The Role of creatinine phosphokinase (CPK) & B-Human Chorionic Gonadotropin (BHCG) in the Early Diagnosis of Ectopic Pregnancy

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Abstract: Introduction: Despite advanced detection methods, ectopic pregnancy may be missed in 40% to 50% of patients on an initial visit.' Most women with Ectopic pregnancy have no risk factors and the classic triad of a history of amenorrhea, abdominal pain, and irregular vaginal bleeding is absent in more than half of cases. Early diagnosis not only decreases maternal mortality and morbidity; it also helps preserve future reproductive capacity--only one third of women with ectopic pregnancy have subsequent live births. **Objective**: to discover the role of creatinine phosphokinase in early diagnosis of tubal ectopic pregnancy & integrity of tube [intact or rupture]. **Study Design**: Cross sectional study. **Aim of the work**: Decrease maternal mortality and morbidity. **Place and Duration**: Department of Obstetrics & Gynecology, Faculty of Medicine AL-Azhar University from February to June 2011. **Patients and Methods**: Thirty women with ectopic pregnancy were enrolled in this study, for all patients' complete history taking and physical examination was done. A venous blood sample was collected for serum creatinine phosphokinase (CPK) & serum beta human chorionic gonadotropin followed by routine investigations and ultrasongraphy of abdominal and transvaginal ultrasound. **Results**: 10 patients had ruptured ectopic pregnancy (42.6%), 14 patients had intact Ectopic pregnancy (58.2%), mean of BHCG ratio was 1.428.The mean of CPK was 111.182 IU/l in the intact tube and 440.625 IU/L in ruptured tube . The mean of BHCG was 1146.20IU/L in intact tube and 1667.66 IU/L in ruptured tube. **Conclusion**: Maternal serum level of CPK was significantly higher in women with tubal pregnancy particularly if it is ruptured ectopic pregnancy.CPK is consider an important adjuvant in the early diagnosis of ectopic pregnancy. So CPK not useful for the primary diagnosis of ectopic pregnancy. only serum ß-hCG assays were used to exclude ectopic pregnancy

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1. Introduction

Ectopic pregnancy is defined as the implantation of the fertilized egg that occurs outside the uterine cavity. It is practically synonymous with tubal pregnancy, as 98% occur in the Fallopian tube. It is a leading cause of pregnancy-related death in the first trimester **(Shaw*, et al (2010)).***

The introduction of highly sensitive methods, such as transvaginal sonography and measurement of serum b-human chorionic gonadotropin, has dramatically improved ectopic pregnancy diagnosis in recent years. Despite advanced detection methods, ectopic pregnancy may be missed in 40% to 50% of patients on an initial visit ***(Condous, et al 2005 & Kirkand Bourne2009).***

Most women with ectopic pregnancy have risk factors(Previous tubal surgery, Tubal ligation, Previous ectopic pregnancy, In utero DES exposure, Current IUD use and Tubal pathology/abnormality) and the classic triad of a history of amenorrhea, abdominal pain, and irregular vaginal bleeding is absent in more than half of cases ***(Murray et al2005 & Shaw et al 2010).***

An empty uterus with low serum levels of beta-HCG may be an evidence of tubal pregnancy but may also be consistent with an intra-uterine pregnancy, which is too small to be seen on ultrasound. In attempts to reduce the risk coincident with the time required for serial testing, at a gestational age when ultrasound is indeterminate, a test that distinguishes Ectopic from intra-uterine gestation obviously would be of value ***(Sameena Wazir et al 2009).***

Early diagnosis is the key to successful and conservative management of women with ectopic pregnancy; however, approximately 50 percent of such women are initially misdiagnosed, resulting in significant morbidity and mortality. Early diagnosis not only decreases maternal mortality and morbidity; it also helps preserve future reproductive capacity—only one third of women with Ectopic pregnancy have subsequent live births ***Shepherd et al 1990).***

Management strategies for patients with Ectopic pregnancy have evolved rapidly, with ambulatory medical therapy becoming an option for

more patients. In order to improve diagnosis, several serum markers are being investigated including progesterone, CA 125, pregnancy-associated plasma protein-A, vascular endothelial growth factor, and maternal creatinine kinase. Measurement of serum maternal creatinine kinase, alone or together with other markers, could be a promising method for earlier and more accurate differential diagnosis ***(Birkhahn et al 2001& Develioglu et al2002)***.

The lack of a sub mucosal layer in the fallopian tube allows the zygote to penetrate the epithelium and lay next to the muscular layer in tubal pregnancies. The trophoblast usually invades the muscle layer and maternal blood vessels are eroded, allowing muscle cell products such as CPK to enter the circulation; therefore increased serum CPK levels are normal during ectopic pregnancy. In consequent to early smooth muscle destruction in tubal pregnancy the maternal serum creatinine phosphokinase (CPK) levels should be higher in comparison to those having normal intra-uterine pregnancy ***(Chandra etal1995, Saha etal 1999 & Katsikis etal2006).***

2. Patients and Methods:

A one year prospective study was conducted at the obstetrics and Gynecology department at Al-Zahra university hospital.

Thirty women with Ectopic pregnancy were conducted in this study; all the patients were subjected to the following:

Clinical assessment with careful history taking including:

Age – Parity – Gestational age and complain of the patient.

Vital signs of the patients including pulse, blood pressure and level of consciousness.

Meticulous physical examination was done. On admission a venous blood sample was collected for serum creatinine phosphokinase (CPK) & serum beta human chorionic gonadotropin followed by routine investigations and ultrasongraphy of abdominal and transvaginal ultrasound.

Women with history of heart disease, nervous system disease, thyroid disease, renal disease, myopathy, recent trauma and/or recent history of multiple intramuscular injections were excluded from the study.

Serial serum B-hCG was taken from the patients at least two B- hCG measurements, at least 48 hours apart for follow up and decision for management except in the cases of heamodynamic unstable.

Statistical Analysis:

The data was performed with SPSS version 12 using the 0.05 level of significance. Beside descriptive statistics, t-test, logistic regression were also used.

3. Results:

Thirty women with suspected ectopic pregnancy were enrolled in this study. Twenty four(24) cases were submitted for laparotomy,(14) cases with intact tubal ectopic pregnancy&(10) cases had ruptured tube with active bleeding as judeged at surgery .While 6 patients submitted for medical treatment by methotrexate who are haemodynamically stable and have minimal symptoms and a low volume of free intraperitoneal fluid on ultrasound scan.

Table (1) summarizes the clinical characteristic of studied group the gestational age of the study group was ranged between 4to 8 weeks.

Table (2) show frequencies of dominant complain of studied group, vaginal bleeding 93.3% and abdominal pain 86.7%.

Table (3) summarizes finding of ultrasound in studied group, 86.7% of patients had free fluid in the Douglas pouch &their uteri were empty.

Table(4) shows distribution of integrity of tube, intraperitoneal haemorrahge& adnexal mass within women who examined by laparotomy.Fourteen patients with intact tube,ten cases with ruptured tube & active bleeding, twenty cases with intraperitoneal haemorrahge & six cases with adnexal mass.

Table(5)demonestrateB HCG ratio was significant&no doubling increase in the second reading of serum BHCG which also significant.

Table(6)shows that the mean of CPK was significantly higher in patients with ruptured ectopic tube than patient with intact ectopic tube, [(440.625±769.502) & (111.182±152.344)] respectively ($P<0.003$).

Table (7) shows that the mean of BHCG was significantly higher in patients with ruptured ectopic tube than patient with intact ectopic tube,[(1667.66 ±1096.07iu/ml versus1146.20 ±1025.13iu/ml)$P<0.001$ respectively].

4. Discussion

Ectopic pregnancy, in which the gestational sac is outside the uterus, is the most common life-threatening emergency in early pregnancy. Although spontaneous resolution of ectopic pregnancy can occur, patients are at risk of tubal rupture and catastrophic hemorrhage (Murray etal2005 & Lobo, 2007).

Ectopic pregnancy remains an important cause of maternal death, Despite the relatively high frequency of this serious condition, early detection can be challenging. In up to half of all women with Ectopic pregnancy presenting to an emergency department, the condition is not identified at the initial medical assessment (Houry and Salhi, 2009).

Table 1: Demographic Characteristics Of Studied Group

Variables	Mean ±SD	Range
age (mm)	28 ± 4.487	23 - 39
Parity	3.20 ± 1.827	
Gestational age(week)	5.714±1.181	4 – 8
Creatinine phosphokinase CPK (iu/l)	260.733 ± 587.0305	34 - 2364
1st Beta human chorionic gonadotrophin(iu/ml)	1650.571 ± 1947.242	160 - 8000
2nd Beta human chorionic gonadotrophin	803.666 ± 998.780	259-2934
3rd Beta human chorionic gonadotrophin	2346 ± 2398.313	269 - 4423
Beta human chorionic gonadotrophin ratio	1.428 ± 0.842	0.41-2.93
Gestational sac (mm)	1.250 ± 0.462	
Adnexal mass of right ovary(mm)	55.222 ± 17.107	45 - 80
Adnexal mass of left ovary(mm)	62.500 ± 20.207	37 - 92
Endometrim thickness(mm)	8.807 ± 5.404	4 - 21

Table 2: Frequencies of women complain of bleeding and pain and receive medical treatment

Items	Women with ectopic pregnancy No	%
Bleeding: Present	28	93.3
Absent	2	6.7
Pain: Present	26	86.7
Absent	4	13.3
Treatment with methotrexate: Take treatment	6	20
Not take treatment	24	80
Total	30	100

Table 3: frequency of women with ectopic pregnancy has free fluid in the Douglas pouch and in abdominal cavity and uterine contents through the use of ultrasound

Items By using ultrasound	Women with ectopic pregnancy No	%
Free fluid: Present in Douglas pouch	26	86.7
Not Present in Douglas pouch	4	13.3
Free fluid: Present in abdominal cavity	4	13.3
not Present in abdominal cavity	26	86.7
Uterine content: Empty	86.7	
Twins(with heterotropic ectopic)	26	
	6.7	2
Loop in situe	6.7	2
Total	100	
	30	

Table 4: Distribution of Women with Ectopic Pregnancy Who Examined By Laparotomy.

Items By using laparotomy	Women with ectopic pregnancy No =24	100%
Ectopic tube: Ruptured tube :right tube	6	25
Left tube	4	16.6
Intact tube : right tube	10	41.6
Left tube	4	16.6
Intra-peritoneal hemorrhage: Present	20	83.3
absent	4	16.6
Adnexal mass: Right rupture	2	8.3
hemorrhagic corpus luteum	2	8.3
left ovarian cyst	2	8.3
right ovarian cyst		
Total	24	100

Table 5: Monitoring of beta human chorionic gonadotrophin for evaluation of ectopic pregnancy in pregnant women

Items	Mean ±SD	t-test	Degree of freedom Df	Significance (2-tailed)
Beta human chorionic gonadotrophin ratio	1.428 ± 0.842	-117.422	11	0.000
1st Beta human chorionic gonadotrophin	1650.571±1947.242	4.404	27	0.000
2nd Beta human chorionic gonadotrophin	803.666 ± 998.780	2.683	11	0.021
3rd Beta human chorionic gonadotrophin	2346 ± 2398.313	1.931	3	0.149

***Table (6) comparison of serum Creatinine phosphokinase (CPK) levels between* patients with intact ectopic tube (unruptured) and patients with (ruptured) ectopic tube.**

CPK level (IU/L)	Minimum	Maximum	Mean	SD	Median	Result P- value
Intact tube	34	577	111.182	152.344	60	P=0.003
Rupture tube	50	2364	440.625	769.502	102	

Table (7) comparison of serum Beta human chorionic gonadotropin (HCGB) levels between Patients with intact ectopic tube (unruptured) & patients with (ruptured) ectopic tube.

BHCG level (miu/ml)	Minimum	Maximum	Mean	SD	Median	Result P- value
Intact tube	160	2457	1146.20	1025.13	541	P=0.001
Rupture tube	160	8000	1667.66	1096.07	822	

Although the incidence of ectopic pregnancy in the general population is about 2%, the prevalence among pregnant patients presenting to an emergency department with first-trimester bleeding or pain, or both, is 6% to 16%.Thus, greater suspicion and a lower threshold for investigation are justified (Murray 2005)

Transvaginal ultrasounds and serial β-hCG determinations are currently the most common methods used for diagnosis. Despite the use of high-resolution transvaginal sonography and sensitive assays for β-hCG, it is believed that 40 to 50% of cases are initially misdiagnosed. Transvaginal sonography has been proposed as helpful only when intrauterine gestation or an adnexal mass is observed, and serum β-hCG measurements can distinguish a normal intrauterine pregnancy (IUP) from a non-viable pregnancy, but cannot distinguish arrested IUP from EP (Kirik et al, 2007& 2008).

Ultrasound is inconclusive in up to 18% of women for whom measurement of serial β-hCG concentrations is necessary to guide management, so we used another chemical marker (CPK) beside the vaginal ultrasound and serum B-hCG to see if it will be helpful in early diagnosis of Ectopic pregnancy.

In this study the gestational was ranged between 4-8 weeks, the parity was ranged between 1-3 and the age was ranged between 23-39 years.

The Beta human chorionic gonadotropin ratio was ranged between 0.41 -2.93 and was significant in the diagnosis of ectopic pregnancy. These results are goes with the study of (Wang, 2008).

who conducted a retrospective clinical study to determine the value of B-hCG ratio in the early diagnostic and prognostic assessment of ectopic pregnancy, he observed that the B-hCG ratio was higher in ectopic pregnant subjects (median 4.07) than in patients with intrauterine pregnancy (median 0.6).

In this study women had serial serum B-hCG at least two B- hCG measurements, at least 24 hours apart, no doubling increase in the second reading of serum BHCG.

all ectopic pregnancies have normally rising B-hCG levels of at least 66% in 2 days. In early healthy intrauterine pregnancies, serum levels of B-hCG double approximately every 2 days (1.4-2.1 d). Kadar et al1994, established that the lower limit of the reference range to which serum B- hCG should increase during a 2-day period is 66%.An increase in B-hCG of less than 66% is associated with an abnormal intrauterine pregnancy or an extra uterine pregnancy. 15% of healthy intrauterine pregnancies do not increase by 66% and that 13% of all ectopic pregnancies have normally rising B-hCG levels of at least 66% in 2 days (Seeber et al 2006, 2006, Horne et al, 2001

Even though ectopic pregnancies have been established to have lower mean serum B-hCG levels than healthy pregnancies, no single serum B-hCG level is diagnostic of an ectopic pregnancy. So serial serum B-hCG levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of ectopic pregnancy once therapy has been initiated (Seeber et al, 2006).

In our study serum BHCG was higher significantly in ruptured tubal ectopic pregnancy than intact tubal pregnancy.

Ackerman and his colleague in 1982 found a positive correlation between serum BHCG level and tubal rupture however in contrast to Roussos etal, 2000 reported that serum BHCG level does not predict tubal rupture.

Galstyank and Kurzel , 2006 reported that serum BHCG by itself cannot predict whether a tubal ectopic pregnancy is likely to be rupture; there is no safe lower limit in hCG titer below which ruptured ectopic is not seen.

While Pinar and his colleague , 2010 agree with our fndings, who reported that mean level of BHCG were significantly higher in patients with ruptured ectopic compared with patient with unruptured ectopic (8735.3± 11317.8 mIU/ml versus 4506±5673.7 mIU/ml) P<0.0001, respectively.So higher BhCG levels seem to be significant risk factors for rupture of an ectopic pregnancy.

On the other hand La Vonne and leslie,2011 concludes that BHCG level of 1500 m IU/ml or greater was significant in determining those who ruptured 57%, it did not discriminate among those who will rupture .Without discriminating test for rupture ,there is always a risk in discharging patients with a possible ectopic pregnancy.

In the present study mean CPK was higher in ruptured tubal ectopic pregnancy than in intact tubal pregnancy.

The first study of CPK as marker of fallopian tube damage produced some encourrging results (lavie etal, 1993).

Serum CK concentrations were significantly higher in those with tubal pregnancy (n=17) as opposed to those with missed abortion (n=17) or normal pregnancy (n=17). There was considerable overlape in the value& with cut off 45 IU/L had a sensitivity of 57% and specificity of 67% Duncan et al, 1995.

Some studies have shown no significant increase in tubal ectopic pregnancy (Darai etal ,1996 & Plewa etal 1998 Birkhahn et al, 2001).

The difference in these studies maybe because serum CPK concentration may actlually is a marker of potential rupture rather tubal ectopic pregnancy (Develioglue etal, 2002).

Other study performed by sameena Waizur & his colleague in 2009; conclude that sensitivity and specificity of serum CPK level at 70 IU/L was 95% and98% respectively. The positive predictive value was 99%and the negative predictive value was 90.7% for the diagnosis of tubal pregnancy. In the present study the mean level of CPK with intact ectopic tube was 111.182 IU/L versus 440.625IU/L in ruptured ectopic tube.

In the present study CPK is higher in isthmical tubal ectopic pregnancy than ampullary ectopic pregnancy, one case CPK level 2364 IU/L with right isthmical rupture tube, second case with CPK 577 IU/L with intact isthmical ectopic pregnancy and third case with CPK 124 IU/L with intact isthmical tubal ectopic pregnancy while intact ampullary pregnancy mean CPK ranging from (34IU/L) to (74 IU/L) but rupture ampullary pregnancy mean CPK 80IU/L.

So CPK concentration appeared to be affected by ectopic tubal location as they were significantly higher in those with isthmic as opposed to ampullary pregnancies .This observation has been confirmed in a more recent study where CPK levels were also higher in isthmic tubal ectopic pregnancies and ruptured ectopic pregnancies, (Soundravally etal, 2007).

So can depend on CPK for diagnoses isthmical rupture tubal ectopic pregnancy. It is likely that as tubal ectopic pregnancy grows & progresses toward rupture, then serum CPK concentrations are increased.

Develioglu & his colleague reported in 2002 that CPK were higher in isthmic than ampullary ectopic pregnancy (P = 0.011) , and higher in ruptured than in unruptured cases (p= 0.003) and normal pregnancies (p<0.0001) .

A CPK value >120 IU/L was 65% sensitive and 87%specific in discriminating ruptured from unrupture ectopic pregnancies. Serum creatine phosphokinase may help in discriminating ruptured from unruptured tubal ectopic pregnancies, while it is not useful for the primary diagnosis of ectopic pregnancy (Develioglu 2002).

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References

1- Ackerman R, DeutschS , krunhdz B . Leve l of human chorionic gonadotropin in unruptured & ruptured ectopic pregnancy. Obstet Gynecol 1982, 60:13-4.

2-Pinar Cilesiz Goksedif B., Seyfettin Kef, Aysuakca, R Nida Ergin. Risk factors for rupture in tubal ectopic pregnancy. Eur JObstet Gynecol Reprod Biol Vol 154(1):96-99,2010.

3-Birkhahn RH, Gaeta TJ, Paraschiv D,Bove JJ, Suz uki T, Katoh H & Nagai . Serum levels of myoglobin, creatine phosphokinase, and smooth muscle heavy-chain myosin in patients with ectopic pregnancy. Ann Emerg Med 2001, 38(6):628-32.

4- Chandra L, Jain A. Maternal serum creatine kinase as a biochemical marker of tubal pregnancy. Int J Gynecol Obstet 1995; 49(1):21-23.

5- Condous G, Kirk E, LuC. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location, Ultrasound Obstet Gynaecol 2005, 26:770-775.

6-Darai E, Vlastos G, Benifla JL, Sitbon D, Hassid J, Dehoux M, Madelenat P, Durand Gaucher G & Nunez E, Is maternal serum creatine kinase actually a marker for early diagnosis of ectopic pregnancy? European Journal of Obstetrics and Gynecology 1996,68 25–27

7- Develioglu OH, Askalli C, Uncu G, Samli B, Daragenli O. Evaluation of serum creatine kinase in ectopic pregnancy with reference to tubal status and histopathology. BJOG 2002; 109(2):121-28.

8-Duncan WC, Sweeting VM, Cawood P & Illingworth PJ. 1995 Measurement of creatine

kinase activity and diagnosis of ectopic pregnancy. British Journal of Obstetrics and Gynaecology **102** 233–237.
9- Galstyank& Kurzel RB. SerumB-HCG titersdo not predict rupture ectopic pregnancy.Int J Fertil womens Med.2006,51(1),14-6.
10- Horne AW, McBride R, Denison FC. Normally rising hCG does not predict live birth in women presenting with pain and bleeding in early pregnancy. Eur J Obstet Gynecol Reprod Biol. 2011;156:120–121.
11- Houry De, Salhi BA Acute complications of pregnancy. In: Marx JA, ed. Rosen's Emergency Medicine: Concepts and Clinical Practice. 7th ed. Philadelphia, Pa: Mosby Elsevier; 2009: chap 176.
12- Kadar N, Bohrer M, Kemmann E, Shelden R. The discriminatory human chorionic gonadotropin zone for endovaginal sonography: a prospective, randomized study. Fertil Steril. Jun 1994; 61(6):1016-20.
13- Katsikis I, Rousso D, Farmakiotis D, et al. Creatine phosphokinase in ectopic pregnancy revisited: significant diagnostic value of its MB and MM isoenzyme fractions.Am J Obstet Gynecol 2006;194(1):86-91.
14- Kirk K,Daemen A,Papageorghiou AT, Condous G.The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy.Hum Reprod2007,22:2824-2828.
15- Kirk K, Daemen A, Papageorghiou AT .Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial trans vaginal ultrasound examination? ActaObstet Gynecol Scand 2008,87(11):1150-1154.
16- Kirk E, Bourne T Diagnosis of ectopic pregnancy with ultrasound, Best Practice & Research Clinical Obstetrics and Gynaecology(2009)1-8.
17- Lavie O, Beller U, Neuman M Maternal serum creatine kinase: a possible predictor of tubal pregnancy. Am J Obstet Gynecol 1993; 169(5):1149-50.
18-Lavonne A Downey&LaslieZun.Indicators of potential for rupture ectopic seen in the emergency department. J Emerg Trauma Shock, 2011, 4(3):374-377.
19- Lobo RA. Ectopic pregnancy: Etiology, pathology, diagnosis, management, fertility prognosis. In: Katz VL, Lentz GM, Lobo RA, Gershenson DM, eds. Comprehensive Gynecology. 5th ed. Philadelphia, Pa: Mosby Elsevier; 2007: chap 17.
20- Murray H, Hanadi Baakdah, Trevor Bardell, and Togas Tulandi. Diagnosis and treatment of ectopic pregnancy. CMAJ. 2005 October 11; CMAJ. 2005 11; 173(8): 905–912.
21- Nama V, Manyonda I. Tubal ectopic pregnancy: diagnosis and management. Arch Gynecol Obstet. 2009; 279:443–453.]
22-Plewa MC, Ledrick D, Buderer NF & King RW. Serum creatine kinase is an unreliable predictor of ectopic pregnancy. Academic Emergency Medicine1998, **5**300–303.
23-R W Shepherd; P E Patton; M J Novy; K A Burry Serial beta-hCG measurements in the early detection of ectopic pregnancy**.**Obstetrics and gynecology 1990;75(3 Pt 1):417-20
24- Roussos D, Panidis D, Neonaki M , Factors that may predispose to rupture of tubal ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol 2000,89(1):15-7.
25- Saha PK, Gupta I, Ganguly NK. Evaluation of serum creatine kinase as a diagnostic marker for tubal pregnancy. Aust N Z J Obstet Gynaecol 1999; 39(3):366-67.
26- Sameena Wazir, Shagufta Yasmeen, Shaheena Prarveen, Syed Nisar Shagufta Parveen, Samreen Chesti*, Asifa Jan 2009 Reliability of Maternal Serum Creatinine
27- Seeber BE, Sammel MD, Guo W, et al. Application of redefined human chorionic gonadotropin curves for the diagnosis of women at risk for ectopic pregnancy. Fertil Steril. 2006; 86:454–459.
28- Shaw J,L Dey,S K Critchley,H O Home.Current knowledge of the aetiology of human tubal ectopic pregnancy. Oxford Journal,human reproduction update2010,16(4):432-444.
29-Soundravally R, Soundravally R Soundara Raghavan & Selvaraj. Serum creatine kinase as a predictor of tubal ectopic pregnancy. International Journal of Gynaecology and Obstetrics2007, **98:**253–254.

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