ORIGINAL ARTICLE

Infertility Associated with Anovulatory Menstrual Cycles in Women of Quetta

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ABSTRACT

Infertility and childlessness are one of the most important health problems in women. The present study was designed to evaluate the infertility associated with anovulatory menstrual cycles in women. A total of hundred (n=100) women of reproductive age were included in the study. Group A having fifty (50) women with the history of infertility served as the research group. While, Group B contain of fifty (n=50) women with apparently normal history was taken as a control. Of the fifty (n=50) from Group A women 68% (n=34) and 32% (n=16) were diagnosed as cases of primary and secondary infertility respectively. By using Lutenizing hormone (LH) Surge detection method, 20% (n=10) women were found to have anovulatory menstrual cycles. Further confirmation of cause of anovulation was made by serum prolactin test in those women (n=10) in which LH-Surge was negative. In the present study high serum prolactin was observed 40% (n=4) women. Similarly, thyroid profile of women (n=10) showing negative LH-Surge was carried out and of these 30% (n=3) women were diagnosed as cases of hypothyroidism. The study revealed that some health issues are more pronounced in women, such as thyroid disease, malnutrition, stress and lack of education. These factors could be cause of anovulation and infertility.

Key words: Anovulation, Lutenizing hormone (LH), Prolactin, Hypothyroidism.

INTRODUCTION

Infertility is defined as the inability to conceive after one to two years of unprotected intercourse (Hull, et al., 1985). In the general population, conception is expected to occur in 84% of women within 12 months and in 92% within 24 months (Te-Velde et al., 2000). According to the European Society of Human Reproduction and Embryology Classification, infertility is defined as the diminished ability, or the inability to conceive. Infertility is also defined in specific terms as the failure to conceive after at least one year of intercourse without contraception (Vayena, et al., 2002).

One of the most important and underappreciated reproductive health problems in developing countries is the high rate of infertility and childlessness reported by Bergstrom, 1992 and Leke, et al. 1993. The inability to procreate is frequently considered a personal tragedy and a curse for the couple, impacting on the entire family and even the local community. In many cultures, womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. Moreover, in the absence of social security systems older people are economically dependent on their children. Childless women are frequently stigmatized, resulting in isolation, neglect, domestic violence and polygamy (Van Balen and Gerrits, 2001; Richards, 2002). Several studies have demonstrated that anxiety has a detrimental effect on fertility (Demyttenaere, et al., 1988) and that reduction of anxiety increases pregnancy rate (Sarrel and Decherney, 1985).

Infertility is divided on the basis of etiopathology in to five groups; unexplained 28%; male factor 24%; ovarian dysfunction 21%; tubule factors 14% and others13% (Hull, et al., 1985). Infertility and childlessness are one of the most important reproductive health problems in developing countries. It is associated with social and psychological consequences. Infertility is also associated with martial instability. Childless women usually experiences emotional tensions such as anxiety, interpersonal problems, anger, frustration, inferiority feeling and depression. Therefore, the aims and objectives of my study are to study the incidence of infertility associated with anovulatory menstrual cycles in women in Quetta. In addition to find out the causes of ovulatory infertility, to evaluate the contribution of historical factors associated with anovulation hyperprolactinemia, premature ovarian

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failure and hypothyroidism and to recommend suggestions to control this problem.

MATERIALS AND METHODS

The present study was conducted for three months period from (March to May, 2010) at Sandeman Provincial Hospital Quetta and Bolan Medical Complex Hospital Quetta, Balochistan, Pakistan. A total of hundred (n=100) women of reproductive age, attending open door patient (OPD) of these two major Hospitals of the Province were selected. One Group A of fifty (n=50) women having the history of infertility served as the research group, whereas the Group B of fifty (n=50) women, with apparently normal history served as control group.

All women with the history of infertility, including primary and secondary were included in study group. Women with polycystic ovaries were not included in study, because the kit which we used for ovulation test was contraindicated in these patients. This is due to the fact that the increased lueitinizing hormone levels in these patients may give the false positive results. Data was collected from the patients attending the OPD from different areas of Balochistan with the history of infertility. History was taken and general physical examination was performed. History and relevant information was collected through a performa/questionnaire.

General physical examination was performed with particular indication to the thyroid gland, fascial and body hair. The days 21 progesterone for confirmation of the ovulation was not performed as it was too costly for a large number of subjects, for research purposes. Instead in present use the LH surge kit for the determination of ovulation. After performing the LH surge test for confirmation of the ovulation, the other tests such as: hysterosalpingography for the determination of tubule blockage and semen analysis for detection of male factor infertility were not performed. Only those tests which confirm the anovulation like serum prolactin and serum thyroid hormone levels were performed.

LH Surge- (Ova Surge) which is the ovulation prediction test kit for detecting the luteinizing hormone (LH) occurring approximately one to two days prior to ovulation. The test was conducted each day for a period of five days, until the LH-Surge has been detected. An ultrasound probe was moved over the stomach. Ultrasound gel was rubbed over the patient's belly to facilitate the movement of the probe. The gel also acts as transducer for the sound waves to travel through. In order to produce the best picture we did the procedure with a full bladder. This helped to push the bowel away from the uterus, providing a better image. It also aids in transmitting the sounds waves produced by the ultrasound machine.

Electro chemiluminescence is based on the technique of using streptavidin coated solid phase along with ruthenium complex labeled antibodies for detection of analytes. The sample, the biotinylated antibodies, antibodies labeled ruthenium complex, and straptavidin coated micro particles were mixed into a reaction cup and incubated. The reaction mixture was aspirated into an electrochemical measuring cell, and unbound conjugate was washed away by TPA (Tri Propylamine) and magnet. Electrical current was then used to excite the ruthenium complex and initiate signal generation to detect the antigen anti-body complexes in the sample.

Radio immune Assay (RIA) procedure for determination of Tri-iodothyronine (T_3) was conducted and result was taken in the numerical form (Surks, et al., 1990). RIA procedure for determination Tetra-iodiothyroxine (T_4) was performed (Ericsson and Therell, 1986). RIA procedure for determination of Thyroid Stimulating Hormone (TSH) (Eggertsen, et al., 1988).

RESULTS

LH-Surge Profile: LH-Surge, the ovulation test was performed in all the 50 subjects with the history of infertility including primary and secondary types. Out of these 50 subjects, 10 women showed LH-Surge negative on ova surge kit as no visible band appeared on the test zone of the kit, showing anovulation, while remaining 40 subjects showed LH-Surge positive, showing ovulation (Table 4). The LH-Surge test from the control group (50 women with normal family history) was also performed. Out of these 50 women, 46 women showed LH-Surge positive while the remaining 4 showed LH-Surge negative on ova surge kit showing anovulation. The LH-Surge was positive in 40 and negative in 10 cases. An LH-Surge positive case shows that ovulation would likely to occur with in 24-48 hours. The LH-Surge negative cases showed that no ovulation has occurred.

Table-1: Age wise distribution of subjects (n=50)

Age (Years)	n=	%age
13 to 22	8	16
23 to 32	20	40
33 to 42	20	40
43 to 49	2	4

*(n=50) = Total number of observation

Prolactin Profile: In anovulatory women, further tests like serum prolactin levels were measured. Serum prolactin test was performed in those ten

patients in whom the LH surge was negative to detect the cause of anovulation. Raised serum prolactin was seen in 5 women (Fig. 1 and Table 5).

Table-2: Infertility wise distribution of subjects **(n=50)**

Type of Infertility	n=	%age
Primary Infertility	34	68
Secondary Infertility	16	32

*(n=50) = Total number of observation

Table-3-: Occupation Wise Distribution of Subjects **(n=50)**

Occupation	n=	%age
House-Wives	31	62
Working Women	19	38

*(n=40) = Total number of observation

Table-4: LH Surge Wise Distribution of Subjects **(n=50)**

n=	Type of Investigation	Results		%age of Anovulation
		+ve	-ve	
50	LH Surge	40	10	20

*(n=50) = Total number of observation

Table-5: Distribution of subjects according to results of serum prolactin levels (n=10)

n=	Test Performed	Raised	Normal
10	Serum Prolactin	4 (40%)	6 (60%)

*(n=10) = Total number of observation

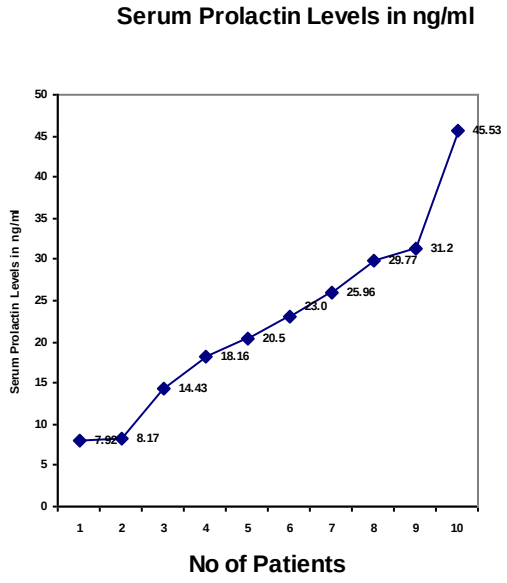

Figure-1: Showing the serum prolactin levels measured by Electro Chemiluminescence method. Serum prolactin was performed in ten anovulatory women. Normal Ranges: (4.79 – 23.3 ng/ml).

Thyroid Profile: The Thyroid profile was also performed in those ten subjects in whom the LH surge was negative. Results show decreased T_3, T_4 and increased TSH levels in three subjects showing hypo-thyroidisim. While the remaining 7 subjects showed normal thyroid hormone levels**.** (Normal Ranges for T_3: 2.5 – 5.8 n mol/L; T_4: 11– 23 pmTSH: 0.17 – 4. 0 m IU/L) (Table 7)

Ultra-Sonography: Ultrasound was performed in all the 50 women with the history of infertility. Fibroid was found in five women, small size uterus in one woman and thickened endometrium with fluid in the culde-sac was also seen in one of subjects (Table 8).

Table-6: Distribution of subjects according the serum T_3, T_4 and TSH levels**.**

n=	Thyroid Profile Test	Decreased	Normal	%age of hypo-thyroidism
10	T_3, T_4 & TSH	3 (30%)	7 (70%)	30%

*(n=10) = Total number of observation

Table-7: Results of thyroid hormone levels

n=s	Hormone Levels		
	T_3,(n mol/L)	T_4, (pm)	TSH (m IU/L)
1	1.8	7.1	5.8
2	1.8	8.7	29.8
3	2.3	9.1	5.5
4	4.9	13.9	3.3
5	4.5	11.8	2.4
6	5.4	23.0	1.8
7	3.6	12.2	1.2
8	5.4	13.1	2.0
9	2.5	13.2	1.4
10	4.5	14.5	2.0

Normal Uterus: Uterus was normal in size and anteverted. Longitudinal segment measures 5.3 cm and endometrial thickness was 7.7 mm. No focal lesion seen. Both ovaries were normal in size and shape. Right ovary measured 3.3 cm, while left ovary measured 3.0 cm No mass or cyst was seen in either ovary (Table 8).

Table-8: Distribution of subjects on the basis of ultrasound examination

n=	Test	Abnormality	Normal
50	Ultrasonography	7 (14%)	43(84%)

*(n) = Total number of observation

Fibroid Uterus: Uterus was anteverted in position. Uterus showed a large rounded mass of 11.9×9.8cm in size. Feature was suggestive of fibroid uterus. Endometrium was normal in thickness. Endometrial cavity showed no evidence of fluid collection. No free fluid was seen at the cul-de-sac. Both ovaries were

normally visualized; which showed normal sizes and shapes. No focal mass, cyst or other lesion were seen on either ovarian side. It is concluded that uterus showed a large rounded, solid and heterogeneous mass; suggestive of fibroid (Table 8).. **Small Size Uterus:** Uterus was small in size and measures longitudinal segment 3.9 cm. endometrial lining was normal. Right ovary measured 1.8 cm and left ovary measures 2.0 cm (Table 8).

Table 9. Distribution of subjects according to causes of anovulatory infertility.

n=	Cause of Infertility	%age
4	Hyerprolactinemia	40
3	Hypothyroidism	30
1	Premature Ovarian Failure	10
2	Unknown Causes	20

Out of ten (10) anovulatory women, four (n=4) were hyperprolactinemic three (n=3) were hypothyroid and one (n=1) woman was diagnosed as a case of premature ovarian failure. The remaining three (n=3) cases of anovulation were not diagnosed. The ultrasound examination of five subjects showed fibroid uterus, which was an associated problem with infertility (Table 9).

DISCUSSION

Abnormal uterine bleeding or dysfunctional uterine bleeding (DUB) can be categorized as anovulatory bleeding or ovulatory bleeding. Anovulatory DUB is caused by failure of the corpus luteum to sustain the developing endometrium. This type of bleeding can be episodic or continuous. Although some authors characterized DUB as bleeding without identifiable structural or systemic cause (Brenner, 1996). Others also consider anovulation as a part of DUB (Apgar, 1997). More then 75 percent cases of DUB in adolescents are associated with anovulatory cycles. For most of the women (95% to 98%) the presence of monthly menstrual cycles with premenstrual symptoms indicates an ovulatory cycle. Taking basal body temperature (BBT) can be helpful and inexpensive indication of ovulation. A biphasic temperature pattern suggests ovulation. Common signs of anovulation other than the alteration in menses are galactorrhoea, signs of androgen excess, such as facial hair or male pattern hair growth, alteration in thyroid or adrenal functioning and weight changes. Regular menstrual cycles in the range of 26-36 days are usually indicative of ovulation (Collins, 1988). However, it is possible that up to 9%, of regular menstrual cycles are anovulatory (Landgren, et al; 1980).

Age has a profound affect on fertility with increasing age vigorous and balanced interplay of reproductive hormones begins to decline, which results in reduced fertility. As age increases, the presence and /or quality of cervical mucus may decline as a result of hormonal imbalance. Fertile cervical mucus is supported by the estrogens, so any kind of reproductive hormonal deficiency with estrogen may interrupt both ovulation regulation, as well as the production of cervical fluids that supports conceiving. Data from historical populations estimated rates of prevalence of infertility to be 5.5%, 9.4% and 19.7 % at ages 25-29 years, 30-34 years and 35-39 years, respectively (Bongaarts, 1982). Metcalf and Mac Kenzie (1980) recorded a much higher incidence of anovulatory menstrual cycles among women under the age of 25 than among older women, an observation that appeared to conflict other studies which suggests that women reach their peak of fertility between 20 and 25 years of age. According to our study the infertility cases were more common at the age group from 23 to 42 years. The percentage was found to be 40% in this age group. From 13 to 22 years the percentage was 16%, whereas from the age group 43 to 49 years the percentage was only 4%. The decreased incidence in this group may be due to the fact that less number of patients comes for the infertility treatment after the age of 43 years.

A recent community based study of 28 Sub-Saharan African countries found that secondary infertility was prevalent, while primary infertility was relatively low (Larsen, 2000). Primary infertility exceeded 3% in less then a third of the 28 Sub-Saharan African countries analyzed. In contrast, elevated levels of secondary infertility prevailed among women age 20-44 in most countries, ranging from 5% in Togo to 23% in Central African Republic. According to our study the incidence of primary infertility was more as compared to the secondary infertility. The percentage of primary infertility was 68% and secondary infertility 32%. A study performed by Rehana and Shamim, (2004) in Lady Reading Hospital Peshawar, for the period of 1990-1999, showed a higher incidence of primary infertility that is 73.31% and 26.82% secondary infertility. The most comprehensive study of infertility involving 5800 cases of infertility, found that most infertile couples around the world suffer from primary infertility.

Latin America also had a relatively high rate of secondary infertility that is 40%, in contrast, only 25% of infertile couples in Asia and 16% in North Africa, suffer from secondary infertility (Cates, et al; 1985). The results of WHO study suggest that repeated pregnancy place a greater role in the etiology of infertility in Africa and Latin America, while repeated

abortions are important in Asia and developing countries (WHO, 1987 and 1991).

In our study the incidence of anovulatory menstrual cycles in women with the history of infertility is 20% excluding the cases of polycystic ovaries (PCO). The incidence of anovulatory cycles in this study was greater as compared to the reported overall incidence of 21% in some studies including the cases of polycystic ovaries (Hull, 1985). The reason for this high incidence in Bolan Medical Complex, Hospital and Sandeman Provincial Hospital, Quetta may be due to the fact that these two hospitals are the main Government Hospitals in Balochistan. The polycystic ovaries are one of the most common causes of anovulatory menstrual cycles. But these cases were excluded as the kit which we use for the detection of anovulation was contraindicated in these patients. So the causes of anovulation other then the PCO were included in our study.

Hyperprolactinemia is a very common disorder, especially among reproductive age women. Its prevalence is common in those women presenting with reproductive or menstrual disorders. In the present study the prevalence of infertility due to hyperprolactinemia is 40% according to the serum prolactin levels preformed in ten anovulatory women. According to the previous studies, hyperprolectinemia accounts for 17% cases of anovulatory cycles (Balen, et al; 1993). The commonest menstrual disorder among hyperprolactinemic woman was found to be oligomenorrhoea according to some studies. Present findings show oligomenorrhoea in three women and amenorrhea in one woman out of four hyperprolactinemic patients. Galactorrhoea was present in three women with hyperprolactinemia.

Similarly, in other studies hyperprolactinemia is seen in 70% women with history of amenorrhea and galactorrhoea (Josimovich, et al; 1987). But we found that the incidence was more in women with history of oligomenorrhoea and galactorrhoea. In one of the hyperprolactinemic woman, the serum thyroid hormone levels were low; whereas the levels of serum thyroid stimulating hormones were raised showing hypothyroidism.

Premature ovarian failure or premature menopause refers to the development of amenorrhea due to cessation of ovarian function before the age of 40 years. Women with premature ovarian failure suffer from anovulation and hypoestrogenisim and present with primary or secondary amenorrhea, infertility, sex steroid deficiency and elevated gonadotrophins (Kalantaridou, et al; 1998).

This condition affects approximately 1% of women, occurring in 10-28% of women with primary amenorrhea and 4-18% in those with secondary amenorrhea (Anasti, 1998). One case of premature ovarian failure was found during the study period. It was a known case of ovarian failure with the history of ammenorrhoea at the age of 35 years and raised F.S.H levels. Intracavitory lesions such as sub mucosal fibroids and endometrial polyps can co exist with anovulatory and ovulatory cycles. Fibroid may not be a direct cause of infertility, if it is not causing ovulation problems. But fibroid can cause infertility in a number of ways. A fibroid may cause compression on the fallopian tubes resulting in blockage of the passage of sperms or eggs. A large fibroid may distort the pelvic anatomy sufficiently to make it difficult for the fallopian tube to capture an egg at the time of ovulation. If a fibroid protrudes into the uterine cavity, it may present a mechanical barrier to implantation.

Infertility is a very common condition affecting the female population of Balochistan, Pakistan. The numbers of cases due to anovulatory cycles were observed higher in present study as compared to the other reported studies. The incidence of infertility due to hyperprolactinemia was also raised. The increased number of anovulatory cycles in the females of Balochistan may be due to the factors like stress and poor nutrition. When we are under stress, regardless of the source, our adrenal glands secrete the hormone cortisole. Cortisole has a direct impact on the sex hormones estrogens, progesterone and Dehydro Epi Andosterone (DHEA). Poor nutrition physically changes the proteins in the brain, so they can no longer send signals for normal ovulation.

CONCLUSION

Pakistan is relatively an underdeveloped country in general, majority of the population of have a lot of health related problems. Some health issues are more pronounced in women, such as thyroid disease, malnutrition, stress and lack of education. It has been observed that, all above mentioned factors can cause anovulation and infertility. As the investigations are expensive, at times the patients can not afford so they also act reluctantly. Sometimes patients do not report on the given time. As the ovulation time is very important, it is essential that the patient should visit the doctor as suggested. Lack of punctuality also creates hindrance towards treatment.

REFERENCES

1. Anasti JN. Premature Ovarian Failure: an update. Fertil Steril 1998; 70: 1-15.
2. Apgar BS. Dysmenorrhea and dysfunctional uterine bleeding. Prim Care 1997; 24: 161.

3. Balen AH. Hypersecretion of luteinizing hormone and the polycystic ovary syndrome. Human Reproduction. 8 supplement 1993; 2: 123 –128.
4. Bergstrom, S. Reproductive failure as a health priority in the Third World: a review. East Afr. Med. J. 1992; 69: 174–180.
5. Bongaarts J. Infertility after age 30: a false alarm. Fam Plan Perspect 1982; 14: 75-8.
6. Brenner PF. Differential diagnosis of abnormal uterine bleeding. Am. J. Obstet. Gynecology 1996; 175: 766.
7. Cates W, Farley TM and Rowe PJ. Worldwide patterns of infertility: is Africa different? Lancet 1985; 2: 596–598.
8. Collins JA. Diagnostic assessment of the infertile female partner. Curr. Prob. Obstet. Gynecol. Fertil 1988; 11: 6-42.
9. Demyttenaere K, Nijs P, Steeno O, Koninckx PR, Everse-Kiebooms G. Anxiety and conception rates in donor insemination. J. Psychosom. Obstet. Gynaecol. 1988; 8: 175–181.
10. Eggertsen R, Petersen K and Lunberg PA. Screening for thyroid disease in a primary care unit with a thyroid stimulating Hormone assay with a low detection limit Br. Med. J., 1998; 297: 1586-1592.
11. Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA and Hinton RA, Population study of causes, treatment, and outcome of infertility. Br. Med. J., 1985; 291: 1693-1697.
12. Josimovich JB, Lavenhar MA, Devanesan MM, Sesta HJ, Wilchins SA and Smith AC Heterogeneous distribution of serum prolactin values in apparently healthy young women, and the effects of oral contraceptive medication. Fertil Steril 1987; 47: 785-791.
13. Kalantaridou SN, Davis SR and Nelson LM. Premature Ovarian Failure. Endocrinology and Metabolism Clinics of North America 1998; 27: 989–1005.
14. Landgren BM, Unden AL and Diczfalusy E. Hormonal profile of the cycle in 68 normally menstruating women. Acta Endocrinal (Copenh) 1980; 94: 89-98.15.
15. Larsen U. Primary and secondary infertility in sub-Saharan Africa. International Journal of Epidemiology 2000; 29:285-291.
16. Leke RJ, Oduma JA, Bassol-MS, Bacha, AM and Grigor KM. Regionaland geographical variations in infertility: effects on environmental, cultural, and socioeconomic factors. Environ. Health Perspect 1993; 101 (Suppl. 2):73 – 80.
17. Metcalf MG and Mackenzie JA. Incidence of ovulation in young women. J. Bio. Sci. 1980; 12: 345.
18. Rehana R, Shamim SM. “Aetiological factors of infertility” 2004; 18 (2): 166 - 171.
19. Richards SC. “Spoiling the womb”: definitions, aetiologies and responses to infertility in North West province, Cameroon. Afr J Reprod Health 2002; 6: 84–94.
20. Sarrel, P and Decherney, A. Psychotherapeutic intervention for treatment of couples with secondary infertility. Fertil Steril 1985; 43: 897–900.
21. Surks MI, Chopra IJ, Mariash CN. American Thyroid Association guidelines for use of laboratory tests in thyroid Disorders. JAMA 1990; 263:1529-1532.
22. Te-Velde ER, Eijkemans R and Habbema HDF. Variation in couple fecundity and time to pregnancy, an essential concept in human reproduction. Lancet 2000; 355: 1928-1929.
23. Van Balen, F and Gerrits, T. Quality of infertility care in poor-resource areas and the introduction of new reproductive technologies. Human Reproduction 2001; 16:215 – 219.
24. Vayena E, Rowe, P and Griffin, D. Current practices and Controversies in assisted reproduction, Geneva. Word Health Organization, 2002.
25. World Health Organization. Infections, pregnancies and infertility: perspectives on prevention. Fertil Steril. 1987; 47: 944–949.
26. World Health Organization (WHO). Infertility: A Tabulation of Available Data on Prevalence of Primary and Secondary Infertility. Geneva. 1991; WHO / MCH / 91.9.