

Expectant Management of Heterotopic Pregnancy

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Heterotopic pregnancy or the coexistence of an intrauterine and an extrauterine pregnancy occurs in about 1 out of 30,000 pregnancies. Between assisted reproductive techniques and ovulation induction, it is said to occur more commonly with the former. The patient presented in this case is a 29 year old primigravid who underwent ovulation induction with clomiphene citrate and was later on diagnosed to have both an intrauterine and a non-viable extrauterine pregnancy. The management for this kind of pregnancy can be medical, surgical or expectant. The patient in this case was managed expectantly. This case study presents a review of literature on heterotopic pregnancy, and describes how this rare type of pregnancy developed in this index patient, how it is diagnosed and managed, and to showcase how expectant management can be a safe option for cases of heterotopic pregnancy.

Key words: heterotopic pregnancy, ectopic pregnancy, Clomiphene citrate

Introduction

A heterotopic type of pregnancy is considered a complication and not a natural consequence because it usually happens to women who are at high risk for having an ectopic pregnancy or those who undergo ovulation induction¹, as seen in the index case. It is a simultaneous occurrence of an intrauterine and an ectopic pregnancy which can implant anywhere outside of the endometrial cavity. In 93.9 percent of cases, the ectopic pregnancy usually occurs in the fallopian tubes but other sites such as the ovaries and the abdomen can also be involved², as in the case of this patient. It is potentially dangerous and it presents with non-specific signs and symptoms such as vaginal bleeding and abdominal pain, so it is imperative to consider this as a differential diagnosis in patients presenting with these complaints.

Heterotopic pregnancy was initially reported in the early 1700's, and over the decades, its incidence has raised steadily.² It was said to occur

in 1 out of 30,000 spontaneous pregnancies, but since the advent of assisted reproductive technology and ovulation induction, its recent incidence has been reported to occur more frequently, approximately 1 out of 100 pregnancies.^{1,3}

This case study aims to review literature exploring the possible theory on how this patient developed this type of ectopic pregnancy, and showcase a different and less popular approach on the management and surveillance of heterotopic pregnancy, the prudent use of diagnostic imaging in confirming the diagnosis, and patient's prognosis on carrying both a live intrauterine pregnancy and a non-viable extrauterine pregnancy, managed expectantly.

The Case

A 29 year-old primigravid, consulted a private physician at 6 weeks age of gestation where an

ultrasound was initially done revealing a single live intrauterine pregnancy with cardiac activity (Figure 1). The patient did not have any complaints of vaginal spotting nor bleeding at this time and she was just prescribed with prenatal vitamins. On her subsequent follow up at 8 weeks age of gestation, a repeat ultrasound revealed uterine didelphys and a twin pregnancy with good cardiac activities (Figure 2). On her 9th week age of gestation, she started experiencing vaginal spotting and hypogastric pain. A follow up ultrasound revealed a multiple pregnancy with the 2nd twin having no cardiac activity (Figure 3). The patient was then admitted for Threatened Abortion, and

was maintained on Isoxuprine drip. A few days after being discharged from the hospital, she again started to experience hypogastric pain described as crampy in character with no associated vaginal bleeding. On repeat transvaginal ultrasound, heterotopic pregnancy was considered, with a single live intrauterine pregnancy that was 9 5/7 weeks age of gestation, with good cardiac activity (Figure 4), and a left adnexal mass measuring 4.93cm x 5.87cm x 4.48cm, containing a gestational sac equivalent to 9 1/7 weeks age of gestation and an embryo with no cardiac activity (Figure 5). The patient was readmitted for further observation.

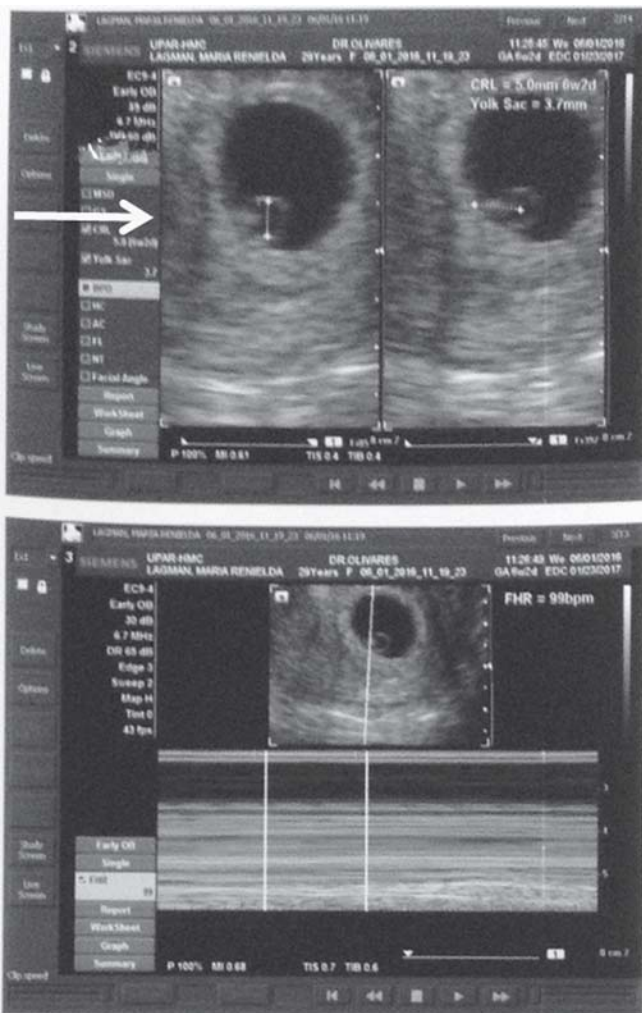


Figure 1. Ultrasound showing a single live intrauterine pregnancy at 6 weeks and 2 days age of gestation by crown rump length (0.52cm), with a positive yolk sac and an embryo (arrow) with cardiac activity of 99 beats per minute.

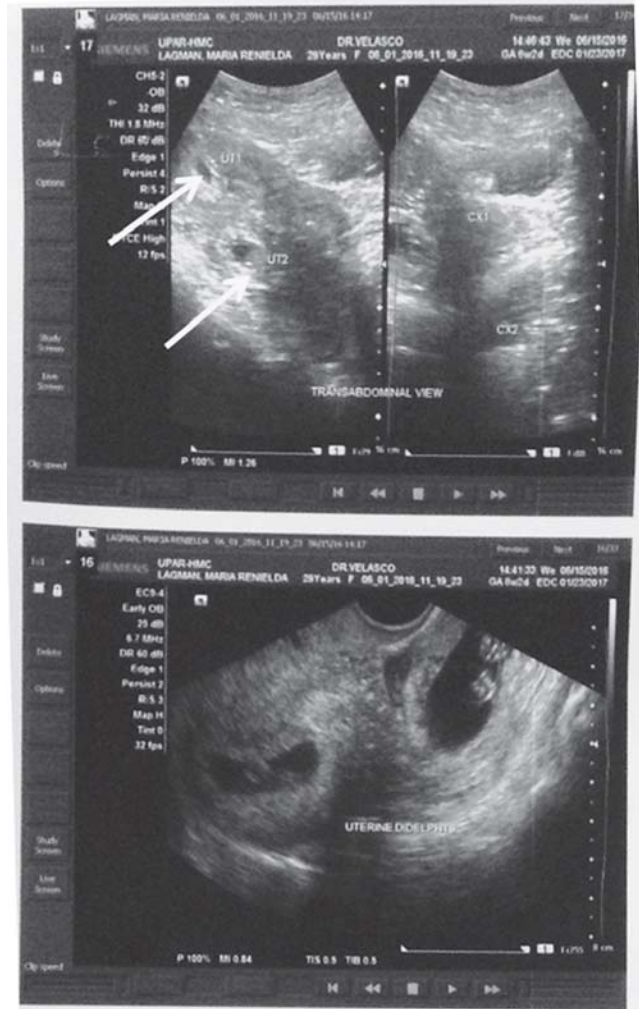


Figure 2. An ultrasound showing Uterine Didelphys (arrows) and a twin intrauterine pregnancy of about 8 weeks age of gestation.

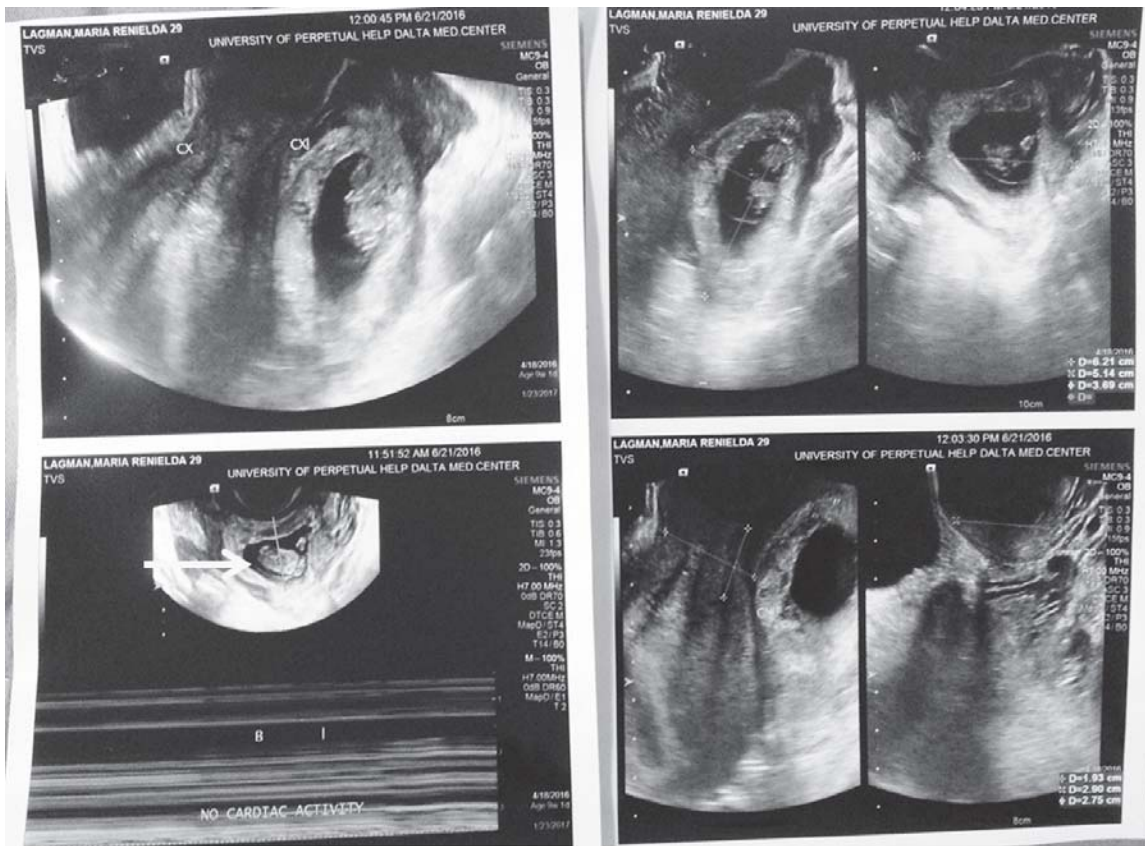


Figure 3. Ultrasound at 9 weeks age of gestation with Twin B having no cardiac activity (arrow).



Figure 4. Ultrasound of an intrauterine pregnancy at 9 weeks age of gestation with good cardiac activity of 185 beats per minute.



Figure 5. Ultrasound showing a left adnexal mass (arrow) measuring 4.93cm x 5.87cm x 4.48cm, containing a gestational sac equivalent to 9 1/7 weeks age of gestation.

The patient has a history of treatment for primary infertility with clomiphene citrate 50mg for 2 cycles. She has no co-morbidities.

On admission, patient had stable vital signs. Other physical examination findings were unremarkable. On speculum examination, the cervix was pink, smooth, with scanty, brownish vaginal discharge. On internal examination, the cervix was soft, closed, with uterus slightly enlarged, no cervical motion tenderness and no adnexal mass. A magnetic resonance imaging was then requested which revealed no signs of uterine didelphys, a gravid uterus and a lobulated heterogeneous structure with fluid signal at its central portion at the posterior cul-de-sac representing an abdominal ectopic pregnancy with a mild mass effect to the uterus, cervix and superior rectum with a demonstrated distinct plane of cleavage in relation to the left ovary (Figures 6 & 7).

Attending physician opted to observe the patient, rather than do immediate surgical exploration, since at this time patient was stable, with no signs of acute abdomen. On discharge, she was maintained on Dydrogesterone (Duphaston[®]) and was advised close follow-up, with regular assessment of complete blood count and bleeding



Figure 6. Plain MRI of the pelvis showing a lobulated structure (arrow) with inhomogeneous thick rim with a bright fluid signal at the central portion measuring 4.1cm x 4.8cm x 6.4cm located at the posterior cul-de-sac, representing an abdominal ectopic pregnancy.

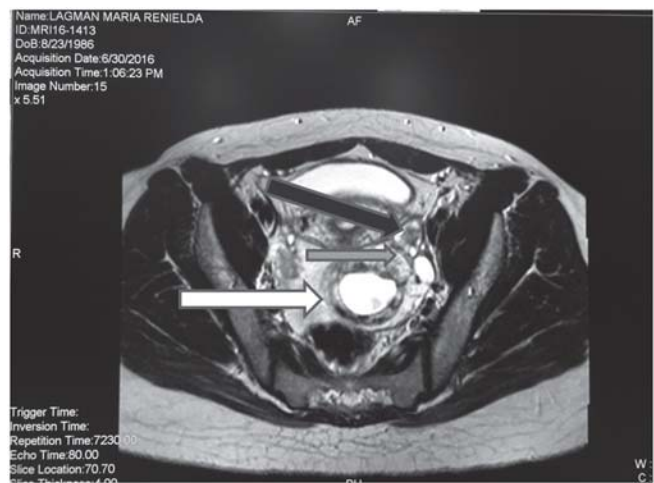


Figure 7. Plain MRI of the pelvis showing a lobulated structure (white arrow) representing an abdominal ectopic pregnancy, with a thin, distinct plane of cleavage (black arrow) in relation to the left ovary (gray arrow).

parameters, as well as sonographic surveillance of the intrauterine and ectopic pregnancies.

The patient was stable throughout her antenatal period. Complete blood count and bleeding parameters were all within normal limits. There was only a slight increase in the size of the ectopic mass (approximately 1 cm), but she did not experience any adnexal pain nor vaginal bleeding. Fetal growth and development was normal.

At 40 weeks age of gestation, patient went into spontaneous labor, and underwent emergency low segment cesarean section for dystocia (failure of descent) on the 14th hour of labor. She delivered a live, term baby boy, 3.35 kg, with APGAR score of 9,9 and 39 weeks on pediatric aging. On inspection of the adnexa, the distal portion of the left fallopian tube was dilated to a 4cm x 3cm x 3cm violaceous mass, which on cut section revealed a brownish solid non necrotic mass with placenta-like tissues. The fimbriae were noted to be clubbed (Figures 8 & 9). The surgeon proceeded to do a left total salpingectomy.

Histopathologic examination of the left fallopian tube revealed degenerated immature villi, consistent with tubal pregnancy.

Patient was discharged stable 3 days post-operatively, with regular postnatal and postoperative instructions.

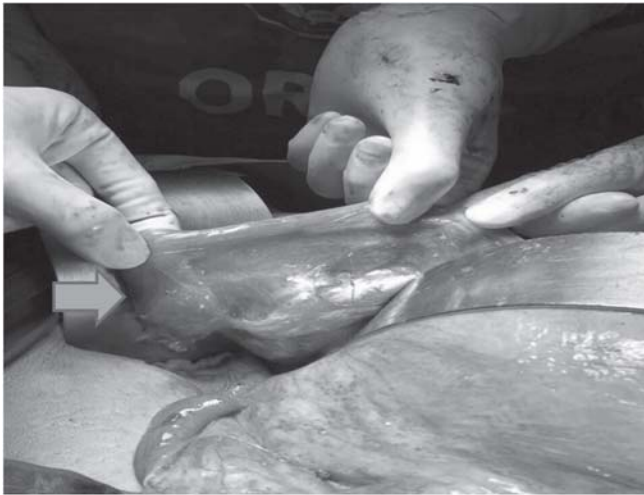


Figure 8. Intraoperative inspection of the adnexa revealed a dilated violaceous distal portion of the left fallopian tube.

Discussion

Heterotopic pregnancy is defined as the coexistence of an intrauterine and an extrauterine gestation. It occurs in 1:30,000 pregnancies, but in the advent of assisted reproductive technology, its incidence has gone up to 1:100 pregnancies.¹ The increasing incidence in these pregnancies may be related to the high proportion of patients with tubal disease, high levels of estradiol and progesterone, or high numbers of transferred

embryos or ovulated oocytes in this population. Other factors, such as volume and viscosity of transfer medium and the technique of embryo transfer, may also play a role. A history of pelvic inflammatory disease has also been cited as a predisposing factor for heterotopic pregnancy. Heterotopic pregnancy, however, is rare following induction with clomiphene citrate.³

Ghandi, et al.³ reported a similar case of heterotopic pregnancy following ovulation induction using clomiphene citrate. Clomiphene citrate was theorized to have caused a hyperstimulation of the ovaries and probably altered the myoelectrical activity responsible for propulsive action of fallopian tubes, therefore increasing the rate of a twin and ectopic pregnancy, and eventually a higher rate of heterotopic pregnancy. This could have been the effect of clomiphene in the index case.

Diagnosis

Early diagnosis of heterotopic pregnancy is difficult because of lack of specific symptoms. Thus, a high index of suspicion for this diagnosis is important, especially in patients who have undergone IVF and who experience abdominal pain or vaginal bleeding.¹

Serial β hCG concentrations are not interpretable in the presence of both a viable

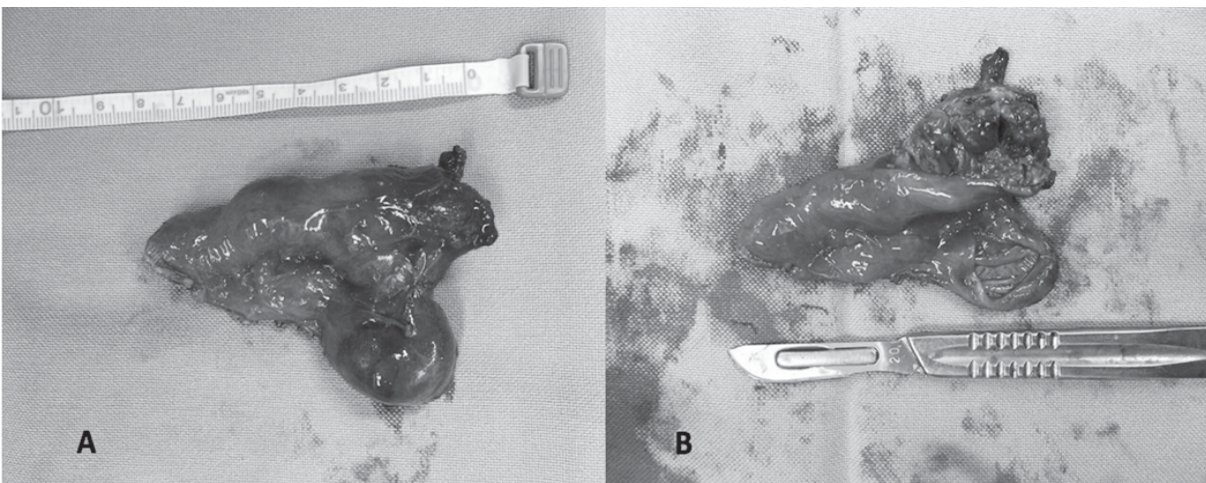


Figure 9. Left fallopian tube specimen (s/p salpingectomy). The distal end of the left fallopian tube was cystically dilated to a 4cm x 3cm x 3cm mass (A), which on cut section revealed a brownish solid non necrotic mass, with placenta-like tissues (B).

intrauterine and ectopic pregnancy, thus it is not useful in this case.⁴ On ultrasound examination, the diagnosis is suggested by visualization of both an ectopic pregnancy and intrauterine pregnancy (IUP) or the presence of echogenic fluid in the posterior cul-de-sac in the presence of an IUP. Heterotopic tubal pregnancies have been reported as late as 16 weeks of gestation, while abdominal or rudimentary horn pregnancies can continue to develop late in gestation.⁵

The ultrasonographer should carefully examine not only the uterus, but also the adnexae, especially in women who conceived following IVF. Women with a confirmed IUP who are experiencing abdominal pain or vaginal bleeding should undergo serial transvaginal ultrasound examinations every week until the possibility of a concomitant tubal ectopic pregnancy can be eliminated.

The patient in this case presented with abdominal pain on her second admission and underwent another transvaginal ultrasound in which a heterotopic pregnancy was revealed. Ultrasonography is still the imaging modality of choice in diagnosing both intrauterine or ectopic pregnancy.⁵ The ectopic pregnancy is found in the fallopian tube in 90 percent of cases; other sites include the cornua (4%), ovary, cervix, and abdomen. A few cases have been diagnosed as late as 16 weeks of gestation.⁵ For confirmation of this finding, a Magnetic Resonance Imaging (MRI) was requested. According to a Clinical Practice Guideline by Sherbrooke, et al.⁶ the use of MRI during the first trimester pregnancy has not been associated with any long term sequelae and should not raise clinical concern.

Management

An extrauterine pregnancy can either be managed surgically, medically or expectantly. According to a case report by De Silva, et al.⁷, surgical management has been the traditional mainstay of treatment since it eliminates the risk of ectopic pregnancy rupture as well as the consequences associated with intraperitoneal hemorrhage.⁷ In the case cited by Ghandi, et al¹, the patient had a tubal ectopic pregnancy which would require a surgical management since tubal

pregnancies outgrow the tube and would eventually result to a rupture and hemorrhage.¹ Furthermore, extrauterine pregnancies could also be managed conservatively through medical management, or expectantly. One of these non-surgical managements that can be done is the administration of Potassium Chloride (KCl) or methotrexate to facilitate fetal reduction. Potassium chloride (KCl) injections have been widely used for selective reduction in multiple pregnancies and this has found favor with heterotopic pregnancies as well. KCl is used to provide cardiac asystole while Methotrexate is also injected for trophoblast destruction. Monteagudo et al. and Kiri, et al. have the largest experience of conservative management of heterotopic pregnancy by injecting either potassium chloride intracardiac or in the gestation sac or methotrexate systemically. The intervention carried out by these authors resulted in successful pregnancy termination without any major complications.^{8,9,10} This option however, is still undocumented locally.

According to a journal by Sivalingam, et al.¹¹, some patients with a concomitant ectopic pregnancy can be managed expectantly by placing them under close observation on whether it would continue to resolve spontaneously through either regression or tubal abortion without any intervention, given the following criteria: no evidence of a ruptured ectopic pregnancy, a clinically stable and asymptomatic patient, and declining β -hCG concentrations.¹¹ Like the management that was chosen for the patient in this case, she was placed under expectant management since she was clinically stable and asymptomatic. However, serial serum β -hCG determination was not done for this case.

One possible complication monitored for this patient as part of the long term management was the possible occurrence of Disseminated Intravascular Coagulation (DIC). Sultana, et al, 2011¹² referred to DIC as a classic complication of obstetric conditions occurring in more than 50 percent of patients with obstetric causes. In this case, the authors have a retained dead fetus. In DIC, an unregulated thrombin explosion causes release of free thrombin into the circulation that leads to the clinical features of DIC, with thrombin

and plasmin responsible for the thrombotic and hemorrhagic manifestations. In addition to this, normal pregnancy is associated with a range of alterations to hemostatic component, which when combined with the patient's condition, puts her in an increased risk of hemorrhage, thrombosis and DIC. DIC occurring in patients with retained dead fetus is more complicated because thromboplastic substances from the dead fetus are slowly but continuously absorbed, producing a picture of progressive DIC. Unless the dead fetus is retained for three weeks or longer, clinically evident coagulation disorders are rare.

The patient did not have any evidence of such complications based on her regular follow-up check-ups, with serial complete blood count, prothrombin time and partial thromboplastin time, She was stable and asymptomatic and she did not have any recurrence of vaginal spotting or bleeding during her subsequent antenatal course.

Summary and Conclusion

An intrauterine pregnancy together with a co-existing ectopic pregnancy does not entail a bad prognosis all the time. It would largely depend on the location of the ectopic pregnancy, an early diagnosis and close surveillance or follow-up. Since it usually presents with a non-specific symptom of an abdominal pain and bleeding, it is necessary to keep a high index of suspicion and consider heterotopic pregnancy as an important differential diagnosis to be able to do the necessary diagnostic exams and arrive at a definite diagnosis, and thus institute a prompt and proper management. Expectant management is a safe option for these patients, for as long as they are clinically stable, asymptomatic, and with declining β -hCG concentrations.

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