

# Pregnancy of unknown location

**I Boshoff**

Department of Obstetrics and Gynaecology, University of Pretoria, Pretoria, South Africa

## Introduction

A pregnancy of unknown location (PUL) is defined as visualising an empty uterus on transvaginal ultrasound scan (TVS), with no signs of an intrauterine pregnancy (IUP) or an ectopic pregnancy, in a woman with a positive pregnancy test. The majority of women will subsequently be diagnosed with spontaneously resolving pregnancies (failing PULs) or intra uterine pregnancies (IUPs) that were too early to visualise on TVS, but a few will be diagnosed with ectopic pregnancies that were too early to visualise or were missed on the initial TVS. The failing PUL group will include both ectopic pregnancies and failing IUPs, since the location of the pregnancy may never be determined.

## Diagnostic tests for PUL

### 1. Transvaginal ultrasound examination (TVS)

This is the most useful test for determining the location of a pregnancy.

### 2. Serum human chorionic gonadotropin (*s*-hCG)

Done if the TVS imaging is non diagnostic. In early pregnancy the mean doubling time ranges from 1.4 to 2.1 days. In most ectopic and nonviable intrauterine pregnancies the hCG concentration rises at a much slower rate. A falling hCG concentration implies a failing pregnancy.

The hCG level above which a gestational sac is visualized on ultrasound examination if an intrauterine pregnancy is present, is defined as the discriminatory zone of hCG.<sup>1</sup> With TVS, the hCG level is 1500 - 2000 IU/L<sup>2</sup>, with transabdominal ultrasound the level is higher (6500 IU/L). TVS is sensitive for detecting an intrauterine pregnancy if hCG >1500IU/L (can't exclude heterotopic pregnancies).<sup>3</sup> If TVS does not reveal an intrauterine pregnancy and shows a complex adnexal mass, an extrauterine pregnancy is almost certain. If hCG <1500IU/L, then TVS is not sensitive for determining the pregnancy location. The hCG should be repeated in two to three days to follow the rate of rise.

### 3. Progesterone

Progesterone concentrations are higher in viable than in failed intrauterine and ectopic pregnancies. A level < 5 ng/mL is unlikely to be associated with a viable pregnancy - but it isn't possible to distinguish ectopics from failed intrauterine pregnancies.<sup>4,5</sup>

An ectopic pregnancy is reasonably excluded with a progesterone level greater than 20 ng/mL.

Progesterone concentrations merely confirm diagnostic impressions already obtained by hCG measurements and TVS and is therefore not monitored.<sup>6</sup>

### 4. Doppler

Blood flow in the arteries of the fallopian tube containing an ectopic pregnancy is 20 – 45% higher than in the opposite tube and the Doppler waveform shows low impedance.<sup>7,8</sup> Not often used.

### 5. Laparoscopy

Laparoscopy is rarely required for diagnostic purposes only.

## Ectopic pregnancies (EP)

Possible distribution sites of ectopic pregnancies:	Distribution
Tubal	98% of ectopics
Cervical	<1% of ectopics
Interstitial	1-3% of ectopics
Ovarian	1:2100 – 1:60000 pregnancies
Heterotopic	1:30000 pregnancies, but 1% in Artificial Reproductive Therapy
Cesarean scar	1:2000 pregnancies
Abdominal pregnancies Pregnancy after hysterectomy	1:5000 – 1:10000 pregnancies Unknown

### Tubal ectopics

It accounts for 98% of all EP, with 75% occurring in the ampullary portion of the fallopian tube.<sup>9,10</sup>

### Cervical ectopics

A rare form of EP (<1%) in which the pregnancy implants in the lining of the endocervical canal. The causes include local

## Correspondence:

Dr I Boshoff  
email: henk@s-curve.co.za

pathology related to previous cervical or uterine surgery<sup>11,12</sup>, or rapid transport of the fertilized ovum into the endocervical canal before it is capable of implantation. The most common symptom is profuse painless vaginal bleeding.<sup>11,12</sup> Examination reveals a soft cervix that is disproportionately enlarged compared to the uterus – an "hour-glass" shaped uterus.

TVS shows intracervical localization of a well formed gestational sac surrounded by an echogenic rim. A closed internal cervical os with trophoblastic invasion of the endocervical tissue is also seen.<sup>11</sup> Additional signs: visualisation of a fetus in the intracervical area, a gestational sac below the level of the uterine arteries and an empty uterine cavity. It needs to be differentiated from a cervical abortion, (an aborting intrauterine pregnancy that is trapped in the endocervical canal because of resistance from the external cervical os).<sup>13,14,15</sup> Repeating the TVS the next day to see if the sac has moved will help in making the diagnosis.

### Treatment

#### Medically

- This results in ablation of the ectopic and preserves the uterus in at least 80% of cases.
- hemodynamically stable patients
- intraamniotic and/or intrafetal injection of local potassium chloride when fetal cardiac activity is present<sup>16</sup>
- multidose methotrexate therapy

#### Surgically

Heavy vaginal bleeding when the pregnancy is involuting may require pre-op measures to control hemorrhage:

- intra-arterial embolisation, transvaginal ligation of the cervical branches of the uterine arteries, Shirodkar cerclage, angiographic uterine artery embolisation or intracervical vasopressin injection<sup>11</sup>
- This is followed by dilation and evacuation
- A Foleys balloon catheter can be used as tamponade and is secured on the cervix with purse-string suture.
- Hysterectomy is a last resort.

### Interstitial ectopics

It is easily misdiagnosed as intrauterine pregnancy. Rupture of the uterus is a common presentation. On TVS it's located eccentrically, < 5 mm from the myometrial mantle and appears as a gestational swelling lateral to the insertion of the round ligament.<sup>17</sup> Treatment consists of wedge resection of the EP.

### Ovarian ectopics

Occurs in 1:7 000 pregnancies.<sup>18</sup> Previous pelvic inflammatory disease or the use of an intrauterine contraceptive device does not increase the risk, as it appears to be a random event. Diagnosis is typically made at the time of surgery. Strict histopathological criteria (Spiegelberg) are used to distinguish ovarian pregnancies from those originating in the fallopian tube. Treatment is usually by surgical excision of the involved organs. Medical treatment with methotrexate has been successful in case reports.<sup>19</sup>

### Heterotopic pregnancy

This is a combination of an intrauterine and a concurrent pregnancy at any ectopic location. As the number of

pregnancies derived from assisted reproductive technology (ART) increases, the incidence is rising. Some tubal heterotopic pregnancies are diagnosed as late as 16 weeks of gestation, while abdominal or rudimentary horn pregnancies can continue to develop to an even later gestation.<sup>20,21</sup> Early diagnosis is difficult because of lack of symptoms, but one must have a high index of suspicion, especially in pts who have undergone ART and who experience pelvic pain. Serial hCG concentrations are not interpretable in the presence of heterotopic pregnancy. TVS will show both an ectopic and intrauterine pregnancy or the presence of echogenic fluid in the Pouch of Douglas in the presence of an intrauterine pregnancy.

Salpingectomy is the standard treatment of heterotopic pregnancy with a tubal component, since the intrauterine pregnancy is a contraindication to medical therapy. If unruptured - local injection of potassium chloride (guided sonographically) into the sac is another option.<sup>22,23,24</sup>

### Cesarean scar pregnancy

This pregnancy is located in a previous cesarean (hysterotomy) scar. There is migration of the embryo through either a wedge defect in the lower uterine segment or a microscopic fistula within the scar.<sup>25</sup> The pregnancy is surrounded by myometrium and connective tissue. Risk factors include adenomyosis, ART, previous dilatation and curettage and manual removal of the placenta. On ultrasound one can visualise an enlarged cesarean scar with an embedded mass, which may bulge beyond the anterior contour of the uterus. There may also be trophoblastic tissue between the anterior uterine wall and the bladder, no fetal parts seen in the uterine cavity or absence of myometrium between the gestational sac and the bladder.<sup>22,26,27</sup> Cervical ectopic pregnancy and placenta accreta must be excluded. If the ectopic is partially implanted in the uterine cavity it can proceed to term, although deeply implanted ectopics are predisposed to rupture in the first trimester.

Patients can present with symptoms ranging from vaginal bleeding to uterine rupture.

A specific treatment recommendation can't be made, because too few cases are currently reported. Hemodynamic stability, desire for future fertility, size and gestational age of the pregnancy should be considered. Expectant management is not advised.

Medical therapy - disadvantage of slow resolution of the pregnancy (can take months) with risk of rupture, hemorrhage and maternal death.

Surgical therapy - advantage of removing the pregnancy and repairing the defect. Options include wedge resection of the pregnancy, local excision or hysterectomy.

Recurrent scar implantation may occur in subsequent pregnancies.

### Abdominal pregnancy

A pregnancy that has implanted in the peritoneal cavity, external to the uterine cavity and fallopian tubes. It may be as a result of intra-abdominal fertilization of sperm and ovum, with primary implantation in the abdomen or secondary implantation from an aborted tubal pregnancy. Serial hCG values seem to be normal. Risk factors include tubal damage, pelvic inflammatory disease and endometriosis.<sup>28</sup>

Because of the variable locations, patients present with a wide range of symptoms. Fetal movements may be painful and the fetus may assume an unusual lie if undetected until an advanced gestational age. Acute abdomen and shock may follow severe intra-abdominal hemorrhage from placental separation or rupture of maternal blood vessels or viscera. A high index of suspicion should be raised if there is inadequate cervical and myometrial response to induction of labour.

Ultrasound findings include absence of myometrial tissue between the maternal bladder and the pregnancy, an empty uterus, poor definition of the placenta, unusual fetal lie and oligohydramnios.

First trimester treatment: operative laparoscopy/laparotomy. Methotrexate has had minimal success.

The risk of maternal complications is high as gestation increases. Cases with expectant management to gain fetal maturity have been described.<sup>29</sup> A viable infant can be delivered via laparotomy, although the potential for delivery of a healthy infant is poor. Removal of placenta can lead to life-threatening maternal hemorrhage, therefore ligation of the umbilical cord and leaving the placenta in situ is advised.

Active intervention using uterine artery embolisation can be instituted to hasten involution.<sup>30</sup> Methotrexate causes rapid destruction of the abdominal placenta, resulting in accumulation of a large amount of necrotic tissue. This provides a favorable medium in which colonic bacteria can grow and increases the frequency of maternal complications. If no other options available - ligate the placental blood supply and remove the placenta.

Fetal deformations and perinatal death occur more often than maternal death.<sup>31</sup>

Sometimes the fetus from an undiagnosed abdominal pregnancy may die, calcify and form a lithopedion ("stone child"). This may not be detected for decades and may cause a variety of complications (intra-abdominal abscess, adhesions, mass).<sup>32</sup> Mostly the diagnosis is made by X-ray, often as an incidental finding.

### **Pregnancy after hysterectomy**

Very rare.<sup>33,34</sup> Presents with pelvic pain in reproductive-aged woman after hysterectomy. It can be classified as pre-existing or late occurring. Pre-existing: patient was pregnant as the hysterectomy was done and the conceptus was present either as an implanted tubal pregnancy or a fertilized egg in transit in the fallopian tube.

Late-occurring: 8 reports were found of fertilisation occurring up to 12 years post surgery, mostly after vaginal hysterectomies. On fistulography, fistulous channels were discovered through the vaginal cuff.

Only 1 case of post-hysterectomy abdominal pregnancy that was successfully carried to term, has been reported.

Prevention: do hCG instead of non-sensitive urine gravindex before surgery, and perfecting surgical technique to prevent post-op vaginal cuff fistula formation.

### **Conclusion**

Pregnancy of unknown location needs to be closely followed up to make a correct, timely diagnosis. 8 to 40% are ultimately diagnosed as ectopic pregnancies.<sup>35</sup> TVS and hCG levels are

the gold standard in diagnosing an intrauterine or ectopic pregnancy. A high index of suspicion is important for making a diagnosis of ectopic pregnancy, as over 90% of EP are located in the fallopian tube, while the remainder implant in other locations such as the abdomen, cesarean scar, cervix, and ovary.

If these pregnancies are not accurately diagnosed, it can lead to increased maternal morbidity and mortality.

### **References**

1. Kadar, N, DeVore, G, Romero, R. Discriminatory hCG zone: its use in the Sonographic evaluation for ectopic pregnancy. *Obstet Gynecol* 1981; 58:156.
2. Paul, M, Schaff, E, Nichols, M. The roles of clinical assessment, human chorionic gonadotropin assays, and ultrasonography in medical abortion practice. *Am J Obstet Gynecol* 2000; 183:S34.
3. Barnhart, KT, Simhan, H, Kamelle, SA. Diagnostic accuracy of ultrasound above and below the beta-hCG discriminatory zone. *Obstet Gynecol* 1999; 94:583.
4. Mol, BW, Lijmer, JG, Ankum, WM, et al. The accuracy of single serum progesterone measurement in the diagnosis of ectopic pregnancy: a meta-analysis. *Hum Reprod* 1998; 13:3220.
5. McCord, ML, Muram, D, Buster, JE, et al. Single serum progesterone as a screen for ectopic pregnancy: exchanging specificity and sensitivity to obtain optimal test performance. *Fertil Steril* 1996; 66:513.
6. Tulandi, T et al. Clinical manifestations, diagnosis, and management of ectopic pregnancy. *Uptodate* 2009; 17:2.
7. Kirchler, HC, Seebacher, S, Alge, AA, Muller-Holzner, E. Early diagnosis of tubal pregnancy: changes in tubal blood flow evaluated by endovaginal color Doppler sonography. *Obstet Gynecol* 1993; 82:561.
8. Pellerito, JS, Taylor, KJ, Quedens-Case, C, Hammers, LW. Ectopic pregnancy: evaluation with endovaginal color flow imaging. *Radiology* 1992; 183:407.
9. Bouyer, J, Coste, J, Fernandez, H, et al. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. *Hum Reprod* 2002; 17:3224.
10. Senterman, M, Jibodh, R, Tulandi, T. Histopathologic study of ampullary and isthmic tubal ectopic pregnancy. *Am J Obstet Gynecol* 1988; 159:939.
11. Ushakov, FB, Elchalal, U, Aceman, PJ, Schenker, JG. Cervical pregnancy: Past and future. *Obstet Gynecol Surv* 1997; 52:45.
12. Vela, G, Tulandi, T. Cervical pregnancy: The importance of early diagnosis and treatment. *J Minim Invasive Gynecol* 2007; 14:481.
13. Jurkovic, D, Hackett, E, Campbell, S. Diagnosis and treatment of early cervical pregnancy: a review and a report of two cases treated conservatively. *Ultrasound Obstet Gynecol* 1996; 8:373.
14. Monteagudo, A, Tarricone, NJ, Timor-Tritsch, IE, Lerner, JP. Successful transvaginal ultrasound-guided puncture and injection of a cervical pregnancy in a patient with simultaneous intrauterine pregnancy and a history of a previous cervical pregnancy. *Ultrasound Obstet Gynecol* 1996; 8:381.
15. Hofmann, HM, Urdl, W, Hofler, H, et al. Cervical pregnancy: case reports and current concepts in diagnosis and treatment. *Arch Gynecol Obstet* 1987; 241:63.
16. Yao, M, Tulandi, T. Practical and current management of tubal and non-tubal ectopic pregnancies. *Current Problems in Obstetrics, Gynecology and Fertility* 2000; 23:89.
17. Tulandi, T et al. Incidence, risk factors, and pathology of ectopic pregnancy. *Uptodate* 2009; 17:2.

18. Comstock, C, Huston, K, Lee, W. The ultrasonographic appearance of ovarian ectopic pregnancies. *Obstet Gynecol* 2005; 105:42.
19. Habbu, J, Read, MD. Ovarian pregnancy successfully treated with methotrexate. *J Obstet Gynaecol* 2006; 26:587.
20. Onan, MA, Turp, AB, Saltik, A, et al. Primary omental pregnancy: case report. *Hum Reprod* 2005; 20:807.
21. Shinohara, A, Yamada, A, Imai, A. Rupture of noncommunicating rudimentary uterine horn at 27 weeks' gestation with neonatal and maternal survival. *Int J Gynaecol Obstet* 2005; 88:316.
22. Ash, A, Smith, A, Maxwell, D. Cesarean scar pregnancy. 74. *BJOG* 2007; 114:253.
23. Goldstein, JS, Ratts, VS, Philpott, T, Dahan, MH. Risk of surgery after use of potassium chloride for treatment of tubal heterotopic pregnancy. *Obstet Gynecol* 2006; 107:506.
24. Gyamfi, C, Cohen, S, Stone, JL. Maternal complication of cervical heterotopic pregnancy after successful potassium chloride fetal reduction. *Fertil Steril* 2004; 82:940.
25. Ash, A, Smith, A, Maxwell, D. Cesarean scar pregnancy. *BJOG* 2007; 114:253.
26. Rotas, MA, Haberman, S, Levigur, M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. *Obstet Gynecol* 2006; 107:1373.
27. Vial, Y, Petignat, P, Hohlfeld, P. Pregnancy in a cesarean scar. *Ultrasound Obstet Gynecol* 2000; 16:592.
28. Ludwig, M, Kaisi, M, Bauer, O, Diedrich, K. The forgotten child--a case of heterotopic, intraabdominal and intrauterine pregnancy carried to term. *Hum Reprod* 1999; 14:1372.
29. Beddock, R, Naepels, P, Gondry, C, et al. [Diagnosis and current concepts of management of advanced abdominal pregnancy]. *Gynecol Obstet Fertil* 2004; 32:55.
30. Cardosi, RJ, Nackley, AC, Londono, J, Hoffman, MS. Embolization for advanced abdominal pregnancy with a retained placenta. A case report. *J Reprod Med* 2002; 47:861.
31. Ayinde, OA, Aimakhu, CO, Adeyanju, OA, Omigbodun, AO. Abdominal pregnancy at the University College Hospital, Ibadan: a ten-year review. *Afr J Reprod Health* 2005; 9:123.
32. Odom, SR, Gemer, M, Muyco, AP. Lithopedion presenting as intra-abdominal abscess and fecal fistula: report of a case and review of the literature. *Am Surg* 2006; 72:77.
33. Binder, DS. Thirteen-week abdominal pregnancy after hysterectomy. *J Emerg Med* 2003; 25:159.
34. Fader, AN, Mansuria, S, Guido, RS, Wiesenfeld, HC. A 14-week abdominal pregnancy after total abdominal hysterectomy. *Obstet Gynecol* 2007; 109:519.
35. Condous, G, Kirk, E, Lu, C, et al. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2005; 26:770.