–21 years and 15–21 years) as the number of new POI diagnoses divided by the total number of females. The current incidence for non-Turner POI among 15–21 years was based on the average incidence rates during the years 2013–2016.

### *Statistical analysis*

Analysis of variance was used to compare continuous variables, and the chi-square test was used to compare categorical variables among the three groups. Univariate logistic regression was used to assess the trend of POI incidence over the years by type of etiology. Multivariate logistic regression was used to determine the association of etiology with secondary amenorrhea. The trends of incidence over the years were analyzed using the Cochran–Armitage trend test. A $p$ value below .05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

## Results

The study cohort comprised 130 females who met eligibility criteria. The distribution according to the etiologies was Turner syndrome/mosaicism in 56 (43%), idiopathic in 35 (27%), and other (genetic, autoimmune, etc.) in 39 (30%) females.

The incidence rate of new POI diagnoses per 100,000 person-years under age 21 years increased throughout the study period ($p$ value = .003; Figure 1A, Table 1). The incidence of POI increased in both the idiopathic and the “other” etiologies groups ($p$ value = .003 and $p$ value = .03, respectively), yet the incidence of POI with Turner syndrome remained static ($p$ value = .7). During the years 2008–2010, the rise in POI incidence appeared to accelerate. For further analysis, the study period was divided into two periods: 2000–2008 and 2009–2016. During the period 2009–2016 compared with 2000–2008, the incidence rate of new POI diagnoses per 100,000 person-years was increased twofold (4.5 vs. 2.0; $p$ value $\leq$.0001) and the incidence rates of both idiopathic and “other” etiologies were increased by 2.6 (1.3 vs. .5; $p$ value = .008) and by 3.0 (1.5 vs. .5; $p$ value = .02), respectively. These trends contrast with a steady rate for Turner syndrome ($p$ value = .2). In all the analyses of changing incidence of POI, statistically and clinically significant increases were observed.

As primary amenorrhea is usually not evaluated before age 15 years, we calculated POI incidence in the age group of 15–21 years. For this group, the incidence of non-Turner POI was one per 100,000 person-years. The incidence rate of POI diagnoses in the age range of 15–21 years was increased by 2.7-fold during 2009–2016 compared with the years 2000–2008 (incidence rates 4.1 and 1.5 per 100,000 person-years, respectively; $p$ value = .002). The incidence rate of idiopathic etiology increased sharply, 6.3-fold ($p$ value = .003). These data contrast with the incidence of Turner syndrome, which did not change ($p$ value = .8) and the “other” category, for which an increase of 2.5-fold was not statistically significant ($p$ value = .06; Figure 1B).

The idiopathic group presented at a mean 2.4 years later than the Turner group and .2 years later than the “other” group ($p$ value = .002; Table 2). The height SDS of the idiopathic group was greater and the body mass index SDS was lower than for the other two groups ($p$ value = .001 and $p$ value = .0004; respectively). Of the 108 patients with data available regarding the type of amenorrhea (primary/secondary), 26 (24%) presented with

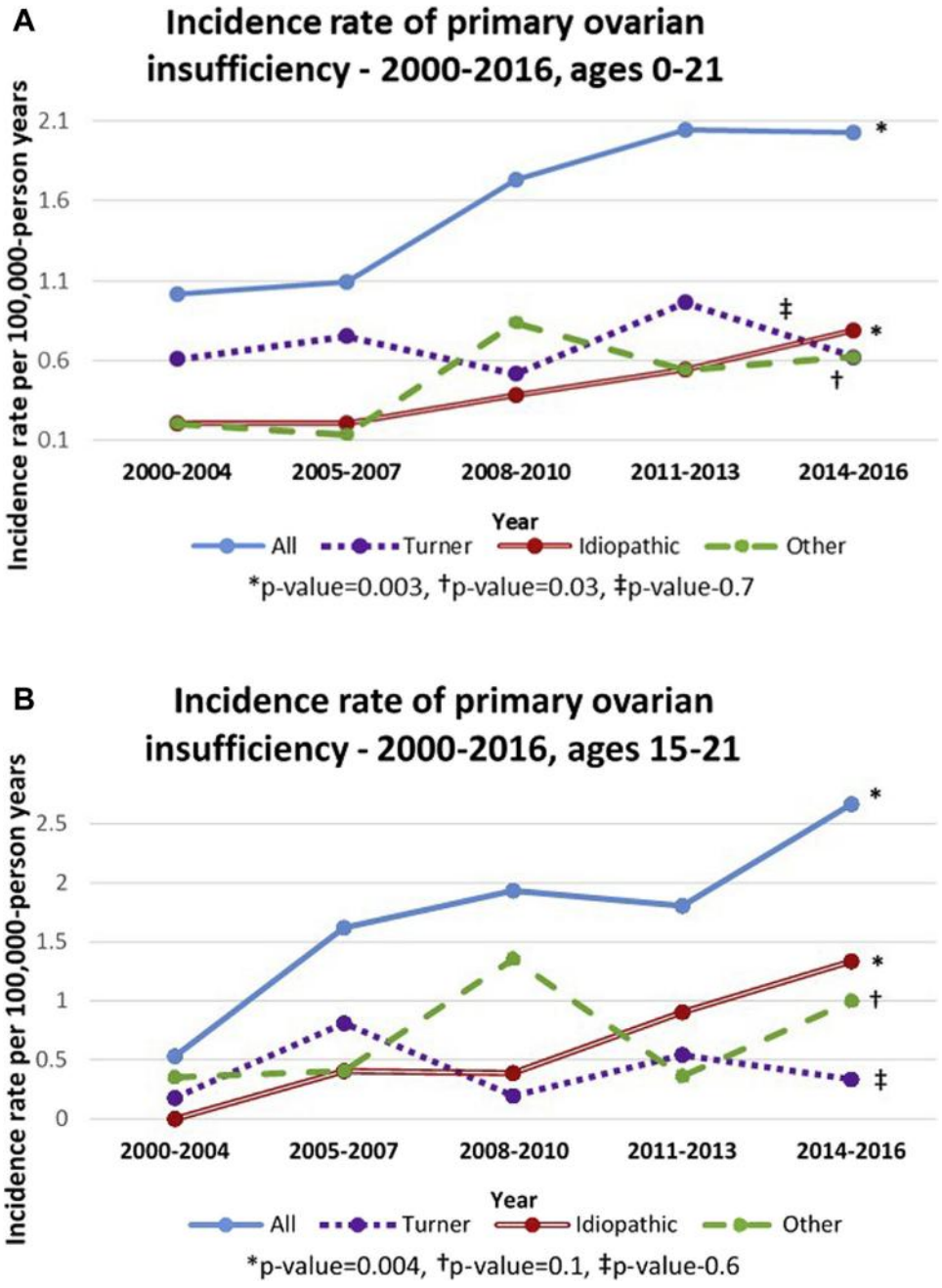


**Figure 1.** Incidence rates of primary ovarian insufficiency between the years 2000 and 2016 among Israeli adolescents. (A) Ages 0–21 years, (B) ages 15–21 years.

secondary amenorrhea. Of those aged >15 years (n = 49), 40% presented with secondary amenorrhea. The highest prevalence of secondary amenorrhea was in the idiopathic group—4.7-fold higher than in the Turner group, and 1.3-fold higher than in the "other" group ($p$ value = .007). A family history of POI was most prevalent among the "other" group ($p$ value = .0008). The mean FSH level was 78.7 ± 42 IU/L, without a significant difference between the three groups. However, in the idiopathic group, the mean LH level was significantly higher and the mean FSH/LH ratio significantly lower than for the other two groups ($p$ value<.0001 and $p$-value = .0002, respectively).

The workup for POI included a genetic analysis, a pelvic ultrasound, and endocrine and metabolic tests. Karyotype was performed for 87% (113/130) of the patients. Of the 17 patients who did not have a karyotype test, 16 had POI because of a known condition (the "other" group). Of the 74 patients who had a 46XX karyotype, additional genetic tests were performed in 59 (80%). For the 59 patients who had a genetic elaboration performed, a mutation in a specific gene was identified in 33 (56%); 43 (73%) of these genetic tests were performed after 2009. Pelvic ultrasound was abnormal in 83% (63/76) of those who underwent this test. Thyroid antibodies were found

**Table 1**
Incidence rates of primary ovarian insufficiency per 100,000 person-years, ages 0–21 years

| | Years of diagnosis | Person-years at risk | Number of cases | Incidence rate per 100,000 person-years | *p* value[a] |
|---|---|---|---|---|---|
| All | 2000–2004 | 1,478,880 | 15 | 1.01 | .003 |
| | 2005–2007 | 1,465,898 | 16 | 1.09 | |
| | 2008–2010 | 1,558,156 | 27 | 1.73 | |
| | 2011–2013 | 1,660,308 | 34 | 2.05 | |
| | 2014–2016 | 1,769,792 | 36 | 2.03 | |
| Turner | 2000–2004 | 1,478,880 | 9 | .61 | .7 |
| | 2005–2007 | 1,465,898 | 11 | .75 | |
| | 2008–2010 | 1,558,156 | 8 | .51 | |
| | 2011–2013 | 1,660,308 | 16 | .96 | |
| | 2014–2016 | 1,769,792 | 11 | .62 | |
| Other | 2000–2004 | 1,478,880 | 3 | .20 | .03 |
| | 2005–2007 | 1,465,898 | 2 | .14 | |
| | 2008–2010 | 1,558,156 | 13 | .83 | |
| | 2011–2013 | 1,660,308 | 9 | .54 | |
| | 2014–2016 | 1,769,792 | 11 | .62 | |
| Idiopathic | 2000–2004 | 1,478,880 | 3 | .20 | .003 |
| | 2005–2007 | 1,465,898 | 3 | .20 | |
| | 2008–2010 | 1,558,156 | 6 | .39 | |
| | 2011–2013 | 1,660,308 | 9 | .54 | |
| | 2014–2016 | 1,769,792 | 14 | .79 | |

The incidence rate of primary ovarian insufficiency per 100,000 person-years in ages 0–21 years was calculated for each period.
[a] Chi-square for trend.

abnormal in 37% (25/67) of those tested. Of the 12 patients (of 35 who were idiopathic) whose adrenal and/or ovarian antibodies were tested, none was found to have positive antibody titers. No adrenal or ovary antibodies were found to be abnormal in any of the 12 with results of such. No statistically significant differences were found between the groups in the endocrine or metabolic parameters studied, apart from vitamin 25OHD, which was the lowest in the "other" group ($p$ value = .01). Diagnoses of the "other" group are presented in Table 3. Additional conditions diagnosed in the idiopathic group included one of each of the following: asthma, hypothyroidism, epilepsy, familial Mediterranean fever, dyslipidemia, mild left ventricular hypertrophy with atrial septal defect, past hyperprolactinemia, and isolated growth hormone deficiency.

In a univariate logistic regression model, for each additional calendar year, an 11% increase was observed in diagnoses of idiopathic and "other" etiologies combined, compared with Turner syndrome ($p$ value = .02; 95% confidence interval [CI]: 1.0–1.2). When the idiopathic etiology was compared alone with Turner syndrome, an 11% increase was also observed in diagnoses of the idiopathic etiology for each additional calendar year ($p$ value = .04; 95% CI: 1.0–1.2). In a multivariate logistic regression model of the entire cohort, in which secondary amenorrhea was adjusted for age, an increase in 1 year of age increased the risk of presenting with secondary amenorrhea in 40% ($p$ value = .002; 95% CI: 1.13–1.74). The odds ratio of presenting with secondary amenorrhea among the idiopathic group was 7.4 ($p$ value = .004; 95% CI: 1.9–29.1) compared with the Turner group; and among the "other" group, the odds ratio was 4.8 ($p$ value = .02; 95% CI: 1.2–19.2) compared with the Turner group. For both comparisons, statistical significance remained after adjustment for year of birth and year of diagnosis.

## Discussion

Our data from a national sample show an incidence of non-Turner POI of one per 100,000 person-years among 15- to

**Table 2**
Characteristics of adolescents with primary ovarian insufficiency

| | Parameter, mean ± SD | All (n = 130) | Turner (n = 56) | Other (n = 39) | Idiopathic (n = 35) | *p* value |
|---|---|---|---|---|---|---|
| Clinical | Age at diagnosis (years) | 13.6 ± 3.7 | 12.2 ± 3.8 | 14.4 ± 4.0 | 14.6 ± 2.4 | **.002** |
| | Height SDS | −1.8 ± 1.6 | −2.4 ± 1.0 | −1.7 ± 1.9 | −.9 ± 1.7 | **.001** |
| | Weight SDS | −1.1 ± 2.1 | −.7 ± 1.4 | −1.8 ± 2.3 | −.7 ± 2.5 | **.05** |
| | BMI SDS | −.03 ± 1.2 | .5 ± .9 | −.6 ± 1.1 | −.2 ± 1.4 | **.0004** |
| | Birth weight (g) | 2,813 ± 614 | 2,693 ± 601 | 2,896 ± 644 | 2,907 ± 601 | .3 |
| | Secondary amenorrhea, n (%) | 26/108 (24%) | 3/39 (8%) | 10/35 (29%) | 13/34 (38%) | **.007** |
| Familial | MPH SDS | −.2 ± 1.7 | −.1 ± .7 | −.1 ± 2.6 | −.5 ± .9 | .6 |
| | Maternal menarche age (years) | 13.5 ± 2.2 | 13.5 ± 1.5 | 12.7 ± 3.3 | 14.1 ± 1.3 | .2 |
| | Arab ethnicity, n (%) | 46/99 (46%) | 8/27 (30%) | 14/25 (56%) | 13/29 (45%) | .15 |
| | Positive family history of POI, n (%) | 15/98 (15%) | 1/31 (3%) | 11/32 (34%) | 3/27 (11%) | **.0008** |
| Laboratory | FSH (IU/L) | 78.7 ± 42.2 | 76.3 ± 43.4 | 74.9 ± 45.2 | 86.8 ± 36.5 | .4 |
| | LH (IU/L) | 25.4 ± 20.8 | 17.3 ± 16.0 | 27.0 ± 20.1 | 36.8 ± 23.2 | **<.0001** |
| | FSH/LH ratio | 6.4 ± 7.5 | 9.2 ± 8.4 | 5.4 ± 7.7 | 2.8 ± 1.2 | **.0002** |
| | Estradiol (pmol/L) | 81.1 ± 46.6 | 77.6 ± 43.1 | 79.8 ± 36.4 | 88.5 ± 59.7 | .8 |
| | AMH (μg/L) | .4 ± .7 | .3 ± .3 | .15 ± 0 | .5 ± 1.0 | .7 |

AMH = Anti-Mullerian hormone; BMI = body for mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MPH = midparental height; POI = primary ovarian insufficiency; SDS = standard deviation score.
Bold values are the statistically significant.

**Table 3**
Characteristics of adolescents with primary ovarian insufficiency, categorized as "other"

| Category | Number | Details |
|---|---|---|
| Developmental/ congenital | 6 | Gonadal dysgenesis |
| | 1 | Atypical Rokitansky–Kuster–Hauser syndrome |
| Metabolic/neurologic | 2 | Galactosemia |
| | 1 | Cystinuria hypotonia syndrome |
| | 1 | Congenital disorder of glycosylation type 1a |
| | 1 | Perrault syndrome |
| Adrenal | 1 | 17-20 lyase deficiency |
| Genetic | 7 | Ataxia telangiectasia |
| | 3 | Woodhouse–Sakati syndrome |
| | 2 | BRCA2 mutation |
| | 2 | Kabuki syndrome |
| | 2 | SPIDR mutation |
| | 2 | SYCE1 mutation |
| | 1 | NUP-107 mutation |
| | 1 | Noonan syndrome |
| | 1 | NOBOX mutation |
| | 1 | Translocation chromosome 11,X |
| Autoimmune | 4 | Autoimmune polyglandular syndrome type 1 |

21-year-old females; this indicates a pronounced increase in incidence during the last decade.

Since Coulam et al. [4] established an incidence of POI in adolescents in 1986, most studies and reviews on this subject cite their findings regarding POI incidence for this age group. Of 1,850 women born during 1930–1935 and followed from 1950 to the 1980s, nine were diagnosed with POI and did not display stigmata of Turner syndrome or another chromosome abnormality. Two adolescents aged 15–19 years and none aged 20–29 years were diagnosed with non-Turner POI. Accordingly, an incidence rate of 10 per 100,000 person-years was extrapolated. From our cohort, we estimated the incidence of non-Turner POI in adolescents in Israel as only one per 100,000 person-years in the age group of 15–21 years. The 10-fold difference in incidence is likely because of methodological factors, such as the 30-fold larger person-years at risk in our study, and the differences in age group (15–21 vs. 15–29 years) and in trial design. In corroboration with our findings, a recent investigation that was unable to establish an association between adolescent vaccination and POI reported POI incidence of 4.6 per 100,000 person-years in the 15–22 years age group [28].

Our data concur with the only other multicenter study that characterized POI in adolescents; that retrospective study identified 57 cases over 7 years [11]. The increasing trend in incidence reported in the present study supports data of a retrospective study, in which 13 of the 15 females identified with idiopathic POI presented in the last 5 years of the study [7]. Moreover, the etiology distribution in our cohort is similar to studies published in the U.S. [7,12].

The increased incidence in Israel of non-Turner POI in adolescents over the last decade is worrisome. Several explanations are possible. Awareness may have increased after publication of Nelson's landmark article in 2009 [1], the ACOG guidelines in 2014 [3], and the ESHRE guidelines in 2016 [2]; however, POI was first described in 1942 by Albright [29] and multiple articles characterizing this phenomenon were published long before 2009 [18,30,31]. New genetic technologies, discoveries of genes involved in POI, and the rise in prevalence of autoimmune diseases may have contributed to the increase in "other" POI cases. The increased incidence of idiopathic POI is of particular concern [6–8,11] because environmental and epigenetic factors may be involved.

An important finding of the current cohort is the prevalence of secondary amenorrhea as a presenting symptom of POI in adolescents. Many caregivers consider any pattern of the menstrual cycle in the first years postmenarche to be normal. Among the idiopathic group, secondary amenorrhea was much more prevalent, about sevenfold higher, than in the Turner group. This concurs with other reports [6,7,12] and highlights the importance of evaluating adolescent females after 4 months without menses [32,33]. Moreover, among the idiopathic group, one of the ovarian reserve parameters, the FSH/LH ratio [34,35] was better compared with the other groups. This also highlights the importance of early evaluation and discussion of fertility preservation [36].

Karyotype in the present study was performed in 87% of the patients, similar to another recent study [11]. The ACOG does not mention autosomal genetic testing, whereas the ESHRE recommends such testing when evidence suggests a specific mutation. Genetic testing was performed in 80% of those with normal karyotype in our study; this proportion is higher than in other studies. TSH was tested in 92% of patients, similar to other reports [12]. Adrenal and ovary antibodies were not found to be abnormal in any of the patients in our cohort; this corroborates the low sensitivity of these tests [37].

The retrospective design is a limitation of this report. Yet, this 14-center study included all pediatric endocrinology centers in one country. Although unusual in Israel, if a patient was advised only at a gynecological clinic, the patient would have been missed. A referral bias, because of a greater tendency to refer patients with POI to gynecologists than to pediatric endocrinologists during 2000–2008 than during 2009–2016, seems unlikely because no changes occurred in this regard in national or international guidelines. Incomplete workup may have resulted in misclassification of a few patients in the "idiopathic" rather than the "other" group; however, this would not obscure the increasing incidence of non-Turner POI. We have no information regarding EDCs during the study period.

In conclusion, we established a current incidence of POI in adolescents and demonstrated a remarkable increase in POI for this age group. Increased awareness of this condition will promote more efficient and earlier evaluation and treatment and may result in reducing complications of POI, such as in relation to cardiovascular and bone health [32]. Investigating the potential impact of EDCs is highly important for determining their role in the alarming increase of idiopathic POI.

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