

Spontaneous and Successful Pregnancies After Premature Ovarian Insufficiency: Case Series

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Abstract

Premature ovarian insufficiency (POI) formerly referred to as premature menopause, premature ovarian failure or primary ovarian failure (POF) implies quantitative and qualitative alterations in the functional integrity of the ovarian follicles leading to irregularity of menses, clinical manifestations of signs and symptoms of menopause and impaired fertility performance. This phenomenon tends to occur in about 1% of the women population in their reproductive years and arbitrarily below the age of 40 years.

We hereby present case series of seven subjects who were specifically complaining of infertility or low fertility from a total of 242 women with presumed diagnosis of premature ovarian insufficiency. These were extracted from a pool of 10,090 clients that were documented over a year's period i.e. from January 1, 2020 up to December 31, 2020. Our patients achieved spontaneous pregnancies and underwent a normal course of the pregnancies that culminated in uneventful childbirths. The deliveries invariably took place in private setups. We maintained a close contact telemetrically and physically; and followed them up during their course of the delivery and the postpartum period since they were denoted as very high risk pregnancy.

To the best of our knowledge, there is no isolated similar case report or publication in the Ethiopian setting. The objective of the case series presentation is linked with the intention of adding to the world literature highlighting its relevance, desire to create more awareness and establish the basis for further inspiration to develop future undertakings in the understanding of diminished ovarian reserve vis-a-vis premature ovarian insufficiency and spontaneous pregnancy.

Keywords: Diminished ovarian reserve, Premature ovarian insufficiency, Infertility, Pregnancy, Ethiopia

Introduction

Premature ovarian insufficiency (POI) is characterized by diminished ovarian reserve and consequently pronounced by dramatic depletion and dysfunction of the ovarian follicles at a much younger age leading to a state of hypergonadotropic hypogonadism. Thus, the premature decline of the total follicular population as a consequence of apoptosis, increased destruction of the ovarian follicles as a result of disease conditions, over stimulation or treatment sequelae as in chemo and radiotherapy are all incriminated factors though in 90%, the cause is astoundingly idiopathic [1, 2].

The diagnosis is established by taking comprehensive family, personal, reproductive and gynecological history coupled with

laboratory investigations of significant emphasis (FSH, LH, estrogen, progesterone AMH, vitamin D and calcium). Moreover, it has been instrumental to employ abdominal and pelvic ultrasound evaluation for obvious pathologies and in particular transvaginal sonography for diminished ovarian volume (shriveling) and follicle count as deemed necessary [3-6].

It is worth reiterating that POI occurs in 1% the women population under 40 years of age though higher rates have been reported and put at 2.4% for Ethiopia and 1.2% for Sweden [7-11]. Unlike complete ovarian failure with fulminant menopausal symptom complexes of amenorrhea and infertility in the absolute sense, there exists intermittent resumption of ovarian functions resulting

in normal ovulation and spontaneous pregnancy in about 5-10% worldwide and 2.3% of the women in Ethiopia with POI [10, 12].

The conservative and prospective treatment approach would ideally be to anticipate for a spontaneous resumption of the normal ovarian activity with an ultimate chance or occurrence of a pregnancy. However, for the nulliparous, infertile or of low fertility women who are in dire desperation to achieve a pregnancy and have their own children, a multitude of interventions comprising of prepubertal ovarian tissue cryopreservation, donor egg, hormone replacement therapy (HRT), clomiphene citrate challenge test (CCCT), Dehydroepiandrosterone (DHEA), IVF (In Vitro Fertilization) and ovulation induction modalities are available when feasible economically and/or at last resorting to adoption. More importantly, patients with such clinical disorders require psychosocial and psychosexual support to bring them out of the associated health impairment in conjunction with treatments for related medical untoward effects of hypergonadotropic and hypogonadism state [2].

In so far as there are no published reports and short of our mention in our previous publication on POI, the purpose of this presentation is to assert the fact that such a clinical phenomenon is not a rare occurrence and create awareness among the practicing young obstetrician-gynecologists, and contribute to the field from our perspective in an Ethiopian setup.

Case Series

General Remarks

The clients constituting the case series at the Yehuleshet Higher Clinic, Gyn-Obs unit were previously menstruating and became amenorrhoeic for more than three or more months or were complaining of oligo-amenorrhea and more often of infertility and low fertility excluding cases with primary amenorrhea and/or chromosomal abnormalities. Their menarche was invariably between ages 11-16 years. Their age range spanned from 33 to 38 years and the average years thus computed was 35. They accounted for a 2.4% (242/10,090) prevalence rate of POI among the patient population seen in the stated period of time; and yielded a 2.9% (7/242) successful spontaneous pregnancy rate after clinically confirmed premature ovarian insufficiency. Their data was collected from January 1 to December 31, 2020. They are residents of Addis Ababa with the exception of one from its vicinity. They were all followed up for the first four months of 2021 to wrap up the data compilation, proceed with the analysis and finalize the write up.

The data extracted from their history included the socio-demographic information, presenting complaints and their associated symptom complexes, family history and elaborate medical, in particular autoimmune disorders, chemotherapy and radiotherapy for gynecological or colorectal cancers, and surgical anamnesis (bilateral oophorectomy) pertaining to possible and contributing elements towards aetio-pathologic processes of POI. Unless and

otherwise these factors were of pertinent relevance to the presentation, they would not be further elaborated upon since they are totally lacking.

The specific laboratory investigations that were carried out to establish the diagnosis of POI included the fertility panel (FSH, LH, estrogen, progesterone, prolactin and testosterone) and AMH which were very strongly implicated in cementing the diagnosis of POI. Vitamin D influences fertility; and along with calcium improves fertility and pregnancy outcomes and hence both were studied. These investigated parameters were considered fair enough for such a low resource setting like ours. The additional tests like fasting blood sugar, thyroid function tests, hepatitis B and C virus antibody, tests for syphilitic acquisitions and Human Immune-deficiency Virus infections were unremarkable and did not warrant any causal relationship. The abdomino-pelvic ultrasound evaluations were routinely ordered to rule out gross pelvic pathologies whereas the transvaginal ultrasound studies mainly focused on the exclusion of polycystic ovaries, appreciation of the shrinkage of ovarian volume or, if any, the number of antral follicles.

Synopsis of their Presentation

The individual brief description of the background history upon the initial presentation and prior to their success story of achieving additional, unexpected and successful spontaneous pregnancy and childbirth is illustrated hereunder.

1. Case 1 (1993/11)

E T, a housewife, aged 37 years old government employee who was married four years ago and encountered four spontaneous abortions at 2 twice, 3 and 5 months of pregnancy, respectively. She started to experience irregular menses with up to six month's interval a year and half ago with minimal vasomotor symptoms and failure to achieve a clinical pregnancy.

2. Case 2 (623/09)

W A is a 32 years old housewife and a primipara with a normal vaginal delivery 3 years ago. She complained of oligo-amenorrhea of two year's duration and failure to attain a renewed pregnancy. The associated vasomotor and decreased libido as well as disharmony with the husband was annoying and threats of divorce were looming. This became more pronounced with the surge of their financial and material wealth.

3. Case 3 (1093/06)

A K is 33 years old Para II Abortion II. She a banker by profession and presented with amenorrhea of six months, hot flushes, sweating, mood swings, sleeplessness and decreased libido as well as strong desire to have a child in fulfillment of the husband's strong desire.

4. Case 4 (2013/11)

E G is a 38 years old nulliparous with three consecutive and spon-

taneous abortions of less than three months of gestational ages. She is a government employee who presented with oligo-amenorrhea spanning up to 3-6 months and ineptitude to achieve a viable term pregnancy.

5. Case 5 (429/12)

B A is a 33 years old, Para 0 Abortion II. She is self employed from the vicinity of Addis Ababa and presented with complaints of irregular menses with intervals of more than three months and more importantly failure to procure a term pregnancy that climax in live childbirth.

6. Case 6 (265/05)

T N is 39 years old Para III Abortion 0. She is a banker by profession and presented with amenorrhea of 6 months and fulminant signs and symptoms of postmenopausal syndrome. The male part-

ner's pressure forced her seek medical help to abate the symptoms, improve on their sexual relationship and demandingly have more children.

7. Case 7 (606/10)

S F is 35 years old self employed merchant, Para II Abortion 0. Her last delivery was 5 years ago and presented with complaints of unpredictable menstrual patterns with intervals longer than three months and menopausal symptoms; and inability to have more children.

Selected and Specific Results

The essential laboratory investigations that were employed and contributed to the basis of the diagnosis of POI are tabulated and presented in the following table.

Variables		Case Series							Units
		1	2	3	4	5	6	7	
Fertility panel	FSH	57.56	87.59	44.26	30.00	33.08	66.70	128.30	mIU/ml
	LH	38.00	45.00	25.00	45.00	35.02	35.00	30.01	mIU/ml
	Estrogen	45.00	57.00	38.00	58.00	31.00	38.00	5.00	pg/ml
	Progesterone	0.45	0.25	0.30	0.38	0.94	0.62	0.68	ng/ml
	Testosterone	0.35	0.80	0.19	0.25	0.13	0.45	0.33	ng/ml
	Prolactin	14.00	12.00	19.00	20.00	15.00	21.00	9.70	ng/ml
AMH		0.02	0.08	0.29	0.34	0.02	0.09	0.01	ng/ml
Vitamin D		12.00	16.26	15.00	17.58	6.00	11.00	17.04	ng/ml
Serum calcium		8.80	9.80	9.20	9.10	9.00	9.40	9.50	mg/ml

Management Approach

All of our patients were counseled on the available provisions of ART. In the light of financial constraints and the improbability of getting the required advanced comprehensive treatment outside the country, they are hinted that pregnancies can still happen. Alternatively, they were all voluntarily put on folic acid, vitamin D and calcium supplementation without coercion or inducements. Whenever the unexpected and spontaneous pregnancies were suspected and confirmed, they were electively put on oral 10 mg dydrogesterone therapy in combination with weekly 250mg 17-a-hydroxyprogesterone-caproate (17-OHPC) depot injections for up to 14 weeks of pregnancy as a prophylaxis in the prevention and lowering of the risk of miscarriage thereby ensuring the maintenance of the pregnancy and also achieve the quiescence of the uterus.

Discussion

The normal spontaneous fertility performance of women and the number of individual reproductive years is very much dependent on the physiological synchronization of the function of the pituitary gland (FSH, LH) with the ovarian reserve, production of estrogen and progesterone with the cyclical and natural release of a mature Graafian follicle. Furthermore, these qualities and their re-

sponsiveness to stimulation are fully and meaningfully expressed provided that the axis pertaining to the fallopian tubes, uterus and the vaginal tract is intact and functional [13]. Our clients were normally menstruating, engaged in normal sexual activity and were capable of becoming pregnant as evidenced by their parity and history of miscarriages up until the onset of the POI.

The hallmark of the presentation of POI is more importantly distinguished by the low fertility or infertility. The diagnostic measures employed, especially the fertility panel and AMH, are explicit tools to basically establish the diagnosis of idiopathic POI in a low resource setting. As opposed to subjects with primary amenorrhea as in congenital disorders like Fragile or Turner's syndrome, or those who underwent bilateral oophorectomy and/or were subjected for chemo-radiation for cancer treatment or have had history of pelvic infections, endometriosis and autoimmune disorders resulting in absolute ovarian failure, patients with POI as in our presentation, can unpredictably get pregnant without any intervention [14].

The possibility of such an event which is in the range of 5-10% worldwide and a 2.3% rate in our earlier publication and 2.9% in

our current study is strikingly a matter of concern as our results are of low percentages which can be attributed to drop outs in favor of individual preferential medical or traditional treatment modalities or lost to follow ups in general. At this juncture, it is worth speculating that previous reproductive performances, family history, genetic and environmental factors, socio-economic influences and nutritional disadvantages may exert their negative detrimental effect.

The chances of a successful spontaneous pregnancy, no matter how remote, are always thoroughly discussed as a mandatory counseling process from and in line with reproductive rights perspective [10, 15-17]. Furthermore, in order to alleviate their feeling of hopelessness and despair, management options that include hormone replacement therapy, donor egg and IVF within the scope of ART, if affordable and acceptable by travelling abroad, were put forth for them and advised to never give in or give up despite the bothersome vasomotor and neurovegetative symptoms, if time is of the essence to primarily overcome their infertility issue rather than the low fertility related desire.

Therefore, in a high parity population like ours, the cultural desire to have more children is rather governed by the male partner, relatives or clans, their religious or mystic beliefs and the common concept that the child is born with its bounty and that there is no limit for procuring a child. The failure to do so results in an emotional trauma with sullen faces and desperation; and at times threats of possible divorce or separation. More often, our patients initially go into a denial state during counseling and express a displaced anger and vow to resort to unspecified traditional medicines, religious practices including holy water baths and drinking.

As a part of our counseling, we routinely and emphatically differentiated our earthly knowledge from the unexpected miraculous godly surprises or provisions of nature in the glimmer of hope that pregnancy can still occur without intervention despite the diagnosis of POI. It is thus imperative to enlighten academicians and practitioners alike in the understanding of the clinical entity and the complexity of its management.

Conclusion and Recommendation

Premature ovarian failure (POF) or premature menopause implies absolute/ cessation of menses, failure to ovulate and present with overt clinical manifestations of symptom complexes of menopause. POI patients, however, can resume menstruating, ovulate intermittently, get pregnant unexpectedly and deliver as demonstrated in these case series and also corroborated in other such publications. It is apparent and commendable to co-opt of standardized set of criteria to diagnose and manage the clinical entity as tailored towards the individual need. Moreover, it is worth contemplating to undertake such a longitudinal prospective study in the future by interested groups or individuals in multicenter setups involving a larger segment of the population.

Limitations

This is just a case series presentation and no significant predictive scoring system to determine ovarian activity, as in the Swedish study involving a larger population composed of 358 patients, was adopted. The main variables of relevance that they accounted for included age at diagnosis, presence of follicles at ultrasound, inhibin b, and estradiol levels [18].

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