Archives of Reproductive Medicine and Sexual Health

Volume 1, Issue 1, 2018, PP: 31-46

Evaluating the Prevalence, Management and the Psychosocial Impact of Premature Ovarian Insufficiency on Patients Attending an Academic Hospital Reproductive Endocrine Clinic

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Abstract

***Context:** To assess the prevalence, etiology, and management of patients with premature ovarian insufficiency in the Reproductive Endocrine Unit at Tygerberg Academic Hospital, Cape Town, South Africa.*

***Primary Objective:** To measure the prevalence of premature ovarian insufficiency (POI).*

***Secondary Objective:** To determine the etiology, to review the management process and approach and to assess the impact of the diagnosis on patients with POI.*

***Design:** Cross-sectional study.*

***Setting:** Reproductive Endocrine Clinic in an Academic Hospital.*

***Patients:** Patients living with a diagnosis of POI.*

***Materials and Methods:** Patients interviews, review of medical records including bone scans, clinical evaluation of patients as they present at the clinic. The study was undertaken over 12 months from August 2016 to July 2017.*

***Primary Outcome Measure:** The prevalence of POI in our setting.*

***Secondary Outcome Measures:** The management of POI, and impact of the diagnosis on the women.*

***Results:** There were 47 patients living with a diagnosis of POI and the total number of all patients seen during this period at the above clinic was 561. The prevalence of POI in our setting is 8,4% (Confidence interval 6.28%-11.06%).*

The etiology of POI in 32% of the patients was idiopathic, 19% genetic syndromic disorder, all of which were Turner Syndrome, 10% were non-syndromic genetic disorders. A familial disorder was found according to family history and accounted for 2% of the causes.

Auto-immune causes accounted for 6%, infective causes 6%, cancer and chemotherapy 6%, obstetric complications 6%, iatrogenic 4% and endometriosis 2%.

A dual energy X-ray absorptiometry (DEXA) scan was done of which32% had osteopenia, 11% had osteoporosis 21% patients a DEXA scan was requested but not done. Patients with normal DEXA scans were re-assessed 5 years later and patients with osteopenia and osteoporosis were re-assessed every 2 years while on treatment. Eighty-one percent of patients with osteoporosis were treated with bisphosphonates.

There were 55% of patients with depression and they were treated with various antidepressants.

***Conclusion:** The prevalence of POI in our clinic is reported to be 8.4%, which is much higher than the prevalence quoted in literature of 1%. This large difference may be due to a bias caused by a smaller sample size relative to the total number of patients seen. All patients received the standard treatment protocol and various specific treatment modalities.*

Keywords: *Premature ovarian insufficiency (POI), amenorrhoea, infertility, genetic, psychosocial.*

Introduction

Premature ovarian insufficiency (POI) is considered a rare disease. As such, in the past it did not attract the attention of researchers, stake-holders and advocacy groups. Recently, there is more urgency towards recognizing POI as a serious condition that requires attention, research and guidelines of management. In 2012, there was a call from the American Society of Reproductive Medicine (ASRM) and other stake-holders for an international database of POI [1]. The database would at least measure the quantum effect of POI and improve reporting of the condition.

In 2014, the Guideline Development Group of European Society of Human Reproduction and Embryology (ESHRE) convened, and guidelines for the management of POI were developed and published [2]. Previously, these patients were either left unmanaged, incompletely managed or managed as menopausal women depending on the health system.

Considering that POI was first described in 1942, there was no urgency in developing guidelines for the management of POI. Marriages and conception happened much earlier than in recent times, masking the effect of POI and its sequelae, especially the loss of fertility.

Prior to the publication of the recent ESHRE Guidelines on POI, there was no consensus on the management of POI. The management differs from one unit to the other and the impact of POI is not well captured in the literature, particularly in patients from Low to Middle Income Countries (LMIC). Therefore, the aim of the study was to report on the prevalence of POI in a tertiary hospital, and to evaluate the management process and the impact of the disease.

Literature Review on Premature Ovarian Insufficiency

Premature ovarian insufficiency (POI) is a clinical syndrome of loss of ovarian function before the age of 40, characterized by menstrual disturbances, oligomenorrhoea or amenorrhoea, primary or secondary, with elevated gonadotropins and low estradiol levels.

POI is a complex, heterogeneous disease that may lead to infertility, medical sequelae and impair quality of life in poorly managed cases [3].

The prevalence of POI is reported as 1% in the literature [3]. The age distribution of POI is 90% of cases between ages 30 to 40 years, and 10 % of cases below the age of 30 [2].

There are more than 23 genes identified in various stages of ovarian development. The critical regions are proximal deletions in the regions Xq13-26 and distal deletions in the region Xq13.3 and Xq21.3-27[]. X chromosome anomalies can be numerical defects such as monosomy X, X-chromosomal mosaicism, deletions, translocations, X-iso-chromosomes and other X-chromosome re-arrangements [4].

Clinical Presentation

The clinical presentation varies from primary amenorrhoea, secondary amenorrhoea, abnormal uterine bleeding, andsymptoms of estrogen deficiency such as vasomotor symptoms, fatigue and mood swings [3, 4]. Patients with syndromic POI will have a particular phenotype, such as a short stature in Turner Syndrome or stigmata associated with a particular syndrome such as ptosis, acanthosis, opthlamoplegia and others. A history of mental retardation could point to Fragile X permutation [4].

Diagnosis of POI

A practical cost-effective approach is to get a thorough medical, personal and family history, a physical examination and blood investigations. An ultrasound is used to identify internal genitalia in patients with primary amenorrhoea. An FSH level of more than 40 on 2 separate occasions is diagnostic of POI [5]. Karyotype in patients below 30 or in patients with primary amenorrhoea is indicated [5]. Further investigations are done on clinical suspicion of the underlying etiological factors.

Certain specific gene mutations and single gene defects can be isolated with specific cytogenetic probes. Enzymatic defects such as 17-hydroxy-progesterone levels and galactose-1-phosphate deficiency can be detected by enzyme assays [5]. Thyroid and adrenal auto-antibodies should be included in the investigation profile. Twenty percent of women with anti-thyroid antibodies develop POI [5]. Gonadotropin receptor mutation, and rare inborn errors of metabolism can be done in some centers where available.

To assess fertility prognosis, an antral follicle count, AMH, LH and E2 levels can be measured to detect remaining follicular activity [6].

A dual energy X-ray arbsorptiometry (DEXA) scan for bone density measurement is a baseline test for all women with POI to detect reduced bone mineral density due to E2 deficiency, to stratify fracture risk and to detect patients with osteoporosis [5, 6].

Etiology of POI

The etiology of POI is varied, the majority of cases being idiopathic [5]. Other causes include genetic syndromes, familial inheritance, steroidogenic enzyme defects, gonadotropin receptor mutations, auto-immunity, early physiological ovarian ageing in rare cases, ovarian insult from various causes and iatrogenic causes[5,6]. Genetic causes of POI can be classified as syndromic and non-syndromic [5-7].

The commonest etiological factor of POI is idiopathic, approximately 30% as reported in literature [7]. This may be due to a lack of studies to determine the underlying cause(s) of POI. Recently, the research is expanding to determine these causes, to mitigate against complete loss of fertility before it is established in women with POI who would otherwise be advised on options of fertility preservation or decide on early childbearing [7].

Ovarian insult includes in utero exposure to environmental toxins, and medications such as DES, maternal and index patient smoking, chemotherapy, radiotherapy and infections of the pelvis including ovaries[5-7]. Smoking reduces the size of ovarian follicular pool and advances ovarian aging though accumulation of mitochondrial-DNA (mt-DNA) deletions as a result of oxidative stress [8].

Iatrogenic causes of POI are generally rare, and occur during pelvic organ surgery including the adnexa, endometriosis and myomectomy using intermittent tourniquet to control blood loss during surgery [9]. Lately uterine artery embolization has been associated with POI by compromising part of ovarian blood supply [9,10].

Known genetic syndromes in POI are Turner Syndrome, Turner mosaic, 47XXX or 47XXY individuals, Fragile X pre-mutation 1 (FMR1) Xq27.3 causing Fragile X Syndrome, Blepharophimosis, ptosis and epicanthus inversus syndrome (BPES) is an autosomal dominant syndrome caused by a mutation in the FOXL2 3q23, either with POI (BPES type1) or without (BPES type 2)[8-10]. Families with the FMR1 gene should receive counselling about the risk of transmission and the consequence of Fragile X syndrome mental retardation. Galactosemia, GALT 9p13, is a cause of ovarian failure due to excess galactose toxicity that impairs folliculogenesis, induces resistance to gonadotropins and accelerates follicular atresia [5,6].

Mitochondrial genes causing syndromic POI include polymerase DNA directed gamma (POLG) 15q25 causing progressive external opthalmoplegia (PEO) [10,11]. POLG is responsible for mt-DNA replication and repair[10,11]. The clinical features of PEO are proximal myopathy, sensory ataxia, Parkinsonism and POI[10,11]. Perrault syndrome is caused by mutations in genes that encode mt-RNA synthetase, chambered protease and primase helicase [10,11].

The mature oocyte has the greatest number of mitochondria of any human cell. Mitochondrial biogenesis plays an essential role in oocyte maturation, fertilization and embryo development [11].

Single gene defects causing non-syndromic POI are X and Y chromosome autosomal translocations, Robertsonian and reciprocal translocations and parental consanguinity [11]. The ones that have been proven causative by functional validation are bone morphogenic protein 15 (BMP15), Xq11.2, which cause impaired folliculogenesis in homozygotes, and a missense mutation in heterozygotes causing ovarian failure in both cases [11].

Progesterone receptor membrane component 1 (PGMC1) Xq22-q24, a putative progesterone binding membrane receptor is involved in progesterone signaling in the reproductive system. PGMC1 mediates anti-apoptotic effects on granulosa cells [10].

A mutation with an X autosome translocation that caused reduced expression of PGMC1 abolishes binding of cytochrome P450 7A1 (CYP7A1) to PGMC1 and attenuates PGMC1's ability to mediate the anti-apoptotic ability of progesterone in ovarian cells. These findings suggest that mutant or reduced PGMC1 may cause POI through impaired activation of the microsomal CYP450 and increased apoptosis of ovarian cells [10,11]

The following mutations were all found to cause POI in highly consanguineous pedigree. Premature ovarian failure 1 (POI1B) Xq21.2, folliculogenesis specific bHLH transcription factor (FIGLA 2p13.3), follicular

receptor hormone (FSHR) mutation, newborn ovary homeobox gene (NOBOX) 7q35 loss of function mutation, nuclear receptor subfamily 5 (NR5A1), steroidogenic factor 1 (SF1) 9q33, NANOS3 mutation, and stromal antigen 3 (STAG3) 7q22.1 [10,11].

More mutations and microdeletions found in homozygous consanguineous families with POI are synaptonemal complex element 1 (SYCE1) 10q26.3 microdeletions, minimicrosome maintenance complex 8 (MCM8) 20p12.3 and 9 (MCM9) 6q22.31, two homozygous mutations that cause germ cell depletion.

A compound heterozygous mutation of ATP-dependent DNA helicase homolog (HFM1) 1p22.2, a meiotic gene encoding helicase necessary for homologous recombination and synapsing during meiosis in germ cells has been found in women with idiopathic POI [10,11].

Genome wide associated studies (GWAS), cytogenetic studies using array-CGH,genome wide sequencing of exomes (WES) and in the future next generation sequencing are contemporary genetic strategies being used to locate susceptible loci and genes causing POI in the idiopathic group. Thus far, a number of genes, responsible for POI are being identified [10,11].

Auto-immune thyroiditis is associated with POI in 20% of the cases. Other autoimmune conditions associated with POI are parietal cell auto-antibodies, myasthenia gravis. Some further 2-10% of patients with POI have chronic adrenal insufficiency (Addison's disease). Auto-immune Polyglandular Syndrome (APS) Type 1 and type3 causes POI by causing an immune response to the side-chain cleavage of the steroidogenic enzymes causing a disturbance of normal ovarian function [11].

Counselling patients with familial POI and their siblings regarding the earlier onset of disease and fertility preservation is necessary. The risk of developing POI in a woman with a first degree relative is more than 4%. Parental consanguinity is also a major risk factor for developing POI.

The presence of Y chromosome carries the risk of gonadal malignant tumour. It is important to counsel the patient for removal of the gonads after the completion of puberty, to reduce the risk of developing a gonadoblastoma [9-11].

The Management of POI

Management is directed to a specific cause of POI if found or known. A multi-disciplinary approach is recommended for all patients with POI. The team includes reproductive endocrinologists, medical endocrinologists,physicians,radiologists,nutritionists, psychologists, psychiatrists, social workers, nurses and administrative personnel who co-ordinate the movement of patients between several clinics and disciplines for adequate management [10,12].

The management of POI should start with preventive measures. Lifestyle modification including smoking cessation, drug use and alcohol cessation is necessary [13]. Obesity causes a chronic inflammatory state in the body which causes excess accumulation of free radicals and oxidative stress on various organs including gonads [14]. Healthy nutrition and exercise are advocated in patients with obesity and high body mass index (BMI). Weight loss, weight-bearing exercise and long-term maintenance of a healthy weight with within normal BMI parameters are advocated[15].

Other preventive measures to preserve fertility include laparoscopic transposition of ovaries prior to pelvic radiotherapy [16]. Oocyte and/or embryo cryopreservation in older patients prior to chemotherapy is a well-established modality for fertility preservation [16].The experimental label on ovarian tissue cryopreservation has been lifted. This is a method of choice in younger patients prior to undergoing gonadotoxic therapy [16].

Estrogen (E2) replacement is the cornerstone in the management of POI. It is essential for induction and completion of puberty in POI [17]. The goal of hormone therapy in patients with POI extends beyond the treatment of symptoms caused by low E2. It is essential and required for the prevention of decline in bone mineral density (BMD), mainly osteoporosis caused by E2 depletion, the risk of morbidity and mortality secondary to cardiovascular and metabolic changes. It is also helpful self-esteem and better sexual health for women with POI [17].

Estrogen replacement must be started from the onset of diagnosis and continued until the natural age of menopause is reached. E2 is initially given for 12 months in patients with primary ovarian insufficiency, and then followed by combined therapy with cyclic

progesterone[17]. The initiation of therapy alone is based on the fact that patients require physiological doses of E2 to treat symptoms of hypo-estrogenism and prevent bone loss, cardiovascular sequelae, vulvo-vaginal atrophy and vasomotor symptoms. The dosage required is higher than that given for treatment of menopausal symptoms. Continuous combined therapy is given to patients who do not desire a period [17].

Combined oral contraceptive (COC) replaces E2 and it is also a contraceptive. It contains supra-physiological doses of E2 and younger women may find it more suitable as it does not distinguish them from their peers [17, 18]. It is also the most convenient and cheapest hormone therapy; however, it contains supra-physiological doses of E2 and carries a higher risk of venous thromboembolism [17, 18].

Patients are given anti-resorptive agents by supplementation in the form of Vitamin D 50000 IU every 2 weeks. The rationale for this is compliance and supplementation in a LMIC group where the dietary calcium may be insufficient. The prophylactic dose of Vitamin D is 1000IU per day [19]. Vitamin D maintains normal bone through its action on intestinal calcium absorption [19]. Calcium supplementation is given in the form calcium carbonate, taken with meals as HCl is required for intestinal absorption. Calcium acts as a vital controlling link in many intercellular and in bone strength. Vitamin D and calcium are anti-resorptive agents associated with a moderate risk reduction of fracture [20]. Patients with osteoporosis and/or have a high risk of fracture are commonly treated with bisphosphonates [20]. Bisphosphonates are anti-resorptive agents regarded as first-line treatment in patients with severe osteoporosis due to estrogen deficiency and in secondary causes of osteoporosis [19, 20].

Other options include Teripatide, a parathyroid hormone (PTH 1-84) or the PTH fragment (hPTH 1-34), which are potent anabolic agents that stimulate bone formation and reduce vertebral and non-vertebral fractures [20]. Teripartide has specific indications; which include failed anti-resorptive therapy, severe fracture disease and glucorcoticoid therapy with a markedly reduced BMD. The use of Teripartide is limited by its expense and certain contra-indications [20]

Patients with symptoms of depression are referred for psychological counselling to deal with the consequences of POI and to acquire coping mechanisms in adjusting to the changes that are caused by POI.

For severe depression patients are treated with various available anti-depressants [21,22] Counselling of patients with POI and family members is all-encompassing and necessary for understanding of the disease, the diagnosis if known, the long-term and multi-disciplinary nature of management and adherence as well as compliance to treatment [21, 22].

Family and community support is important and should not be overlooked [22]. It has been shown that in patients with chronic diseases like HIV, pre-treatment counselling of the patient and family members is required to assist to engage the family to support the patient emotionally. This leads to better compliance, general well-being and routine follow-up [22].

Options for Fertility and Conception

For patients who desire conception the fertility specialist can lookfor any remaining antral follicles with pelvic ultrasound, and if present an attempt is made to administer several therapeutic interventions such as DHEA, enzyme Co-Q10, testosterone gel, with subsequent performance of controlled ovarian stimulation for ART. However, in a systematic review of therapeutic interventions for women with POI, there was no evidence of effectiveness of any therapy[23]. An evidence-based option is the use of donor oocytes in IVF/ICSI cycles to assist with conception. Adoption is always an option for involuntary childlessness [23, 24]

Sequelae of POI

Bone Mineral Density Loss

Studies show that BMD in women with POI is approximately one standard deviation (-1SD) below mean compared with age-matched cohorts despite sufficient E2 replacement [25]. There is a 2.6 fold increased risk of hip fractures in patients with POI. Therefore, POI patients require higher doses of E2 compared to menopausal patients, with or without cyclic progesterone. In younger patients, combined oral contraceptives with higher E2 levels may be appropriate for peer acceptability and if pregnancy is not desired [5,25,26]. This should be accompanied by smoking cessation, good nutrition and weight-bearing exercise [5, 25, 26].

Possible Loss of Fertility

Although POI is associated with infertility, it is not uniformly associated with complete depletion of available oocytes [24, 27]. Research has established that approximately 25% of women diagnosed with POI can have a brief period of spontaneous resumption of ovulation and spontaneous conception in 5% of these patients [5, 24, 27]. Therefore, patients with POI who do not desire fertility should be made aware of this possibility[5, 24, 27].

Cardiovascular Risk

The risk of mortality in women with POI due to cardiovascular disease is 2-fold higher than that of age-matched cohorts, with an odds ratio for mortality of 1.95 (CI 1.24-3.07). The major contributing factor to excess mortality is secondary to carotid intima thickness and plaque formation causing coronary artery disease and stroke [5, 28, 29].

The lipid profile of women with POI shows an elevated level of triglycerides. Elevated triglycerides indirectly interfere with lipoprotein metabolism and are associated with obesity and insulin resistance and metabolic syndrome [5, 30].

Depression and Quality of Life

Depression is a threat to longevity in patients with POI. If left untreated, it could lead to suicidal ideation and subsequent dementia [2, 21-24, 27]].

Primary Objective

To measure the prevalence of premature ovarian insufficiency (POI) at a Reproductive Endocrine Unit

Secondary Objective

To determine the etiology, to review the management process and approach, and to assess the impact of the diagnosis on patients with POI.

Diagnosis and Routine Investigations

FSH levels are done 2 months apart to establish the diagnosis of POI. Estrogen levels, thyroid function tests, prolactin levels are done. Karyotype in patients with primary amenorrhoea or if clinically indicated is included. A pelvic ultrasound is done if indicated as explained above. In our clinic, not all patients receive a pelvic ultrasound because we have one ultrasound machine used for ART patients, general gynecology patients, reproductive endocrinology patients, and family planning clinic patients. A baseline DEXA scan is always requested for all patients. Other investigations are done on clinical findings or suspicion.

Standard Treatment Protocol

Depending on the age of the patient, treatment includes estrogen alone (Premarin 0,625mg daily) or in combination with progesterone (Provera 10mg daily for the last 10 days of the cycle), or a combined oral contraceptive (COC) in young women who have attained maximum pubertal development and growth in height. Vitamin D 50000IU every 2 weeks and calcium carbonate 1500mg daily are supplemental for bone protection. The follow–up protocol included 6 to months in our unit. For routine medication, patients collected medication from their local or the nearest clinic.

Management of Bone Loss

Patients with reduced bone mineral density (osteopenia) and osteoporosis are advised on lifestyle modification, by smoking cessation, good nutritional intake, especially food high in calcium, vitamin D and protein, and introduction of weight-bearing exercise in their daily routine.

A base-line DEXA is routinely requested through a computerized booking system on initial contact [2,]. Once the request is received, the clinical radiology department contacts the patient and offers them an appointment date for the scan.

Patients with osteoporosis are referred to the clinical endocrinology unit for assessment to exclude secondary causes of osteoporosis and the need for bisphosphonate treatment.

The standard treatment protocol (hormone therapy, Vitamin D and Calcium carbonate) is adhered to and the patient is counselled for compliance with treatment. A DEXA scan is repeated every 2 years

Management of Patients with Depression

Patients with depression are initially referred to a psychologist for counselling and to assist the patients with coping strategies to manage with the disease long-term as well as to adhere to treatment protocols. Patients with symptoms of severe depression are treated with Fluoxetine 20-40 mg daily by a psychiatrist, and followed up for improvement of symptoms.

Climacteric Symptoms

Hormone therapy as outlined above is the mainstay of treatment to manage climacteric symptoms. Alternative treatment if systemic hormone therapy is contra-indicated, is available, such as, clonidine, selective serotonin re-uptake inhibitors (SSRI's) and non-SSRI's. Vaginal estrogen cream is given to prevent changes in the urogenital tract and maintain vaginal health.

Fertility Prognosis

Patients seeking a pregnancy are counselled for the loss of fertility associated with POI. They are informed of choices such as IVF through oocyte donation or adoption. Patients are further made aware that there may be a brief spontaneous resumption of ovulation in about 25% of patients with POI which may result in a possible conception in 5% of cases. Patients who do not desire pregnancy are counselled to strictly adhere to contraceptive or hormone therapy as prescribed.

Results

Data was analyzed using Statistical analysis was performed by a bio-statistician using the Statistical Package for the Social Sciences (SPSS) software, using frequency tables for categorical variables and summary statistics such as mean and standard deviation for continuous variables and order analysis. Descriptive statistics will be used to present the different variables within the data set. These will be presented in the form of tables, graphs and charts.

Demographic Data

The median age was 35years (range 15-50 years), median age at diagnosis was 28years (range 13-40 years) and the median duration of the disease was 6 years (range 1-23 years) [Table 1]

Table 1. *Age*

Total number of patients: 47	Current Age	Age at Diagnosis	Duration of the disease
Mean Age	33.62	26.85	6.79
Median Age	35.00	28.00	6.00
Standard deviation	9.461	8.648	5.938
Minimum Age	15	13	1
Maximum Age	50	40	23

Sixty-eight percent (68%) of the women were nulliparous and 32% of the women had one or two children. [Table2]

Table 2. *Parity*

Number	Frequency	Percent
0	32	68.1
1	9	19.1
2 0r more	6	12.8
Total	47	100.0

Primary Outcome Measure

The prevalence of POI in our setting is 8,4% (Confidence interval 6.28%-11.06%).

Secondary Outcome Measures

The etiology of POI in 32% of the patients was idiopathic, 19% genetic syndromic disorder, all of which were Turner Syndrome, 10% were non-syndromic genetic disorders.

A familial disorder was found according to family history of a patient with a sibling that has POI, and accounted for 2% of the causes. All other causes are outlined in Table 3, pie chart 1.

Table 3. *Probable Etiological Factors*

Etiology	Frequency	Percent
Idiopathic	15	31.9
Genetic Syndrome	11	23.4
Genetic Non-Syndromic	3	6.4
Familial	1	2.1
Auto-immune	3	6.4
Cancer/Chemotherapy	3	6.4
Obstetric complications	3	6.4
Infective	3	6.4
Endometriosis	1	2.1
Iatrogenic	2	4.2

Sixty percent of the patients who were nulliparous had a desire to conceive and only 4% could afford low cost IVF with donor oocytes. [Table 4] and [Graph 1]

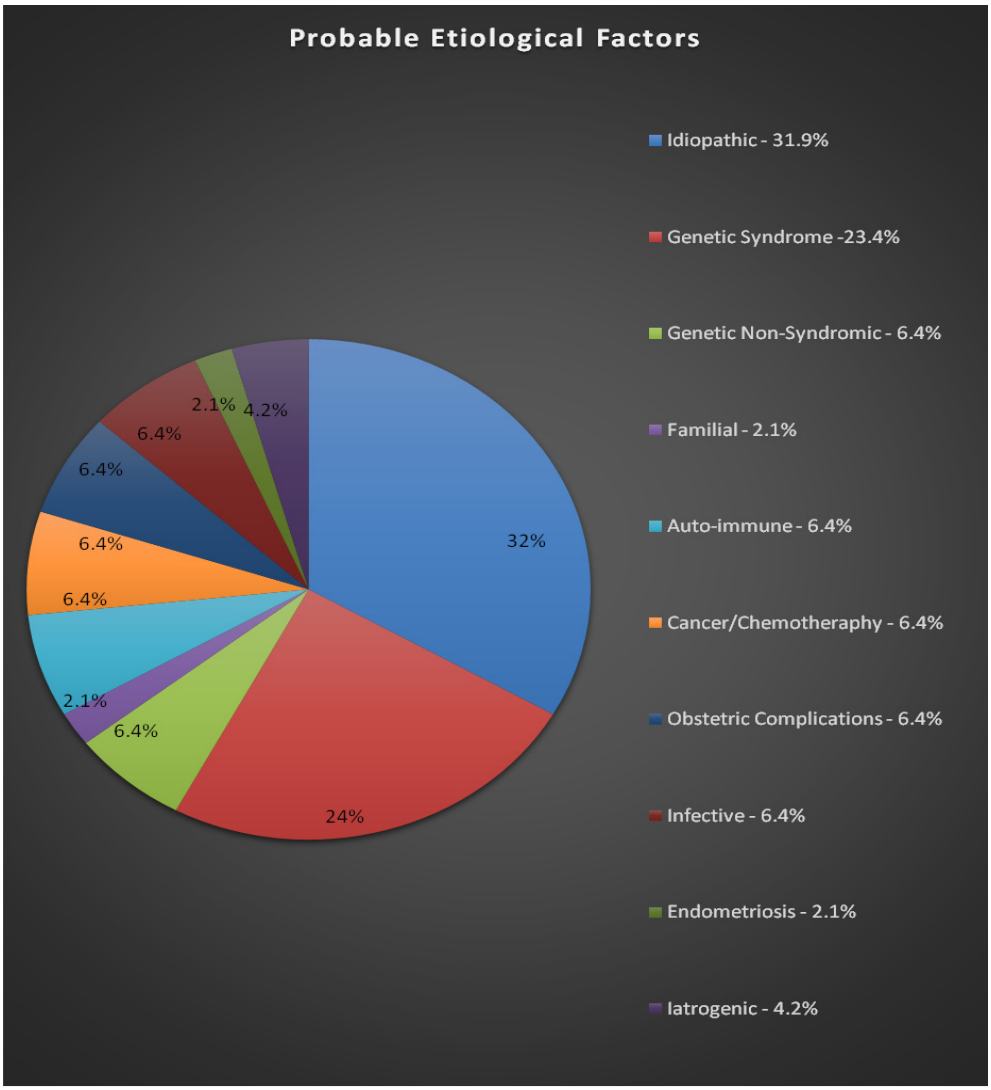


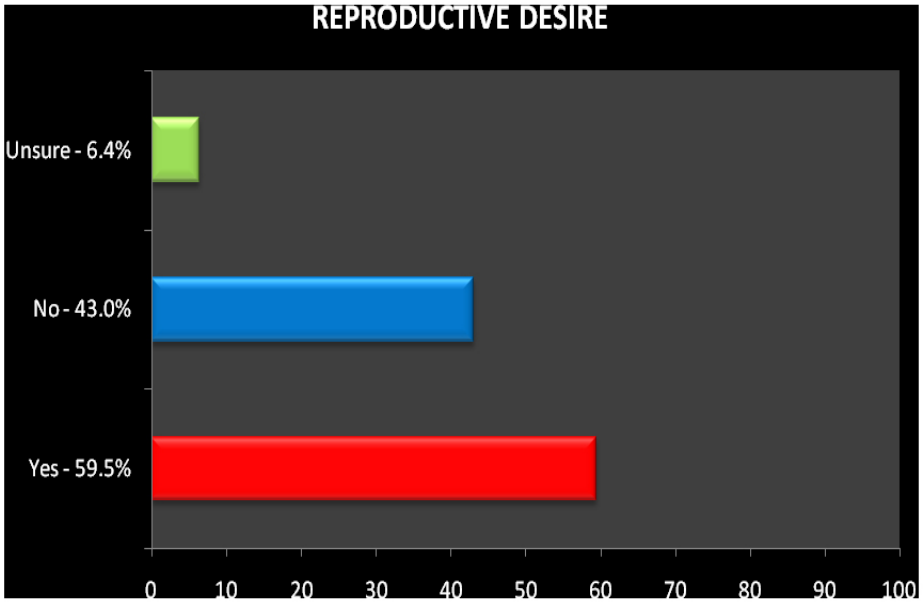
Table 4. *Reproductive Desire*

Desire	Frequency	Percent
Yes	27	60.0
No	16	43.0
Unsure	3	7.0
Total	47	100.0

Depression was found in 55% of patients. They were treated with various anti-depressants, the least expensive of which was fluoxetine 20-40mg daily. [Table 5] and [Graph 2]

Table 5. *Depression (DSM-V Classification)*

Depression	Frequency	Percent
Yes	26	55.3
No	21	44.7
Total	47	100.0

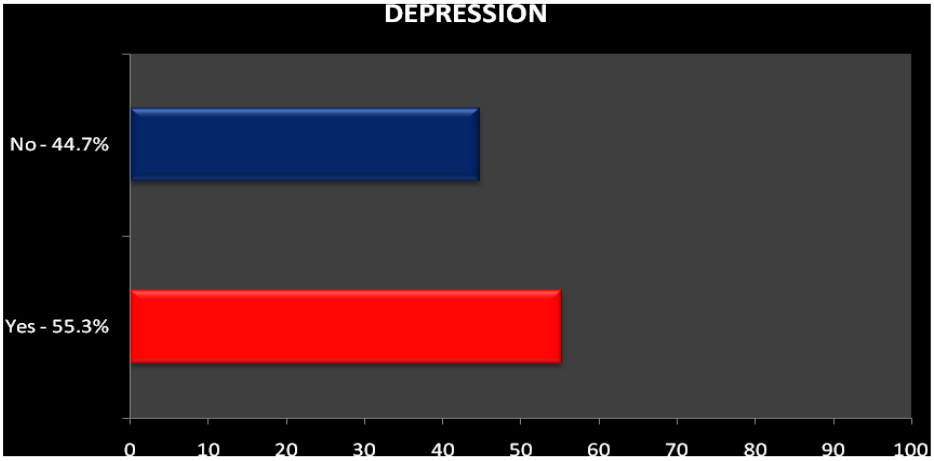


A dual energy X-ray absorptiometry (DEXA) scan was done in 79% of cases, of which32% had osteopenia, 11% had osteoporosis and in 21% patients a DEXA scan was requested but not done.

Patients with normal DEXA scans were re-assessed 5 years later and patients with osteopenia and osteoporosis were re-assessed every 2 years. Eighty-one percent (81%) of patients with osteoporosis were treated with bisphosphonates in the clinical endocrinology unit. [Table 6] and [Graph 3]

Table 6. *DEXA*

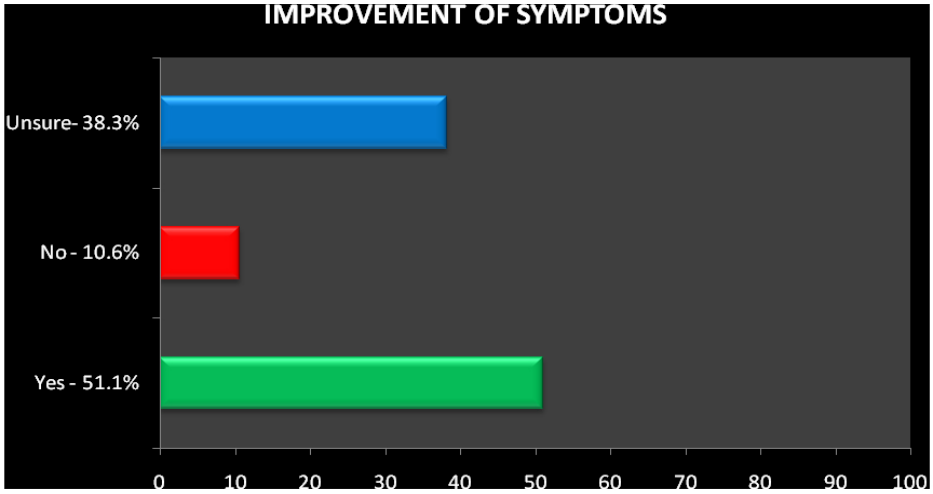
Number	Frequency	Percent
Not done	10	21.3
Normal BMD	16	34.0
Low BMD/Osteopenia	13	27.7
Osteoporosis	8	17.0
Total	47	100.0



The majority of patients (51%) were satisfied with their long-term management and with the standard treatment protocol as outlined above. Even though 39% of the patientswere unsure of their therapeutic progress they continued with the routine follow-up, and 11% of the patients did not observe any change with treatment. [Table 7] and [Graph 4]

Table 7. *Improvement of Symptoms*

Improvement	Frequency	Percent
Yes	24	51.1
No	5	10.6
Unsure	24	38.3
Total	47	100.0



Discussion

The prevalence of POI in this study is higher (8.4%) than the reported figure in the literature of 1% (0.9%-3.1%). The difference may be due to a bias caused by a smaller sample size relative to the total number of patients seen at our clinic.

In the context of the current total earth population estimated at 7.8 billion people, and the female population estimated at 3.8 billion (49.6%) of the total, the population of women in the reproductive age (15-49 years) estimated at 1.6 billion in 2016 [31]. The prevalence of 1% means that approximately 16 million women of reproductive age are affected by POI world-wide.

16 million women may appear small relative to the total world population, but if we imagine that there are countries with a population of approximately 16 million people, then the impact of the disease becomes significant.

The low fecundity rate in most parts of the world, and the high maternal, neonatal and childhood mortality statistics world-wide, especially in LMIC become important when the prevalence of POI and the age distribution of POI, with 90% of cases occurring between ages 30-40.

Patients in LMIC usually receive fragmented care for various reasons such as internal infrastructural deficiencies in some hospitals, frequent change and movement of medical staff who rotate between different units, the difficulty they encounter with inter-departmental referrals, and various other reasons that may pertain to the patient themselves.

Management of POI in our Study

The patients were managed according to standard protocol described above. To some extent it was in keeping and supported by best practice and current guidelines. However, we fell short on some key areas like cardiovascular health, metabolic disease screening and special investigations for rare causes of POI, which may have been classified as idiopathic. This may be due to the fact that our investigations are limited by financial constraints, and therefore we mainly concentrate on the routine investigations as described in the literature.

Patients with suspected cardiovascular compromise and metabolic syndrome are referred to the internal medicine department. Ideally, this service should be provided to all patients, but it is limited by the patient load in ourhospital.

Thus far, we have not been effective in protecting the fertility potential of our patients because cost and resources [32]. We also have not been effective in providing a cost-effective and concessionary fertility program to suit patients with POI because our ART program is already overloaded with patients paying for low-cost IVF. Under these circumstances the unit cannot accommodate patients whose ART treatment is complicated by need of donor oocytes, making the cost greater [33].

To overcome this hurdle, we could suggest and encourage altruistic oocyte donation from younger patients who are good responders, who have a higher than normal yield compared to their peers. Furthermore, public-private collaboration could initiate an altruistic oocyte donor program through patients that can afford conventional IVF with a higher yield of oocytes. With thorough counselling family member donation should be encouraged [34].

The Impact of POI on Our Study Patients

The commonest etiological factor of POI is idiopathic 32% (Table 3). Idiopathic causes of POI are reported as 30% as in the literature, similar to the findings in our study.

The commonest finding in our study was the devastation of loss of fertility (Table 4). For patients desiring conception, donor oocyte programs are available. In our study, most of the patients desired a pregnancy (60%) and only 2 patients (4%) in the whole cohort could afford donor-IVF through altruistic oocyte donation from patients with an excess number of oocytes in our IVF program.

Unfortunately, a large number of patients had to give up the desire for a child due a lack of affordability. Social isolation due to infertility is common in our society, aggravating symptoms of anxiety and depression. Psychological devastation, anxiety, and sexual dysfunction were as high as 50%-70% of the patients in a sub-analysis of the results.

The phenomenon of unequal access to health care is common in LMIC [35]. ART coverage is South Africa confirms our finding regarding reproductive desire and the inability to for the patient to access ART service [36]. Barriers to care include infrastructure, costs, and affordability [35,36].

Government and academic institution collaboration could alleviate the situation by increasing government subsidized Reproductive Medicine training centers, as well as increasing training posts to bolster numbers of available specialists to provide this specialized service to the community.

Fertility preservation is now a possibility and a priority for women with POI. Currently, research is expanding to determine idiopathic causes of POI. The findings could mitigate against complete loss of fertility before it is established in women with POI who would otherwise be advised on options of fertility preservation or decide on early childbearing [37]. Some centers are doing research to find ways to prolong the fertility window for all women, including women with POI [38].

With the changes in the age of conception occurring later than previous years, there will be an overlap of POI patients with reproductive desire and patients seeking assisted reproductive technologies (ART) at the end of their reproductive potential. This means more people with a poor prognosis will seek ARTrequiring donor-IVF [39].

This is a challenge faced by institutions in the majority of state reproductive units that are not funded [40]. In some areas, such as our institution, there is an on-going collaboration and assistance form private reproductive units that generate income. Most of our patients have to save money over 12-24 months or longer in order to afford low-cost IVF [40].

Depression was the secondmost common long-term outcome affecting patients in this study (Table. 5). Current literature shows a linear relationship between depression and dementia [22,31,41]. If depression is left untreated over an extended period, it affects memory and eventually leads to dementia [22,31,41]. Alzheimer disease could be a consequence to chronic low E2 levels, but studies are inconclusive regarding causation [42].

Regrettably, two patients in our study population attempted suicide with rodenticides. They were fortunately taken to hospital on time. One patient required an emergency laparotomy for an acute abdomen. Clinicians should increase their vigilance and lower their tolerance for symptoms of severe depression, as some patients may not be forthcoming with the information. Patients with severe depression have to be treated with anti-depressants to prevent such tragic incidents.

Our results show that 20% of the patients did not fulfil their appointment for a DEXA scan (Table 6). We can only speculate that those patients either did not understand the necessity of a baseline DEXA or they could not honor the appointment due to work commitment or a lack of financial resources to travel to hospital.

Most of the patients were accompanied by family members or care-givers. Those who were found to be depressed received appropriate management through counselling and anti-depressant medication as described above. Most of the young women with Turner syndrome were anxious and depressed by their body stature and had a poor body image, stating that they want to look like their peers

It is encouraging that only 10% of the patients were not satisfied with their treatment and reported no improvement in symptoms (Table 7). They cited a dissatisfaction with being seen by different clinicians in the same clinic. Their preference would be a follow-up with the same clinician. This is not possible in a public setting because of restricted resources, therefore, it is important to educate and inform patients at their first visit on how the system functions and what to expect in order to minimize the levels of dissatisfaction.

Currently, in most LMIC, patients with POI are still treated as patients with natural menopause [41], because of lack of awareness of changes in nomenclature from “Premature Menopause” to Premature Ovarian Insufficiency. There is alsoa lack of awareness of the latest published guidelines in the primary and secondary health sector.

Natural menopause is not considered a disease condition but a continuum in the natural aging of a woman. Furthermore, E2 replacement therapy required in patients with POI is generally higher than that required in menopause for bone and cardiovascular protection. Therefore, patients in LMIC are actually being under-treated for their condition.

Estrogen deficiency also causes vasomotor symptoms, a reduced quality of life and compromises the general functional level of the patient. In a sub-analysis, 25 to 60% of patients in our cohort reported poor body image, sexual dysfunction, reduced functional level and social isolation due to the diagnosis of POI and living with the disease. This was similar to a study published in journal of clinical oncology in young patients who have undergone gonadotoxic therapy [41].

Educating the patient about changes secondary to E2 decline in non-medical language may bring understanding to the patient, as well as compliance to treatment.

Strengths and Limitations of the Study

POI, being a low prevalence condition, makes it difficult to accrue enough sample sizes for research purposes. The number of patients in our study did not give sufficient power to obtain a good Confidence Interval (CI). Therefore our biggest limitation was sample size.

The strength of the study is that to our knowledge, this is the first audit of women living with POI locally and in LMIC. After an exhaustive literature search, we found several, but few publications from different African countries, none of which are similar or related to our study [34,44]. Through the findings of this study, we hope to improve our services to women with POI, especially where there are deficiencies, including fertility preservation and assisted reproductive technology (ART). Furthermore, we hope to encourage further good quality and robust studies on this subject in LMIC.

African research and publications on POI are the rarest of all in published media on POI. With varying healthcare problems, scarce resources and prioritization of epidemic diseases, POI is regarded as a small, albeit tragic condition. This could be due to the fact that POI is considered a rare condition and therefore not receiving due attention. This leads to the suffering observed in women with POI [42].

New Frontiers and Future Areas of Research in POI

The ultimate in any disease process is prevention, followed by accurate and cost-effective diagnosis and treatment.

Currently, several robust genetic studies are on-going to find other causes of POI, especially in the idiopathic group. New methods for cytogenetic screening such as new generation sequencing may expand identifiable causes in women with idiopathic POI.

Although fertility preservation has been established in centers of excellence locally and abroad, it is still not widely available. Fortunately, awareness is increasing regarding all methods of fertility preservation through continuous medical education and media. The missing link is information to the patient, as well as access and cost to centers of excellence.

Vitrification methods are still not uniformly well performed in all reproductive centers, but the improvement from slow freezing of oocytes to rapid vitrification has improved the survival of oocytes and has lowered the high attrition rate experienced with previous methods [43].

It is reasonable to think that a specific screening test or a clinical biomarker to identify women with reduced ovarian reserve remote from the end of the reproductive potential could be found.

AMH is currently used in assisted reproductive programs. Women with low AMH values are expected to have a limited to muted response (poor responders) to controlled ovarian stimulation [44]. A study looking at a minimum critical value outside of the normal range for age could be useful as a screening test for POI.

LH is another promising biomarker. In one study, investigators found that the remaining few follicles of women with POI undergo premature luteinization [45]. Therefore, an elevated LH as an early biomarker could identify women whose follicles could be rescued before manifestation of POI [45,46].

Another study showed that although AMH was an important and superior marker in differentiating both women with elevated FSH who otherwise have regular cycles and women with POI from controls; LH had a higher resolution than AMH in differentiating women with POI from women with elevated FSH who otherwise have regular cycles [46]

Age is a critical factor in such a screening program, as this would alert the clinician to counsel not only the patient, but siblings who may have the same syndrome causing POI, before it manifests.

In vitro maturation (IVM) of antral follicles is currently used as a modality in ART in some centers [47]. Refining this technique and sharing of information in ART centers would make IVM another established modality of fertility preservation.

The concept that germ-line stem cells are not present in the ovary, and that follicular renewal intrinsic to the ovary does not occur in the postnatal mammalian ovary has been challenged. Recently investigators are looking at ovarian stem cells and some germ-line stem cells have been found in animal studies [48]. There are trials of stem cell therapy on the ovary with resumption of follicle formation [49].

This new paradigm may change the way the ovary is currently viewed as a gonad with a linear downward trajectory, but rather as a dynamic organ with a population of cells capable of undergoing renewal.

In some working environments, employers offer their female employees egg freezing for future use as an employee benefit for future use [50]. This trend is seen locally in social media where some ART centers encourage young women to freeze their eggs. This

aims to counter the effect of loss of fertility through late marriages and busy early careers with long working hours in the female population. Although not universal, this forward thinking may save some women who may experience POI in their 30's.

Conclusion

The study reported a high prevalence of 8,4% of POI. Without an international database, it remains uncertain whether the prevalence has in fact remained the same, or changed. Therefore, there is a need for a database and robust studies on POI.

The patient management was on par with some of the current ESHRE guidelines, but it fell short in some crucial areas. Patients are generally from low-income families, and therefore, cannot always afford to follow-up regularly. This causes "non-compliance", with patients missing important appointments scheduled for investigations and inter-departmental referrals.

The other challenge is a burdened national health systems in many LMIC, and therefore compromising optimal service delivery.

The on-going initiatives from various organizations and societies suggesting an international database and developing of evidence based guidelines are encouraging and should be supported.

The growing interest in POI and advances in scientific research will hopefully yield tangible results that can be translated into clinical use. We hope that this study will increase awareness in our region and other LMIC. This would help clinicians to manage these patients with current guidelines.

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Citation: **Mmaselemo Tsuari, Thabo Matsaseng.** *Evaluating the Prevalence, Management and the Psychosocial Impact of Premature Ovarian Insufficiency on Patients Attending an Academic Hospital Reproductive Endocrine Clinic. Archives of Reproductive Medicine and Sexual Health. 2018; 1(1): 31-46.*