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Original Article

Evaluation of Female Infertility by Cyto-Hormonal, Endometrial Biopsy and Endocrinological Study

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Abstract
Objective: *The present study was undertaken to know the role of vaginal hormonal cytology, endometrial biopsy and endocrinological evaluation in the detection of ovulation and various ovulatory dysfunction.*
Material & Method: *A total of 34 infertile female patient were studied.*
Result: *On the basis of cytological finding of 34 patients, 10 patient were found to be ovulatory, 22 patients were anouvlatory (including 5 case of atrophic changes) and 2 patients were inconsistent due to inflammatory changes. Endometrial biopsy showed evidence of ovulation in 11 patients and anovulation in 23 patients. Hormonal evaluation indicated endocrinological disorders in 10 patients which may underline anovulatory infertility. In these patients, results were within normal range in rest 24 patients.*
Conclusion: *Vaginaland endometrial biopsy showed correlation in respect to ovulation in 91.44 % of the cases.*
Keywords: *Vaginal cytology, Infertility, Endometrial biopsy, Hormonal analysis.*

Introduction

Infertility in a female or male can be defined as "the inability of a couple to achieve conception after a year or more of regular unprotected sexual intercourse". The WHO estimates that approximately 8-10% of couples experience some form of infertility. The primary diagnosis in the couples are ovulatory disorders (27%), abnormal semen parameter (25%), tubal defect (22%), endometriosis (5%), others(4%) and unexplained (17%). The most common causes of adult onset anovulation are hypothalamic dysfunction (38% of cases), pituitary disease (17%) and ovarian dysfunction. The most common cause of hypothalmic dysfunction are abnormalities in weight and body composition, stress and strenuous exercise. The most pituitary disorder that causes anovulation is prolactinoma, followed by empty sella syndrome, Sheehan's syndrome and Cushing's disease. The most common ovarian causes of anovulation are ovarian failure, ovarian hyperandrogenism (polycystic ovarian syndrome).

Thyroid disease can occasionally be associated with anovulation.

Disorders of ovulation accounts for approximately 30-40% of all cases of female infertility. These disorders are generally among the most easily diagnosed and most treatable causes of infertility. Various methods to detect ovulation are available with varying degree of sensitivity and specificity. Among these are basal body temperature charting, cervical mucus study, vaginal hormonal cytology, endometrial biopsy, mid luteal progesterone assay and serial ultrasonographic monitoring. Anovulatory patients can further be subjected to evaluation of hormonal status to determine various endocrinological abnormalities.

Evidence of ovulation and causes of ovulataory dysfunction can be obtained by study of serial vaginal cytology, endometrial biopsy (EB) and hormonal assessment. The extreme sensitivity of the epithelium of the vagina to various hormonal agents has long been recognized. Cytohormonal evaluation of a polychrome stain of lateral vaginal wall scraping, obtained at the time of initial examination can be a valuable adjunct to the total evaluation of hormonal status. Vaginal epithelium undergoes cyclical changes under the effect of hormones like estrogen and progesterone. On the basis of such changes various indices have been developed to quantify the estrogenic stimulation of the vaginal epithelium. The two most commonly used are maturation index and maturation value. Endometrium is another end-organ for the action of ovarian hormones thus EB gives evidence of ovulation or anovulation and luteal phase deficiency besides giving information regarding various endometrial pathology eg. Tuberculous endometritis. Abnormality of luteal phase results in underdevelopment or irregular ripening of endometrium. Evaluation of etiology of anovulation can be complex. Measurement of serum follicle stimulating hormone (FSH) luteinizing hormone (LH), Thyroid stimulating hormone (TSH), prolactin and androgens can help identify that cause of anovulation.

Material & Method

Present study was conducted in the Department of Pathology, Sri Krishna Medical College, Muzaffarpur with the help of Department of Obstetrics and Gynecology during the period of October 2017 to May 2018.A total of 34 infertile females were studied. A detailed history including menstrual history in every patient was taken and thorough physical examination carried out with special attention being paid to body weight, secondary sexual character, status of vagina, etc. Of the 34 patients, 10 gave history of regular and spontaneous menstrual cycles, while 24 patients had menstrual irregularities in terms of duration, flow and cycle length. Eight patients gave history of secondary amenorrhea.

Serial vaginal scrape smears from lateral vaginal wall were made with Ayer's spatula on the days 5^{th}, 11^{th}, 14^{th}, 20^{th} and 26^{th} of the menstrual cycle in 24 patients and same time interval was also followed in amenorrhoeic patient starting from the date of next visit. Smears were fixed in 95% alcohol and stained with Papanicolaou stain. EB was performed on day 28 in patients with regular menstrual cycle, on day 1 in patients with irregular cycle and on next visit in amenorrhoeic patients. Biopsy fixed in 10% formalin, processed and stained with haematoxylin and eosin. Sera for evaluation of various hormones like gonadotropins (FSH and LH), prolactin, TSH, thyroxine (T4), triiodothyronine (T3) were collected on the 3^{rd} day of cycle, while testosterone level estimation was done in selected cases.

Result

On vaginal hormonal cytology, follicular phase was characterized by progressive rise in karyopyknotic index with shift of maturation index to right and predominance of superficial squamous cells distributed singly against clear background. Ovulation was characterized by predominance of intermediate cells showing crowding, edge curling against dirty background with lots of Doederlein's bacilli and lowering of

KPI and shift of MI to left. Atrophic pattern was noted by presence of parabasal cells which ranged 30-40% of total cells. In 2 cases hormonal change were not commentable due to inflammatory changes.

In Endometrium Secretory changes, non-seceretory changes, cystic glandular hyperplasia and atrophic changes were seen. Tuberculous endometritis in non-secretory endometrium was noted in 2 patients.

Endocrinological assessment revealed values within normal range in 24cases and abnormal values were found in 10 cases. These cases with abnormal results were further evaluated and findings were confirmed in next cycles. Two patients, one presenting with amenorrhea and other with oligomenorrhea, both having serum LH: FSH ratio>2 and serum testosterone >1.5 mg showed bilateral enlarged ovaries with multiple small follicles. All the patients with history of amenorrhea were given progesterone. All but four exhibited withdrawal bleeding. Of these 4 cases, one patient had low serum FSH and LH level (<5m IU / ml) along with low serum TSH level, while other 3 had high levels of serum FSH and LH.

Discussion

Present study was conducted with a view to detect ovulation and various causes of anovulation. Engineer et al studied serial vaginal smear to detect ovulation and concluded that vaginal epithelium responded to estrogen with more sensitivity and earlier than any other accessible sites of genital tract such as cervix and endometrium. Presence of mature epithelial cells and abundant cornified squamous cells with pyknoticnuclear confirmed the presence of adequate estrogen level and finding of predominant intermediate cells on vaginal cytology provided evidence of adequate progesterone secretion. The main feature of anovulatory cycle was the lack of change in the maturation index at the time of expected ovulation. Cells did not show crowding, folding curling of cells edges and presence of predominant intermediate cells population. Endometrial biopsy afforded best single index of ovarian function in the study of infertile patients. Presence of secretory changes in premenstrual EB, proved that cycle has been ovulatory. Also EB helped in detecting chronic endometritis, tuberculous endometritis, cystic glandular hyperplasia and atrophic endometrium. Non-secretory endometrium with evidence of cystic glandular hyperplasia indicated presence of anovulatory cycles for long period, which results from unopposed estrogenic action on endometrium.

Evaluation of hormonal profile yielded important information pointing towards specific abnormality. Amenorrhea patients were subjected to progesterone stimulation test. One patient did not manifest withdrawal bleeding, who also had low serum FSH, LH, TSH and prolactin values below baseline. Kustin and Rebar described hypogonadotropic hypogonadism in such case due to disturbance in hypothalamic pituitary axis. In three amenorrhoeic patients serum FSH and LH were raised above 45 m IU / ml. In these cases there is a strong possibility of hypogonadotropic hypogonadism or ovarian failure. High serum testosterone level well above baseline along with high serum LH value and LH: FSH ratio more than two, clinical history of oligomenorrhea and amenorrhea, hirsutism obesity and USG findings lead to the diagnosis of polycystic ovarian syndrome. Both patients had episode of withdrawal bleeding after progesterone challenge test. Hyperprolactinaemia was manifested in seven patients. Prolactin in excess inhibits ovulation by blocking the effects of gonadotrophins on the ovary, impairs granulosa cell maturation and ovarian steroidsecretion. Thyroid dysfunction is associated with menstrual irregulatory and anovulation .Pregnancy occurring in woman with hypothyroidism has been reported to be uncommon.

Conclusion

Vaginal hormonal cytology is a simple, safe, non-invasive, inexpensive and fairly reliable outdoor test to detect ovulation. While endometrial biopsy is highly reliable in detecting ovulation with various endometrial pathology, but being an invasive test. Hormonal analysis is useful to detect and treat endocrinological pathology responsible for anovulation.

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