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The Clinical Characteristics of Infertile Women with Premature Ovarian Insufficiency: A Retrospective Analysis

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Abstract:

Objective: *To explore the clinical profile of infertile women with premature ovarian insufficiency, previously termed premature ovarian failure presenting to a public health facility.*

Materials and methods : *A retrospective study was carried out in which the data collected over three years from 2015-2017 in the Gynae Endocrine Clinic of Infertility unit of the Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University. A total of 36 infertile women diagnosed as premature ovarian insufficiency were included in the study. Detailed data from the records of the clinic regarding symptoms, history related to possible etiology, investigations including endocrine profile and karyotype were included in the analysis. A follow up interview over cell phone was carried out in 2020 to have the information about any pregnancy and compliance with drug over 2- 5 years.*

Results: *A total of 36 women with infertility which were due to premature ovarian insufficiency were included. The mean age was 30.35±5.16 years. Four women were under 25 years and one of them had primary amenorrhoea. Median values with interquartile range of serum FSH, serum AMH and estrogen were 47IU/L ,0.16ng/ml and 22.83pg/ml respectively.Hypoestrogenic symptoms like hot flush and vaginal dryness were present in 50% and 38.9% of the women respectively. While the possible causes of premature ovarian insufficiency were predicted from history, examination and investigations, autoimmune cause was most common (41.7%) followed by genetic/familial causes (25%). Two (5.6%) women conceived spontaneously. None of the women was compliant with the hormone replacement therapy we prescribed.*

Conclusions: *Detailed evaluation with history, examination and investigation for possible causes of premature ovarian insufficiency should be done though the primary concern is infertility. Counseling should emphasize on the need of hormone replacement therapy and the probability, though small, of spontaneous pregnancy.*

Key words: *Premature ovarian insufficiency, Premature ovarian failure, Hormone replacement therapy*

Introduction:

Premature ovarian failure is cessation of ovarian activity before the age of 40 years[1]. Since spontaneous pregnancy can occur in 5-10% cases due to random ovulation, the term is now replaced with premature ovarian insufficiency[2]. Premature ovarian failure was diagnosed when the women had amenorrhoea with the raised basal FSH above 40IU/L on two occasions at 4 weeks apart. Now according to European Society of Human Reproduction and Embryology (ESHRE), premature ovarian insufficiency is diagnosed when women below 40 years have at least four months of amenorrhoea and basal FSH raised to more than 25 IU/L on at least

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two occasions at 4 weeks apart. As far as fertility is concerned, pregnancy is unlikely even by in vitro fertilization (IVF) with her own oocyte if basal FSH is higher than 25IU/L.

Hypergonadotropic anovulation (WHO type III anovulation), is the second most common (20-30%) cause of anovulation in women, the first one being polycystic ovary syndrome(75-85%)[3]. Nothing less than IVF with donor oocyte can increase the chance of pregnancy in this group of infertile women.The prevalence of premature ovarian insufficiency is 1 in 100 below 40 years of age, 1 in 1000 below 30 years of age and 1 in 10000 below the age of 20 years[4]. Most of the cases are idiopathic. Causes identified for follicular depletion and dysfunction are genetic, autoimmune and iatrogenic. Genetic causes include Turners syndrome and its variants, FMRI gene permutation carrier state etc. Autoimmune causes are autoimmune oophoritis, sometimes associated with autoimmune disorders of other endocrine glands such as thyroid or adrenal gland. Iatrogenic causes include ovarian surgery (eg in endometriosis), radiotherapy/ chemotherapy for malignant disease or connective tissue disorder (eg systemic lupus erythromatosus). Premature ovarian insufficiency is diagnosed in infertile women when they present with oligomenorrhoea or amenorrhoea and are screened with basal FSH. When basal FSH is high, the investigation is repeated four weeks later. The diagnosis is confirmed when basal FSH is more than 25 IU/L on at least two occasions at 4 weeks apart. They are counseled about the poor prognosis of treatment other than IVF with donor oocyte. The women informed about the 5-10% chance of pregnancy without treatment, prescribed hormone replacement therapy and advised for follow up visit. Investigative regimes of ovarian stimulation are expensive,of no proven benefit and so better not to try.

When an infertile woman is diagnosed as premature ovarian insufficiency and she is counselled about the prognosis, it is devastating for her. In vitro fertilization with donated ova is not acceptable to our patients due to financial and ethical reasons. Third party reproduction is not a practical option in this country with Sunni Muslim dominance. Bangladesh is a country where early marriage is prevalent and childlessness is socially unacceptable. The purpose of our study was to explore the clinical characteristics and relevant causes in the infertile women who presented with premature ovarian insufficiency and to investigate their present situation regarding spontaneous pregnancy or otherwise.

Methods:

This was a retrospective analysis of data recorded in the Gynae Endocrine Clinic of the Infertility unit of the Department of Obstetrics and Gynaecology at Bangabandhu Sheikh Mujib Medical University during three years from 2015 to 2017. There was a follow up interview of the women over telephone in March 2020 and the data about the possible events of spontaneous pregnancies and compliance with drugs were included in analysis. The criteria for diagnosis of premature ovarian insufficiency in infertile women were oligomenorrhea or amenorrhea combined with basal FSH higher than 25 IU/L on two occasions at 4 weeks apart. The higher value of FSH was included in the analysis. Then they were interviewed and investigated in an attempt to define the cause. Not all women were amenorrhic for more than four months though all were oligomenorrhic. They were interviewed about hypoestrogenic symptoms like hot flushes, vaginal dryness and presence of any associated autoimmune diseases like diabetes mellitus, hypothyroidism, hypoparathyrodism, addisons disease, recurrent respiratory tract infection suggestive of IgG deficiency or pernicious anaemia, any previous ovarian surgery, chemotherapy or radiotherapy. Genetic and familial cause was suspected when she had family history of secondary amenorrhea or any history of mental retardation, autism or tremor ataxia in elderly male relatives suggestive of FMRI gene permutation. They were advised to have investigations in an attempt to exclude autoimmune diseases. Tests for anti-ovarian or anti-adrenal antibodies were not available. Serum TSH was done and anti thyroid antibodies were advised when serum TSH was more than 2.5 mIU/L . Complete blood count with peripheral blood film was advised to exclude pernicious anaemia. Fasting blood sugar and blood sugar two hours after 75 gm glucose was done to exclude diabetes mellitus. Serum calcium and serum phosphate was advised to exclude hypoparathyroidism. If she had history of recurrent respiratory tract infection than serum total protein

and albumin -globulin ratio was advised to exclude IgA deficiency. Karyotype was advised when the woman was less than 30 years and height less than 60 cm. Following evaluation the women were counselled about her fertility potential. They were put on a regime of hormone replacement therapy (HRT) consisting of conjugated equine estrogen 0.625 mg daily and medroxy-progesterone acetate 5-10 mg daily for 10 -12 days cyclically. They were told to continue the therapy up to 50 years of age and asked for follow up visits if any problem arises.

Results:

There were a total of 36 infertile women with premature ovarian insufficiency presenting in the Gynae Endocrine Clinic of the Infertility unit of the Department of the Obstetrics and Gynecology over 3 years from January 2015 to December 2017. The follow up interview was done in March, 2020.

Table I and II summarize the general characteristics of the study subjects. The mean age was 30.35±5.16 years. The median age was 30 years with range 22-39 years, four women under 25 years. Only one woman had primary amenorrhea. The mean age at menarche of others was 12.27±2.69 years or 13 years (median) with range 10-17 years. Most (66.7%) of the women had primary infertility,the maximum duration being 18 years. Hypo-estrogenic symptoms were present in around half of the women. The serum levels of basal FSH, AMH and estradiol did not have normal distribution,but skewed significantly.The estimated levels are more appropriately described as median values, basal FSH 47IU/L, AMH 0.16 ng/ml and estradiol 22.83 pg/dl. Serum E2 at 50th percentile was 22.83 pg/ml, 44% had levels more than 30pg/ml. This explains the hypo-estrogenic symptoms in around half of the women. Four of the women had serum AMH levels more than 1ng/dl, which may be the cases of ovarian resistance syndrome or technical failure in AMH estimation.

Table III describes the possible causes of premature ovarian insufficiency as predicted from history, examination and investigations. Nine women had karyotype of whom two were Turner variants. Both were cases of secondary amenorrhea. One was Turner Mosaic (47XXX, 45XO), the other had terminal deletion of the long arm of one X chromosome. Autoimmune causes were more common than familial, genetic cause or iatrogenic cause. There was no case of previous chemotherapy or radiotherapy. There were four women who had personal or contact history of tuberculosis and suspected to have genital tuberculosis unless proved otherwise.

The women were contacted over cell phone after about 2-5 years but twenty one women were unreachable. All of the women who were interviewed said they discontinued our prescription and sought treatment elsewhere. Two women conceived spontaneously. The proportion was 5.6%. One was 24 year old at the time of diagnosis. She had secondary amenorrhea. She conceived spontaneously and delivered a healthy male baby 4 years back. The secondary amenorrhea persisted and she is recently pregnant for second time. The other woman who is 39 years old conceived spontaneously but had an early abortion. One woman said she had adopted a child.

Table-I

General characteristics of the subjects (N=36)

Parameters	Mean	Standard deviation	Median	Interquartile Range
Age (years)	30.34	5.16	30	26-36
Duration of infertility (years)	6.43	4.09	6	3-9
Basal FSH (IU/L)	58.31	29.55	47.3	35.7-79.3
AMH (ng/dl)	0.53	1.20	0.16	0.02-0.49
Estradiol (pg/dl)	40.10	37.52	22.83	15.52-65

Table-II

Clinical characteristics of the subjects (N=36)

Parameters	Number	Frequency (Percentage)
Primary infertility	24	66.7
Secondary infertility	9	25
Oligomenorrhea	18	50
Amenorrhoea	14	38.9
Hot flushes	18	50
Vaginal dryness	14	38.9

Table-III

Etiology of premature ovarian insufficiency, when available (N=36)

Possible Cause	Number	Frequency (percentage)
Genetic/familial		
Turner syndrome variants	9	25
Suspected Fragile X	2	5.6
permutation	2	5.6
Family history of secondary	5	13.9
amenorrhoea		
Autoimmune disorder		
Hypothyroidism	15	41.7
Diabetes mellitus	9	25
Diabetes mellitus and	3	0.08
hypothyroidism	1	0.02
Bronchial asthma	2	0.05
Suspected genital tuberculosis	4	11.1
Iatrogenic: ovarian surgery	2	5.6

Discussion:

Premature ovarian insufficiency is relatively a rare cause of infertility. The European Society of Human Reproduction and Embryology (ESHRE) defined premature ovarian insufficiency as a clinical syndrome where there is loss of ovarian activity before the age of 40[2]. POI is characterized by menstrual disturbance (amenorrhea or oligomenorrhea), with raised gonadotropins and low estradiol[1]. Previously the condition was called premature ovarian failure. Diagnostic criteria was amenorrhea more than 4 months and basal FSH 40IU/L or more on at least two occasions at 4 weeks apart. Now the criteria has been set to basal FSH elevated to more than 25IU/L on two occasions at more than 4 weeks apart. They limit cycle length to at least 4 months. The previous terms like premature ovarian failure or premature menopause imply permanency and so are inappropriate because there is still around 25% chance of spontaneous ovulation and 5-10% chance of spontaneous pregnancy[4-6]. In our population of infertile women we did not emphasize on cycle length or hypo-estrogenism because serum FSH levels rise even when cycle length is less than 4 months or estrogen levels are normal[4,5]. The finding of basal FSH >25IU/L is ominous in infertile women because in this situation all ovarian stimulation protocols are ineffective. No usual treatment other than IVF with oocyte or embryo donation will increase her chance of conception to more than the spontaneous pregnancy rate of 5-10%.

The hypo estrogenic symptoms like hot flushes and vaginal dryness were present in around half of the women. Hypoestrogenism is not persistent in these women[5,6]. This is explained by the fact that not all of our women had amenorrhea for more than a year. In some women serum AMH was more than 1 ng/dl. This indicates that there were still some residual preantral follicles capable of recruitment and ovulation. They may otherwise indicate resistant ovary syndrome (Savage syndrome) or technical failure in AMH estimation. Prolonged storage of blood samples may lead to falsely high estimate of AMH levels[7]. Savage syndrome is a rare endocrine disorder with hyper-gonadotropic hypogonadism. Ovarian follicles are present but unresponsive to FSH, endogenous or exogenous[8]. Transvaginal ultrasound to visualize the ovaries could further evaluate the diagnosis. Women with ovarian resistance are offered oocyte donation programs though there have been few reports of pregnancy following in vitro maturation of retrieved oocytes[9].

Regarding etiology of premature ovarian insufficiency of the study population, 5.6% were Turner variants, 13.9% had positive family history and 41.7% were associated with autoimmune disorder. Though our population was infertile women, the prevalence was almost similar to that of other studies[4,5,8,10-13].The chromosomal anomalies like Turner variants was 5%, family history of secondary amenorrhea or any history of mental retardation, autism or tremor ataxia in elderly male relatives was present in 20-30%. Turner's variants are responsible for rapid follicular depletion. Familial causes include single gene defects or fragile X premutation. FMRI gene, responsible for fragile X syndrome is present on chromosome Xq27. Tandem repeats of CGG less than 45 is normal, but more than 200 repeats in FMRI gene in female carrier exposes her to risk of POI and leads to fragile X

syndrome in male relatives[8], the second most common congenital cause of mental retardation in males, only next to Down's syndrome. Autoimmune disorders varied from 10-30%[13]. Thyroid autoimmunity was most prevalent (25-60%) among autoimmune disorders[10, 13] as is in our study. The prevalence of autoimmune disorders may be overestimated in our study as inference was made from history without complete investigation of auto antibodies. Ovarian auto antibodies are not validated cause of premature ovarian dysfunction. Screening for autoimmunity should begin with asking about associated autoimmune disorders even before investigations. This screening is essential for future health surveillance[10]. The women presented with infertility, so all of them were married. No woman had the history of chemotherapy or radiotherapy. Those having this sort of treatment may have been already informed about their fertility potential and so not presenting to us for fertility treatment. Two women had ovarian surgery. Bilateral cystectomy of ovaries carries the risk of ovarian failure in around 2.4% cases [12]. Four women were suspected to have genital tuberculosis. Genital tuberculosis can cause oligomenorrhea or amenorrhea as a sequele of endometritis. Mycobacterium tuberculosis can induce oophoritis or autoimmune destruction of ova by development of autoantibodies[14].

Most of the women were unreachable for follow up interview which may indicate a difficulty in practicing telemedicine in our country. There was no compliance with HRT. The HRT was advised not only to treat and prevent hypo estrogenic symptoms but also to prevent prolonged effect of hypo-estrogenic state leading to osteoporosis and risk of cardiovascular death[8].The reasons behind non compliance may lie in inadequate counseling by our doctors in Gynae Endocrine Clinic or the women's preoccupation with infertility problem. The exogenous estrogen may sensitize the granulocytes and estrogen-progesterone down regulate the LH and FSH receptor, thus favor ovulation and pregnancy [11,13].However one of the women got pregnant even when she had amenorrhea and was not on any HRT. The spontaneous pregnancy rate was 5.6% as expected. One of the women who was pregnant aborted. The rate of abortion in these women is 20%, not more than general population of pregnant women[10].

Limitations of the study were that it was a retrospective analysis of the data obtained on women who declined investigations on the believe that it would not benefit their fertility potential. Fragile X premutation screening was too expensive to do even when history was suggestive. Many auto antibodies like anti adrenal antibodies could not be determined due to non-availability of the facility.

Conclusion:

For infertile women diagnosis of premature ovarian insufficiency is unexpected and distressing. Fertility is of more concern to them than hormone replacement therapy for long term health. They need more personal and emotional support in the form of counseling and follow up to help them deal with the impact of diagnosis. Counseling should stress on the fact that pregnancy is possible without treatment in 5-10% cases. Detailed evaluation beyond fertility competence should be emphasized to ensure quality of life and long-term survival.

Conflict of Interest

The authors decline any conflict of interest.

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