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Clinical and Laboratory Characteristics of Infertile Women with Premature Ovarian Insufficiency

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Abstract

Background: Premature ovarian insufficiency (POI) is the preferred term for the condition that was previously referred to as premature menopause or premature ovarian failure. The condition differs from menopause in that there are varying and residual ovarian functions. This study aimed to analyze the clinical characteristics of infertile women with premature ovarian insufficiency. **Material & Methods:** This prospective study was conducted at the OPD of Impulse Fertility Center, Impulse Hospital, Dhaka, Bangladesh. The study was conducted for a period from January 2022 to December 2022. A total of 23 patients who received outdoor treatment during the study period were purposively selected as sample size. A purposive sampling technique was followed in this study. After approval by the Ethics committee of the Hospital, informed consent from the respondents was obtained after explaining the purpose of the study to them. To be included in the study, respondents should have met the classical definition of infertility defined by the WHO as the inability of a sexually active non-contraceptive using woman to have a live birth after 12 or more months of regular sexual intercourse without a malefactor. Women who had male-factor infertility were excluded. In this study live birth was used as a measure of proven fertility (Because couples desire children, not simply pregnancies, infertility affects couples regardless of whether the etiology lies in conception or the progression of the pregnancy). All the necessary laboratory investigations were done. A questionnaire was developed and data were collected by interviewing the patients and some data were collected from the laboratory results. Data were processed and analyzed by SPSS 19 version. **Results:** All patients had normal puberty, and menarche occurred at ages 11–15, followed by a regular menstrual cycle. Women who presented with oligomenorrhea were younger than patients with infertility. The mean period of oligomenorrhea before diagnosis was 0.9 years in the oligomenorrhea group and 1.8 years in the infertility group. The mean age when the infrequent periods started was 28 years in the group with oligomenorrhea and 29 years in the group with infertility, and their anthropometric characteristics were not different. In most patients, the FSH levels on day 3 of their menstrual cycle were less than 25 mU/ml. FSH levels >25 mU/ml were confirmed in two patients with oligomenorrhea and five patients in the infertility group. AMH levels were low than 1.0 ng/ml (considered to be in poor ovarian reserve ranges: from 0.13 to 1.0 ng/ml in patients with oligomenorrhea and from 0.13 to 0.9 ng/ml in the infertility group.

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Transvaginal ultrasound-determined AFC on menstrual cycle days 4–8 was accessed in all patients. We consider AFC < 6 small follicles (diameters 3–9 mm) as a low ovarian reserve indicator. The lowest AFC (one small follicle) was noted in one infertile patient with oligomenorrhea. **Conclusion:** This study concluded that the subjects usually present with menstrual irregularity (oligomenorrhea) or infertility, and after proper evaluation, their poor ovarian reserve can be confirmed and an occult form of POI established. women who presented with only oligomenorrhea were younger than infertile patients; therefore, menstrual irregularity may be the earliest clinical symptom of occult POI.

Keywords:- Premature Ovarian Insufficiency (POI), AMH, FSH.

INTRODUCTION

Premature ovarian insufficiency (POI) previously known as premature menopause or premature ovarian failure (POF) is a common occurrence.[1] It affects 1 in 100 women of age greater than 40 years and 1 in 1000 women aged less than 30 years.[2] European society of human reproduction and embryology (ESHRE) describes POI as the presence of amenorrhea for 4 months or more before the age of 40 in women, accompanied by a serum FSH level of >25 IU/l on two occasions four weeks apart.[3] The main presenting symptom of the condition is amenorrhea but due to the residual function of ovarian follicles, around half of the women have oligomenorrhea and spontaneous ovulations.[4] According to an estimate, 5–10% of women with POI conceive spontaneously. These women are said to have a variant of POI which is called "occult primary ovarian insufficiency" associated with diminished ovarian reserve (DOR).[5] Occult ovarian failure was first described as a triad of regular menstruation, infertility, and high plasma levels of Follicle Stimulating Hormone (FSH).[6] These women with occult POI are not recognized until they present infertility.[5] POI is a genetically heterogeneous condition but the current understanding of its genetic basis is far from complete, with the cause remaining unknown in the majority of patients. The genes that regulate DOR have been reported but the genetic basis of DOR has not been explored in depth. Both conditions are likely to lie along a continuum of degrees of decrease in ovarian reserve.[7] In most cases, multiple factors contribute to the premature depletion of the primordial follicle pool.[8] Genetic abnormalities, autoimmunity, radiotherapy, chemotherapy, or surgery can all contribute to this disease.[8,9,10,11,12] The most common symptoms are menstrual irregularities, low-level estrogen, and high follicle-stimulating hormone (FSH); however, some POI patients have unexplained idiopathic causes.[13] POI at an early age has an undesirable impact on the reproductive system and may result in infertility. Furthermore, estrogen deficiency is linked to low bone density, cardiovascular diseases, sexual dysfunction, and high mental distress.[14,15] Though POI is a polygenic disease,[16] the precise etiology and molecular mechanisms of POI remain unknown. AMH could potentially help assess the progression of

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ovarian senescence, as serum AMH levels are independent ofhypothalamic–pituitary–gonadal axis function and decrease to undetectable levels at menopause. In cancer survivors, serum AMH levels correlate with the extent of gonadal damage. In this Review, we provide an overview of the current studies that have measured AMH in women with POI of various aetiologies and discuss its possible application as a marker to determine ovarian reserve.[17] Given the limited treatment options for women with POI, treatment of POI is performed with two proposals: the first is hormone replacement therapy (HRT) to reduce complications due to impaired endocrine function of ovaries, and the second is for fertility concerns. Infertility treatments available for POI which may be used before or during ovarian failure, especially in cancer patients, include fertility preservation such as ovarian cortex, oocyte and embryo cryopreservation, oocyte or embryo donation, and adoption in women without any ovarian function.[18]

Objective

General Objective

- To analyze the clinical and laboratory characteristics of infertile women with premature ovarian insufficiency.

Specific Objectives

- To see sociodemographic characteristics of the study population.
- To know the length of the menstrual cycle among the patients.
- To know AMH levels in the patients.
- To know day 3 AMH and FSH levels in the patients.

MATERIAL AND METHODS

This prospective study was conducted at the OPD of Impulse Fertility Center, Impulse Hospital, Dhaka, Bangladesh. The study was conducted for a period from January 2022 to December 2022. A total of 23 patients who received outdoor treatment during the study period were purposively selected as sample size. A purposive sampling technique was followed in this study. After approval by the Ethics committee of the Hospital, informed consent from the respondents was obtained after explaining the purpose of the study to them. To be included in the study, respondents should have met the classical definition of infertility defined by the WHO as the inability of a sexually active non-contraceptive using woman to have a live birth after 12 or more months of regular sexual intercourse without a malefactor. Women who had male-factor infertility were excluded. In this study live birth was used as a measure of proven fertility (Because couples desire children, not simply pregnancies, infertility affects couples regardless of whether the etiology lies in conception or the progression of the pregnancy). All the necessary laboratory investigations were done. A questionnaire was developed and data was collected by interviewing the patients and some data were collected from the laboratory results. Data were processed and analyzed by SPSS 19 version. The confidentiality of the respondents was maintained.

Inclusion Criteria

- Women with diagnosed cases of infertility
- Patients who had given consent to participate in the study.

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- Patients with premature ovarian insufficiency.

Exclusion Criteria

- Male infertility.
- Patients who did not give consent to participate in the study.
- Patients with chronic diseases etc.

RESULTS

Out of 23 study subjects, most of the patients (10, 43.47%) belonged to the 31-35 years age group, followed by 8 (34.78%) in the age group of 26-30 years, followed by 3 (13.04%) of patients belonged to the 36-40 years age group, Concerning occupation, more than half (56.52%) of the patients were unemployed, and the rest 10 (43.47.0%) were employed. Regarding religion, 13 (56.52%) of the subjects were Muslims, 8 (34.58%) were Hindu, and the rest 2 (8.69%) patients were from other religions. In terms of income of an individual family, most of the patients (15, 65.21%) belonged to low income, followed by (5, 21.73%) middle income, and the rest (3, 13.04%) had a high income. [Table 1]

Table 1: Sociodemographic characteristics of the study subjects (N=23).

Parameters	**N**	**%**
Age (years)		
26-30	8	34.78
31-35	10	43.47
36-40	3	13.04
>40	2	8.69
Occupation		
Employed	10	43.47
Unemployed	13	56.52
Religion		
Muslim	13	56.52
Hinduism	8	34.78
Others	2	8.69
Income		
Low	15	65.21
Middle	5	21.73
High	3	13.04

Table 2: Clinical characteristics and laboratory parameters of the study subjects (N=23).

Characteristics	**Oligomenorrhea (n=12)**	**Infertility (n=11)**
Age of POI diagnosis	30.4±2.7	34.5±3.9
BMI (kg/m^2)	20.3±0.02	21.5±0.03
Age of menarche (years)	12.4±1.29	12.6±0.8
Menstrual cycle length (days)	21-90	24-67
Length of menstrual disturbances (years)	0.9±0.1	1.8±0.2
Pregnancy (n)	00	00

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Day 3 FSH (mu/ml)	5-37	8-30
Day 3 estradiol (pmol/ml)	13-300	30-259
AMH (ng/ml)	0.4±0.7 (0.13-1.0)	0.3±0.6 (0.13-0.9)
AFC (n)	4.2±0.9 (3-5)	3.8±0.8 (1-5)

All patients had normal puberty, and menarche occurred at ages 11–15, followed by a regular menstrual cycle. Women who presented with oligomenorrhea were younger than patients with infertility. The mean period of oligomenorrhea before diagnosis was 0.9 years in the oligomenorrhea group and 1.8 years in the infertility group. The mean age when the infrequent periods started was 28 years in the group with oligomenorrhea and 29 years in the group with infertility, and their anthropometric characteristics were not different. In most patients, the FSH levels on day 3 of their menstrual cycle were less than 25 mU/ml. FSH levels >25 mU/ml were confirmed in two patients with oligomenorrhea and five patients in the infertility group. AMH levels were low than 1.0 ng/ml (considered to be in poor ovarian reserve ranges: from 0.13 to 1.0 ng/ml in patients with oligomenorrhea and from 0.13 to 0.9 ng/ml in the infertility group. Transvaginal ultrasound-determined AFC on menstrual cycle days 4–8 was accessed in all patients. We consider AFC < 6 small follicles (diameters 3–9 mm) as a low ovarian reserve indicator. The lowest AFC (one small follicle) was noted in one infertile patient with oligomenorrhea. [Table 2]

DISCUSSION

The Bologna ESHRE consensus labels women as "poor ovarian responders" when at least two of the following three criteria are satisfied: (i) advanced maternal age (≥40 years) or any of the risk factors for POR, (ii) a previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol), and (iii) an abnormal ovarian reserve test (i.e., antral follicular count (AFC) <5–7 follicles or Anti Mullerian Hormone (AMH) <0.5–1.1 ng/ml).[19] Concerning the present study, in most of the patients, the FSH levels on day 3 of their menstrual cycle were less than 25 mU/ml. FSH levels >25 mU/ml were confirmed in two patients with oligomenorrhea and five patients in the infertility group. AMH levels were low than 1.0 ng/ml (considered to be in poor ovarian reserve ranges: from 0.13 to 1.0 ng/ml in patients with oligomenorrhea and from 0.13 to 0.9 ng/ml in the infertility group. According to a study, menopausal levels of follicle-stimulating hormone (FSH > 40 IU/L) and low estradiol levels, were assessed in two separate settings at least four weeks apart besides amenorrhea from 4–6 months in women under the age of 40.[20] Resembling the current study, FSH levels on day 3 of their menstrual cycle were less than 26 mU/ml. FSH levels >26 mU/ml were confirmed in 3 patients with oligomenorrhea and 4 patients in the infertility group in another study. AMH levels were low than 1.0 ng/ml (considered to be in poor ovarian reserve ranges: from 0.13 to 1.0 ng/ml in patients with oligomenorrhea and from 0.13 to 0.9 ng/ml in the infertility group which was quite similar to the present study.[21] Another study showed, AMH was 0.69±1.46 ng/mL and estradiol was 3.69±2.82 ng/mL in patients with POI, which was relatable to the present study.[22] In this study, patients had normal

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puberty, and menarche occurred at ages 11–15, followed by a regular menstrual cycle. Women who presented with oligomenorrhea were younger than patients with infertility. The mean period of oligomenorrhea before diagnosis was 0.9 years in the oligomenorrhea group and 1.8 years in the infertility group. The mean age when the infrequent periods started was 28 years in the group with oligomenorrhea and 29 years in the group with infertility, and their anthropometric characteristics were not different. Transvaginal ultrasound-determined AFC on menstrual cycle days 4–8 was accessed in all patients. We consider AFC < 6 small follicles (diameters 3–9 mm) as a low ovarian reserve indicator. The lowest AFC (one small follicle) was noted in one infertile patient with oligomenorrhea. Another study also showed similar results.[23] Moreover, otherwise healthy women of advanced maternal age, as well as perimenopausal and even menopausal women similarly explore alternative options in their quest to achieve a pregnancy. Additionally, diminished ovarian reserve is coupled with poor oocyte quality, entailing a heavily compromised fertility status-irrespectively of age.[24]

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSIONS

This study concluded that the subjects usually present with menstrual irregularity (oligomenorrhea) or infertility, and after proper evaluation, their poor ovarian reserve can be confirmed and an occult form of POI established. women who presented with only oligomenorrhea were younger than infertile patients; therefore, menstrual irregularity may be the earliest clinical symptom of occult POI.

Recommendation

A thorough evaluation with history, examination, and investigation for possible causes of premature ovarian insufficiency should be done. Counseling should emphasize the need for hormone replacement therapy and the probability, though small, of spontaneous pregnancy. Moreover, to get robust data, further studies should be conducted involving a large sample size and multiple centers.

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