



The importance of accurate evaluation of the adnexa to diagnose a heterotopic pregnancy: a retrospective case-series

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ABSTRACT

Heterotopic pregnancy is the contemporary presence of intrauterine and ectopic (most frequently tubal) pregnancy. This condition is rare; yet, recently, it has been reported increasingly, due to diffusion of both assisted reproduction techniques and pelvic inflammatory disease following sexually transmitted infections. Although difficult, diagnosis is crucial. Currently, diagnosis is most frequently posed at ultrasound, provided that accurate evaluation of adnexa is performed, even after demonstration of the intrauterine location of a pregnancy. Treatment and outcome are highly influenced by the intrauterine component of heterotopic pregnancy. Conservative treatment, involving use of potassium chloride or a hyperosmolar solution injection, may be chosen to selectively terminate the ectopic pregnancy. Methotrexate may be utilised, if the intrauterine pregnancy evolves to miscarriage spontaneously or following the patient's decision. Expectant management may be considered in some cases. Survival of the intrauterine component reaches approximately 70%; the outcome of live

SOMMARIO

La gravidanza eterotopica è la contemporanea presenza di gravidanza intrauterina ed ectopica (più frequentemente tubarica). Questa condizione è rara; tuttavia, recentemente, è stata segnalata in aumento, a causa della diffusione sia delle tecniche di riproduzione assistita che della malattia infiammatoria pelvica in seguito a infezioni trasmesse per via sessuale. Sebbene difficile, la diagnosi è cruciale. Attualmente, la diagnosi è più frequentemente posta tramite ecografia, a condizione che venga eseguita un'accurata valutazione degli annessi, anche dopo la dimostrazione della posizione intrauterina della gravidanza. Il trattamento e l'esito sono fortemente influenzati dalla componente intrauterina della gravidanza eterotopica. Il trattamento conservativo, che prevede l'uso di cloruro di potassio o di una iniezione di soluzione iperosmolare, può essere scelto per terminare in modo selettivo la gravidanza extrauterina. Il metotrexato può essere utilizzato se la gravidanza intrauterina si evolve spontaneamente in aborto o su decisione della paziente. In alcuni casi, è possibile

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births does not differ from that of singleton pregnancies. This article analyses the world literature about the topic and reports on a series of five cases diagnosed and treated at Sandro Pertini Hospital in Rome.

Keywords: heterotopic pregnancy; ectopic pregnancy; ultrasound; diagnosis; treatment.

prendere in considerazione una gestione di attesa. La sopravvivenza della componente intrauterina raggiunge approssimativamente il 70%; l'esito delle nascite non differisce da quello delle gravidanze singole. Questo articolo analizza la letteratura mondiale sull'argomento e riporta una serie di cinque casi diagnosticati e trattati all'ospedale Sandro Pertini di Roma.

INTRODUCTION

During pregnancy, a series of more or less serious complications can occur with consequent risk to the health of both the mother and the fetus⁽¹⁻⁶⁾.

Among these complications, heterotopic pregnancy (HP) is one of the most rare. It is defined as the simultaneous presence of intrauterine and ectopic pregnancy firstly described by Duverney in 1708 and has a spontaneous incidence of 1/30000 pregnancies^(7,8). Nevertheless, a significant increase in the incidence of ectopic pregnancy and, as a consequence, heterotopic pregnancy too, has been noted during the last decades. The reason for this phenomenon is attributed to several factors, including a higher incidence of pelvic inflammatory disease (PID) and the widespread use of assisted reproductive technologies (ARTs). Most frequently, the ectopic component of a HP is located within a fallopian tube (88.2%)⁽⁹⁾.

Diagnosis is difficult, since the presence of an intrauterine pregnancy may induce the clinician to a wrong interpretation of the symptoms and clinical signs of the ectopic pregnancy. In addition, the monitoring of haematic levels of beta-human chorionic gonadotrophin (hCG) is not useful for diagnosis in such cases. Despite ultrasound represents the cornerstone for gynecological and obstetric diagnosis in pregnant woman who cannot undergo other diagnostic procedures⁽¹⁰⁻¹⁶⁾, the ultrasonographic diagnosis in case of HP may be difficult and/or delayed, when the finding of the intrauterine location of a pregnancy leads to omit careful evaluation of adnexa and the anatomic morphology outside the uterine cavity.

Given the possibility to be undiagnosed or diagnosed too late and the elevated morbidity and mortality that this condition shares with an ectopic pregnancy, HP is highly dangerous for both the mother and

the intrauterine pregnancy.

The aim of this study is to provide an overview of the diagnosis and treatment of HP, retrospectively analyzing 5 cases of HP diagnosed and treated at the Department of Obstetrics and Gynaecology of Sandro Pertini Hospital of Rome.

MATERIAL AND METHODS

This is a retrospective case-series. Five cases of HP referred to Sandro Pertini Hospital between October 2005 and August 2015 were retrospectively collected. Maternal age, parity, gestational age at diagnosis, spontaneous or induced occurrence of the pregnancy through ARTs, other risk factors, symptoms, diagnostic assessment, treatment and outcome have been considered. Diagnosis was made in every case through ultrasound. In particular, the combination of a transabdominal (TA) and transvaginal (TV) approach has always been used. The sonographic demonstration of an intrauterine pregnancy associated with an ultrasound finding indicating the coexistence of an ectopic pregnancy⁽¹⁷⁾ allowed diagnosis of a HP. In particular, the tubal location of the ectopic pregnancy was indicated by the presence of an ectopic mass separate to the ovary⁽¹⁸⁾. We followed the ultrasound criteria for diagnosis of ectopic tubal pregnancy described in the world literature: an inhomogeneous adnexal mass⁽¹⁹⁾, an empty extra-uterine sac with a hyperechoic ring or a yolk sac and/or foetal pole with or without cardiac activity within an extra-uterine sac. Additional possible ultrasound features were the finding of free fluid within the pelvis and/or the abdomen.

The monitoring of haematic β -hCG in addition to ultrasound was used in the follow-up of one of those patients undergoing a conservative treatment.

This study obtained the local institutional

review board approval (N.:0001433/2016) released by the Sandro Pertini Hospital. Written informed consent was provided by each of the subjects.

RESULTS

During the considered period, HP was diagnosed in five cases. Maternal age ranged between 27 and 38 years. The gestational age at diagnosis ranged between 6 weeks' and 9 weeks + 4 days of gestation. Four patients conceived spontaneously: one of these patients had undergone salpingectomy previously, due to ectopic pregnancy; the other three patients presented no known risk factors. In one case, pregnancy was induced through in vitro fertilization with embryo transfer (IVF-ET). Symptoms included pelvic/abdominal pain and vaginal blood losses in women with a previous biochemical diagnosis of pregnancy. In the IVF-ET case, a hyperstimulation syndrome (OHSS) was also present. Diagnosis was always made at ultrasound according to the above-mentioned criteria. In particular, with regard to the adnexal findings, a "tubal ring" was found in four cases. Whereas the presence of both an embryo measuring 14.7 mm without cardiac activity and a yolk sac within the right fallopian tube was found in one case, whose intrauterine component was at 9 weeks + 4 days of gestation (**Figure 1**).



Figure 1.
Heterotopic pregnancy: presence of an embryo measuring 14.7 mm within the right fallopian tube associated with intrauterine viable pregnancy (embryo measuring 26.4 mm).

Remarkable abdominal free fluid was found in one patient. As regards treatment, laparotomic salpingectomy was performed in one patient, in whom a massive haemoperitoneum was drained;

this patient underwent blood transfusion too. Two patients underwent laparoscopic salpingectomy (**Figure 2**).



Figure 2.
Heterotopic pregnancy: the same case as Figure 1, at laparoscopy

In two cases of internal miscarriage associated with the ectopic pregnancy, uterine curettage was needed. The IVF-ET patient underwent a conservative treatment consisting of clinical, ultrasound and haematological follow-up (blood cell count, haemoglobin, etc.): as soon as discharged from the hospital, she was made aware of the need of urgent new admission, in the case of onset of remarkable abdominal pain and/or lipotimia. One of the two patients treated through uterine curettage, underwent ultrasound and β -hCG follow-up until spontaneous resolution of the ectopic pregnancy. This patient refused surgery, because she had undergone previously removal of the contralateral fallopian tube due to ectopic pregnancy; she refused therapy with methotrexate as well. In all cases, treatment was performed after informed consent was obtained. One patient terminated her endouterine pregnancy at 20 weeks gestation, because of subsequent diagnosis of trisomy 18 at amniocentesis. One patient underwent caesarean section at 37 weeks gestation because of onset of labour and breech presentation in primipara: a female healthy baby weighing 3020 g, was delivered; the infant is currently 2 years-old and doing well. The IVF-ET patient had initially an intrauterine triplet; pregnancy continued as a twin pregnancy, subsequently. This patient had threatened abortion during the first two trimesters and severe threatened premature delivery during the third one. She underwent caesarean section at 31 weeks' gestation: a male

baby, weighing 1400 g, and a female baby, weighing 1250 g, were delivered. The infants are currently 10 years-old and doing well. Data are summarized in **Tables 1 and 2**.

Table 1
Features and risk factors of Patients

| Case | Age | Race | Parity | Gestational Age (weeks + days) | Risk Factors |
|------|-----|-----------|--------|--------------------------------|-------------------------------|
| 1 | 36 | Caucasian | 0 | 6 + 2 | IVF-ET induced Pregnancy |
| 2 | 29 | Caucasian | 1 | 6 + 4 | No |
| 3 | 38 | Caucasian | 0 | 9 + 4 | No |
| 4 | 30 | African | 0 | 8 + 2 | No |
| 5 | 27 | Caucasian | 0 | 7 + 3 | Previous salpingectomy for EP |

EP: Ectopic Pregnancy

Table 2
Treatment and Outcome of HP

| Case | Symptoms | Location of EP | Treatment | Outcome of intrauterine pregnancy |
|------|---|----------------|-------------------------------|-----------------------------------|
| 1 | OHSS in Intrauterine Triplet, vaginal blood losses | Right F.T. | Conservative US | C.S. (31 weeks) 2 live babies * |
| 2 | Abdominal pain, vaginal blood losses | Right F.T. | Laparoscopy salpingectomy | Pregnancy Termination (Trisomy18) |
| 3 | Abdominal pain | Right F.T. | Laparoscopy salpingectomy | C.S. (37 weeks) 1 healthy baby |
| 4 | Incomplete miscarriage, haemoperitoneum, metrorrhagia | Left F.T. | Laparotomy salpingectomy + UC | Miscarriage |
| 5 | Incomplete miscarriage, metrorrhagia | Left F.T. | UC + US + β -hCG | Miscarriage |

*Intrauterine pregnancy was initially a triplet, went on as a twin pregnancy; the babies are currently doing well
EP: Ectopic Pregnancy; F.T.: Fallopian Tube; OHSS: Ovarian Hyperstimulation Syndrome; US: Ultrasound; UC: Uterine Curettage; β -hCG: beta-Human Chorionic Gonadotrophin; C.S.: Caesarean Section

DISCUSSION

In a HP, the most frequent site of implantation of the ectopic component is within a fallopian tube. However, further possible locations of the ectopic pregnancy in cases of HP have been described in the ovary, the cervix uteri, the cornual region, the scar of a previous caesarean section, the abdominal cavity⁽¹⁸⁻²¹⁾. In our series, the ectopic pregnancy was located within a fallopian tube in all cases.

As mentioned above, the incidence of HP has been estimated as much as 1 in 30,000 pregnancies. The risk factors appear to be identical to those predisposing to ectopic pregnancy. Moreover, recently the rate is considered to be higher because of the larger use of new ARTs in infertile couples reaching approximately 1 in 7000 in these cases⁽²²⁻²⁴⁾.

In the ovulation-induction procedures, a excessive number of induced follicles and subsequent obtained oocytes are reported to raise the incidence of HP between 33/10,000 and 1/100⁽²⁵⁾. On that basis, it is of paramount importance a correct stimulation protocol in these assisted reproduction procedures, and it is mandatory to use the different available approaches and precautions to avoid excessive stimulation, particularly in high risk population such as woman affected by polycystic ovary syndrome or interrupt the procedure in case of high number of induced follicles^(24,26,27). Differently, in IVF-ET procedures transferring four or more embryos has been reported as a further risk factor⁽²⁸⁾, this is a iatrogenic complication and is mandatory to limit the number of transferred embryos, favouring other approach to improve

outcomes in these patients⁽²⁹⁻³¹⁾. All these elements may enhance the risk of altered implantation and twin pregnancies⁽³²⁻³⁴⁾.

Gruber et al. described the role of the hydrostatic forces generated during an embryo transfer as a possible contributor that might increase the risk of both ectopic and heterotopic pregnancy⁽²²⁾. Another possible explanation for this phenomenon is that the transferred embryos that migrate into the damaged tubes are not expelled by peristaltic movements^(35,36).

An increased risk for HP also derives from a previous history of PID secondary to a sexually transmitted infection. Evidence shows a 7- to 10-fold increased risk of ectopic pregnancy in women with a history of PID compared to a healthy cohort, as a consequence of both, anatomical damage or distortion of the adnexa and the presence of pelvic adhesions⁽³⁷⁾.

Another confirmed predisposing factor for ectopic pregnancy (and therefore, HP as well) would include tubal ligation⁽³⁸⁾. Further risk factors are represented by previous tubal surgery and another previous ectopic pregnancy⁽³⁹⁾.

Nevertheless, HP may occur even in the absence of any predisposing factors at all⁽⁴⁰⁾.

In our series, in one case HP was diagnosed in a patient who obtained the pregnancy through IVF-ET. Another patient had a history of a previous ectopic pregnancy treated with salpingectomy. Three patients with HP conceived spontaneously and presented no known predisposing factors.

Diagnosis of HP is often hard, even in the presence of symptoms. The most common clinical presentation is represented by abdominal pain (83% of HP) and/or blood losses^(25,28). Abdominal pain is secondary to peritoneal irritation often due to haemorrhagic fluid collection, which could eventually lead to hypovolemic shock. Nevertheless, pain could be aspecific and related to other pathologies, such as adnexal masses or growing uterine fibroids^(41,42). When vaginal bleeding occurs, it is explained as retrograde from the ectopic pregnancy, since the endometrium of the intrauterine pregnancy is intact⁽²⁸⁾. Other possible clinical signs are the findings of an adnexal mass and enlarged uterus. Differential diagnosis with low urinary tract symptoms, bowel symptoms, and other gynaecological/obstetric disorders such as the rupture of ovarian cysts (especially in cases of ovulation-induction), ovarian torsion, haemorrhagic corpus luteum, threatened abortion of an intrauterine pregnancy, needs to be done.

Ultrasound plays a key role in detection

of HP: the rate of ultrasound diagnosis before surgery increased from 41%, as reported in the investigation by Tal et al.⁽⁴³⁾, to 66% reported in the study by Talbot et al.⁽⁴⁴⁾. On the contrary, in previous investigations diagnosis was found to be mainly posed at surgery⁽²⁵⁾. It has been speculated that there are two major reasons to explain this phenomenon: the constant increase in quality of ultrasound imaging; the widespread use of ARTs, which increased awareness, besides the prevalence, of HP⁽⁴⁵⁾.

It is crucial for diagnosis of HP to consider that the ultrasonographic demonstration of intrauterine location of a pregnancy does not exempt from accurate evaluation of the adnexa. It is crucial that early diagnosis of HP is obtained, since this condition is potentially associated with high mortality and morbidity for both the mother and the intrauterine pregnancy.

The ultrasound criteria for diagnosis of ectopic pregnancy, as elucidated above, include: an inhomogeneous adnexal mass, an empty extra-uterine sac with a hyperechoic ring or a yolk sac and/or foetal pole with or without cardiac activity in an extra-uterine sac⁽¹⁷⁾. Additional possible ultrasound features are the finding of free fluid within the pelvis and/or the abdomen. However, even following accurate evaluation of the adnexa, the diagnosis may be missed in the presence of obesity, intense bowel meteorism or other factors hampering diagnosis. In addition, the nosologic entity of pregnancy of unknown location (PUL) is a well-known one. Therefore, the ultrasound finding of an intrauterine location of the gestational sac with exclusion of ectopic pregnancy, if obtained very early in pregnancy, needs to be confirmed by a subsequent ultrasound with careful evaluation of adnexa, in order to exclude definitively heterotopic pregnancy. In any case, ultrasound diagnosis is missed when adnexal evaluation is not performed.

Ultrasonographic differential diagnosis may be somewhat difficult amongst the following conditions: haemorrhagic corpus luteum with an intrauterine gestation, rupture of an ovarian cyst associated with an intrauterine pregnancy, ectopic pregnancy with an intra-uterine pseudogestational sac. In some cases, the association of an incomplete miscarriage with an ectopic pregnancy may not be excluded. This diagnosis is even more difficult, in the absence of a previous ultrasound scan demonstrating the presence of an endouterine pregnancy.

In our cases, the diagnosis was performed through ultrasound. An accurate transvaginal

and transabdominal ultrasonic evaluation of the adnexa allowed us to find a “tubal ring” in four cases and the presence of both an embryo without cardiac activity and a yolk sac within the fallopian tube in one case (**Figure 1**).

In our opinion, the combination of transabdominal with transvaginal ultrasound should always be used and represents the key diagnostic approach to reduce the incidence of false negative, as regards diagnosis of ectopic pregnancy as well. In fact, in some cases the adnexa are located much cranially and surrounded by intestine: therefore, an ectopic pregnancy could be unrecognized with the sole transvaginal approach. In some other cases, the fallopian tubes are prolapsed under the weight of the ectopic pregnancy and hematoma, and therefore badly or unidentifiable at all with the sole transabdominal approach.

The management of HP remains controversial. The options for the treatment consist in surgical or conservative approach, as a result of the clinical assessment and the ultrasound findings, as well as the patient’s choice (if possible and after adequate information⁽⁴⁶⁾).

In case of surgical approach for ectopic pregnancy, laparoscopy represent the first feasible choice even in complicated cases^(47, 48). Laparoscopy is extensively used in many field of gynecological surgery, from endometriosis^(49,50) to oncological disease⁽⁵¹⁻⁵⁶⁾ with appropriate post operative management^(57,58), and the surgical skills are usually available. As regards the surgical procedure, salpingectomy is the most frequent surgical operation reported in the world literature, in the case of tubal location of an ectopic pregnancy (59). It has been demonstrated that salpingotomy does not significantly improve fertility prospects as compared to salpingectomy. Furthermore, it is difficult to follow-up evolution of the ectopic component of HP in patients who undergo salpingotomy, since monitoring of haematic levels of beta hCG is not helpful. Thus, salpingotomy has not been frequently chosen as an option in surgery of HP. In one case of very rare condition of bilateral HP, salpingotomy of one fallopian tube in association with salpingectomy of the contralateral one was chosen, for the absence of informed consent for bilateral salpingectomy (a monolateral ectopic pregnancy was ultrasonographically diagnosed prior to surgery) and the opportunity to preserve at least one of the adnexa. The difficulty in diagnosis poses, in turn, the question of the need to carefully control the contralateral fallopian

tube, during surgery for both ectopic and heterotopic pregnancy⁽⁶⁰⁾.

The nonsurgical approach has been increasingly used through the last decades, increasing from 6% during the period 1971–1993 up to 26% during the period 2005–2010⁽⁴⁵⁾.

Oral methotrexate is the first line option for women with HP who decide not to preserve their intrauterine pregnancy⁽⁶¹⁾. On the other hand, the need to preserve the intrauterine component may involve the use of either potassium chloride or a hyperosmolar solution injection to selectively terminate the ectopic gestation. This therapeutic solution may be considered, especially when the extrauterine locations involve high technical surgical difficulties and/or risks. Selective ultrasound-guided potassium chloride injection into the ectopic pregnancy has been reported to be successfully applied to cases of tubal⁽⁴³⁾, cervical⁽⁴⁴⁾, caesarean scar⁽⁶²⁾, cornual or interstitial⁽⁶³⁾ and abdominal pregnancies⁽⁶⁴⁾. Benefits from this therapy include the absence of potential teratogenicity of methotrexate and the uterotonic effects of prostaglandins, that may affect prognosis of the intrauterine pregnancy. Unlike the ectopic pregnancy, actually the prognosis of the intrauterine pregnancy is the factor that mostly affects treatment of HP, besides maternal health.

A further possible conservative approach may be the clinical follow-up of women, by monitoring the symptoms and signs, ultrasound features and haematic parameters: such as, respectively, abdominal pain and tenderness, haemodynamic parameters (blood pressure), the presence and evolution of a pelvic fluid collection, the trend of the red blood cell count and haemoglobin.

We have chosen the “wait and see” management in one patient of our series, who showed the contemporary presence of an intrauterine triplet and a right tubal pregnancy following IVF-ET, due to both the maternal choice and the risks of surgery: she presented with a OHSS too. In this patient, the serial clinical and sonographic follow-up (as far as possible) showed the spontaneous resolution of the ectopic component, while the haematic parameters kept stable. Another patient in our series has undergone the same management, following the uterine curettage for an incomplete miscarriage of the intrauterine component; in fact, this patient refused surgery and therapy with methotrexate as well. Three patients in our series underwent surgery. One of them underwent laparotomy, which was preferred due to massive

haemoperitoneum, besides uterine curettage for incomplete abortion; blood transfusion was needed in this patient. In two cases, laparoscopic approach was chosen. In all the surgery patients, salpingectomy was performed.

As noted above, the prognosis of the intrauterine component of a HP is the key factor which affects management and prognosis of this condition, besides maternal health. Currently, miscarriage of the intrauterine component is the most frequent evolution reported in the case of a HP⁽⁶⁵⁾. However, a remarkable raise in the survival rate has been described: reportedly, from approximately 50% in 1957 to 69% in 2007^(66,67). It may reasonably be speculated that a more precocious diagnosis allows better management of the condition, resulting in a better outcome. Furthermore, no significant difference amongst HP and singleton intrauterine pregnancy has been reported in outcome of the live births, in particular with regard to the incidence of low birth weight and preterm birth^(45,65).

CONCLUSION

The incidence of HP is significantly increased as a result of the currently wide diffusion of the ARTs and the high incidence of PID following sexually transmitted infections. Diagnosis of HP is a very difficult one. Nevertheless, it is crucial given the elevated maternal mortality and

morbidity, which shares with the condition of ectopic pregnancy. Diagnosis is possible only at ultrasound prior to surgery, provided that careful evaluation of the adnexa is always warranted even after evidencing an intrauterine pregnancy. From a technical point of view, the combination of the transabdominal and the transvaginal approach appears to be important in our experience. Diagnosis of HP allows treatment. Prognosis and treatment are strongly affected by the intrauterine component of HP. Treatment may be conservative, including the pharmacological options and/or clinical-ultrasonographical observation. Treatment is conditioned by the clinical and ultrasound findings, but also the maternal choice whenever possible alternative options exist. The rate of ultrasound diagnosis prior to surgery is remarkably increased through the last decades. This might be one of the factors explaining the improved outcome of HP observed during the same period (up to approximately 70% of live births). Given the possibility of a good outcome appropriate counselling regarding all of the above issues to the patient should be warranted.

DECLARATION OF INTEREST

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper. No specific funding was obtained.

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