RELIABILITY OF COLPOSCOPY DURING PREGNANCY

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ABSTRACT

The high specificity of colposcopy in pregnancy for the diagnosis of invasive carcinoma allows selecting with reasonable certainty patients to be subjected to diagnostic excision in case of suspected colposcopic invasion (low rate of false positives). However, sensitivity values may impose the need to target patients with high-grade colposcopy to target biopsy, to avoid the risk of non-diagnosis of invasive carcinoma (false colposcopy negative). Colposcopy is a reliable diagnostic tool, especially in the first half of pregnancy. After the 20th week of gestation, the accuracy and reliability of colposcopy are reduced, hence these patients should be cautiously evaluated, considering a higher risk of colposcopic underestimation of the lesions. However, regardless of the gestational age, each pregnant woman with abnormal cervical cytology should be evaluated by experienced colposcopists.

KEYWORDS: colposcopy, pregnancy.

INTRODUCTION

Squamocellular cervical cancer (SCC) is the most common gynecological neoplasia occurring during pregnancy, with an estimated incidence ranging from 1 per 1,200 to 1 per 10,000 pregnancies.[1]

About 30% of women diagnosed with cervical cancer are in reproductive age, and approximately 3% of cervical cancers are diagnosed during pregnancy.

In addition, the peak incidence of high grade cervical intraepithelial neoplasia (CIN) is between 25 and 35 years old, the same decade in which most pregnancies occur.[2] However, the natural history of CIN seems not to be influenced by the pregnancy itself and most of CIN regresses or persists after delivery.[3]

In women with biopsy proven CIN2 during pregnancy, the risk of microinvasive cancer at the postpartum visit is negligible, whereas the risk after CIN3 is less than 10% and deeply invasive cancers are very rare.[4] For these reasons, the treatment of high grade CIN is contraindicated during pregnancy, since excisional procedures can result in a fetal loss, preterm delivery or maternal hemorrhages.[5] During pregnancy, the only diagnosis that may alter management is invasive cancer. Thus, the primary aim of the cytological screening and subsequent colposcopy performed during pregnancy should be the exclusion of invasive cancer.[6]

According to the current guidelines, all pregnant women in which a recent cervical cancer screening test is not available, are recommended to perform the test and, if abnormal, a colposcopy.[7] However, in most of the cases, the optimal phase of the pregnancy in which to perform the colposcopy is not clearly defined. Some authors recommend performing the cytological screening and the colposcopy in the first trimester or early in the second trimester.[8]

Indeed, the modification of the hormonal milieu occurring during pregnancy could influence the interpretation of pap smears, especially when performed in the second half of pregnancy, determining a high rate of falsely positive results.[9] Furthermore, the pregnancy-related hormonal changes seem to affect not only the pap smears evaluation but also the diagnostic accuracy of colposcopy.[10] On the other hand, after 20 weeks of gestation the endocervical mucosa everts and the squamo-columnar junction may become visible, making the colposcopic evaluation easier.[11] In non-pregnant women, colposcopy is an accurate diagnostic tool, and a reliable correlation between the colposcopic impression and the histopathological diagnosis on biopsy (colposcopic accuracy) can be observed in most of the cases.[12]

More precisely, the detection rates of colposcopy currently reported in the literature are: 68% for CIN1, 73.3% for CIN2, 81.4% for CIN3 and 88.9% for invasive cancer.[13] Furthermore, the reported overall sensitivity, specificity, positive predictive value and negative predictive value of colposcopy are 92%, 67%, 52% and 96%, respectively.[14]

During pregnancy, the reliability of colposcopy is debated. Colposcopy during pregnancy is challenging, mostly because of cervical hyperemia, hyperplasia of endocervical glands with mucus overproduction, prolapsing vaginal walls and contact bleeding.[15]

In addition, the development of prominent normal epithelial changes can mimic the appearance of the preinvasive disease.[16] Hence the management of an abnormal pap smear in pregnant women should be performed by gynaecologists with expertise.[17] The aim of the present study was to investigate the reliability of colposcopy during pregnancy and the concordance between colposcopic in women.

BACK GROUND

Colposcopy and pregnancy

The physiological changes of pregnancy (with the increased rate of squamous metaplasia, the increase in vascularity and the changes in the size and shape of the cervix) together conspire to make both cytological interpretation and colposcopic assessment a particular challenge.[18]

Benign lesions may appear to be suspicious of abnormality, but simply represent deciduosis, whereas active squamous metaplasia may be associated with a fine mosaic or punctuate surface pattern that may be indistinguishable from a low-grade cervical intraepithelial neoplasia (CIN).[19]

An awareness of this is reflected in the National Health Service Cervical Screening Programme guidance for management: In countries in which routine screening is not available, however, opportunistic screening, whether by cytology or visual inspection of the cervix, with acetic acid may be of value.[20]

Although colposcopy is a safe and effective method of evaluating abnormal cytology, carrying it out in pregnancy may produce particular technical challenges. The vaginal walls are often lax, and there may be vulval and vaginal varicosities. On examination it is recommended that a large speculum is used.[21] To keep the vaginal walls apart, a latex glove with the tip of the finger portion removed may be inserted in order to cover the speculum blades. It is then opened once inserted into the vagina[22] condom instead of the finger of a glove may also be used**.**

The value of colposcopy in pregnancy

The aim of colposcopy during pregnancy is to exclude malignancy. Paraskevaidis et al.2 investigated the evolution of CIN and evaluated the safety of cytological and colposcopic surveillance of women with CIN during pregnancy.[23]

Ninety-eight women with the antenatal cytological, colposcopic impression of CIN, or both, were followed up during pregnancy with cytology and colposcopy every 2 months.

A cytological and colposcopic re-evaluation 2 months postpartum was carried out, and large loop excision of the transformation zone (LLETZ) (or loop electrosurgical excision procedure as it is known in North America), carried out if appropriate. Punch or loop biopsies were only taken in pregnancy if micro-invasion was suspected.[24]

In 14 out of 39 (35.9%) and in 25 out of 52 (48.1%) women with an antenatal impression of CIN I and CIN 2 and 3, respectively, a postnatal impression of regression was evident. Seven women with findings suspicious of micro-invasion underwent small loop biopsies during pregnancy, but early stromal invasion (< 1 mm) was seen in just one case. One more case of micro-invasion (1.5 mm of stromal invasion) was diagnosed postnatally in which the antenatal impression was of CIN 3.[25] The investigators concluded that a considerable regression rate of CIN occurs after pregnancy, possibly attributable to the loss of the dysplastic cervical epithelium during cervical 'ripening' and vaginal delivery. However, without biopsy confirmation of the epithelial abnormality in pregnancy, and with the possibility of an over-call of cytological features in the pregnancy smear, the true regression rates may have been overestimated. In concordance with other earlier studies, the investigators concluded that frequent cytological and colposcopic evaluation seemed to be safe, and small loop biopsies are recommended for tissue diagnosis in suspected cases of possible micro-invasion.[26]

METHODS

This is a multicenter observational study of pregnant women diagnosed with abnormal cervical cytology, who subsequently underwent a colposcopy with cervical biopsy.

All the pregnant women with abnormal cervical cytology underwent a colposcopy, as recommended by the most recent international guidelines[27]; all the colposcopies were performed by gynecologists with expertise in diagnosis and management of lower genital tract intraepithelial lesions. All the colposcopic examinations were recorded accordingly to the 2011 revised colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy (IFCPC).[28] Fine mosaic; fine punctuation and thin acetowhite epithelium were considered as "grade I abnormal colposcopic findings" (minor) while dense acetowhite epithelium; coarse mosaic; coarse punctuation; rapid appearance of

acetowhitening; cuffed crypt (gland) openings; sharp border; inner border sign and ridge sign were considered as "grade II abnormal colposcopic findings" (major).[29] The detection of atypical vessels and/or additional signs such as fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration characterized a "suspicious for invasion" colposcopy.[30]

For the present analysis, only pregnant women who underwent a colposcopy-guided biopsy were considered. The biopsies were performed only on areas with abnormal colposcopic findings and random biopsies were not performed. In case of wide lesions, multiple biopsies were taken and in case of different histopathological results (e.g CIN1 in one sample and CIN2 in the other), the worse result (and the relative colposcopic pattern of the biopsied area) were considered for the analysis.

Exclusion criteria were inadequate colposcopy and current HIV infection or immunodepression (e.g. ongoing immunosuppressive therapies). Cases with a concomitant high grade vaginal intraepithelial lesion or vaginal cancer were excluded as well.

RESULTS

During the study period, 67 women were diagnosed with an abnormal PAP smear during pregnancy in the institutions involved, and subsequently underwent a colposcopy.

Among them, 10 women were excluded from the present analysis: 13 were excluded because patients refused the biopsy; 5 because of an inadequate colposcopy. The remaining 35 women, fulfilling the study inclusion/exclusion criteria, constituted the study cohort.

Abnormalities on referral cytology while the remaining 14 women had "lesser cytological abnormalities". In the study cohort, no case of AGC on the referral pap smear was observed.

Considering the colposcopic examination, 4 women showed "grade I abnormal colposcopic findings", 12 showed "grade II abnormal colposcopic findings" and the remaining 5 women had a "suspicious for invasion" colposcopy. No case of "normal transformation zone" was detected.

The baseline clinical, cytological and histopathological characteristics of the study cohort.

At inclusion, the mean (±SD) age of the entire study cohort was 31.1 (±4.6) years (range 22-42). Comparing women with grade I and grade II colposcopic findings, no significant difference in the mean age was found (29.6 ± 5.7 vs 31.4 ± 4.3, p=0.20).

The mean (±SD) gestational age of the entire study population was 17.5 ± 6.4 weeks.

In women with gestational age ≤ 20 weeks (n= 13), 10 cases of "grade I abnormal colposcopic findings", 10 cases of "grade II abnormal colposcopic findings" and 2 cases of "suspicious for invasion" colposcopy were found.

In women with a gestational age > 20 weeks (n= 18), 4 cases of "grade I abnormal colposcopic findings" and 14 cases of "grade II abnormal colposcopic findings" were found.

In women with a gestational age > or ≤ 20 week, no significant difference in the rate of "grade II abnormal colposcopic findings" (77.8% vs 74.5%, p = 0.969) and in the rate of "grade I abnormal colposcopic findings" (22.4% vs 19.6%, P = 0.930) emerged.

Data about the performance of colposcopy in the diagnosis of invasive carcinoma (sensibility, specificity, positive and negative predictive values - PPV and NPV respectively).

The outcome of colposcopy and the histopathological findings of the 5 patients who underwent an excisional treatment during pregnancy are reported: in two cases the final diagnosis was CIN 3, although the biopsy showed the suspicion of invasive carcinoma.

Data about the agreement between colposcopy and guided biopsy (Cohen's weighted kappa) and the rates of colpo-histopathological concordance are reported.

Considering the gestational age (≤ 20 weeks vs > 20 weeks of gestation), we found a better agreement between colposcopy and guided biopsy (K= 0.65; CI 0.42-0.87) in women ≤ 20 weeks pregnant and when colposcopy was performed in the firsts two trimesters of pregnancy (K= 0.56 and K=0.62, respectively). No difference in the colposcopic overestimation or underestimation was found respect to the gestational age.

As a secondary analysis, in the present study we evaluated the potential concordance between the referral pap smear and the histopathological diagnosis, finding an overall "cyto-histopathological concordance" in 12 cases, with a cytological underestimation in 8 cases and a cytological overestimation in 15 cases. In the whole study cohort, we found a moderate agreement (K= 0.29; CI 0.06 – 0.52) between cytology and histopathological analysis performed during pregnancy.

DISCUSSION

This study showed that the follow-up of atypical smears during pregnancy, including colposcopy, is a safe approach. It does appear that the reliability of both colposcopic diagnoses made by a skilled colposcopist was not significantly altered by the physiological changes observed in the cervix during pregnancy.

The cervical smear is an effective screening test but it often fails to give the precise diagnosis of a lesion.[31]

In our study, cytology tended to underestimate the final diagnosis in 20.5°/0 of pregnant patients and to overestimate it in 24.0%. Other authors have reported similar rates.[32] Therefore, the suggestion that pregnant women with an abnormal smear should be monitored with repeated smears[33] seems to be unwarranted. According to our results, every woman with an abnormal smear during pregnancy should be referred for colposcopy.

In our study, the colposcopic impression obtained during pregnancy was in complete agreement with the final diagnosis in 72.6% of patients and, not surprisingly, overestimation was more frequent than underestimation. Similar colposcopic results have already been reported.[34]

Despite the tendency with colposeopy to overestimate physiological changes in pregnant patients more often than in controls, the reliability of colposeopic diagnosis was not significantly different between the two groups. The modifications of cervical colposeopic appearance during pregnancy are well known. Their intensity varies with individuals and parity.[35]

The increased vaseularity of the cervix exaggerates the reaction of the immature metaplastic epithelium to acetic acid and produces a confusing angioarchitecture which may give a suspicious aspect and mimic severe lesions.[36] Therefore, even an experienced eolposcopist may overestimate some physiological changes or, conversely, overlook a lesion.[37]

Some authors have reported false negatives in the antepartum colposeopic assessment of malignancy.[38] In a survey including 73 patients, Nahhas et al.[39] failed to diagnose the single case of invasive carcinoma, because of an antepartum colposcopic impression consistent with low-grade CIN. Benedet et al.[40] Reported that in five out of nine patients, the

diagnosis of invasive carcinoma was not made during pregnancy, because of an antepartum colposcopic impression consistent with carcinoma in situ.

In a review of the literature on the colposcopic management of abnormal cervical cytology in pregnancy[41] only 17 out of 25 (68%) patients with invasive cervical cancer had a suggestive anteparturn colposeopic impression. Colposcopy predicts micro-invasion more accurately when the depth of invasion increases.[42]

Thus, overlooking invasive lesions at the time of antepartum colposcopy is thought to be due to the fact that some lesions may not display a pattern sufficiently specific to enable identification[43]. For this reason, we believe that a biopsy should be performed in most pregnant patients.

This study, as with previous ones, indicates that a directed biopsy may be carried out with very minimal risks to both mother and fetus.[44]

For that reason, proper management of abnormal pap smear during pregnancy is mandatory. The current guidelines recommend a colposcopic evaluation and, if necessary, a biopsy.[45]

More precisely, the primary aim of colposcopy during pregnancy should be the exclusion of invasive cancer. Therefore, limiting biopsy to lesion suspicious for high grade CIN or cancer is preferred, but a biopsy of any lesion is acceptable.[46] Interestingly, biopsy during pregnancy has not been linked to fetal loss, preterm delivery or other obstetric complications, whereas failure to perform biopsies during pregnancy has been linked to missed invasive cancer.[47]

However, the colposcopic evaluation of pregnant women is challenging because of several pregnancy-induced modifications that can alter the cervical appearance: cervical hyperemia, hyperplasia of endocervical glands with mucus overproduction, prolapsing vaginal walls and contact bleeding are typical in pregnancy.[48]

In addition, the development of prominent normal epithelial changes can mimic the appearance of the preinvasive disease.[49] Therefore, the reliability of colposcopy during pregnancy is debated. Previous studies evaluated the reliability of colposcopy in pregnant women, even with a comparison to non-pregnant controls.[50]

Baldauf et al, reported a "colpo-histopathological concordance" of 72.6 %, with an overestimation and underestimation rate of 17.6% and 9.8%, respectively. Interestingly, the "colpo-histopathological concordance" appeared not to be influenced by the pregnancy status.[51]

However, data reported by Baldauf are related to the biopsy performed after delivery (post-partum follow-up) with the risk of bias linked to the spontaneous progression/regression of the lesions. The study of Fader et al.[52] reported a "colpo-histopathological concordance" of 62.9 % but the colposcopic impression was not inflrnced by the the gestational age.

These findings highlight the importance of a cytological screening assessment with eventual, subsequent colposcopic evaluation, as soon as possible during pregnancy.

The lower reliability of colposcopy and the theoretically higher risk of bleeding after the 20th week of gestation, suggest the opportunity to perform the cervical biopsy in the first half of pregnancy.

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