Retrospective observational study: the natural history of cervical intraepithelial neoplasia during pregnancy

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ABSTRACT

Aims: To assess the persistence, regression and progression of cervical dysplasia in pregnancy, within a tertiary London hospital.

Methods: All cases referred for colposcopy at Kings College Hospital during pregnancy, between September 2011 and August 2017, were retrospectively identified. Women underwent a tissue biopsy only if clinically indicated. All women were seen for colposcopy between 3 and 6 months postnatally. Women were excluded from the final analysis if they were referred for reasons other than an abnormal smear, and if follow-up data were not available.

Results: 82 pregnant patients (median age: 35 years, range: 27-48 years) were seen during this period. 56 cases were referred for colposcopy due to abnormal smears and had complete follow-up data; the other cases were excluded. 24 had high-grade cervical intraepithelial neoplasia (CIN). Of these, CIN regressed in 6/24 (25%) cases and persisted, necessitating excisional treatment, in 18/24 cases (75%). No cervical cancer cases were diagnosed. The regression, persistence and progression rates of the remaining 32 cases with low-grade smear abnormalities during pregnancy were: 20/32 (63%), 6/32 (19%) and 6/32 (19%) respectively.

Conclusion: This study shows high rates of regression of low-grade abnormalities following pregnancy. Additionally, there were no cases of progression of high-grade CIN to cancer, thus supporting safe conservative management of these women. Post-partum follow-up remains essential for those with high-grade CIN due to significant levels of persistence.

KEYWORDS

Colposcopy, CIN, pregnancy, pregnant.

Introduction

Cervical cancer is the most common gynaecological malignancy diagnosed during pregnancy. Its incidence is estimated to be 1.2-4.5 per 10,000 women [1-3]. Most pregnancies occur between the ages of 18 and 35 years, the same range that sees the peak incidence of cervical intraepithelial neoplasia (CIN). Accordingly, the prevalence of CIN in the pregnant population is approximately 1% [4].

Several studies have looked at the evolution of CIN in pregnancy. The risk of progression of low-grade CIN is thought to be small (6-14%) [5,6] with high rates of regression to normal after pregnancy, compared with matched non-pregnant controls [6]. This is in concordance with British Society of Colposcopy and Cervical Pathology (BSCCP) guidelines, and the American Society for Colposcopy and Cervical Pathology Consensus guidelines (ASCCP), which recommend colposcopic examination in pregnancy, if CIN 1 or less is suspected, and to repeat colposcopic examination 3 months postnatally [7,8].

Studies examining the regression, persistence and progression rates of high-grade CIN are much more variable. Serati *et al*., in one of the most cited studies, prospectively followed up 78 women who underwent a PAP smear at between 8 and 17 weeks' gestation and had abnormal cytology [6]. In their cohort of patients, at the first postpartum follow-up appointment, 53% of the women who had shown high-grade disease had persistent high-grade CIN and subsequently underwent large loop excision of the transformation zone (LLETZ), 27% showed complete regression, and 20% regression to CIN 1.

Fader *et al*. retrospectively analysed 1079 pregnant patients referred for colposcopy, of whom 164 had high-grade cytology [9]. Of these, only 36 patients had either biopsy-confirmed CIN 3 or colposcopic impressions of CIN 3. The regression rate was lower than Serati *et al* study, at 32%, with persistence rate of 68%. Due to the retrospective nature of this study, the follow-up rate was low, at approximately 50%. Other studies have reported regression rates of between 17 and 70% for high-

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grade CIN [10,11].

The aim of this study was to assess the persistence, regression and progression of cervical dysplasia in pregnancy, within a tertiary London hospital.

Methods

All women referred for colposcopy at Kings College Hospital during pregnancy, between September 2011 and August 2017, were retrospectively identified.

Data collected from ViewPoint software used for colposcopy included: demographic details, such as age and smoking history. In addition, gestational age at time of colposcopy, referral cytology, colposcopic impression and results of biopsy (if performed) were recorded. All patients underwent colposcopic examination performed by one of two highly experienced colposcopists. Women only had a tissue biopsy if clinically indicated, for example, those with suspicious lesions on colposcopy, or if there was a significant discrepancy between colposcopic and cytological findings.

The inclusion criteria were all women referred for colposcopy during pregnancy with an abnormal smear and seen both during pregnancy and between 3 and 6 months postnatally. The colposcopy findings had to be documented.

Women were excluded from final analysis if they were referred for reasons other than an abnormal smear, and if follow-up data were not available.

Results

82 pregnant patients were seen during this period. Their median age was 35 years (range 27-48 years). Seventy-three percent were parous and 10% were smokers. Twenty-three percent of the women had previously undergone LLETZ treatment. The women were seen at the colposcopy clinic antenatally at between 3 and 36 weeks' gestation.

Twenty-nine (35%) patients were referred due to high-grade smear abnormalities, and 38 due to low-grade abnormalities (46%). The remaining women were referred for reasons other than an abnormal smear, including: follow up of glandular disease (2%), vaginal bleeding (9%) and an abnormal-looking cervix (6%) – all these were excluded from further analysis.

Patients were also excluded if they had inadequate follow-up data (15 cases).

A total of 56 cases remained; of these 24 had high-grade CIN and 32 low-grade CIN. Only one patient underwent a punch biopsy during pregnancy for an abnormal-looking cervix. No complications associated with the punch biopsy were recorded.

Among the cases with high-grade abnormality in pregnancy, CIN regressed in 6/24 (25%) cases and persisted, necessitating excisional treatment postnatally, in 18/24 cases (75%). The 6-month test of cure smear was normal in all those who underwent treatment. No cervical cancer cases were diagnosed.

Among the women who showed low-grade smear abnormalities during pregnancy, the regression, persistence and progression rates were 20/32 (63%), 6/32 (19%) and 6/32 (19%) respectively. All those who progressed had LLETZ treatment postnatally, which confirmed high-grade CIN on histology.

Pregnancy outcomes were available only for 19/56 cases. Of these, 14/19 (74%) had vaginal deliveries, 4/19 had Caesarean sections (21%) and 1/19 had a miscarriage (5%).

Discussion

This study supports the BSCCP guidelines on conservative follow up of pregnant women with low-grade smear abnormalities postnatally, given the high rate of regression observed (63%). This finding is also consistent with other studies [5,6,12] that showed high regression rates of CIN 1, particularly when compared with a non-pregnant cohort [6].

It is well known that the cervix undergoes many physiological changes during pregnancy, which can make colposcopic examination challenging. It has been suggested that some of the physiological changes, such as those due to the interaction between oestrogen and HPV, may play a role in the increased regression rates seen postnatally [6]. There has also been some debate as to whether mode of delivery is associated with higher rates of regression [13-15]. Inadequate pregnancy outcome data in the present study limits any analysis focusing on mode of delivery.

Women with a history of treatment of cervical dyskaryosis are at higher risk of future abnormalities later in life [16]. In keeping with this, in this study, a significant proportion (23) of women with abnormal smears in pregnancy had already had at least one LLETZ treatment in the past.

Reassuringly, there were no cases of micro-invasive or invasive cancer in this cohort. This supports expectant management of high-grade CIN, in pregnancy too, and is in concordance with other studies which found very low rates of evolution to cancer [11]. There was, however, a very high rate of persistence of high-grade CIN (75%), which underlines the need for close follow up of these women postnatally. The variations in high-grade CIN regression and persistence rates observed in different studies (0-70% and 38-100%, respectively) may be due to differences in follow-up durations and populations and to variations in the methods used to confirm regression and persistence [5,11,17].

Many studies have shown that cervical biopsy is safe in pregnancy [18]. Indeed, because cytology and colposcopic examination alone can be inadequate for the evaluation of cervical abnormalities during pregnancy [18-20], patients with suspicious lesions should undergo a biopsy if there is doubt. There is significant variation amongst colposcopists regarding thresholds to perform cervical biopsies in pregnancy. In the present study only one patient had a cervical biopsy in pregnancy, with no complications. Many additional studies have shown that excisional treatment with LLETZ is also safe in the first trimester [21,22]. Siegler *et al*. performed LLETZ (also known as the loop electrosurgical excision procedure) in 43 pregnant patients with high grade CIN during the first 15 weeks of gestation [22]. There were no cases of major haemorrhage. Additionally, 92% had term deliveries.

One of the difficulties in evaluating studies of the evolution of CIN in pregnancy lies in the heterogeneous nature of diagnosis of high-grade CIN. In the present study, the diagnosis was based on smear and colposcopic examination, as biopsy was only performed if clinically indicated. This is different to several studies in which biopsy confirmation of CIN was among the inclusion criteria [6,11,17,23]. In the absence of histology there is a risk of misdiagnosis, given the difficulty of obtaining accurate colposcopic assessment in pregnancy [18,19]. In the present study, this difficulty was mitigated by the fact that all assessments were performed by one of two experienced colposcopists.

A limitation of this study is the size of the cohort, even though it is comparable with those of other studies looking at the evolution of CIN in pregnancy. In addition, due to its retrospective nature, 18% of the original cohort were lost to follow up, which could introduce potential bias.

In conclusion, this study showed a high rate of regression of low-grade abnormalities following pregnancy. Additionally, there were no cases of progression of high-grade CIN to cancer, thus supporting safe conservative management of these women. Post-partum follow-up remains essential for all pregnant women with dyskaryosis, although this applies particularly to those with high-grade CIN due to significant levels of persistence.

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