CLINICAL VIGNETTE

Primary Ovarian Insufficiency: A Primary Care Overview

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Case Presentation

A 25-year-old female, with a history of hydrocephalus status post VP shunt placement as a child, presented to establish primary care. Her major concern for the initial visit was a lack of menses for 5 years. She reported her first menstrual cycle occurred in middle school at the age of 12 years old, and occurred monthly until she turned 16, when her periods lightened and changed in frequency. At this point, she was told by her prior physician that her menstrual changes were due to her weight. She had less than 15% body fat and was 15 to 20 lbs lighter at that time. She had been playing softball and exercising daily. Her irregular menstrual cycle eventually became amenorrhea with no vaginal bleeding for five years. She reported being evaluated by several providers in the past. Most recent testing excluded a thyroid disorder; pelvic ultrasound showed normal ovaries and no endometrial findings. No other recent testing was performed. The patient denied hair or skin changes, including acne. She reported no headaches or vision changes, and specifically no peripheral vision loss. Her breasts had been normal with no changes in size or galactorrhea. Her body weight had remained stable and she was exercising a few times per week. She reported being sexually active with one partner and denied dyspareunia or vaginal dryness. She also denied mood symptoms or hot flashes. On exam she was thin, well appearing woman. Vital signs included BP 118/70 | Pulse 83 | Temp 36.4 °C (Oral) | 5' 5" (1.651 m) | Wt 112 lb (50.8 kg) | SpO2 99% | BMI 18.64 kg/m²

Thyroid was normal size with no nodules; Cardiovascular: No murmurs, rubs, or gallops, normal S1/S2; Abdomen: Non distended, non tender without hepatosplenomegaly.

GU was remarkable for No hair, pink, moist vaginal mucosa, without adnexal masses. Cranial nerves intact bilaterally, peripheral vision intact on confrontation. Skin: Minimal acne over chin, no excessive hair growth, no vitiligo

Labs included: Testosterone 54 ng/dL, DHEA 3640 ng/mL, FSH 70.3 mIU/mL, LH 31.8 mIU/mL, Estradiol <12 pg/mL, Progesterone 0.4 ng/mL, PRL 9.6 ng/mL, TSH 1.1 mcIU/mL, and TPO Ab 9.6 IU/mL. Based on these labs, a diagnosis of premature ovarian insufficiency was suspected. She was referred to reproductive endocrinology for further evaluation and discussion on future fertility. Reproductive endocrinology confirmed the diagnosis of premature ovarian insufficiency and discussed management with estrogen replacement. She did not desire any children in the future, so fertility options were not investigated. The patient was hesitant to start estrogen therapy with concerns that she would "feel different" than her current state. Generally, she felt well despite low estrogen levels. The following tests were ordered subsequently to look for other causes, though none was found.

Anti-Mullerian Hormone <0.003 ng/mL
21 Hydroxylase Antibody <0.2 U/mL
Adrenal Antibody Negative
HIV-1/2 Ag/Ab 4th Generation negative

Karyotype
46, XX
Female Chromosome Analysis with no apparent abnormalities

Fragile X Mutation
No evidence of a fragile X FMR1 (CGG)n mutation

DXA Scan (bone mineral density):

1. The left hip and femoral neck Z-score's of -1.8 and -1.1 respectively, lie within the expected range for age.
2. The PA lumbar spine Z-score of -1.4 also lies within the expected range for age.

Discussion

Pathophysiology: The loss of primordial follicles, the follicles that grow into graffian follicles before ovulation, is a main cause of primary ovarian insufficiency (POI) and the same mechanism for menopause. There are three major causes of early follicle loss, with damage by toxins being one type of insult. Possible toxins include chemotherapy, radiation, surgery and environmental exposures. One study reported sixteen cases of exposure to a cleaning solvent that led to premature ovarian insufficiency.[1] A detailed history is key to picking up on these etiologies. Some chemotherapy agents are well known to have high risk for ovarian toxicity. Cyclophosphamide has been documented to lead to in the 1970s.[2] The mechanism is direct DNA damage in the first 24 hours to the primordial follicles that lead to apoptosis.[3] Other alkylating agents similar to cyclophosphamide carry the same risk. Additional measures to prevent this when initiating alkylating chemotherapy. There is debate whether viral infections can lead to POI through follicle damage, but no studies documenting a direct link. Smoking has also been studied and is not directly associated

with POI, although typical smokers transition into menopause 2 years earlier than the average population.[4]

Autoimmunity is nother important cause for primordial follicle loss. This has been seen in patients with polyglandular syndromes. Both type 1 and type 2 polyglandular syndromes typically involve adrenal insufficiency, with type 2 having a higher occurrence. Adrenal insufficiency, secondary to autoimmunity, represents a large population within these syndromes with concomitant ovarian insufficiency. This more common association is seen because the immune system targets steroid producing cells in both glands and specifically in the follicular, theca cells. Lymphocyte aggregation has been documented on biopsiesa. Autoimmunity to theca cells eventually leads to loss of the follicle. Interestingly, this raises the possibility of immunosuppressive treatment, which continues to be studied.[5] That said, polyglandular syndrome patients with premature ovarian insufficiency does not always present with adrenal insufficiency.

Lastly, genetic abnormalities can lead to POI, due to an insufficient starting numbers of primordial follicles with accelerated loss. The most common genetic disorder associated with POI is Turner's Syndrome, a condition in which the second X chromosome is missing. Studies have examined whether this is due to abnormal follicular development versus early loss. It appears that Turner Syndrome patients have normal follicle development in utero, but months into gestation the follicles degenerate with collagenous tissue replacing them.[6] These patients can have multiple presentations with primary amenorrhea or secondary amenorrhea, reflecting the variability in timing and severity of ovarian atresia. The second most common genetic disorder associated with POI is fragile X syndrome, which is also one of the most common syndromes associated with intellectual disability. This disorder involves repeats of a CGG sequence in the FMR gene region. The disorder presents with varying degrees of severity depending on the length of the repeats. The reason behind follicle loss is uncertain, but is theorized to be secondary to toxic effects of the FMR protein, as POI occurs only in those patients where the sequence length leads to FMR protein production.[7] There are other much less common genetic disorders that can cause POI. Some of these disorders involve production of metabolites that lead to follicular damage, genetic changes that cause damage of DNA impacting certain cells of the follicle necessary for development, and genetic changes impacting cellular division.

The second mechanism for ovarian insufficiency includes follicle dysfunction not follicle loss. Though there are a normal number of follicles, they are not able to mature due to underlying pathology. This can be due to rare changes in the follicular stimulating (FSH) or luteinizing hormone (LH) receptor, changes in the G protein that is linked to FSH and LH receptors, or an enzyme deficiency or enzyme inefficiency leading to low estrogen biosynthesis.

Though several causes of premature ovarian insufficiency are known, most patients have no identifiable mechanism.

Presentation: Symptoms are similar to menopausal transition and estrogen deficiency. These include vasomotor symptoms like hot flashes and night sweats, changes in mood and sleep patterns, and vaginal dryness leading to vaginal pain. Menstrual cycle changes can include either amenorrhea or oligomenorrhea. Because POI patients can still have intermittent follicular development and intermittent menses, the lack of estrogen deficiency symptoms does not exclude the diagnosis. One in 1000 women by the age of 30 years old and one in 100 by the age of 40 years old experience premature ovarian insufficiency.[8] Although most cases are sporadic, from 10-15% of women have a first-degree relative with premature ovarian failure, so a complete history is important.[9,10] If family history is significant for a female relative affected by this condition, then the patient should be referred to a reproductive specialist. Referrals should be placed even prior to detection of any menstrual abnormalities, as studies suggest an occasional autosomal dominant sex linked transmission or x-linked inheritance with incomplete penetrance.[10] Given the association with the developmental disorder Fragile X, a family history of persons with ataxia, developmental delay, and seizures should be obtained. Furthermore, Turner syndrome features such as short stature, shield chest, and webbed neck should be assessed. As autoimmunity can occur in relation with POI, other autoimmune signs can be seen, including enlarged thyroid, vitiligo, or features of adrenal insufficiency.

Differential Diagnosis: Given no specific menstrual history is pathognomonic for POI, the differential can include a few other conditions. Primary amenorrhea occurs in only 10% of cases.[11] Classically the history of POI includes a female with normal menses at puberty that subsequently becomes oligomenorrheic or polymenorrheic, followed by amenorrhea. A minority of cases present with abrupt cessation of menses. Many POI patients can have intermittent ovulation and thus, intermittent menses. Therefore, strict amenorrhea is not necessarily the predominant presentation. The differential for this disorder includes secondary amenorrhea etiologies, most commonly polycystic ovarian syndrome, hypothalamic amenorrhea, and hyperprolactinemia in addition to POI. Pregnancy should also be ruled out.

Gold Standard Diagnosis: Traditionally, to diagnose POI, a woman must be amenorrheic for more than 4 months, with an elevated follicular stimulating hormone (FSH) on two occasions. FSH level must be in the post-menopausal range and checked one month apart. This change must occur before the age of 40 years old, as that is considered the cut off for prematurity.[12] However, POI patients do have intermittent follicular development leading to ovulation, and thus occasional menstruation.[13] An updated definition is now used that includes a variety of menstrual patterns in the setting of post-menopausal FSH levels. Patients with oligomenorrhea represent around 50% of POI cases. Patients that are still menstruating, should have FSH levels checked during day three of their cycle, which is usually the time FSH is lower. Checking an estrogen level simultaneously is helpful in the event follicular development occurred, causing elevated estrogen

levels which would temporarily suppress FSH, leading to a falsely low value in a POI patient. 50% of patients observed over a four-month period achieved elevated estrogen levels due to follicular development, but not necessarily ovulation.[13]

Evaluating for Underlying and Associated Conditions: On presentation, a pregnancy test is the first lab indicated in evaluation of secondary amenorrhea or oligomenorrhea. This is followed by testing for prolactin, thyrotropin stimulating hormone, and follicular stimulating hormone (FSH). If FSH is in the menopausal range, a repeat is indicated in a month. Once the diagnosis is confirmed to be POI with a second elevated FSH level, the mechanism behind the disorder should be determined. With most cases, no underlying cause is identified, though it is suspected to be of some genetic etiology.[10] A karyotype analysis, FMR 1 premutation, adrenal antibodies, as well as 21 hydroxylase immunoprecipitation tests should be performed. These look for evidence of Turner's Syndrome, Fragile X, and autoimmunity/polyglandular syndromes. Among the autoimmune diseases, the two most common are adrenal autoimmunity and Hashimoto's thyroiditis. There is a 50% risk of developing adrenal insufficiency, if adrenal autoantibodies are positive. If adrenal antibodies are present, then the patient should have annual checks of adrenal function.[14] Up to 30% of patients are discovered to have hypothyroidism secondary to autoimmune thyroid destruction, necessitating testing thyroid horomone levels as well as TPO antibodies.

Effects on Health: The average age of menopause in North America is 51 years old. Therefore, the health consequences of lacking physiologic estrogen levels in the body are the main concern for POI patients. Obvious concerns include bone and cardiovascular health, but others should be considered. Women who experienced surgical menopause earlier than the average age of menopause have been studied and findings can be extrapolated to a primary ovarian insufficiency population, who also have no detectable estrogen similar to oophorectomy patients. A Mayo Clinic Cohort study from the 1950s to 1980s, found women who underwent unilateral or bilateral surgical oophorectomy for non-cancerous pathologies prior to transitioning into menopause experienced cognitive impairment and dementia more often than their reference group. The younger the women were at the time of surgery, the greater the risk of dementia. Women receiving estrogen therapy had no increased risk of dementia.[15] Another cohort study, published 7 years later, demonstrated a more rapid cognitive decline with early surgical menopause with increased cerebral plaque formation, typically seen in Alzheimer's disease. If women received estrogen therapy within 5 years of surgical menopause, these risks were not found.[16] A retrospective cohort study on "Impact of a premature menopause on cognitive function in later life" separated women into two groups, those that underwent surgical menopause versus those who had premature ovarian failure prior to the age of 40 years old. Both groups demonstrated trouble with verbal fluency and visual memory compared to women transitioning through menopause between ages of 41 to 50. There was no significant difference between the two types of early menopausal groups – surgical versus physiological transition. Unlike the prior studies, this study did not find a significant improvement in cognitive performance when receiving hormone replacement therapy following menopause.[17] This study reported similar outcomes in both surgical menopause cases and POI. Thus, effects of Estrogen replacement in preventing cognitive decline has been seen, but not in every study. There is also debate about whether estrogen therapy helps relieve symptoms that lead to a better quality of life and sleep, which in turn impacts cognition.[18]

Estrogen's role in maintaining bone health is well understood. Early menopause has been associated with lower bone mineral density, which is associated with high fracture risk.[19] POI patients demonstrated a 2-3% lower bone density compared to the control group.[20] Multiple studies have demonstrated the positive impact of estrogen replacement on bone health. The most recent randomized control trials completed in 2014 and 2016 demonstrated improvement in femoral neck T scores and decrease in bone turnover markers, while on estrogen therapy, either transdermal or oral.[21,22] In the setting of premature ovarian insufficiency, a dexa scan should be obtained to screen for any negative impact on bone density. The standard recommendations for those in perimenopause and menopause transition are typically applied to POI patients. 1200mg of calcium intake per day, maintaining a vitamin D level greater than 30ng/mL, and weight-bearing activities are advised to maintain appropriate bone density. If found to be osteoporotic, bisphosphonates are generally held until the patient determines there is no future pregnancy plans due to their teratogenic effects.

Cardiovascular health is also impacted by lack of normal estradiol levels. There is a two-fold increase in cardiovascular mortality in POI patients. An Adventist Health Study demonstrated that early natural menopause between the ages of 35-40 increases the incidence of ischemic heart disease.[23] Another prospective cohort study looked at women aging from 40 to 54 years old. These non-premature ovarian insufficiency women transitioned through menopause naturally without smoking nor hormone replacement use. Women transitioning into menopause between the ages of 40-44 years old had higher mortality due to coronary artery disease compared to those aged 50-54.[24] There has been no conclusive evidence that estrogen replacement improves this risk. A systematic review looked at 12 different studies to evaluate whether hormone replacement/ maintenance therapy decreased cardiovascular mortality. Unfortunately due to limitations in study construction and reliance on surrogate outcomes, the review could not definitively comment on impact of estrogen therapy on cardiovascular deaths.[25] The reviewers favored estrogen therapy, given its limited risk and potential benefits. More studies on this are required to show a more direct link between hormone replacement and mortality benefit.

Another major impact on health is the psychological consequences of early menopause and infertility. Majority of women are dissatisfied with the way the diagnosis is communicated, which leads to patient distress.[26] POI patients, when compared

to matched controls, exhibit higher rates of anxiety and depression due to perceived lack of purpose in life.[27] How patients are educated on this condition and supported can impact how they handle the diagnosis. Screenings for these mood disorders should be a part of their overall care.

Treatment: Five to ten percent of women conceive and deliver a child following this diagnosis, so pregnancy prevention is necessary if it is not desired.[28] This is part of the reason premature ovarian failure has been removed as a diagnosis and replaced with premature ovarian insufficiency. Oral birth control is not considered effective at preventing pregnancy in this patient population, given past case reports of pregnancy while on oral contraceptives and lack of actual studies.[29] The theory is that birth control is unable to suppress follicular stimulating hormones at high (postmenopausal) values. The main goal in treatment is giving physiological levels of estrogen back with the lowest associated risk profile. Treatment with the lowest risk profile can be accomplished with transvaginal or transdermal estrogen in addition to progesterone 10mg daily for 12 days out of the month for endometrial protection. The dosing of estrogen is typically around 100 micrograms/day which is close to physiologic levels. Both vaginal and dermal administration, bypass liver metabolism and lowers risk for venous thromboembolism.[30] A progesterone IUD can take the place of the oral progesterone, and would serve as a form of birth control as well. Oral contraceptives are an option, but not typically used as first line treatment due to their pharmacologic dosing and first pass metabolism having unfavorable effects on lipids and coagulability. One study showed improved bone health in POI patients using transdermal estrogen rather than oral.[21] Per ACOG guidelines, treatment should extend to the ages of 50 or 51 years old, the time of natural menopause.[31] Fertility is the major concern for most women. There is a small percentage of women who can become pregnant and have remission of POI for up to a few years. If this is not the case, adoption and egg donation are other possibilities.

Summary

Primary Ovarian Insufficiency is a disorder that can present in a variety of fashions. Many patients retain some ovarian function, so evaluation may not demonstrate typical menopausal symptoms as with our case nor true amenorrhea. The causes are numerous, but in the end, most women have no identifiable etiology. Those conditions most associated with POI need to be ruled out, and thus, a standard investigation for Turner Syndrome, Fragile X, Thyroid Disorder, and Polyglandular Disorders specifically encompassing adrenal insufficiency should be assessed. Estrogen therapy addresses hot flashes and genitourinary symptoms, and improves quality of life, bone health, and likely cardiovascular health. The ideal method of estrogen replacement is transdermal 17 Beta estradiol. There are few options regarding fertility management, which was not thoroughly discussed in this review. Primary care physicians should be aware of POI's psychological impact to facilitate better communication regarding diagnosis and care, and to diagnose concomitant depression and anxiety.

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