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Categorization of reproductive hormone profile abnormalities in women with infertility: A retrospective study

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Abstract
Objective: To review the pattern of reproductive hormone abnormalities among women with infertility at Bingham University Teaching Hospital.
Method: A retrospective review of the patients who had hormonal assay done as part of their infertility workup from January 2021 to December 2022.
Results: During the period of the study, there were132 women who had hormonal assay done. Of the 132 women, 50(37.9%) women had abnormal hormonal profile. Normogonadotrophic normogonadism occurred in 41(82.0%) of all the patients, while hyper-gonadotrophic hypogonadism occurred in 6(12.0%) and hypogonadotrophic hypogonadism occurred in 3(6.0%) of the patients. Sixteen (32.0%) had decreased progesterone suggesting luteal phase deficiency, and 21(42.0%) had hyperprolactinemia (Increased prolactin levels).
Conclusion: The commonest reproductive hormone abnormalities in our facility are normogonadotrophic anovulation (distorted LH/FSH ratio often caused by polycystic ovary disease), hyperprolactinemia, and luteal phase defect. This is important as these women can be adequately counseled and their infertility managed medically even in our environment, while those with hypergonadotrophic hypogonadism, hypogonadotrophic hypogonadism can be counseled appropriately for assisted reproductive techniques (ARTs).

Keywords: Reproductive hormones, hormone profile, infertility, reproductive hormone abnormality

Introduction
The desire for reproduction is a basic human instinct especially in Africa where infertility is a major reproductive health problem with regional prevalence rates of 20-30% [1] and premium is placed on having children to continue the lineage. Infertility is an extremely important personal concern for many couples and a significant health problem for the medical profession. The WHO estimated that between 8-12% of couples experience some form of infertility during their reproductive lives, thus affecting 50-80 million couples worldwide with 20-35 million couples in Africa and 3.4 million Nigerian couples suffer from infertility [2]. Infertility forms a major part of gynaecological consultation and couples seeking help can place a heavy burden on limited health workers. Infertility is defined as the inability of a couple to get pregnant after one year of regular unprotected sexual intercourse and could be primary if there's no pregnancy at all in the couple or secondary if there was a past history of pregnancy [3, 4].
The psychosocial consequences of infertility include anxiety, depression, marital disharmony, physical violence and social discrimination. Increasing female literacy and employment has resulted in a rise in the age at which women conceive. With the changing roles and aspirations for women, postponement of marriage, delayed age of childbearing fertility starts to decline with advancing age therefore more women are facing the problem of infertility and are seeking medical attention to overcome this problem [2, 5]. The etiology of infertility has been grouped into male factor (15%), ovulatory (27%), tubal/uterine (22%), others (9%), unexplained (17%) in developed societies while in developing societies like Nigeria the commonest causes of infertility are tubal and peritoneal (30 - 40%), male (30 - 40%), ovulatory dysfunction (15%) [1, 4, 6]. The reproductive hormones are especially important for ovulation, menstruation and implantation of the fertilized ovum.

Unlike the other causes of infertility, hormonal factor has been the least considered, researched or discussed among professionals within the health care community in Africa, with attention being paid to tubal factor infertility and seminal fluid analysis. In a study carried out in Sagamu, Lagos state, low levels of progesterone, estradiol and gonadotrophins (LH, FSH) were observed in 80%, 90% and 100% of the infertile women studied respectively [2]. In a study carried out in Zaria 71.1% of the infertile women had hormonal abnormalities and 46.6% of the infertile women had elevated LH, LH/FSH, low progesterone and estradiol which are biochemical evidence of androgen excess an indication that infertility in these women may be due to Polycystic Ovarian Syndrome which is amenable to treatment [7].

The reproductive cycle depends on the cyclic interactions between hypothalamic gonadotrophin releasing hormone (GnRH), the pituitary gonadotrophins follicle stimulating hormone (FSH) and luteinizing hormone (LH), prolactin inhibitory factor the ovarian sex steroid hormones estradiol and progesterone [4]. Thyroid hormone also influences the menstrual pattern directly through the impact on the ovaries and indirectly through sex hormone binding globulin, prolactin and GnRH secretion [8]. Thyroid disorders can result in menstrual irregularities, luteal phase defects, and can cause infertility or recurrent miscarriages [9]. Before ovarian follicles are expelled oocyte maturation demands a favorable endocrine environment including normal levels of thyroid hormones [8, 10]. Thyroid function and prolactin are closely related, long standing untreated hypothyroidism is associated with ovulatory dysfunction and in 1-3% of cases with galactorrhea [8, 9, 12]. Any derangement of hypothalamic pituitary ovarian (HPO) axis results in menstrual irregularities and ovulation disorders with consequent infertility [10].

The normal ovulatory menstrual cycle is controlled by hormones as follows [7, 13]:

1. The menstrual cycle starts with the recruitment of cohort of follicles
2. FSH promotes the conversion of androgens to estrogens, increase estradiol concentrations within the follicles and peripheral circulation.
3. The dominant follicle continues to grow with increasing estradiol concentrations and decreasing LH and FSH pulse amplitude
4. The dominant follicle acquires LH receptors; LH stimulates the synthesis of androgens which are metabolized into estrogens. Estradiol is highly mitogenic and potentiates several local growth factors thus the selected follicle will grow rapidly and in a few days become a fully mature follicle (Graafian follicle).
5. Maturity of the Graafian follicle is marked by high circulating concentrations of estradiol which signals the hypothalamus and pituitary that the follicle is ready for the ovulatory signal. The long loop estradiol positive feedback is activated and as a result the gonadotrophin surge occurs.
6. The high gonadotrophin concentrations during the surge arrest granulosa cell proliferation and secretory activity in the Graafian follicle, estradiol secretion declines rapidly, granulosa cells begin to luteinize and as a consequence a small pre- ovulatory rise of progesterone occurs. Ovulation occurs about 12 hours following the gonadotrophin peak or at least 36 hours after the initiation of LH surge.
7. After the release of the oocyte the granulosa layer becomes vascularized and it completes the process of luteinization whereby it acquires de novo steroid synthesis capacity. LH stimulates the secretion of progesterone and estrogen from the corpus luteum, which activates the hypothalamic opiate center decreasing the gonadotrophin pulse frequency.
8. The corpus luteum is a transient organ that lasts for 12 - 14 days, with estrogen and progesterone secretion peaking about 5 - 7 days after its formation.
9. Luteolysis results in a rapid decline in progesterone and estrogen concentrations leading to menstruation if there's no fertilization of the ovum.
10. Through a combination of several factors which may include the long period of decreased pulse frequency during the luteal phase, a decrease in inhibin secretion, progesterone and estrogen secretion, FSH concentrations increase relative to those of LH and a new cycle is initiated.

Methodology/ materials

This was a hospital based retrospective study of women with infertility who had hormonal assay done from January 2021- December 2022. Blood sample was collected by venipuncture and analyzed using ELISA. The patients last menstrual period was used to determine the date for sampling. For amenorrhoiec patients however, the blood was drawn at presentation and they were assumed to be in the follicular phase of the menstrual cycle.

The records of patients with infertility who had hormonal assay done within the period were retrieved, from the patient's case notes and the reference ranges of hormones from hospital laboratory were used. The number of women with abnormal reproductive hormone, their age range, and the hormonal values were correlated with patient's age. The patients were grouped into ovulatory and anovulatory and were further sub-classified based on the type of ovulatory disorder; hypogonadotrophic hypogonadism, normogonadotrophic normogonadism, hypergonadotrophic hypogonadism and hyperprolactinemia. Patients with luteal phase deficiency were also determined. The data was analyzed using Epi Info version 7.2.2.2

Results

During the study period 132 patients had hormonal assay done and 50 patients had abnormalities in their hormonal profiles giving a prevalence of 37.9%. Table 1 shows the age distribution of the patients with hormonal abnormalities. Table 2 reveals that, of the 50 patients with hormonal imbalance, 6(12.0%) had hypergonadotrophic hypogonadism suggestive of ovarian failure. The highest age range among patients with hypergonadotrophic hypogonadism was in the 36 - 40 years group, 3(42.9%) followed by the >40 group with 2(28.6%) and the 30 - 35 years group with 1(14.9%).

Table 3 shows that 41(82.0%) had normal serum levels of gonadotrophins and estradiol (normogonadotrophic normogonadism), however 33 out of the 41(80.5%) had an increased LH: FSH of at least 2-3:1, while the remaining 8(19.5%) had normal LH to FSH ratio. The 20 - 29 age group had the highest number of patients with increased LH to FSH 13(40.0%) followed by the 30 - 35 with 11(35.0%),

then the 36- 40 with 7(20.0%) and finally those greater than 40 years with 2(5.0%).

Table 4 represents patients, 3(6.0%) with low serum levels of FSH and estradiol (Hypogonadotrophic hypogonadism). These patients were all among the 20-29 years age group.

Table 5 shows 16(32.0%) with low levels of progesterone suggesting a possible luteal phase deficiency while 34(68.0%) had normal levels. Twenty-one (42.0%) of the women had raised serum levels of prolactin hormone.

Table 1: Age range of the patients

Age (Years)	Frequency (n=50)	Percentage (%)
20 – 29	17	33.3
30 – 35	18	36.7
36 – 40	12	23.3
>40	3	6.7
Total	50	100.0

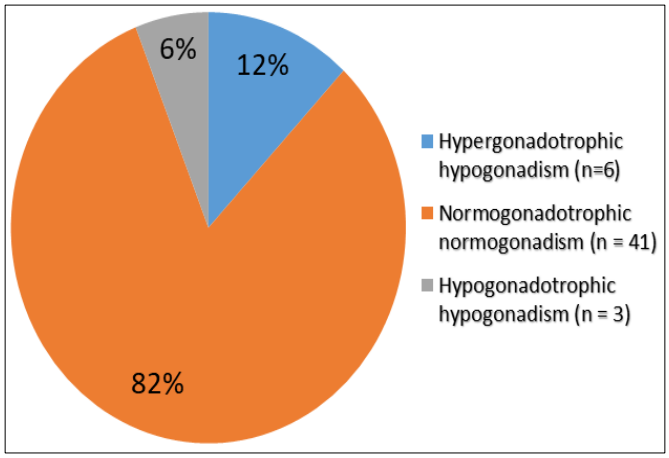

Fig 1: Patients with abnormal hormone profile results

Table 2: Age of patients compared with increased FSH values (Hypergonadotrophic hypogonadism)

Age (Years)	Increased FSH(>35mIU/ml)
20-29	0
30-35	1
36-40	3
>40	2
Total	6

FSH= follicle stimulating hormone

Table 3: Age range compared with increased LH: FSH ratio

Age (Years)	Increased LH: FSH ratio (2-3:1)
20-29	13
30-35	11
36-40	7
>40	2
Total	33

FSH= follicle stimulating hormone LH= luteinizing hormone

Table 4: Age compared with decreased FSH values (Hypogonadotrophic hypogonadism)

Age (Years)	Decreased FSH(< 3mIU/ml)
20-29	4
30-35	0
36-40	0
>40	0
Total	4

Table 5: Age compared with prolactin and progesterone levels

Age (Years)	Increased prolactin (>19.5ng/ml)	Decreased progesterone(<2ng/ml)
20-29	8	5
30-35	8	5
36-40	4	5
>40	1	1
Total	21	16

Discussion

Ovulatory dysfunction is one of the major causes of female infertility and results from dysfunction of hypothalamic-pituitary-ovarian axis. In this study, 132 women were evaluated for infertility and 50(37.9%) of them showed evidence of hypothalamic-pituitary-ovarian axis dysfunction based on serum levels of LH, FSH, prolactin and mid-luteal phase progesterone. These dysfunctions were present in different patterns of hormonal abnormalities. Most forms of hormonal imbalances ultimately lead to anovulation. This finding was consistent with reports from other studies within and outside Nigeria [6, 13].

The various patterns of anovulation noted among our study population are similar to WHO's classification of anovulation. Three patients (6.0%) had hypogonadotrophic hypogonadism which is consistent with 5 – 10% of WHO class I, 82.0% had Normogonadotrophic normogonadism with distortion in LH/FSH ratio and is in keeping with 70 – 85% of WHO class II and 12.0% hypergonadotrophic hypogonadism similar to 10 – 30% of WHO class III. Hyperprolactinemia which is class IV anovulation account for 42.0% ovulatory dysfunction. From the study anovulation from distorted LH/FSH ratio and or hyperprolactinemia and decreased mid luteal phase progesterone were the top three hormonal abnormalities encountered in our study population [3-5]. These observations are similar to studies from Awka, South-eastern and Zaria North-western Nigeria where hyperprolactinemia, normogonadotrophic normogonadism with distorted LH/FSH ratio, and decreased progesterone were the top three disorders noted in various proportions [7, 10]. In Chennai, India hyperprolactinemia also accounted for 42.9% of the abnormal hormone levels noted [6].

From the study 80.5% of the patients with normogonadotrophic normogonadism had an elevated LH/FSH ratio which is suggestive of polycystic ovarian syndrome, this accounts for most of the patients in this group and is higher than the 46.6% observed in Zaria [7, 14]. The diagnosis of PCOS does not rely on laboratory findings alone but also factors in clinical evidence of hyperandrogenism, menstrual regularity and morphologic features of the ovaries on ultrasonography [14]. This study looked at laboratory support in infertility evaluation alone and this may have been responsible for this high difference. PCOS is a heterogeneous clinical entity characterized by signs and symptoms of hyperandrogenism and anovulatory disorders often associated with infertility and obesity [2, 5, 7, 14].

Elevated plasma FSH, LH during the reproductive life is an early manifestation of ovarian ageing and this was observed among those greater than 36 years compared to those less than 35 years [4, 15]. This suggests that infertile women with elevated FSH are in the peri-menopause despite having regular ovulatory and apparently normal cycles [15-17]. In Lagos low levels of gonadotrophins was observed in 100%

of cases while in Zaria hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism occurred in 1.7% each [2, 7].

Hyperprolactinemia occurred in 42.0% of the patients in this study and is less than the observation in Zaria were it occurred in 50% and is higher than the study in Sagamu were it occurred in 28% [2, 7]. Hyperprolactinemia usually coexists with other hormonal disorders like PCOS (10-20%), hypergonadotrophic hypogonadism and hypogonadotrophic hypogonadism [2, 3, 5]. It coexisted with normogonadotrophic normogonadism in 33% of cases in Zaria [7]. Some of the causes of hyperprolactinemia include stress, exercise, trauma, breast feeding, dopamine receptor antagonists and prolactinomas [7, 11, 12]. Exclusion of these factors were however not documented in the case note. Hyperprolactinemia can result in anovulation, galactorrhea, and oligomenorhea [2, 4, 5]. Most of the patients on follow for infertility are actually under a lot of psychological stress which can explain the prolactin levels noted.

Decreased progesterone level as was seen in 32.0% of the patients, is similar to a study in the Netherlands and Sheffield were the progesterone level was lower in women with unexplained infertility compared to the control group [14, 16, 18]. In Sagamu there was a decrease in progesterone in 80% of the patients studied far higher than in our study population [2]. Low serum progesterone interferes with endometrial development which in turn interferes with nidation resulting in infertility [5, 6, 16, 19].

Conclusion

The commonest reproductive hormone abnormalities in our facility are normogonadotrophic anovulation (distorted LH/FSH ratio often caused by polycystic ovary disease), hyperprolactinemia, and luteal phase defect. This is important as these women can be adequately counseled and their infertility managed medically even in our environment, while those with hypergonadotrophic hypogonadism, hypogonadotrophic hypogonadism can be counseled appropriately for assisted conception.

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