Endometrial biopsy collection from women receiving Norplant®

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Abstrak

Dalam upaya melakukan eksplorasi penyebab perdarahan sebagai efek samping utama dari wanita pengguna implan di Indonesia, maka Pokja Reproduksi Universitas Indonesia melakukan beberapa penelitian dasar yang salah satunya adalah penelitian biopsi endometrium. Untuk itu telah dilakukan biopsi endometrium terhadap 191 wanita pemakai kontrasepsi Norplant® dengan lama pemakaian antara 2 dan 12 bulan. Delapan puluh tujuh biopsi dilakukan dengan menggunakan mikrohisteroskopi, dan 104 biopsi dilakukan dengan memakai kanula Pipelle atau kanula Karman dengan metode aspirasi. Dari hasil biopsi histeroskopi, hanya 50% sampel dapat dianalisis adanya sel endometrium, oleh karena sering didapatkan hanya miometrium dari sampel tersebut. Pada metoda biopsi dengan kanula baik Karman maupun Pipelle tidak sampai mencapai miometrium. Sedangkan pada analisis kadar estrogen, didapat perbedaan bermakna antara kadar estrogen pada biopsi hari ke 90 dengan biopsi hari ke 14, yaitu masing-masing (26,5 ± 2,1 v 16,2 ± 1,8 pmol/l P=0,0003) dan (439 ± 35 v 289 ± 33 pmol/l P=0,0018). Disimpulkan bahwa setelah 3-12 bulan pemakaian Norplant®, 50% menunjukkan endometrium yang sangat tipis untuk dapat diambil sampelnya. Dengan gambaran klinis kadar estrogen yang sangat rendah dan berkurangnya darah haid.

Abstract

This paper reports a series of 191 endometrial biopsy procedures performed on Indonesian women who had received between 3 and 12 months exposure to Norplant®. 87 biopsy procedures were attempted with a microhysteroscope using biopsy forceps, and 104 procedures were attempted with either Pipelle or Karman suction curettes. Regardless of biopsy method, diagnosable endometrium was only obtained in approximately 50% of procedures. Myometrium was often found in microhysteroscope but not suction biopsies. Analysis of a number of clinical characteristics showed that women from whom diagnosable endometrial tissue was obtained had higher mean peripheral oestrogen levels in the 2 weeks prior to biopsy (439 ± 35 v 289 ± 33 pmol/l. P=0.0018), and significantly more days when endometrial bleeding occurred in the 90 days prior to biopsy (26.5 ± 2.1 v 16.2 ± 1.8. P=0.0003). These results suggest that after 3-12 months exposure to Norplant® about 50% of women have an endometrium that too thin to sample, and that this group is characterised by lower peripheral oestrogen levels and reduced menstrual bleeding.

Keywords: endometrial biopsy, Karman cannula, microhysteroscope, Norplant®, Pipelle suction curette.

Prolonged and/or irregular breakthrough bleeding is one of the major complications of most progestogen-only contraceptive. In particular, a significant number of women using the subdermal contraceptive implant, Norplant®, is seriously inconvenienced by unwanted alterations in menstrual bleeding pattern. Recently, research into the causes of Progestogen-induced breakthrough bleeding has focused on the role of local factors acting within the endometrium. In the absence of good animal models, this work has been carried out almost entirely on endometrial biopsy samples obtained from women using progestogen-only contraceptive methods. In a majority of the patients using Norplant contraception, drop out is due to menstrual disorders (menorrhagia, spotting etc.). This paper will very briefly describe the endometrial biopsy procedures and results from Raden Saleh Klinik in Jakarta where a group of 191 women underwent endometrial biopsy following 3-12 months of exposure to Norplant®. The aim of this study is to compare three difference methods of biopsy, i.e. Hysteroscopy, Pipelle biopsy and Karman cannula, in getting accurate tissue samples.

METHODS

Three different outpatient endometrial biopsy techniques were utilised in this study. The first was microhysteroscopy, the second was Pipelle suction curette (Prodimed 60530, Neuilly-en- Thelle, France) and the third was Karman cannula. Microhysteroscopic biopsies were performed with a rigid 4 mm

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Storz hysterescope with a 30° angle of view. Carbon dioxide was used to distend the uterine cavity and this was delivered by a Hamou hysteroflator. Prior to hysteroscopy, the external cervical os was exposed, wiped clear of mucous and swabbed with mild antiseptic (providone iodine, 10%). 5-10 ml of 1% lignocaine was infiltrated into the anterior lip of cervix to provide local anaesthesia. Small rigid biopsy forceps were inserted through the operative canal on the hysteroscope into the distended uterine cavity. Endometrial biopsy was performed either under direct vision or from video images on a nearly monitor. Preparation for biopsies with either the Pipelle or Karman cannula was essentially similar to that for microhysteroscopy except that no local anaesthetic was used. The Pipelle suction curette is a narrow flexible device that is widely used for out-patient endometrial biopsy procedures. The Karman cannula is 4 mm in diameter and made of flexible polyethylene. Suction is provided by attaching a standard disposable syringe.

These procedures were performed on volunteers who had consented to take part in a WHO funded and ethically approved study, without anaesthetic. A total of 191 women who had received an average Norplant® exposure of 219 ± 7.2 days (mean ± S.E.M) are reported in this study.

The average weight of these women was 51 ± 0.7 kg, the average age was 30 ± 0.3 years, and each woman had an average of 2.6 ± 0.1 pregnancies. Endometrial biopsies were taken by 2 operators, over a period of almost 3 years. All endometrial materials obtained from each procedure were immediately transferred to the laboratory and processed using buffered formalin fixation, prior to wax embedding and routine histological examination. Biopsies were sceened by at least two people for evaluation of diagnosable endometrial tissue.

All subjects completed a daily menstrual record card for at least 90 prior to biopsy, recording bleeding, spotting or no bleeding for each day. Bleeding and spotting days were combined for the analysis to give a figure for total number of bleeding and spotting days during the 90 days prior to biopsy. In the 2 weeks prior to biopsy, six peripheral blood samples were taken at 2-3 day intervals to evaluate circulating oestradiol concentrations (Coat-A-Count Oestradiol; Diagnostic Products Corporation, Los Angeles, CA, USA; coefficients of variation, intra-assay 5.6% at 290 pg/ml, interassay 5.5% at 262 pg/ml).

RESULTS

The results for 191 biopsy procedures are given in Table 1. In summary, from 87 biopsies with a microhysteroscope, 51% produced endometrial tissue that could be adequately evaluated by histopathology. Using either a Pipelle or Karman cannula, from 104 procedures, exactly 50% of biopsies produced enough diagnosable endometrial tissue.

Table 1. Results for 191 endometrial biopsy procedures using either a microhysteroscope, or Pipelle or Karman cannula. Operator 1 performed all microhysteroscope procedure (N = 87) while 2 operators (1 and 2) performed the remaining 104 procedures using either a Pipelle or Karman.

Microhysteroscope		Pipelle / Karman	
Operator	1	1	2
Diagnosable endometrial tissue	44 (51%)	22 (42%)	30 (58%)
Myometrium only	40 (46%)	-	-
Inadequate or no tissue	3 (3%)	30 (58%)	22 (42%)
Totals	87 (100%)	52 (100%)	52 (100%)

In a subsequent study by a third operator, only 5 out of 30 (17%) biopsies taken using a microhysteroscope had adequate tissues for diagnosis. However, 105 out of 152 (69%) biopsies taken with a Karman cannula produced suitable tissues for histopathological diagnosis.

The use of the microhysteroscope often resulted in full thickness endometrium being collected, including a small amount of myometrial tissue. Histologial evaluation of these full thickness biopsies showed that the endometrium was always very thin or absent. In contrast, both the Pipelle and the Karman collected endometrial tissue only. Where a biopsy was successful, there was often a relatively large amount of tissue broken into small and medium size fragments contained within blood and mucous. However in the 50% of biopsies where no tissue was obtained, mucous and blood were usually the only findings on histology. Sometimes a limited number of epithelial and glandular cells was also found within the mucous and blood obtained in these unsuccessful procedures.

In a brief analysis of a number of clinical parameters, some significant differences were found between those patients from whom a successful biopsy was obtained, and those from whom no endometrium was collected. These data are listed in Table 2 and show very significant differences in both bleeding days, and average peripheral estrogen levels between women from whom endometrial tissue was obtained and those from whom tissue was not obtained. Similar analyses for body weight and length of Norplant® exposure showed no significant differences between the two groups.

Table 2. Differences in bleeding days, (number of days in which bleeding or spoting were recorded in the 90 days prior to biopsy), and average peripheral estrogen levels (based on 6 bloods taken during the 2 weeks prior to endometrial biopsy) between women from whom an endometrial biopsy was obtained, and women from whom no endometrial tissue was obtained (values are mean ± SEM).

	N	Bleeding Days	Average Estrogen (pmol/l)
Biopsy	88	26.5 ± 2.1	439 ± 35
No Biopsy	93	16.2 ± 1.8	289 ± 33
P Value		0.0003	0.0018

DISCUSSION

The results from this study show that in women who have received Norplant® contraception for between 3 and 12 months, only about 50% have an endometrium that can be biopsied. These results suggest that in approximately 50% of these women, there is very little or no endometrium present. There may be some differences depending on the experience of individual operators. The microhysteroscope provides a small biopsy that usually contains full thickness endometrium. The epithelium is often missing from these biopsies, presumably due to shearing damage during the biopsy procedure. In contrast, the Pipelle and Karman cannula often provide quite large amounts of tissue, although this may be broken into numerous fragments and often combined with large amounts of blood. It is much more difficult to orient the tissue obtained from the Pipelle or Karman cannula biopsy compared to those obtained by microhysteroscopy.

The finding of significant differences in both bleeding days and average estrogen levels between the groups from which a biopsy was obtained versus those from which no biopsy was obtained, is somewhat suprising. This suggests that women taking Norplant from whom succesful endometrial biopsies were obtained are not representative of the whole population, but rather define a sub- group that have an average of a higher level of bleeding, and greater endogenous estrogen levels. This information needs to be considered whenever analysis of clinical data is undertaken for women from which biopsies were successfully obtained.

In conclusion, this short paper outlines the typical success rate that can be anticipated when endometrial biopsies are being obtained from women during the first year of Norplant® use. It also demonstrates for the first time, that the group from which successful biopsies are obtained may not be representative of the whole population, and this issue should be borne in mind during further analyses of clinical parameters.

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