13 Cervical Cancer Screening in Pregnancy

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13.1 Introduction

Cervical cancer is the most common genital malignancy diagnosed during pregnancy. Around 3% of newly diagnosed invasive cervical cancer occurs in pregnant women [1]. The prevalence of abnormal Papanicolaou (Pap) test result in pregnancy does not differ from the age-matched non-pregnant population. In some populations up to 20% of pregnant women have an abnormal Pap test result during pregnancy [2]. The objective of this chapter is to review the existing guidelines on cervical cancer screening in pregnancy and also diagnosis and management of cervical intraepithelial neoplasias (CIN) in pregnancy.

13.2 Current Scenario of Screening Programs in Developed and Low- and Middle-Income Countries

Annual incidence of 122,000 new cervical cancer cases and 67,000 cervical cancer-related deaths clearly show the burden of this totally preventable cancer in India [3]. The screening program available in India is very sporadic, opportunistic, and non-population based. According to the India HPV report, in 2012, only 2.6% of the rural women and 4.9% of the urban women have been screened in the country [4]. Tamil Nadu is the only state in the country that has initiated systematic screening of the women after conducting a pilot project in three districts [4]. In high-income countries, a Pap test linked with definitive treatment has prevented millions of women from cervical cancer but failed to achieve optimum utilization in most developing countries. In the last two decades, various research works have convincingly established the utility of visual inspection on acetic acid (VIA) and human papillomavirus test (HPV) in low- and middle-income countries (LMICS) including India [5–7]. The evidence was evaluated by the World Health Organization (WHO) in recently published recommendations for comprehensive cervical cancer control strategies for the low- and middle-income countries [8]. The existing guidelines are almost the same for the specified age

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group of 21–65 years irrespective of the pregnancy status with few modifications according to the gestational age of the women and severity of abnormality on screening test.

Prenatal care provides an opportunity for screening because many women seek health care only when they are pregnant. This is especially true for low- and middle-income countries where catching up the reproductive age group women may be the only opportunity to screen all pregnant women who are older than 21 years when they present for their first prenatal visit.

13.3 Physiological Changes of the Cervix in Pregnancy

Due to increased estrogen and progesterone, the cervix becomes soft and swollen with resultant hypertrophy and hyperplasia of the elastic and connective tissues. Estradiol stimulates growth of columnar epithelium resulting in exposure of the columnar line of endocervical canal into the vaginal secretions. This condition is also known as ectropion. Due to increased mucus production, clinical examination of the cervix becomes difficult (Fig. 13.1). Decidualization of the cervical stroma often causes increased friability, polyps, and plaque-like changes that can be seen grossly and also on colposcopy examination (Fig. 13.2).

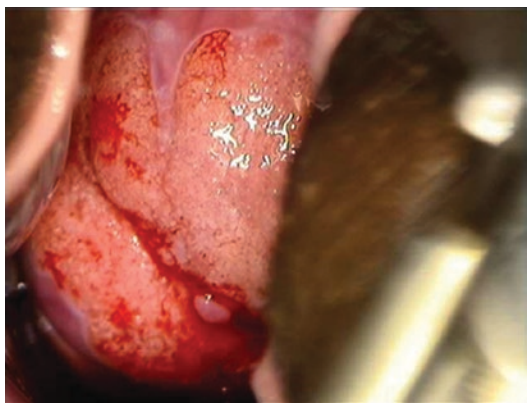

Fig. 13.1 Difficult colposcopy examination due to large ectropion in pregnancy

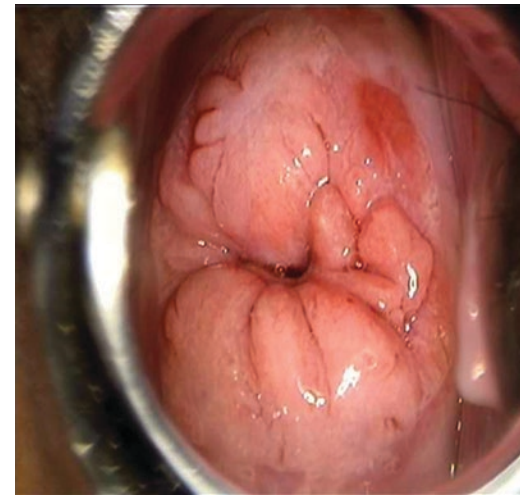

Fig. 13.2 Hypertrophy of columnar epithelium in pregnancy

13.4 Guiding Principles of Cervical Cancer Screening in Pregnancy

The cervical cancer screening algorithm has undergone significant changes after the introduction of HPV DNA and VIA tests as an option. Both anatomical and physiological changes in the cervix during pregnancy make the screening procedure a different scenario altogether as the management principles are directly related to obstetric outcome of the women.

13.4.1 Screening Methods

13.4.1.1 Cytological Tests

In the developed countries with an established cytology-based screening program, the need of opportunistic screening by Pap smear as a routine prenatal examination to increase rate of detection of cervical abnormalities is rarely necessary. Due to availability of routine screening covered up by health insurance, the incidence of cervical cancer has dramatically gone down and rarely addressed in high-resource countries. But for low-resource countries, visit to the antenatal clinic may be the only time, when women will attend the healthcare facility and will remain compliant to her

clinician's advice. Thus opportunistic screening at the time of their routine prenatal visit is required, and this plays a key role in diagnosis and management of cervical pre-cancers. However, interpretation of conventional or liquid-based Pap testing is difficult due to high mucus production and large number of navicular, reactive glandular, and even trophoblastic cells in the smear. To rule out misdiagnosis and resultant over treatment, interpretation of Pap test results should be done carefully especially during pregnancy and postpartum period.

13.4.1.2 Noncytological Tests

Under the hormonal influence, significant change in anatomy and physiology of the cervix during pregnancy can make the result of any visual screening tests like VIA with 5% freshly prepared acetic acid or visual inspection with Lugol's iodine (VILI) harder to interpret and could be inaccurate. Moreover, the younger the age, the probability of false-positive VIA test is also high. The role of molecular tests like HPV mRNA test and hybrid capture 2 (HC2) test, which detects 13 high-risk types of oncogenic HPV DNA (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) by nuclear hybridization technique, is more reliable. The interpretation of results with these tests is not observer-dependant, and results are highly sensitive and specific [9].

Various researchers in different studies have shown that the pooled estimates of sensitivity and specificity of VIA, Pap smear cytology, and human papillomavirus DNA to be 67.65% and 84.32%, 62.11% and 93.51%, and 77.81% and 91.54%, respectively [9, 10].

13.4.2 Time to Perform Screening Tests During Pregnancy

During pregnancy, the time of performing cervical cancer screening tests also depends on which trimester the lady is reporting to the clinic. The National Health Service (NHS) trust cervical screening program recommends that routine cervical screening tests can usually be delayed in pregnant women till 6 weeks postpartum provided they are up to date with their routine Pap test prior to the conception [11]. Apart from suspicion of invasive cancer definitive diagnostic tests and further management can be postponed till delivery. This is because of the fact that even left untreated, only 2–5% of CIN3 cases will progress to invasive cancer in the future [12, 13].

13.4.3 Screening Interval

The current recommendation of screening interval for pregnant women remains same as the non-pregnant individuals.

13.4.4 ASCCP Guidelines on Cervical Cancer Screening in Pregnancy

In 2012, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), United States Preventive Services Task Force, and ACOG released updated recommendations for cervical cancer screening in pregnancy [14, 15]. As there is an already established cytology-based screening practice available, the recommendations are strongly based on abnormal Pap smear results. The following are the special recommendations for management of abnormal cytological findings in pregnancy (Table 13.1):

1. Management of screen test positive result depends on the severity of abnormality on cytology.
2. In case of any suspicion of invasive cancer, further referral for colposcopy and biopsy is mandatory.
3. Treatment of any grade of CIN is contraindicated during pregnancy as there is no immediate harm to the mother or fetus, while unnecessary treatment may be associated with adverse fetal and maternal outcome.
4. In case of CIN2 and CIN3 lesions, repeat colposcopy and cytology can be done at a minimum of 6 weeks interval.

Table 13.1 Summary of abnormal Pap smear management in pregnancy

Pap test result	Management
Atypical squamous cells of undetermined significance (ASC-US)	• Defer colposcopy 6 weeks postpartum • No ECC
Low-grade squamous intraepithelial lesion (LSIL)	• Colposcopy 6 weeks postpartum acceptable • No ECC • If no evidence of high-grade lesion follow-up as per non-pregnant guidelines
High-grade squamous intraepithelial lesion (HSIL)	• Colposcopy • No ECC • Diagnostic excision only if suspected invasive disease • Treatment only in case of invasive cancer
Atypical glandular cells (AGC)	• Colposcopy • No ECC • If no evidence of high-grade lesion, repeat cytology and HPV postpartum

5. Treatment by excision methods is only recommended to rule out suspected invasive cancer.
6. Glandular abnormality in Pap smear should be referred for further evaluation by colposcopy; however, endocervical curettage (ECC) is not recommended during pregnancy.
7. Plan for pregnancy and/or mode of delivery should not be altered unless invasive disease is present.
8. The 2012 recommendations include the utility of molecular testing as an adjunct test to cytology screening for certain women and provide guidance to the treating physicians based on different risk-benefit considerations for different ages [16].

The increase in cost with very few benefits of picking up true high-risk cases which require further evaluation makes co-testing with HPV DNA and Pap smear a questionable method in a resource-constrained setup. The World Health Organization (WHO) has strongly recommended HPV DNA test as a primary screening test if feasible [17, 18]. However, the main objective of preventing cervical cancer should be addressed by using any screening method according to public health resources and country-specific need.

13.4.5 Age of Screening

According to the ASCCP guidelines, cervical carcinoma screening by cytology should begin at 21 years of age, regardless of age of coitus or vaccination status, until age 30. For women more than 30 years of age, co-testing with cytology and HPV testing every 5 years is the preferred method of screening [14, 15], although cytology screening every 3 years is acceptable. When HPV testing is used as a primary screening test, the screening should start at 30 years of age. Majority of studies utilizing VIA as a screening method has reported the starting age of VIA at more than 25 years [19, 20]. This is to avoid unnecessary false-positive results due to immature squamous metaplasia and inflammation at younger age.

Studies report that 10–70% of cervical intraepithelial neoplasias, CIN1 and CIN2, diagnosed during pregnancy regress and sometimes even disappear postpartum, while persistence in the severity of cervical neoplasia is reported in 25–47% of cases and progression in 3–30% of cases [21, 22]. In absence of strong recommendations, data obtained are mainly based on personal experiences and retrospective studies of pregnant women.

13.5 Colposcopy Examination in Screen-Positive Cases

Indications for colposcopy in pregnant and non-pregnant women are same. The only exception in the ASCCP guidelines is that colposcopy examination may be deferred until the postpartum period in low-grade squamous intraepithelial lesions (LSIL) or atypical squamous cells of undetermined significance (ASC-US) with HPV-positive status (Fig. 13.3). As more than 80% of HPV infection gets cleared within a year, the co-testing for HPV DNA is recommended after 6 weeks in the postpartum period if early trimester co-testing with cytology and HPV DNA were positive [23]. Due to hormonal changes interpretation of colposcopy, findings are difficult during pregnancy. The pregnant cervix may be easily seen or may be difficult to visualize than the non-pregnant state. It is usually easier to see the entire

TZ due to eversion of cervical epithelium colposcopically described as large ectropion which reverts postpartum. On colposcopy, the cervix becomes more hyperemic with prominent ectropion, and the vaginal rugosities also are more prominent and hyperemic. As pregnancy progresses, vaginal walls may become highly patulous especially in multiparous women making visualization of cervix more difficult. The use of lateral vaginal speculum or condom may help to hold back the vaginal walls. Vulvovaginal varices may also become prominent in pregnancy due to high blood supply.

As the pregnancy progresses, decidualization of stroma often becomes prominent, appearing as hyperemic-raised plaque-like lesions, which becomes acetowhite after application of 5% acetic acid. Even in the first trimester, edema and increased vascularity make colposcopy examination difficult. Active immature metaplasia often produces thin patchy acetowhite areas with fine mosaics and fine punctations, making it difficult to distinguish between low-grade dysplasia and squamous metaplasia. Due to vasodilation, intraepithelial blood vessels become larger, which makes the low-grade lesions look more severe (Fig. 13.3). Subtle signs of invasive cancer can be easily missed within a high-grade intraepithelial lesion. Regarding the positioning of the patient, no changes in position is required in early pregnancy, whereas in late trimester, lying down in left lateral position is preferable to avoid supine hypotension during colposcopic examination.

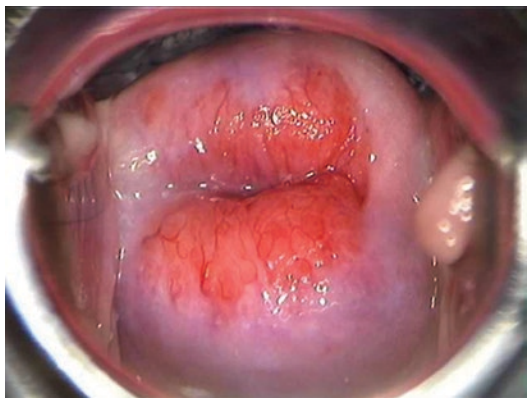

Fig. 13.3 Vasodilatation of intraepithelial blood vessels due to hormonal changes in pregnancy

13.6 Hispathological Examination

A sharp cut with a punch biopsy from the worst affected area under colposcopy guidance is recommended. Biopsy should only be done in high-grade lesions on colposcopic examination to rule out invasive cancer. As cytology test results, interpretation of histopathological findings is also challenging with prominent decidual changes and Arias-Stella reaction in the pregnant cervix. Due to high vascularity of the cervix, securing hemostasis becomes difficult but should be obtained with pressure gauze or Monsel's solution.

13.7 Management of CIN Lesions in Pregnancy

Repeated colposcopy examination with no evidence of high-grade lesions on colposcopy and biopsy is unnecessary and is categorized as unacceptable in ASCCP guideline. The majority of CIN lesions regresses in the postpartum period. The reasons for the regression may be the following [21, 22]:

- Due to natural history of the disease itself.
- The typical hormonal pattern during pregnancy may induce a viral activation that spontaneously leads to higher clearance rates postpartum.
- Misinterpretation of histopathological findings in antenatal period.
- The process of childbirth possibly leads to loss of abnormal cervical epithelium in intrapartum period.

Only high-grade lesions need further evaluation by colposcopy and guided biopsy to rule out invasive cancer. In case of absence of any invasive component in histology, treatment of even high-grade pre-cancers CIN2 and CIN3 can be deferred until 6 weeks postpartum with reevaluation by colposcopy and/or biopsy. Treatment methods available are as same as in non-pregnant women. Ablative methods by cryotherapy, thermocoagulation, laser ablation or excisional method by loop electrosurgical excision

procedure (LEEP), cold knife conization (CKC), and laser conization are the standard modes of treatment available for management of cervical pre-cancerous lesions.

13.7.1 Ablative Treatment

In case of high probability of loss to follow-up or if additional opportunities to treatment are unlikely, treatment during pregnancy by ablative method can be considered [24, 25]. The limited evidence does not suggest that either cryotherapy or thermocoagulation treatment during pregnancy is related to any adverse pregnancy outcomes; however, an increased risk of pregnancy loss cannot be ruled out, and further evidence is required. There also are possible negative perceptions if ablative treatment is accidentally associated with pregnancy loss by women.

13.7.2 Excision Method

Both LEEP and CKC in pregnancy should be performed if required to rule out invasive cancers. LEEP in the first trimester is a safe procedure with unclear evidences regarding comparison of obstetric outcome between cryotherapy and LEEP [25–27]. Meta-analysis on early pregnancy outcomes for CIN states increased risk of miscarriages when LEEP is performed in the second trimester possibly as a result of cervical incompetence after proportionally large excision during the LEEP procedure [27–29]. However, cold knife conization is associated with increased second-trimester miscarriages and more chances of cesarean delivery [30]. This may be due to larger depth of cone than the LEEP specimen with increased risk of cervical incompetence.

Unnecessary treatment of cervical pre-cancers can lead to cervical stenosis, preterm delivery, and preterm premature rupture of membranes [31]. The treatment of cervical pre-cancers in young women should be minimized with individual case assessment of risk-benefit ratio and chances of future fertility and adverse obstetric outcome.

13.8 Treatment of Invasive Cancer

Biopsy-proven invasive cancer cervix (ICC) in pregnancy should be referred to an oncology center. ICC requires a multidisciplinary approach according to the stage of the disease and gestational age of the current pregnancy.

13.9 Mode of Delivery

An abnormal screening test is not an indication for cesarean delivery. Even histologically proven high-grade pre-cancer is not a contraindication for vaginal delivery. In case of invasive cancers only, delivery by cesarean section is advised due to high probability of micrometastasis in locoregional area and/or obstruction of birth canal due to large growth [32].

13.10 Screening for HPV-Vaccinated Pregnant Women

After the introduction of HPV vaccination in 2007, there is a cohort of women who are vaccinated against high-risk oncogenic types 16 and 18 of HPV. Irrespective of their pregnancy status, current recommendation is as same as the routine screening protocol of non-vaccinated women [33, 34]. More studies are required to establish an evidence-based cervical cancer screening strategies for the HPV-vaccinated girls.

13.11 Conclusion

Cervical cancer screening guidelines are not different in pregnant population from non-pregnant population. In low-grade abnormalities, colposcopy and/or biopsy may be deferred until 6 weeks postpartum. In case of high-grade lesions, biopsy should be performed to rule out invasive cancers. Treatment options are also same as non-pregnant women but shall be reserved for highly selected cases and in suspicion of invasive cancers. In invasive cancer cases, appropriate referral to oncology center with multidisciplinary team

approach can influence the obstetric outcome as well as the prognosis of the disease.

Key Points

- The current indication for cervical cancer screening is same in both pregnant and non-pregnant women.
- Colposcopy may be deferred at least 6 weeks postpartum for atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions but should be used to triage high-grade abnormalities.
- Cervical biopsy in pregnancy is indicated only in suspicion of invasive cancer.
- Cervical pre-cancers should be monitored during pregnancy and reevaluated after delivery, which may be done vaginally.
- The treatment of cervical pre-cancers in young women should be minimized with individual case assessment of risk-benefit ratio and chances of future fertility and adverse obstetric outcome.
- More studies are required to establish evidence-based cervical cancer screening strategies for the HPV-vaccinated girls.

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