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Short Communication

Primary Ovarian Insufficiency: Time to Diagnosis and a Review of Current Literature

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Abstract

Background: Prompt recognition of symptoms and subsequent diagnosis of primary ovarian insufficiency (POI) are critical given its consequences on quality of life and long-term health. Poor access to care in underrepresented minority women and/or low-income populations may contribute to delayed diagnosis. Our group previously demonstrated a dearth of board-certified reproductive endocrinology (RE) physicians providing care for Medicaid patients in New Jersey. Given the adverse effects of prolonged hypoestrogenism, we aimed to evaluate length of time to diagnosis of POI in a low-resource/low-income population presenting to an urban university-based RE clinic, as well as provide a review of the current literature. **Methods**: This retrospective case series included all new patients seen at the RE clinic at University Hospital in Newark, NJ from June 2014 through June 2018. POI was diagnosed in women with oligo/amenorrhea and menopausal levels of follicle stimulating hormone. The primary outcome was time to diagnosis from onset of symptoms. **Results**: Of 524 new patients seen, 19 (3.6%) were diagnosed with POI. Median time to diagnosis of POI from onset of symptoms was 48 months. 57.9% of our patients identified as Black and 31.6% as Hispanic. 13/19 (68.4%) reported hypoestrogenic symptoms at time of referral. 21.1% were diagnosed with Turner mosaicism. 14 of 19 patients completed DEXA scan, of which 35.7% were diagnosed with low bone mass or osteoporosis. Of those diagnosed prior to referral to RE (9/19, 47.4%), only 4 had initiated hormone therapy. **Conclusions**: Our study demonstrates a need for more aggressive evaluation of oligo/amenorrhea in underrepresented minority women. Prolonged time to diagnosis of POI has adverse effects, as reflected by hypoestrogenic symptoms and decreased bone mineral density. Delayed diagnosis and management of POI may be related to health care disparities facing these women and warrants action to improve access to care.

Keywords: primary ovarian insufficiency; delay to diagnosis; underrepresented minorities

1. Introduction

Primary ovarian insufficiency (POI) is a condition defined by the loss of normal ovarian function before the age of 40. Although presentation can be variable, women diagnosed with POI may experience amenorrhea, irregular menstruation, difficulty conceiving, and vasomotor or other symptoms associated with estrogen deficiency. In most cases, the cause of POI remains unknown, however genetic, environmental, infectious, metabolic and iatrogenic causes have been identified, along with certain autoimmune diseases which are associated with an increased risk for developing the condition [1,2].

POI affects 1% of women overall, but prevalence varies greatly by age. POI affects 1 in 10,000 women between ages 18–25, 1 in 1000 women between ages 25–30, and 1 in 100 women between ages 35–40, making the latter the most common age group for onset of this condition [3]. Epidemiological studies have also demonstrated variation in the prevalence of POI among women in different ethnic and socioeconomic groups. In one analysis, African American, Hispanic, and Caucasian women had a relatively higher occurrence of POI (1.4%, 1.4%, and 1%, respectively), followed by Chinese (0.5%) and Japanese (0.1%) women [4]. This study also assessed variables such as income and level of education, and determined that low socioeconomic status was associated with a higher prevalence of POI [4].

Early diagnosis is imperative to the proper treatment and management of POI, as POI has been linked with other comorbidities including low bone density, depression, and increased risk of cardiovascular disease [5–7]. A substantial delay between presentation of symptoms and the diagnosis of POI is not uncommon—most experiencing about a 5-year delay between symptom onset and diagnosis [8], and may be attributed to insufficient understanding and awareness regarding the condition, on the part of women as well as their providers. Further, since low socioeconomic status is associated with poorer self-reported overall health as well as higher mortality, socioeconomic status likely contributes to delay in diagnosis via limited access to care [9]. Indeed, a large cross-sectional study from the Korea National Health and Nutrition Examination Survey demonstrated a significantly increased prevalence of POI in patients with lower socioeconomic status [10]. Delay in diagnosis proves detri-

mental to patient care, as it results in delayed treatment for comorbidities, which can ultimately increase the risk for all-cause mortality in women with POI [6].

In view of the above, our aim was to investigate the time to diagnosis in a population that often faces barriers to medical care. Our group previously demonstrated a dearth of board-certified reproductive endocrinology and infertility subspecialists providing care for Medicaid patients in New Jersey [11]. We assessed time from initial symptoms to diagnosis of primary ovarian insufficiency for women presenting to the Reproductive Endocrinology and Infertility Clinic at the University Hospital Ambulatory Care Clinic in Newark, New Jersey, a referral center which provides care for a patient population largely comprised of Black and Hispanic women, including immigrants and underserved communities who have historically faced limited access to medical care. Herein we also provide a review of POI etiologies, clinical implications and associated comorbidities, diagnosis, and management of POI.

2. Methods

This is a retrospective case series including all women presenting to the Reproductive Endocrinology and Infertility clinic at University Hospital in Newark, New Jersey between June 2014 and June 2018. The study was approved by the institutional review board of Rutgers Biomedical and Health Sciences. Inclusion criteria were defined as new patients, aged less than 40 years old, presenting to the Reproductive Endocrinology and Infertility clinic, diagnosed with POI based on oligo/amenorrhea and menopausal follicle-stimulating hormone (FSH) levels (>25 mIU/mL). Of note, not all patients had two FSH measurements, thus for our calculations we used the highest FSH value for patients with two measurements. This decision was based on data supporting that the maximum FSH value is more predictive of ovarian reserve [12]. Data obtained via retrospective chart review included age at symptom onset, body mass index (BMI), serum estradiol (E2), FSH and anti-mullerian hormone (AMH) levels, ethnicity, race, history of smoking, parity, symptoms of POI on presentation, hormone therapy initiated prior to presentation, and etiology of POI. Oligomenorrhea was included as a symptom and was defined as cycles more than 35 days in length or less than 6 cycles a year. The primary outcome measured was time from onset of symptoms until confirmed diagnosis of POI. Secondary outcome was presence or absence of osteopenia or osteoporosis as determined by dual energy x-ray absorptiometry (DEXA). Shapiro-Wilk test was performed to determine whether or not data were normally distributed. Statistics were descriptive and presented as mean $\pm$ standard deviation for normally distributed data, or median + interquartile range (IQR) for non-normally distributed data.

3. Results

A total of 524 patient charts were reviewed, of which 3.6% (n = 19) met inclusion criteria. The mean age at onset of POI-related symptoms was 25 years. The racial/ethnic makeup of the patients included was 57.9% Black, 10.5% White and 31.6% other; 31.6% identified as Hispanic, an overall similar distribution to that of our general Obstetrics and Gynecology clinic at University Hospital. The majority (73.6%) of the women included were nulliparous. Of the 19 patients, 12 (63.2%) had Medicaid, 6 patients (31.6%) were uninsured, and one patient (5.3%) had private insurance. Median time to diagnosis from onset of symptoms was 48 (IQR, 23–120) months. Mean serum FSH and median estradiol levels were 82.0 $\pm$ 31.5 mIU/mL and 8.5 (IQR, <5–19) pg/mL, respectively. AMH was undetectable (<0.015 ng/mL) in 100% (10/10) of patients in whom AMH was measured. Of the 19 patients included, 3 (15.8%) did not complete the diagnostic workup for etiology of POI. This workup included measurement of serum FSH, estradiol, TSH (thyroid stimulating hormone), karyotype, FMR1 premutation testing as well as antithyroid and anti-adrenal antibody testing. A specific etiology of POI was identified in 42.1% of patients with 21.1% being diagnosed with Turner mosaicism, 10.5% with Fragile X premutation and 10.5% having a history of previous chemotherapy. With regards to POI-related morbidity, 73.2% (14) of patients underwent a DEXA scan and 35.7% of screened patients were found to have osteopenia or osteoporosis. In addition, 63.6% reported vasomotor symptoms and 31.6% reported vaginal symptoms. With regards to fertility, 68.4% of patients reported desire for future child-bearing, however only 5 (26.3%) were actively trying to achieve pregnancy for at least one year. Five patients (26.3%) were already on hormonal therapy with combined oral contraceptives prior to presenting to our practice. Results are presented in detail in Table 1.

4. Discussion

The aim of this study was to shed light on the time to diagnosis of POI in underserved, underrepresented minority women. Several studies outside of the U.S. have highlighted that women of lower socioeconomic status are at higher risk of developing POI, but lack diversity in terms of race/ethnicity of the population studied. More specifically, large cross sectional studies from India have shown that women living in rural areas, who are less educated or of lower economic status, are at greater risk of developing POI [13,14]. A prospective study from the United States demonstrated that social class and psychosocial stress are important predictors of an earlier age at menopause in African American women, but did not evaluate these factors in women with POI [15]. In age-related menopause, women of lower income and educational status experience more menopausal symptoms, while another cross-sectional study found that women who are homeless or uninsured reported

Table 1. Baseline demographics, hormonal profiles and morbidity in women with POI (n = 19).

Variables	Values
Follicle stimulating hormone (M ± SD)	82.0 ± 31.5 mIU/mL
Estradiol [Mdn (IQR)]	8.5 (<5–19) pg/mL
Anti-mullerian hormone (% undetectable)	100%
Age at symptom onset in years (M ± SD)	25.1 ± 10.0
Age at diagnosis in years (M ± SD)	29.9 ± 7.7
Time to diagnosis from symptom onset in months [Mdn (IQR)]	48 (23–120)
Ethnicity	
Hispanic	6 (31.6)
Non-Hispanic	13 (68.4)
Race	
White, n (%)	2 (10.5)
Black, n (%)	11 (57.9)
Other, n (%)	6 (31.6)
History of smoking, n (%)	4 (21.1)
BMI (M ± SD)	25.6 ± 5.4 kg/m^2
Nulliparous, n (%)	14 (73.6)
Symptoms on presentation to reproductive endocrinology	
Vasomotor, n (%)	12 (63.2)
Vaginal, n (%)	6 (31.6)
Hormone therapy initiated prior to referral, n (%)	5 (26.3)
Etiology identified, n (%)	8 (42.1)
Chemotherapy, n (%)	2 (10.5)
Turner mosaic, n (%)	4 (21.1)
Fragile X premutation, n (%)	2 (10.5)
DEXA completed, n (%)	14 (73.7)
Low bone mass or osteoporosis, n (%)	5 (35.7)
Hormone therapy	
Combined oral contraceptive pills, n (%)	6 (31.6)
Cyclic estrogen and progestin, n (%)	12 (63.2)

DEXA, Dual energy X-Ray Absorptiometry; M, mean; SD, Standard Deviation; BMI, Body Mass Index; Mdn, median; IQR, interquartile range.

more severe vasomotor symptoms, depression and anxiety [16,17]. In view of the above, it was important to investigate the time to diagnosis of POI in a high risk population, such as that of our clinic, which is mostly comprised of underinsured minority women. Our retrospective study showed a substantial delay from onset of symptoms to diagnosis (median 48 months). Importantly, more than one-third of women in our study were diagnosed with osteopenia or osteoporosis, a finding that further supports the need for timely diagnosis and management. To the best of our knowledge, this is the first study to address delay in diagnosis of POI in an urban U.S. population comprised largely of underserved, underrepresented minority women who face multiple barriers to care. Given the significant health implications and symptomatology associated with the diagnosis of POI, which we will review herein, a delay in diagnosis is likely to be detrimental to the overall health and quality of life of these patients.

4.1 Pathophysiology

Primary ovarian insufficiency occurs because of accelerated depletion of follicles via apoptosis or a disruption in normal follicular function. Follicular dysfunction may be due to a number of causes, including disruption in follicular response to gonadotropins (e.g., due to FSH or luteinizing hormone (LH) receptor mutations), steroidogenic enzyme deficiency, or autoimmune lymphocytic infiltration of the theca layer of antral follicles [18]. However, regarding possible etiologies that contribute to the loss of follicular function, idiopathic causes make up 74–90% of cases [2]. Follicular dysfunction or loss of ovarian follicles interrupts the menstrual cycle, resulting in oligo/amenorrhea, reduced fertility, and accompanying menopausal symptoms experienced by women with POI.

About 10–20% of POI cases can be attributed to genetic causes, thus many efforts have been made to identify candidate genes associated with disease onset [19]. Since no single gene has been identified as the sole cause of

POI, it is theorized that POI is the result of multiple gene mutations—*FMR1* being among the many genes that has been linked to the development of POI [2,20]. A premutation in the *FMR1* gene is the most common single gene abnormality associated with the development of POI—12.9% to 24% of women with the *FMR1* premutation experience primary ovarian insufficiency [2,3,21,22]. Chromosomal abnormalities are a more common etiology of POI than single gene mutations, with Turner Syndrome making up most of the cases [2,23].

POI is associated with autoimmune diseases. Hashimoto's disease/autoimmune thyroiditis and autoimmune adrenal insufficiency are the more common autoimmune diseases found in women with POI [2]. Iatrogenic and environmental causes have also been implicated in the development of POI [2,3,24–27]. Most iatrogenic cases of POI are associated with cancer treatment and may develop in women with a past medical history of cancer during childhood or adolescence [2]. Chemotherapy and radiation therapy can impede follicular development and can also cause a decrease in primordial follicles [27]. Certain environmental factors induce toxic effects on ovarian function and increase the risk for developing POI, a common toxic agent being cigarette smoke. Noxious agents found in cigarette smoke expose the follicles to extensive damage via oxidative stress and apoptosis, resulting in decreased follicles [28].

4.2 Clinical Presentation

Given the variable clinical presentation of POI and importance of early diagnosis, the provider must recognize symptoms and have a low threshold for screening. Amenorrhea is the classic clinical symptom associated with POI; however, POI does not cause an abrupt cessation of menstruation. Changes in menstrual regularity, especially after pregnancy or discontinuance of hormonal birth control pills, is a relatively common presentation of POI [29–31]. Few women may present with signs of hypoestrogenism—night sweats, hot flashes, vaginal dryness, mood disturbances, dyspareunia, and decreased sexual desire [29–31]. Infertility is also a common symptom of POI, and its presentation is gradual [27]. Because the disorder is progressive, some women with POI can become pregnant, especially during earlier stages of the condition. When compared to women experiencing age-appropriate menopause, women with POI are more likely to experience higher levels of stress as well as labile mood, depression, and anxiety [32]. Importantly, unlike age-appropriate menopause, the symptoms associated with POI do not gradually subside [32]. Women diagnosed with POI experience their symptoms long after diagnosis, if left untreated.

4.3 Diagnosis

Since menstrual irregularities can be varied and no single presentation is necessarily specific for the diagnosis of POI, a careful history and physical are always the first component of the evaluation. Unfortunately, there are no universally agreed upon criteria for the diagnosis of POI, nor universal recommendations for further workup once the diagnosis is confirmed. A recent review of clinical practice guidelines (CPGs) for early menopause and primary ovarian insufficiency demonstrated that most CPGs are of low to average quality and have significant variation in their recommendations [33]. For example, with regards to diagnostic criteria, the European Society of Human Reproduction and Embryology (ESHRE) recommends FSH levels >25 IU/L at a cut-off whereas the International Menopause Society (IMS) recommends ≥ 40 IU/L. In addition, only ESHRE had CPG specifically for POI. This inconsistency in recommendations between different organizations is likely due to the paucity of high-quality data available. Furthermore, most CPGs were developed based on data from European and North American studies, which brings into question whether these guidelines would be applicable in other populations.

Diagnostic criteria according to the American College of Obstetrics and Gynecology (ACOG) include amenorrhea or other abnormal bleeding patterns for a minimum of three months, and menopausal levels of FSH at least a month apart in a patient aged less than 40 years [34]. Two FSH measurements are recommended, as the diagnosis is of particular psychological burden to the patient and it is important to have confidence in the diagnosis, especially given the fluctuation in clinical status and hormonal levels [23].

Obtaining a complete medical history, including screening for autoimmune disease, is imperative for diagnosis of POI. Although Turner Syndrome, the most common chromosome abnormality causing POI, commonly arises from a spontaneous genetic alteration, a detailed family history remains important as a genetic cause is implicated in 10–20% of cases [19]. Physicians should note pertinent family history of intellectual disability, ataxia, or primary ovarian insufficiency as these could be indicative of premutations in the *FMR1* gene, which is a common genetic etiology of POI [30]. In addition, a chromosome analysis should be performed on all women with POI.

Prolactin and thyroid stimulating hormone level testing is recommended to evaluate for other causes of oligomenorrhea. Once the diagnosis is established, the minimum evaluation per ACOG, in addition to karyotype analysis and testing for *FMR1* premutation includes anti-thyroid and anti-adrenal antibodies (either by 21-hydroxylase immunoprecipitation or indirect immunofluorescence) as well as pelvic ultrasound [18,34]. Ultrasound may not be useful in predicting disease progression but is important in evaluation for fertility preservation and may also aid in acceptance of the diagnosis. Despite the potential for detection of ovarian antibodies, this is a low specificity test that is not indicated. In addition, an ovarian biopsy is not recommended as it does not yield information that can help dictate manage-

ment; biopsies indicating no follicles can be inaccurate due to sampling error and patients may still achieve pregnancy [35].

4.4 Morbidity/Clinical Implications

The deteriorating ovarian function and resulting hypoestrogenism characteristic of POI can have severe health implications [36]. One of the major health risks that women with POI face is osteopenia/osteoporosis and subsequent fractures. Multiple studies have demonstrated that women with early menopause (defined as onset prior to age 45) as well as POI have lower bone mineral density (BMD) than control women [5,36,37]. A cross-sectional study comparing BMD between women with POI and controls found that women with POI on average had 2–3% lower BMD as measured by dual energy x-ray absorptiometry. Importantly, it was found that a 1-year delay in diagnosis was a significant risk factor for low bone mass. In addition, the length of time that the patient was not on hormone replacement therapy (HRT) was also highlighted as a risk factor for reduced bone mass [5]. Physiologic hormone replacement including estrogen and progestin has been shown to improve BMD in patients with POI, to become equivalent to that of women without POI [38].

Increased risk of cardiovascular disease is another significant clinical implication of POI. The dysregulation of endothelial function and metabolic changes associated with estrogen deficiency may be the etiology of the increased risk of cardiovascular morbidity and mortality in women with POI [6,36,37]. A systematic review and meta-analysis of studies assessing cardiovascular disease (CVD) risk and morbidity and age of menopause, demonstrated increased risk of coronary heart disease, stroke, CVD mortality and overall mortality in women with early onset menopause [6]. In view of the above, it would stand to reason that hormone therapy would improve CVD outcomes for patients with POI. However, this benefit has been demonstrated mostly in studies assessing naturally menopausal women [39]. Further research addressing this question in women with POI is needed.

One of the most distressing complications of POI is infertility, often unresponsive to traditional infertility treatments. A case-control study of women with POI demonstrated that despite the presence of antral follicles, these follicles did not respond appropriately to ovarian stimulation as estrogen levels did not increase significantly after the administration of recombinant FSH [40]. Options for women with POI who desire children include *in vitro* fertilization using donor oocytes, use of donor embryos, or adoption [39], any of which may not be feasible for patients without the financial means. Timely diagnosis is therefore critical.

Depression and mood disorders have also been associated with estrogen deficiency and POI. The subsequent loss of fertility can be a particularly devastating diagnosis and a cause of significant emotional distress to the patient. In addition to a grief-like reaction, a new or ongoing diagnosis of POI may be a source of lower self-esteem and well as lower perception of social support [41]. One study administering the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders 4th edition to women with POI showed an increased prevalence of major and minor depression, as well as overall mood disorders, when compared with the general community [7]. Assessment and treatment for mental health disorders should become a routine part of care for patients with POI.

Autoimmune thyroid disease is commonly associated with POI. Hashimoto's disease has been linked to POI in about 14–32.7% of cases [2]. Despite no official recommendations for thyroid screening, it is reasonable to test for thyroid disease with thyroid-stimulating hormone (TSH) levels every 1–2 years [18,34]. Furthermore, Addison's disease is a known autoimmune comorbidity in patients with POI. In a study with 123 participants, 3.2% of women with a previous POI diagnosis had occult adrenal insufficiency [42]. Testing for adrenal auto-antibodies could therefore be a high-yield screening test, with corticotropin stimulation testing if adrenal antibodies are found to be present [18,34]. Other endocrinopathies and autoimmune diseases associated with POI include rheumatoid arthritis, diabetes mellitus, myasthenia gravis, pernicious anemia, systemic lupus erythematosus and dry eye syndrome. Patients should be tested for these in the case of symptoms.

4.5 Treatment

Despite the lack of consensus regarding management guidelines, it is widely accepted that hormone therapy is a critical component of treatment. The current regimens recommended by ACOG include transdermal or oral 17beta-estradiol or conjugated equine estrogen, with either continuous or cyclic progestin in the form of medroxyprogesterone or micronized progesterone [36]. In women who prioritize contraception, replacement with combined oral contraceptive pills is recommended. In addition, in women who prefer physiologic estrogen dosing but desire contraception, a levonorgestrel intrauterine device (IUD) may be used instead of oral progestin [36].

High quality randomized controlled trials have shown the benefit of hormone therapy in patients with POI with regards to bone mass. A three-year study comparing bone mineral density (BMD) between patients on transdermal estradiol 100 μg/d and cyclic oral medroxyprogesterone acetate (10 mg/d $\times$ 12 days monthly) with or without transdermal testosterone (150 μg) showed that BMD in women with POI on estrogen and progesterone replacement was comparable to that of control women. The addition of testosterone was not shown to be beneficial in improving BMD [38]. Low dose hormone therapy was also shown to be more effective in increasing BMD when compared to combined oral contraceptive pills in a 2-year randomized trial [43]. In addition to hormone therapy, risk factors for osteopenia

should be addressed, such as vitamin D deficiency, low calcium intake, smoking and a sedentary lifestyle [5].

With regards to infertility, women with POI have a 5–10% possibility of a spontaneous pregnancy and no treatment has been shown to definitively improve this rate [44]. A single randomized, placebo-controlled study investigating the effect of pre-treatment with estrogen on ovulation after ovarian stimulation in patients with POI showed a significant increase in ovulation rates in the treatment group as opposed to placebo. The authors suggested that the mechanism of this improvement in ovulatory function was due to down-regulation in gonadotropin levels [45]. Future directions regarding infertility treatment for women with POI include research into activation of primordial follicles. This so far includes animal and human *in vitro* studies to identify (and potentially harness) signaling pathways, transcription factors, growth factors and other molecules that regulate follicle activation [46].

5. Conclusions

POI is frequently under-diagnosed due to either low suspicion on the part of the physician or limited patient access to a qualified specialist. Our study illustrates a substantial delay in diagnosis, specifically in an underserved community consisting of largely underrepresented minority women who lack easy access to a reproductive endocrinologist. To our knowledge, this study is the first to assess time to diagnosis of POI specifically in a population of underinsured, underrepresented minority women who face multiple barriers to care. Median time to diagnosis in our patient population was 48 months, a disheartening result given the lost opportunity for early treatment, especially since 35.7% of patients that underwent DEXA screening had osteopenia or osteoporosis and 73.6% of total patients were nulliparous.

It is critical that obstetrician/gynecologists and other providers of primary care are educated to have a high index of suspicion for POI in women with menstrual irregularities and a low threshold for referral to a reproductive endocrinologist. Further research is warranted with joint efforts from major scientific organizations to develop high quality, agreed upon, guidelines. Equally important is patient education as a vital part of patient advocacy, allowing women to make appropriate decisions regarding their own health and wellbeing. Educating women on POI and providing them with information and resources is important to reduce the time between onset of symptoms and diagnosis. In particular, access to reproductive endocrinologists should be facilitated for underserved patients, in order to secure timely care for them and minimize the risk of long-term comorbidities.

Author contributions

EM and LP performed literature search and wrote the manuscript. SB designed the study and performed data collection. VO performed data collection. NCD and SSM designed the study and wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Rutgers Biomedical and Health Sciences Institutional Review Board [Protocol ID Pro2018001738]. Consent to participate was not applicable as this was a retrospective study.

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Conflict of interest

The authors declare no conflict of interest.

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