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Cervical Intraepithelial Neoplasia (CIN) in pregnancy: the state of the art

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Abstract. – OBJECTIVES: Cervical cancer is the most commonly diagnosed malignancy in pregnancy and cervical screening should be accordingly performed in this particular situation. Occurrence of a preneoplastic cervical disease in pregnancy has for a long time represented a challenge for the clinician, both in terms of diagnostic accuracy, treatment options and risk of obstetrical complications. For these reasons, lack of uniformity in diagnosis and management is still commonly observed and the need for evidence-based clarifications is strongly required. Consistently with the literature evidences and accordingly with international guidelines, this review aim to overview the most significant aspects of the issue and trace simple and practical indications for an evidence-based correct workout and management of these conditions.

MATERIALS AND METHODS: The most significative and focused-on results from literature as well as recent international guidelines have been considered and summarized in order to clarify the key-points of the topic; epidemiology, pathophysiology, natural history, treatment modalities and procedure-related risks have been approached and discussed.

RESULTS: Risk factors, prevalence and progression rate of cervical intraepithelial neoplasia in pregnancy are comparable to those observed in non-pregnant patients; thus, pregnancy does not have to be considered a condition at higher risk. Cytology, histology and colposcopic patterns must be evaluated by experienced professionals because of pregnancy-induced modifications that can lead to misinterpretations. Each diagnostic step should be directed to exclusion of invasive cervical cancer.

CONCLUSIONS: Once invasive cancer has been excluded through a comprehensive diagnostic workout, treatment of cervical intraepithelial neoplasia can be safely deferred after delivery.

Key Words:
CIN, Screening, Cervical Intraepithelial Neoplasia, Pregnancy, Guidelines.

Introduction

Cancers of the female genital tract are the most common malignancies encountered during pregnancy. Among them, cervical cancer is the most frequent one, accounting for almost 70% of genital tract neoplasia[1-3]. It is estimated that it occurs in 1.5-12 of every 100,000 pregnancies[4] and that an overall 3% of cases of newly diagnosed cervical cancer occurs in pregnant women[5]. The direct precursor of cervical cancer is represented by Cervical Intraepithelial Neoplasia (CIN), that is usually detected and managed through the Papanicolaou (Pap) test cytological screening and/or high-risk Human Papillomavirus (hr-HPV) DNA testing. The incidence of abnormal cervical cytology during pregnancy is at least as high as that reported for non-pregnant women. As matter of fact, almost 1% of the population of childbearing women annually screened for cervical cancer will be diagnosed with CIN of various degrees[6]. Thus, it is strongly recommended that all pregnant patients undergo cervical screening at the time of their initial prenatal visit, as pregnancy can represent a unique opportunity to approach otherwise unscreened women[7,8]. The age group at highest risk for the development of CIN and/or cervical cancer is 30-40 years[9-12]. Thus, cervical cytology is strongly recommended especially in women older than 25 years-old or sexually active from more than 3 years[13]. Moreover, cervical cancer screening at the moment of initial pregnancy very often also provides an important chance to screen for premalignant and malignant cervical disease women who do not seek or do not have access to routine healthcare facilities and organized screening programs[7,8]. For a long time, pregnancy has represented a sort of "not-written contraindication" towards any kind of procedures to be performed on the uterine cervix, as the gestational state has widely been seen as a particularly weak

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condition and exposed to complications for pregnant women. Heavy bleeding, infections and even the risk of miscarriage have represented the major worries that have significantly reduced any diagnostic procedure needed on the cervix. On the other hand, the incident diagnosis of a cervical preneoplastic disease in pregnancy has sometimes lead to the dramatic decision of pregnancy termination in view of the risk of progression to invasive cancer. In recent years, the natural history of cervical cancer precursors has been widely studied and reassuring evidence is available from literature data, so that these conditions in pregnancy have started to be approached in a different perspective. Nevertheless, the diagnosis and management of premalignant cervical lesions in pregnancy still represent a strong challenge for clinicians and patients and definitely deserve an extensive clarification. Actually, diagnosis and management clinical options for cervical dysplasia in pregnancy are not well defined worldwide and mainly take origin especially from data in non-pregnant women, expert opinions, anecdotal personal experiences or retrospective series of pregnant women. In this review we refer to the most recent updated consensus guidelines of international scientific societies and to large clinical trials results that studied women with abnormal cervical cancer screening in pregnancy. Our purpose is to summarize the current knowledge on the diagnosis and treatment of CIN in pregnancy, to highlight the key elements of the topic and to provide practical algorithms that will guide the clinical management of the childbearing patient affected by cervical dysplasia.

Human Papillomavirus (HPV) Infection in Pregnancy

Currently, the precise effects of pregnancy on HPV infection course are not fully known. In theory, the "paraphysiological" immunological tolerance that characterizes pregnancy may promote the infection or, at least, may reduce the immune system effectiveness in clearing the infection itself. In fact, immunosuppressed subjects are, in general, known to be at higher risk for HPV infection, HPV-correlated lesions onset and cervical cancer development[14,15]. On the other hand, an active host's immune response is demonstrated to be positively correlated with virus elimination and lesions regression[16,17] even in subjects treated with immunosuppressive drugs for transplanted organs control[18]. Consistently with these immunological aspects, some authors[19] found an increased incidence of high-risk subtypes (HPV types 16, 18, 31, 35, 45, 51, 52 and 56) when they compared pregnant with non-pregnant women. It was also described that younger mothers and those with higher parity had higher rates of HPV infections[7,20], while age of the patient of 25 years or more, HSILs, and HPV type-16 infections were significative risk factors for the progression or persistence of intraepithelial lesions of the cervix in the postpartum period[21]. Another large cohort population-based study compared pregnant healthy women and pregnant women with cervical cancer or CIN. Authors found that women with CIN were younger, while women with cancer tended to be older than healthy women, and that CIN or cervical cancer affected women tended to be of lower income brackets than healthy ones, and were more likely to be treated in urban teaching hospitals[9]. However, the vast majority of published data, comprising extensive meta-analysis of the last decades and longitudinal studies, all agree with the evidence that pregnancy does not represent an increased risk for HPV detection. The overall prevalence of HPV-DNA positivity detected in pregnant women does not significantly differ from the prevalence detected in non-pregnant matched controls[5], resulting in the evidence that pregnant women do not represent a high-risk subgroup of subjects for the development of HPV-correlated cervical intraepithelial lesions and HPV-related cervical cancer.

Diagnostic Procedures in Pregnancy

For the management of the abnormal Pap smears, colposcopy with targeted biopsy and histological examination of cervical abnormalities suspicious for dysplasia is the procedure of choice. However, it is important to note that in pregnant women the morphological alterations of the cervix and the maternal-fetal potential risks related to diagnostic and therapeutic procedures, require that the management of these patients being performed by experienced physicians.

Colposcopic Examination

The colposcopic appearance of the cervix changes greatly throughout pregnancy. On one hand, colposcopic evaluation is easier to be performed because the Squamo-Columnar Junction (SCJ) and the Transformation Zone (TZ) are better exposed due to the physiological eversion of the columnar pattern. On the other hand, oedema, cyanosis, friability, the increased pelvic conges-

tion of the cervix, and vaginal walls protrusion may determine objective limitations to colposcopic subjective interpretation. Moreover, copious thick mucus production is frequently observed, making the complete visualization of the cervix around the external os more difficult. It is important to use the largest (in width and depth) speculum a patient can tolerate and/or a vaginal sidewall retractor or a condom placed over the speculum and opened at the distal tip to obtain the optimal visualization. Cervical mucus is usually thick, opaque and tenacious and, sometimes, twisting it around a dry cotton swab may be useful. Despite these changes may markedly distort colposcopic findings, several authors suggested that the colposcopic appearance of cervical dysplasia do not appreciably differ between pregnant and non-pregnant women. Differently, other authors reported that pregnancy-induced modifications can overestimate the colposcopic lesion severity[22,23]. As matter of fact, as pregnancy progresses, decidualization of the stroma often becomes prominent, colposcopically appearing as densely aceto-whitening plaque-like lesions with spidery superficial blood vessels, often creating ring shaped aceto-whitening decidualized area surrounding normal capillaries, which causes a "starry sky" appearance. Also, the development of active immature metaplasia can promote thin aceto-whitening areas with fine mosaic and punctuation vessels, making these aspects particularly difficult to the unexperienced colposcopist to be distinguished from low grade intraepithelial lesions (LSIL).

If the colposcopic evaluation is unsatisfactory early in the gestation, it should be repeated in the second trimester[22] when a complete eversion of the SCJ and TZ are more likely to be detected. A ring forceps may be used in place of an endocervical speculum to dilate the external os and reach a complete visualization of the endocervical canal. If the TZ cannot be still entirely visualized, the risk of complications associated with a diagnostic conization must be balanced against the likelihood of an underlying malignancy[5].

Cervical Cytological and Pathological Changes

Several factors can complicate the sampling and analysis of cervical cytology in pregnancy. As regards cervical cytological sampling, some clinicians may be concerned about the use of the cytobrush for the Pap test collection. It was already previously reported that no difference in complications (including bleeding and spontaneous abortion) exists between the use of the cytobrush and the Dacron swab[24]. Thus, the use of the cytobrush (or comparable broom) for the collection of a prenatal Pap smear is widely accepted and recommended as safe. According to the cytological and pathological analysis, pregnancy-related hormonal changes can promote modifications in squamous and glandular epithelial cells, including hyperplasia and reactive atypia. Inflammation and endocervical gland hyperplasia and hypersecretory appearance (the Arias-Stella reaction) make the identification of atypical glandular cells on Pap smear and biopsies particularly difficult[25]; stromal decidualization results in large cells with large nuclei that may frequently be misinterpreted as dysplastic cells. Cytotrophoblast and syncytiotrophoblast cells and immature metaplastic cells may also be seen in the cytologic specimen, misleading to an inappropriate diagnosis of high-grade intraepithelial lesions (HSIL)[26]. Overall, the Papanicolaou test, both with conventional and liquid-based cytology, has demonstrated an equivalent diagnostic accuracy in pregnancy and in the non-pregnant patient[4], with a sensitivity for detecting HSILs between 70% and 80%[27,28].

Cervical Biopsy in Pregnancy

Although no evidence exists that performing a cervical biopsy of the pregnant patient is at higher risk compared to the non-pregnant patient[29,30], concerns over excessive or uncontrollable bleeding from the hyperemic and congested pregnant cervix, prevent many physicians from performing biopsies in such cases[4,24]. Actually, biopsies are only indicated when the results could potentially impact the patient's management options, such as lesions colposcopically suspicious for invasive cancer[31]. Some authors suggested to perform biopsies in the second trimester to avoid the potential association of the procedure with a spontaneous, unrelated, miscarriage, while others considered the use of a stiff brush as a biopsy substitute for a less invasive diagnosis[32]. To prevent excessive bleeding after biopsy has been taken, it is recommended to apply a prolonged pressure with a large swab and, in selected situations when bleeding persists, the use of a hemostatic preparation (e.g. Monsel's paste or silver nitrate) may be safely considered, taking care to use the smallest effective quantity because of the caustic effect of these substances. If bleeding is significantly excessive or still uncontrollable, electrosurgical cautery, fine suture or vaginal packing may be

considered. Despite these possible complications, adverse effects are unlikely to happen[5]. However, it should be cautioned that endocervical curettage (ECC) is strongly contraindicated in pregnant patients[31].

Natural History of CIN in Pregnancy

As far as it concerns the natural history of CIN in pregnancy, it has been diffusely demonstrated that the progression to invasive carcinoma is extremely rare, occurring between the 0% and the 0.4% of cases; thus, most of the intraepithelial dysplastic lesions remain stable or regress. In fact, spontaneous regression occurs from 48% to 70% of HSIL or CIN2-3 lesions[33-36]. Whether the delivery mode can affect the possibility of regression of dysplastic lesions remain is controversial[33,36-39]. Ahdoot et al[35] reported a spontaneous regression in 60% of women with HSIL who had a vaginal delivery, whereas none of the patients who delivered by cesarean section showed regression. Inconsistently, Yost et al[33] found an overall regression of HSIL lesions in 70% of patients, independently from the mode of delivery. It has been speculated that the cervical trauma occurring during second and third stage of labour and during delivery can lead to an inflammatory reaction in the cervix epithelium which can promote repair mechanisms. Another theory advocates the transient ischemic changes occurring to cervical tissues during ripening as responsible of lesions regressions. For these evidences, the present indications for delivery in women with intraepithelial cervical lesions do not comprise elective cesarean section for non-obstetrical indications.

Management of Abnormal Pap Test Results

Indications for colposcopic examination are similar for pregnant and non-pregnant women. In 2013, the American Society of Colposcopy and Cervical Pathology (ASCCP) published the revised 2006 Consensus for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors; in this update, pregnancy is considered a particular condition and detailed recommendations are presented[31,40,41]. Actually, the current consensus recommendations reflect an overall conservative approach to abnormal Pap smear in the absence of a frankly invasive cancer during pregnancy. In general, when invasive cancer can be excluded, all procedures, both diagnostic and therapeutic are deferred after delivery[41].

Negative Pap Test with Positive HPV-DNA Testing

Although HPV-DNA testing is usually performed only in the presence of atypical squamous cells of undetermined significance (ASC-US), there are some programs that perform high risk HPV-DNA testing in combination with the Pap smear in all women over 30 years of age (co-testing screening)[11,42,43]. Thus, it may happen a woman having a normal Pap test with a positive high risk HPV; it was reported that in this case the probability to have CIN2 or higher lesions is 4%[44] and usually women with such findings have only a transient HPV infections. The ASCCP recommends that non pregnant women with positive high risk HPV and negative Pap smear being followed up with repeat co-testing at 12 months; for pregnant women, it is reasonable to undergo a repeat co-testing at 6 week post partum visit[7,31].

ASC-US and LSIL Cytology

According to the ASCCP guidelines, colposcopy is deferred until 6 weeks postpartum in women with LSIL cytology[31], as these abnormalities are very likely to regress spontaneously and very unlikely to harbor an occult invasive malignancy. Fader et al[45] reported 86% of postpartum regression of LSIL lesions diagnosed during pregnancy, with no case of invasive cancer identified. Another study[37] found that 62% of patients with antepartum LSIL cytology had disease regression after delivery, 32% had persistent LSIL, and only 6% had progression to HSIL; no progression to invasive cancer occurred during pregnancy. However, colposcopy is reasonable for women with persistent dysplasia or who may not have easy access to health care facilities after pregnancy. The risk of cancer is relatively low among pregnant women with ASC-US, as it is demonstrated for non-pregnant patients, and the likelihood of finding an invasive lesion following either antepartum or postpartum biopsy is less than 1%. Of note, although HSILs may be diagnosed in up to 17% of patients with ASC-US Pap smears, some studies have found that antepartum colposcopic evaluation does not add prognostic significance to management[46]. Thus, colposcopy is recommended only in case of atypical squamous cells favoring high grade lesions (ASC-H). In the other cases, in presence of an ASC-US Pap smear, is recommended the use of the HPV triage in women older than 20 years of age, because of its higher sensitivity than the Pap smear in detecting high grade cervical intraepithelial lesions

(CIN2-3)[47,48]. Women who are high-risk HPV positive should undergo colposcopy 6 week post partum, while high-risk HPV negative women can be followed up with cytology at 6 weeks postpartum[31,49].

Atypical Glandular cells (AGC), Adenocarcinoma in Situ (AIS) and HSIL

Colposcopy is the procedure of choice in the triage of HSIL, AGC and AIS conditions during pregnancy, and pivotal in directing cervical biopsies of suspicious lesions. Because of the cervical changes in pregnancy, colposcopy could be challenging and should be performed by experienced clinicians who are familiar with pregnancy-induced cervical changes. Cervical biopsies during pregnancy are recommended in women with persistent untreated dysplasia or significative risk factors for persistent dysplasia or progressive disease, such as smoking, immunosuppression or noncompliance, or in case of lesions colposcopically suspicious for invasive cancer. Economos et al[22] reported 95% of concordance between the directed biopsy and the colposcopic impression. However, following biopsy, 54% of normal colposcopic findings turned out to be CIN1-2 and 14% of CIN1 colposcopic impressions turned out to be CIN3. Despite this, such discrepancies would not have led to major modifications in the management of cervical lesions, essentially because the mainstay of management of cervical dysplasia during pregnancy is observation, with the exception of suspected or confirmed invasive cancer. As already stated, a regression rate of 68% and 70% for CIN2 and CIN3 lesions respectively was reported[33]. Only in 7% of cases a progression from CIN2 to CIN3 on postpartum evaluation was observed; no CIN lesions progressed to invasive cancer. Thus, in case of a colposcopic impression of CIN2-3, biopsies or repeated colposcopy may be deferred in the postpartum as these lesions demonstrate a regression chance of 35% within the first year after pregnancy and are unlikely to progress, with a risk of invasive carcinoma of 0.45-1/1000 live births[45]. Patients with a histological diagnosis of CIN2 or 3 may be followed with repeated colposcopy at intervals no shorter than 12 weeks[5]. Pregnant women with cytological HSIL who are not diagnosed a CIN 2-3 should undergo revaluation with cytology or colposcopy at least 6 weeks postpartum. However, this reccomendation is based on expert opinion without strong evidence to support it[5], and repeated colposcopy every 12 weeks during pregnancy is an acceptable option[31]. Finally, it should be considered that, although the approach to the management of CIN in pregnancy is conservative, it is important that these patients will be reassessed in the postpartum, without stopping medical checks. A study demonstrated the importance of a postpartum follow up in pregnant women with a diagnosis of HSIL; 28 women with HSIL on a first trimester antepartum cytology were followed with colposcopy and biopsy 6 to 8 weeks post partum[36]. HSILs persisted in 89% of patients and microinvasive disease was found in 11% of women. These data also support why in case of patients who could not follow controls and medical care after pregnancy colposcopy and biopsy may be performed before delivery. As concerns AGC results, they are relatively rare and frequently caused by benign conditions, such as reactive changes and polyps. Despite this, it is not uncommon for AGC to be associated with significant underlying neoplastic conditions, including adenocarcinomas of the cervix, endometrium, ovary, and fallopian tubes. Several series in non-pregnant patients have reported that 9-38% of AGC underlying CIN2-3, AIS or cancer and 3-17% invasive cancer[50-53]. CIN is the most frequent significant finding identified in women with AGC[54], while malignancies are less common in women under 35 years of age than in older women[44], and pregnancy does not appear to change the underlying associations between AGC and gynecologic neoplasia[31]. Definitely, colposcopy is recommended for pregnant women with AGC and AIS; however, differently from non-pregnant patients, endocervical curettage is considered as unacceptable[31].

Cervical Treatments

The only accepted indication for therapy of cervical dysplasia in a pregnant women is the exclusion of an invasive cancer[31]. As matter of fact, different meta-analysis showed an increased risk of adverse obstetric outcomes after conservative treatment for CIN. The causes remain unclear and may include anatomical changes, abnormal healing of the cervix, immunological factors and alteration of the cervicovaginal flora[55,56].

Large Loop Excision of the Transformation Zone (LLETZ)

Several authors reported that the depth of the cone of removed cervical tissue during a Large Loop Excision of the Transformation Zone

(LLETZ) predicts the degree of prematurity at birth, particularly if it exceeds 10-12 mm[57-59]. However, other studies suggested that despite different degrees of shortening of the residual cervical length, LLETZ does not appear to predispose to patients' obstetrical complications (including preterm delivery) in a subsequent pregnancy[60-64]. Shanbhag e al[65] evaluated the risk of spontaneous preterm labor and Premature Preterm Rupture of Membranes (PPROM) in CIN3 patients, comparing the obstetrical outcome between women who had an excisional procedure and those with no treatments. The authors found that the rate of preterm delivery was 12% and 15% in the two groups respectively, without any statistically significant difference. Despite LLETZ can also be performed in pregnancy with a reasonable degree of maternal safety, according to the most recent ASCCP Consensus Guidelines[31], it should be only indicated in a diagnostic fashion, and for this with minimal cervical reduction, for patients in whom invasive disease is strongly suspected at colposcopy or confirmed with biopsy.

Cold Knife Conization

Cold knife cervical conization has been associated with heavy vaginal bleeding in 5-15% of pregnant patients[66,67] and with spontaneous abortion in more than 25% of cases[7]. A recurrent CIN1 secondary to a smaller than usual excision has been reported in 50% of cases[68,69]. A significant reduction in the mean gestational age at delivery (38.23 ± 2.51 weeks vs. 39.15 ± 1.56 weeks) was observed, together with a higher rate of premature rupture of the membranes, premature onset of labor, premature delivery and neonatal hospitalization in patients with history of conization[68]. Moreover, newborns from women who had cervical conservative surgery had a significantly lower weight and size at birth than those of the control group: these children were also more frequently admitted in the neonatal intensive care unit[10]. For all these considerations, and according to the present indications for treatment of CIN in pregnancy, cold knife should no longer be indicated and performed.

Complications

A review of 2,480 cases during and 11 years observation period revealed significant correlations between the presence of high-risk human papillomavirus HPV-DNA and preterm births and placental abnormalities[70]. These results seem to suggest that a high-risk HPV cervical infection detected in pregnancy is a risk factor for preterm birth and that cervical cytology is an effective tool for screening women during pregnancy and also for predicting pregnancy outcome. Other authors reported that women with cervical cancer, but not with CIN, where at higher risk of delivering prematurely. They also did not find any correlation between CIN or cervical cancer and increased risk of IUGR, PPROM and intrauterine death. However, it is not known what proportion of women had undergone any kind of treatment for CIN[9]. Another study[71] compared the prevalence of HPV detection in placentas from women with spontaneous abortions (occurred between the 6th and the 16th week of pregnancy) and from a control group of women after delivery at term; results from this experience did not reveal any significant difference between the two groups. In this regard, the only evidence-based obstetrical complication correlated with the presence and treatment of a CIN in pregnancy is represented by a significant increase in preterm deliveries in patients treated with a deep cone excision[72,73].

Conclusions

Cervical cancer is demonstrated to be the most frequently diagnosed cancer during pregnancy. The finding of an abnormal cytology is as high in frequency as it is detected in non-pregnant conditions. Moreover, the rate of high-risk HPV types identified in pregnant women is comparable to what is found in gynecological practice. In consideration of the evidence that the present mean age at the first pregnancy is in the range of 30-32 yrs., the occurrence of a CIN diagnosis in pregnancy is a common observation. This aspect underlines the importance of cervical cytological screening in the antenatal care or at initial obstetrical consultation for pregnancy. Also, pregnancy promotes structural and morphological changes at the level of the cervical tissues which can make particularly challenging the correct interpretation of cytologic, histologic, and colposcopic findings, requiring management by experienced physicians. The progression rate of dysplastic lesions of the cervix in pregnancy is very low and the risk of invasive cancer almost insignificant. This evidence indicates a more conservative approach compared to the non-pregnant woman, reserving surgical treatment only in case of strong suspicion or certainty of cervical cancer. A simplified man-

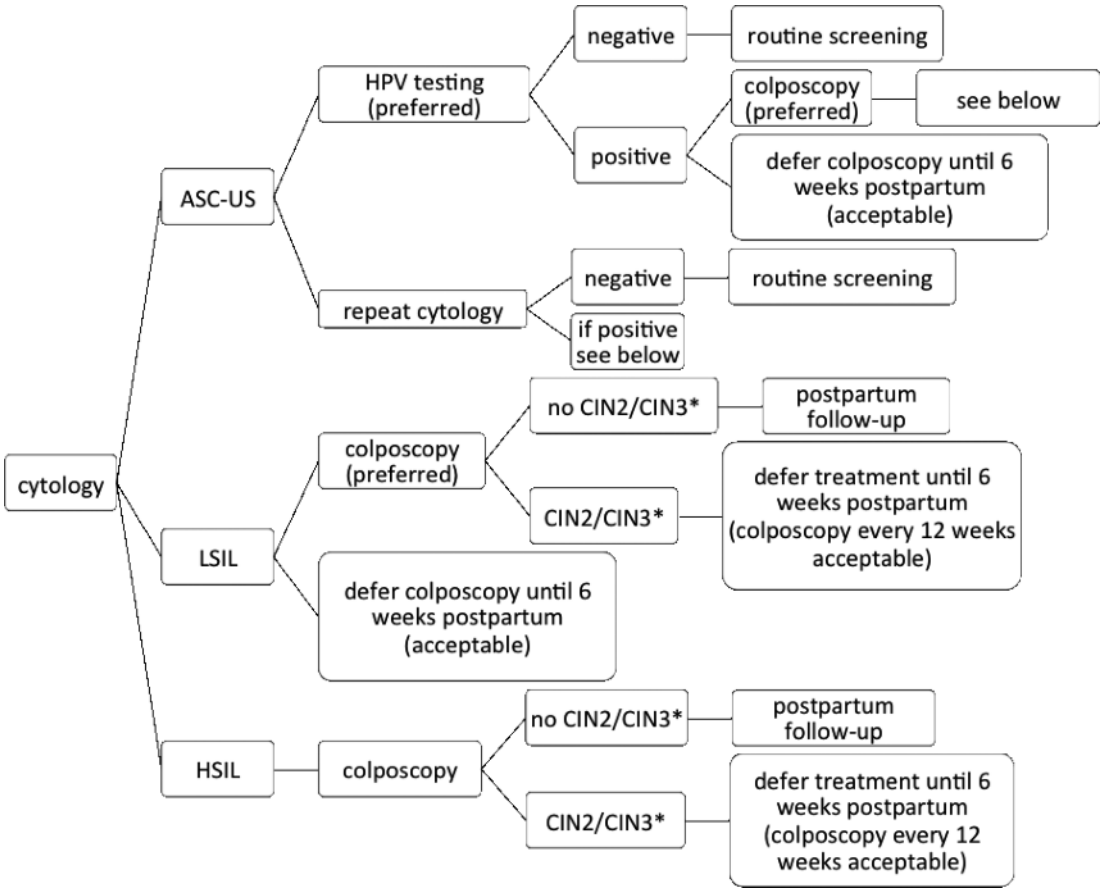

Figure 1. Simplified algorythm of clinical management (*for detailed and specific situations see text and reference 41).

agement algorithm is illustrated in Figure 1. In clinical practice, once invasive cervical cancer has been excluded by colposcopy and/or targeted biopsy, every adjunctive procedure, either diagnostic or therapeutic, should be deferred after delivery.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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