PRESERVING FERTILITY: NEW SURGICAL APPROACHES TO THE MANAGEMENT OF EARLY CERVICAL CANCER

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Abstract

The diagnosis of cervical cancer is particularly devastating when it occurs in young women who have yet to complete, or even start their family. In the past, the options for treatment, either radical hysterectomy or radical radiotherapy, rendered women infertile. In the 1990s the technique of radical trachelectomy was developed which potentially preserved fertility in these young women while treating their cancer. Experience with this technique has grown in the past 10 years such that there is evidence that in highly select patients, who are highly motivated to preserve their fertility and whose cancers fulfill strict criteria (early stage disease, tumours less than 2cm and otherwise suitable for surgical treatment), survival rates are equivalent to radical hysterectomy. The procedure is not without risk and the pregnancies that may ensue are to be considered high-risk with the incidence of second trimester loss (11%) and the incidence of pre-term birth (18%) more than double that of the general population.

Cancers, in general, are often thought to be diseases of 'old' people. Nothing could be further from the truth with cervical cancer. It has its peak incidence in the 45 to 49 year-old age group and over 30% of all cervical cancers are diagnosed in women in their prime reproductive years (ages 20 to 40).[1] Given the increasing trend for women in Australia and in other developed countries to delay childbearing into their thirties and later, it is not surprising that some patients are faced with a diagnosis of cervical cancer when they have yet to complete or even start their family. For young women, the otherwise successful treatment of early cervical cancer with radical hysterectomy or radical radiotherapy can still be devastating because they are rendered infertile in the process.

It was in response to this difficult clinical scenario that Daniel Dargent first developed the technique of radical vaginal trachelectomy in order to preserve the uterus in women diagnosed with early stage cervical cancer.[2]

Technique

The radical vaginal trachelectomy described by Dargent involved removal of the upper vaginal cuff, paracervical tissue and cervix up to the isthmus of the uterus. A pelvic lymphadectomy was also performed. The lower uterine segment was then rejoined to the vagina. Subsequently, there have been modifications to this technique. Plante and Roy described leaving up to 1cm of upper cervix to try and optimise a woman's reproductive potential.[3,4] Smith et al have described the technique of radical abdominal trachelectomy, stating it is an easier technique to master for surgeons more familiar with the technique of radical abdominal hysterectomy than radical vaginal surgery.[5] As world-wide experience with all these techniques grows it can be said that, for best results, the technique should be limited to women who would otherwise be candidates for radical hysterectomy, but who have a strong desire to preserve fertility and have a tumour size less than 2cm.[3]

For patients who fulfill the above criteria and choose fertility sparing surgery, a pelvic lymphadectomy with frozen section is first carried out, either laparoscopically or via open technique, to ensure that there is no evidence of extra-cervical spread. If the nodes are involved, then the radical trachelectomy procedure is abandoned in favour of definitive surgery or radiotherapy as the preferred treatment as individual circumstances dictate. If the nodes are negative, then radical trachelectomy is performed, with the upper margin of the cervical specimen being assessed by frozen section to ensure a tumour free margin of at least 5mm. Then the upper cervix, or what remains of it, is sutured to the vagina. A catheter may be inserted to prevent scarring and narrowing of the newly formed cervical os and a permanent cervical suture may also be inserted.

Safety

Radical hysterectomy has been a highly successful treatment of early cervical cancer for many years, with five year survival rates of over 90% for small tumours. There is no doubt that when the new technique of radical trachelectomy was described, there were misgivings about the wisdom of meddling with such success. Concerns were expressed that patients undergoing radical trachelectomy would have an unacceptably high central recurrence rate. No randomised controlled trials have been done comparing radical hysterectomy with radical trachelectomy and it would be considered impractical because of low patient numbers. Thus, any information regarding the success of the treatment in oncological terms rests with comparing reported outcomes in patients who have undergone radical trachelectomy with those who have undergone radical hysterectomy.

To date, the outcome of 548 patients undergoing radical vaginal trachelectomy have been reported.[4, 6-14] With a median follow-up time of 44 months (range 1-176),

there have been 22 recurrences (4.0%) and 14 deaths (2.6%). This is certainly comparable, or even better than, the results expected with conventional treatment. It should be remembered that the patients undergoing radical trachelectomy were highly selected and even included patients who might have been adequately treated with cone biopsy alone. In addition, those with adverse prognostic features such as lymphatic space invasion, tumour size greater than 2cm and high grade histology, were often excluded.

Outcomes with radical abdominal trachelectomy have also been published, however the reported cases are much fewer. In total, three investigators have reported their results on a total of 37 patients who have undergone radical abdominal trachelectomy.[15-17] Follow-up information is available on only 33 patients. With a median follow-up of greater than three years (range 9-75 months), there have been no recurrences and no deaths.

Surgical morbidity, including intra-operative and post-operative complications, appears to be lower in patients undergoing radical vaginal trachelectomy than radical hysterectomy because the procedure is less extensive. Shepherd's group reported that blood loss, analgesic requirements and length of hospital stay were all shorter with the radical vaginal trachelectomy group as compared to radical hysterectomy group.[18] In addition, bladder hypotonia was also less frequent. On the other hand, patients undergoing radical vaginal trachelectomy had more problems with dysmenorrhea (24%), dyspareunia, irregular vaginal bleeding (17%), amenorrhea (7%) and cervical stenosis (10%).

Obstetric outcomes

The 'raison d'etre' for performing radical trachelectomy rather than radical hysterectomy is to allow the patient to successfully carry a pregnancy and deliver a healthy baby. Accordingly, obstetric outcome is of paramount interest. Because the procedure radically compromises the cervix, in its early days there were concerns expressed about the ability of patients to conceive a pregnancy and to carry a pregnancy to viability, let alone term.

Obstetric outcomes have been reported in 484 patients undergoing radical trachelectomy (see Table 1).[13,14,19] Of the 484 patients, less than half (214) have attempted conception with 118 patients succeeding (70%). As shown in Table 2, there have been 213 pregnancies. Ninety-three patients have had a live birth at greater than 36 weeks. Eighteen per cent have had a first trimester loss or spontaneous abortion, which is comparable to the general population. Of concern is that 18% have had a live birth at less than 36 weeks (preterm birth) and 11% have had second trimester losses. This compares unfavourably to the general population, where the incidence of pre-term birth is 7-8% and the incidence of second trimester loss is 3%.

All would agree that these pregnancies should be considered high-risk with a substantial risk of pre-term birth and second trimester loss. This is felt to be related to decreased cervical length, alteration in cervical mucous and presence of a cervical suture leading to infection.[19]

Frequent antenatal visits will be required and some investigators advocate serial cervical length measurement.[20] Given that increased incidence of pre-term birth is felt to be due to ascending infection and premature rupture of membranes, other investigators advocate screening for bacterial infection and use of prophylactic antibiotics.[21] Those with a cervical suture in place will need delivery by caesarean section.

There is little guidance in the literature as to how to best manage these high-risk and much wanted pregnancies.[22] No consensus exists on the timing of the pregnancy or even whether there should be a waiting period after the procedure before attempting pregnancy.

It is interesting to note that less than half of the women undergoing this procedure have actually attempted pregnancy. The reasons for this are varied, however may relate to short follow-up of some studies, lack of partner at follow-up, or early age at diagnosis of cancer, with desire to maintain options or changed circumstances.

The future

Patients who are being evaluated as candidates for radical trachelectomy often have had a cone biopsy prior to definitive treatment to adequately assess their disease and size of tumour. One of the interesting observations from several studies on radical trachelectomy is the high rate of no residual disease on the final trachelectomy specimens. Shepherd, in the largest radical trachelectomy study to date, reported that 63% of patients had no residual disease on final pathology.[13]

This raises the question as to whether even less aggressive surgery may provide similar outcomes to radical trachelectomy in early stage, low volume disease. Rob et al has reported on a less aggressive approach, in which 26 women who underwent large cone biopsy or simple trachelectomy, combined with laparoscopic sentinel pelvic node identification for early stage cervical cancer.[23] With a median follow-up of 49 months, he reported one central recurrence which was treated with chemo-radiation, with no evidence of disease 36 months later. Fifteen out of 26 women planned a pregnancy, with 11 succeeding (15 pregnancies). Of these pregnancies, there were eight children delivered, three of which were pre-term deliveries at 24 weeks, 34 weeks and 36 weeks, respectively.

There have been no other reported studies to date and much larger numbers of patients will be required to determine whether this could be a reasonable option for highly selected patients in the future.

Patient expectations

The option of radical trachelectomy provides hope to a woman diagnosed with invasive cervical cancer that she may still be able to have a child of her own. In the face of a diagnosis of a life-threatening disease, this is often the most positive piece of information she is given. Are the expectations of women in this situation valid, and what are their concerns about their reproductive future?

Carter et al addressed the reproductive concerns of women treated with radical trachelectomy in a study of 29 patients undergoing the procedure.[24] She found that pre-operatively, patients had relative high expectations of successful conception and childbirth in that 85% of patients rated their chances of conceiving at 50% or greater. By six months post-operatively, expectations had declined such that only 63% of patients rated their chances at 50% or greater. Six months post-operatively, 85% of women had concerns about pregnancy and 27% had concerns about time pressures ie. 'clock ticking'. Clearly, while radical trachelectomy offers hope for future fertility, it does not remove anxieties and concerns women may have about future fertility.

Conclusions

Radical trachelectomy is slowly gaining acceptance among the gynaecologic oncology community as a valid option for a highly select group of patients with early cervical cancer who wish to preserve their fertility options. Given that the incidence of cervical cancer in Australia continues to fall, this is not a procedure that will commonly be performed by all gynaecological oncologists. In expert hands, the survival rates following the procedure are comparable to that of radical hysterectomy. However, patients need to be fully informed about the risks of infertility, early pregnancy loss, pre-term delivery and neonatal complications. The challenge for gynaecological oncologists in the future is to recognise how safely we can push the limits of conservative treatment without jeopardising outcome and survival.

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