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Case Report Open Access

Successful Surgical Management of a Heterotopic Tubal Pregnancy following Ovulation Induction using Clomiphene Citrate

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Introduction

Heterotopic pregnancy (HP) is a rare form of multiple pregnancy where a combined intrauterine gestation develops simultaneously with an extrauterine pregnancy. The majority of extrauterine implantations are tubal. Other uncommon sites can include ovaries, cervix and the abdomen [1,2]. There have been documented cases of higher order multiple heterotopic gestations; spontaneous triplet HP with two sacs seen in one tube [3] and in another case an ectopic pregnancy in each tube with a single intrauterine gestation [4] Quadruplets HP have also been reported [5].

The advent of Assisted Reproductive Techniques (ART) and the use of ovulatory drugs such as Clomiphene Citrate (CC) have led to an upsurge in the frequency of this previous rarity. In 1948, 1 in 30,000 gravidas presented with HP [6]; recent studies report 1 in 3,800 [7]. With assisted reproductive techniques, it is 1 in 100 [2,8]. Clomiphene Citrate (CC) is associated with a HP rate of 1 in 900 [9].

CC can hyperstimulate the ovaries leading to the release of multiple mature follicles. This results in a 5-10% risk of multiple pregnancy, with majority being twins, although higher order multiple pregnancies have been reported [10]. HP may be the resultant effect of retrograde flow of the embryo into the fallopian tubes [11]. Also, CC alters the local progesterone / estradiol ratio and may disturb the oviductal peristalsis, resulting in extra uterine implantation of the embryo [12]. This may be further enhanced by any pre-existing tubal disease [13]. HP appears to share similar risk factors as for multiple pregnancy a nd ectopic pregnancy (EP). In general, 1-2 % of pregnancies result in spontaneous EP [15], while 5% of ART result in EP [2].

Case Report

A 34 year old primigravida with a 3 year history of unexplained primary infertility had induction of ovulation with clomiphene citrate in our centre. She conceived after two cycles of treatment.

She presented in our Early Pregnancy Assessment Unit at 7 weeks gestation with mild vaginal bleeding and lower abdominal pain. Her serum β-HCG was 45 904 units/litre. An ultrasound scan showed a viable intrauterine pregnancy corresponding to 7 weeks (Figures 1 and 2) and a right adnexal mass measuring approximately 6 cm. The suspected diagnosis was a ruptured corpus luteum. She was kept under observation as her pain progressively worsened. A second opinion was sought and a diagnosis of a ruptured ectopic pregnancy was made (Figures 3-5).

She was managed surgically by mini-laparotomy and right salpingectomy. The surgical findings revealed a large 6 cm haematosalpinx. There was a gestation sac in the right tube with a large haematoma in the fimbrial end with more than 100 ml of haemoperitoneum. The uterus was bulky corresponding to 7 weeks gestation and the left tube and both ovaries appeared normal.

The histology result reported a tubal ectopic gestation. A subsequent ultrasound scan revealed a viable intrauterine pregnancy. She was discharged three days post-operatively.

Serial ultrasound examinations showed a normal developing foetus. She spontaneously laboured at 41+2 weeks and was delivered by forceps for a delayed second stage of labour. Her male baby weighed 3500 g and had an Apgar score of 8 and 9, at 1 and 5 minutes respectively.

Discussion

The preoperative diagnosis of HP is difficult [15]. The finding of an intrauterine pregnancy (IUP) on ultrasound scan may offer false reassurance and thus prevent further meticulous abdomino-pelvic search for a co-existing EP. This delays the diagnosis of this sinister pathology [16]. In contrast, an empty uterus would trigger a prompt active investigation for an extra-uterine gestation even in an asymptomatic patient. Over half (54%) of HP cases could present asymptomatically [13]. The presence of a haemorrhagic corpus luteum can also confuse and delay the diagnosis of a HP [2,17], especially in hyperstimulated ovaries, as in our case. Also, Ovarian Hyperstimulation Syndrome (OHSS) may occur following induction of ovulation with CC. This presents a preoperative diagnostic challenge as ascites and haemoperitoneum may be difficult to distinguish hence justifying the use of laparoscopy [15].

Despite advances made in ultrasound, the preoperative diagnosis of HP has not improved. A review of literature between 1971 and

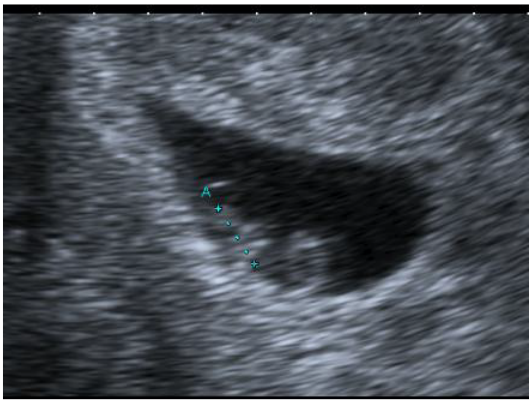

Figure 1: Viable intrauterine pregnancy.

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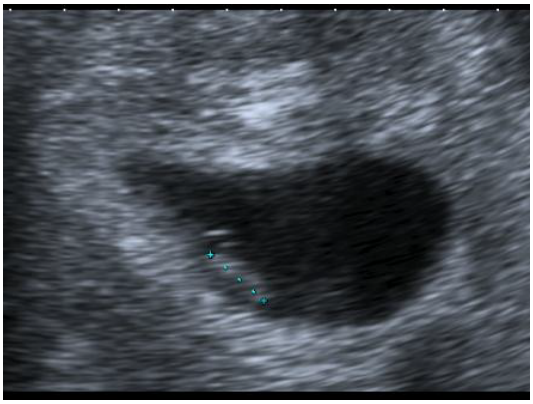

Figure 2: Viable intrauterine pregnancy.

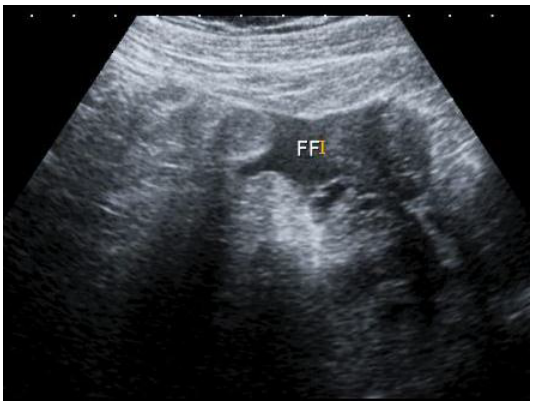

Figure 3: Pelvic free fluid (haemoperitoneum).

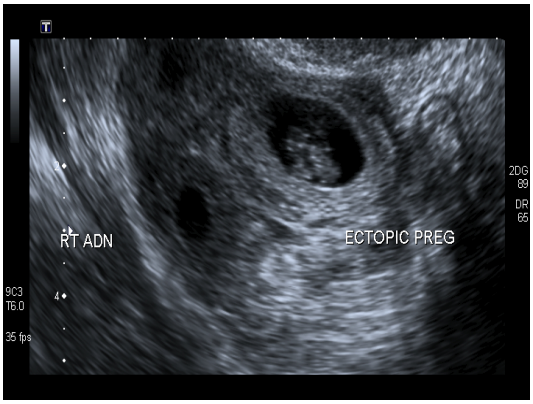

Figure 4: Ectopic pregnancy in the right adnexia.

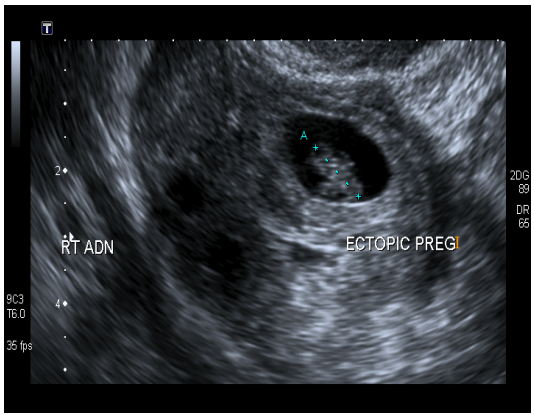

Figure 5: Ectopic pregnancy in the right adnexia.

1993 revealed 112 cases of HP; only 46 were diagnosed by ultrasound (41.07%), whereas 66 were diagnosed by laparoscopy or laparotomy (58.93%). A similar review from 1994 to 2004 showed that out of 80 cases, 21 were diagnosed by ultrasound (26.25%) and 59 at surgery (73%) [18]. HP is definitely diagnosed by laparoscopy or laparotomy in 60 to 73% of cases and by ultrasound scan in 26 to 41% of the cases [9]. However, Tal et al. reported that 70% of heterotopic pregnancies were diagnosed between 5 and 8 weeks of gestation, 20% between 9 and 10 weeks and only 10% after the 11th week [2]. Furthermore, Tal et al. reported that more than 50% of HP were identified by USS or laparoscopy more than 2 weeks after the initial visualisation of the IUP [2], although 85% of cases remain undiagnosed prior to rupture.

Clinicians should hence have a high index of suspicion when dealing with women of child bearing age presenting with lower abdominal pain in the first trimester, especially if there is a preceding history of fertility treatment.

Treatment presents a challenging dilemma in dealing with the extrauterine gestation and its associated complications whilst conserving the viable IUP. The treatment options are influenced by the clinical presentation, haemodynamic status, clinician's expertise and the patient's fertility wishes. With early diagnosis and management, 70% of patients have a viable pregnancy at term [9], compared with 60% reported by Louis-Sylvester et al. [15].

Surgical management has been the traditional mainstay as it offers immediate results and eliminates the risk of EP rupture and the morbidity and mortality associated with intraperitoneal haemorrhage. However, the surgical and anaesthetic risks to both to the mother and the developing IUP have been reported to result in up to 40% loss of viable IUP [9,15].

Laparoscopic surgery has been compared with open surgery in 228 women in three randomised controlled trials. Laparoscopic procedures were associated with shorter operation times, less intraoperative blood loss, shorter hospital stays and lower analgesic requirements [19]. Laparoscopy allows both diagnosis and treatment, and the outcome of the intrauterine pregnancy is comparable with laparotomy [15]. Laparoscopic approach is preferred over laparotomy in the management of suspected HP due to minimal uterine manipulation [11].

In this era of advancing medical science, non-surgical management of HP, which aims to preserve the IUP, could be employed. These methods are indicated in early asymptomatic cases. They decrease the potential surgical and anaesthetic complications but there remains an ongoing risk of rupture of the HP; hence, strict clinical and sonographic surveillance are mandatory. These treatment modalities include local injection with potassium chloride (KCl) or hyperosmolar glucose into the EP sac [9,20,21].

A literature review of HP cases treated with KCl injection noted that 55% resulted in failure and required surgical intervention [22]. Also, Habana *et al.* studied the outcome of women undergoing surgery versus medical treatment, and demonstrated the benefits of surgery in terms of miscarriage (13% versus 50%, $p<0.05$) and live birth rate (60.9% versus 50%) [7].

There have been reported cases of expectant management of heterotropic pregnancy [23].

Conclusion

In our case, intraabdominal bleeding was suspected hence an emergency mini-laparotomy and salpingectomy was justified. IUP does not exclude EP or vice versa, as the diagnosis of HP can be inconclusive even after thorough abdomino-pelvic sonographic assessment. It should be seriously considered as a differential diagnosis for early pregnancy lower abdominal pain. Clomiphene induction of ovulation should trigger early sonographic surveillance. An early diagnosis and prompt treatment is of great importance in reducing maternal morbidity, blood transfusion and mortality. It is more likely to conserve the IUP and the patient's future chances of reproduction.

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