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RESEARCH ARTICLE

AN ECTOPIC PREGNANCY WITH A VERY HIGH B-HCG AND THE SUCCESS OF METHOTREXATE AS A CHOICE OF TREATMENT

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ABSTRACT

A 31 years old woman has undergone treatment with methotrexate because of ectopic pregnancy (EP). She had a typical ultrasound appearance of ectopic pregnancy in her right adnexa. She followed the therapeutical protocol of methotrexate (MTX) in our clinic but the unusual point of view in our case was that her first value of β-hCG was very high, starting from 13827 IU and was increasing the following days. This was in controversy with the until today, guidelines choosing methotrexate for the treatment. The results and her clinical appearance is discussed in the following text.

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INTRODUCTION

Ectopic pregnancy is defined as implantation of a fertilized ovum outside the endometrial lining of the uterus, and it most commonly occurs in the fallopian tube with 90% to 95% occurring in the ampullary or isthmic portions. Clinically, the classic triad of signs and symptoms of ectopic pregnancy consists of vaginal bleeding, abdominal or pelvic pain, and a tender adnexal mass. Unfortunately, this triad is only seen in about 50% of women presenting with ectopic pregnancy. A delay in diagnosis of ectopic pregnancy is straightforwardly connected with increasing mortality of the woman.

Untreated ectopic pregnancy can lead to massive hemorrhage, infertility and death. With the introduction of high-resolution transvaginal ultrasound, in conjunction with serum assays for the β-subunit of human chorionic gonadotropin (β-hCG), rapid and precise diagnosis of this entity is now possible.

Although surgical intervention such as laparotomy or laparoscopy used to be the main way of treatment, earlier detection has allowed a shift towards more conservative, nonsurgical management for stable patients. For those ones with an ectopic pregnancy detected at an early gestational age, treatment with methotrexate has become a safe, available choice. In select patients, expectant management is now also considered as a choice (Beckmann *et al*, 2010; Schorge *et al*, 2008; Merz, 2005).

Methotrexate has become a regular treatment for ectopic pregnancy. It has been used for the management of malignancy, rheumatic disorders, and psoriasis and termination of intrauterine pregnancy. It is a folic acid antagonist that inhibits dihydro folate reductase, resulting

in a block in the synthesis of thymidine and inhibition of DNA synthesis. Folic acid is an essential vitamin needed to help quickly dividing cells in pregnancy, and methotrexate is a powerful drug, which works by temporarily interfering with the managing in the body of folate. It stops the pregnancy developing any further, and the body, leaving the fallopian tube complete, gradually reabsorbs the pregnancy (Hyoun *et al*, 2011).

Methotrexate is most effective in the earlier stages of pregnancy, usually when the pregnancy hormone ‘beta-human Chorionic Gonadotropin’ (β-hCG) level is below 5000 mIU/mL.

The risk of rupture is higher in pregnancies with levels greater than this. However, in some of them like cornual ectopic pregnancy, it is not unusual to try and treat ectopic pregnancy with the drug with higher levels of β-hCG. We need to mention, that in a case of a ectopic pregnancy, it is not really the stage of pregnancy (as in the number of gestational weeks), but the size of the ectopic, which can vary over the first few weeks, depending on the rate of growth, that is important. (Schorge *et al*, 2008; Kirchner, 2000).

We present an interesting case of an ectopic pregnancy with a very high value of β-hCG from the beginning, diagnosed by ultrasound at 7 weeks of amenorrhea. The β-hCG and the size of the sac have increased even more the following days, as the first doses of treatment have started. We follow up the β-hCG, the size of the sac, the thickness of endometrium, and the Doppler indices (PI and RI) of the crown. We also present a brief review of the literature about treatment of an ectopic pregnancy with a methotrexate.

Case report

A 31 years old, Para 1 woman, came in A & E because of 7 weeks amenorrhea and a positive urine test pregnancy. She didn't have any clinical symptoms and her first value of β -hCG was 13827 in this day. From her past obstetric medical history, she had one normal delivery, one miscarriage and two dilatation and curettages. She left home for personal reasons and she came back 7 days later when she was admitted for second time. Her β -hCG was 16414 IU that day and 17826 two days later (nine days from the first) (Figure 1).

As she was clinically stable, and she would not consent for surgical treatment, the medical team decided to start the medical protocol with methotrexate for her treatment under her consent, and after all the risks and possibilities of failure were thoroughly explained to her. She had the first dose of MTX, 50 mg IM, the next day, and two more of the same dosage every second day. Each day after the MTX, she had a dose of Buaderon injections. The woman stayed as an inpatient for one week, to confirm that the β -hCG was dropping and she was stable. After her discharge, she was seen weekly for a follow up and measurement of serum β -hCG with the rest of the ultrasound indices.

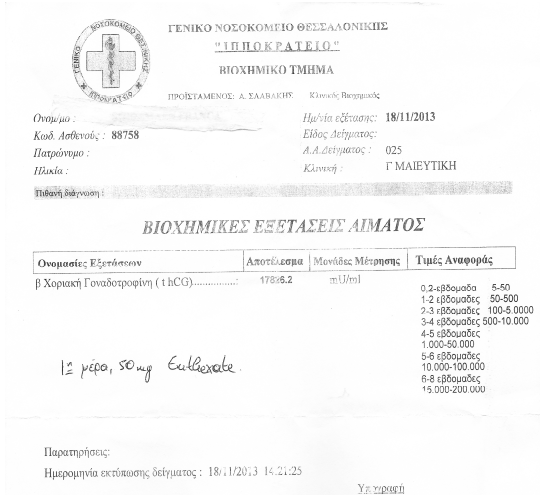


Figure 1 β -hCG value during patient's admission

The patient didn't have any clinical symptoms and her vital signs were normal. All her blood tests were within normal limits during all the treatment. The value of β -hCG started to fall down slowly after the third dose of methotrexate reaching the value of 12604 and became negative two months after the end of the treatment.

The pelvic ultrasound showed a lecithic sac, a crown but without the presence of the fetal heart activity. The trophobalst started with a size of 0,8 cm, reached 5,7cm almost 4 weeks after the third dose and disappeared two months later as well. The thickness of the endometrium started in 0,6cm, reached 1, 1 cm in 2 weeks after the third dose and started to decrease the next weeks.

During our research, we observed the Doppler indices PI and RI around the crown of the ectopic mass as an extra index of the management and success of the treatment with methotrexate (Figure 2). We discovered that they were high in the beginning and they fell down slowly after the third dose of the methotrexate and at the same time as the β -hCG has began

to decrease too. To exclude any malignancy, serum bloods analyzed for CA indices like AFP, CA 15.3, CA 125, CA 19, 9, CEA and they were found to be within normal levels (Safdarian *et al*, 2008; Yamashita *et al*, 2011; Nowak-Markwitz *et al*, 2009).

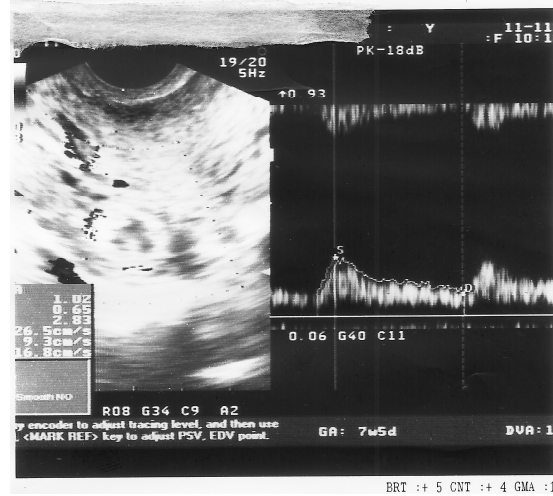


Figure 2 Doppler indices around the crown of the Ectopic pregnancy

DISCUSSION

We have presented a case where a woman of ectopic pregnancy, with a very high value of β -hCG, accepted and received the treatment of MTX in contrast with the criteria of the guidelines. Our case prompts several interesting considerations. As we have already mentioned, MTX is an antimetabolite chemotherapeutic folate antagonist, which disrupts purine nucleotide production. Although criteria may vary from institution to institution, worldwide a patient is considered a candidate for MTX treatment if they are clinically stable, a serum β -hCG levels are less than 5,000 mIU/ mL, the gestational sac is less than 3.5 cm and there is no positive fetal heart activity. It is also referred that the lower values of β -hCG areas associated with a higher likelihood of successful treatment.

We could speak for a possible failure of medical management when there is a rising or a plateau in β -HCG levels, and when we have some changes in ultrasound appearance, such as an increase in the size of the sac or detectable cardiac activity of the fetus. It has been reported, that the fallopian tube or the size of ectopic pregnancy may increase initially post treatment, and that vascularity may increase on color Doppler flow imaging.

Transvaginal Doppler sonography has an excessive diagnostic value in the follow up of the treatment of ectopic pregnancy, because of the studying and analyzing the values of the indices PI and RI around the crown (Vaswani, 2014; Shobairi *et al*, 2013; Ramanan *et al*, 2006; Atri, 2003). As a conclusion, in contrary to the until now results and criteria, there is a possibility for the medical treatment with MTX, to succeed in a woman with ectopic pregnancy, which starts with very high values of β -hCG from the beginning and during the first steps of the management.

The patient should be under a systematic control and review to keep her health safe, and all the information have to be

given to her. Except for the β -hCG and the usual blood results, it is very interesting to study some other indices for the follow up like trophoblastic size, the Doppler indices (PI and RI), the thickness of the endometrium and the presence of fetal heart activity (Atri, 2003; Kirchler *et al*, 1993; Stomati *et al*, 2012).

Disclosure

The authors hereby, report no conflict of interest and no financial interest with companies, concerning the information provided in the above paper.

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