

## Heterotopic Pregnancy, It is Such a Rare Finding?

Francesco Giacomello<sup>1-2\*</sup>, Giovanni Larciprete<sup>2</sup> and Herbert Valensise<sup>1-2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Tor Vergata University, Rome, Italy

<sup>2</sup>Department of Obstetrics and Gynecology, Fatebenefratelli Isola Tiberina Hospital, Rome, Italy

**\*Corresponding Author:** Giacomello Francesco, Department of Biomedicina e Prevenzione, Tor Vergata University, Rome, Italy.

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### Abstract

Heterotopic pregnancy is a multiple pregnancy with simultaneous implantation of the embryos at two or more distinct locations. Risk factors, epidemiology, signs, symptoms, sonographic findings and management options are reviewed. Literature data indicates an increase of the prevalence of heterotopic pregnancy and a trend increase toward sonographic diagnosis at an earlier stage, before rupture. In order to facilitate early diagnosis, the dictum “think heterotopic” is never overemphasized also in the sonographic evidence for an intrauterine pregnancy. Diagnostic vigilance is particularly recommended in in-vitro fertilization with multiple embryo transfer even in the case of intrauterine twin visualization. Finally management options are examined. Changing trends toward less invasive treatments could be the basis of an improved prognosis both for the patients and for the intrauterine gestation.

**Keywords:** Assisted reproductive technologies; Coexistent pregnancy; Coincident Pregnancy; Combined Pregnancy; Ectopic Pregnancy; Heterotopic Pregnancy; Ovulation Induction

### Introduction

Heterotopic pregnancy (HP) is a multiple pregnancy with simultaneous implantation of the embryos at two or more separated locations [1,2]. “Heterotopic” has indeed a Greek etymology (*hetero* = other and *topos* = place) hints at the coexistence of intrauterine pregnancy (IUP) with any site of ectopic pregnancy (EP) (tubal, tubal stumps, ovarian, abdominal, cornual or interstitial, angular, cesarean section scar, cervical). Therefore, HP can occur in many clinical forms very different from each other. In high risk patients for HP, such as those who have undergone assisted reproductive technology (ART), many combinations of sites of implantation and numbers of pregnancies are possible, as described in the literature. As a consequence, HP is also called combined pregnancy [2,3].

The first report of HP in 1708 by Duverny was essentially the description of an autopsy finding [4]. In 1971, Payne *et al.* described one HP after administration of clomiphene citrate and corticosteroids [5]. In 1972, Robertson and Grant reported HP after induction of ovulation with gonadotropins [6]. In 1985, Sondheimer *et al.* reported for the first time HP after ART [7]. One year later Abdalla *et al.* described the first case of HP after with *in vitro* fertilization and embryo transfer (IVF-ET) [8]. Other unprecedented descriptions involve HP associated with premature ovarian failure after hormonal replacement therapy and egg donation [9] and HP after transfer of frozen-thawed embryos in a spontaneous cycle [10].

### Epidemiology

HP is very rare in the general population, in everyday clinical practice. In 1948 its incidence was theoretically calculated around 1:30000 deliveries from natural conceptions [11]. The HP rate was estimated 1:27500, 1:7963 and 1:3889 deliveries in 1965 [12], 1983 [11], and 1986 [2], respectively. Over the years HP has been gradually rising; recently, its prevalence has increased up to 1-3% [13,14], due to the emergence of ART such as ovulation induction [2], IVF-ET and the rate of tubal and pelvic inflammatory disease (PID) [3]. The

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incidence of HP thus strongly depends on the incidence of both EP and multiple pregnancies in a certain population. Accordingly, the HP rate can be calculated from annually published reproductive health reports. In the case of ART, with unreasonable transfer of more than 4 embryos, the risk of HP has been reported as high as 1:45 [9]. When more than 3 embryos are transferred, the odds ratio for HP versus EP increases 10-fold [15].

The majority of HP consists of singleton IUP associated with an EP, however triplets [16,17] quadruplets [18,19] and even sextuplets [20] have been reported, albeit extremely rare. Even the coexistence of three different sites of implantation has been described following IVF-ET in Taiwan [21]. Therefore ART can be considered the main risk factor for HP, which becomes an increasingly common complication in the case of unlimited IVF-ET. Other risk factors predisposing to HP are identical to those predisposing to EP. Tubal abnormalities and PID are considered among the strongest risk factors for HP [3,22]. In any case, multiple ovulations (natural or induced) are always a prerequisite for its occurrence. In addition to ART, technical factors may play key roles in determining the rate of HP: the unsound transfer of large number of embryos [15], the site of transfer, excessive medium or pressure on the syringe [23], increased depth of catheter insertion [24,25], embryonic quality, hormonal administration and pelvic adhesions. Recurrent heterotopic pregnancy has also been reported in the same patient who underwent repeated IVF-ET in a year period [26]. In the case of ART, HP has been described even in a patient who underwent bilateral salpingectomy [27], being the main risk factor for the occurrence of cornual pregnancy.

### Early diagnosis

HP is a very dangerous life threatening mixture and carries a significant mortality and morbidity, similar to that of EP. To a lesser extent, also the development of the IUP is jeopardized. Actually, maternal and fetal prognosis is tightly linked to early diagnosis, preventing unexpected rupture of the ectopic component and avoiding maternal hemorrhage, shock, blood transfusions and miscarriage of the IUP. Very often, the IUP ultrasound visualization and description by the unaware sonographer may produce a false reassurance for the clinician, even in symptomatic women. In such case the missed detection of the ectopic component is the determinant factor for its unexpected rupture. Nevertheless, successful obstetrical outcome of the IUP is still possible even in the case of tubal rupture [28,29]. The most commonly observed signs and symptoms of HP are the following: abdominal pain, adnexal mass, peritoneal irritation and uterine enlargement [3,22]. Symptoms can be also those of IUP or EP or something between them. The clinical findings are therefore unspecific, being common in other normal or abnormal kind of pregnancy. The identification of risk factors such as ART [2] or tubal damage [3], the history of previous EP or the use of intrauterine device are the clue to heighten diagnostic vigilance for an early detection [30].

Around 50% of HP is asymptomatic [31] and also, compared to EP, in HP vaginal bleeding occurs rarely [30,32]. Its origin may be retrograde from the EP rather than from a well-implanted IUP [15]. In HP a further diagnostic challenge may derive from the normal production of beta HCG by the IUP, which masks the abnormal secretion of the ectopic component, possibly giving reliable results also in serial determinations [28].

### Ultrasound diagnosis

Simultaneous visualization of both embryos with heart activity is the easiest diagnosis of HP, when the mirror artifact is ruled out [33,34]. This effect can very rarely occur when multiple echo reflections of the product of conception are determined by posteriorly flat anatomical surfaces acting as a mirror (colon distended by gas, psoas muscle). However the gestational sacs and embryos of HP are usually of different size, and also heart rate can appear at a different time minimizing the danger of a misdiagnosis [23,28]. In addition, the "one frame", simply recognizable pattern of progressive HP is a rare ultrasound finding, which occurs in less than 10% of cases [34]. The most common differential diagnosis for HP is IUP with hemorrhagic corpus luteum and EP with intrauterine pseudo gestational sac [36,37]. Bicornuate uterus with pregnancies in both horns may rarely occur, mimicking HP [38]. Indeed HP in non-communicating horn of bicornuate uterus has also been described [39].

ART may add diagnostic problems. Pelvic anatomy may acquire an extraordinary complexity in the case of ART. Additional complications for the sonographic interpretation may originate from severe ovarian hyperstimulation syndrome (OHSS) with multiple luteinized follicles and ascites, since distinction from hemoperitoneum may be difficult. This fact may explain the low sensitivity of ultrasound

diagnosis in case of OHSS reported by some authors [40,41,42]. Paradoxically, as recently recognized, ART may improve diagnostic vigilance and expertise of sonographers with resulting increased diagnostic efficiency [22].

The ectopic component of HP may consist of three sonographic patterns:

1. inhomogeneous adnexal mass or “blob sign” adjacent to the ovary, that the sonographer can move separately from it or observe spontaneously sliding,
2. empty sac with hyper echoic ring “bagel sign”,
3. sac containing a yolk sac and/or a fetal pole with or without pulsations [43,44]. The implantation of the ectopic component is most commonly tubal though it has also been described as interstitial, cervical, scar pregnancy [45], intramural and cornual. Cornual pregnancies are often diagnosed later than other forms of EP with life-threatening rupture and hemorrhage, due to the rich blood supply derived both from branches of the ovarian and uterine arteries. Therefore scan of adnexa, interstitium, cornua and cervix is recommended whenever pelvic fluid with a “ground glass” appearance (hemoperitoneum) is occasionally found in a first-trimester scan showing a normal IUP.

### Diagnostic ultrasound

In spite of the introduction of ultrasound since 1970-1980 and of the increasingly extensive medical knowledge, early diagnosis of HP was not provided for long, and the majority of cases resulted only at laparoscopy or at laparotomy [30]. Most probably, in the first decades of TVU and ART, the presence of an IUP was giving a false sense of security to clinicians disregarding signs or symptoms of the coexistent EP. The French aphorism “think ectopic” was therefore easily forgotten whenever a well-implanted, normal gestational sac was found, despite the presence of acute abdomen in a pregnant woman. Many case reports of early ultrasound diagnosis including our [46] represented an exception rather than the rule. This unexpected low detection rate of TVU is the critical finding in the review article concerning all HPs reported from 1971 to 1993 [47], with only 46 out of 112 (41%) being diagnosed with TVU before surgery. Even the introduction and wide diffusion of TVU in clinical practice from 1994 to 2004 [30] did not produce any diagnostic improvement, as only 21 out of 80 cases (0,26%) of HP were diagnosed before surgery. Most cases were unexpectedly seen at by laparoscopy or laparotomy performed in emergency, mostly because of severe symptoms related to the rupture of the ectopic component. The diagnostic efficiency of ultrasound changed significantly in recent years as reviewed by Talbot *et al.* [48], who reports 82 cases of HP 66% of which was conclusively diagnosed by TVU. In a recent huge retrospective series from China [22], the progress of ultrasound diagnosis has been strongly confirmed (Table I). The study includes 16483 women after IVF-ET examined by means of TVU; here 174 cases of HP were correctly diagnosed and only 10 were missed. This study also demonstrates that failure of early TVU diagnosis of HP not only may favor unexpected tubal rupture and severe hemorrhagic complications, but also determine the miscarriage of the IUP.

Improving ultrasound imaging and increasing clinicians awareness of HP, in case of ART, may explain the aforementioned encouraging trend in diagnostic efficiency of TVU. Moreover, besides increased sensitivity of TVU the review of recent literature also reveals a much earlier detection of HP than previously reported. Gestational age at diagnosis ranges from 5 to 34 weeks of gestation [49]. Nevertheless full term undiagnosed HPs were described at cesarean section [50] also in a Tanzanian woman who continued to feel fetal movements of the forgotten child and abdominal pain the day after her spontaneous delivery [51]. In the study by Talbot *et al* [48], 70% of HP was identified at 5-8 weeks' gestation, 20% at 9-10 weeks and 10% after 11 weeks. For comparison, in the last available and most comprehensive published study [22], 72% of HP was identified at 5-6 weeks gestation, 15.9% at 7-8 weeks and only 4.5% after 9 weeks (Table II). In this study the role of IVF-ET in increasing diagnostic vigilance and ultrasound sensitivity cannot be overemphasized. A high degree of suspicion of HP is always required for early and timely diagnosis. Actually, as reported by Han *et al.* [52], HP after ART has a better IUP outcome than cases occurring spontaneously. Therefore early TVU of HP is strongly advisable; it would be possible mostly in ART environment where early and repeated sonographic examinations are usually performed, to assess the number and the location of resulting pregnancies. In the study by Li *et al.* [22] further ultrasound examination was needed in 37 cases of HP, probably because some of the EP was too small at the time of the first TVU [53]. Interestingly, in recent years the diagnostic efficiency is improved thanks not only to technological advances but also to the increased rate of HP. Therefore, to suggest that the sonographer must always be aware of HP, the new aphorism “think heterotopic” [32] has been proposed whenever women with symptoms suggesting a diagnosis of EP are

shown to have an IUP. Nowadays, the demonstration of a viable IUP must never be taken as exclusion of EP. Even with intrauterine twin visualization, in patients undergoing unrestricted ART, repeated ultrasound is advisable in order to exclude HP [17,20,54,55]. Professional societies and the legislative power of many countries have issued guidelines or laws to limit the number of embryo transfer, in an attempt to reduce complications including EP and HP. According to the NICE (National Institute for Health and Care Excellence) 2014 quality standards, concerning fertility problems, the number of embryos transferred in a cycle should never exceed the number of two. A recent case of HP in a cross border reproductive care occurred to an Italian patient, treated in Spain with oocyte donation, outlines also the need of cooperation between international centers of ART in order to favor early diagnosis of HP [56].

GA at UD	(1971-93) 112 cases 46 UD	(1994-2004) 80 cases 21 UD	(2005-2010) 82 cases 54 UD	(2005-2011) 132 cases 122 UD
5-8 weeks	76 %	86 %	70%	72% (5-6 weeks) 16% (7-8 weeks)
9-10 weeks	11 %	14 %	20 %	4,5 % (> 9 weeks)
> 11 weeks	6 %	0 %	10 %	

**Table 1:** Gestational age (GA) at ultrasound diagnosis (UD) of heterotopic pregnancy (HP).

Tal et al. 1996	Barenetxea et al. 2007	Talbot et al. 2011	Li et al. 2013
112 cases	80 cases	82 cases	132 cases
46 UD (41 %)	21 UD (26 %)	54 UD (66 %)	122 UD (92 %)
66 SD (59 %)	59 SD (74 %)	24 SD (29 %)	10 SD (7%)

**Table 2:** Diagnostic efficiency of ultrasound diagnosis (UD) of HP [ultrasound versus surgical diagnosis (SD)].

### Management options

Treatment of HP has a twofold therapeutic goal for the gynecologist. The former is to avoid the risk of life threatening hemorrhage from the EP, and the latter is to allow uneventful development of the IUP until viability. Even after escaping a potentially fatal condition, the good outcome of IUP is a clear expectation for a patient who is only concerned about becoming mother. Due to the rarity and variability of the clinical presentation of HP, no standard guidelines for management options are available, each case being treated according to surgical skill and expertise, side effects, resource availability and individual patient's preference.

The treatment of the ectopic component is mainly surgical; nonetheless, minimally invasive options are developed over the last decade in order to increase the likelihood of uneventful outcome of the IUP until viability. Of course, early diagnosis may also allow a conservative management [43], in reliable and selected patients, under close observation. In general, patients that are asymptomatic with small ectopic mass (mean diameter less than 3 cm) are considered for hospitalization and serial observation [22], after informed consent, being aware that rupture of the ectopic component may occur at any time. Surgery for HP should be minimally invasive in order to preserve IUP from miscarriage. Particular care is devoted to respect ovarian blood supply in the side bearing the corpus luteum, and progesterone support is suggested before 12 weeks of gestation.

The usual treatment for HP is laparoscopy or laparotomy with minimal manipulation of the pregnant uterus, in order to avoid uterine contractions during and after the procedure and to spare the residual IUP. Laparoscopy is the first choice surgery in hemodynamically stable women with HP, due to its safety in pregnancy and the prompt postsurgical recovery time [57,25]. The excellent field exposure with minimal uterine manipulation [58] and the reduction of hospitalization with consequent early mobilization may decrease thromboembolic complications [48]. The advantage over medical treatment is the prompt result and lower cost [59]. However the procedure requires the highest laparoscopic skill and experience.

Sometimes the adoption of conservative or radical laparoscopy may be a difficult choice, however salpingectomy is the simplest one as it reduces the risk of complications associated with salpingotomy [60]. Laparotomy is usually limited to severe acute bleeding with hemodynamic instability due to hemorrhagic shock. Nowadays, early ultrasound diagnosis of HP, before its rupture, allows a wide spectrum of management options besides surgery [22]. In addition, non-surgical management of early-diagnosed HP sounds a good treatment option, since it eliminates the need for anesthesia. As a matter of fact, the non-surgical approach for HP was increased from 6% (1971-1993) to 18% (1994-2004) and then to 26% (2005-2010) [47], respectively. Injection of potassium chloride (KCl) or Hyperosmolar solution into gestational sac, under ultrasound guidance, may be performed, whenever possible (clear visualization, absence of rupture) [61]. Methotrexate is best avoided due to the risk of toxicity for the surviving IUP. Moreover, the injection of KCl becomes the first choice treatment [48], if the site of EP is interstitial, cornual, cervical [62], cesarean scar [63,64], abdominal [65,66], and whenever surgical approach is dangerous or even impossible.

HP associated with abdominal pregnancy is particularly challenging, its management being recently reviewed by Yeh *et al.* [66]. Non-surgical approach is particularly suited for abdominal implantation with the selective injection of potassium chloride (KCl). This injection is a minimally invasive procedure with high rate of success reported also in ampullar HP [43]. Nevertheless, a recent review has found that 55% of tubal HP treated by transvaginal ultrasound guided salpingocentesis required subsequent salpingectomy, raising concern about the opportunity of this management when other more suited possibilities are available [67]. Systemic methotrexate, RU486 and prostaglandins may be freely used in those women who chose to interrupt the IUP [68]. HP associated with cervical pregnancy involves other technical problems. Moragianni *et al.* [69] described a case report and reviewed all the described available management options in 39 cases of cervical HP. Surgical methods include removal by aspiration, extraction, dilatation and curettage, and hysteroscopy. Hemostasis can be achieved by cauterization, Foley catheter insertion, cerclage and ligation of the uterine arteries. Medical selective embolization of uterine arteries can also be performed, as recently described [70]. In a small proportion of cases a combination of treatment modalities was employed.

Caesarean scar pregnancy associated with IUP is a rare subtype of HP. Very recently Ouyang *et al.* reviewed such cases so far published in the literature and found only 14 case reports [45]. Vaginal bleeding or no symptoms were the findings at early diagnosis performed by transvaginal color Doppler. Selective embryo reduction under sonographic guidance (aspiration, drug injection, both methods) was the most popular treatment (10 patients) to preserve IUP. Laparoscopic and hysteroscopic excision was performed in 2 cases and expectant management in one case [45].

### Prognosis of intrauterine pregnancy

Favorable outcome of intrauterine component has been reported in most studies. Nguyen-Tran and Toy [71] demonstrated that 70% of IUPs in HP can proceed normally with early diagnosis and treatment, confirming a previous study by Han *et al* [51] who reported that ART may lead to a prognostic improvement in HP versus spontaneously occurring cases. In HP the risk of miscarriage seems to be increased for the intrauterine component [72]. Parallel to the increase of early ultrasound diagnosis, the survival rate for the IUP has been improved with time, rising from the rate of 48-51% reported in early studies [73] to 69% in 2007 [30] and 88% in 2014 [54], respectively. In addition, the risk of low birth weight or preterm delivery is not increased in pregnancies progressing to live birth [72].

In conclusion, the notion of HP as a rare finding proves to be a misconception. This is particularly true in the case of unrestricted ART. Careful ultrasound inspection of the whole pelvis is mandatory even in the case of IUP visualization. This caution can help preventing unexpected hemorrhage from the ectopic site of implantation and hence favor continuation of the normal IUP, until viability, in almost 70% of cases [22].

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