Comparison of adequacy of endometrial biopsy using endosampler and hysteroscope guided sampling

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INTRODUCTION

Endometrial sampling is one of the most common gynaecological procedure carried out in patients with abnormal uterine bleeding and infertility. The methods of endometrial sampling are unguided and guided. The reported sensitivity and specificity of various unguided methods of endometrial sampling like Novak curette, Vabra aspirator, pipelle aspirator, endosampler are 57% and 97%, 88.2% and 88.7%, 60-100% and 51.4-100%, 93% and 100% respectively while the sensitivity and specificity of guided endometrial biopsy using hysteroscopy is 100% and 72.8-91%.1-15

The endometrial biopsy obtained by any method of endometrial sampling should provide adequate tissue for proper histopathological diagnosis. One of the common challenges for sampling procedures is obtaining sufficient amount of tissue for diagnosis, especially in the postmenopausal women. Sometimes the tissue obtained is so small that the pathologists report it as insufficient for...
When the data sets were not normally distributed, the sample size with the other chronic medical or surgical illness leading to AUB and infertility fulfilling the inclusion criteria were enrolled and patients with genital infections, other chronic medical or surgical illness leading to AUB were excluded, and the protocol was approved by the ethics committee of the institute.

A consensus recommendation published in a commentary on the management of endometrial precancers stated that devices that yielded crushed (jawed devices) or very small (jawed devices) samples were not reliable in terms of tissue adequacy.

Common observation is that the size of biopsy obtained by hysteroscope guided technique is very small as compared to that obtained by unguided methods like endosampler due to the small diameter of grasping biopsy forceps. The objective of this study was to find out whether hysteroscope guided biopsy (obtained using jawed biopsy forceps) provided adequate tissue in comparison to endosampler aspiration.

**METHODS**

This cross-sectional study was performed between 2017 to 2019 in a Medical college hospital of Delhi, India. Ninety patients with AUB and infertility fulfilling the inclusion criteria were enrolled and patients with genital infections, other chronic medical or surgical illness leading to AUB were excluded, and the protocol was approved by the ethics committee of the institute.

A detailed history and clinical examination was done after written informed consent. Endometrial biopsy was done in the minor gynecology operation theatre. A tablet containing a combination of 400 mg ibuprofen and 325 mg paracetamol was given to all study subjects 45 minutes prior to endometrial biopsy.

Hysteroscopy was done using office hystroscope, endometrial cavity was examined and guided biopsy was taken if any suspicious looking area was seen, otherwise random endometrial biopsy was taken, later endosampler was used for taking endosampler aspiration biopsy. Both the procedures were performed in the same sitting.

The hystroscope used in our study was a 0° scope with a 4 mm inner sheath diameter and a length of 22 cm. A 5fr biopsy forceps was used for taking guided endometrial biopsy.

The endosampler used in the study was a low-pressure endometrial sampling device, 23 cm in length and 3 mm in diameter. The negative pressure was created by a 10 ml syringe and the endometrial aspirate obtained.

All the samples obtained were preserved in 10% formalin. Biopsy obtained by hysteroscope was labelled as ‘A’ and biopsy obtained by endosampler was labelled as ‘B’. The samples were sent for histopathological evaluation but pathologist was blinded to the method of obtaining biopsy. The criteria used by pathologists in our institute regarding tissue adequacy was the presence of at least a single intact endometrial gland with stroma.

**Sample size calculation**

On the basis of previous studies around 13% of tissue samples were inadequate in hysteroscope guided biopsies and 7% in the specimens obtained by endometrial aspiration techniques. Taking this value as reference, the minimum required sample size with 7.5% margin of error and 5% level of significance is 78 patients. So total sample size calculated was 80.

The total sample size taken in the study is 90.

Formula used in this study was

\[
N \geq \frac{p(1-p)}{(ME)^2} \left(\frac{Z_{a}}{2}\right)^2
\]

Where,

- \(Z_a\) is value of \(Z\) at two-sided alpha error of 5%.
- ME is margin of error and \(p\) is proportion of adequate samples.

**Type of study**

The type of study was cross sectional study.

**Statistical analysis**

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used.

Statistical tests were applied as follows- (a) quantitative variables were compared using independent t test/Mann-Whitney test (when the data sets were not normally distributed) between the two groups and (b) qualitative variables were correlated using chi-square test/Fisher’s exact test. P value of <0.05 was considered statistically significant.

The data was entered in Microsoft excel spreadsheet and analysis was done using statistical package for social sciences (SPSS) version 21.0.
RESULTS

Clinical characteristics and histopathology report depicted in Table 1 shows that the maximum number of patients were in the age group of 40-50 years with the mean age of 44.3 years and maximum patients were multiparous with mean parity of 2.7.

Around 53.33% women had presented with complains of heavy menstrual bleeding. On evaluating the endometrial thickness by ultrasound, 70% (63) patients had ET>4 mm while for the remaining patients ET was ≤4 mm. The hysteroscopic findings were found to be normal in 37.78% patients and polyps were detected in 26.67% patients. The size of the biopsy obtained using hysteroscope guided method was in the range of 0.001-0.002 cm³ (mean size- 0.0015 cm³) in 62.22% patients and that obtained by endometrial aspiration was in the range of 0.011-0.1 cm³ (mean size- 0.055 cm³) in 33.33% patients. On histopathological evaluation, more than 50% of the patients had proliferative endometrium (Table 1).

Table 1: Adequacy of endometrial biopsy.

| Factors                                      | Number (%)       | Number (%)       | Number (%)       | Number (%)       | Number (%)       |
|----------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Age (years)                                  |                  |                  |                  |                  |                  |
| 21-30 (11.11)                                | 21-30 (24.44)    | 41-50 (47.78)    | 51-60 (12.22)    | >60 (4.44)       |
| Parity                                        |                  |                  |                  |                  |                  |
| (Nulliparous)                                | 2                | (Primiparous)    | 8                | (Multiparous)    | 80               |
| Chief complaints                             |                  |                  |                  |                  |                  |
| (Hmb*)                                       | 48               | (Imb*)           | 22               | (Pmb*)           | 18               |
| Clinical findings on per vaginal examination |                  |                  |                  |                  |                  |
| (Uterus normal size)                         | 81               | (Uterus bulky)   | 5                | (Uterus 6-8 weeks) | 4               |
| ET on USG (in mm)                            |                  |                  |                  |                  |                  |
| (≤4 mm)                                      | 63               | (>4 mm)          | 27               |                  |                  |
| Hysteroscopic findings                       |                  |                  |                  |                  |                  |
| (Normal)                                     | 34               | (Polyp)          | 24               | (Fibroid)        | 18               |
| Size of endometrial biopsy using hysteroscope in mm³ | (0.001-0.002)   | (0.003-0.006)   | (0.007-0.010)    | (0.011-0.1)      | (0.101-1)       |
| Size of endometrial biopsy using endosampler in mm³ | (0.001-0.002)   | (0.003-0.006)   | (0.007-0.010)    | (0.011-0.1)      | (0.101-4)       |
| Histopathological findings                  |                  |                  |                  |                  |                  |
| (Proliferative endometrium)                  | 39               | (Secretory endometrium) | 27 | (Hyperplastic endometrium) | 4 |
| (Atrophic endometrium)                       |                  |                  |                  |                  | (Chronic endometrium) | 1 |
| Hysteroscopic findings                       |                  |                  |                  |                  |                  |
| (Normal)                                     | 34               | (Polyp)          | 24               | (Fibroid)        | 18               |
| Size of endometrial biopsy using hysteroscope in mm³ | (0.001-0.002)   | (0.003-0.006)   | (0.007-0.010)    | (0.011-0.1)      | (0.101-1)       |
| Size of endometrial biopsy using endosampler in mm³ | (0.001-0.002)   | (0.003-0.006)   | (0.007-0.010)    | (0.011-0.1)      | (0.101-4)       |
| Histopathological findings                  |                  |                  |                  |                  |                  |
| (Proliferative endometrium)                  | 39               | (Secretory endometrium) | 27 | (Hyperplastic endometrium) | 4 |

*Hmb- heavy menstrual bleeding, Imb- irregular menstrual bleeding, Pbm- post menstrual bleeding
Regarding adequacy of endometrial biopsy, Table 2 shows that it was adequate in 35 patients (38.89%) and inadequate in 18 patients (28%) by both methods. Out of the rest 37 women, in 24 women endometrial biopsies were inadequate by hysteroscope guided method but adequate by endosampler method. In the remaining 13 women endometrial biopsy was inadequate by endosampler but adequate by hysteroscope guided method. The number of patients who had adequate biopsy results by hysteroscope guided method and inadequate by endosampler were 14.4% out of which majority (69.2%) were focal lesions, and those having adequate results by endosampler and inadequate results by hysteroscope guided biopsy were 26.67% out of which 50% were focal lesions (Table 2).

**Table 2: Adequacy of endometrial biopsy.**

| Tissue adequacy of endometrial biopsy | Number | Percentage (%) |
|--------------------------------------|--------|----------------|
| Adequate by both devices             | 35     | 38.89          |
| Inadequate by both devices           | 18     | 20.00          |
| Adequate in hysteroscope guided biopsy and inadequate in EA* | 13 (69.2=F) | 14.44 |
| Inadequate in hysteroscope guided biopsy and adequate in EA* | 24 (50=F) | 26.67 |
| Total                                | 90     | 100.00         |

*EA-endometrial aspiration, F=focal lesions

Correlating adequacy of endometrial biopsy with various parameters (Table 3), the endometrial biopsy samples were adequate in 71.43% women between the age group of 22-45 years while it was adequate in only 28.47% cases in the age group of >45 years by both devices. Out of 35 patients in the age group of >45 years, 18 were post-menopausal and the rest 17 were pre-menopausal. The tissue adequacy of endometrial biopsy decreased as the age advanced which showed a statistically significant correlation (p value<0.0001). The maximum number of cases with adequate biopsy results by both devices were of heavy menstrual bleeding (68.57%) and minimum were of post-menopausal bleeding (5.71%). Regarding endometrial thickness on ultrasound, endometrial biopsy was adequate in 91.43% patients when ET was >4 mm. The correlation observed between the endometrial thickness on ultrasound and tissue adequacy was significant with a p value of <0.0001.

**Table 3: Correlation of tissue adequacy with respect to various factors.**

| Factors                      | Classification | Adequate by both methods | Inadequate by both methods | P value |
|------------------------------|----------------|--------------------------|----------------------------|---------|
| Age (years)                  |                |                          |                            |         |
| 22-45                        | 25             | 4                        |                            |         |
| >45                          | 10             | 14                       |                            | 0.001   |
| Parity                       |                |                          |                            |         |
| Nulliparous                  | -              | -                        |                            |         |
| Primiparous                  | 2              | 2                        |                            | 0.56    |
| Multiparous                  | 33             | 16                       |                            |         |
| Clinical indications         |                |                          |                            |         |
| Hmb*                         | 24             | 6                        |                            | <0.0001 |
| Imb*                         | 9              | 1                        |                            |         |
| Pmb*                         | 2              | 11                       |                            |         |
| Infertility                  | -              | -                        |                            |         |
| ET on USG (mm)               |                |                          |                            |         |
| ≤4 mm                        | 3              | 18                       |                            | <0.0001 |
| >4 mm                        | 32             | 0                        |                            |         |
| Hysteroscopic findings       |                |                          |                            | 0.12    |
| Normal                       | 12             | 12                       |                            |         |
| Polyp                        | 12             | 3                        |                            |         |
| Fibroid                      | 8              | 1                        |                            |         |
| Hyperplasia                  | 3              | 2                        |                            |         |
| Subseptate                   | -              | -                        |                            |         |
| Calcification                | -              | -                        |                            |         |

*Hmb- heavy menstrual bleeding, Imb- irregular menstrual bleeding, Pmb- post menstrual bleeding

On taking endometrial biopsy by hysteroscopic guided method, the biopsy tissue was adequate in 48 patients (55.3%) while biopsy was adequate in 59 patients (65.56%) when endometrial biopsy was taken by endometrial aspiration techniques. The difference in the tissue adequacy of endometrial biopsy by both these methods was not found to be statistically significant (p value=0.129) (Table 4).
DISCUSSION

There are various sampling devices available for obtaining endometrial biopsy and the ultimate aim of the procedure is to obtain adequate tissue sample for reporting which is important for further management.

Hysteroscopic guided biopsy is advocated as an ideal method. However, this facility may not be available in many places specially in low resource settings. The consensus recommendation published in a commentary on the management of endometrial precancers stated that devices that yielded crushed (jawed devices) or very small (jawed devices) samples were not reliable in terms of tissue adequacy.\textsuperscript{17} The criteria used for reporting adequate tissue has not been clearly defined. In our study pathologist used the criteria of intact gland with stroma. Various studies have also emphasized the presence of intact gland in reporting tissue adequacy.\textsuperscript{16,19}

In our study the size of endometrial biopsy obtained using hysteroscope guided method was in the range of 0.001-0.002 cm\(^2\) (mean size 0.0015 cm\(^3\)) in 62.22\% of patients and for endometrial aspiration biopsy it was 0.011-0.1 cm\(^2\) (mean size 0.055 cm\(^3\)) in 33.33\% of patients. The size of endometrial biopsy obtained using hysteroscope guided method was comparatively smaller than the size of biopsy obtained using endosampler due to smaller diameter of the grasping forceps used in the procedure.

From our results it became evident that the size of endometrial biopsy did not affect the tissue adequacy (p>0.05) which meant that the number of intact glands to stroma ratio mattered more than simply the size of endometrial biopsy obtained. No published literature is available on this issue, with which we could compare our results.

Hysteroscopy guided biopsy has been used in various clinical conditions to study sensitivity and specificity but there are very few studies where tissue adequacy has been reported using hysteroscope guided biopsy.\textsuperscript{12-15}

Comparison of hysteroscope guided biopsy with other sampling devices in terms of tissue adequacy has not been extensively studied.

A prospective observational study on 150 perimenopausal women with AUB, showed both hysteroscope guided biopsy and pipelle biopsy to be comparable in terms of tissue adequacy.\textsuperscript{20} In this study further it was stated that the hysteroscope guided biopsy diagnosed more cases of hyperplasia as compared to those diagnosed by pipelle, but this marginal difference was not statistically significant. Another similar study where endometrial tissue was obtained by both hysteroscope guided biopsy and pipelle aspiration in 130 women with AUB and both the methods proved to have a comparable tissue adequacy.\textsuperscript{15}

We found adequate tissue in 53.33\% and 66.67\% of the patients by hysteroscope guided biopsy and endosampler aspiration respectively. Although endosampler endometrial biopsy reported a higher percentage of tissue adequacy but this difference was not statistically significant (p value=0.126) and was comparable to above mentioned studies. These observations reiterates the fact that endometrial biopsy can be obtained adequately by sampling devices other than hysteroscope.

There are variable reports addressing the adequacy of endometrial biopsy related to age.

On comparing tissue adequacy with other demographic parameters, we found that out of 90 patients 43 patients were in the age group of 41-50 years. A statistically significant correlation was found between age and tissue adequacy which implied that more the age (>45 years) less is the tissue adequacy (p value=0.001).

Bakour et al in their univariate analysis on 248 women with AUB reported that chances of inadequate tissue specimen increased with increasing age (p value=0.001).\textsuperscript{21} Similarly Dina Kandil et al in their retrospective study on 17522 women reported an inverse correlation between age and tissue adequacy.\textsuperscript{16} In contrast some other studies showed no significant correlation between age and tissue adequacy.\textsuperscript{16,22} The probable reason in these two studies could be variable distribution of patients in the various age spectrums and also that the data was analysed retrospectively.

The first step in evaluation of AUB is the assessment of thickness of endometrium by TVS.

We observed that the thickness of endometrium on ultrasound in mm was directly related to adequacy of endometrial biopsy. Of the 90 patients, 63 patients (70\%) were having endometrial thickness of >4 mm and out of these 32 patients had been adequately sampled by both methods. In the remaining 27 patients of endometrial thickness ≤4 mm, 18 (66.67\%) patients had inadequate biopsy reports. It was inferred from these findings that thickness of endometrium (>4 mm) was directly correlating with tissue adequacy (p value<0.0001). Similar results were reported in a study by Aue et al in a prospective study done on 233 patients where a statistical correlation was seen between endometrial thickness and tissue adequacy.\textsuperscript{22}

### Table 4: Comparison of tissue adequacy of hysteroscope guided biopsy with endometrial aspiration biopsy.

| Tissue adequacy | Hysteroscope guided biopsy (%) | Endosampler aspiration (%) | P value |
|-----------------|-------------------------------|---------------------------|---------|
| Adequate        | 48 (53.33)                    | 59 (65.56)                |         |
| Inadequate      | 42 (46.67)                    | 31 (34.44)                | 0.129   |
| Total           | 90 (100.00)                   | 90 (100.00)               |         |
Various other studies have also established that the endometrial thickness is directly related to tissue adequacy.22,23

On the contrary some studies found no significant correlation between endometrial thickness and tissue adequacy because of exclusion of patients with ET ≤ 4 mm and influence by other secondary factors like type of device, type of provider and uterine volume etc.24,25

The strength of our study is that it is the first study to compare hysteroscope guided biopsy and endosampler aspiration in terms of tissue adequacy. There’s no observer bias as both procedures were conducted by the same observer in the same setting. The limitation of our study was that since no previous studies have been conducted comparing tissue adequacy of hysteroscope guided biopsy with endosampler, we could not compare our results.

CONCLUSION

For obtaining adequate endometrial biopsy, endometrial aspiration by endosampler and hysteroscope guided biopsy, both are comparable.

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