



## PERSISTENT RISE OF BHCG AFTER SURGICAL TREATMENT OF ECTOPIC PREGNANCY

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### ABSTRACT

#### Keycontent

- Bhcg measurements after treatment of ectopic pregnancy is justified to rule out persistent trophoblastic activity.
- Management of persistent rise of Hcg after surgical treatment of ectopic remains a clinical challenge and leads to pressure on resources. The aim should be to exclude persistent ectopic and non pregnancy sources of Bhcg and to minimise morbidity and mortality associated with it.
- The mechanisms which underlie this persistent rise of Bhcg are poorly understood.
- Appropriate counselling, investigations and multidisciplinary approach should be offered.

#### Learning objectives

- To gain knowledge of the various causes of persistent rise of Hcg measurements after treatment of ectopic pregnancy, especially after surgical management.
- To learn how to tailor the treatment regimen to the individual woman's situation.

#### Ethical issues

- Mismanagement of ectopic pregnancy.
- Inappropriate use of methotrexate for treatment of presumed persistent ectopic pregnancy.
- Maintaining patient choice in relation to the management of ectopic and persistent ectopic pregnancy.

**KEYWORDS:** ectopic pregnancy/rise in Bhcg after treatment/ Bhcg.

### INTRODUCTION

An ectopic pregnancy is any pregnancy implanted outside of the endometrial cavity.

In the UK, the incidence is approximately 11/1000 pregnancies, with an estimated 11000 ectopic pregnancies diagnosed each year. The incidence of ectopic pregnancy in women attending early pregnancy units is 2-3%. Unfortunately, women still die from ectopic pregnancy, with 6 maternal deaths reported between 2006 and 2008. However, the case fatality rate has decreased over recent years, suggesting that early diagnosis and treatment may have made an impact.

The various ectopic pregnancies include: tubal, cervical, caesarean scar, interstitial, cornual, ovarian, endometrial and heterotopic.<sup>[1]</sup>

### Pathophysiology

Human chorionic gonadotropin [hcg] is a heterodimeric glycoprotein composed of an alpha and a beta chain. Hcg is a hormone produced by proliferating trophoblast. The urine pregnancy kits available these days are very sensitive and pick up levels as low as 25 IU and levels less than 5 IU are consistent with cessation of trophoblastic activity.<sup>[2]</sup> However, the levels of this hormone cannot reliably diagnose the site of pregnancy, but only aid the subsequent management of pregnancy. Falling levels of hormone reflect falling pregnancy cells wherever in the body and used in determining the success of treatment.

Risk factors for ectopic pregnancy include tubal damage following surgery or infection, smoking and in vitro fertilisation. However, the majority of women with an ectopic pregnancy have no identifiable risk factor.

Ectopic pregnancy can present with a variety of symptoms. Common symptoms include abdominal/pelvic pain, amenorrhea and vaginal bleeding with or without clots. Other less common symptoms are breast tenderness, gastrointestinal symptoms, dizziness, fainting and syncope, shoulder tip pain, urinary symptoms, passage of tissue and rectal pressure or pain on defecation.<sup>[3]</sup>

Transvaginal ultrasound is used as first line investigation to diagnose/exclude ectopic pregnancy. In expert hands, TVS has a sensitivity of 87%, specificity of 94%, and positive predictive value of 92.5% in the diagnosis of an ectopic pregnancy.<sup>[4]</sup> Repeat TVS or MRI abdomen and pelvis can be used if the results are inconclusive on initial ultrasound and patient is clinically stable. Laparoscopy is justified when women is hemodynamically unstable and there is strong clinical suspicion of ectopic pregnancy. In some instances, laparoscopy can be negative or equivocal, even in the presence of convincing ultrasound images, particularly in early ectopic pregnancies, which poses therapeutic dilemma to the surgeons. It has been suggested that ERPC should be performed in such cases where laparoscopy is equivocal.

Management includes conservative, medical and surgical options, which encompasses removal of ectopic pregnancy. Conservative and medical management with methotrexate is usually given after a thorough evaluation has been done and certain criteria are met. The National Institute for Health and Care Excellence [NICE] recommends that women managed expectantly or by methotrexate and/or conservative surgery should be followed by serial Hcg measurements afterwards to demonstrate fall in hcg levels. Post operative Hcg measurements sometimes is justifiable when the laparoscopic findings are not convincing or there is some suspicion about the exact location of the ectopic gestation as happened in our case below.

#### OUR CASE

A 31 year old lady, G2P1, with no risk factors for ectopic pregnancy came to early pregnancy unit with positive pregnancy test and left iliac fossa pain. TVS was suggestive of left interstitial ectopic measuring 1.5cm with empty uterine cavity. Bhcg was 11608. Decision for laparoscopic left cornual excision of ectopic pregnancy was made. The following day after surgery, Bhcg came back as 12852. bhcg measurements 48 hrs later was found to be still rising at 15781. A repeat scan revealed only post surgical scarring, but no pregnancy. At this point, ERPC was done in suspicion of persistent intrauterine trophoblastic tissue, which revealed decidual cast on histology, with no evidence of products of conception. Histology of the tube revealed no ectopic in the cornual part of the tube. MRI abdomen and pelvis was organised, which came back as negative for any ectopic pregnancy and possible tumour which can account for the rising Hcg. MDT meeting agreed for observation alone with

hcg measurements and to consider methotrexate in case of continued rise. However, bhcg levels started declining and patient was discharged when levels became negative in 8 weeks time.

#### DISCUSSION

##### Persistent rise of Bhcg after surgical treatment of ectopic pregnancy

The mechanisms underlying persistent rise of bhcg after surgical management of ectopic are poorly understood and different theories have been put forward for its etiology. The risks of persistent trophoblastic tissue after conservative surgery is well known. Secondary pregnancy by an implant in a laparoscopic trocar site has been recently reported.<sup>[5]</sup> Other causes include the presence of persistent omental trophoblastic implantation following salpingectomy. Omental and peritoneal secondary trophoblastic implantation are probably the result of disruption of the ectopic pregnancy or morcellation of the fallopian tube at salpingectomy. These implants present with persistent Bhcg titres post operatively and needs to be considered especially in cases of persistent disease following salpingectomy.<sup>[6][7][8]</sup>

The occurrence of simultaneous ectopic pregnancies in two extrauterine locations although rare, particularly in spontaneous pregnancies; and heterotopic simultaneous ectopic and intrauterine pregnancy after spontaneous conception have been reported.<sup>[9][10][11]</sup>

Cases have been reported where woman presented with persistently elevated Bhcg after a salpingectomy for a left tubal ectopic pregnancy. Follow up led to the discovery of a simultaneous right tubal ectopic pregnancy. Another case, where splenectomy was carried out, as bleeding was noted from the spleen on laparotomy after positive hcg and hemoperitoneum on transvaginal ultrasound presented with rising hcg levels postoperatively. Subsequently, a failed intrauterine pregnancy was diagnosed.<sup>[12]</sup>

Cases where laparoscopy showed normal salpinges, but hysteroscopy identified the gestational sac in the uterine angle have been reported in literature, thus highlighting the use of different management tools, which otherwise would have caused a confusion in rise of Bhcg level have been put forward.<sup>[13]</sup>

This reinforces that persistent trophoblastic disease can occur not only after salpingotomy but also after salpingectomy and complete removal of ectopic, hence the need for postoperative serum beta human chorionic gonadotropin in all cases, even if chorionic villi are present in the initial surgical specimen.

##### Non pregnancy sources of BHCG

In the absence of any pregnancy, intrauterine or extrauterine, other possible causes for hcg should be considered.

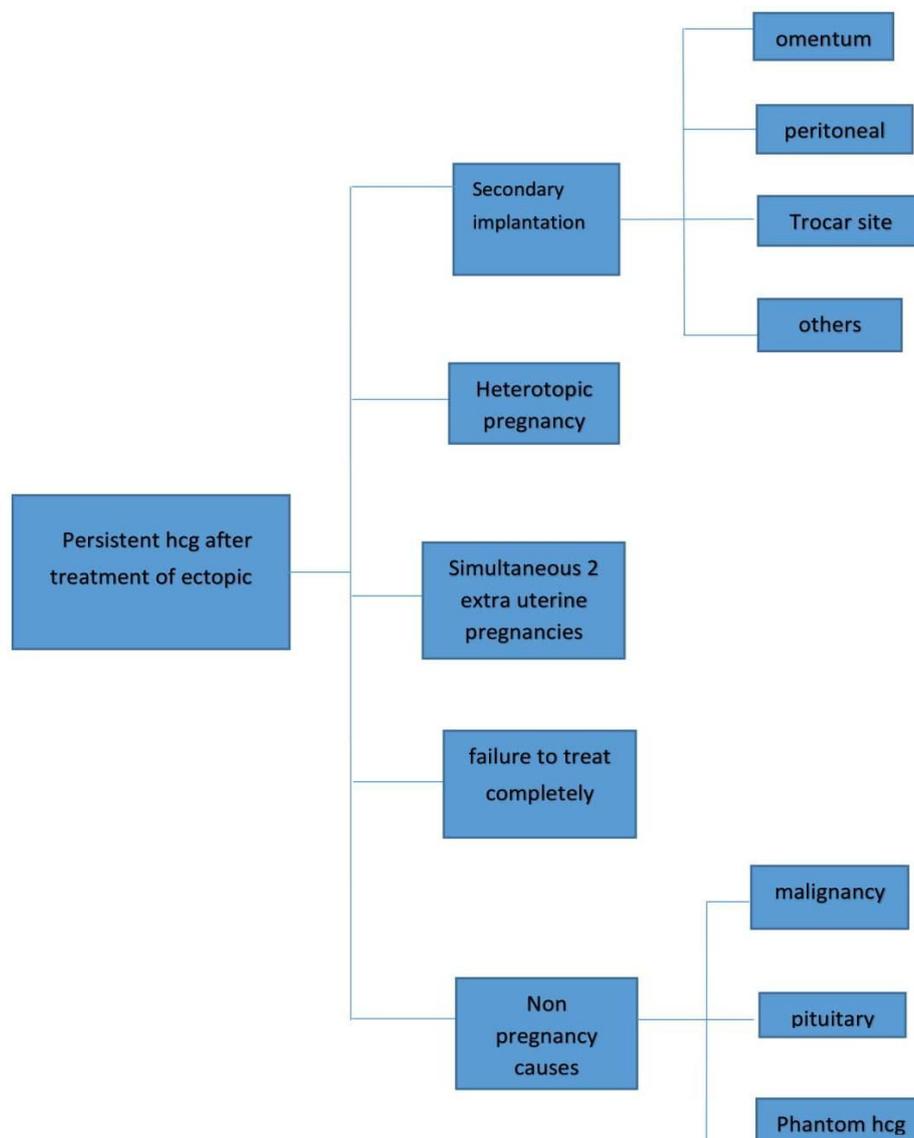
- **Malignancy:** Cancer cells sometimes make hcg. While many different types of cancer have been shown to make the hormone, it is most commonly associated with gestational trophoblastic diseases and certain types of germ cell tumours.

Although gynaecological malignancies are a common reason for elevated serum hcg, it has also been described in association with paraneoplastic syndrome in other non gynaecological malignancies including cancer of the bladder, kidney, GI-tract, breast and lung.

- **Pituitary hcg:** Although placenta normally produces hcg during pregnancy, it can be made by the pituitary gland. Interestingly, three hormones normally produced by the pituitary gland [thyroid stimulating hormone, FSH and LH] are structurally similar to hcg. Pituitary hcg is more commonly detected in

women greater than 55 years of age, but can be detected in young women as well. Non pregnant women with pituitary hcg usually have low concentration of hcg present in blood and urine. Importantly, concentrations of hcg produced by pituitary gland don't show the rapid increases that occur during pregnancy.

- **Interfering antibodies:** Some women have antibodies in their blood that can interfere with hcg tests and cause a positive or elevated result in the absence of hcg. Only hcg tests performed on blood can be affected by this problem because the interfering antibody molecules aren't normally present in urine.<sup>[14]</sup>



**Figure 1: Depicts the various causes of persistent bhcg after ectopic treatment.**

In the case report mentioned above, the most likely explanation was, the excised ectopic pregnancy might have been missed in retrieval, but fortunately didn't

implanted in any other site, explaining the initial rise of hcg and then persistent decrease with out any further intervention.

### Investigation

The most important reason to investigate B<sub>hcg</sub> rise after treatment of ectopic is to exclude persistent ectopic and there by avoid life threatening hemorrhage. It is best to ascertain what treatment the woman had, observe the trend in B<sub>hcg</sub> levels and review the images of the ultrasound or laparoscopy before further assessment. In the absence of any pregnancy, non pregnancy causes for B<sub>hcg</sub> rise should be considered.

### Transvaginal ultrasound

Several studies have demonstrated that using transvaginal ultrasound as an initial tool in the investigation and evaluation of women with persistent B<sub>hcg</sub> rise is safe and cost effective without compromising efficacy. The technique is rapid, highly effective, relatively painless and less invasive than laparoscopy.

Transvaginal ultrasound allows the simultaneous evaluation of the pelvis and lower abdominal region, and this can lead to detection of other pathologies that may have gone undetected such as ovarian tumour.

Following a negative scan showing no persistent ectopic, further imaging needs to be considered.

### Further imaging

Further imaging such as computed tomography or particularly magnetic resonance imaging may be needed in the event of negative ultrasound to rule out any abdominal/ omental pregnancy and ovarian tumours. Since secondary implantation and simultaneous two extrauterine pregnancies is a possibility in persistent disease, thorough examination of the pelvis, the peritoneal and serosal surfaces is mandatory.<sup>[15]</sup> X-ray of the skull may be needed in rare cases of suspected pituitary hcg.

### Laparoscopy

Laparoscopy is the gold standard diagnostic and therapeutic option. However, laparoscopy is invasive, expensive and can lead to post operative morbidity such as infection or post operative pain. In addition, intraoperative complications can occur including risks of injury to abdomino-pelvic structures. Hysteroscopy is useful to diagnose angular pregnancy where in some cases laparoscopy/ultrasound miss the diagnosis.

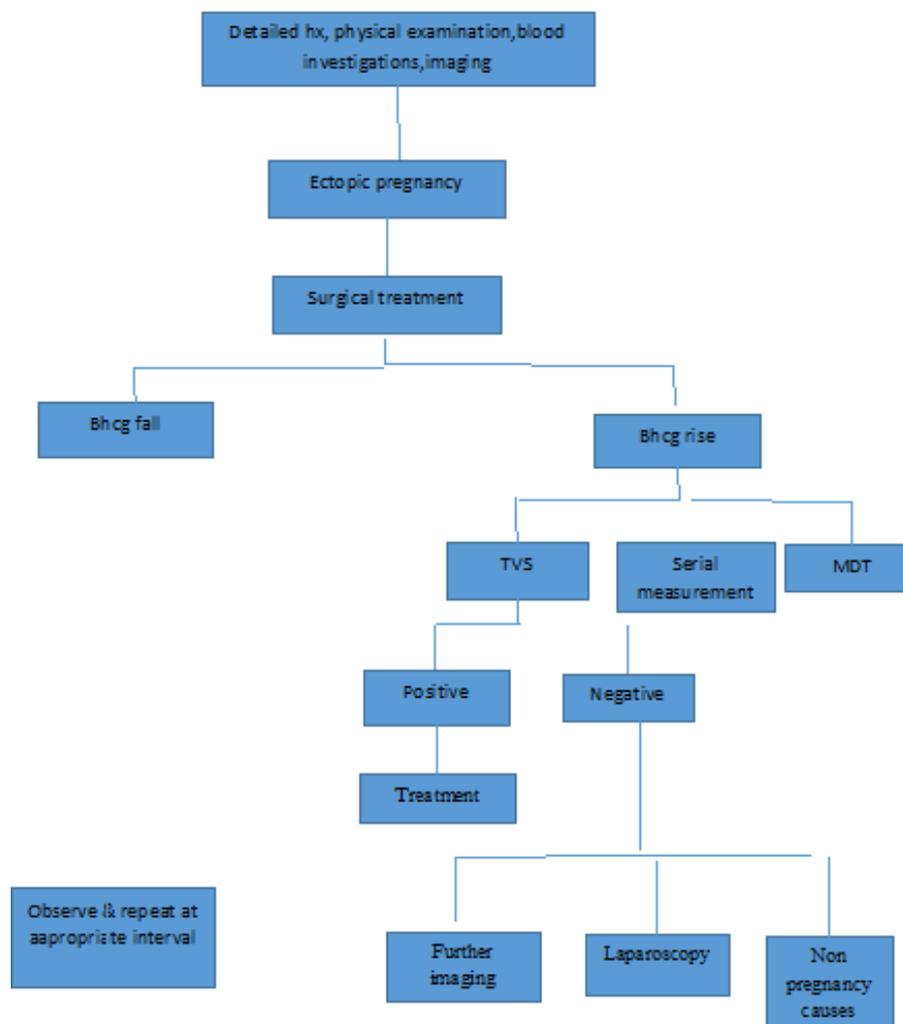


Figure 2: Depicts The Assessment Plan For Persistent Hcg Rise.

### Management

Different treatment modalities can be offered depending on the case. For some women with persistent hcg despite negative investigations, after multidisciplinary team discussion, careful observation and follow up by serial hcg measurements until the values become negative can be adopted. A single methotrexate injection is a safe and successful treatment for persistent ectopic pregnancy. Delayed hemorrhage may be a rare complication, and close surveillance is necessary.<sup>[16]</sup> Surgery can be offered to women who have a poor response to methotrexate or otherwise not suitable for medical management.

### CONCLUSION

Persistent bhcg after ectopic treatment is poorly understood. It may be due to persistent ectopic/ non pregnancy related causes. But the situation leads to significant anxiety in women and poses greater degree of challenge to clinicians. In a small percentage of woman, with negative investigations, this concern may be justified with observation alone. However, for a great number of women, further treatment with methotrexate or surgery is needed. While minimising the adverse effects on health and fertility, finding the appropriate type of treatment for each woman requires multidisciplinary input and compliance from the patient as well. Appropriate counselling regarding the condition should be offered from the outset.

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