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Prior cervical conization and uterine sparing cervical cancer surgery

Imran Hamzawala and Charlotte Chaliha

INTRODUCTION

Cancer of the cervix is the second most common female cancer, with more than half a million cases occurring annually worldwide. Approximately 30% of women with cervical carcinoma are less than 35 years of age and, for many of these women, fertility is a major issue[1]. Cervical screening programs have significantly reduced the incidence and death rates due to cervical cancer in developed countries with a concomitant increased rate of detection of early cervical cancer accompanied by a peak incidence of preinvasive disease (cervical intraepithelial neoplasia (CIN)) at around 30 years of age[2]. Thus, women may present earlier in reproductive life with issues regarding fertility and future pregnancy which could be compromised depending on the treatment offered. Whilst the benefits of cervical screening are regularly cited, it has not been implemented worldwide, and deficiencies are particularly apparent in resource poor nations.

Large loop excision of the transformation zone is presently the standard treatment of precancerous cervical changes in those areas of the world where such technology is available. Cervical conization is often used for superficially invasive or microinvasive carcinoma of the cervix (FIGO stage 1A1) in women wanting to preserve fertility as the risk of parametrial extension and lymph node metastasis in stage 1A1 carcinoma of the cervix is less than 1%[3]. FIGO stage 1A2 tumors have a 7.8% incidence of nodal metastases, whereas this increases to 16–18% with FIGO stage 1B tumors[4]. The traditional treatment of cervical cancer is either radical hysterectomy or radiotherapy to the pelvis, both of which inevitably compromise fertility[5]. The obvious impact on fertility of traditional surgery has led to the introduction of techniques to preserve uterine function such as the radical trachelectomy. However, in order to offer fertility sparing surgery, patients must be carefully selected by specific examination under anesthetic and careful review of available histology obtained from previous biopsies. A magnetic resonance imaging (MRI) scan should be performed for careful assessment of cervical and paracervical tissues to exclude more aggressive extension of disease in order to accurately stage the tumor[6,7].

Both the treatment of CIN and early stage cervical cancer with uterine sparing surgery may have an impact on fertility and pregnancy outcomes, and all patients seeking a fertility sparing procedure must be counseled with regards to potential oncologic and obstetric outcomes. This chapter discusses the current fertility sparing procedures and their effect on future fertility and pregnancy.

RADICAL TRACHELECTOMY

Radical trachelectomy can be performed either vaginally or abdominally depending on the surgeon's preference and level of expertise. In a vaginal trachelectomy, the cervix is removed along with parametrial tissue and a cuff of vagina by the vaginal route with a simultaneous laparoscopic pelvic lymphadenectomy[8,9]. The uterine body is left intact and a non-absorbable suture, acting as a cervical cerclage is placed around the uterine isthmus to maintain uterine competency for future pregnancies. Abdominal radical trachelectomy is essentially a similar procedure, albeit involving an abdominal approach. Postoperative morbidity with trachelectomy includes dysmenorrhea (24%), dysplastic Pap smears (24%), irregular or intermenstrual bleeding (17%), problems with cervical sutures (14%), excessive vaginal discharge (14%), isthmic stenosis (10%), amenorrhea (7%) and deep dyspareunia[10]. Posttrachelectomy, in the absence of adverse prognostic factors, patients are advised to use contraception for 6 months before they consider pregnancy to ensure that no oncological concerns are present prior to a pregnancy[11]. If prognostic factors such as positive lymph nodes and involved histologic margins are present, these warrant completion of treatment in the form of radical hysterectomy or chemo/radiotherapy. Such additional therapy should be undertaken at a suitable postoperative time which is usually 4–6 weeks postoperation[12]. All trachelectomy cases require close gynecological oncology follow-up at 3 monthly intervals for the first year, 4 monthly intervals for the second year, 6 monthly intervals until 5 years and then yearly until 10 years. After 10 years, if no evidence of recurrence is present, patients should be able to return to the 3 yearly screening program or a similar program that is acceptable to the requisite bodies of different nations[12]. Consideration of pregnancy during this follow-up period should be in liaison with a gynecological oncologist for advice and follow-up during and after pregnancy.

Oncologic prognosis of trachelectomy procedures

Radical vaginal trachelectomy

A total of 790 patients have reportedly undergone radical vaginal trachelectomy in published studies which noted 4% recurrences and 2% deaths from these recurrences[13]. These results are comparable to those of radical hysterectomies for similar sized lesions[14]. With a tumor size of less than 20 mm and a depth of invasion of less than 10 mm, the incidence of parametrial involvement is 0.6%[15]. Hence, radical vaginal trachelectomy is reserved for women with tumors less than 20 mm in diameter and with invasion of less than 10 mm[16].

Dursun *et al*. in their critical literature review of radical vaginal trachelectomies reported the median age as 31 years and median follow-up time of 48 months (1–176 months). Some 60% of patients had a diagnosis of squamous cell carcinoma and 40% had adenocarcinoma. The overall recurrence rate was reported as 4.2% and the death rate as 2.8%[17].

Radical abdominal trachelectomy

Some 116 patients have undergone radical abdominal trachelectomy in published studies worldwide which also report two recurrences[13]. Ungar *et al.* reported the largest series of 33 patients with a mean age of 30.5 years (25–37 years) who underwent radical abdominal trachelectomy. During follow-up (median 47 months), no recurrences were observed. These authors suggest that the radical nature of the parametrial, sacrouterine, vesciocervical and pelvic lymphatic tissue resection with the abdominal approach may contribute to high levels of disease free survival rates[18].

Fertility and pregnancy outcomes postradical trachelectomy

Radical trachelectomy offers hope of future fertility; however, posttrachelectomy, patients express distress and significant concerns regarding conception and pregnancy lasting for up to 6 months[19]. Apart from the physical recovery from an operative intervention, the uncertainty of conception and the acknowledgment of the potential for a high-risk pregnancy are obvious concerns for these patients. Accordingly, the immediate months postsurgery represent an ideal time for readdressing potential concerns (stenosis, sexual function, reproduction) and providing referrals for further support if needed[20]. The use of vaginal dilator therapy and vaginal moisturizers is extremely beneficial in addressing vaginal stenosis, scarring and/or dyspareunia following cancer treatment[21]. These modalities also could be beneficial in treating trachelectomy patients with the above symptoms. Stretching of tissues due to dilator therapy may reduce fibrosis and scarring if initiated early on and may beneficially improve oxygenated blood flow to the requisite tissues[22]. The complexity of aftercare, which may vary greatly from patient to patient, is markedly enhanced by the addition of a nurse specialist and mental health professional to the multidisciplinary team looking after trachelectomy patients.

Fertility and miscarriage

In their summary of fertility data on patients who had undergone radical trachelectomy (six series), Plante *et al.* reported an overall fertility rate of 13% (40 of 310 patients). In this group, 14 conceived with reproductive assistance, as the adjusted fertility rate was 8% (26 of 310 patients). It was also noted that patients with infertility secondary to cervical causes or ovulatory dysfunction had a reasonable chance of conceiving with assisted reproductive techniques such as *in vitro* fertlization (IVF) or intrauterine insemination (IUI). However, patients with infertility secondary to male factor, uterine factor or unexplained factors were less likely to conceive[23]. Existing data on radical trachelectomy suggest factors such as cervical stenosis or adhesion formation may cause subfertility[15,23 24,], as is also the case when lack of cervical mucus, subclinical salpingitis and subclinical chronic endometritis are present[24–26].

Given the above circumstances, it is important to assess prior medical issues that may adversely impact future fertility. Ideally, collaborations with fertility specialists should be developed for optimal counseling and management[23]. Boss *et al.*, reviewing the literature, which included 16 studies involving 355 radical trachelectomy patients, noted that 43% of patients had attempted pregnancy and that 70% conceived. In those who became pregnant, 21% had a first trimester miscarriage, 8% had a second trimester miscarriage, 21% delivered in the third trimester before 36 weeks, whereas only 50% delivered after 36 weeks[27]. In a further series, Plante *et al*. reported a series of 50 pregnancies in 31 patients (retrospective review of 72 patients treated from October 1991 to October 2003) following fertility preserving vaginal radical trachelectomy. In this study, the rate of first trimester miscarriages was similar to that of the general population (16%), as was the rate of second trimester miscarriage (4% vs 3–5%). In their series, 72% were able to carry their pregnancies to the third trimester and, of these, 78% reached term (>37 weeks). The preterm delivery rate was higher than in the general population (16% vs 12%)[23].

Chorioamnionitis and premature rupture of membranes

The increased risk of preterm delivery may be related to premature rupture of membranes

secondary to chorioamnionitis as reported in several series. In the series reported by Schlearth *et al*. in 2003, one pregnancy ended at 22 weeks with chorioamnionitis and another ended at 26 weeks with fetal death[28]. In another series reported by Shepherd *et al*., six of the seven preterm births were preceded by spontaneous rupture of membranes without contractions[24]. This is similar to a series by Bernardini *et al*. where spontaneous rupture of membranes occurred without contractions in four of the six premature deliveries. Expectant management was carried out and all four women delivered within 4 days, three showing signs of infection at the time of delivery[25].

The etiology of premature rupture of membranes is thought to be either mechanical or infectious and most probably a combination of both[24,25,29]. Shepherd *et al*. suggested that the permanent cerclage placed around the isthmus at the time of radical trachelectomy, even though buried under vaginal mucosa, may still act as a source of bacterial contamination[24]. Kolomainen *et al*. reported a case of a postvaginal radical trachelectomy in a woman whose Pap smear showed presence of *Actinomyces*. Since *Actinomyces* have been associated with chorioamnionitis resulting in preterm labor, the authors recommended that anaerobic cultures be done on pregnant patients after a radical trachelectomy either as a routine or if signs of premature labor develop[30].

The cervical mucus plug may function to protect against ascending vaginal infection. In patients who undergo radical trachelectomy, however, disruption of endocervical glands results in inevitable reduction of mucus secretion. Thus impaired or absent production of mucus can facilitate the access of micro-organisms to the choriodecidual space and uterine cavity. Decidual cells, resident macrophages of decidua and neutrophils initiate a cytokine response. This elevation of cytokines is considered to be a cause of preterm labor and the subsequent occurrence of preterm premature rupture of membranes[31,32]. Accordingly, little benefit may derive from being conservative with trachelectomy patients who present with premature rupture of membranes, as they are likely to deliver within 2–3 days and a delay may lead to serious neonatal and maternal infection complications[23]. However, it has been suggested in one study that expectant management is a reasonable option until 32–34 weeks of pregnancy in patients with premature rupture of membranes without signs of chorioamnionitis[33].

Management of miscarriage

If first trimester miscarriage occurs, expectant management or induction with misoprostol is generally successful. If necessary a dilatation and curettage can be performed under a general anesthetic but cervical dilatation should be kept to a minimum to reduce the risk of breaking the cerclage around the isthmus[23].

The management of second trimester loss is more difficult. In the series by Plante *et al*. two patients spontaneously miscarried at 17 and 20 weeks, respectively[34]. In the series of Bernardini *et al*. the patient with second trimester loss delivered after removal of cerclage and induction with misoprostol[25]. Hysterotomies should be reserved for patients who fail the expectant/medical management or show signs of sepsis.

Antenatal care

Due to the increased risk of cervical incompetence, these patients need to be followed more frequently. A visit in a high-risk obstetric clinic every 2 weeks is recommended from 18 to 28 weeks and weekly thereafter. If cervical incompetence is diagnosed, placement of another cervical cerclage around the uterine isthmus should probably be attempted, depending on the stage of pregnancy[11].

Obstetricians caring for women who have undergone radical trachelectomy should be familiar with the procedure and aware of potential complications. If possible, a high-risk consultant with expertise in management of cervical incompetence and preterm labor should take the lead in managing these women.

Obstetricians should also stringently aim to reduce the risk of introducing infections. Hence, digital examinations should be reduced to a minimum and cervical cytology should probably be avoided beyond the first trimester[23]. Cessation of coitus is advisable between 20 and 36 weeks of pregnancy[35]. Cervical length may be followed up by serial vaginal ultrasounds[36]. This procedure has been used in non-trachelectomy patients where transvaginal ultrasound is found to be a good predictor of cervical incompetence with a good negative and poor positive predictive value[37].

Although, serial fetal fibronectin has been suggested for use in the third trimester to predict preterm birth, no data exist with regards to its use in trachelectomy patients[38,39]. Extrapolating from the data on premature birth in the general population, progesterone suppositories could be considered in pregnant women posttrachelectomy as they appear to significantly reduce preterm birth secondary to cervical incompetence in high-risk populations such as women with prophylactic cerclage and women with previous preterm birth[40–42].

Routine prophylactic steroids to accelerate fetal lung maturity are recommended in view of risk of premature delivery[24,25].

For patients with recurrent miscarriages a Saling technique was described in 1981. This is performed by excising and undermining the vaginal mucosa near the cervical opening, stretching it over the cervix and resuturing it in place to completely cover the cervical os to prevent ascending infection. It is usually performed at 14 weeks of gestation and patency of the cervical opening is restored at the time of cesarean section[43].

Mode of delivery

In view of the permanent cerclage placed at radical trachelectomy, delivery by cesarean section is indicated. In general, cesarean sections after radical trachelectomy are performed via a classical incision in order to prevent extension of the wound[44]. Generally 37–38 weeks is considered an optimal time for elective delivery[13].

Postnatal follow-up

No data suggest that pregnancy affects the cancer prognosis. Following delivery, the patient is advised to follow-up with her routine oncology appointments.

CONIZATION SURGERY

Factors affecting treatment of CIN include size and site of lesion, severity on colposcopic examination or histology of previous biopsy, anatomical characteristics of the transformation zone and suspicion of glandular neoplasia or microinvasive disease[45]. Two types of treatment are used for management of preinvasive disease: excisional and ablative procedures. Excisional procedures include cold knife conization, large loop excision of the transformation zone and laser conization. Ablative procedures include laser ablation, cryotherapy and diathermy.

Ablation in general is used to treat smaller, superficial and less severe areas. Excision treatment is used when there is a suspicion of invasion, a larger area, or transformation zone deep in the endocervical canal. Hence a larger area of cervix will be removed with excisional treatment. Studies show that treated women remain at higher risk than the general population for developing subsequent invasive cervical cancer, even many years after treatment[46–48].

Pregnancy outcome after conization surgery

A meta-analysis of 27 studies executed by Kyrgiou *et al*. in 2006 evaluated pregnancy outcomes in women previously treated for CIN. This pooled analysis reported that the risk of preterm delivery amongst women with large loop excision of transformation zone or cold knife conization was 1.7 and 2.6 times higher, respectively, than that of untreated women. A significantly increased risk was also noted for low birth weights with both methods, for premature rupture of membranes after large loop excision of the transformation zone and for cesarean delivery after cold knife conization. Laser ablation was not associated with adverse obstetric outcomes[49].

In a recent meta-analysis, Arbyn *et al*. looked at severe obstetric or neonatal outcome in women treated for CIN with excisional procedures (cold knife conization, large loop excision of transformation zone) and ablative procedures (laser ablation, cryotherapy and diathermy). Criteria for severe obstetric and neonatal outcome included perinatal mortality, severe (<32/34 weeks) and extreme (<28/30 weeks) preterm delivery, and severe low birth weight (<2000 g, <1500 g and <1000 g)[50]. This meta-analysis showed that cold knife conization was associated with severe adverse pregnancy outcomes, which included increased risk of perinatal mortality, severe preterm delivery and extreme low birth weight infants. The meta-analysis by Kyrgiou *et al*. in 2006 had previously suggested an increased risk of preterm delivery and low birth weight babies was associated with large loop excision of the transformation zone, but in the more recent meta-analysis large loop excision of the transformation zone did not significantly affect the more serious adverse obstetric outcomes; however, it was also suggested that it cannot be considered as completely free of adverse pregnancy outcome. Both meta-analyses showed that ablation with laser had no effect on pregnancy outcomes.

Laser conization may increase the risk of preterm delivery[51] and outcome after conization may be influenced by cone size and height[52,53], with women whose cone height is greater than 10 mm having a higher rate of preterm delivery than those with a cone height of less than 10 mm[54]. Inevitably the knife excises more tissue than the loop. Loop excisions that remove large amounts of cervical tissue probably have the same effect as knife cone biopsies. Most loop excisions in young women with fully visible transformation zone need to be only 1 cm deep and this conservatism should protect against serious obstetric outcomes[50].

Transvaginal ultrasound scan can predict preterm birth in women who have had large loop excision of the transformation zone procedures. The negative predictive value of the ultrasound scan is 95.2% for spontaneous preterm birth at less than 37 weeks in women with large loop excision of transformation zone[55]. Hence, this may be a valuable tool in pregnancy management along with serial scans for fetal growth in view of the increased risk of low birth weight babies.

Mode of delivery after conization

Vaginal delivery is not contraindicated after excisional procedures on the cervix. Paraskevaidis *et al*. looked at delivery outcomes after loop electrosurgical excision procedures for microinvasive cervical cancer. Their study showed that treated women did not have more delivery complications compared with controls, apart from a shorter duration of labor[56]. Another study by Klaritsch *et al*. looked at delivery outcomes after cold knife conization of the cervix and showed that cold knife conization is a risk factor for preterm birth and premature rupture of membranes and seems to be a risk factor for cervical tears; however, no difference was noted in mode of delivery, duration of labor, chorioamnionitis and use of oxytocin[57]. In contrast, an increased risk of

cesarean section after cold knife excision was reported by Kyrgiou *et al*.[49].

CONCLUSION

Cervical cancer is a disease that often affects women in their reproductive years. This is important, as with recent delays in childbearing in many developed countries, women may not have started their families when a diagnosis is made. Issues regarding fertility and conception therefore are highly important to them and have prompted a move from the very radical procedures of the past to fertility sparing procedures.

Treatments such as conization of the cervix and radical trachelectomy have shown promise with regards to future fertility and pregnancy; however, they are not without complications including premature rupture of membranes and preterm labor, both of which may lead to significant neonatal concerns and physical and emotional distress for the mother. Hence, patients undergoing radical trachelectomy/conization, need to be thoroughly counseled regarding issues of fertility sparing surgery on prognosis of disease, fertility and pregnancy. It is also important to note that these patients need to be managed in an obstetric department with a high-risk obstetrics consultant specialized in looking after such patients. Multidisciplinary input is essential with involvement of gynecological oncologist, neonatologist, nurse specialist and mental health professional.

Ultraconservative fertility sparing surgery for very early invasive cervical cancer (1A2 and early 1B1) is now under consideration. This involves a simple trachelectomy or a large cold knife cone with laparoscopic pelvic lymphadenectomy. However, the concept of an ultraconservative treatment approach warrants further investigation to evaluate the oncological safety and long-term prognosis[34]. Human papilloma virus (HPV) testing may help with the follow-up of women after treatment for CIN. Due to its high negative predictive value, it can clearly identify those women who are at a low risk of residual or recurrent disease[58–60]. This may give more confidence to clinicians to resort to less aggressive treatment practises. The introduction of HPV vaccine may also decrease the incidence of cervical cancer and precancerous lesions requiring treatment, which may subsequently reduce adverse obstetric outcomes.

REFERENCES

1. Office of National Statistics. *Cancer Statistics: Registration of Cancer Diagnoses 1991, England and Wales*, Series MB1, no 24. London, UK: Her Majesty's Stationery Office, 1997
2. Herbert A, Smith JA. Cervical intraepithelial neoplasia grade III (CINIII) and invasive cervical carcinoma: the yawning gap revisited and the treatment of risk. *Cytopathology* 1999;10:161–70
3. Jones WB, Mercer GO, Lewis JL, *et al*. Early invasive carcinoma of the cervix. *Gynecol Oncol* 1993;51:26–32
4. Sevin BU, Nadji M, Averette HE, *et al*. Microinvasive carcinoma of the cervix. *Cancer* 1992;70:2121–8
5. Morrow CP, Curtin JP, Townsend DE, eds. *Synopsis of Gynecologic Oncology*, 4th edn. New York: Churchill Livingstone, 1993:111–52
6. Peppercorn PD, Jeyarajah A, Woolas R, *et al*. Role of MRI imaging in the selection of patients with early cervical carcinoma for fertility-preserving surgery: initial experience. *Radiology* 1999;212:395–9
7. Sahdev A, Wenaden AET, Sohaib SA, *et al*. Magnetic resonance imaging in gynaecological malignancies. *Cancer Imaging* 2005;5:539
8. Dargent D. A new future for Schauta's operation through a pre-surgical retroperitoneal pelviscopy. *Eur J Gynecol Oncol* 1987;8:292–6
9. Querleu D, Leblanc E, Castelain B. Laparocopic pelvic lymphadenectomy in staging of early carcinoma of the cervix. *Am J Obstet Gynecol* 1991;164:579–81
10. Alexander–Sefre F, Chee N, Spencer C, *et al*. Surgical morbidity associated with radical trachelectomy and radical hysterectomy. *Gynecol Oncol* 2006;101:450–4

11. Roy M, Plante M. Pregnancies after radical vaginal trachelectomy for early stage cervical cancer. *Am J Obstet Gynecol* 1998;179:1491–6
12. Shepherd JH. Uterus-conserving surgery for invasive cervical cancer. *Best Pract Res Clin Obstet Gynaecol* 2005;19:577–90
13. Shepherd JH, Milliken DA. Conservative surgery for carcinoma of the cervix. *Clin Oncol* 2008;20:395–400
14. Marchiole P, Benchaib M, Buenerd A, *et al*. Oncological safety of laparoscopic assisted vaginal radical trachelectomy: a comparative study with laparoscopic assisted vaginal radical hysterectomy. *Gynecol Oncol* 2007;106:132–41
15. Covens A, Shaw P, Murphy J, *et al*. Is radical trachelectomy a safe alternative to radical hysterectomy for patients with stage 1A-B carcinoma of the cervix? *Cancer* 1999;86:2273–9
16. Dargent D, Martin X, Sacchetoni A, *et al*. Laparoscopic vaginal radical trachelectomy: a treatment to preserve fertility of cervical carcinoma patients. *Cancer* 2000;88:1877–82
17. Dursun P, LeBlanc E, Nogueira MC. Radical vaginal trachelectomy: a critical review of literature. *Eur J Surg Oncol* 2007;33:933–41
18. Ungar L, Palfalvi L, Hogg R, *et al*. Abdominal radical trachelectomy: a fertility – preserving option for women with early cervical cancer. *Br J Obset Gynaecol* 2005;112:366–9
19. Carter J, Sonoda Y, Abu-Rustum NR, *et al*. Reproductive concerns of women treated with radical trachelectomy for cervical cancer. *Gynecol Oncol* 2007;105:13–16
20. Carter J, Sonoda Y, Chi DS, *et al*. Radical trachelectomy for cervical cancer: Postoperative physical and emotional adjustments and concerns. *Gynecol Oncol* 2008;111:151–7
21. Denton AS, Maher EJ. Interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy. *Cochrane Database Syst Rev* 2003;(1):CD003750
22. Decruze SB, Guthrie D, Magnani R. Prevention of vaginal stenosis in patients following vaginal brachytherapy. *Clin Oncol (R Coll Radiol)* 1999;11:46–8
23. Plante M, Renaud M-C, Hoskins IA, *et al*. Vaginal radical trachelectomy: A valuable fertility – preserving option in the management of early – stage cervical cancer. A series of 50 pregnancies and review of literature. *Gynecol Oncol* 2005;98:3–10
24. Shepherd JH, Mould T, Oram DH, Radical trachelectomy in early stage carcinoma of the cervix: outcome as judged by recurrence and fertility rates. *Br J Obstet Gynaecol* 2001;108:882–5
25. Bernardini M, Barrett J, Seaward G, *et al*. Pregnancy outcomes in patients after radical trachelectomy. *Am J Obstet Gynecol* 2003;189:1378–82
26. Aust T, Herod J, Macdonald R, *et al*. Infertility after fertility preserving surgery for cervical carcinoma: the next challenge for reproductive medicine? *Hum Fertil (Camb)* 2007;10:21–4
27. Boss E, Van Golde RJT, Beerendonk CCM, *et al*. Pregnancy after radical trachelectomy: a real option? *Gynecol Oncol* 2005;99:S152–6
28. Schlaerth JB, Spirtos NM, Schlaerth AC. Radical trachelectomy and pelvic lymphadenectomy with uterine preservation in the treatment of cervical cancer, *Am J Obstet Gynecol* 2003;188:29–34
29. Mathevet P, de Kaszon EL, Dargent D. Fertility preservation in early cervical cancer. *Gynecol Obstet Fertil* 2003;31:706–12
30. Kolomainen DF, Herod JJ, Holland N, *et al*. Actinomyces on a papanicolaou smear following a radical trachelectomy. *Br J Obstet Gynaecol* 2003;110:1036–7
31. El-Shazly S, Makhseed M, Azizieh F, *et al*. Increased expression of pro-inflammatory cytokines in placentas of women undergoing spontaneous preterm delivery or premature rupture of membranes. *Am J Reprod Immunol* 2004;52:45–52
32. Sakai M, Sasaki Y, Yoneda S, *et al*. Elevated interleukin-8 in cervical mucus as an indicator for treatment to prevent premature birth and preterm, pre-labour rupture of membranes: a prospective study. *Am J Reprod Immunol* 2004;51:220–5
33. Jolley JA, Battista L, Wing DA, *et al*. Management of pregnancy after radical trachelectomy: case reports and systematic review of literature. *Am J Perinatol* 2007;24:531–9
34. M Plante. Vaginal radical trachelectomy: an update. *Gynecol Oncol* 2008;111:S105–10
35. Hill JA. Recurrent pregnancy loss. In: Maternal–*Fetal Medicine: Principles and Practices*, 5th edn. Philadelphia: WB Saunders, 2004:579–601
36. Petignat P, Stan C, Megevand E, *et al*. Pregnancy after trachelectomy: a high-risk condition of preterm delivery. Report of a case and review of literature. *Gynecol Oncol* 2004;94:575–7

37. Berghella V, Daly SF, Tolosa JE, *et al*. Prediction of preterm delivery with transvaginal ultrasonography of the cervix in patients with high risk pregnancies: does cerclage prevent prematurity? *Am J Obstet Gynecol* 1999;181:809–15
38. Daskalakis J, Papantoniou NE, Koutsodimas NB, *et al*. Fetal fibronectin as a predictor of preterm birth. *J Obstet Gynaecol* 2000;20:347–53
39. Lowe MP, Zimmerman B, Hansen W. Prospective randomized controlled trial of fetal fibronectin on preterm labour management in a tertiary care centre. *Am J Obstet Gynecol* 2004;190:358–62
40. ACOG Committee Opinion #291. Use of progesterone to reduce preterm birth, Nov 2003. *Obstet Gynecol 2003*;102:1115–6
41. Meis PJ, Klebanoff M, Thorn E, *et al*. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348:2379–85
42. da Fonseca EB, Bittar RE, Mario HB, *et al*. Prophylactic administration of progesterone by vaginal suppositories to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo controlled double – blind study. *Am J Obstet Gynecol* 2003;188:419–24
43. Saling E. Def fruhe muttermundverschluss zur Vermeidung habitueller Aborte und Fruhgeburten. *Z Geburtshilfe Perinatol* 1981;185:259–61
44. Ishioka S, Endo T, Hayashi T, *et al*. Pregnancy related complications after vaginal radical trachelectomy for early stage invasive uterine cervical cancer. *Int J Clin Oncol* 2007;12:350–55
45. Prendiville W, De Camargo M, Walker P. The use and abuse of LLETZ. *CME J Gynecol Oncol* 2000;5:85–7
46. Kalliala I, Anttila A, Pukkala E, *et al*. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia : Retrospective cohort study. *BMJ* 2005;331:1183–5
47. Soutter WP, Sasieni P, Panoskaltsis T. Long term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer* 2005;118:2048–55
48. Strander B, Andersson-Ellstrom A, Milsom I, *et al*. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: Population based cohort study. *BMJ* 2007;335:1077
49. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, *et al*. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;367:489–98
50. Arbyn M, Kyrgiou M, Simoens C, *et al*. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ* 2008;337:a1284
51. Hagen B, Skjeldestad FE. The outcome of pregnancy after CO2 laser conisation of the cervix. *Br J Obstet Gynaecol* 1993;100:717–20
52. Ricciotti HA, Burke L, Kobelin M, *et al*. Ultrasound evaluation of cervical shortening after loop excision of transformation zone (LETZ). *Int J Gynaecol Obstet* 1995;50:175–8
53. Gentry DJ, Baggish MS, Brady K, *et al*. The effects of loop excision of transformation zone on cervical length: implications for pregnancy. *Am J Obstet Gynecol* 2000;182:516–20
54. Raio L, Ghezzi F, Di Naro E, *et al.* Duration of pregnancy after carbon dioxide laser conisation of the cervix: influence of cone height. *Obstet Gynecol* 1997;90:978–82
55. Crane JM, Delaney T, Hutchens D. Transvaginal ultrasonography in the prediction of preterm birth after treatment for cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2006;107:37–44
56. Paraskevaidis E, Koliopoulos G, Lolis E, *et al*. Delivery outcomes following loop electrosurgical excision procedure for microinvasive (FIGO stage 1A1) cervical cancer. *Gynecol Oncol* 2002;86:10–3
57. Klaritsch P, Reich O, Giuliani A, *et al*. Delivery outcome after cold knife conisation of the uterine cervix. *Gynecol Oncol* 2006;103:604–7
58. Paraskevaidis E, Arbyn M, Sotiriadis A, *et al*. The role of HPV DNA testing in the follow up period after treatment for CIN: a systematic review of literature. *Cancer Treat Rev* 2004;30:205–11
59. Arbyn M, Paraskevaidis E, Martin-Hirsch P, *et al*. Clinical utility of HPV DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN. An update of pooled evidence. *Gynecol Oncol* 2005;99:7–11
60. Arbyn M, Sasieni P, Meijer C, *et al.* Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine* 2006;24:78–89