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MAIN RESEARCH ARTICLE

Ectopic pregnancy: using the hCG ratio to select women for expectant or medical management

EMMA KIRK[1], BEN VAN CALSTER[2], GEORGE CONDOUS[3], ARIS T. PAPAGEORGHIOU[1,4], OLIVIER GEVAERT[2], SABINE VAN HUFFEL[2], BART DE MOOR[2], DIRK TIMMERMAN[5] & TOM BOURNE[5,6]

[1]*Early Pregnancy and Gynaecological Ultrasound Unit, St George's, University of London, UK,* [2]*Department of Electrical Engineering (ESAT-SCD), Katholieke Universiteit Leuven, Belgium,* [3]*Early Pregnancy Unit and Advanced Endosurgery Unit, Nepean Clinical School, University of Sydney, Nepean Hospital, Sydney, Australia,* [4]*Fetal Medicine Unit, St George's, University of London, UK,* [5]*Department of Obstetrics and Gynecology, University Hospitals Leuven, Belgium, and* [6]*Imperial College London, Hammersmith Campus, London, UK*

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Correspondence
Dr Emma Kirk, Early Pregnancy and Gynaecological Ultrasound Unit, St George's, University of London, London, UK.
E-mail: ejkirk@hotmail.co.uk

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Abstract

Objective. To identify variables that can be used to select women with an ectopic pregnancy for expectant or medical management with systemic methotrexate. *Design.* Cohort study. *Setting.* Early Pregnancy Unit of a London teaching hospital. *Population.* Women with a tubal ectopic pregnancy managed non-surgically. *Methods.* The diagnosis of tubal ectopic pregnancy was made using transvaginal sonography. Human chorionic gonadotrophin (hCG) levels had to be taken at 0 hour and 48 hours pre-treatment. Other recorded variables include presenting complaints, gestational age, progesterone levels, size of the ectopic mass and appearance of the ectopic on transvaginal sonography. Women were followed up until the outcome (success or failure) of management was known. *Main outcome measures.* Univariable analysis was performed to identify the variables associated with successful management using area under curves and relative risks. *Results.* Thirty-nine women underwent expectant management (overall success rate 71.8%) and 42 had medical management (overall success rate 76.2%). The pre-treatment hCG ratio (hCG 48 hours/hCG 0 hour) was related to the failure of both expectant (area under curve 0.86, 95% CI 0.67–0.94) and medical (area under curve 0.79, 95% CI 0.58–0.90) management. History of ectopic pregnancy was related to failure of expectant management only (relative risk 0.46, 95% CI 0.16–0.92). *Conclusions.* The most important variable for predicting the likelihood of successful non-surgical management was the pre-treatment hCG ratio. New studies are required to validate the use of this variable and of history of ectopic pregnancy to predict the likelihood of successful non-surgical management in clinical practice.

Abbreviations AUC, area under curve; CI, confidence interval; EPU, early pregnancy unit; hCG, human chorionic gonadotrophin; IU, international unit; PUL, pregnancy of unknown location; TVS, transvaginal ultrasound scan.

Introduction

Historically, histological confirmation after visualization at the time of surgery is thought to be the gold standard for diagnosis of an ectopic pregnancy. However, transvaginal ultrasound (TVS) is now becoming the diagnostic technique of choice. It has been reported to have an overall sensitivity of 90.9–99.0% for the detection of ectopic pregnancy (1–3). Between 73.9 and 85.9% of these ectopic pregnancies diagnosed on TVS can actually be visualized on the initial TVS examination performed (3,4). As the majority of ectopic pregnancies are now diagnosed non-surgically, there has been an increasing trend to manage suitable cases either expectantly or medically.

Expectant and medical management have been shown to be safe and effective in selected cases of ectopic pregnancy.

For expectant management, reported success rates vary from 48 to 100% (5–9), while success rates of 65–95% have been reported for systemic low dose methotrexate (9–13). Much of this variation in success rates depends on patient selection. Currently, it would appear that a number of women with an ectopic pregnancy that would have resolved with non-surgical management have surgery, and many who would have successfully resolved with expectant management have unnecessary methotrexate treatment.

Various predictors of the likely success of non-surgical management in ectopic pregnancies have been studied, including a previous history of ectopic pregnancy, gestational age, the ultrasound appearance of the ectopic, initial serum human chorionic gonadotrophin (hCG) levels and changes in serum hCG levels (13–17). However, to date, no single factor has been identified to help the clinician decide between expectant and medical treatment when considering non-surgical management. In general, most offer expectant management if the hCG levels are decreasing and give methotrexate if the hCG levels are increasing, but it is often down to the clinician's and woman's own preference. However, there are issues regarding the definition of an increasing or decreasing hCG level and what is the best form of management when the hCG level appears to be plateauing.

The aims of this study were to identify which biochemical and morphological features of ectopic pregnancies can be used to predict the success of non-surgical management and can aid the clinician in deciding whether management should be expectant or medical.

Material and methods

This was a cohort study on women with a tubal ectopic pregnancy undergoing expectant or medical management under the care of the Early Pregnancy Unit (EPU) of a London teaching hospital over a 3-year period. A diagnosis of unilateral tubal ectopic pregnancy was made on the basis of the transvaginal ultrasound (TVS) findings using a 5-MHz transducer for B mode imaging. The criteria for the diagnosis of ectopic pregnancy on TVS were based upon the absence of an intra-uterine gestational sac and the presence of one of the following: 1) an inhomogeneous adnexal mass separate from the ovary, 2) an empty extra-uterine gestational sac with an hyperechoic ring ('bagel sign') in the adnexal region, or 3) a yolk sac or fetal pole with or without cardiac activity in an extra-uterine sac in the adnexal region (2,18). Ten sonographers performed the TVS examinations during the study period. These were either doctors or specialist nurses/midwives who were competent in transvaginal ultrasound. Women were diagnosed with an ectopic pregnancy either on the basis of their first TVS examination or after follow-up examinations if they were initially classified as pregnancies of unknown location (PULs).

Women undergoing surgery as the primary treatment for ectopic pregnancy were excluded from this study. Indications for primary surgical treatment were: hemodynamic instability, an acute abdomen, hemoperitoneum on TVS, positive fetal cardiac activity, an initial serum human chorionic gonadotrophin (hCG) level of >5000 IU/l, liver or renal impairment and/or poor likely patient compliance with conservative management. Surgical management in these women was either laparoscopic or open, with salpingectomy or salpingostomy. In addition, women with non-tubal ectopic pregnancies and heterotopic pregnancies were excluded.

Women were included in this study if they underwent expectant or medical management as the primary treatment and had had at least two serum hCG measurements taken, 48 hours apart, before a management decision was made (Figure 1). The following were documented: gestational age according to the last menstrual period, indications for presentation, scan findings and serum hCG and progesterone levels at presentation (time 0 hour) and 48 hours later. The pre-treatment hCG ratios were calculated for each woman. The pre-treatment hCG ratio was defined as the serum hCG 48 hours/serum hCG 0 hour. The largest diameters of the entire ectopic mass were measured in three dimensions on TVS, and their mean was calculated.

The decision to manage expectantly or medically was made by the attending clinician at 48 hours. The general policy of the EPU was that women with a decreasing hCG level could be managed expectantly. This was defined as an hCG ratio of <1. If the hCG ratio was ≥ 1, treatment with methotrexate was advised. There were some women who declined methotrexate and wished to be managed expectantly and some who preferred to have methotrexate rather than to be managed expectantly even though their serum hCG levels would have allowed this.

Expectant management involved monitoring serum hCG levels initially every 48 hours for the first week and then weekly until the levels were less than 10 IU/l. If the hCG level was not decreasing (<10% decrease between any two measurements), or if there was a change in the clinical situation, a repeat TVS was performed and then methotrexate given or surgery performed as indicated.

Medical management was in the form of systemic methotrexate and a single dose (50 mg/m^2) was given (10). If the serum hCG decreased by more than 15% between days 4 and 7 post-administration, hCG levels were monitored on a weekly basis until they were less than 10 IU/l. If hCG levels failed to decrease by more than 15%, a second dose of methotrexate (50 mg/m^2) was given. Surgery was performed if indicated by deterioration in the clinical situation or if the hCG level failed to decrease (>15% days 4–7) after two doses of methotrexate.

The success of expectant and medical management was determined. For expectant management, success was defined

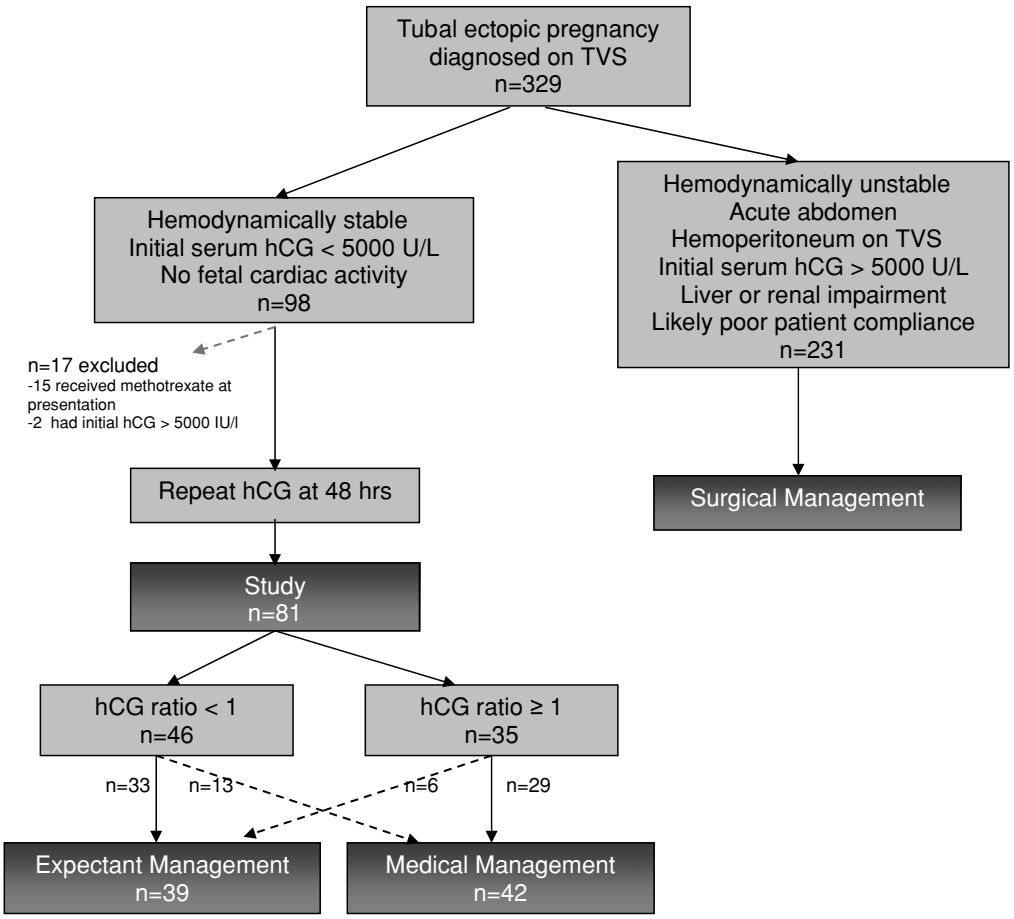

Figure 1. A flow chart summarizing patient selection.

as there being no requirement for methotrexate or surgical intervention. Failure of expectant management resulted in methotrexate treatment if there was a rising hCG or plateauing hCG, defined as a decrease of <10% between two measurements. Surgery was performed in women who presented with pain, became hemodynamically unstable or developed a hemoperitoneum. Successful medical treatment was defined as not requiring surgical treatment and this was undertaken if there was pain, hemodynamic instability or hemoperitoneum.

Statistical analysis

The statistical analysis was performed using SAS v9.1 (SAS Institute, Cary, NC, USA) and MATLAB 7.0.4.352 (R14). A univariate analysis was carried out to identify the variables associated with successful conservative management. This was done using the area under the curve (AUC) for continuous variables and relative risks for categorical variables, with 95% confidence intervals (CIs) computed using Newcombe's method and the Cox–Hinkley–Miettinen–Nurminen method, respectively (19,20). For the most important variable(s), sensitivity (i.e. percentage correctly predicted failures) and specificity (i.e. percentage correctly predicted successes) were investigated by varying the cut-off in case of a continuous variable.

Results

During the study period, 13 312 consecutive women attended the EPU or Acute Gynaecology Unit with a positive pregnancy test and underwent a TVS. Of the 329 women diagnosed with a tubal ectopic pregnancy (2.5%), 231 (70.2%) were managed surgically and 98 (29.8%) conservatively in the EPU. Of those 98 women, 17 women were excluded from subsequent analysis: 15 because they received methotrexate at the time of presentation and two because their initial serum hCG levels were greater than 5000 IU/l. Of the remaining 81 women, 39 (48%) were managed expectantly and 42 (52%) medically; these were included in the final analysis. Of these 81 women, 67 (82.7%) had their ectopic pregnancies visualized

Table 1. Descriptive data for women managed expectantly ($n = 39$)

Variable	Successful expectant management ($n = 28$)		Failed expectant management ($n = 11$)		Effect size
Continuous	*n*	*median (range)*	*n*	*median (range)*	*AUC (95% CI)*‡
Age (years)	28	30 (20–41)	11	27 (21–38)	0.60 (.40–.77)
Gestation (days)	25	43.0 (13–94)	9	42.0 (30–59)	0.56 (.35–.75)
hCG 0 hour (IU/l)	28	174.0 (10–1604)	11	320.0 (19–2852)	0.64 (.43–.79)
Prog 0 hour (nmol/l)	27	6.0 (1–56)	7	13.0 (4–35)	0.68 (.44–.85)
hCG ratio	28	0.58 (0.16–1.81)	11	0.93 (0.39–1.95)	0.86 (.67–.94)
Mean size (mm)	27	16.5 (8.5–33.7)	9	19.3 (9.5–37.3)	0.65 (.43–.81)
Categorical	*n*	*% yes*	*n*	*% yes*	*Relative risk (95% CI)*‡
Parous	24	42	10	50	0.90 (0.54–1.43)
History of EP	24	13	10	50	0.46 (0.16–0.92)
Reason for scan	28		10		
Bleeding		21		40	0.76 (0.39–1.18)
Pain		14		30	0.74 (0.31–1.19)
Both		54		10	1.59 (1.10–2.46)
Other		11		20	–
USS appearance of EP	28		11		
Inhomogeneous mass		89		100	–
Bagel		7		0	–
CRL		4		0	–

‡ 95% CI of the AUC using the method of Newcombe (2006); 95% CI of the relative risk using the Cox–Hinkley–Miettinen–Nurminen method (Miettinen and Nurminen, Stat Med 1985).

on the first TVS and 14 (17.3%) were initially classified as PULs with visualization of ectopic pregnancies on subsequent TVS examinations. The ultrasound appearance of the ectopic pregnancy was an inhomogeneous mass in 76.5% of cases (62/81), an empty extra-uterine gestational sac in 7.4% of cases (6/81) and a fetal pole without cardiac activity in an extra-uterine sac in 16.1% of cases (13/81).

Expectant management

Thirty-nine cases were managed expectantly and this resulted in successful resolution in 28 (72%) cases (Table 1). Of the 11 women with failed expectant management, six were successfully treated with methotrexate, two received methotrexate but subsequently required laparoscopic salpingectomies and three underwent surgery – two laparoscopic salpingectomies and one diagnostic laparoscopy that confirmed a tubal miscarriage. The pre-treatment hCG ratio and history of ectopic pregnancy were most strongly related to the outcome of expectant management. Women with unsuccessful management had a median hCG ratio of 0.93, whereas women with successful management had a median ratio of 0.58 (Table 1). The AUC was 0.86 (95% CI 0.67–0.94). A history of ectopic pregnancy was observed in half (5/10) of the women with unsuccessful management and in 13% (3/24) with successful management. The relative risk of success was 0.46 (95% CI 0.16–0.92): 38% for women with a history of ectopic pregnancy (3/8) compared to 81% for women without (21/26). In contrast, presenting with both bleeding and pain was more common in patients with successful (15/28, 54%) vs. failed (1/10, 10%) management. The relative risk of success was 1.59 (95% CI 1.10–2.46): 94% for women with both presenting complaints (15/16) compared to 59% for other women (13/29). The effects of the initial hCG, initial progesterone level, and mean diameter of the ectopic pregnancy were all in the expected direction but were not strong. Of ectopic pregnancies managed expectantly, 41% (16/39) had an initial hCG of <175 IU/l and the success rate was 88% (14/16). The success rate in those with an hCG of ≥ 175 IU/l was 61% (14/23).

Medical management

Forty-two cases were managed medically and the success rate of this treatment was 76% (32/42, Table 2). The pre-treatment hCG ratio was the only variable that was related to the outcome. Women with unsuccessful management had a median hCG ratio of 1.42, whereas women with successful management had a median ratio of 1.07 (Table 2). The AUC was 0.79 (95% CI 0.58–0.90). The effect of initial hCG was in the expected direction but, nevertheless, the AUC was low. Of the 42 women, 62% (26/42) had an initial hCG level of <1000 IU/l. The success rate in those with an hCG level <1000 IU/l was 80.8% (21/26) compared to 68.8% (11/16) in those

Table 2. Descriptive data for women managed with systemic methotrexate ($n = 42$)

Variable	Successful medical management ($n = 32$)		Failed medical management ($n = 10$)		Effect size
Continuous	*n*	*median (range)*	*n*	*median (range)*	*AUC (95% CI)‡*
Age (years)	32	30 (18–42)	10	29 (20–38)	0.54 (.35–.72)
Gestation (days)	30	43.5 (16–72)	9	38.0 (19–54)	0.59 (.38–.77)
hCG 0 hour (IU/l)	32	549.5 (43–3438)	10	928 (166–3317)	0.57 (.37–.75)
Prog 0 hour (nmol/l)	28	18.5 (3–170)	9	15.0 (2–70)	0.59 (.37–.77)
hCG ratio	32	1.07 (0.44–2.43)	10	1.42 (1.07–1.85)	0.79 (.58–.90)
Mean size (mm)	31	15.3 (8–22.5)	10	14.1 (11–16.7)	0.57 (.37–.75)
Categorical	*N*	*% yes*	*N*	*% yes*	*Relative risk (95% CI)‡*
Parous	32	41	10	50	0.91 (0.60–1.31)
History of EP	32	22	10	20	1.03 (0.58–1.44)
Reason for scan	32		10		
Bleeding		34		30	1.05 (0.67–1.48)
Pain		6		10	0.87 (0.26–1.34)
Both		34		30	1.05 (0.67–1.48)
Other		25		30	–
USS appearance of EP	32		10		
Inhomogeneous mass		63		60	1.03 (0.72–1.59)
Bagel		6		20	0.63 (0.19–1.14)
CRL		31		20	1.14 (0.72–1.58)

with an initial hCG $\geq$ 1000 IU/l. In 36 women a single dose of methotrexate was given, while six women required two doses of methotrexate. The success rate in those requiring one dose was 27/36 (75%), while in the six women requiring two doses, five (83%) had successful medical management and one (17%) was unsuccessful.

Pre-treatment hCG ratio

The pre-treatment hCG ratio was the only predictor of success for both expectant and medical management, with lower ratios being a predictor for successful management. Figure 2 shows box plots of the hCG ratio stratified by management (expectant vs. medical) and outcome (success vs. failure).

Figure 3 shows the evolution of sensitivity and specificity by varying the cut-off to predict the outcome of expectant management. Based on this information, a cut-off of 0.8 appears ideal. It detects most cases for which expectant management turned out successful (26/28, specificity 93%, 95% CI 77–98%) while still detecting the majority of failures (7/11, sensitivity 64%, 95% CI 35–85%). This implies that if the hCG ratio is at least 0.8, expectant management is considered likely to fail (7/9, positive predictive value 78%), and if the hCG ratio is <0.8, it is considered likely to be a success (26/30, negative predictive value 87%).

In our data, having a history of ectopic pregnancy and/or presenting with pain and bleeding further influences the likelihood of successful management, but due to the limited sample size we refrained from multivariable modeling.

Figure 4 shows the evolution of sensitivity and specificity by varying the cut-off to predict the outcome of medical management. A cut-off of 1.2 appears sensible, and prioritizes the detection of cases for which medical management will fail over the detection of successes. It detects most cases for which medical management turns out unsuccessful (8/10, sensitivity 80%, 95% CI 49–94%) while still detecting a majority of successful cases (21/32, specificity 66%, 95% CI 48–80%). This means that if the hCG ratio is at least 1.2, medical management is considered likely to fail (8/19, positive predictive value 42%). If the hCG ratio is <1.2 there are 21/23 successes (negative predictive value 91%).

Discussion

In this paper we have developed a strategy on which to base the clinical management of a hemodynamically stable woman with a tubal ectopic pregnancy with no fetal cardiac activity and an initial serum hCG level <5000 IU/l. This involves waiting 48 hours following the diagnosis of an ectopic pregnancy in order to calculate the pre-treatment hCG ratio. The pre-treatment hCG ratio can then be used to predict the likelihood of success of conservative management and has the potential to assist in selecting women for either expectant management or treatment with single-dose systemic methotrexate. Few studies have examined the change in serum hCG prior to expectant or medical management as a possible predictor of management success (15,21,22). A study in which expectantly managed ectopic pregnancies had

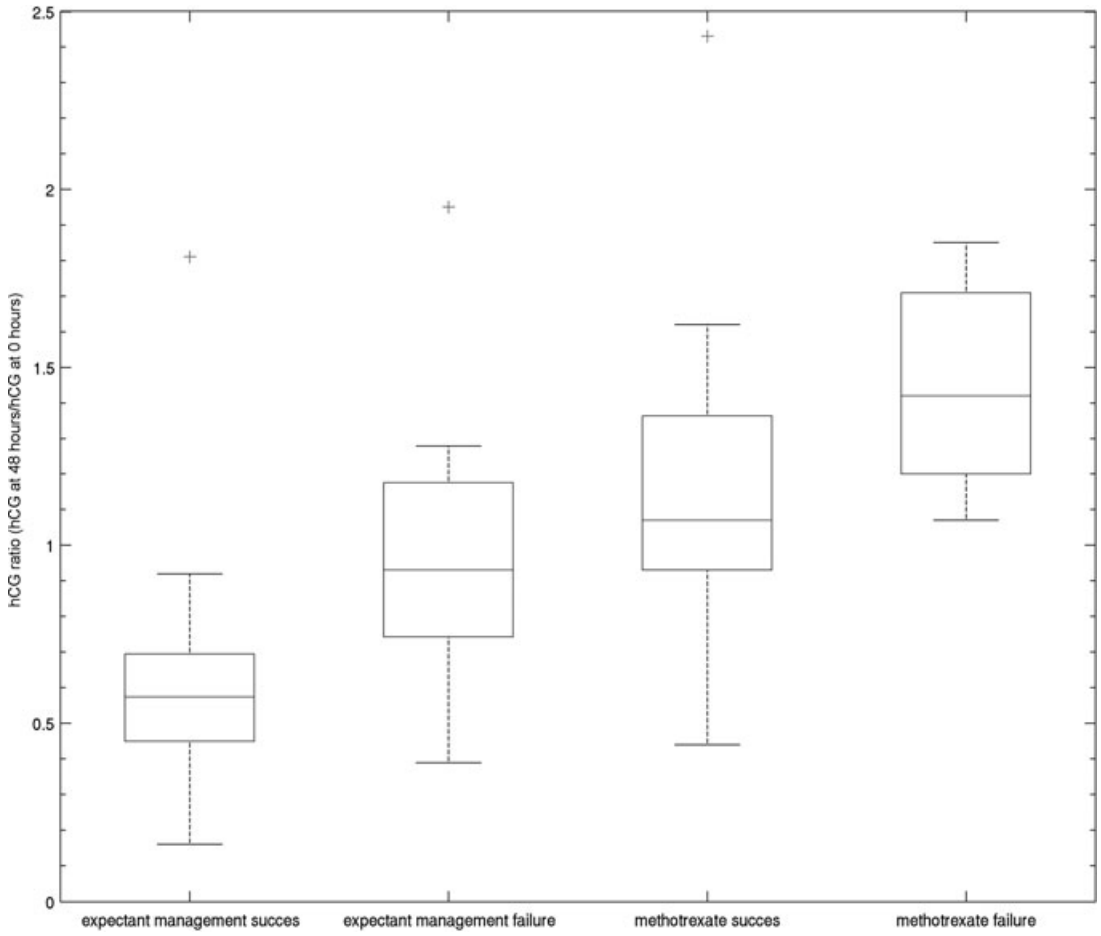

Figure 2. Box plot of the pre-treatment hCG ratios in successful and unsuccessful expectant and medical management.

hCG levels monitored initially twice weekly and then weekly, showed that a decrease in hCG levels was significantly more common among women with a successful outcome (15). However, the decrease in hCG levels was not quantified. The trend in hCG levels before and after methotrexate administration has also been found to be associated with a successful outcome (21). Da Costa Soares et al. (2008) found that a $\leq$11% rise in serum hCG prior to the administration of methotrexate was indicative of treatment success (22). Women who had failed methotrexate treatment had a mean increase in hCG of 36.2% (22).

One of the limitations of our study is that women were selected for expectant or medical management on the basis of the trend in hCG levels over 48 hours. Therefore there are limited data on the expectant management of women with increasing hCG levels and on the use of methotrexate when the hCG was decreasing over the initial 48 hours. We felt that withholding treatment in women with ectopic pregnancies whose hCG levels were increasing was inappropriate, due to the risk of rupture. However, six women refused methotrexate treatment and were initially managed expectantly despite a pre-treatment hCG ratio of $\geq$1. Expectant management was only successful in one of these women (16.7%). Similarly, we did not feel it was appropriate to give methotrexate routinely to ectopic pregnancies with features of probable spontaneous resolution. However, in the 13 women with a pre-treatment hCG ratio $<$1 who did receive methotrexate, the success of treatment was 100%. This success rate is far higher than the success of expectant management alone, so it is possible that there is some advantage in giving methotrexate to women with a decreasing serum hCG level. We therefore decided not to exclude these women from our analysis. It may also be thought that withholding methotrexate for an initial period of expectant management may result in a lower success rate from medical management. However, in our study there was no difference in the success rate of methotrexate when it was given as the primary treatment (success rate 76%) or after a period of initial expectant management (75%).

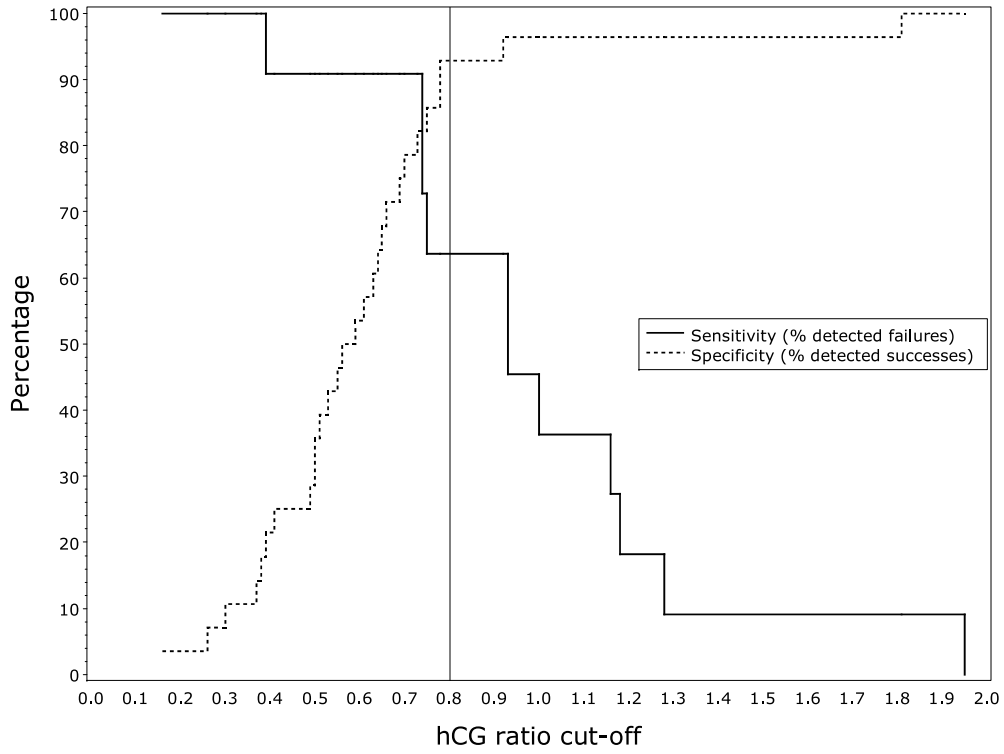

Figure 3. Sensitivity and specificity of expectant management for varying hCG ratio cut-offs.

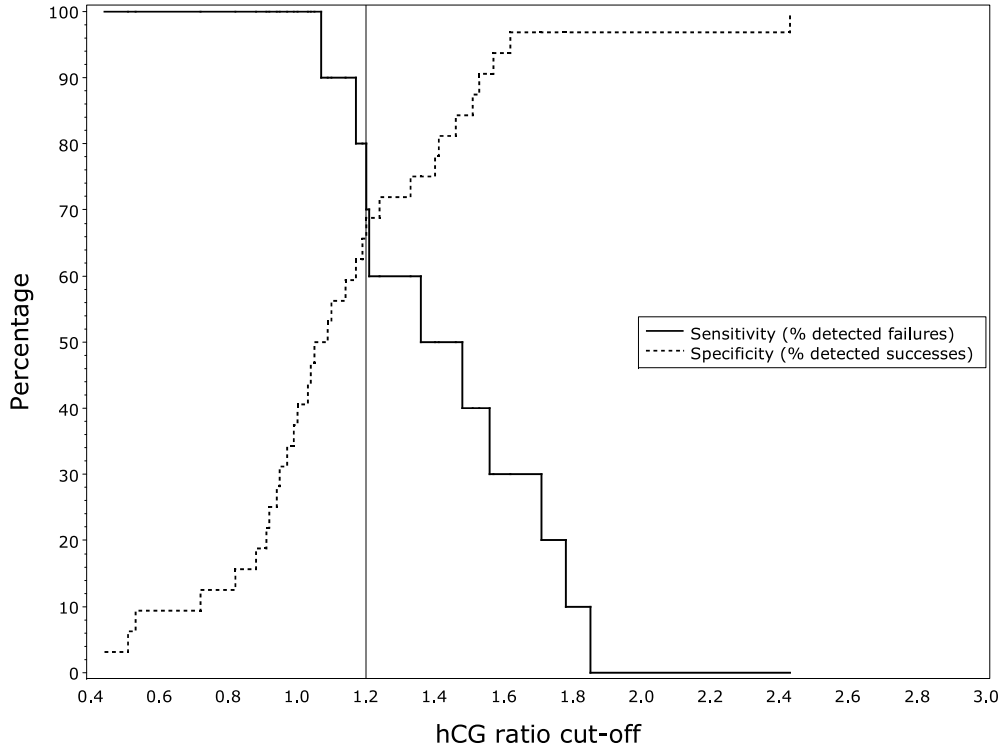

Figure 4. Sensitivity and specificity of medical management for varying hCG ratio cut-offs.

In our EPU population, we have shown that women with a pre-treatment hCG ratio of less than 0.8 can be managed expectantly with resolution in about 80% of cases. If the pre-treatment hCG ratio is greater than 0.8, methotrexate should be given and this has a similar success rate to expectant management up to a ratio of 1.2. Above this hCG ratio, surgery may be the most appropriate primary treatment. We considered it more important to detect failure of medical treatment than to detect failure of expectant management. After failed expectant management, methotrexate may be an option, but with failed medical management the only option is surgery. However, these are only suggested cut-offs given the small sample sizes.

According to this study, the size of the ectopic pregnancy was not important for determining the likely outcome of conservative management. This is in agreement with other studies (16,23). The ultrasonographic appearance of the ectopic pregnancies in this study was also not an important predictor of success. This may be due to the very high proportion of ectopic pregnancies (76.5%) in this study that were visualized as an inhomogeneous mass. However, the ultrasonographic appearance of an ectopic has been shown in other studies to be a significant predictor of success for expectant management (15,16). In those studies, the absence of a gestational sac was shown to be significant. The presence of a yolk sac has been shown to be a poor predictor of success for management with methotrexate (24,25) but this variable was not examined in our study due to the small number of ectopic gestational sacs (21.4%). Fetal cardiac activity was a contraindication to conservative management in our study on the basis that ectopic fetal cardiac activity has previously been shown to be a significant predictor of failure with methotrexate treatment (13).

In this study, we also found that the success of expectant management is higher if the woman has pain and bleeding. We can speculate that this is due to the symptoms signifying a tubal miscarriage. Also, women with a history of a previous ectopic pregnancy were less likely to undergo successful expectant management. These findings should be investigated further.

To date, studies have suggested that the initial serum hCG is probably the most significant predictor of the success for both medical and expectant management. In a study of expectant management, a success rate of 96% was reported if the initial hCG was <175 IU/l (23). However, our data suggest this approach will only be helpful in a small number of women. In our study, although the success rate of expectant management was 87.5% (14/16) when the hCG was <175 IU/l, only 41% (16/39) of ectopic pregnancies had an initial hCG of <175 IU/l. Similarly, for management with methotrexate, the failure rate has been found to be significantly higher when the initial serum hCG level is greater than 1000 IU/l (21). While we acknowledge that we excluded ectopic pregnancies with an initial hCG of >5000 IU/l, for ectopic pregnancies with initial hCGs below this threshold our data suggest that the initial serum hCG is not a significant variable for the prediction of outcome.

Conclusion

According to our study, the pre-treatment hCG ratio is the most important variable to consider when selecting women with an ectopic pregnancy for non-surgical management. In women where TVS shows a tubal ectopic pregnancy without embryonic heart activity; who have an initial hCG of less than 5000 IU/L; and who are clinically stable, we advocate waiting 48 hours in order to calculate the pre-treatment hCG ratio (hCG 48 hours/hCG 0 hour). The use of the pre-treatment hCG ratio needs to be further investigated to validate its performance and assess its impact on the non-surgical management of ectopic pregnancies. The additional usefulness of other markers, such as initial hCG, history of ectopic pregnancy, or presenting with pain and bleeding, should also be further investigated in a multivariable analysis, and may result in an individualized likelihood of success for both expectant and medical management.

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