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Spontaneous Pregnancy in the Setting of Primary Ovarian Insufficiency and Breastfeeding: Does Immunosuppression Play a Role?

Authors' Contribution:

Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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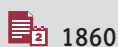
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Conflict of interest: None declared

Patient: Female, 34-year-old
Final Diagnosis: Pregnancy • premature ovarian insufficiency
Symptoms: Amenorrhea • pregnancy
Medication: —
Clinical Procedure: —
Specialty: Obstetrics and Gynecology

Objective: Unusual clinical course
Background: Primary ovarian insufficiency is defined as primary hypogonadism in a woman under the age of 40 years. It commonly presents clinically with amenorrhea and infertility. It is often thought to be an autoimmune process. Breastfeeding also reduces the rate of conception by reducing pulsatile gonadotropin secretion, resulting in lactational amenorrhea.
Case Report: Here, we present a case of a patient with primary ovarian insufficiency. FSH and LH levels at diagnosis were in the menopausal range. After undergoing fertility treatments and failing to become pregnant, she achieved a first pregnancy with donor eggs through *in vitro* fertilization. After delivery, while solely breastfeeding her first baby, menses returned to normal and FSH and LH levels returned to normal. She then spontaneously conceived. She delivered a second baby without the need for assisted reproductive technology.
Conclusions: Pregnancy alters the maternal immune system to produce maternal-fetal tolerance through complex mechanisms that are not completely understood. The immunosuppression of pregnancy in this patient may have repressed the autoimmune process in her ovaries, allowing her to ovulate and thus reverse her primary ovarian insufficiency. Several previous case reports and studies show that immunosuppression has reduced the symptoms of primary ovarian insufficiency and allowed conception in some patients. These studies and this case report raise the question of immunosuppression as a treatment for infertility caused by primary ovarian insufficiency.

MeSH Keywords: Autoimmune Diseases • Breast Feeding • Infertility, Female • Primary Ovarian Insufficiency

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Background

Primary ovarian insufficiency (POI) is defined as ovarian failure in a woman under the age of 40 years. It most commonly presents with infertility, oligomenorrhea, and/or amenorrhea. Only 5–10% of women with POI are able to spontaneously conceive [1]. There are many causes of POI, including genetic, enzymatic, autoimmune, chemical, and environmental causes (Table 1). However, the cause remains unknown in 75–90% of patients [3,4]. In addition to POI preventing pregnancy, breastfeeding is thought to reduce the rate of conception by reducing pulsatile secretion of GnRH and LH by an unclear mechanism [5].

Here, we present a patient with a diagnosis of POI, who failed to become pregnant with initial fertility treatments. She subsequently conceived with donor eggs. After delivery, her menses returned to normal despite her history of amenorrhea due to POI. She also, remarkably, spontaneously conceived while solely breastfeeding her first baby.

Case Report

A 34-year-old woman, gravida 1, para 1, with past medical history significant for POI, prior pregnancy achieved through *in vitro* fertilization with donor eggs, and subclinical hypothyroidism presented for preconception counseling. The patient had delivered her first baby via primary low-transverse cesarean section (PLTCS) 8.5 months earlier. This patient's first pregnancy was complicated by gestational hypertension for which she had an induction of labor at 38 weeks 1 day of gestation. After failure to progress and recurrent fetal decelerations, she had a PLTCS. At this appointment for preconception counseling, she was still solely breastfeeding her 8.5-month-old child. She was currently having regular menses (25-day cycles), which had not been the case for approximately the last six years before delivery. Roughly four months postpartum, she had labs re-checked due to the return of cyclic, monthly bleeding. FSH was 7.3 mIU/mL and Anti-Müllerian hormone (AMH) was 0.545 ng/mL, despite previous levels from the patient's previous obstetrician/gynecologist and reproductive endocrinologist in the menopausal range, which had given her the diagnosis of POI (Figure 1). At the time of this appointment, her menses were three days late, and she was concerned that she was pregnant. A urine pregnancy screen was obtained and was positive.

This patient's history was significant for menarche at age 13. She initially had regular periods with dysmenorrhea and menorrhagia. At age 15–16 years, she began taking combination oral contraceptives (COCs), starting with norgestimate and ethinyl estradiol. After some years of taking this medication, she switched to taking drospirenone and ethinyl estradiol. She had irregular cycles

Table 1. Autoimmune causes of primary ovarian insufficiency [3,4].

Autoimmune and related diseases	Increase of CD4+ T and B cells
	Addison's disease
	Alopecia
	Autoimmune hemolytic anemia
	Autoimmune polyglandular syndrome
	Celiac disease
	Chronic active hepatitis
	Chronic candidiasis
	Crohn's disease
	Grave's disease
	Hashimoto thyroiditis
	Hypophysitis
	Oophoritis
	Ovarian antibody
	Idiopathic thrombocytopenic purpura
	Parathyroid disorders
	Pernicious anemia
	Primary biliary cirrhosis
	Myasthenia gravis
	Rheumatoid arthritis
	Sjögren's syndrome
	Systemic lupus erythematosus
	Type 1 diabetes mellitus
	Vitiligo
	Zona pellucida antibody

with continued dysmenorrhea and menorrhagia while on COCs. She then had a levonorgestrel-releasing intrauterine device (IUD) placed at approximately age 28 years. She had the IUD for 2.5 years, during which time she had no menses. It was removed because of the patient's desire for pregnancy. Five months after the IUD was removed, the patient presented to the clinic for evaluation of secondary amenorrhea as she had had no menses after removal of the IUD. At this clinic visit, she was prescribed a 10-day oral progesterone challenge. She experienced minimal spotting after this challenge, but no true menses. Labs were drawn by her primary obstetrician/gynecologist, which showed FSH 58.1 mIU/mL, LH 31 mIU/mL, and estradiol 64 pg/mL. FSH and LH were elevated, consistent with POI. Since estradiol was within normal limits, the patient was started on clomiphene cycles to induce ovulation. She was instructed to use ovulation predictor kits and timed intercourse. After failing to achieve pregnancy with five cycles of clomiphene, the patient went to see a reproductive endocrinologist, where AMH was <0.05 ng/mL. Around this time, per patient report, repeat FSH was elevated at 51 mIU/mL on cycle day 2 and 31 mIU/mL on day cycle day 5. TSH and prolactin, when checked, had been within normal limits. The patient was subsequently diagnosed with POI. After this diagnosis, the patient decided to proceed with donor eggs, and she achieved her first pregnancy one year later through IVF. This first pregnancy was complicated by gestational hypertension, and the baby was delivered via PLTCS, as described above.

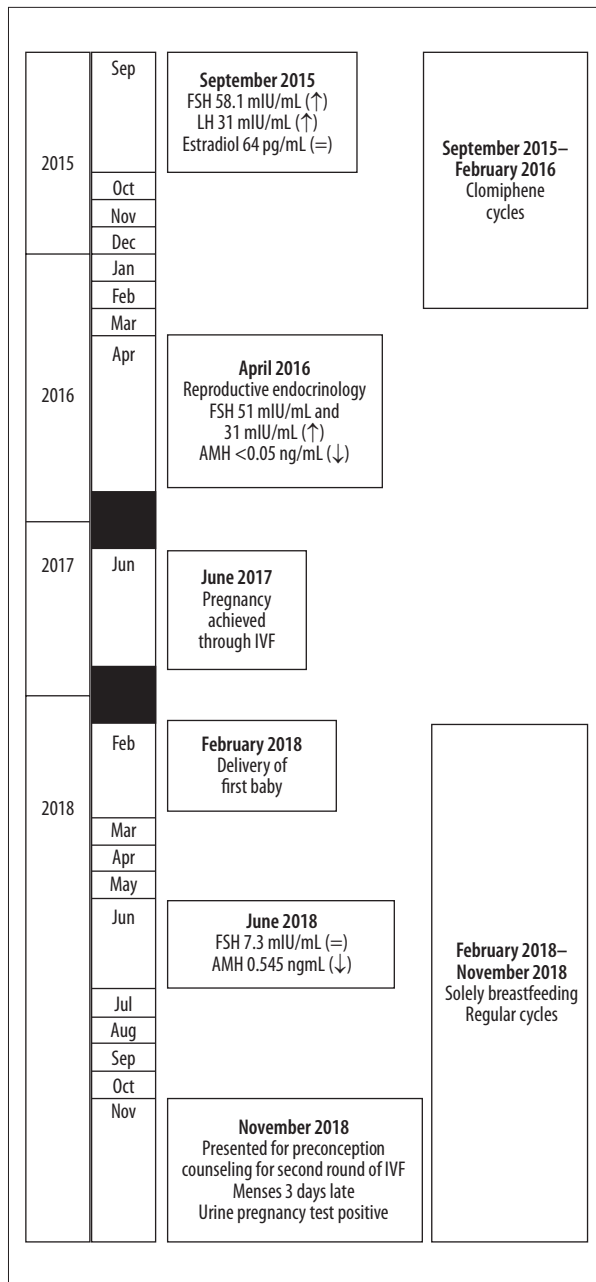


Figure 1. This figure indicates the patient's time course of fertility workup, treatments, and pregnancy. The patient had labs drawn at three points: first with her primary obstetrician/gynecologist for fertility workup (September 2015), second with reproductive endocrinology (April 2016), and third with our office upon resumption of normal menses after delivery of her first child (June 2018). Symbols indicate the following ↑ – increased, ↓ – decreased, = – normal.

Of note, this patient's workup for an etiology of POI did not determine a specific cause. There was no documentation of stigmata of Turner syndrome, prior ovarian surgery, chemotherapy, or family history of POI or fragile X syndrome. She had normal chromosome studies (46,XX). With her history of subclinical hypothyroidism, a possible autoimmune etiology was suspected. A personal or family history of autoimmune disease implies that a potential polyglandular autoimmune syndrome may exist.

This patient's second pregnancy, achieved spontaneously, was complicated by advanced maternal age at delivery. She took daily aspirin after the first trimester due to her history of gestational hypertension. The healthy baby was delivered via repeat low-transverse cesarean section at term.

Discussion

A salient complication of POI is infertility, and it is one of the major clinical presentations of this diagnosis. While the patient discussed here did have infertility for years, necessitating the need for donor eggs, she then became pregnant spontaneously while solely breastfeeding. This occurrence is remarkable, considering the combination of POI and breastfeeding, which both reduce fertility. To theoretically explain this patient's achievement of spontaneous pregnancy is difficult, since the cause of POI is unknown in most patients. As stated in the details of this case report, the only clue to an etiology in this patient is her history of subclinical hypothyroidism, suggesting an autoimmune cause.

Given the likely autoimmune nature of this patient's POI, pregnancy-related immunosuppression may have contributed to suppressing her POI enough to become pregnant. Pregnancy is a semi-allograft, since half of the genetic material is paternal, necessitating immunosuppression for fetal tolerance. Elements of immunosuppression during pregnancy are well-established, although not fully understood. Research has focused on the immune function of specific molecules, types of immune cells, and hormones.

Important regulatory molecules for immunosuppression in pregnancy include indoleamine 2,3 dioxygenase (IDO), CD95L, Crry, and MHC class II antigens. IDO is a molecule that disables local T cell response. It is produced by maternal uterine mucosa and fetal syncytiotrophoblasts. Mice with pharmacologic inhibition of IDO suffered from fetal loss [6–9]. CD95L (Fas ligand) is expressed by fetal trophoblasts and promotes apoptosis of activated lymphocytes expressing CD95 (Fas). Mutant strains of mice lacking functional CD95L had small fetuses and resorption of fetuses. Crry is a complement inhibitor in mice. In mice with this gene deleted, gestational failure ensued due to

compliment deposition and inflammation at the maternal-fetal interface. Fetuses were rescued from gestational failure with the addition of gene deletion of the C3 complement component. There is no Crry in humans, but alternative mechanisms of complement suppression exist [10–12]. Lastly, MHC antigens have a role in the immunosuppression of pregnancy. MHC class II antigens are usually limited to professional antigen-presenting cells. However, they can be induced in other tissues by exposing them to the cytokine IFN- γ . However, this is not possible in trophoblasts, suggesting that even in the setting of inflammation, antigen presentation via MHC II is prevented in these cells. Some subtypes of MHC class I molecules are also absent in the placenta. An allelic difference in HLA-G, a type of MHC class I molecule, was found in fertile couples versus couples with at least two unsuccessful fresh embryo transfers [13–15].

With respect to immune cells, uterine natural killer (NK) cells are not cytotoxic, as opposed to peripheral NK cells, which are. Regulatory T (Treg) cells increase in the spleen and lymph nodes that drain the urogenital tract, starting at day 2 of pregnancy in mice. The absence of these cells led to early gestational failure in pregnancy [16,17]. Studies have also found increased Tregs in the human decidua and blood during pregnancy. These Tregs suppress proliferative responses of T cells to allogeneic dendritic cells. Lastly, in the population of T helper cells, Th2-predominance over Th1 is proposed to aid in immunotolerance to pregnancy, based on evidence from both human and murine pregnancy [18–21].

With respect to hormones, pregnancy produces a high estrogen and progesterone state. These hormones are postulated to play a role in the immunosuppression of pregnancy via several mechanisms. Progesterone induces a Th2-dominant cytokine production, uterine homing of NK cells, and increase in leukemia inhibitory factor, an IL-6 that inhibits myeloid cell differentiation. In patients who miscarried, a decline in estrogen and progesterone correlated with skewing of Th1/Th2 balance toward the Th1 response. There is also evidence that estrogen has anti-inflammatory effects, although this has been studied in the context of osteoarthritis [22–24]. Another important pathway in which sex hormones affect immune function involves myeloid-derived suppressor cells (MDSCs). These cells expand during cancer, inflammation, and infection, and suppress T cell responses. According to one study, patients who miscarried had lower functional MDSC levels [25–27]. Furthermore, MDSCs accumulate in the cord blood of healthy newborns and in the peripheral blood of healthy pregnant women [28]. In a study of mice with systemic lupus erythematosus, female mice had a higher frequency of MDSCs in peripheral blood mononuclear cells, and 17 β -estradiol was positively correlated with frequency of MDSCs [29]. In patients who miscarried, a decline in estrogen and progesterone was correlated with a decline in MDSCs [23].

With respect to POI, there is some research to suggest that immunosuppressive therapy can be effective. There are two case reports of patients with comorbid myasthenia gravis (MG) and POI treated with immunosuppression (corticosteroids, intravenous immunoglobulin, plasmapheresis) with subsequent return of menses. In one case, gonadotropins nearly normalized. Similarly, there are case reports of patients with POI who resumed menses after being treated with corticosteroids [30–34]. In one report, the patient subsequently conceived [32]. In a prospective study, 2 of 11 women with POI treated with corticosteroids had return of menses, biochemical normalization, and conception [35].

This research on immunosuppression in the context of our case report raises the question: did this patient's first pregnancy create the perfect immunologic milieu to suppress the autoimmune process in her ovaries so she could conceive again? In other words, did her pregnancy treat her POI? This postulation is theoretical and would be helped if more frequent measurements of FSH, LH, estrogen, AMH, and immune markers such as Th1 and Th2 cells and cytokines could have been obtained, to see in real-time when her POI improved and how her immune status changed. Monitoring of these levels in patients with POI has potential for prospective studies.

While the role of immunosuppression in reversing POI is theoretical, it does raise interesting questions about the role of immunosuppression as a management strategy for infertility in POI as opposed to the costly option of utilizing donor eggs. It also raises questions regarding the interplay of POI, immunosuppression, and pregnancy, including whether a first pregnancy in a patient with POI might make it easier to achieve future pregnancies.

Conclusions

Infertility is a major complication of POI, which is often caused by an underlying autoimmune process. Limited previous studies have shown that treatment with various methods of immunosuppression have improved symptoms of POI and have even allowed some women to achieve pregnancy. Similarly, pregnancy itself is immunosuppressive, resulting in maternal-fetal tolerance. These facts and our case report raise the question of whether pregnancy itself can help treat the infertility associated with POI.

Conflict of interest

None.

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