**Case report**

A case report of spontaneous pregnancy during hormonal replacement therapy for premature ovarian failure

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**Abstract**

**Background:** Premature ovarian failure (POF) is a common condition; its incidence is estimated to be as great as 1 in 100 by the age of 40 years. Physiologic replacement of ovarian steroid hormones seems rational until the age of normal menopause. Temporary return of ovarian function and pregnancy may occur rarely in women with POF. We report a case of POF who conceived during hormone replacement therapy.

**Case:** A 30 years-old woman with confirmed POF after pelvic surgery and severe emotional stress conceived spontaneously.

**Conclusion:** Return of ovarian function and achievement of pregnancy is possible in women with POF.

**Key words:** Premature ovarian failure, Transient ovarian failure, Hypergonadotropic hypogonadism, Hypergonadotropic amenorrhea, Hormone replacement.

**Introduction**

Premature ovarian failure (POF) is a mysterious disorder. It is defined by the association of amenorrhea, hypoestrogenism and elevated (menopausal) levels of serum gonadotropins before the age of 40 years (1). It is not a rare condition; its incidence is estimated to be as great as 1 in 100 by the age of 40 years, and 1 in 1000 by the age of 20 years (2). Although, the most cases of POF are idiopathic, with no identifiable etiology even after a thorough evaluation, diverse etiologies have been associated with POF: genetic aberrations, iatrogenic factors, autoimmune ovarian damage, infectious agents, toxins and environmental factors (3, 4). Netter et al have suggested that severe emotional stress could be cause of POF (5). Despite the absence of controlled evidence for this specific population, physiologic replacement of ovarian steroid hormones seems rational until the age of normal menopause (6, 7). This condition differs from normal menopause in several important ways.

Temporary return of ovarian function, as indicated by elevated estradiol levels, follicle development, and even pregnancy may occur in women with idiopathic, iatrogenic or psychogenic ovarian failure (5-9).

Here, we report a case of POF who conceived during hormone replacement therapy.

**Case report**

A 30 years-old woman was referred to our infertility clinic, for evaluation of primary infertility with 7 years duration. She recalled experiencing thelarche at 11 years of age and did not recall the timing of adrenarche. She had menarche at 12 years and reported regular menstrual cycles, lasting 3 to 5 days. The significant points in her
personal and past medical and family history were
occasional migrane headaches without associated
neurological deficits and mental retardation in her
maternal uncle. Her physical examination revealed
a healthy appearing woman with body mass index
(BMI) of 26, Tanner stage V development, normal
pelvic examination, including a well estrogenized
vaginal epithelium. In this time, she was 25 years
old. Routine infertility work-up including
hormonal assay on 3rd day of cycle (basal FSH
level=6 IU/ L; LH level=5.5 IU/ L; E2 level= 27
pg/m L), semen analysis, hysterosalpingography,
and transvaginal ultrasound revealed no
abnormality with impression of unexplained
infertility, controlled ovarian hyper stimulation
(COH) and IUI was recommended. She conceived
in the second cycle of COH and IUI. She had an
ectopic gestation in ampullary portion of right tube
that was treated with laparoscopic salpingectomy
at the seventh week of gestational age. In
laparoscopic view, uterus and left adnexa were
unremarkable and right salpingectomy was
performed by using electrocautery. No surgical
complication occurred. The patient had one
episode vaginal bleeding 4-5 weeks after
operation. Then she experienced severe emotional
stress (death in her family), and after this event,
her menses ceased. Eight months later, she began
experiencing hot flushes, dysparonia, and loss of
libido. In this time, she was 26 years old. History
and physical examination were unremarkable
except for secondary amenorrhea with 8 months
duration and hypoestrogenized vaginal epithelium.
In vaginal smears, intermediate cells were seen.
Transvaginal ultrasonography demonstrated normal
size uterus with thin endometrum and small
ovaries (right ovary 2.1cm³, left ovary 2.3cm³)
with 3-4 primordial follicles in each ovary.
Progesterone–withdrawal test was negative. Serum
FSH and LH levels were high (FSH=62 IU/ L, LH
=34.8IU/ L).Progesterone level was (0.3ng/m L),
and estradiol level was less than (10pg/ m L). The 3rd
day hormonal assay was repeated 4 months later
(basal FSH level=135 IU/ L, LH level=88 IU/ L,
E2 level= 10 pg/m L). CBC, ESR, FBS, serum
creatinine, prolactin, androgen, ANA, Anti-ds
ANA, U/A, and liver, thyroid, adrenal function
tests were in normal ranges. Adrenal autoantibody
tests were negative. DEXA study revealed mild
osteopenia. Karyotype was 46 XX, fragile X
mutation testing revealed normal size alleles with
normal ranges of CGG repeats. Because of the
unknown clinical value, serum anti ovarian
antibody tests and ovarian biopsy did not request
(9). She had serial hormonal (FSH, LH) assay. The
last one belongs to 9 months prior to the recent
pregnancy, which was showed high (menopausal)
levels of gonadotropins. Hormone replacement
as sequential regimen with 1.25mg of conjugated
equine estrogen daily for 25days / month and 10
mg of medoxy progesterone acetate for 14days/
month was initiated. Daily weight bearing exercise,
and calcium and vitamin D taking were advised.
For infertility treatment, assisted conception with
donated oocyte was suggested, but she did not
accept this advice. Four years after starting
sequential hormone replacement therapy, she
noticed no return of vaginal bleeding for 6 weeks.
At this time, her β-hCG level was positive,
transvaginal ultrasonography showed an early
intrauterine pregnancy. E2/progesterone
replacement therapy was stopped. She is currently
in second trimester (23weeks) of an uneventful
pregnancy.

Discussion

Women with POF are not necessarily sterile; they have %5 chance of conceiving at some time
after diagnosis (6). So the term POF is medically
inaccurate. The terms "hypergonadotropic
hypogonadism" and "premature ovarian
insufficiency” are more accurate. However the
most of spontaneous pregnancies occur while
patients are receiving HRT, but this may not imply
a cause-and- effect relation (7).

Our patient had the pelvic surgery and
emotional stress before spontaneous cessation of
her menstruation. The effect of pelvic-adnexal
surgery on ovarian function has been evaluated
(10). Although no prospective studies of ovarian
function and gonadotropin levels before and after
pelvic-adnexal surgery have been done, some
evidences indicate that such surgery sometimes
affects ovarian function by compromising ovarian
blood flow. Recovery after interventions that
compromise ovarian blood supply would seem to
be possible if sufficient collateral circulation
develops and the resting follicles resume their cycles.

Although, the mechanism involved in stress-induced ovarian failure is unknown, transient loss of ovarian function has been described in cases of major emotional stress (5). Netter et al reported hypergonadotropic hypogonadism secondary to emotional stress in 10 women 18 to 38 years of age. Only one of these patients had subsequent return of menses (5). While we cannot rule out idiopathic premature ovarian failure in our case, the sequence of events implies that the pelvic surgery and emotional stress influenced her ovarian function.

Although, we know that ovarian “failure” in POF does not mean permanent cessation of ovarian function, “but the likelihood of recovery of ovulation is not possible to predict POF (7). Although, different drug intervention such as various dosage of corticosteroids, estrogen, clomiphend, high-dose gonadotropin, recombinant FSH, danazol, and apoptotic inhibitors were recommended to induce ovulation in patients with POF, “but the few randomized controlled trials that are available fail to demonstrate any significant improvement in ovulation and pregnancy rates(7, 9). Assisted conception (IVF) with donated oocyte was documented to be choice in these patients (6,7). Advanced in technology of cryopreserved ovarian tissue transplantation and in-vitro maturation of oocytes derived from stem cells, may make it possible for some women with POF to use their own egg for IVF (11, 12.). The women with a significant family history of POF may consider oocyte or embryo cryopreservation since there are currently no entirely reliable tests to predict ovarian reserve (13, 14).

Pregnancy in the patients with POF is associated with significant fetal and maternal mortality and morbidity such as increased risk of a child with fragile X syndrome, intra uterine fetal death, pregnancy-induced hypertension, and postpartum adrenal crisis (15-17). So women who wish to avoid pregnancy should use a barrier method, because HRT or use of oral contraceptive pills will not prevent conception, perhaps due to the elevated gonadotropin levels in this condition (18).

References
