

Premature Ovarian Insufficiency: Under-Diagnosis and Diagnostic Opportunities

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ABSTRACT

Background: Premature ovarian insufficiency (POI) is basically cessation of menses, irregular menstruation or reduced fertility before the age of 40 years. It occurs in about 1% of the women population although younger women are not immune. The ultimate pathophysiology centers on the depletion of follicles and/or loss of endocrine function of the ovaries. Most commonly, it is idiopathic but possibly could be secondary to iatrogenic factors or a multitude of clinical conditions. Unlike natural menopause or acute ovarian failure, pregnancy is possible.

Objective: The study will provide valuable information in the prevalence, clinical presentations and counseling of patients regarding the management options for the affected individuals.

Setting: A clinical setting in the Ob-Gyn specialty clinic.

Methods: All prospective, consecutive patients attending Ob-Gyn clinical services with complaints of irregular menstrual bleeding including amenorrhea and those visiting us for preconception fertility counseling and infertility. The study was conducted during the period extending from January 1, 2020 to June 30, 2020. Variables considered included socio-demographic characteristics like age, religion, ethnicity, residence, socioeconomic status (educational achievement, family monthly income) along with their obstetric performance and menstrual history. Transvaginal ultrasonographic findings and laboratory tests, especially and more importantly of the fertility panel and Anti-Müllerian hormone (AMH) were determined and documented. The variables extrapolated ensured accuracy, avoided redundancy and maintained confidentiality. The data was entered, cleaned and analyzed using Epi-Info statistics software program. Descriptive statistics like mean and median for quantitative and proportion/percentage for qualitative variables were used, respectively. Level of significance was set at P -value <0.05 .

Inclusion and exclusion criteria were set so that only patients with established scenario of hypergonadotrophic hypogonadism and diminished ovarian reserve vis-à-vis the AMH were availed.

Results: Out of a total of 5348 gynecological patients, 130 were diagnosed to have premature ovarian insufficiency giving a prevalence rate of 2.4%. Among the subjects with POI, three (2.3%) achieved spontaneous pregnancy with folic acid and vitamin D with calcium prenatal supplementation, despite guarded prognostication and suggestion for donor egg or embryo transfer and intent to liaise them to where it is routinely practiced. The mean age was $34.8 \pm SD4.8$ with the range being between 21-39 years. Their clinical presentations in the order of frequency were predominantly secondary and primary infertility and oligo-amenorrhea of up to three months followed by sign and symptom complexes of postmenopausal syndrome. The diagnosis was ascertained by ovarian reserve testing with ultrasound, blood tests that encompassed AMH, FSH, LH, estrogen, progesterone, thyroid function tests, serum prolactin and serum vitamin D and calcium levels.

Conclusion: The study provides us with mounting evidence supported by the laboratory results that premature ovarian insufficiency is not a rare phenomenon and cites similarities reinforcing the fact that it is relatively more common than we anticipate. The available diagnostic means in such a low resource setting comfortably enables the capturing of the patients timely and channeling them for proper and comprehensive management options as deemed necessary.

Keywords

Premature Ovarian Insufficiency (POI), Premature Ovarian Failure (POF), AMH (Anti-Müllerian hormone), Ethiopia.

Abbreviations

AMH: Anti Müllerian hormone; ART: Assisted Reproductive Techniques; FSH: Follicle Stimulating Hormone; HBsAg: Hepatitis B Surface Antigen; HCV Antibody: Hepatitis C Virus Antibody; HIV: Human Immuno-deficiency Virus; HRT: Hormone Replacement Therapy; ITPP: Idiopathic Thrombocytopenic Purpura; IUI: Intra Uterine Insemination; IUTPI/DIPI/FSP: Intrauterine Tuboperitoneal Insemination; Direct Intraperitoneal Insemination; Fallopian tube Specialist Perfusion Program; IVF-ET: In-Vitro Fertilization and Embryo Transfer; LH: Luteinizing hormone; PCOS: Polycystic Ovarian Syndrome; POF: Premature ovarian failure; POI: Premature Ovarian Insufficiency; RPR: Rapid Plasma Reagin; TPHA: Treponema Pallidum Haemagglutination Antigen; TFT: Thyroid Function Test; VDRL: Venereal Disease Research Laboratory.

Introduction

Premature ovarian insufficiency (POI) entails a conundrum of semantic issues for an entity expressing overlapping pathophysiologic changes with similar clinical signs and symptoms but implying differences in the physical, mental and social well being of the individual. It was first described as POI by Fuller Albright in 1942 [1,2]. The connotation of premature menopause/premature precoce (praecox) if defined with low estrogen levels and higher values of FSH in the menopausal range and with the ultimate cessation of menses for over a year is quite troubling to the client and family as opposed to premature ovarian insufficiency which may be expressed with intermittent resumption of function, occasional menstrual periods and pregnancy achievements. Primary ovarian failure with no menarche is invariably and strongly associated with gonadal dysgenesis or X-chromosome anomalies. Premature ovarian insufficiency (POI) and decreased ovarian reserve tend to be reconciliatory than premature ovarian failure (WHO III) which denotes an irreversible hypergonadotrophic/hypogonadism state or the aforementioned terminologies that do not imply permanent ovarian failure bearing in mind that pregnancies can spontaneously occur in 5 to 10% of such a population [2-4].

Hence, premature ovarian insufficiency (POI) is the loss or depletion of function (diminished ovarian reserve), dysfunction of the ovaries or loss of eggs resulting in variable estrogen and FSH levels with marked fluctuation of menstrual patterns characteristically before the age of 40 years but surely after menarche. It tends to occur in about 1% of the women population as opposed to the natural physiological menopause that occurs at 51 ± 5 years of age. The hallmark of the diagnosis in POI is based on menstrual irregularity for at least in three consecutive months with variable fertility patterns and deranged fertility hormonal panel [5,6].

The causes are diverse and could be spontaneous or induced. Though not exhaustive, may include autoimmune diseases like

Hashimoto's disease, Grave's disease, hypoparathyroidism, pernicious anemia, auto-immune hemolytic anemia, ITPP, Type I Diabetes Mellitus (DM), vitiligo, idiopathic Addison's disease and myasthenia gravis, karyotyping vis-à-vis gonadal dysgenesis Turner's and Fragile X syndrome as well as pelvic irradiation, excessive surgical removal or drilling of ovarian tissue (acute ovarian failure), chemotherapy and immunosuppression. Other incriminated factors include viral infections, tuberculosis, chemicals, toxins and cigarette smoking. A series of investigations commensurate with the management plan need to relate or correspond with the causal factors [7-9].

The treatment options comprise of high doses of ethinylestradiol (EE) for breast development, pubertal growth and sexual maturity, mental, physical and social support in the very young. Prevention of osteoporosis and cardiovascular diseases and promotion of sound sexual health and provision of treatment options like donor egg with IVF and adoption are in the order of management plan. The administration of DHEA (Diethylepiandrosterone) increases a spontaneously conceived pregnancies, decrease spontaneous miscarriage rates and improve IVF success rates in women with POI. When considering options like IVF, IUI, IUTPI/DIPI/FSP or natural conception, one ought to exercise caution for fear of aortic rupture in Turner's syndrome patients during pregnancy. Advanced management choices include ovarian tissue cryopreservation in prepubertal individuals at risk, fragmenting of ovaries with Akt stimulators and autografting and hormonal therapy, and treatment with estradiol skin patch or vaginal ring by-passing the first pass effect on the liver and medroxyprogesterone acetate per day for days one through 12 of each calendar month [10].

More important in the management is counseling of patients and families regarding their future fertility, risk of comorbidities, and potential for genetic inheritance. Psychological counseling for the impaired self esteem, emotional distress and HRT for sexual health and prevention of osteoporosis and cardiovascular diseases ought to be part of the order of treatment. Furthermore, annual general checkup for comorbidities and genetic inheritance should be part of the future plan [11,12].

The prevalence of premature ovarian insufficiency is far more beyond case presentations [13] and deserves comprehensive analysis and documentation. Furthermore, an Ethiopian study on prevalence and severity of symptoms on peri, menopause and post menopause was conducted on age range of 30-49 which is also inclusive of the very young without delineation from POI [14]. Therefore, the study highlights the existence of limited data, appreciates the diversity of clinical presentations and addresses the individual personal desires regarding fertility.

Materials and Methods

All consecutive patients visiting the gynecology outpatient services at YHC in Addis Ababa, Ethiopia with complaints of infertility and oligo-amenorrhoea were recruited for the purpose of this study during the period extending from January 1 through June 30, 2020.

The time interval of six months was set under the assumption that enough cases would be collected by then. A total of 5348 patients were seen and those with the aforementioned symptom complexes making up for a rate of premature ovarian insufficiency (POI) of 2.4%. The cut-off age for POI was less than 40 years of age. Amazingly, three patients spontaneously achieved pregnancy with folic acid, vitamin D and calcium supplements.

A complete set of information pertaining to premature ovarian insufficiency (POI) in general as an instrument to diagnose and plan the clinical management was obtained. Thus, an amalgam of the present and past medical history including family history with infertility, obstetric history and general physical examinations were routinely performed and documented.

Relevant laboratory investigations that encompass karyotyping whenever indicated, blood tests for fertility panel, thyroid function assessment, prolactin level, quantitative β HCG or urine pregnancy tests and transvaginal ultrasound to study for the shriveling, enlargement or polycystic nature of the ovaries were part of the detailed investigations.

An emphasis was put on the serum Anti-Müllerian hormone, a biomarker of ovarian reserve, follicle development and to assess for menopausal status and premature ovarian failure as well as for the evaluation of the functional intactness and responsiveness of the ovaries for infertility and success of IVF-ET. In the female, it is also an auxiliary aid in the diagnosis, recruitment and analysis of POI patients and exclusion of ambiguous genitalia/intersex, PCOS and granulosa cell tumors of the ovaries. Pregnancy was ruled in or ruled out in all of the studied population presenting with history of delayed or absence of menses.

Inclusion criteria included all non-pregnant clients who consented, were less than 40 years of age, have had their menarche and those who were never subjected for non-invasive or invasive operations along the hypothalamo-pituitary-ovarian-uterine and vaginal axis that resulted in a detrimental impact on the obstetrical and gynecological performance of the individual.

The exclusion criteria encompassed all clients with completed age of 40 or more years; and patients with polycystic ovaries, hyperprolactinemia, gonadal dysgenesis or those who had underwent bilateral salpingo-oophorectomy with or without hysterectomy and those subjected for chemotherapy, radiotherapy and those who experienced primary amenorrhea and never registered or experienced menarche. Under scrutiny were also those who were found to have hypogonadotrophic/hypogonadism (WHO I) as hypothalamic pituitary failure and normogonadotropic/anovulatory (WHO II) designated as hypothalamic pituitary dysfunction. Those with mental retardation, teens of less than 18 and those who were not able to give a verbal consent for whatever reason were also excluded from the study.

The data collected for the study period was entered, cleaned, and analysis for mean with standard deviation or median for

quantitative variables and proportions/percentages for qualitative variables were made. The statistics software employed was Epi-info Version 3.5.1.

Results

Out of 5348 clients, 130 were diagnosed to have premature ovarian insufficiency and the computed prevalence rate was put at 2.4%. Among the studied subjects with spontaneous-onset POI, 3(2.3%) achieved spontaneous pregnancy and no attempt for ovulation induction was made as their AMH levels were less than 0.5ng/ml which was labeled as a level “predictive of poor response”. A significant proportion of the clients were referred by physicians, and some being self referrals mainly for infertility workup and counseling.

The scope of the age range of the studied population extends from 21-39 with a mean age of 34.8 ± 4.8 years; and noteworthy is that about 112 (86%) of them fall within the range of 30-39 years (Table 1). As presented in Table 1, most of them were married 113 (86.9%) with relatively low parity rate as accounted for by 84 (64.1%) of nullipara and a cumulative percentage of 102 (78.4%) when primiparas are included. Majority of the patients were of Christian faith followed by Muslims mainly coming from Addis Ababa and Somaliland, respectively and most are housewives with diverse distribution of their educational status, occupation, family income; and ethnic wise they were mainly Amharas and Somalis (Table 1).

Of the patients, 41 (31.5%) and 3 (2.3%) have had history of miscarriage and ectopic pregnancy, respectively. All of them were sero-negative for HIV, HBsAg and HCV Antibody and furthermore their VDRL, TPHA and RPR tests were not yielding. Their thyroid function tests and serum prolactin levels were within normal ranges.

Their mean age at menarche was 13.7 ± 1.9 years with a median of 14 years and a range of 10-19 years; and its relevance is very much dependent on the dictum that early menarche and early menopause, late menarche and late menopause could be in the interplay (Table 2) although no statistical significance was established as evidenced by Correlation Coefficient: $r^2=0.00$, P-value=0.427.

The primary complaints upon presentation in the order of frequency, as shown in Table 3, were secondary and primary infertility and oligo-amenorrhea of up to three months followed by sign and symptom complexes of postmenopausal syndrome. These clinical manifestations among POI patients are not as pronounced as in postmenopausal women though they hardly accept the reality that they are basically in similar clinical states.

The pertinent laboratory parametric values are presented in Table 4. The laboratory results when properly dissected and plotted markedly enrich their clinical significance. The FSH, LH, estrogen and progesterone levels are impressively commensurate with the postmenopausal ranges and their relationships are well established

Characteristics		Number	Percent
Age (years)	20-24	7	5.4
	25-29	11	8.5
	30-34	27	20.7
	35-39	85	65.4
Marital status	Single/Cohabiting	17	13.1
	Married	113	86.9
Parity	Nullipara	84	64.6
	Primipara	18	13.8
	Secundipara & three	16	12.3
	Para 4 or more	12	9.2
Religion	Orthodox Christian	69	53.1
	Muslim	56	43.1
	Protestant	5	3.8
Ethnicity	Amhara	56	43.1
	Oromo	16	12.3
	Guraghe	13	10.0
	Somali	42	32.3
	Tigre	3	2.3
Address	Addis Ababa	72	55.4
	Somaliland	42	32.3
	Regions	14	10.8
	Eritrea	2	1.5
Occupation	Housewife	62	47.7
	Self employed	30	23.1
	Government employee	26	20.0
	Private institutions	8	6.1
	NGO	4	3.1
Educational status	Illiterate	37	28.5
	Primary	27	20.8
	High school	30	23.1
	College and above	36	27.7
Family income	Less than 2,000*	1	0.8
	2,001-5,000	72	55.4
	5,001-10,000	29	22.3
	More than 10,000	28	21.5

* Ethiopian currency; 1USD = 38 Ethiopian Birr at the time of analysis

Table 1: Socio-demographic Features, January-June, 20.

Age of Menarche	Frequency	Percent	Cum Percent
10	4	3.1%	3.1%
11	16	12.3%	15.4%
12	22	16.9%	32.3%
13	14	10.8%	43.1%
14	19	14.6%	57.7%
15	32	24.6%	82.3%
16	16	12.3%	94.6%
17	6	4.6%	99.2%
19	1	0.8%	100.0%
Total	130	100.0%	100.0%

Mean 13.7 ± 1.9, Median 14 years, Age range 10-19 years

Table 2: Age of menarche.

(Figures 1-3). As shown in Figure 1, as age increases, the level of AMH tends to decrease (Correlation Coefficient: $r^2=2$, P-value <0.05). AMH levels define an inverse, negative, relationship but strong correlation with FSH values with Correlation Coefficient: $r^2=2$, P-value <0.05 (Figure 2). AMH and estradiol levels, as depicted in Figure 3, show a weak but positive correlation (Correlation Coefficient: $r^2=0.03$, P-value <0.05).

The salient points from the clinical interpretations of AMH (Table 5) provide clear information from severely diminished to ovarian reserves that would be considered of limited response if they were to be challenged with ovulation inducing drugs and stimulated as part of evaluation for assisted reproductive techniques/technology.

The relative vitamin D deficiency which is rampant among the population is also reflected in the scatter plot and is substantiated by the correlation in the Figure 4. The close association of vitamin D and total serum calcium level demonstrates strong and positive correlation (Correlation Coefficient: $r^2=0.06$, P-value <0.05) though may not establish a cause and effect relationship but yet can impact individual fertility potential. The prolactin and serum testosterone levels did not weigh in as clinically of great relevance.

Discussion

The ovaries are paired organs of 3-5 x 1.5-3 x 0.6-1.5 cm in size and weighing 5-8gm (15). They produce 6-7 million follicles at about 20 weeks of gestation of the female fetus in utero; of which 1-2 million are around at birth, 300,000-400,000 during the reproductive life span and 300-400 ovulate during a woman's reproductive age at a rate of 20-30 follicles per cycle just to release one mature Graaffian follicle. Most of them undergo atresia and this is a continuous process that tends to be unaffected by the age of onset of menarche and POI. Thus the end result is scarification from the follicles that constantly undergo the process of atresia/apoptosis thereby contributing towards the depletion of the primordial follicles and undermining the continuity of its hormonal and biological functionality in reproduction [16-18].

Climacterium is the time interval depicting a transitional phase from the end of the reproductive periods starting at 40 or more years of age and entering senility at 60 years of age which is characterized by the hallmark of involution and atrophy of the reproductive systems secondary to a hypergonadotropic hypogonadism state. In contrast, premature ovarian insufficiency with raised gonadotrophins and hypogonadism condition occurs after menarche but before the age of 40 years deviating from an

Variables	Number	Percent
Primary infertility	43	33.1
Secondary infertility	52	40.0
Amenorrhea of > 3 months	32	24.6
Menopausal signs & symptoms*	3	2.3

Table 3: Presenting complaints.

*Hotflushes, sweating, vertigo, tingling sensations/hands, chest pain/prickly sensation, tachycardia, hypertension, headache, tinnitus, psyche {hypomania/ depression/ melancholic/ hysterical}, irritability, decreased libido, amnesic forgetfulness, decreased performance, sleeplessness, loss of breast and adipose tissues, osteoporosis, atherosclerosis, diabetes mellitus.

Variables	Mean with SD	Median	Range
Anti Müllerian hormone (AMH) in ng/ml	0.153 ± 0.215	0.0375	0.010-0.850
Follicle Stimulating hormone in mIU/ml	48.077 ± 17.765	44.350	25-99
Luteinizing hormone in mIU/ml	39.754 ± 12.188	40.555	40.555-40.555
Estradiol in pg/ml	45.446 ± 15.463	45.000	12,000-87,000
Progesterone in ng/ml	0.717 ± 1.421	0.400	0.050-10.200
Testosterone in ng/ml	0.537 ± 0.508	0.360	0.040-3.210
Prolactin in ng/ml	13.431 ± 4.997	12.500	5.000-27.000
Vitamin D in ng/ml	15.379 ± 4.997	15.010	0.900-27.980
Serum calcium in ng/ml	9,054 ± 0.330	9.000	8.010-10.000

Table 4: Laboratory results.

AMH level in ng/ml*	Result		Remarks
	Number	Percent	
<0.5	116	89.2	Predictive of poor response
0.5 - <1.0	24	10.8	Suggestive of limited reserve
1.0 - <3.5	-	-	Predictive of optimal response
>3.5	-	-	Predictive of hyperstimulation/PCOS

Table 5: Clinical interpretation of AMH.

AMH (adopted from Star Metropolis Clinical Laboratories, 802-803 8th Floor Al Musalla Towers, Bur dabi, Dubai, UAE).

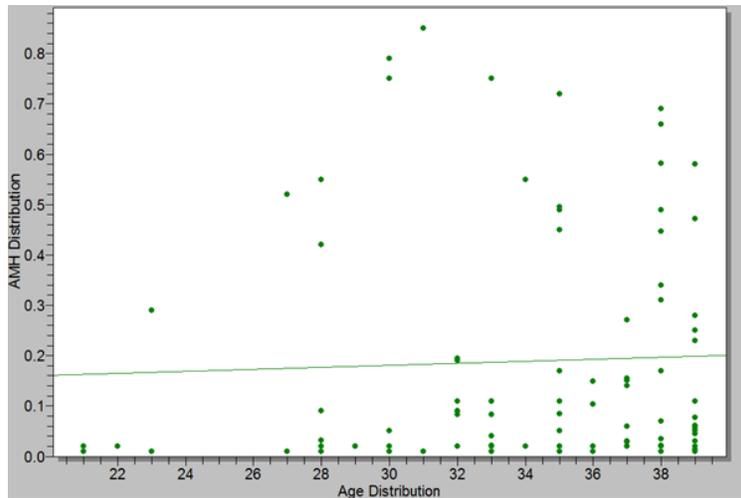


Figure 1: Scatter plot of Age vs. AMH levels.

Correlation Coefficient: $r^2= 0.00$, P-Value <0.05 .

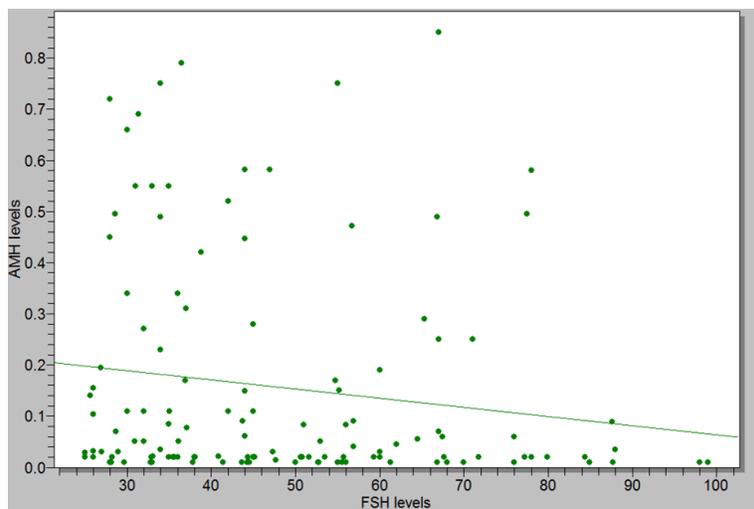


Figure 2: Scatter plot of relationship of AMH and FSH levels.

Correlation Coefficient : $r^2= 0.02$, P-Value <0.05

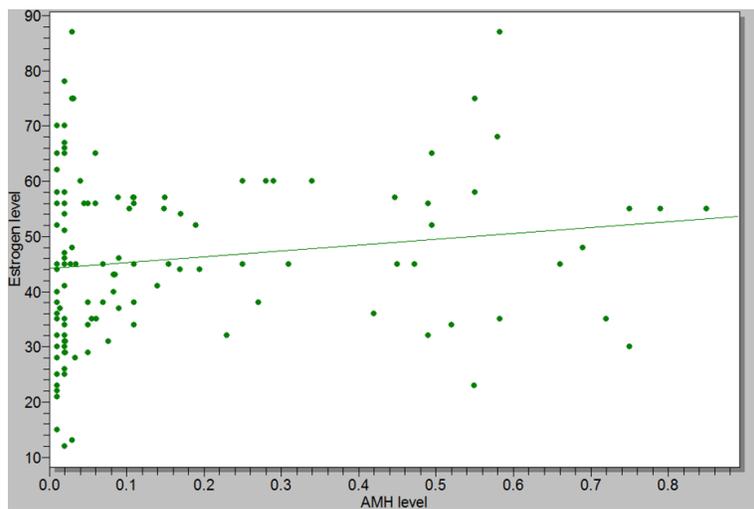


Figure 3: Scatter plot of relationship between estrogen and AMH levels

Correlation Coefficient : $r^2= 0.03$, P-Value <0.05

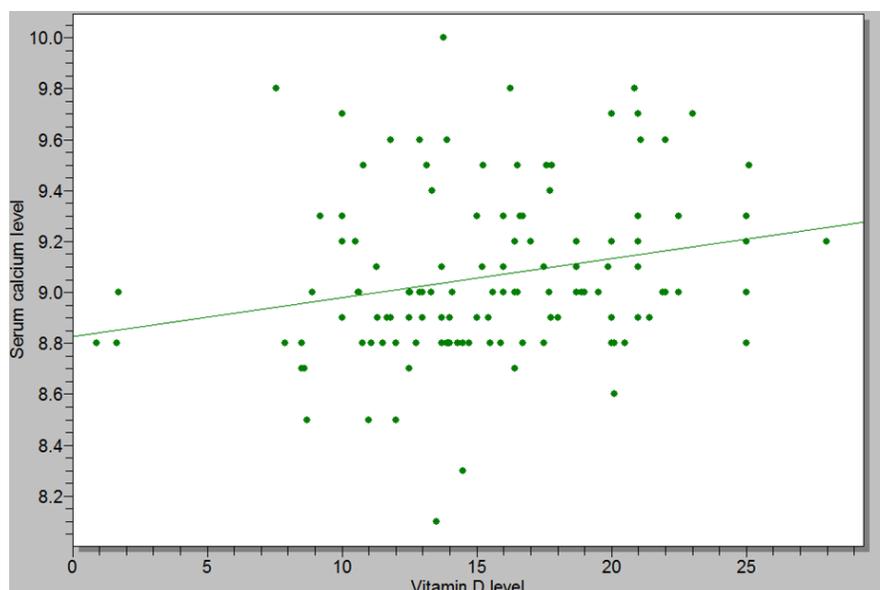


Figure 4: Scatter plot of relationship of vitamin D and serum calcium.

Correlation Coefficient : $r^2=0.06$, P-Value <0.05 .

Ethiopian study on menopause between the ages 30-49 as our current undertaking considers the POI as an entity distinct from menopause and its subgroupings [14].

A total of 130 patients with a fertility panel suggestive of hypergonadotrophic hypogonadism (WHO III) labeled as premature ovarian insufficiency are represented in current study. The hypogonadotrophic hypogonadism (WHO I) i.e. hypothalamic pituitary failure and normgonadotrophic anovulatory (WHO II) that implies hypothalamic pituitary dysfunction were excluded from the study in order to retain a homogenous population possibly with diminished or ovarian reserve. It is often stated that it is idiopathic in 90% of the cases but other attributed or incriminated factors are autoimmune diseases and chromosomal abnormalities in addition to treatment sequelae like pelvic irradiation, excessive removal and/or drilling of ovarian tissue, chemotherapy, and immunosuppression as well as toxins, cigarette smoking and infectious causes [8,9,19]. It is thus a universal phenomenon demanding attention especially in the presence of improved diagnostic capabilities and availing a variety of management options.

Furthermore, in establishing the diagnosis as in other studies, AMH, fertility panel, prolactin level, TSH, vitamin D and other parameters were utilized as instruments to define the diagnosis [19-21]. Through these means, it was possible to distinguish the four clinical states of occult POI, biochemical POI, overt POI, and the irreversible permanent cessation of menses with climacteric syndromes of premature ovarian failure in the extreme with follicular depletion and hypergonadotrophic hypogonadism. The overall calculated prevalence rate was 2.4% and is quite similar with the often quoted rate of 1-2% as in the Swedish study. In conclusion, it is an acceptable and established phenomenon that the

incidence in those less than 40 years of age as corroborated in the present study is not a rare condition and its incidence is estimated to be as great as 1 in 100 by the age of 40, and 1 in 10,000 by the age of 20 years, 1 in 1000 by 30 years of age. It is to be highlighted that in women with primary amenorrhea the prevalence rate is 10-28%; and in those with secondary and/or iatrogenic amenorrhea, premature ovarian failure occurs in 4-18% [6,19,22-24].

It is a common understanding that fertility declines past the age of 35 which is regarded as an advanced maternal age. Our study is indicative of the fact that there is aggregation of diminished ovarian reserve towards the age of 40 years which can be verified by employing ovarian reserve tests with AMH and complementary transvaginal ultrasonographic evaluation for shriveling ovaries but holds true that the correlation exists only past ≥ 35 years of age [4,15,23-25].

The quantitative antral follicle counts (AFC) and the qualitative properties of the follicles because of ovarian senescence with marked increase in chromosomal/genetic abnormalities of the follicles poses a challenge in deciding for ART. AMH starts declining years prior to rise in FSH and is a sensitive biomarker of ovarian primordial follicular reserve. It has age specific ranges and also broader clinical interpretations for ovarian reserve but with the former, the values are at times out of range and falling in the much advanced age groups. Its low values with increase in age and its preponderance past the age ≥ 35 years provides an opportunity in establishing the diagnosis of POI as vividly demonstrated in this study. The diagnosis was mirrored by the performed diagnostic opportunities though admissibly no blanket approach was assumed and patients were not tailored/subjected to have their inhibin B levels, in conjunction with AMH, determined. The peptide inhibin B blood levels decline in advanced maternal age especially in

the presence of fewer follicles and diminished secretion by the granulosa cells and it would have been strongly complementary with AMH, had it been possible and available in the country.

Delayed diagnosis based on the quest for an answer to their immediate clinical presentations were likely due to oligo-amenorrhoea, primary or secondary infertility; and sign and symptom complexes of menopause which are not as pronounced as in natural or iatrogenic menopause although they may overlap [8,9,12,15,26]. They fared better with vasomotor, neurovegetative and psychological impacts that may include anxiety, depression, insomnia, irritability, and worry about aging, identity crisis and loss of prestige. However, once the diagnosis of premature ovarian insufficiency is established and it is only then after the implications of untimely ageing, inability to have or procure more children, social withdrawal in addition to hopelessness and depression/including melancholy, marital disharmony and being disavowed, sexual incompatibility or disharmony tend to be an immediate discussion points [27].

In a relatively high parity population as in our country and Somalia in general, such a low parity level among the studied population is analogous with subfertility designated population. Intermittent and unpredictable ovarian functions can result in spontaneous pregnancies and hence the fertility panel patterns unpredictably highly variable in time relating to the poor ovarian reserve both in quality and quantity with low numbers of ovarian follicles or impaired folliculogenesis [15,19]. This is attested by the three individuals who spontaneously achieved pregnancies and are nearing term at about the time of this analysis and reporting.

The association of vitamin D and infertility is well established and hence vitamin D supplementation along with calcium in order to fulfill their extra needs in the prenatal and natal periods is highly recommended. The low levels of vitamin D, depicting deficiency as observed in our study population in the absence of malabsorption syndrome and intake of certain medical drugs is unbelievably high especially when one considers the abundance of sunshine in the region. The “sunshine hormone” in a “Land of 13 months of sunshine” is simply odd and thinking of it in conjunction with infertility unrealistic; but a factual phenomenon [28]. The relationship of vitamin D and calcium with osteoporosis in a hypergonadotrophic-hypogonadism state should not be understated and underestimated.

There exists management difficulties and the approaches are measured. The availability of management options in government institutions is practically non-existent and its affordability at a private setup is allegedly soaring and causes financial constraints. The wider options of introducing ovulation inducing drugs and availability of assisted reproductive technology including oocyte, ovarian tissue or embryo cryopreservation as in advanced services is very much center focused and expensive. The least, non-invasive and cheap approaches, we can offer them include hormone replacement therapy (HRT) with estradiol valerate,

phytoestrogens or combined oral contraceptive pills as other combined postmenopausal preparations are not available; calcium and vitamin D supplements, regular physical activity and a healthy body weight and treatment for any associated conditions and assuring them of a glimmer of hope that there exist a possibility of intermittent resumption of ovarian functions and a 5-10% rate of spontaneous pregnancy [29-34]. In desperate situations in terms of time and ultimate option in delayed infertility cases, the clients are liaised to infertility clinics both at home and abroad with available assisted reproductive technology services depending on their choice and financial capability. In general, it demands a multidisciplinary approach involving gynecologists, psychologists and counselors, reproductive subspecialists, endocrinologists and internists with broader scale of diagnostic facilities and treatment of co-morbidities.

The study demonstrated that premature ovarian insufficiency is not a rare phenomenon. An elevated gonadotrophic hormones and hypogonadism with resultant clinical manifestations of involuntary infertility and abnormal uterine bleeding with diminished ovarian reserve as verified with AMH determinations establish the basis of the diagnosis. POI is divergent from the usual complex heralding manifestations of physiologic, anatomical and pathological changes with vasomotor, genitourinary and psychological clinical signs and symptoms.

The limitations include a clinical setup with clustering of referred patient population for fertility workup, limited to the specified time frame, expensive laboratory investigations and the financial burden incurred by the patients and difficulty in conducting a comparative study. A multi-centered national comparative study supported with adequate funding should be carried out on this very important topic.

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