CERVICAL PREGNANCY: DIAGNOSIS AND MANAGEMENT OPTIONS.

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ABSTRACT

Ectopic pregnancy is associated with significant morbidity and mortality in the first trimester. With *in vitro* fertilization and better early diagnosis, the incidence of ectopic pregnancies has increased. Although cervical pregnancies are <1% of all ectopic pregnancies, they could be associated with life-threatening bleeding. Transvaginal ultrasonography is the mainstay of diagnosis of cervical pregnancy, but beta-human chorionic gonadotrophin may be helpful in monitoring treatment outcomes. Current therapeutic options for cervical pregnancies include conservative management which could be medical, surgical or both, and 'radical' surgery.

The advent of real-time transvaginal ultrasound examination has allowed earlier diagnosis which has in turn permitted life-saving and fertility-sparing treatment options. Various conservative haemostatic measures may be used if bleeding occurs during conservative management. Clinicians should watch carefully for a possible increased risk of preterm labour or incompetent cervix, while reassuring patients that most pregnancies after a cervical ectopic will lead to term deliveries.

Keywords: cervical pregnancy, transvaginal ultrasonography, methotrexate.

INTRODUCTION

Ectopic pregnancies are situated outside the normal endometrial lining of the uterus. These conceptuses are also regarded as extrauterine pregnancies. This may not be strictly correct however, as pregnancies located in the interstitial, cornual and cervical portions of the uterus, though ectopic, are still regarded as uterine in location.

Varying incidences for ectopic pregnancies have been quoted. These figures are sometimes difficult to reconcile because different denominators have been employed in the calculations e.g. the figures from Lithuania are 23.8/1000 live births, 11.2/reported 1000 pregnancies and 10.1/10,000 women aged 15-44 years! However, a review of the trend suggests that the overall incidence is increasing due to the development of highly-sensitive pregnancy detection kits (able to identify cases that would otherwise have spontaneously resolved) and transvaginal ultrasound imaging techniques.

Cervical pregnancy refers to an uncommon form of ectopic pregnancy implanted within the cervical mucosa. It is estimated that 0.15 % (< 1%) of all ectopic pregnancies are cervical pregnancies, and they make up about 1 in 18000 deliveries.[1]

Ectopic pregnancy was the cause of eight of the 129 direct maternal deaths in the United Kingdom (1994 - 96) and is an important cause of maternal mortality in the first trimester. Also cervical pregnancies could result into life-threatening haemorrhage, requiring hysterectomy in about 50% of cases.[4] Thus, a high index of suspicion, close surveillance of at-risk patients and a knowledge of the evidence-based management options of this rare pregnancy complication will reduce its case fatality rate.

The use of sensitive kits for the detection of beta-human chorionic gonadotrophin levels and high-resolution ultrasonography has resulted into earlier diagnosis, thus shifting the management from inpatient surgical therapy to selective outpatient management.

This review will highlight the diagnostic clues and also discuss the various modalities of management of cervical ectopic pregnancies and the outcome from the available literature.

MATERIALS AND METHODS

An electronic search of the published literature was conducted using the search terms “cervical pregnancy,” “ectopic pregnancy” and “management.” Pub Med, and other indexed journals specifically addressing management of cervical ectopics were searched. An Internet Google search with the terms “pregnancy/ectopic/cervix” was also done. Websites of international

organizations and private foundations with a bearing on the topic were also searched. All original articles that addressed various management options of cervical ectopic pregnancy and their outcomes were included in the study. The search was restricted to English language articles.

RESULTS

Historical background

Before 1970, the diagnosis of cervical pregnancy was commonly made when dilatation and curettage for presumed incomplete abortion resulted in unexpected haemorrhage. The use of cervical imaging techniques has however made earlier diagnosis with more certainty possible. This was initially done transabdominally, making the diagnosis obvious before the onset of severe haemorrhage,[7] and later transvaginally.[7] Recently, magnetic resonance imaging of cervical pregnancies has also been documented.[7]

Traditionally, due to delayed diagnosis, hysterectomy used to be the only life-saving option. However with earlier diagnosis, non-surgical methods e.g. local or systemic methotrexate administration have been successfully used.[7] The use of methotrexate in the treatment of cervical ectopic was first reported by Farabow *et al* in 1983, and this has been followed by other documented cases.[13, 14] Surgical evacuation of products of conception with subsequent cervical cerclage,[5] local sonographically-guided potassium chloride injection or prostaglandin instillation and the use of a Foley catheter[9, 16] to prevent severe haemorrhage have also been documented.

Tamponade of the bleeding implantation bed in the cervix using the inflated balloon of a Foley catheter was first documented by Kuppuswami *et al*. Subsequently, reports employing balloon tamponade alone or in conjunction with other measures were documented.[7]

Aetiology and Risk Factors

The aetiology is obscure, although accelerated migration of the fertilized ovum through the uterus (such that there is rapid transportation of the fertilized ovum to the cervical canal before it is capable of nidation), damage to the endocervical canal and *in vitro* fertilization have all been postulated as possible mechanisms.[4, 9,]

Thus, the risk factors include previous dilatation and curettage, previous cervical pregnancy[13] or uterine scar, pelvic inflammatory disease and endocervical inflammation from intrauterine contraceptive device.[4, 9, 26] Other risk factors include multifetal pregnancy, embryonic chromosomal anomalies, tumours of the reproductive tract and decidual proliferation of the endocervical epithelium due to hyperoestrogenaemia.

Cervical ectopics have been documented after *in-vitro* fertilization and embryo transfer and even after intra-fallopian transfer, suggesting that the incidence of cervical pregnancies increase with increasing use of assisted reproductive technologies.[3] However, a study by Kirk *et al* including seven cases of cervical pregnancies showed that all the ectopics were products of spontaneous conceptions. It is yet to be decided therefore, whether these risk factors are more of postulations than proofs.

Clinical Presentation

The clinical presentation is usually that of painless first-trimester vaginal bleeding after a variable period of amenorrhoea, although cramps have been described by some patients. Pelvic examination could reveal a bluish cervical lesion, soft but enlarged cervix (sometimes disproportionately so in comparison with the uterus), a partially dilated cervical os and profuse haemorrhage on manipulating the cervix.[10]

Diagnosis

Using trans-vaginal ultrasonography, Timor-Tritsch *et* al[13] described their diagnostic criteria for cervical pregnancy: (i) the placenta and entire chorionic sac containing a live fetus are below the internal os, (ii) the uterine cavity is empty and (iii) the cervical canal is significantly dilated and barrel-shaped. It could also be sonographically diagnosed when a gestational sac with peri-trophoblastic blood flow or a live embryo is seen within the cervix. Magnetic Resonance Imaging (MRI) could also help to identify the pregnancy and assess its location within the cervix.[15,16,31]

The products obtained should necessarily be sent for histology. To confirm cervical nidation, Rubin's criteria has been suggested: (i) cervical glands must be attached to the placenta, (ii) the placenta must be implanted below the place where the uterine vessels reach the uterus and (iii) the attachment between the placenta and the cervix must be intimate.

Management Options

This could be divided into Conservative (with the preservation of the uterus) or 'Radical' modalities. The conservative options could be further subdivided into Medical, Surgical or Combined Medical and Surgical.

Conservative

Medical Management

This involves the use of pharmacological agents like methotrexate, potassium chloride and prostaglandins. Studies have been done more with methotrexate than with any other agent.

Methotrexate has been administered systemically by intravenous infusion[18] or intramuscular injection. Sometimes, a single dose[18, 27, 31] may be all that is needed whereas, other patients may require two doses.[6] The use of high-dose systemic methotrexate without surgical procedures has been linked with resolution of the ectopic gestational sac.

Many studies have also recorded successful outcomes with ultrasound-guided local injections of methotrexate into the gestational sac to cause fetal death. These have been done transabdominally,[6] transvesically[6] and transvaginally.[14, 19] Spontaneous expulsion of the products of conception may follow (as was reported of an 11weeks and 4day-old cervical pregnancy with intact gestational sac spontaneously expelled following commencement of methotrexate therapy accompanied by minimal bleeding not requiring surgical intervention) or bleeding may occur necessitating the use of surgical options to avoid catastrophic outcomes. Suzumori *et al* described the management of an 11-week cervical gestation which was accompanied by heavy bleeding after systemic methotrexate treatment. The bleeding continued despite ligation of the descending branches of the uterine arteries and application of a cervical cerclage, but was successfully controlled by a unilateral internal iliac artery embolization on the same side as the ectopic gestation. Two-and-a-half years later, the 33-year old woman had a vaginal delivery of a healthy baby at 38 weeks gestation.

Surgical Management

Dilatation of the cervix and Curettage of the products of conception from the endocervical canal has been used alone or in conjunction with tamponading of the bleeding implantation site using the inflated balloon of the Foley's catheter,[9, 16, 23, 24, 25] occlusion of the site using a cerclage[5] or roller – ball ablative technique. Maschiach *et al* reported 4 cases of CP including one heterotopic pregnancy (intrauterine and cervical) treated successfully with placement of Shirodkar cerclage.

Bleeding may continue despite these measures and interventions like ligation of the descending branches of the uterine arteries or unilateral (on the same side as the ectopic pregnancy) angiographic embolization of the internal iliac artery could be done to control haemorrhage and preserve the woman's reproductive potential.[35]

Combined Medical and Surgical Approach

This involves the initial commencement of treatment using a pharmacological agent e.g. to cause cessation of the fetal cardiac activity followed by dilatation and curettage with or without the other surgical options mentioned above.

The surgical option could also precede the use of a pharmacological agent. Cepni *et al* treated a 9-week old cervical pregnancy with transvaginal ultrasound-guided aspiration of the contents of the sac followed by single systemic dose of methotrexate.

'Radical'

Other treatment options include surgical interventions like internal iliac artery ligation or total abdominal hysterectomy to arrest life-threatening pelvic haemorrhage.[5]

CERVICAL PREGNANCIES

SUMMARY OF MANAGEMENT OPTIONS (already referenced)

Lead Author	Year	Number of Cases	Gestational Age (days)	Medical Treatment	Surgical Treatment	Outcome
Leon[48]	2003	1	49. Fetal heart present	MTX	Curettage	Foley catheter balloon tamponade used to assist with haemostatsis
Monteagudo[14]	1996	1		MTX; TV route.		IUP continued
Spitzer[22]	1997	1		PG; intra - amniotic	Adjuvant Curettage	
Goldberg[5]	2000	1	Viable	Systemic MTX.	Curettage	Cervical Cerclage inserted

Tuncer[31]	2001	1	72		Curettage	Uterine artery ligation, cervical hysterotomy and eventually hysterectomy due to uncontrolled haemorrhage.
Maschiah[37]	2002	4	44 - 59	MTX	2 each had emergency and elective cerclage	Successful.
Suzumori[35]	2003	1	77	MTX	Ligation of descending branches of uterine artery, cervical cerclage and unilateral internal iliac artery embolization	Successful delivery two - and-half years later.
Cepni[38]	2004	1		Aspiration of sac via TV route, then MTX	Curettage	Successful.
Doubilet[21]	2004	1		Intra-amniotic KCl		
Kim[45]	2004	31		14 had MTX alone while 8 had MTX with simple curettage, curettage & Foley catheter tamponade, cervical cerclage, ligation of descending branches of uterine artery or ligation of hypogastric arteries	1 had D & C only, 5 had D & C with other haemostatic measures (as with the MTX group) while 3 had hysterectomy	The uterus was preserved in all those in the MTX group. 3 women had healthy babies in subsequent pregnancies.
Sherer[34]	2004	1	81	MTX		The dead fetus was expelled with its intact sac on the 2 nd day with minimal bleeding.
Mesogitis[6]	2005	9	42 - 54	25mg MTX; TA route. 2 women had repeat MTX doses. All had outpatient management	Curettage 1-week later if fetus was dead, sac regressing and β -hCG declining	No admissions or side effects noted.
Kirk[30]	2006	7	36 – 80. Fetal heart present in 3 cases	3 had single dose MTX, 1 each had multiple doses and intra-amniotic MTX, 1 had expectant management while 1 had initial single dose, later multiple dose regimen and then intra - amniotic KCl (due to persistent fetal heart tones)	5 had Curettage while one was managed expectantly	No mortality or morbidity. Median hospital stay was 18days, median number of follow-up scans was 4 and median number of serum β - hCG tests was 12.

MTX: Methotrexate; **TV**: Transvaginal; **IUP**: Intra-uterine pregnancy; **PG**: Prostaglandin; **KCl**: Potassium chloride; **D & C**: Dilatation and curettage; **TA**: Transabdominal; **β-hCG**: beta-subunit human chorionic gonadotrophin.

Beta-human Chorionic Gonadotrophin (β-hCG) monitoring

The levels of β-hCG have been used serially to monitor the response of the woman to the management option offered to her. In fact, high initial levels have been found to correlate well with failure of treatment with methotrexate.''

Successful treatment is regarded as one that resulted in appropriate lowering of the beta hCG levels. Treatment with methotrexate with or without surgery resulted in a fall in β-hCG levels to non-pregnant levels within a variable period depending on the initial value, presence of a yolk sac e.t.c. While one study[27] reported a return to normal in 13 days from onset of treatment, another study[6] reported 22 to 72 days. The level begins to fall from a median time of 14 days (range 9 - 17) and complete regression would be noticed in 68 (range 19 – 143) days after treatment.[33]

The disparity in the rates of regression of the cervical pregnancy compared with the β-hCG levels was noted by Song *et al*.[33] While the cervical gestational mass appeared to start regressing from a median of 40 days (range 10 – 88 days), the β-hCG levels began to return to normal from a median of 14 days (range 9 - 17) after treatment. The regression of the cervical pregnancy from a gestational sac into a mixed echoic lesion on transvaginal evaluation took 86 (range 48 - 181) days while the median time for complete regression of the β-hCG was 68 (range 19 - 143) days after treatment. This shows that resolution of the cervical mass on sonography lags far behind the resolution of the β-hCG.

DISCUSSION

Although the advent of ultrasonography has made the diagnosis more accurate, making a diagnosis with certainty may still remain a problem in developing countries where access to and experience in ultrasonography is limited.

One differential diagnosis of a cervical ectopic is spontaneous abortion. The distinction is made from follow-up scans because while the position of the cervical pregnancy does not alter, the spontaneous

miscarriage changes in size and position.[31]

A suspicion of cervical ectopic makes radiological evaluation mandatory since the detection of the pregnancy before the occurrence of torrential bleeding, for example, would reduce the unfavourable outcomes of management.[43] In a study of 31 cervical pregnancies in which 22 had methotrexate treatment and 9 had surgical interventions without methotrexate, the findings suggested that early diagnosis and methotrexate chemotherapy, sometimes with concomitant conservative surgeries like dilatation and curettage, cervical cerclage, Foley catheter tamponade and ligation of the descending branches of the uterine arteries could contribute to successful treatment with preservation of the uterus and future reproductive ability.

Early diagnosis has resulted in the detection of increasing numbers of cervical pregnancies with active fetal cardiac activity. The presence of a viable fetus with relatively advanced gestational age coupled with high beta human chorionic gonadotrophin levels have been linked with higher rates of treatment failure.[39, 40] Also, Bai *et al*[41] found no significant relationship between efficacy of treatment and women's parity, size of the conceptus and presence of fluid in the peritoneal cavity, but they noted that those cervical pregnancies that presented with serum beta human chorionic gonadotrophin levels >10,000 mIU/mL and fetal cardiac activity were associated with a higher failure rate of primary methotrexate treatment. Other prognostic factors include conceptus >9weeks and crown-rump length (CRL) >10mm.[27]

A Boston, United States' study[42] on the other hand, identified a yolk sac on transvaginal sonography in 88% of women with ectopic pregnancies who had treatment failure. It was not noted in any patient who had a successful treatment. Although the beta hCG level was a useful adjunct, the most reliable predictor of failure of the treatment when the size of the ectopic mass, the presence of a pseudogestational sac, amount of free fluid, presence of a yolk sac and fetal heart motion were considered, was the presence of the yolk sac. Also, Lipscomb *et al* in a study of tubal pregnancies, found that 16 women had failed treatment out 73 (21.9%) who had a yolk sac compared with 36 of 486 (7.4%) without a yolk sac [p=0.0003].

The injection of methotrexate locally has been shown to be more effective in stopping the fetal cardiac activity and reducing the risk of treatment failure than systemic administration.[27,] A total dose of 1mg/kg body weight of methotrexate or 1 – 3mls of potassium chloride (concentration of 2mEq/ml)[21] is injected under ultrasonic guidance into the gestational sac or into the embryo if it is >5mm in length. This has the advantages of ablating the abnormal pregnancy, allowing a concomitant intrauterine pregnancy (in heterotopic cases) to continue and preserving the uterus for future pregnancies.[31]

Although conservative management with methotrexate has been reported to be successful, each case should be managed individually and the need for surgical intervention should always be considered.

Patients with cervical pregnancies tend to bleed more profusely because the cervix has little contractile tissue. Thus, treatment with dilatation and curettage may result into heavy bleeding compared with the treatment of an intrauterine gestation.[31]

It is unclear whether advanced cervical ectopics should be managed primarily by surgical evacuation or by the more conservative medical management with chemotherapeutic agents. As the gestational age increases so the need for radical surgery increases and therefore the risk of complications.[4, ,]

The inevitable need for hysterectomy despite initial conservative surgical management in an advanced cervical pregnancy has been reported by Tuncer *et al*. In that case, methotrexate administration was not chosen due to the presence of active tuberculosis. Dilatation and curettage did not control the hemorrhage. At laparotomy, despite bilateral uterine artery ligation, profuse bleeding continued necessitating hysterectomy. In another report, misdiagnosis allowed a pregnancy to proceed until the 22nd week of gestation and made its management more complicated. An abdominal hysterectomy with preservation of the adnexa was performed.[49]

The benefit of medical therapy is the avoidance of surgery, but the disadvantages include the cost of serial β-hCG monitoring and sonograms, anxiety over the uncertain outcome and the possibility of an emergency surgical intervention should bleeding ensue.[31]

Some authors have commented on pregnancies after treatment for a cervical pregnancy. The incidence of a recurrence appears to be low as the information on it is sparse.[14] On the contrary, the commoner report is that of vaginal delivery of healthy babies without

congenital malformations after the cervical pregnancy, which is quite reassuring.[35, 43, 46] However, because dilatation and curettage is one of the management modalities, the subsequent possibility of an incompetent cervix, mid-trimester miscarriage and the risk of preterm labour should be borne in mind.[10]

CONCLUSION

As the incidence of ectopic pregnancies, in general, increases, so will that of cervical pregnancies. The need for a more wide-spread use of transvaginal ultrasonography in developing countries cannot be over-emphasized as this, along with a high index of suspicion, will enable earlier diagnosis and improve prognosis for the affected women.

After diagnosis, the management options need to be individualized to each patient so that the best outcome is achieved. Predictors of failed medical treatment should be considered so that there could be earlier recourse to conservative surgical measures if deemed appropriate.

Various options of managing cervical ectopics with preservation of the reproductive potential of the patients exist. However, hysterectomy might still be an inescapable option especially to preserve the life of the woman.

Successful pregnancy outcomes without congenital malformations in pregnancies following conservative treatment of cervical pregnancies have been noted. This will likely make earlier diagnosis and conservative management options the way forward in the treatment of cervical ectopics.

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