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The Correlation of Diagnostic Accuracy For The Endometrial Lesions Between Aspiration Cytology, Cell Block Preparation and Histopathology -An Overview

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ABSTRACT

Background: Accurately diagnosing malignant tumors is a key function of endometrial cytology. In certain cases, the endometrial cytology alone cannot diagnose endometrial malignancies. In such cases, an invasive procedure, endometrial tissue collection is necessary to validate the final diagnosis.

Material & Methods: Keywords and tools were used to search the related articles in the main electronic databases. The keywords and tools adopted for the search ensured a comprehensive and systematic approach to search for the articles reviewing necessity for endometrial tissue biopsy as a definitive method

Results and discussions: The insights gained from this overview provide a foundation for future research about the cytology and cell block preparation of endometrial aspirate to be reliable and accurate screening tool for endometrial lesions. The cytology is a cost-effective procedure and it has the extra benefit of not requiring anesthesia during the acquisition of sample from patients while the other procedures have issues including perforation.

Conclusions: Amongst perimenopausal and post- menopausal women presenting with abnormal uterine bleeding (AUB), aspirate cytology and cell block preparation could be considered as primary investigation for screening of early detection of various endometrial diseases especially hyperplasia and malignancy thereby leading to better prognostic outcome and significantly contribute in the reduction of morbidity and mortality.

Keywords: *Cytomorphological Findings, Endometrial Aspirate, Cell Block, Endometrial Cytology. Perimenopausal , Post-Menopausal Women , Aspirate Cytology*

1. INTRODUCTION

More than half million hysterectomies are performed annually [1]. Spectrum of common pathologies includes polyps. fibroids, dysfunctional uterine bleeding, adenomyosis, chronic cervicitis, adnexal mass, endometrial hyperplasia, atrophic endometrium, and endometrial carcinoma [2-3].

The common conditions affecting the uterus include the following-

Polyp: The patients with endometrial polyps may presents as irregular uterine bleeding or sometimes with infertility [4]. Small, symptomless polyps may go away on their own. Progestins and gonadotropin-releasing hormone agonists may alleviate polyp symptoms if they are present, but surgical excision is the only effective treatment [5].

Leiomyoma (fibroid): Because of its oestrogen sensitivity, it grows larger during pregnancy and shrinks after menopause [6]. It frequently results in miscarriage and typically causes irregular uterine bleeding. It typically gives the uterus an uneven contour if it is large or many. By squeezing the rectum posteriorly, it may even result in constipation. Surgery, such as a hysterectomy or myomectomy are done depending on the symptoms [7].

Endometrial hyperplasia: An abnormal endometrial gland proliferation is caused by excess of estrogenic stimulation. An increased risk of endometrial carcinoma is usually associated with it [8].

Adenomyosis: It usually presents with dysmenorrhea and menorrhagia. In adenomyosis, hyperplasia of the endometrial basal layer results in glandular endometrial tissue expansion into the uterine myometrium. Medical treatment includes NSAIDs and hormonal therapy while hysterectomy is considered the gold standard treatment.

Endometritis: It is a condition in which the endometrium due to retained material in the uterus can get infected by bacterial flora [9].

Endometriosis: The ovary, pelvis, and peritoneum are the most frequently affected areas. It emerges in the ovary as a blood-filled chocolate cyst or endometrioma. It has been identified in the scar site of cesarean section [10]. It can be present on the outside surface of the uterus. Retrograde flow of menstrual blood is considered as one of the causes of endometriosis. Medical treatment includes NSAIDs and hormonal therapy [11].

2. ABNORMAL UTERINE BLEEDING (AUB:

In developing countries, AUB has remains as one of the most frequent indications for hysterectomy but in 40% of cases no definitive organic pathology is associated with AUB. It is a common condition in which there is an irregular or untimed bleeding from the uterine corpus. In India, prevalence of AUB is around 17.9% [11].

3. RADIOLOGICAL ANATOMY OF THE NORMAL ENDOMETRIUM

Age, postmenopausal exposure to hormone replacement treatment, gestational status, and menstrual cycle phase all affect the endometrial thickness [12]. It undergoes periodic remodeling in response to cyclical hormonal changes hence, correlation with the patient's clinical history is crucial to make accurate interpretations. The thickness of the endometrium depends upon the phase of the menstrual cycle [13]. It is thin in the early proliferative phase and it's thickness reaches up to 16 mm in the secretory phase [14,15]. Sonography correctly estimates about the endometrial thickness. In premenopausal women, the correlation with the last menstrual period (LMP) becomes important.

Postmenopausal women typically have endometrial thicknesses of 5 mm or less, which can accurately rule out cancer in women who are asymptomatic [14]. The etiology may then be confirmed or premalignant or malignant disease may be ruled out with additional research [16, 17].

4. HISTOLOGICAL CHARACTERISTICS OF ENDOMETRIUM

The endometrium engages in a regular cycle of change that consists of distinguish phases: menstruation, proliferation, and secretion [17]. There is wide variation amongst normal women but a typical menstrual cycle is 28 days in length. In the menstrual phase, the endometrial shedding occurs only if there is failure of fertilization and/or implantation of the ovum [17]. In the proliferative phase, The endometrial stroma proliferates. Simple tubular glands elongate and becomes tortuous and begins to produce secretions which are coincident with ovulation. The proliferative phase starts and sustains until ovulation, since the developing ovarian follicles keeps producing increased production of estrogens [17].

When ovulation takes place, the secretory phase starts, which concludes with the start of menstruation on around day 28. Average menstrual phase is for about 5 days. The proliferative phase lasts until around day 14 [17].The endometrium, histologically as well as functionally can be divided into three distinct layers [18-20].

Adjacent to the myometrium, is the deepest or basal layer, the stratum basalis, which do not shed during menstruation and undergoes minimal alteration during the menstrual cycle [17,19]. The intermediate layer, also referred to as the stratum spongiosum, is distinguished by stroma that appear spongy. Both the spongy and compact layers are shed during menstruation and show discernible changes over the course of the cycle [17].These layers together are known as stratum functionalis [19]. A capillary plexus forms around the glands and in the stratum compactum as a result of these long, thick-walled, coiled structures that migrate to the endometrial surface and produce numerous branches. When progesterone secretion stops near the conclusion of the cycle, the spiral arteries tighten, causing an ischemic phase to occur right before menstruation [18]. Light microscopy evaluation of the histological features of endometrial biopsy material continues to be the gold standard for the clinical diagnosis of endometrial pathology [18].

Endometrial carcinoma: It has a variety of histologic subtypes. Amongst the carcinomas of female genital tract, the endometrial carcinoma is most common invasive cancer [21-28]. Given that tamoxifen stimulates the endometrium's estrogen receptors, it increases the risk of endometrial cancer. Additionally, polycystic ovarian syndrome, tumors that secrete estrogen, such as granulosa cell tumors, and obesity are examples of endogenous sources of estrogen [29-31]. Most women who

develop endometrial cancer will exhibit either postmenopausal or atypical vaginal bleeding. Less frequently, they could exhibit bloat, weight loss, altered bowel habits, and abdominal pain [32].

Abnormal Uterine Bleeding:

It is defined as an excessive, unpredictable or irregular bleeding per vagina in absence or presence of intracavitary or uterine pathology. It may be associated with systemic abnormalities or even structural abnormalities [33].

Amongst the reproductive age group, abnormal uterine bleeding (AUB) is a common problem. It sometimes may be accompanied by pain and discomfort, and may cause significant social discomfort, and have a significant effect on health as well as quality of life. AUB leads to loss of productivity and may later on resulting into a surgical intervention [32-34].

5. MATERIALS AND METHODS

Following systematic strategy was used to gather and evaluate the literature needed to write this comprehensive and insightful review article.

1. Defined the research question and identified key themes, terms, and concepts related to our topic.

2. Developed a list of relevant keywords and phrases, including synonyms and variations.

3. **Databases used for literature search strategy were**

- PubMed
- Scopus
- Web of Science
- Google Scholar

4. Reviewed abstracts to identify relevant articles that aligned with our research question.

Refined search strategies by utilizing advanced search features (e.g., filters, categories) in databases.

6. RESULTS AND DISCUSSIONS

The classification system, which is named after the acronym PALM-COEIN, consists of nine primary groups. Women who experience what was once referred to as "dysfunctional uterine bleeding" are more likely to have a main endometrial problem, coagulopathy, or an ovulation disorder [35-37]

Siva Kaliyamoorthy et al studied 58 cases of endometrial aspiration cytology (EAC) and histopathological correlation [25]. Of the cases, 27 (46.6%) had benign endometrium, 24 (41.4%)

had simple hyperplasia, 4 (6.2%) had endometritis, 1 (1.7%) had atypical hyperplasia, and 2 (3.4%) had cancers [29, 38]. Finally, they concluded that endometrial lesions and the cyclical changes can be safely diagnosed by endometrial aspiration cytology which is an easy and safe outpatient procedure. The accuracy was ranging between 98.28% to 100% in identifying inflammatory, benign and malignant lesions making EAC an effective procedure.

7. CELL BLOCKS IN CYTOLOGY

The cell block (CB) approaches are in use for the last many decades. The specimen collection for examination in a single outpatient session is possible by CB cytology. Moreover, use of immunohistochemistry also provides useful information for histological diagnosis. For screening in post-menopausal women, a combination of cell block and conventional cytology and may be a valid method [34, 36]. Cell blocks can be made from almost any kind of sample, such as scraps from traditional smears or from liquid-based preparations [39- 41].

In today's practice of cytopathology, the crucial role of cell block preparation cannot be minimalized. The hematoxylin and eosin stained histologic sections of the cell blocks add crucial diagnostic information and emphasize structural feature that could not have been present or readily noticed in alternative cytologic preparations which make them superior [34,42]. The cell blocks can be preserved and kept for a long time, possibly being used in research or diagnostic studies in the future. Cell blocks include several serial slices that can be utilized for molecular testing, specific stains, immunohistochemistry, and other ancillary investigation [34,43].

Cell block evaluation has been recognized as a crucial supplementary method for the diagnostic evaluation in addition to other cytological preparations [34, 44]. This is for the reason minimally invasive sampling techniques have become more efficient, and the use of cell block techniques for tissue acquisition has increased as the consequence [34, 45-48].

A variety of commercially available and homebrewed techniques are now in use, with the most popular ones being the Histo Gel (27%) and plasma thrombin (33%) techniques[37,50].

Even though cell block techniques have changed throughout time, the fundamental procedure remains the same: the sample's cellular concentration is followed by histologic processing [51]. However, there are significant drawbacks that can restrict their application in real-world scenarios.

For example, inconsistent or poor cellularity has been identified as a primary cause of cell block discontent. This list of drawbacks also includes time and operating expenses [34, 43, 52].

8. BIOPSY

Endometrial biopsies frequently occur in order to evaluate abnormal uterine bleeding. It is a rather quick and economical method of retrieving endometrial tissue so that the endometrium could potentially be directly analyzed histologically [41, 44]. Endometrial biopsy indications are as follows: [42].

- Endometrial hyperplasia or cancer monitoring;
- Endometrial neoplasia or precancerous hyperplasia;
- Abnormal uterine hemorrhage;

Many healthcare professionals and hospital organizations advise patients that it is safe to take a shower or bath right after the surgery, regardless of there are indeed no established regulations [44]. It is recommended to refrain from having sex or inserting any intravaginal devices until any vaginal bleeding has ceased [46, 47]. In order to prevent vasovagal reactions, post-procedure care involves keeping the patient semi-recumbent for as many hours as the patient feels it is required [48].

Endometrial biopsy procedure becomes a valuable office-based diagnostic test to investigate postmenopausal bleeding [46].

Review of existing knowledge of correlation of cytology and cell block preparation of endometrial aspirate with endometrial biopsy

Baijal L et al [1954] conducted research to do a clinicopathological as well as cytological study of endometrium in the cases of infertility, they did this study on endometrial biopsy and uterine aspirates [2]. Two hundred infertile women were selected for the study. There were 153 cases of primary and 47 cases of secondary infertility. The cellular morphology varied according to the phase of the menstrual cycle. The stromal cells were usually seen in small numbers and most often seen singly and it was difficult to phase the cycle on morphology of the stromal cells. Authors concluded that the uterine aspiration for endometrial study is the simplest, easiest and most satisfactory of all aspiration methods. Besides, the technique provides adequate material both for cytological and histological evaluation in one procedure.

Udasimath S et al (2012) conducted a cross-sectional study on malignant ascitic fluid effusions, in which they studied the role of the cell block method in the diagnosis and observed that CB additionally diagnosed 13.63% more cases of malignancy[34].

Kaur N et al (2014) study results showed that age of the patients ranged from 19 to 70 years. 96.94%, 93.88%, and 96.84%, respectively was the accuracy in diagnosing benign and malignant conditions of endometrium [35].

Patil P et al (2014) established a hospital-based study to compare three different endometrial sampling methods in diagnosing cases of AUB in perimenopausal age group, and they observed that the EAC could detect premalignant lesions in 19% cases and benign endometrial pathologies in 44% cases[36]. Dilatation and curettage detected benign pathology in 50% and premalignant lesions in 44%. Pipelle biopsy detected premalignant pathology in 45% and benign pathologies in 49% and in contrast to 4% of endometrial specimens obtained by pipelle biopsy as well as dilatation and curettage techniques, around 37 percent of endometrial samples generated by aspiration cytology were deemed to be insufficient; the sensitivity, specificity, and diagnostic accuracy of endometrial aspiration cytology were 29.09%, 87.04%, and 59%, correspondingly[42].

They therefore came to an understanding that the detection of endometrial diseases using pipelle biopsy and dilatation and curettage had nearly comparable rates of successful diagnosis [42].

Zhang Z et al (2016) study revealed that the endometrial aspirate had 93.8% diagnostic accuracy, 79.3% sensitivity, and 97.4% specificity [37].

Jadhav MV et al (2016) performed a prospective study of the endometrial aspiration cytology and observed that Endometrial cytology had a diagnosis reliability of 90.4%, while morphological hormonal assessment had a diagnostic accuracy about 97.6% [38].

Shashikala K et al (2017) conducted an observational study of the diagnostic efficacy in endometrial aspiration cytology which was 90% when compared to histology [39].

Saikia JB, Sharma A (2017) studied the endometrial aspiration cytology and concluded that the endometrial aspiration was found to be cost effective and acceptable outpatient procedure [40].

Kaliyamoorthy S, Gandhi R (2018) concluded diagnostic accuracy of endometrial aspiration cytology to be 98.28% to 100% in identifying inflammatory, benign, and malignant tumors, EAC is a successful method [25].

Kulkarni S et al (2018) has made an observational study of the cell blocks and concluded that extracted from LBC specimens helped differentiate intraepithelial lesions from carcinoma cervix in the diagnosis of neoplastic lesions of the cervix. Ancillary techniques such as HPV-DNA testing as well as immunohistochemistry might be applied to cell blocks [41].

Aisagbonhi O et al[63] (2018) studied the modified plasma-thrombin method of cell block preparation for fine-needle aspiration biopsies and observed that in a resource limited settings the modified plasma-thrombin method is a reliable cell block preparation method[42].

Wadhwa K et al (2019) concluded that for the diagnosis of benign and malignant lesions, the diagnostic utility of a Cell Block approach combined with immunohistochemistry is found to be superior than FNAC smears [43].

Wang Q et al (2019) did a meta-analysis of 4179 cases of pathology of endometrium and their study suggested that cytological examinations should be utilized as an additional endometrial assessment method to evaluate the endometrium [44].

Amiri Z et al (2019) evaluated peritoneal fluid in gynecological cancers by comparing liquid-based cytology, conventional cytology, as well as cell block [45].

Siva K et al (2020) observed that the sensitivity of the frozen section of simple hyperplasia for forecasting the diagnosis of HPE was 100%. They concluded that for the diagnosis of endometrial pathologies, the efficiency of histopathological examination is at par to the EAC and frozen section which are minimally invasive and simple techniques that could be utilized [46].

Mardi et al (2020) did a cross-sectional study and reported that endometrial aspiration cytology is an effective and minimally invasive procedure [47].

Shivangi et al (2021) It was determined that endometrial sampling employing Pipelle is a convenient and secure method with sensitivity, specificity, and positive and negative predictive values while juxtaposed with hysteroscopy [48].

Manjunath SS, Paul A (2021) narrated that the histopathological analysis of their study revealed that combining FNAC with cell-block can give more accurate diagnosis[49].

Mane AP et al (2022) conducted a cross-sectional observational study and concluded that the abundance of morphological findings varies greatly, and cell blocks provide a greater understanding of morphology than the traditional smear method. Major variations exist in the order of architecture findings, suggesting a greater understanding of architecture on cell blocks [50].

Cervical dilatation and uterine cavity curettage have long been the accepted techniques for evaluating the endometrium [51-58]. Traditionally, which is done under general anesthesia. Hence, a large proportion of hospital beds and operation rooms are occupied which increases the cost of hospital stay significantly [56, 57].

While performed via Karman's plastic cannula, endometrial aspiration has been demonstrated to be an appropriate ambulatory treatment for diagnosing endometrial lesions in patients of any age, while avoiding the need for anesthesia and hospitalization [47,54].

Since the cell block method utilizes the residual material of the sample, it definitely increases the diagnostic yield and increases the accuracy also. Although the cell block approach improves the specificity of gynecologic cytology, Koss suggested using it in addition to endometrial brushings [7, 45]. For over a hundred years, a range of cell block (CB) approaches have been extensively employed [7, 59].

9. CONCLUSIONS

The cell block (CB) technique brings additional tissue architectural information. CB can also be used for the ancillary techniques such as immunocytochemistry and molecular techniques. The present review is undertaken to have better insights into endometrial aspirate cytology comparison versus histopathology in gynecologic patients, so that minimal invasive, time saving and inexpensive endometrial cytology can gain diagnostic acceptance.

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