International Journal of Gynaecology and Obstetrics Research
www.gynaecologyjournal.in
E-ISSN: 2663-3612, P-ISSN: 2663-3604
Received: 21-08-2020 Accepted: 06-09-2020; Published: 23-09-2020
Volume 2; Issue 2; 2020; Page No. 22-25

Management of heterotopic pregnancy and their outcome

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Abstract
The presence of a combined intrauterine and ectopic pregnancy is known as a heterotopic pregnancy. It is an extremely rare, life-threatening and potentially fatal condition. It is usually a consequence of modern reproductive medical technology. Early diagnosis and appropriate management of heterotopic pregnancy can improve the intrauterine pregnancy outcome. The preferred method of treating a heterotopic pregnancy is laparoscopic surgery in order to preserve and protect the viable coexisting intrauterine pregnancy.

Keywords: ectopic pregnancy, heterotopic pregnancy, fatal, laparoscopic surgery

1. Introduction
In a normal intrauterine pregnancy, the blastocyst implants in the endometrial lining of the uterine cavity. Implantation in an area other than the uterine cavity constitutes ectopic pregnancy (EP). Simultaneous occurrence of a potentially viable intrauterine pregnancy and an extra-uterine pregnancy (ectopic pregnancy) is referred to as heterotopic pregnancy (HP) [1]. It is also known as combined ectopic pregnancy, multiple-sited pregnancy, coincident pregnancy or concomitant intrauterine and extra-uterine pregnancy. It is an extremely rare, dangerous and potentially fatal condition.

Most of the extra-uterine pregnancies occur in the fallopian tube and the commonest site is the ampulla. The other locations include ovarian pregnancy, abdominal pregnancy, cervical pregnancy, broad ligament pregnancy and pregnancy in rudimentary horn[2].

1.1 Epidemiology
The estimated incidence of heterotopic pregnancy in spontaneous (natural) conceptions has been found to be 1 in 30,000 pregnancies [3]; however the incidence is significantly increased in women who undergo ovulation induction. A heterotopic pregnancy rate of 1 in 100 pregnancies if conception is due to assisted reproduction techniques (ART) such as In Vitro Fertilization (IVF) and Gamete Intra-Fallopian Transfer (GIFT) [4]. When more than 4 embryos are transferred, the incidence rises to approximately 1 in 50 [5].

1.2 Risk Factors
The major risk factors for an ectopic pregnancy (such as pelvic inflammatory disease, previous ectopic pregnancy, tubal disease or surgery, use of an intrauterine contraceptive device) after natural conception can also lead to heterotopic pregnancy [6]. However, the risk of a heterotopic pregnancy is markedly increased particularly with assisted reproduction techniques (ART) involving multi-follicular development and technical factors in embryo transfer (such as assisted hatching, frozen embryo transfer, higher transfer volume, deep fundal transfer and the practice of multiple embryo transfer) [7, 8].

2. Pathology
One important aspect of ectopic pregnancy is the lack of resistance of the endosalpinx to invasion by the trophoblastthus, implantation occurs beneath the endosalpinx in the muscle and connective tissue next to the tubal serosa. There may be little or no decidual reaction and minimal defense against the penetrating trophoblast. Therefore, the trophoblast invades the blood vessels to cause local hemorrhage. Hemorrhage is the major cause of maternal death in untreated ruptured ectopic pregnancy [9].

3. Clinical manifestation
The common clinical presentations of heterotopic pregnancy include abdominal pain and vaginal bleeding or signs of hemodynamic instability [10]. It may be sometimes asymptomatic. So, it is recommended to all high-risk women to be screened for heterotopic pregnancy despite of confirming a normal intrauterine pregnancy.

3.1 Diagnosis
Taking history in detail and combining symptoms, signs and pelvic examination will be helpful in making diagnosis of a heterotopic pregnancy, however to confirm the diagnosis serial serum quantitative beta human chorionic gonadotropin (HCG) tests and trans-vaginal ultrasound is very important [11]. Doppler ultrasound can also provide additional information which could also be helpful. Sometimes, it is very difficult for doctors to confirm diagnosis even with these methods, because of the

presence of intrauterine pregnancy; it's very easy for an ectopic pregnancy to be missed.

About 70% of heterotopic pregnancies diagnosed between 5-8 weeks of gestation, 20% between 9 and 10 weeks and only 10% after the 11th week. An early diagnosis can prevent potentially fatal complications by managing appropriately on time and preserve the intrauterine pregnancy.

3.2 Differential Diagnosis

To distinguish a heterotopic pregnancy from other related diseases, table (I) could be useful.

Table 1

Appendicitis	Ruptured Corpus Luteal Cyst	Salpingitis	Uterine Abortion
1) Pyrexial disease 2) Epigastric, periumbilical, then right lower quadrant pain; tenderness localizing at McBurney's point, rebound tenderness. 3) Unrelated to menses 4) Negative β-hCG 5) White cell count elevated	1) Unilateral pain 2) No symptoms or signs of pregnancy 3) Temperature and pulse normal 4) Tenderness over affected ovary. No masses. Uterus firm and not enlarged 5) Negative β-hCG. 6) White cell count normal	1) Pyrexial disease 2) Usually in both lower quadrants pain, with or without rebound 3) Hypermenorrhea or metrorrhagia, or both 4) Temperature and pulse37.2-40^{0}C. Pulse elevated in proportion to fever. 5) Negative β-hCG. 6) White cell count elevated	1) Midline cramps 2) Longer amenorrhea, then spotting, then brisk bleeding. 3) To 37.2^{0}C if spontaneous; to 40^{0}C if induced (infected). 4) Cervix slightly patulous. Uterus slightly enlarged, irregularly softened. Tender only with infection 5) Ultrasonography

3.3 Treatment

Surgery (salpingectomy or salpingostomy) is the preferred method of treating a heterotopic pregnancy in order to preserve the intrauterine pregnancy. Indications for surgery include severe intraperitoneal bleeding, old ectopic pregnancy, require sterilization and failure of conservative treatment. Laparoscopy is useful in the diagnosis and management of unruptured ectopic pregnancy [12]. However, it is contraindicated in case of severe hemorrhage and hypovolemic shock where exploratory laparotomy should be considered as soon as possible [13].

Conservative management includes medicines (such as methotrexate, KCl, hyperosmosis glucose) that inhibit trophoblast proliferation, destroy chorion and kill the embryo. It is indicated for non-tubal heterotopic pregnancy (such as the cervical or interstitial EP) where surgical treatment may destroy the co-existing intrauterine pregnancy [14, 15]. Contraindications include severe dysfunction of liver and kidney and defect of coagulation in women. Salpingocentesis with the introduction of methotrexate (MTX) or potassium chloride (KCl) into the gestational sac is still in investigation, as it has a limited role in the management of heterotopic pregnancy as one must try to protect the viable intrauterine pregnancy. Expectant management (watchful waiting) is a conservative strategy in which the ectopic pregnancy is continuing to resolve spontaneously and successfully without doing any intervention. It has also been successfully applied in selected cases.

Table 2: Management of heterotopic pregnancy ant their outcome

		C. Louis *et al*. (1997)	Rumana *et al*. (2010)	Talbot *et al*. (2011)	Jennifer *et al*. (2012)
Total Reported cases		13 ; Non-viable IUP at diagnosis = 3	14	82	13; Viable IUP at diagnosis = 10 (76.9%)
Treatment methods	Salpingectomy	10 = 7 (L) + 3 (Open)	14 (L)	40 (49%)*	9 (L)
	Salpingostomy	3 (L)	-	2 (2%)*	-
	Cornual resection	-	-	5 (6%)	1 (L)
	Injection of KCl/MTX/hyperosmolar solution and/or aspiration	-	-	21 (26%)*	2
	Other	-	-	16 (20%)	1
Outcome of Intrauterine pregnancy (IUP)	Full term delivery	6 (46%)	11 (78.6%)	39	7 (70%)
	Preterm delivery	-	-	14	1 (10%)
	Miscarriage or abortion	3	3 (21.4%)	26%	-
	Other	1	-	-	2
* Two women had more than one type of procedure; L= Laparoscopy.					

C. Louis-Sylvestre *et al*. reported a total of 13 patients with heterotopic pregnancy, 10 (77%) patients were treated laparoscopically and 3 underwent a laparotomy: 1 patient because of significant haemoperitoneum, 1 because of a ruptured cornual pregnancy with significant haemoperitoneum and 1 because of an interstitial pregnancy. Salpingectomy was performed in these 3 patients. In the laparoscopic group, salpingectomy was performed in 7 cases and salpingostomy in 3 cases (2 patients without previous tubal disease and 1 with a previous contralateral salpingectomy). In 3 cases, the intrauterine pregnancy was non-viable at the time of diagnosis of HP. Of the remaining 10 patients, 3 miscarried within 2 weeks of surgery and 1 had in-utero-fetal death of twins after developing chorioamnionitis at 26 weeks. 6 women had an uneventful pregnancy (46%). Among the 8 patients who underwent a laparoscopy with a viable intrauterine pregnancy, 5 proceeded

uneventfully to term (62.5%) [16].

Rumana *et al*. reported a total of 14 patients with heterotopic pregnancy, all underwent laparoscopic salpingectomy. 11 (78.6%) patients delivered live singleton infants at full term via caesarean section while 3 (21.4%) had spontaneous abortion after 10-15 days of surgery [17].

According to Talbot *et al*., a total of 59 of the 82 women (72%) were managed with a surgical approach, with 40 women undergoing a salpingectomy and two women undergoing a salpingostomy. In contrast, 27% were managed purely conservatively; this included all of the pregnancies but one, implanted in the cervix. In 22 cases, the surgical approach was laparoscopic, whereas in 36 cases a laparotomy was used. A total of 39 women delivered healthy infants at term, with only 14 delivering prematurely at <37 weeks' gestation. A total of 26% of pregnancies resulted in miscarriage or abortion [18].

Jennifer *et al*. reported a total of 13 patients with heterotopic pregnancy, out of which 9 patients managed with laparoscopic salpingectomy, 1 managed with laparoscopic resection of cornua, 1 with laparoscopic excision, 1 with intra-amniotic potassium chloride injection and 1 managed with transvaginal aspiration of ectopic gestation. At the time of diagnosis 10 (76.9%) patients had a viable intrauterine pregnancy; of these, 7 (70%) patients went on to have delivery at term, 1 (10%) had a preterm twin delivery at 32 weeks, 1 (10%) patient decided to terminate the pregnancy, and 1 (10%) patient had an uneventful ongoing pregnancy at 35 weeks, as indicated in the last follow-up record at the time of the review [19].

4. Conclusion

A heterotopic pregnancy is an extremely rare, life-threatening and potentially fatal condition. It is usually a consequence of modern reproductive medical technology. Early diagnosis and appropriate management of heterotopic pregnancy can improve the intrauterine pregnancy outcome. The preferred method of treating a heterotopic pregnancy is laparoscopic surgery in order to preserve and protect the viable coexisting intrauterine pregnancy.

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