Successful pregnancy following medical management of heterotopic pregnancy

ABSTRACT

We present a case of sonographic demonstration of quadruplet heterotopic pregnancy consisting of twin intrauterine (IU) pregnancy and a twin adnexal pregnancy after ovulation induction (OI) with clomiphene citrate (CC) and timed intercourse (TI). Both heterotopic pregnancy and spontaneous twinning are frequent after OI, this combination although extremely rare must be kept in mind. The role of early transvaginal sonography and serum beta human chorionic gonadotrophin after missed periods helps in early diagnosis. It gives us an opportunity for medical management, saving the patient the agony of surgery along with loss of pregnancy. The management of heterotopic pregnancy is controversial. This patient did not have a viable IU pregnancy and both the sacs in the adnexa were small. Thus, we treated her successfully by medical management with systemic methotrexate, with regular follow-up. This patient successfully conceived after 6 months with OI and TI, with ovulation occurring from the same side of the previous ectopic. She had a viable IU gestation corresponding to 12 weeks.

KEY WORDS: Heterotopic/ectopic pregnancy, medical management of ectopic gestation, ovulation induction, timed intercourse, transvaginal sonography

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INTRODUCTION

Heterotopic pregnancy is simultaneous presence of intrauterine (IU) and extrauterine pregnancy with an incidence is 1/30,000 of all spontaneous pregnancies. It was first defined by Duverney, in the year 1708, as an autopsy finding in a patient who died of ectopic pregnancy who also had an IU pregnancy.[1] With rampant use of ovulation induction (OI) and assisted reproductive technique, the incidence has increased to 2.9%[2] and 1%,[1] respectively. Hence, screening the adnexa by transvaginal sonography (TVS) is mandatory despite visualization of an IU gestational sac (GS) in patients undergoing ovarian stimulation and assisted reproduction.

About 1% of the pregnancies are in an ectopic location, of which 95–97% are located in the fallopian tube. The most common site is the ampullary portion of the tube (80%), followed by the isthmic segment of the tube (10%), the fimbria (5%) and the cornual and interstitial regions (2–4%).[2]

Clinical examination, serum beta human chorionic gonadotrophin (beta hCG) assay and transvaginal scanning as a diagnostic algorithm has a sensitivity of 100% and a specificity of 99%.[3]

Early treatment of an ectopic pregnancy with the antimetabolite methotrexate (MTX) has proven to be a viable alternative to surgical treatment. If administered early in the pregnancy, MTX can disrupt the growth of the developing embryo causing the cessation of pregnancy. Successful medical treatment using MTX has been reported in the literature, with subsequent good reproductive outcomes.

CASE REPORT

Mrs. TA, 28 years old, married since 1 year, was anxious to conceive due to her irregular cycles as a result of polycystic ovaries. Her menarche was at 12 years, with menstrual cycles being irregular for 1–2 days every 35–45 days. She also had history of (H/O) pre-menstrual pain, tension and spotting with dysmenorrhea. She had undergone ureteroscopy for renal calculi twice. She also had a family history of hemophilia, with two of her brothers being affected and her mother being a carrier. Her three maternal uncles also had hemophilia.

She was obese, with moderate hirsuitism. Clinically, her uterus was normal in size, firm and mobile, with all fornices being clear. At her baseline ultrasound (US), the uterine size was

70.6/33.2/42.2 mm, endometrial thickness was 6.1 mm and both ovaries were enlarged with multiple follicles with increased stroma. The antral follicle count was 11 small follicles in the right ovary and 14 in the left ovary. The right ovarian volume was 12.68 cc and the left ovarian volume was 13.34 cc.

Her baseline hormone levels on Day 2 of the cycle were as follows: Follicle stimulating hormone – 5.6 mIU/ml, luteinizing hormone – 5.3 mIU/ml, dehydroepiandrosterone sulfate – 780 ng/ml, androstenidione – 2.7 ng/ml, estradiol (E2) – 20.73 pg/ml and progesterone (P4) – 3.68ng/ml, thyroid stimulating hormone – 9.4 uIU/ml, free T4 – 1.25 and fasting insulin (FI) – 15.8 μU/ml.

FI levels were repeated after 3 months of metformin (500 mg twice a day), which was 3.1μU/ml.

Semen analysis performed was normal.

In view of family history of hemophilia, she was evaluated to rule out a carrier state. Her prothrombin time was 13.2, control 12; activated partial thromboplastin time 33 s, control 30 s; factor VIII c activity, 86% (60–150); factor IX c assay, 60% (60–150) and factor XIII screening-stable clot.

Her results for polymerase chain reaction (PCR) for carrier state revealed that she was not a carrier for hemophilia. The PCR analysis was as follows:

1. g.20519G > G, p.180 Arg > Arg.
2. g.20422G > A, p.Ala > Thr (Mnl1 polymorphism).

Her Hysterosalphingography showed a normal uterine cavity with good filling of both tubes with bilateral spill. The right tube was morphologically normal, with mild dilatation and clumping of the distal end of the left tube. Tubal pressures were low.

She was started on 50 μg of tablet levothyroxine and tablet metformin 500 mg BD. Metformin was discontinued after 2 months due to gastrointestinal side effects.

The first cycle was monitored without OI drugs. No ovulation was documented after monitoring till day 21 of the cycle. In the second cycle, clomiphene citrate (CC) 100 mg was given from Day 2 to Day 6 and ovulation was documented on day 22. In the next cycles, the dose of CC was increased to150 mg and ovulation was still not documented; hence, the dose was increased to 200 mg in the next two cycles. Ovulation was documented on Days 15 and 17. After four cycles of CC, no ovulation drug was given for two cycles but P4 was given in the second half of the cycle. In the next three cycles, letrazole 5 mg was given from Day 3 to Day 7 and ovulation documented on Day 14 or 15 of the cycle. As there was no pregnancy even with letrazole, CC was given in the seventh cycle. Injection hCG 5000 IU was given intramuscular when she had three mature follicles of more than 19 mm and one follicle of 16.5 mm on Day 12. The other follicles were between 10 and 14 mm. Ovulation was documented on Days 14 and 15. Micronised P4 vaginal pessaries were given for luteal support. Twenty days after ovulation, beta hCG performed on 19-11-07 was 410 mIU/ml, which was less than normal for that gestational age (usually between 900 and 1500 mIU/ml for a single GS). Beta hCG was repeated again on 22-11-07, which had increased to 1085 mIU/ml. The rise was again less than normal as beta hCG doubles every 24–36 h. Ultrasonography (USG) revealed a single IU sac with gestational sac diameter (GSD) 4.4 mm = 5 weeks 1 day.

On 26-11-07, a repeat TVS did not show any increase in GSD (5.8 mm = 5 weeks 2 days). No yolk sac or fetal pole was seen. Repeat TVS after a week on 3-12-07 documented a GS of 8.4 mm = 5 weeks 4 days [Figure 1], with no yolk sac or fetal pole seen. There was minimal tenderness in the right fornix but no ectopic gestational sac (GS) was seen in either fornix [Figure 2]. Beta hCG that day was 9515 mIU/ml, which was too high for an anembryonic pregnancy. Beta hCG was repeated on 6-12-07, which was 11342 mIU/ml and on TVS–IU GS [Figure 3a], it was 10.5 mm = 5 weeks 6 days, with no fetal pole or yolk sac seen. There was another second small GS seen measuring 4 mm [Figure 3b], which could be due to fertilization of the oocyte due to delayed ovulation from the follicle that was 16.5 mm on the day of hCG. There were also two small sacs measuring 4 and 6 mm, seen in the right adenexa [Figure 3c], the left adenexa appearing normal, with no free fluid in the pouch of douglas (POD). There was no abdominal tenderness or guarding. No tenderness in any of the fornices. On 8-12-07, the beta hCG was 12,947 mIU/ml, with an IU GS of 10.5 mm = 5 weeks 6 days, with no fetal pole or yolk sac [Figure 4a]. The two sacs in the right adenexa had increased in size to 8

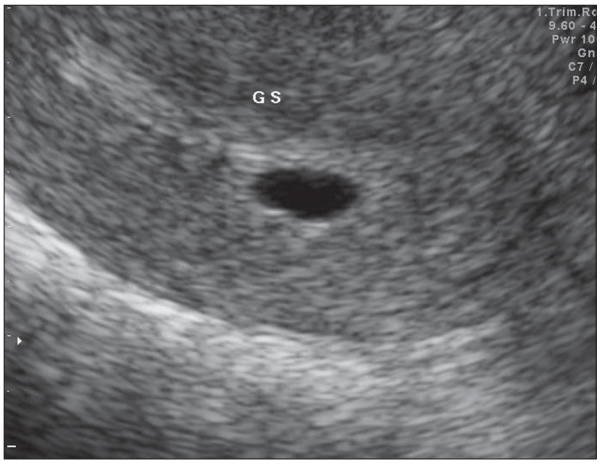

Figure 1: On 3-12-07, showing a single intrauterine gestational sac of 8.4 mm corresponding to 5 weeks 4 days, with no yolk sac or fetal pole seen

and 6 mm [Figure 4b]. There was no free fluid in the POD. The patient was clinically asymptomatic and stable and there was no fetal pole seen in any sac. A decision to start medical therapy was taken. Although a high beta hCG is a contraindication to MTX therapy, here we should consider the presence of four sacs and thus, effectively, the level per sac is 3250 mIU/ml. We used the multiple dose regime of MTX. Inj MTX 1 mg/kg was given IM with Inj. leucovorine 0.1/kg given IM on alternate days. A total of six injections of MTX were given. All her blood parameters were normal throughout the treatment.

The patient was followed-up on regular bases clinically and by TVS. She was also closely monitored for beta hCG, hemoglobin, complete blood count, liver function test and peripheral smears.

The beta hCG levels after MTX injection were as follows:

12-12-07: 11,967 mIU/ml; 14-12-07: 10,164 mIU/ml; 17-12-07: 6292 mIU/ml; 20-12-07: 3232 mIU/ml; 22-12-07: 1088 mIU/ml; 24-12-07: 791 mIU/ml; 28-12-07: 90 mIU/ml; 2-1-08: 9 mIU/ml.

Serial TVS performed showed regression of IU and right adenexal sacs. Once the beta hCG levels were less than 1000 mIU/ml, the patient had per vaginal bleeding. TVS showed the products in the cervical canal that were then removed under aseptic precautions with an ovum forceps under USG guidance.

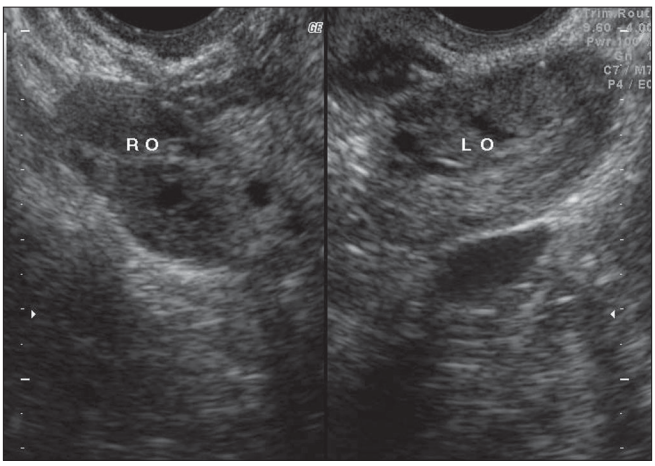

Figure 2: On 3-12-08, bilateral adnexa normal

Once the beta hCG was below 10 mIU/ml, she was advised not to conceive for 6 months with follow-up for beta hCG after 1 and 2 months, which was normal.

After 6 months, she was again given CC for OI. As she had responded to CC 200 mg, the same dose was given. She conceived in the second treatment cycle, with two dominant follicles on the right side. The size of the follicles was 21.2/20.9 and 19.5/19.3 mm on the day of hCG (Day 13 of the cycle). The left ovary on the day of hCG showed multiple small follicles of 10–12 mm in diameter and the endometrial thickness was 13.1 mm. She ovulated on Day 14 (23-08-08), when timed intercourse (TI) was advised. Luteal phase support was given with tablet duphaston 10 mg twice a day for 15 days. Her beta hCG was evaluated on 13-09-08, 21 days after ovulation, which was 3571 mIU/ml. TVS revealed an IU GS of 9 mm, corresponding to 5 weeks 5 days. The hCG levels corresponded to the period of gestation. Corpus luteum was seen on the right side, with no other adnexal pathology. Repeat beta hCG on 20-09-08 [Figure 5] after 1 week was 15,000 mIU/ml. A GS with yolk sac and fetal pole corresponding to 6 weeks and 5 days was seen. Fetal heart was also documented. The patient was regularly followed-up every 8 days till 12 weeks [Figure 6] in view of her previous ectopic sacs appearing late. She was also told to report immediately in case of bleeding per vaginum or in the presence of abdominal pain. At the time of publication of this case history, the gestational age was 12 weeks, with a normal Nuchal translucency.

DISCUSSION

The object of this case report is to discuss the importance of early diagnosis and medical treatment of heterotopic

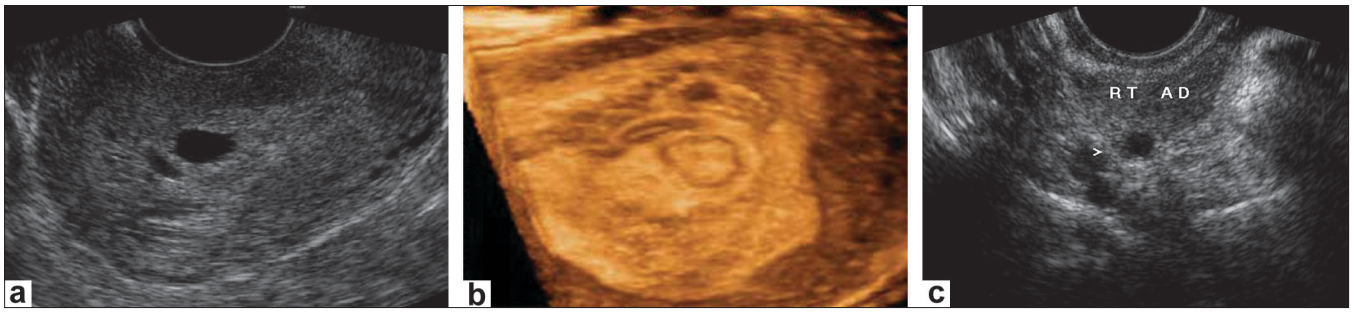

Figure 3: (a) On 6-12-07, showing two intrauterine gestational sacs of 10.5 and 4 mm, with no yolk sac or fetal pole seen; (b) On 6-12-07, showing two intrauterine gestational sacs with no yolk sac or fetal pole seen on a three-dimensional scan; (c) Showing two ectopic sacs in the right adnexal region of 4 and 6 mm

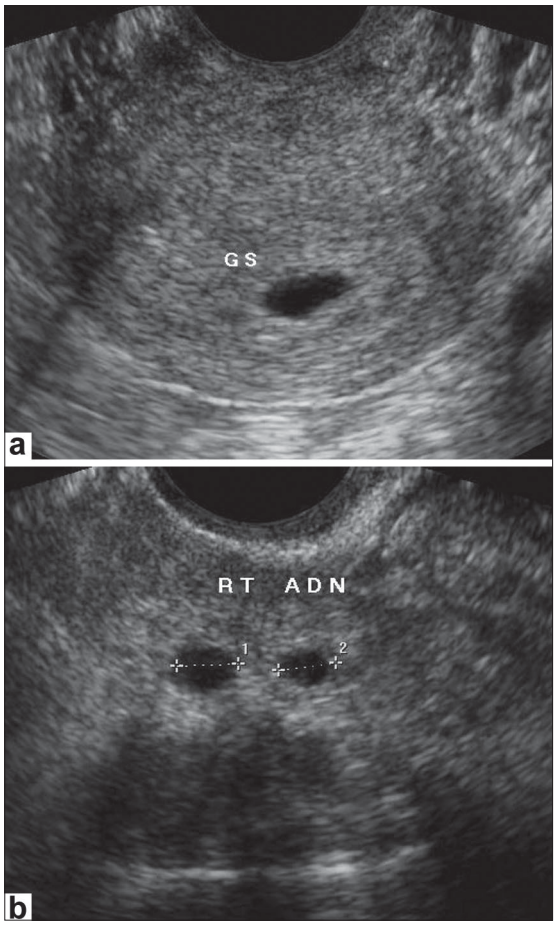

Figure 4: (a) On 8-12-07, showing an intrauterine gestational sac of 10.5 mm with no yolk sac or fetal pole seen; (b) On 8-12-07, two sacs in the right adnexa measuring 8 and 6 mm

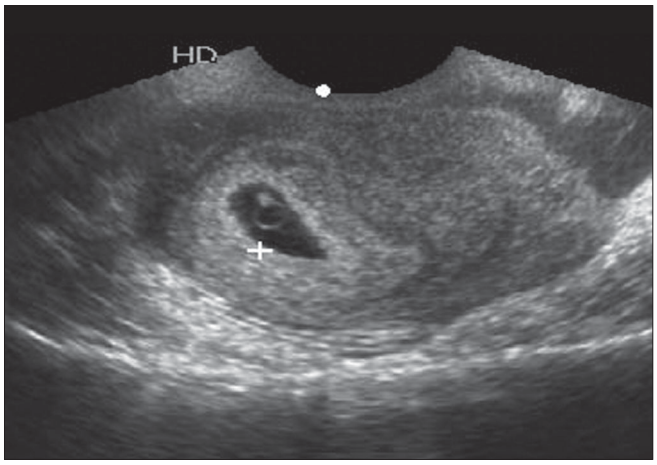

Figure 5: Single intrauterine gestational sac with yolk sac on 20-09-08

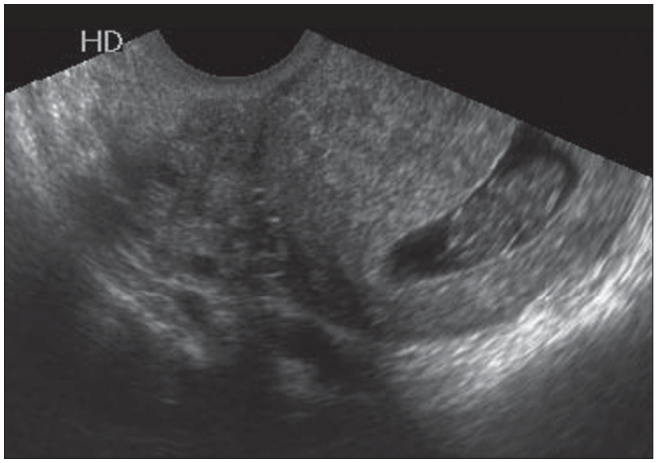

Figure 6: Single intrauterine fetus of 10 weeks of gestational age with normal right adnexa on 11-10-08

pregnancies. In 54% of the cases, the heterotopic pregnancy is asymptomatic,[4] as with our case.

The alteration of the local P4/E2 ratio by CC may disturb the oviductal peristasis, resulting in an ectopic implantation of the embryo.[5]

Early diagnosis of heterotopic pregnancy is difficult because of insufficient clinical symptoms. Classically, an ectopic pregnancy can present with abdominal pain due to peritoneal irritation and adnexal mass with or without bleeding per vaginum and hypovolemic shock if ruptured. Usually, vaginal bleeding with a rising beta hCG titer and no documentation of IU pregnancy is diagnostic of an ectopic pregnancy. This is rarely seen in hetrotopic pregnancies because of the intact endometrium of IU pregnancy.[1]

The recent advances in beta hCG determination and transvaginal US have aided in the early diagnosis of heterotropic pregnancy. US, especially transvaginal scanning, has proven to be an invaluable tool in the diagnosis of this condition. At times, even with TVS, the adnexal sac can be mistaken for a hemorrhagic corpus luteum or ovarian cyst, especially in hyperstimulated ovaries.[2] A heterotropic pregnancy goes unnoticed in the presence of IU pregnancy. Therefore, if the beta hCG levels are more for the period of gestation with an IU pregnancy, one must look for a coexistent tubal pregnancy.

The sensitivity of TVS in diagnosing heterotropic pregnancy is only 56%[1] at 5–6 weeks. In our case too, we could visualise the right tubal pregnancy only after 12 days of confirming an IU pregnancy.

Generally, it is not easy to differentiate anembryonic adnexal ectopic pregnancy from hemorrhagic corpus luteum cyst at TVS.[6] Morphologic ultrasonography findings help in differential diagnosis – seeing a 2–6 mm intense hyperechoic ring around the GS.[1] If the pregnancy is less than 6 weeks, presence of cardiac activity is diagnostic. A case reported that 70% of the heterotopic pregnancies are diagnosed at between 5 and 8 weeks of pregnancy, 20% of them at the

9th to 10th week and 10% after the 11th week.[1]

The management of heterotopic pregnancy remains controversial. The medical armamentarium, although used successfully for an ectopic gestation, has a limited role in the management of heterotropic pregnancy as one must try to preserve and protect the IU pregnancy. Moreover, MTX is also associated with complications of chemotherapy.[6]

Medical therapy with MTX in the presence of ectopic gestation is appealing over surgical options for a number of reasons. These include eliminating morbidity from surgery and general anesthesia and potentially less tubal damage, with less need for hospitalization, which is cost effective. Tanaka *et al*., published the first case report of successful medical treatment of tubal pregnancy with MTX, which has gained considerable popularity and is considered highly effective.[7]

To initiate MTX therapy, the patient must be hemodynamically stable, with no signs or symptoms of active bleeding or hemoperitoneum. Moreover, she must be reliable, compliant and able to return for regular follow-up. The other factors to be considered are size of the gestation, which should not exceed 3.5 cm at its greatest dimension on US, absence of cardiac activity, absence of free fluid in POD and beta hCG, which should not be more than 5000 mIU/ml. Also, the patient must not have any contraindications to medical therapy with MTX.[8]

The follow-up of women treated by MTX includes primarily serial hCG measurements whereas repeated TVS is performed only according to clinical indications.[7]

MTX is a folic acid antagonist. Folic acid is normally reduced to tetrahydrofolate by the enzyme dihydrofolate reductase (DHFR), a step in the synthesis of DNA and RNA precursors. MTX inhibits DHFR, causing depletion of cofactors required for DNA and RNA synthesis. Folinic acid (leucovorin) is an antagonist to MTX that can help reduce otherwise prohibitive side effects, particularly when higher doses of MTX are used.[8]

The multiple dose protocol alternates MTX treatment (1 mg/ kg) with leucovorin therapy until hCG falls by 15% from its peak concentration. In the single dose protocol, MTX is given at a dose of 50 mg/m^2. Beta hCG was repeated on Days 4 and 7. The dose of MTX was repeated only if beta hCG decreased to <15% between Days 4 and 7.[8]

Complete resolution of an ectopic pregnancy usually takes between 2 and 3 weeks, but can take as long as 6–8 weeks when pre-treatment hCG levels are in higher ranges. When declining hCG levels rise again, the diagnosis of a persistent ectopic pregnancy is made.[8]

There are no randomized trials directly comparing the two different MTX treatment protocols and medical versus surgical treatment. In a metaanalysis including data from 26 articles and 1327 cases, the overall success rates after multidose MTX was higher – 92.7% (95% confidence interval [CI], 89–96) as compared with a single-dose regime–88.1%(95% CI 86–90).[8]

One review concluded that MTX treatment was successful in 78–96% of the selected patients. Post-treatment, hysterosalpingography documented tubal patency in 78% of the cases, with 65% of the patients who attempted subsequent pregnancy conceiving and the incidence of recurrent ectopic pregnancy being 13%.[8] In another study, 87.2% of the patients achieved a subsequent IU pregnancy whereas 12.8% experienced a subsequent ectopic pregnancy.

Four Cochrane authors (Fernandez *et al*., 1998; Saraj *et al*., 1998; Sowter *et al*., 2001; El-Sherbiny *et al*., 2003) reported a "non-significant tendency to a higher treatment success with systemic MTX treatment as compared with r laparoscopic salpingotomy (odds ratio 1.8, 95% CI 0.73, 4.6)."[9]

Approximately 40% of the women diagnosed with an ectopic pregnancy are candidates for medical management and 90% of those can be treated successfully without surgery. Whereas the cost of surgery and outpatient medical management vary widely and medical treatments can be administered in an office setting, MTX is less expensive than surgery. Many cost-effective analyses have favored MTX therapy.

CONCLUSION

Serial TVS, beta hCG and regular follow-up diagnosed the coexistent right tubal ectopic pregnancy with an IU GS at an early stage, allowing us to treat this patient medically without any complications. We could treat her with MTX as both IU pregnancy and extrauterine pregnancies were not viable. If the IU pregnancy was viable, laparoscopic treatment would have been preferred, which would have given a good chance for continuation of the IU pregnancy. Although a beta hCG level of >5000 mIU/ml is considered as a contraindication for medical treatment, in our case, we need to consider that she had a total of four GSs – two IU and two extrauterine. Her beta hCG level was as high as 12,947 mIU/ml; thus, effectively, the level per sac is 3250 mIU/ml, when she was started on MTX. The beta hCG took 26 days to reach <10 mIU/ml with a multiple dose protocol.

Benefit of non-invasive treatment includes preservation of fertility with decreased morbidity and decreased cost. Presence of a normal functioning tube after medical management of ectopic pregnancy is evident from our case, who conceived with a viable IU pregnancy despite ovulation from the side of ectopic pregnancy.

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