

Test Papanicolaou During Pregnancy: Perceptions and Reality in Clinical Practice: A Review of the Literature

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Received date: 29 January 2023; **Accepted date:** 16 February 2023; **Published date:** 23 February 2023

Citation: Nektaria Z, Ioannis M, Kyriakos K, George M (2023) Test Papanicolaou During Pregnancy: Perceptions and Reality in Clinical Practice: A Review of the Literature. J Comm Med and Pub Health Rep 4(01): <https://doi.org/10.38207/JCMPHR/2023/FEB04010213>

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Abstract

Background: Test Papanicolaou is an effective screening method for preventing and diagnosing cervical cancer. Pregnancy represents a unique opportunity for many of these women, especially the younger ones, to participate in this life-saving screening program for the first time.

Objective: This review aimed to summarize the evidence from published data regarding the use, assessment, and interpretation of Pap smears during pregnancy.

Sources: We searched PubMed and Scopus databases using a combination of terms, from inception till January 2023, for articles referring to Test Papanicolaou in pregnant women, but our search was mainly concentrated on those published after 2000.

Results: The initial search identified 761 results. We assessed those results by reviewing the titles and abstracts and retrieved 40 articles. The reference lists from retrieved papers were also scanned. After complete text evaluation, 23 studies were finally included in this review. Those studies described the following main topics: **1)** cytology changes of the cervix, **2)** comparisons and suggestions between various sampling devices, **3)** the value of the diagnosis of bacterial vaginosis, and **4)** evaluation of abnormal results.

Conclusion: Generally, a Pap smear should be conducted at the first prenatal visit and no sooner than 4 weeks postpartum. The results are most accurate during the postpartum period due to the regression of cervix changes that occur during pregnancy. The incidence of abnormal cytology is low and tends to regress till the postpartum period.

Keywords: Test Papanicolaou, Cancer Screening, Pregnancy, Pregnant women, Cervical cancer

Introduction

Papanicolaou smear, introduced in the early 1930s, is one of the most widespread and reliable screening tests for cancer in the medical community now [1,2]. Pap smear is mainly used for the early detection of pre-neoplastic lesions [1]. The incidence and mortality of cervical cancer have substantially decreased due to cervical cancer screening programs [1,3]. The leading clues for this widespread use and success derive from its low cost, low false-negative rate, and simplicity of the procedure.

Pregnancy is a period in a woman's life that establishes a more constituent, regular, and complete follow-up by an Obstetrician and Gynecologist. Moreover, a few women may visit an Obstetrician & Gynecologist for the first time, representing an entry point to the health care system. Thus, pregnancy is an opportunity to counsel and educate women not only about the pregnancy but also about the routine gynecological examination and preventive services, especially the significance of Pap smear [4]. Sometimes pregnancy is the only opportunity to screen women for cervical cancer or dysplasia [10]. The American College of Obstetricians & Gynecologists

(ACOG) recommends that women at the age of 21 should start screening for cervical cancer via Pap smear, regardless of the period at first sexual intercourse, contrary to previous guidelines [11,12,22]. According to the literature, many women have their first pregnancy at an increased age, which results in a growing frequency of abnormal cytological findings in pregnant women, such as atypical glandular cells (ACG) [13]. Nevertheless, cervical cancer incidence in pregnancy is rare, varying between 0,8 to 1,5 cases per 10.000 births [23]. Cervical cancer is one of the most common malignancies diagnosed in pregnant women [5,23]. Moreover, one to three out of every hundred women diagnosed with cervical cancer are pregnant or postpartum [3,6,23]. Human Papilloma Virus (HPV) is the leading cause of cervical cancer [14,15].

Moreover, pregnancy is not known to alter the history or progress of the disease [7,8]. Pap smear screening test during pregnancy is essential for detection, prevention, and early intervention in the mother or child's unfortunate occurrence [4]. Another point of interest is the validity of a Pap smear in diagnosing Bacterial Vaginosis (BV)

[9]. The results of a Pap smear in pregnancy can be under-evaluated due to various factors, including cell degeneration with increasing cervical secretions and inadequate samples [18]. In many countries, it is a fact that midwives mainly conduct Pap smear sampling. A study examining the perceptions of midwives in regard to Pap smear during pregnancy indicated a lack of knowledge, especially regarding the exact period that a Pap smear should be performed after delivery.

Methods

Sources

We conducted a search of the literature in English for studies referring to Test Papanicolaou in pregnant women from inception till January 2023. We searched PubMed (1951 up to January 2023) and SCOPUS (1951 up to January 2023) databases using a combination of the terms: "Test Papanicolaou" AND "Pregnancy" OR "Pregnant women." While searching PubMed, we used MESH terms to restrict many results to the most relevant studies. We concentrated our scientific interest on papers mainly published from 2000 onwards, being up to date. We scanned the titles and abstracts for the retrieved studies but focused on the full text for the most relevant studies. In addition, we examined the reference lists from the retrieved papers. All analyses were reviewed carefully to avoid duplicates. A combination of the following factors: large study sample, most representative, and more relevant studies were finally retrieved. The methodology followed to write this review is based on articles describing the content and structure of review papers [19-21].

Results

Our initial search identified 761 results. After assessing the titles and abstracts, 40 studies were further evaluated. The duplicate papers were excluded after the initial assessment. The full-text review was conducted, and we included 23 studies (**Figure 1**) reporting on the Pap smear procedure in pregnant women, evaluation and Management of Pap smear results, and a comparison between the

Midwives are also not keen on conducting a Pap smear during pregnancy [4].

This review aimed to summarize published evidence of the literature regarding the practical use, value, and techniques of Pap smear in pregnancy. Our objective was to present a well-structured review of the interpretation and assessment of the Pap smear results in pregnant women to strengthen the knowledge and enhance the guidance of the Obstetrician & Gynecologist in routine clinical practice.

Study Selection

We included clinical trials describing the Pap smear procedure for screening in pregnancy, an assessment of the results in pregnant women, and a comparison between the prepartum and postpartum periods. Regardless of the article type, all studies referring to Pap smear use in pregnancy, cohort studies, and case reports were eligible for inclusion, too.

Studies referring to the therapy of cervical cancer based on the diagnosis via Pap smear during pregnancy and those referring to Pap smear in non-pregnant women were excluded.

The quality of the included studies was assessed according to (1) the evaluation of Pap smear results with standardized and validated worldwide classification rules compared to informal assessment and (2) the follow-up of an abnormal Pap smear result regarding the national guidelines. We have also taken into consideration the study protocols of included clinical trials and their validity, as well.

prepartum and postpartum period. To be more specific, the main topics of the included studies focused on 1) cytology changes of the cervix in pregnant women, 2) comparisons and suggestions between a variety of sampling devices, 3) the value in bacterial vaginosis diagnosis, and 4) evaluation of abnormal pap smear results. The characteristics of the included studies are shown in **Table 1**.

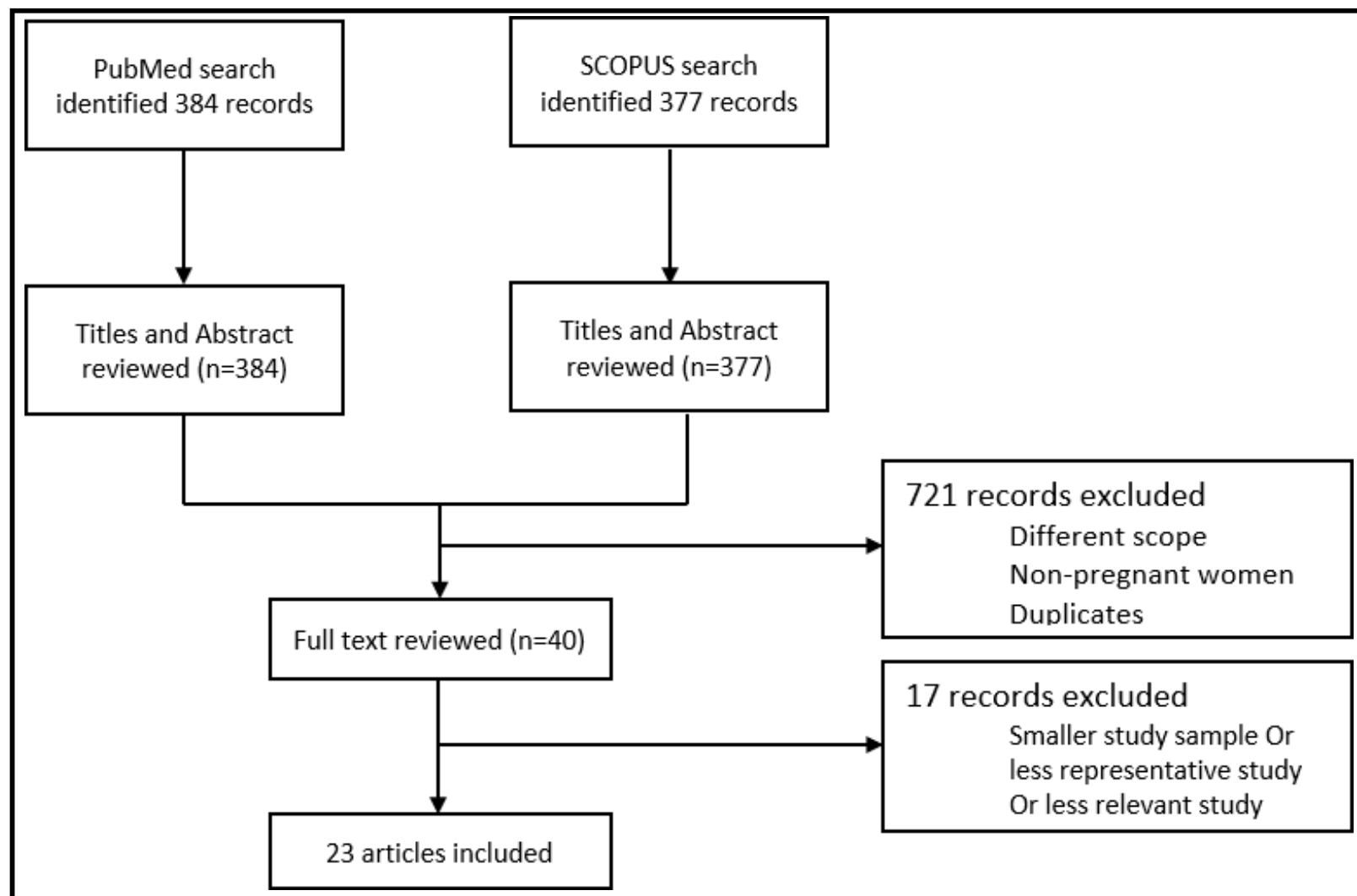


Figure 1. Flow diagram for the selection of included studies.

Table 1. Characteristics of included studies.

First Author (Reference)	Title	Year of Publication	Study Design	Purpose	Population
Sharon Bond [5]	Caring for Women with Abnormal Papanicolaou Tests During Pregnancy	2009	Review	Review guidelines and management strategies for abnormal Pap smear results	Pregnant women
Buchmayer Susanne [25]	Signs of infection in Pap smears and risk of adverse pregnancy outcome	2003	Cohort Study	Investigate the association between signs of infection in Pap smear results and adverse pregnancy outcomes	60,296 women with singleton births in 2 cities of Sweden, who had had Pap smear taken in pregnancy
Yang Y. Kathleen [10]	Abnormal Pap Smear and Cervical Cancer in Pregnancy	2012	Review	Summarize the management of cervical dysplasia and cervical cancer in pregnant women	Case series of pregnant women
Dinc Ayten [3]	Pap Smear Screening Results for Turkish Pregnant Women	2012	Clinical Trial	Evaluate the results of Pap smear screening during pregnancy for prevention of cancer	110 Turkish pregnant women vs 86 Turkish non-pregnant women
Slama J. [13]	Outcomes of pregnant patients with Pap smears classified as atypical glandular cells	2011	Clinical Trial	Evaluate the outcome of patients with AGC diagnosed from Pap smears during pregnancy	17 pregnant women with AGC in Pap smears vs 31 pregnant women with HSIL in Pap smears
Lertcharernrit Jiraporn [24]	Prevalence and Risk Assessment of Cervical Cancer Screening by Papanicolaou Smear and Visual Inspection with Acetic Acid for Pregnant Women at a Thai Provincial Hospital	2016	Clinical Trial	Identify the prevalence of abnormal Pap smears and lesions with VIA in pregnant women and assess risk factors	414 pregnant women between 12-36 gestational weeks in Thailand

Suzuki Kazuhiro [18]	Comparing Papanicolaou test results obtained during pregnancy and post-partum	2017	Retrospective Study	Results of Pap smear taken during pregnancy vs Pap smear in the post-partum	1213 women from January 2010 to December 2014
Dunn Terry S. [8]	Management of the Minimally Abnormal Papanicolaou Smear in Pregnancy	2001	Cohort Study	Evaluate colposcopy in pregnant women with minimally abnormal Pap smear results	200 pregnant women from July 1997 to January 1999
Greene III John F. [9]	The papanicolaou smear: inadequate screening test for bacterial vaginosis during pregnancy	2000	Review	Evaluate Pap smear ability to identify Bacterial Vaginosis	159 pregnant women screened for BV with Amstel criteria
Michael Claire W. [1]	The Papanicolaou Smear and the Obstetric Patient: A Simple Test with Great Benefits	1999	Review	Present information for Pap smear on the obstetric patient	Studies referring to Pregnant women
Chhieng David C. [35]	Significance of AGUS Pap Smears in Pregnant and Postpartum Women	2000	Retrospective Study	Clinical significance of AGUS in pregnant and post-partum women	30 pregnant women and 5 women at post-partum period with AGUS
Holt Jim [27]	Should a nylon brush be used for Pap smears from pregnant women?	2005	Clinical Inquiry	Evaluate Nylon Brush use for Pap smear during pregnancy	Studies including pregnant women
Stonehocker Jody [30]	Cervical Cancer Screening in Pregnancy	2013	Review	Review guidelines and management of abnormal cervical cytology and cervical cancer in pregnancy	Pregnant women
Foster Joyce C. [26]	Use of the Cytobrush for Papanicolaou smear screens in pregnant women	1996	Randomized Clinical Trial	Safety and Efficacy of Cytobrush for Pap smear screening during pregnancy	252 pregnant women
Paraiso M F [28]	Evaluation of the Endocervical Cytobrush and Cervex-Brush in pregnant women	1994	Clinical Trial	Comparison of Pap smear collection techniques and association with adverse pregnancy outcomes	352 pregnant women
Cannon J M [29]	Comparison of the Cytobrush plus plastic spatula with the Cervex Brush for obtaining endocervical cells	1993	Comparative Study	Comparison Pap smear techniques	309 smears (1/3 on pregnant women)
Wetta Luisa A [31]	The management of cervical intraepithelial neoplasia during pregnancy; is colposcopy necessary?	2009	Retrospective Study	Determine the incidence of CIN 2,3 in pregnant patients	625 Pregnant women with Abnormal cytology
Fan Ling [32]	Factors associated with abnormal cervical cytology in pregnant women	2010	Retrospective Study	Investigate risk factors for abnormal cervical cytology in pregnant women	11,906 pregnant women
Kaplan Keith J. [33]	Prognosis and recurrence risk for patients with cervical squamous intraepithelial lesions diagnosed during pregnancy	2004	Review	Examine the prognosis and recurrence risk for SILs diagnosed during pregnancy	157 women with SILs
Jain Astrid G [34]	Management of low grade squamous intraepithelial lesions during pregnancy	1997	Review	Determine the value of colposcopy in pregnant women with squamous atypia, ASCUS, LSIL	253 pregnant women
Perkins Rebecca B [36]	2019 ASCCP Risk-based management consensus guidelines for abnormal cervical cancer screening test and cancer precursors	2020	Guidelines	Consensus guidelines for management of cervical cancer screening abnormalities	NA

Nelson Erin [37]	Management of Abnormal cancer screening tests in pregnancy	2021	Guidelines	Management of abnormal Pap smear results during pregnancy	NA
Neumann Kay [38]	Introducing a new scoring system for pap smear in the detection of high-grade squamous intraepithelial lesions in pregnancy (The Luebeck Score)	2016	Cohort Study	Create a scoring system for Pap smear results appraisal and interpretation	Pap smear results (n=24 in pregnant women, n=28 in non-pregnant women)

Alterations of Cervical Cytology in Pregnancy and Pap smear

A hormonal environment induced by pregnancy causes various changes in the cervix, leading to a potentially ambiguous diagnostic accuracy on Pap smear results [10,13,18]. Firstly, the cervix area shows increased vascularity, and taking a pap smear may easier result in bleeding than in non-pregnant women. Secondly, cervical glands become hypertrophic and hyperplastic, which increases with the progress of gestational age. The proliferative endocervical tissue is either extended or everted; thus, the transition zone is more apparent compared to non-pregnant women, though this is not common in nulliparous women. Moreover, the squamocolumnar junction is visible after 20 gestational weeks in pregnant women, explaining, in some cases, the inability to see the entire transition zone early in pregnancy [24]. However, some cell types originated from the endometrium, identical to pregnancy, including the Arias-Stella reaction and trophoblastic cells [13,24]. These cells' microscopic image could mimic HSIL (High-grade Squamous Intraepithelial lesion) due to its enlarged nucleus and variably staining cytoplasm, leading to a confusing false positive Pap smear [24].

Cell degeneration and increased cervix secretions during pregnancy could result in inappropriate Pap smear samples, but endocervical cells in Pap smear results indicate that the transformation zone was adequately sampled [5]. On the contrary, the hormonal environment in the postpartum period is similar to non-pregnant women. Therefore, a postpartum Pap smear result can be more accurate [18], but this does not signify that Pap smear result during pregnancy is unreliable and should be used as a prenatal screening test [3].

Pregnancy and Pap smear sampling devices

Over the years, various devices have been used to obtain endocervical cell samples for Pap smears. The most commonly used appliances in the clinical routine are Ayre spatula, Cytobrush, and Cervex-brush. These devices were widely tested for efficacy and safety in non-pregnant populations by the time they were first introduced. However, only a few pregnant women were included in these studies [26,27]. The manufacturer of Cytobrush advised not to use the device after 10 gestational weeks [27]. Further studies were conducted to verify the safety of these devices during pregnancy, with data that indicates the same recommendations made for the general population [26,27]. In addition, there was an increased incidence of spotting with each device in pregnant women, compared to non-pregnant women, without being clinically significant [26,27].

The combination of Ayre plus Cytobrush and the Cervex-brush are the most suitable devices for Pap smear performance during pregnancy [28,29]. Paraiso et al. [28] conducted a randomized clinical trial including 352 pregnant women and found no statistically significant difference between those two devices regarding the Pap smear sampling during pregnancy. Moreover, these devices were not associated with severe adverse outcomes. Finally, combining the Ayre spatula with Cytobrush during pregnancy is recommended to obtain an adequate sample of squamous and endocervical cells. [26-28].

Genital tract infections during pregnancy and Pap Smear

Genital tract infections are associated with adverse pregnancy outcomes such as preterm birth, small for gestational age, and stillbirth. It is questionable whether Pap smear results during pregnancy, indicating signs of infection, play a role in the incidence of adverse pregnancy outcomes [25]. Therefore, it is also essential to evaluate the reliability of a Pap smear in diagnosing BV in pregnant women.

Greene et al. [9] compared Pap smear results for the diagnosis of BV in pregnancy to results for the clinical diagnosis of BV, scored by using Amstel Criteria as a control group. The sensitivity and specificity of the Pap smear for BV diagnosis in pregnant women were 49% and 93% based on Greene et al. [9], respectively. In this study, the false negative ratio was 74%, concluding that using a Pap smear screening test in diagnosing BV in pregnancy is unreliable [9]. Another cohort study by S. Buchmayer et al. [25] investigated the association between Pap smear results and inflammation and adverse pregnancy outcomes. The Pap smear results in this study included: inflammation, trichomonas vaginalis, coccobacilli, or fungus. The cohort study's preliminary results show that a decreased time between the Pap smear test and delivery is more likely to identify signs of inflammation in the smear result. The rate of smears with signs of infection increased with the progress of gestational age. S. Buchmayer et al. [25] found that the risk of very preterm birth increased with coccobacilli in a Pap smear taken within 4 weeks before delivery. They also associated either Coccobacilli or Trichomonas vaginalis with increased incidence of SGA delivery. Nevertheless, the fact that a Pap smear with signs of infection predicts the risk of various adverse obstetric outcomes (preterm delivery, SGA, or antepartum death) cannot be generalized [25]. In addition,

several studies in the past recommended that a Pap smear has at least an equal value identifying BV compared to Gram stain use [1,25].

The vaginal origin of BV suggests that Pap smear sensitivity in the diagnosis of BV will be enhanced if a well-performed vaginal component is added to the cervical smear of pregnant women [1,9]. However, few studies have been identified in the literature investigating the Pap smear diagnostic value for BV during pregnancy. These studies conclude that it is unreliable. Due to limitations in sample size or the period the Pap smear was performed, further studies should be conducted to draw safe conclusions.

Pap smear and Abnormal Results

HPV is a sexually transmitted infection that constitutes the leading cause of Cervical Cancer [24,30]. Various parameters, including the hormone level change and the immunosuppressed status during pregnancy, are supposed to affect the incidence of HPV infection, as identified by Lertcharernrit et al. [24] in their study. These rates are 18 % in pregnant women compared to approximately 6 % in non-pregnant in the previous study [24]. On the contrary, another study by Stonehoker [30] suggests that despite its immunosuppressive status, pregnancy does not affect the progress or the prevalence of HPV infection. Nevertheless, HPV infection is still the leading cause of cervical cancer in pregnancy. Finally, up-to-date sources report that pregnancy does not seem to alternate either the HPV or the natural cancer history [36,37]. The rates of HPV progression to cancer are similar between pregnant and non-pregnant women [37].

Several studies have evaluated abnormal Pap smear results during pregnancy, which is of great scientific interest [3,10,31-35]. Dinc [3], in his research, found that almost 1 % of pregnant women have ASCUS (Atypical Squamous Cells of Undetermined Significance) in the pap smear results. In another study, which included 11,906 pregnant women, Fan et al. [32] found that 9,52 % had ASCUS, 0,94 % had AGUS (Atypical Glandular cells of Undetermined Significance), 1,92 %, and 0,62 % had LSIL (Low-grade Squamous Intraepithelial Lesion) or HSIL (High-grade Squamous Intraepithelial Lesion), respectively. Another study found that AGUS incidence in pregnancy and postpartum was 0.26 %, lower than the general population included in their study [35]. A survey conducted by Wetta et al. [31] showed that 25,6 % of women with ASCUS or LSIL in smear results had CIN2 (Cervical Intraepithelial Lesion 2) or CIN3 (Cervical Intraepithelial Lesion 3) on biopsy, while others found a lower rate approximately 10 % [34]. In addition, Kaplan et al. [33] found that 62 % of pregnant women with LSIL regressed postpartum, 32 % of the cases remained stable, and 6 % progressed to HSIL postpartum, respectively. Another study showed that 65 % of

pregnant women with LSIL remained stable, and 3 % went to HSIL postpartum [34]. Both studies conclude that none of their cases progressed to invasive cancer [33,34]. Finally, Suzuki et al. [18], in their research, supported that 66,7 % of their patients with ASCUS or LSIL regressed in the postpartum period. Although, 25 % of pregnant women with HSIL reverted, and 75 % remained stable [18]. Most of the cases in the previous studies either regressed or remained stable during the pregnancy and postpartum follow-up [10,33,34].

In their study, Neumann et al. [38] support that a more systematic approach and assessment of pap smears utilizing the "Luebeck Score" shows good quality in detecting HSIL, especially during pregnancy. This scoring system assesses six parameters, which recommend well-known criteria associated with malignancies or dysplastic lesions such as polymorphology of cells, anisonucleosis, nucleus structure, tissue destruction, Nucleus/plasma ratio, and signs of tumor diathesis [38]. Neumann et al. [38] suggest that the "Luebeck Score" could help interpret complex pap smears, reduce the number of false negative results and avoid discrepancies in the evaluation of pap smear results between different clinicians. Nevertheless, further studies are needed to evaluate the "Luebeck Score" accuracy [38].

Regarding the Management of abnormal Pap smear results during pregnancy, ASCCP recommends following the same guidelines established for non-pregnant women [36]. Although, there are some things in which pregnant women differentiate from the general population. In particular, endocervical curettage, endometrial biopsy, or treatment without biopsy are contraindicated during pregnancy [30,36]. Thus, Colposcopy is the only acceptable method for evaluating AGC in pregnant women [13,30]. For pregnant women with HSIL, the follow-up utilizing Colposcopy and testing (Pap smear or HPV-DNA, depending on age) is advised to be conducted every 12-24 weeks.

Nevertheless, it is acceptable if the Colposcopy is deferred to the postpartum period. Treatment for HSIL is not recommended during pregnancy [30,36]. If the clinician suspects cancer, he should repeat the biopsy or conduct a diagnostic excision. Moreover, if the lesion appearance is getting worse or looks like invasive cancer, a biopsy should be repeated, as well. The Colposcopy in the postpartum period should be conducted no sooner than 4 weeks after the delivery. A well-experienced Colposcopist is more suitable to evaluate a pregnant patient, mainly because of the cervix changes during pregnancy as previously described. In some cases, it would be difficult to distinguish cancer from these changes, which may lead to confusion and misinterpretation of the results [13,36].

Discussion and Conclusion

Pap smear is a worldwide known screening test for cervical cancer and should be a routine at the first prenatal visit of a pregnant woman to an Obstetrician & Gynecologist, which is of great significance if she has never had one before [4,5,10]. A combination of Cytobrush

plus Ayres spatula is recommended for performing Pap smear during pregnancy, mainly because it is likely to obtain an adequate cell yield compared to Cervex-brush [26-28]. Nevertheless, those devices do not have a statistically significant difference [28]. Moreover, various

changes occur in the pregnant cervix due to pregnancy-related hormone changes and immunosuppression [18,24].

Existing data for Pap smear use in the diagnosis of BV and its correlation to adverse pregnancy outcomes suggest that it is not reliable in general and further studies should be conducted. Assessment and Management of abnormal cytology Pap smear results during pregnancy is challenging. Most studies found that most minimally abnormal Pap smear results (ASCUS, LSIL, HSIL) regress during pregnancy or postpartum, and none of these cases progressed to invasive cancer [33,34]. Overall, Obstetricians & Gynecologists should follow the ASCCP guidelines published for the non-pregnant population regarding the Management of abnormal Pap smears during

pregnancy [36]. However, endocervical curettage, endometrial biopsy, and treatment without biopsy are contraindicated in pregnancy. HSIL treatment in pregnancy is not recommended [30,36]. Colposcopy and guided biopsy are safe, but these should be performed by an experienced colposcopist [13,18,36].

In conclusion, considering all studies that examined, compared, and evaluated Pap smear results during pregnancy and postpartum; Pap smear is more accurate during the postpartum period, performed no sooner than 4 weeks after delivery. This statement should not be interpreted as the unreliability of Pap smear results achieved during pregnancy, which should be the possible reference result used as the control group.

Contributors: All authors had the original idea for this review, conducted the literature search and drafted the manuscript. All authors revised and approved the manuscript. GM is the guarantor.

Abbreviations: AGC: Atypical Glandular Cells; AGUS: Atypical Glandular cells of Undetermined Significance; ASCUS: Atypical Squamous Cells of Undetermined Significance; CIN: Cervical

Intraepithelial Neoplasia; LSIL: Low grade Squamous Intraepithelial Lesion; NA: Not Applicable; SILs: Squamous Intraepithelial Lesions; VIA: Visual Inception with Acetic Acid

Funding: We have not received a grant for this research from any funding agency.

Conflicts of Interest: None declared.

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