

# Spontaneous Heterotopic Pregnancy

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## Definition

Spontaneous heterotopic pregnancy (SHP) is a rare condition represented by the synchronous coexistence of an intrauterine and an ectopic pregnancy. It rarely occurs with natural conception and is usually a consequence of assisted reproductive techniques. Diagnosis of SHP can be a challenge for the clinician. The evolution of the intrauterine pregnancy is dependent on many factors, such as the location of the heterotopic pregnancy, gestational age at the time of diagnosis, the surgical procedure, the presence of other risk factors, early or delayed management.

## 1. Introduction

Heterotopic pregnancy is the co-occurrence of ectopic pregnancy and intrauterine pregnancy. It is a pathological form of a dizygotic, biovular twin pregnancy <sup>[1]</sup> where one egg will nidate inside the uterine cavity and the other one will stop progression towards the uterus. The cause of this is an ovulatory abnormality or a difference in the migration speed of the two embryos, due to a delay in the capture of the fertilized egg by the fallopian tube <sup>[2]</sup>. It is a rare condition with an incidence of approximately 1 per 30,000 pregnancies <sup>[3]</sup> and can be potentially fatal <sup>[4][5]</sup>.

The prevalence of heterotopic pregnancy has seen an increasing trend in the last decades, which may be attributed to the increased use of ovulation induction <sup>[6]</sup> and medically assisted pregnancies <sup>[7]</sup>, rarely occurring with natural conception <sup>[8][9][10]</sup>. Additionally, patients who require assisted reproductive procedures often present with tubal pathology, which is one of the main causes of extrauterine pregnancy <sup>[11]</sup>.

The risk factors for heterotopic pregnancy are very similar to those for ectopic pregnancy, including smoking, history of ectopic pregnancy, previous inflammatory pelvic disease, sexually transmitted infections (especially Chlamydia infections), surgery of the fallopian tubes, abdominal surgery, endometriosis, infertility treatments, and some forms of contraception <sup>[7]</sup>.

Diagnosis is often times extremely difficult due to the intrauterine pregnancy masking the ectopic one <sup>[12]</sup>. Lower levels of the  $\beta$ -subunit of human chorionic gonadotropin (HCG) are usually an indicator of ectopic pregnancy <sup>[12]</sup>. Endovaginally ultrasonography allows correct diagnosis in 88.9% of cases by revealing the actual intrauterine and extrauterine pregnancies <sup>[2]</sup>. In case of uncertainty after performing the ultrasound, an exploratory laparoscopic intervention may be performed in order to facilitate diagnosis and subsequent steps in clinical management <sup>[13]</sup>.

The definitive result is provided by the pathology department which may describe chorionic villi in the wall of the tube, confirming the presence of an ectopic gestation. It may also describe inflammation and distortion of plicae, and modifications consistent with chronic salpingitis <sup>[14]</sup>.

The treatment of heterotopic pregnancy consists of surgical intervention in order to remove the extrauterine pregnancy. A laparoscopic approach is usually desirable in the absence of contraindications. In this case, the intrauterine pregnancy is preserved and may advance with normal surveillance and with no additional complications <sup>[15]</sup>. The overall prognosis for spontaneous heterotopic pregnancy (SHP) is similar to extrauterine pregnancy, depending on the management of the extrauterine pregnancy. Fetal prognosis remains reserved and mostly uncertain even after treatment, as approximately 35% of cases eventually develop into miscarriages. Functional prognosis is influenced by the approach used in

treatment and the biological heterogeneity of patients [2].

## 2. Discussion

This systematic review extracted available literature information regarding the diagnosis, treatment options and outcome of SHP after natural conception. Timely diagnosis can be difficult in the absence of specific symptoms.

The majority of patients presented with pelvic pain, accompanied by vaginal bleeding and amenorrhea [4][10]. This triad seems to be encountered by all patients described in the case reports we have identified. However, since these symptoms may be present in normal intrauterine pregnancies, thus early diagnosis can be mistaken for a much less serious condition [4][10]. Medical staff must not underestimate pregnant woman presenting to the emergency department with abdominal pain. It is recommended that intrauterine pregnancies are carefully investigated along with the adnexa and the abdominal cavity. The most common differential diagnoses of SHP are miscarriage, ectopic pregnancy, intrauterine pregnancy with hemorrhagic corpus luteum, and adnexal torsion. Non-gynecological causes, such as appendicitis, cholecystitis, bowel obstruction or pancreatitis, should also be excluded [16].

Ultrasonography is a valuable imaging tool in the challenging process of diagnosing spontaneous heterotopic pregnancy [9]. Since there are no specific investigations available to screen for SHP, clinicians must rely on clinical signs in conjunction with exhaustive ultrasound examination of the uterus and adnexa [4][9][10], or even resort to exploratory laparoscopy or laparotomy in cases where the ultrasonographic findings are unclear [16]. The presence of an intrauterine pregnancy does not exclude the presence of synchronous ectopic pregnancy. Careful examination of patients with normal intrauterine pregnancies who present the triad of amenorrhea, vaginal bleeding and pelvic pain is therefore mandatory [10].

In the majority of cases, diagnosis of SHP is made late, when rupture occurs, and patients present with hemoperitoneum. Early management is essential in order to avoid severe maternal complications. SHP has a higher incidence in patients with a history of infertility, following assisted reproductive techniques [5] and represents the reason why many fertility clinics prefer single-embryo transfers and rigorous ultrasonographical post-implantation follow-up [16]. However, our review highlighted the possibility of encountering this pathology as a consequence of natural conception. Although the presence of extrauterine pregnancy is usually associated with risk factors, we found a number of case reports that presented patients with heterotopic pregnancies in the absence of known risk factors [4][17][18][19][20][21][22][23]. Five articles mentioned the existence of risk factors for the patients, such as a history of pelvic inflammatory disease, history of repeated miscarriages and intrauterine interventions, history of abdominal surgery [24][25][26][27][28], thus emphasizing the importance of identifying patients with risk factors and performing differential diagnosis on individuals with clinical signs of SHP.

Race could not be assessed as a potential risk factor for SHP, since very scarce information is present in the literature. The choice between classic or laparoscopic approaches was reportedly based on the experience of surgeons, location of pregnancy, patient status and preference. Based on the identified evidence, there is no overarching pattern to suggest superiority of a particular surgical approach for SHP. Despite division across surgical techniques, minimal intraoperative manipulation of the uterus is advised in order to prevent ruptures and damage to the intrauterine pregnancy [29]. Emergency surgical treatment is advised in the presence of hemoperitoneum [4][24][17][30][25][18][19][31][32][21][23][27][29].

Medical treatment is described in the literature, such as ultrasound-guided injections of saline solutions in the ectopic sack [32] but none of the articles included in our review described using this technique.

The outcome of the intrauterine pregnancy depends on many factors, such as the maternal status at the moment of admission, the location of the extrauterine pregnancy. Hypovolemic shock of the mother can lead to a poor prognosis of the intrauterine pregnancy. Our review revealed improved outcomes for

intrauterine pregnancies when the extrauterine ones were located in the fallopian tubes, as compared to the interstitial ectopic sack [18]. Almost all articles included in our study reported an unaffected intrauterine pregnancy, with the exception of one article that reported a spontaneous abortion [27]. However, the literature describes an unaffected intrauterine pregnancy in two thirds of cases and spontaneous abortion in one third [16].

### 3. Conclusions

In the case reports identified by our systematic search, successful follow-up and evolution of intrauterine pregnancy have been observed regardless of surgical approach (open or laparoscopic) after SHP. Early diagnosis and treatment are advised, as they impact maternal and fetal outcomes. Evidence on this topic is scarce, predominantly comprised of case reports with variable degrees of adherence to dissemination guidelines. An additional concern when synthesizing information from multiple case reports is publication bias, which should be considered when interpreting the information present in this manuscript, as the tendency is to select cases with successful outcomes. More studies on this topic are required to inform clinical guidelines and to optimize care protocols for the increasing occurrence of SHP.

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## Keywords

heterotopic;ectopic;pregnancy;diagnosis

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