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Abnormal Pap smear among pregnant women – Feasibility of opportunistic cervical screening☆

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ABSTRACT

Objective: The uptake of cervical cancer screening is poor, especially in developing countries. Thus, pregnancy represents a good opportunity to have the test done. The aim of this study is to determine the prevalence of abnormal Pap smear among pregnant women during their antenatal check-ups.

Study design: A prospective study involving five hundred and ninety-six women was recruited over a 1-year duration from 15th January 2018 until 14th January 2019 in a tertiary referral center, in Malaysia. Pap smears were performed on all consented pregnant women using liquid-based cytology and the results were obtained to evaluate the prevalence of abnormal Pap smear during pregnancy. Maternal risk factors associated with abnormal Pap smear were identified and the outcomes of abnormal Pap smear were followed up.

Results: A total of 670 participants were approached and 596 participants agreed to participate, giving a response rate of 89.0 %. Therefore, 587 participants were available for analysis. There were nine unsatisfactory smears (1.5 %). The prevalence of premalignant lesions reported on p % ap smear was 0.8 %. Three respondents had atypical squamous cells of undetermined significance (ASCUS) (0.5 %) and two respondents had low-grade squamous intraepithelial lesions (LSIL) (0.3 %). Almost one-third (30.3 %) of respondents had an infection and 24 (4.1 %) smears were reported as reactive changes associated with inflammation. Respondents between the age of 20–30 years old had a significant association with an abnormal pre-cancerous smear (p = 0.000) as well as nulliparity (p = 0.0.40). There was no significant association between height, weight, BMI, sexual partner, age of first intercourse, smoking habit, history of sexually transmitted disease and history of abnormal Pap smear.

Conclusion: The prevalence of abnormal pre-cancerous smears during pregnancy is low. However, it is desirable to perform cervical screening as it provides an opportunity to no screening at all.

Introduction

Cervical cancer is one of the most common cancers worldwide with 604,127 new cases diagnosed in 2020 and 15 % of new female cancer arise from Southeast Asia [1]. In Malaysia, it was the third most common cancer in females with a lifetime risk of 1 in 116. There were 795 new cases diagnosed in 2011 and the Chinese female population had the highest incidence with an Age-Standardized Rate (ASR) of 9.8 followed by Indian 7.6 and Malays 5.1. About 60 % of cervical cancer was detected at stage I-II [2]. The number of new cases increased to 1740 with 991 deaths in 2020 [1].

Studies have shown that an effective cervical cancer screening program helps to identify the premalignant cervical lesion [3] and also reduces the mortality rate [4]. National cervical cancer screening had been started since the 1960 s but to date, Malaysia still relies on opportunistic screening without an organized program for cervical cancer screening [3]. Despite being free of charge for women attending public clinics and hospitals, cervical cancer screening uptake was poor.

The coverage however remained low and disappointing at around 40 % during the last survey [5]. As compared to the United Kingdom, the uptake of cervical cancer screening is around 80 % [6]. In contrast to Pap smear screening, Malaysia has achieved high coverage for HPV vaccination since 2010 and HPV self-sampling has also been found to be acceptable and effective [7].

The incidence of abnormal Pap smear during pregnancy is about 1.6–9.5 % [8–11]. A study by Kathleen et al. stated that the incidence may be up to 20 % and the prevalence of abnormal Pap test results in pregnancy does not differ from the age-matched nonpregnant population [12]. The incidence of cervical pre-cancerous lesions in pregnancies peaks at the age of 25–35 years [12]. From this perspective, antepartum care presents an opportunity to offer a Pap smear to women who otherwise might not go for a routine health check and a means to increase coverage of the program. A nationwide registry study in Denmark showed that women undergoing routine opportunistic screening were more likely to be diagnosed with abnormal cytology as compared to those with regular screening. This could serve as an important supplement to the systematic screening program [13].

The World Health Organization emphasizes that pregnancy is not the ideal time for taking cervical samples for cytology screening because it might give misleading results. However, if the woman is in the target age group with a high likelihood that she will not return after giving birth, the health professional should proceed with the smear [1]. Risk factors for abnormal Pap smear in pregnant women were the same as those in non-pregnant [3]. Previous studies showed that conducting cervical cancer screening during pregnancy was as reliable as those conducted in non-pregnant women [10,12,13].

It is a routine practice in Western countries such as Northeastern in Brazil, Nigeria, the United Kingdom and New Zealand, for women to have cervical cancer screening during their antenatal visit [14–17]. There is no contraindication for a smear being taken during pregnancy especially if the woman is overdue for a smear or the previous smear is abnormal [17]. Therefore, pregnancy represents a good opportunity and sometimes the only opportunity to have this test done. Thus, the aim of this study is to determine the prevalence of abnormal Pap smear during pregnancy and to identify risk factors associated with abnormal Pap smear.

Materials and methods

Study design

This was a prospective study, over a 1-year duration, from 15 January 2018–14 January 2019 at Hospital Canselor Tuanku Muhriz (HCTM). All pregnant women attending antenatal or admitted through the patient admitted center were approached. Those respondents who fulfilled the inclusion criteria were recruited. Respondents were explained about the study and informed consent was taken if they agreed to participate. Demographic data such as age, ethnicity, gravidity, parity, gestational age, height, weight, body mass index (BMI), number of sexual partners, age of first sexual intercourse, contraception prior to pregnancy, smoking habit, history of sexually transmitted disease and history of abnormal pap smear were recorded.

A speculum examination without an antiseptic solution was performed. Liquid-based cytology technique was used in this study. Thus, a sample of cells was collected from the cervix using cytobrush-spatula [18]. The samples were then immersed into a container of preservative/transport medium, and subsequently sent to the laboratory. In the lab, the cells were separated by centrifugation or filtration and deposited on a slide as a monolayer. The slides were stained, mounted and screened by trained cytoscreeners. Every slide was then interpreted and validated by a consultant cytopathologist. The cervical cytology results were reported according to the Bethesda classification 2014 [19]. The Pap smear results were reviewed during the next available follow-up. Any abnormal cytology result was managed according to the standard guideline [20,21]. The management was either to repeat Pap smear, immediate colposcopy or deferred colposcopy until at least 6 weeks postpartum. The patients were followed up accordingly based on the Pap smear cytology report.

Data analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 23.0. The chi-square test and Fisher's exact test were used to analyse categorical data and the t-test was used for continuous data. A p-value of less than 0.05 was considered statistically significant.

Ethical consideration

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Medical Research and Ethics Committee Universiti Kebangsaan Malaysia (UKM) (Research Code: FF-2018–034).

Results

Demographic data

There were 670 participants approached and only 596 agreed to participate, giving a response rate of 89.0 %. There were nine unsatisfactory smears (1.5 %). Therefore, 587 participants were available for analysis. The majority of the participants were Malay (n = 485, 82.6 %) followed by Chinese (n = 67, 11.4 %), others including Sabahan, Indonesian and non-citizen (n = 19, 3.2 %) and Indian (n = 16, 2.7 %). The number of pregnant women who attended the O&G clinic during the period of recruitment from January 2018 to January 2019 was 11492.

The median age of participants was 31.3 years old. One-third of women were nulliparity (n = 187, 31.9 %). Median gestational age was 30.5 weeks and their body mass index was 28.3 kg/m2. Most women (97.8 %) had a single sexual partner. Five hundred and two respondents (85.5 %) had their first sexual intercourse between 20 and 30 years old. Surprisingly, 323 (55 %) respondents were not on any form of contraception to space the pregnancy. There were six respondents who smoked during pregnancy. None of the respondents had a history of sexually transmitted infection or history of abnormal Pap smear (Table 1).

Table 1
Demographic data.

	$n = 587$
Age, years	31.3 (19, 45)
Ethnicity	
• Malay	485 (82.6)
• Chinese	67 (11.4)
• Indian	16 (2.7)
• Others	19 (3.2)
Nulliparous, n (%)	187 (31.9)
Gestational age, weeks	30.5 (13.0, 40.0)
BMI, (kg/m^2)	28.3 (16.0, 49.9)
Multiple sexual partners, n (%)	13 (2.2)
Age of first Sexual Intercourse, years, n (%)	
• Less than 20	50 (8.5)
• 20–30	502 (85.5)
• More than 30	35 (6.0)
Previous contraception, n (%)	264 (45)
Smoking habit, n (%)	6 (1.0)
History of Sexual Transmitted Disease (STD), n (%)	0 (0)
History of abnormal Pap smear, n (%)	0 (0)

All parameters expressed in median (Quartile); Maternal related factors analyzed were maternal age, BMI, sexual partner, age of first sexual intercourse, previous contraception prior to pregnancy, smoking habit, history of sexual transmitted disease and history of abnormal Pap smear.

Prevalence of normal and abnormal Pap smear

Overall, 380 (64.7 %) respondents' pap smears were negative for intraepithelial lesions or malignancy (Table 2). Almost one-third of respondents (30.3 %) had a concomitant infection, including Candida *spp* (n = 135, 75.8 %), bacterial vaginosis (n = 31, 17.4 %) and both Candida *spp* with bacterial vaginosis (n = 12, 6.7 %). There were 24 (4.1 %) respondents who had smears reported as reactive cellular changes associated with inflammation. The prevalence of premalignant lesions reported on pap smear was 0.8 %. Three respondents had atypical squamous cells of undetermined significance (ASCUS) (0.6 %) and two respondents had low-grade squamous intraepithelial lesions (LSIL) (0.3 %) (Table 3). The two respondents with LSIL were at 37 and 38 weeks gestation, therefore they were advised to have HPV DNA testing at 6 weeks post-partum.

There was a significant association between age and parity with abnormal Pap smear (pre-cancerous lesion). However, there was no significant association between weight, height, BMI, number of sexual partners, age of sexual intercourse, contraception prior to conception and smoking (Table 3).

There were three patients with ASCUS and they had repeated smears three months after delivery. All the repeated smears were reported as negative for intraepithelial malignancy (NILM). One patient with LSIL had persistent LSIL three months after delivery. Her colposcopy biopsy result showed chronic cervicitis. Another patient with LSIL had a normal smear at three months post-partum.

Discussion

For the last three decades, the incidence of cervical cancer has reduced markedly by around 50–70 % with the introduction of HPV testing and vaccination [22]. However, Pap smear is still a must despite the use of these inventions. No other cancer has such a remarkable reduction in mortality rate by having prevention, early diagnosis and treatment than cancer of the cervix [23]. Unfortunately, the uptake of Pap smear is rather disappointing, especially in developing countries like Malaysia.

A local study by Othman in 2009 showed that among 1431 cases of cervical cancer diagnosed in eight major hospitals in Malaysia between 2000 and 2006, up to 88 % of patients had no Pap smear done within 3 years before the development of cancer [24]. This was consistent with another study done in five rural districts in Perak, Malaysia which showed only 48.9 % among 959 respondents had undergone Pap smear at least once in the past three years [5].

Another study was done among women of Russian, Somali and Kurdish origin compared with the general Finnish population, with the odd ratio for screening among Russian (0.92), Somalis (0.16) and Jurds (1.37). Their screening participation was lower among students and retirees. The author suggested that efforts using culturally tailored / population-specific approaches may be beneficial [25]. In Korea, in a study among 15141 women who underwent both HPV testing and cervical cytology, the author concluded that the use of HPV testing showed higher sensitivity than cytology but the specificity of HPV testing varied between the methods used [26].

This was mainly due to the fact that public knowledge and awareness

Table 2
Classification of Pap smear based on Bethesda Classification 2014.

	n = 587
Negative for intraepithelial lesion or malignancy	380 (64.7)
Presence of organism (infection)	178 (30.3)
Reactive cellular changes (inflammation)	24 (4.1)
Epithelial cell abnormalities (pre-cancerous smear)	
• Atypical squamous cells of undetermined significance (ASC-US)	3 (0.5)
• Low grade squamous intraepithelial lesion (LSIL)	2 (0.3)

All parameters expressed in n (%) unless specified

Table 3
Maternal characteristics and Pap smear results.

Characteristic	Abnormal Pap smear (pre-cancerous lesion)	Normal Pap smear	p
Age, years	5	582	**0.000**
Ethnicity			
• Malay	5	480	0.889
• Chinese	0	67	
• Indian	0	16	
• Others	0	19	
Parity			
• Nulliparous	3	184	**0.040**
• Parity 1 – 3	1	368	
• Parity 4 and above	1	30	
Weight, kg	5	582	0.981
Height, cm	5	582	0.487
BMI, kg/m2	5	582	0.393
Multiple Sexual partners	0	13	0.775
Age of first Sexual Intercourse, years			
• Less than 20	0	50	0.775
• 20–30	5	497	
• More than 30	0	35	
Contraception prior to conception	2	262	0.684
History of Smoking	0	6	0.860

of cervical cancer and its prevention were relatively low. A study done recently among 716 pre-university students showed that the majority of them had poor to moderate knowledge with only 8.8 % exhibiting good level of knowledge [27]. Other barriers to screening especially in developing countries included competing health needs, limited human and financial resources, poor access to information and poverty [28]. The poor practice of Pap smear screening also included those aged less than 35 years old, those practicing hormonal contraceptive methods and individuals who perceived barriers to Pap smear testing according to a survey done among secondary school teacher [29]. Besides, 95.8 % of women claimed that Pap smear make them worry and 62.1 % of women gave the reason that no healthcare workers advised them to do so [30].

In China, the cervical cancer burden is as heavy as in Malaysia. Although the Chinese government provides free cervical cancer screening, the screening rates remain low. Only 63 % of the participants underwent screening in a questionnaire study. Related knowledge was higher amongst the screened group relative to the unscreened group. Age, education and income were significantly associated with a higher knowledge level. Education was the only significant factor associated with a positive attitude [31]. Another systematic review by Chua et al., the most common barrier to cervical cancer screening is an embarrassment and poor knowledge of screening [32]. Thus, many studies attempt to find out the efficacy of educational interventions to improve the knowledge and uptake of cervical screening [33,34].

Risk factors for abnormal Pap smear in pregnant women were the same as those non-pregnant [3]. Previous studies showed that conducted cervical cancer screening during pregnancy was as reliable as those conducted in non-pregnant women although there were present of certain challenges [12,14,19]. In fact, a study by Mari Nygard et al. stated that pregnant women were 4.3 times more likely to have Pap smear during follow-up compared to non-pregnant women. Sixty-three percent of the pregnant women did a Pap smear as a response to the invitation letter compared to 28.7 % of the non-pregnant women [35]. Hence it is recommended to screen pregnant women with a pap smear if they would benefit from screening under current screening guidelines.

Challenges in cervical smear interpretation during pregnancy are due to micro glandular hyperplasia of the endocervical gland and pregnancy-related cellular changes such as Arias-Stella reaction, ectropion, decidual cells and trophoblastic cells [36]. Nevertheless, many authors have reported the accuracy of cytology of pregnant women is as

high as 82–100 % which is equal to those in mass-screened, non-pregnant women [11,14]. In this study, the prevalence of abnormal pap smear (precancerous lesion including ASCUS and LSIL) during pregnancy was 0.9 %. This was much lower as compared with a larger study done in China by Fan et al. in 2008, where 12,112 women who underwent antenatal check–up were smeared using thin prep cytology and incidence of ASCUS, atypical glandular cells of undetermined significance (AGUS), LSIL and high grade squamous intraepithelial lesion (HSIL) were 9.52 %, 0.94 %, 1.92 % and 0.62 % respectively [8]. Where in Thailand, a study done by Lertcharernrit et al., over 414 pregnant women found that the prevalence of abnormal Pap smear was 6 % (25/414) and the most common abnormality reported was LSIL (44 %, 11 out of 25 women) followed by ASCUS (36 %, 9/25), Atypical Cells cannot exclude High-Grade Lesion (ASC-H) (12 %, 3/25) and HSIL (8 %, 2/25) [11]. They also demonstrated that the use of Pap smear had higher sensitivity as compared to visual inspection with acetic acid during the same study [11]. The difference in prevalence is probably due to the different populations studied and the number of sample sizes recruited. However, the respondents' response rate to invitations for Pap smear during antenatal check-ups in this study was very encouraging (89.0 %).

There are multiple risk factors associated with the development of cervical cancer including age at first intercourse, number of sexual partners, smoking, multiparity and sexually transmitted illness [37]. In this study, we demonstrated that age and multiparity were associated with an increased risk of abnormal precancerous lesions but due to the number being small, this result must be interpreted with caution. Fan et al., with logistic regression analysis, showed that age of first intercourse, number of sexual partners and smoking were associated with abnormal Pap smear [8]. It was concluded by the author that the risk factors associated with abnormal Pap smear were the same as those of non-pregnant women [8]. Whereas, Lertcharernrit et al. found that low BMI, multiple sexual partners and being a government official were associated with abnormal Pap smear during pregnancy [11].

The strength of this study included the relatively good sample size with a high response rate from the study population. However, there are several limitations to this study. Due to the incidence of abnormal precancerous lesion smears being relatively low in the study, risk factors associated with the abnormal smear must be interpreted cautiously. A further larger study will be needed in the future with multicentre collaboration perhaps to determine the role and usefulness of performing Pap smear screening during antenatal check-ups.

Conclusions

The incidence of abnormal premalignant smear during pregnancy is low. However, it is desirable to perform cervical screening as it provides an opportunity to no screening at all.

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CRediT authorship contribution statement

Conceptualization, N.F.M, B.K.N, N.M.I and P.S.L.; Methodology, N.F.M, B.K.N, N.M.I and P.S.L; Software, N.F.M, B.K.N; Validation, N.F.M, B.K.N and N.M.I.; Formal analysis, S.H.P, Y.P.W, N.F.M and B.K.N.; Investigation, S.H.P, Y.P.W, N.F.M and B.K.N.; Resources, N.F.M, B.K.N, N.M.I and P.S.L.; Data curation, S.H.P, Y.P.W, N.F.M and B.K.N; Writing – original draft preparation, N.F.M, B.K.N.; Writing – review & editing, S.H.P, Y.P.W, N.F.M, S.E.P and B.K.N; Visualization, S.H.P, Y.P.W, N.F.M, S.E.P and B.K.N.; Supervision, B.K.N and N.M.I; Project administration, N.F.M, B.K.N and N.M.I. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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