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Review

Abnormal cytologic findings during pregnancy

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Abstract

Our aim was the illustration of the controversies that occur during pregnancy related to the mode of obtaining and interpreting a cervical smear, specific colposcopic features, as well as the approach of diagnosing, following-up and treatment, based on the findings of the Papanicolaou smear. A review of the literature as well as the updated American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines on the management of abnormal Papanicolaou smears known as 2012 Bethesda Consensus Guidelines, was undertaken. The results of the abnormal smears were categorized according to their severity and the current evidence-based diagnostic and therapeutic management has been overviewed. The diagnostic and therapeutic workup is outlined based on the available guidelines to be followed according to the cytology results, the trimester of the pregnancy, and the scheduled mode of the delivery. The interpretation of abnormal cytology smears during pregnancy is similar to those outside pregnancy. However, the effect of the pregnancy in cytology and colposcopy might hamper the discrimination of normal and abnormal epithelium. The arising issues following an abnormal smear are numerous, both from the patient's and the doctor's side. The knowledge of optimal cytology management during pregnancy is essential to avoid cases of under- or overtreatment.

Key words: cervical cancer; pregnancy; cytology; colposcopy

Cervical cancer (CxCa) represents the third commonest cancer among women, as well as the third most common cause of death among women with malignancies in industrialized countries[1]. Each year more than 530,000 new CxCa cases are being diagnosed globally, while 275,000 deaths are being attributed annually to this etiology[2]. 1 - 3% of individuals with CxCa are pregnant or in the puerperium at the time of diagnosis[3,4]. More specifically, about half of these cases are diagnosed during pregnancy and the remainder within a 12 - month period after delivery[5]. Therefore, CxCa represents one of the commonest malignancies during pregnancy, with a mean frequency of 0.8 to 1.5 cases per 10,000 gestations[5-8].

Those facts have led to the inclusion of obtaining cervical smears among the routine antenatal screening tests. This practice represents an excellent opportunity to implement a diagnostic screening test in a large population of women of reproductive age, who wouldn't otherwise have the opportunity to undergo the exam[9-11]. The rationale of this practice is reflected on the fact that randomized studies illustrated a 3 - fold higher probability of diagnosing

Stage I CxCa in pregnant women while compared to non - pregnant[12]. However, the questions arising on the management of an abnormal smear during pregnancy are numerous, both from the patient's and the doctor's side. In this article we aim to review the particularities and the modes of diagnosis, follow - up and mode of delivery depending on the findings of Papanicolaou exam during pregnancy.

Cervical cytology during pregnancy

The diagnostic accuracy of the Pap smear can be affected during pregnancy, both because of the technical difficulties that arise in obtaining the smear, as well as the physiological cellular cervical changes attributed to pregnancy.

Regarding the issues related in obtaining a smear, many clinicians hesitate to insert the cervical brush in the endocervix of the gravid uterus for the fear of possible complications. Consequently, the percentage of samples with inadequate endocervical harvest is increased. In a retrospective study of 1377 obstetrical cases reviewed by Londo et al, endocervical cells were represented in only 44.1% of the specimens that were obtained during pregnancy. When those women were followed up in the post - delivery period, endocervical cells were sufficiently represented in 82% of samples[13]. A study that assessed alternative methods of obtaining cervical smears during pregnancy, illustrated that the classical method of obtaining endocervical cells with the use of Cytobrush is superb compared to the others in achieving endocervical assessment without increasing the complication rate, including hemorrhage and spontaneous abortions[14]. Consequently, as for the technical part, obtaining a cervical smear at antenatal screening must be cautiously but decisively undertaken by health professionals.

The second factor that affects the reliability of Papanicolaou smears during pregnancy is related to the physiological changes cervical cells undergo under the influence of hormones which often render the discrimination of the abnormal colposcopic findings difficult to extremely complicated.

In particular, there is an abundance of degenerated cells of the decidual layer, which morphologically resemble cells suggestive of high grade squamous intraepithelial lesion (HSIL), from which they can be differentiated mainly because of their enlarged cellular size. Cytotrophoblasts which are distinguished on the basis of their prominent nucleoli, can be also mimic cells desquamated from an HSIL lesion. Additionally, cells originating from the syncytiotrophoblast, characterized by their perinuclear halos and their nuclear atypia, might be incorrectly diagnosed as human papilloma virus (HPV) affected cells. Another usual problem arises with cells illustrating Arias - Stella reaction, with vacuolating cytoplasm and enlarged atypical nuclei with prominent nucleoli which resemble those of endocervical adenocarcinoma[15].

The translocation of the endocervical epithelium externally from the ectocervical os leads to the development of eversion of the glandular epithelium. This results to the easy definition of the squamocolumnar junction after the second trimester; however exposed columnar cells are vulnerable to numerous microabrasions and infections which lead to reactive and repairing cellular changes. The exposure of the columnar cells in the acidic vaginal environment precipitates their immature squamous metaplasia that can be misinterpreted as dysplasia. Furthermore, the hyperplasia of the endocervical glands attributed to harmonic stimuli, induces a spectrum of cellular changes that can be misinterpreted as atypical glandular cells of undetermined significance (AGUS).

Finally, the presence of multinucleated cells of cervical origin during pregnancy broadens the spectrum of differential diagnosis, which should encompass multinucleated histiocytes, syncytiotrophoblasts, decidual cells, multinucleated endocervical cells, HPV and herpes simplex virus (HSV) infection[16].

Provision to the cytologist of basic information from the patients' history and knowledge of the fact that the smear was obtained from a pregnant woman definitely represent the minimal dataset to avoid diagnostic errors.

Diagnostic colposcopy during pregnancy

Colposcopy represents a totally safe procedure which can be performed in any obstetrical patient, regardless of gestational trimester whenever there are aberrations in cervical cytology[17]. A careful colposcopic assessment provides the opportunity of early intervention or even treatment, especially in early pregnancy when concerns over the relevant interventions are minimal both for the mother and the fetus.

The macroscopic impression of the cervix during pregnancy is drastically different from the appearance of the non-gravid state, because of the cervical physiological changes attributed to pregnancy. Pregnancy - related histological changes induce decidual reaction and edema of the cervical stroma, enlargement of the cervical size, increased vascularity, hyperplasia of the endocervical glands leading to excess mucous secretions and prominent ectropion in the ectocervical os[17-20].

The remarkable decidual reaction of the cervical stroma is the dominant feature during pregnancy. Despite occasional difficulties with the colposcopic recognition, it can be very pronounced leading to polypoid cervical projections, known as "decidual polyps". Their discrimination from the common cervical polyps is based on their yellowish hue and absence of epithelial coating.

Additionally, the increased cervical vascularity produces less prominent acetowhite changes, and gives rise to the appearance of abnormal vascular patterns. The former leads to underestimation of high grade lesions; unless a 5% solution is implemented, while the latter might give the false impression of high grade disease or even invasion[21].

Furthermore, as the pregnancy advances the endocervical columnar epithelium migrates towards the ectocervical os, leading to emergence of ectropion. This physiological change facilitates the visibility of the transformation zone in 90 - 100% of patients at the 20th week of pregnancy. Therefore, if a colposcopy is considered unsatisfactory at the initial stages of pregnancy, it can be repeated later with the squamocolumnar junction easily visible[17]. The acidic environment precipitates the process of squamous metaplasia. The metaplastic areas can be more prominent and identifiable, with a whitish hue after immersion with acetic. However, pregnancy - induced metaplastic acetowhite areas are paler, with less clear margins compared to frank dysplastic lesions.

Finally, the presence of acanthosis within areas of the squamous epithelium, leads to their intense reaction to the acetic acid and their clear discrimination from original squamous epithelium, while they might illustrate patterns of mosaicism, punctuation, or both. The small area size and the mosaicism, as well as the fine and without irregularities punctuation assist the differential diagnosis. However diagnostic colposcopy might not be able to discriminate lesions with coarse mosaicism from more severe dysplasias[22].

As for the technical part of the colposcopy, several particularities have to be considered: the increased fragility and possibility of a traumatic bleeding of the cervix because of the aforementioned characteristics, as well as the significantly increased cervical mucus, the laxity of the vaginal walls and the increased cervical volume, all contribute in making colposcopy during pregnancy a laborious procedure. The patients' attitude and co - operation, despite reassurance on the safety of the procedure is often suboptimal or problematic. Thus, this exam during pregnancy should be performed by expert colposcopists acquainted with the peculiarities of this patient subcategory[17-20,22].

In regards to the final histologic diagnosis, Baldauf et al concluded that colposcopy during pregnancy either estimated accurately, overestimated or underestimated the severity of a lesion in 72.6%, 17.6% and 9.8% of patients, respectively. Thus, and bearing in mind that the main aim of colposcopy during pregnancy is to exclude the presence of invasive CxCa, representative biopsies should be obtained from the suspicious areas[17]. As mentioned above, biopsies obtained during pregnancy are safe, accurate and reliable[23]. The colposcopic impression and the final histologic diagno-

sis from biopsies either coincided or ranged within one grade of severity of the lesion, in 83.7% and 95.9% of cases, respectively[17]. The risk of postoperative bleeding is low (1 - 3%) but might be higher in the second trimester; however obtaining biopsies in the third trimester might lead to premature labor[3,23,24]. The reliability of colposcopy and colposcopy - guided biopsies is unrelated to the trimester of the pregnancy[17,19,23,25,26].

Abnormal Pap smear findings suggestive of uncomplicated HPV infection, ASCUS or LSIL lesions and management

It has been conclusively shown that the pregnancy does not accelerate the progression of cervical precancer. Studies suggest that only 3.7% of pregnant women with smears suggestive of atypical squamous cells of undetermined significance (ASC - US) or low - grade squamous intraepithelial lesion (LSIL) harbored high - grade lesions (cervical intraepithelial neoplasia CIN 2 - 3) when a diagnostic work - up was undertaken post labor[27]. Resolution of cervical precancer during the puerperium is quite common. Low - grade lesions resolve in 48 - 62% of cases, and remain unchanged in 29 - 38%. Deterioration of those lesions is uncommon (up to 6% in published studies). Regarding high - grade lesions, despite a lower resolution probability (27.4 - 34.2%), deterioration of the lesions is observed in only 2.7 - 9.7% of cases[20,28,29].

Taking into account the above, and considering that the main scope of colposcopy during pregnancy is the exclusion of invasive disease as well as the avoidance of redundant interventions, the management of pregnant women with moderately abnormal cervical smears is outlined as below[30-34]:

Women below 21 years of age, pregnant or not, commonly exhibit high rates of HPV infection and thus present with borderline cytological changes (ASC - US, LSIL); CxCa risk is negligible among those ages and rates of spontaneous regression of those abnormalities are considerably high, reaching 90%[31]. Therefore, colposcopy during pregnancy can be safely deferred in those patients. However, soon after birth a new cervical smear should be obtained[30,32].

In the category of pregnant women aged between 21 and 24, the management of a mildly abnormal smear, resembles to the management of a smear outside pregnancy. For ASC - US smears, repeating cervical cytology after 12 months is suggested. Triaging those patients with HPV - DNA test is also an acceptable option. If the sample tests are negative for HPV, then cytology is repeated after a 3 - year interval, exactly as in non - pregnant women. However, a positive HPV - DNA result in conjunction with the presence of ASC - US cytology merits repetition of cytology after 12 months. Nor resorting to colposcopy or repeating the HPV tests are indicated. Similarly, if cytology is indicative of LSIL, repeating cytology after 12 months (post partum) is indicated, however colposcopy is not warranted in this age group[30-32].

For women aged over 24, with cytology indicative of ASC - US, an HPV - DNA test is warranted. Those who test positive can be triaged with colposcopy, which can be however postponed for at least 6 weeks post partum. When the HPV - DNA test is negative, it is safe to resort to co - testing 3 years later. Colposcopy is also warranted in cases with LSIL cytology[30,32].

A special category is represented by women with smears harboring atypical epithelial cells for which a high - grade squamous intraepithelial lesion cannot be excluded, known as ASC - H. A cytology report indicative of ASC - H is related with an elevated risk of a subsequent CIN3+ with time, while compared with ASC - US or LSIL cytology. This also applies for women aged 21-24 years, despite that the risk of subsequent CIN3+ lesions, is lower when compared with older patients harboring ASC - H. In these cases, colposcopy is mandatory, irrespective of the HPV - DNA status[30-32].

The most important difference in the management of the above findings between pregnant and non - pregnant women is that in the former colposcopy can be deferred and can be safely performed at least 6 weeks post partum, since progression of a

high-grade lesion to malignancy is highly unlikely to occur in such a short time lapse[33,34]. If however colposcopy is actually performed, repeating the smear in the following trimesters is not mandatory, except if a high - grade lesion (CIN 2 - 3) is confirmed[31].

Abnormal Pap smear findings suggestive of HGSIL lesions and management

This category encompasses the subgroups of moderate dysplasia (CIN2), as well as severe dysplasia formerly known as carcinoma in situ (CIN3)[35]. CIN2 lesions represent an heterogeneous group illustrating a higher propensity for regression during long-term follow - up when compared to CIN3 lesions, and indeed the histologic discrimination of these two entities is often difficult[36-38]. For this reason, to endorse a failsafe mechanism, as in the non - pregnant state, CIN2 is the cut - off limit for surgical interventions; consequently guidelines for the management with histologic CIN2 and CIN3 are uniform[35]. It is accepted that pregnant women with HGSIL should undergo immediate colposcopy. To avoid overestimation of the anticipated cervical changes, the procedure should be performed by an experienced colposcopist, cognizant of the anticipated pregnancy - related colposcopic patterns. If colposcopy is suggestive of CIN2, CIN3, or invasive cancer, the next step is obtaining cervical biopsies[39].

The fear of excessive bleeding of the hyperemic gravid cervix averts many gynecologists from obtaining biopsies. However these concerns have not been corroborated by the literature as several studies encourage obtaining colposcopically - guided biopsies in the course of pregnancy without citing major hemorrhage events or adverse pregnancy outcomes attributed to the procedure[17,23,40,41]. Despite the low risk of hemorrhage in the first trimester, some authorities advocate deferring obtaining the biopsies in the second trimester to avoid correlating this intervention with a possible unrelated spontaneous abortion. Aiming to achieve a less interventional diagnosis, other authors advocate the implementation of a special rigid brush instead of obtaining biopsies[42]. This technique is based in the use of a spiral brush with thick filaments, which can detach tissue specimens when applied on a suspicious cervical lesion, in a comparable manner with those obtained with a conventional biopsy. Regarding endocervical curettage, given that no well - designed randomized studies are available to date, it is considered totally unsuitable during pregnancy[41].

Patients with biopsy - confirmed CIN2 or CIN3 lesions should undergo further cytologic and colposcopic assessment during pregnancy in time intervals no less than 12 weeks. Repeating the biopsies during pregnancy might be necessary for lesions with deteriorating colposcopic features, or when repeat cytology is suggestive of invasive disease. Pregnant women with cytology suggestive of HGSIL, in whom CIN2, CIN3, or invasion has not been detected in colposcopy, can be re - assessed with cytology and colposcopy no earlier than 6 weeks postpartum[9].

Despite diagnostic conization should be performed only when invasion is suspected, more aggressive approaches have been also suggested. Siegler et al[42] consider large loop excision of the transformation zone in the first trimester of pregnancy as a safe procedure, with the advantage of treating definitively CIN2+ lesions. The authors suggest that large loop excision of the transformation zone (LLETZ) should be performed more liberally in the first trimester of pregnancy. This approach has been corroborated by other investigators[44,45].

Atypical glandular cells and adenocarcinoma in situ

Detection of atypical glandular cells (AGCs) in a cervical smear, triggers significant differential diagnosis issues in pregnancy. AGCs only represent 0.1 - 2.5% of the net cytological findings[46-48]. Despite the low prevalence of AGCs, they might be related with a serious underlying situation. According to the literature, CIN2/CIN3, adenocarcinoma in situ (AIS) or invasive carcinoma are detected in 9 - 54%, 0 - 8% and 1 - 9% of AGCs cases, respectively[49-50].

Pregnancy - related cellular changes, encompassing decidual cells, trophoblasts and cells with Ari-

as - Stella reaction, often obscure the interpretation of cervical smears. In particular, Arias - Stella reaction is often misinterpreted as glandular atypia[51,52]. Arias - Stella reaction has been detected in the endocervical canal of 9% of perinatal hysterectomy pathologic specimens[53]. In a group of 21 patients with AGCs during pregnancy who were managed conservatively, Kim et al[54] documented only one case of AIS. Chhieng et al[55] followed up 30 gravidas and 5 puerperas with AGCs who underwent colposcopy and biopsy. Of those, 18% harbored HGSIL and 12% harbored LSIL lesions. No case of adenocarcinoma or AIS was diagnosed. During follow up of these patients, only two showed sustained cellular atypia, one glandular and one squamous.

In patients with AGCs, the first measure is to undergo colposcopy. Should a suspicious lesion be revealed, obtaining a biopsy is mandatory to confirm histology. However, in contrast to the general population, endocervical curettage and endometrial biopsies are unacceptable during pregnancy. More aggressive interventions, like diagnostic conization, should be reserved only when there is high index of suspicion for invasion. In any other case re - evaluation postpartum is necessary[30].

Management of abnormal Pap smear findings indicative of cervical cancer

Approximately 30% of women with CxCa are of reproductive age, while 1 - 3% of CxCa are diagnosed in the course of pregnancy. It is estimated that the incidence of CxCa during pregnancy is 1 - 10 cases every 10,000 pregnancies[3,8,18,19,23]. Zemlickis et al have calculated that pregnant women are in a two or three fold higher risk to be diagnosed with surgically curable stage of the disease[56]. This could be partially attributed to the fact that visual inspection and bimanual gynecologic exam, as well as cytological assessment, represent part of the routine antenatal assessment.

The prevalence of abnormal cytological exams during pregnancy has been estimated between 5% and 8%, which correlates well with the figures from the general population. However, it has been estimated that 1.2% of gravidas with abnormal Pap will eventually harbor cervical cancer[2,3,7,18-20,23,57]. Of the patients who will be eventually diagnosed with cervical cancer, 76% are in stage IB, while 78% of cases represent neoplasms emerging from the squamous epithelium[58].

If the Pap smear is suggestive of invasive disease, colposcopy - guided biopsies should be obtained from any suspicious areas. For biopsies to be diagnostic they should include sufficient stroma, and for this reason many authors using "wedge" biopsies or small loop biopsies instead of punch biopsies. The indication for conization is weaker as the pregnancy advances, given the high morbidity (hemorrhage, miscarriages and preterm labor are commoner in advanced gestational age)[59,60]. Therefore, a similar intervention can be accomplished easier in the early stages of the pregnancy. Therapeutic decisions should be based on cervical length, surgeon's experience, and the index of suspicion for underlying invasive disease.

The management of the pregnant patient who is newly diagnosed with cervical cancer is individualized, based upon the stage of the disease, the gestational week and accordingly the fetal maturity, as well as the mother's wish upon completion of the pregnancy. Patients should be managed in tertiary centers with relevant expertise. In cases of IA1 stage (stromal infiltration less than 3mm), when the disease is diagnosed following conization with clear specimen margins, continuation of the pregnancy until term and vaginal labor are a feasible option.

However, in cases with more advanced disease, the gestational age will dictate management[61]. In pregnancies less than 20 weeks, straightforward initiation of treatment without delays is suggested, in the form of radical hysterectomy with bilateral pelvic lymphadenectomy or radiotherapy, depending on the stage of the disease. If radical surgery is to be performed, the pregnancy should not be terminated before the intervention; despite a perioperative hysterectomy to remove the fetus might help in the technical part of the intervention. If radiotherapy is to follow, radiation can start without prior pregnan-

cy termination, as the fetus is usually aborted in the course of treatment.

In gestational ages exceeding 24 weeks, expectant management is acceptable aiming for a viable fetus. Corticosteroids should be administered aiming to minimize the danger of neonatal respiratory immaturity. All other possible prematurity - related complications should be considered before the decision of elective cesarian section. For this patient category, cesarean section is warranted, despite that the choice of the route of delivery does not seem to affect the mother or the neonate, even in cases with invasive disease. Radical hysterectomy and pelvic lymphadenectomy may be executed immediately following the cesarean section[61,62].

For gestational ages between 20 and 24 weeks, decisions on individualized management must be undertaken by a multidisciplinary oncological board (obstetricians - gynecologists, oncologists, neonatologists and psychologists), after considering all aspects for the mother and fetus. In bulky disease (>4cm) platinum - based neoadjuvant chemotherapy might be beneficial. Lymph node status can be assessed with laparoscopy.

The stage of the disease is the most critical determinant of survival. Finally, the informed decision of the mother on the continuation of the pregnancy should be respected. Patients who opt to continue the pregnancy should be aware that even in cases with apparently early disease stages, progression of the neoplasm cannot be ruled out.

Conclusion

The appreciation of an abnormal cytology test during pregnancy shares the same principles with the non gravid state. However, the effects of the pregnancy on cervical cytology and on colposcopy might hamper the discrimination of the normal from dysplastic cervical epithelium. The aim during the prenatal period is the safe conservative follow - up of the patient and the reliable exclusion of invasive disease. Cervical biopsies, if considered necessary can be safely performed, however other more invasive diagnostic excisional methods are associated with significant morbidity for the mother and fetus. The diagnosis of invasive cervical cancer during pregnancy requires a multidisciplinary approach to obtain all relevant and necessary information to the patient so that she will take an informed decision on the management of this special situation.

Conflict of interest

All authors declare no conflict of interest.

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