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Negative histology with surgically treated tubal ectopic pregnancies – a retrospective cohort study.

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Condensation: Retrospective cohort study of surgically treated tubal ectopic pregnancies demonstrating that approximately 5% are not confirmed on histological examination.

Abstract

Negative histology with surgically treated tubal ectopic pregnancies – a retrospective cohort study.

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Objective: To determine the outcome of histological examinations of surgical specimens obtained from treatment of tubal ectopic pregnancy and to correlate with clinical findings, pre-operative ultrasound scans and the type of surgery.

Study design: A retrospective cohort study of 941 women diagnosed with a tubal ectopic pregnancy in the Early Pregnancy Unit and having surgical treatment at King's College Hospital, London. Clinical and ultrasound data had been entered contemporaneously on our electronic early pregnancy database and hospital clinical records over an 11 year period from 2004-2014. Demographic data, clinical history, ultrasound scan parameters, type of surgical management and histological diagnosis were recorded. The primary outcome measure was the presence or absence of chorionic villi in the surgical specimen. Data were analysed using Mann Whitney U test for non-parametric data, relative risk for categorical data and binomial logistic regression.

Results: A surgical specimen was obtained in 925 cases. Of these, 881/925 (95.2%) were positive for the presence of chorionic villi on histological examination. Patients with negative histology had a lower median gestational age, smaller ectopic pregnancies and lower serum human chorionic gonadotrophin levels. The relative risk of negative histology was significantly higher with a solid ectopic pregnancy on ultrasound (RR1.91, 95% CI 1.07-3.4) and with conservative surgery (RR 3.68, 95% CI 1.25-10.77). The relative risk was significantly lower with the presence of embryonic cardiac activity (RR 0.12, 95% CI 0.02 – 0.85). Only the serum hCG level was a significant predictor of negative histology on logistic regression analysis (p=0.048). In 39/44 women with negative histology, the human chorionic gonadotrophin level declined after surgery with no further intervention. Five of the 44 required a second surgical procedure as the ectopic pregnancy had been missed at the initial surgery and did not resolve.

Conclusion: There is lack of histological confirmation of sonographically diagnosed and surgically confirmed ectopic pregnancies in approximately 5% of cases, making

this a relatively common finding following surgical treatment of tubal ectopic pregnancy. Clinicians should be aware of this when counselling women with tubal ectopic pregnancies about to undergo surgery, include this risk in the consent process and plan post-surgical follow up with this in mind.

Keywords: ectopic; ; ; ; , pregnancy first trimester, ultrasound, histopathology, surgery

Introduction

Although conservative treatments for tubal ectopic pregnancies are increasingly employed, surgery remains the preferred treatment for the majority of women (1). The accuracy of laparoscopic diagnosis of ectopic pregnancy has never been formally assessed, but it remains the accepted gold standard for the diagnosis of an ectopic pregnancy in an acute situation, and the primary approach for surgical treatment (2). We perform an annual audit of ectopic pregnancy in our Early Pregnancy Unit (EPU) and we note a small number of cases where the postoperative histology does not confirm the presence of chorionic villi, despite the ultrasound and surgical diagnosis of an ectopic pregnancy. Previous studies of the diagnostic accuracy of ultrasound did not report any cases of a positive surgical diagnosis of ectopic pregnancy that was not confirmed histologically (3-5). Older reports of diagnostic laparoscopy prior to transvaginal sonography reported ‘false positive’ diagnosis of ectopic pregnancy in approximately 5% of cases (6, 7). The aim of this study was to ascertain the proportion of surgically managed tubal ectopic pregnancies that are unconfirmed histologically and to correlate the absence of chorionic villi with the clinical, ultrasound and surgical findings.

Methods

This was a retrospective observational study carried out at King's College Hospital, London. Data had been collected prospectively over an eleven year period from 2004-2014. Our unit serves a racially diverse, mobile, inner city population with high levels of socioeconomic deprivation. All women included had a spontaneous pregnancy, a positive urinary pregnancy test and had presented to EPU with abdominal pain, vaginal bleeding or for pregnancy dating. All surgically managed cases of tubal ectopic pregnancies were identified by searching our early pregnancy database, theatre records and clinical diagnostic codes. Exclusion criteria were non-tubal ectopic pregnancy, heterotopic pregnancy, non-surgical treatment and emergency surgical treatment without formal pre-operative ultrasound assessment in the EPU. Pregnancies of unknown location (PUL) on ultrasound were not included. Ultrasound scans were performed by experienced Gynaecologists according to a standardised clinical protocol. Scans were performed transvaginally, supplemented by a transabdominal approach when indicated to get a clear view of the uterus and adnexae. An ectopic pregnancy was diagnosed by an empty endometrial cavity with: (i) an inhomogeneous, solid adnexal mass separate from the corpus luteum or corpora lutei or (ii) an empty extrauterine gestational sac seen as a hyper-echoic ring or (iii) an extrauterine gestational sac with a yolk sac and /or fetal pole with or without cardiac activity (4). Women with abdominal pain and evidence of a haemoperitoneum on ultrasound scan were considered to have indirect evidence of an ectopic pregnancy and were included in the study. For each case, the following data was collected: side of the ectopic pregnancy, ultrasound morphology of the tubal ectopic pregnancy (gestational sac containing embryo +/- cardiac activity,

empty gestational sac +/- yolk sac or inhomogenous, solid mass), presence or absence of blood in the pelvis.

For surgically managed cases, the surgical approach (ie laparoscopic or open) and procedure (salpingectomy, salpingotomy, conservative i.e. tubal milking or no active intervention) were recorded. Finally, for all the surgical cases where a tubal ectopic pregnancy was documented as having been confirmed intra-operatively, the histology results were recorded. The primary outcome measure was the presence or absence of chorionic villi in the surgical specimen.

Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY. Mann Whitney U test was used for non-parametric data, relative risk for categorical data and binomial logistic regression to assess multiple independent variables, with multiple imputations for missing values.

The advice of our research and development committee was sought regarding the study and we were advised that formal ethical consideration would not be required.

Results

There were a total of 1491 ectopic pregnancies in EPU over the study period. 1363 (91.0%) of these pregnancies were tubal ectopic pregnancies. Of these cases, 23 patients completed their follow-up elsewhere, thus a total of 1340 tubal ectopics were treated at King's. 941/1340 (70.2%) of tubal ectopic pregnancies were managed surgically, the remainder were managed non-surgically. The study population had a mean maternal age of 30.6 years, 47.0% were black, 26.2% white, 5.4% Asian and 21.4% considered themselves of mixed or other ethnicity. The median gestational age by dates (where known) was 46.9 days. The flow of patients through the study is shown in Figure 1.

On preoperative ultrasound assessment, the ectopic pregnancy was right sided in 533/941 (56.6%), left-sided in 404/941 (42.9%) and was uncertain in 4/941 (0.4%) due to haemoperitoneum. 877/941 (93.2%) had laparoscopic surgery and the remainder had an open procedure. 822/941 (87.4%) underwent a salpingectomy, 86/941 (9.1%) a salpingotomy, and 33/941 (3.5%) had conservative surgery in the form of tubal milking or pelvic washout.

The diagnosis of tubal ectopic pregnancy was confirmed intra-operatively in 932/941 (99.0%) of cases. Of the nine women with negative laparoscopies, three had a persistent ectopic pregnancy on ultrasound and required a second surgical procedure by which time the ectopic pregnancy was visible at laparoscopy. Of the remaining six women, one had a miscarriage and associated haemoperitoneum (she had a suspected ectopic pregnancy but products of conception were found in her vagina at the time of her laparoscopy), and the hCG declined without further surgical intervention or surgical confirmation of the location of the pregnancy in the other five.

The details of the ultrasound findings, first surgical procedure and histological outcome of the 941 women are shown in table 1. A histological specimen was obtained in 922/941 (98.0%) of cases. Of those 922 cases, the histology was negative for the presence of chorionic villi in 44 (4.8%).

Considering the 44 cases with negative histology, 28 showed indirect evidence of an ectopic pregnancy with haemorrhage in the tube, including five cases that also had intraluminal trophoblast. In two of the 23 cases with haematosalpinx alone, the ectopic pregnancy persisted on ultrasound examination and the hCG continued to rise, so second surgery was performed. 16 cases showed chronic inflammation or tubal epithelial hyperplasia, including one case of tubal schistosomiasis. Of these, three women were found to have ongoing ectopic pregnancies requiring second surgery. All five women who required a second surgical procedure had histologically confirmed ectopic pregnancies at second surgery. However, one of these was contralateral to the side of her initially diagnosed ectopic pregnancy. Two of these women had had salpingectomies at their initial surgery. The remaining 39/44 (88.6%) women were asymptomatic post-operatively and their serum hCG levels declined without the need for further intervention.

A comparison between clinical features, USS findings, surgery and final histological outcomes of 925 pregnancies (i.e. including the three cases where the initial surgery failed to identify the ectopic pregnancy) is shown in table 2. Patients with negative histology had a significantly lower median gestational age, smaller ectopic pregnancies and lower hCG levels. The relative risk of negative histology was significantly higher with an inhomogenous, solid ectopic pregnancy on ultrasound and with conservative surgery. The relative risk was significantly lower with the

presence of embryonic cardiac activity. Only serum hCG level was a significant predictor of negative histology on logistic regression analysis (p=0.048).

Comment

Our study has shown that failure to confirm an ectopic pregnancy is a fairly common outcome at histological examination; occurring in just under 5% of cases. Although we found clinical factors that were more frequently associated with negative histological examination, none were sufficiently exclusive so as to be clinically useful. There are two possible reasons that histological examination may fail to confirm an ectopic pregnancy; the diagnosis may have been incorrect (ie. a true false positive) or the ectopic pregnancy may have been present, but either omitted from the surgical specimen or missed during processing in the histopathology laboratory. Omission from the surgical specimen may be because ectopic had already miscarried from the tube and been removed by suction along with the blood and clot in the pelvis - unless all the contents within the suction vacuum are sent for histological analysis, chorionic villi are unlikely to be identified. Another potential reason is that the part of the fallopian tube or tubal mass that contained the chorionic villi was not included in the surgical specimen that was sent to the laboratory. This may be due to an error by the scrub team or omission by the surgeon – the ectopic gestation is often located at the medial aspect of the tubal swelling, and may be smaller than the associated haematosalpinx. However, as long as any remaining chorionic villi are non-viable, which is likely to be the case due to diathermy and devascularisation, surgical treatment will still have been successful. Very occasionally, the wrong part of the tube is removed intra-operatively due to the tube appearing swollen, missing the actual ectopic pregnancy. This was proven to be the case in 5/935 of our patients, 0.53% of all surgically confirmed tubal ectopic pregnancies. We had one case where the ectopic pregnancy was eventually diagnosed contralateral to the side of initial diagnosis (i.e. there was a genuine false

positive diagnosis on both ultrasound and surgery); the initial histology of the tube showed a haematosalpinx and chronic inflammation, but the ectopic pregnancy was located in the interstitial portion of the opposite tube. So although rare, it is important to recognise that not every tubal swelling in a woman with a positive pregnancy test and an empty uterus on ultrasound examination is due to a tubal ectopic pregnancy and that misdiagnosis is a risk. Misdiagnosis and the consequences of misdiagnosis can be minimised both by accurate ultrasound diagnosis and by restricting intervention to women in whom it is clinically justified. The risk of intervention has to be balanced against the risk of a delay in treatment, resulting in tubal rupture or more aggressive surgical treatment than would have been necessary had intervention occurred sooner. It was reassuring that we had no cases of intrauterine pregnancies misdiagnosed as ectopic pregnancies in this surgical series, but the risk of a false positive diagnosis of ectopic pregnancy is reason to caution against the liberal treatment with methotrexate (8). This is particularly the case given that expectant management of ectopic pregnancy is feasible in approximately one third of women, without risking teratogenesis should the diagnosis prove incorrect (9).

The UK Royal College of Obstetricians and Gynaecologists produced guidance for clinicians in obtaining consent of women undergoing laparoscopic salpingectomy or salpingotomy for ectopic pregnancy in 2010 (10). Their advice includes counselling regarding the risks of inability to identify an obvious cause for the presenting complaint (i.e. a negative laparoscopy) and of persistent trophoblastic tissue when salpingotomy is performed. Our study shows that lack of histological confirmation can even occur following salpingectomy for a laparoscopically confirmed ectopic pregnancy, so we believe that this should be included in counselling and accounted for in postoperative follow up. This study also provides benchmarking data that other

hospitals may wish to audit against and that may be quoted in medico-legal cases. As yet, there are no published data from other units in the UK, but there is no reason to suggest that our findings should not be generalisable to other hospitals.

We recommend that units establish a formal means of checking the histology results after surgery for an ectopic pregnancy, following up those women with negative results to ensure that their pregnancy has resolved and allow timely intervention in the small number with ongoing ectopic pregnancies. The alternative is to perform a follow up urinary or serum hCG on all women post-surgery, not solely those who have had conservative surgery or a salpingotomy, so as not to miss the small number of women with persistent ectopic pregnancies that may require further treatment.

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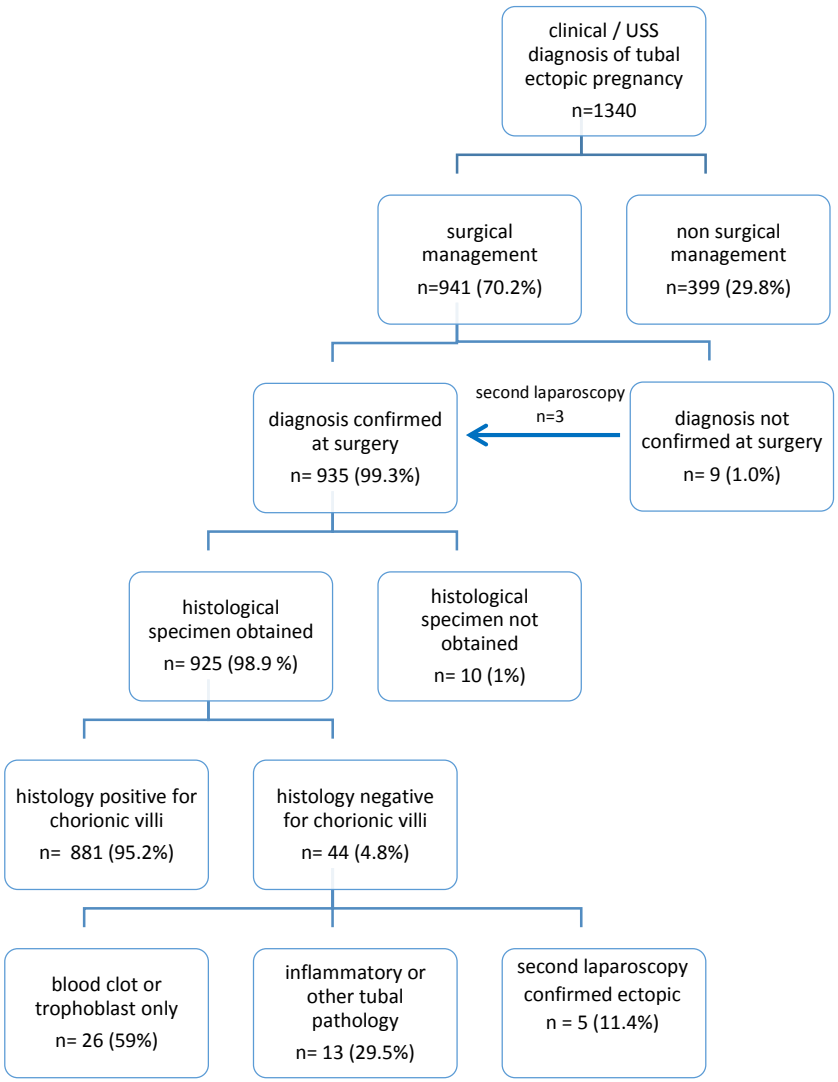
References

1. Varma R, Gupta J. Tubal ectopic pregnancy. BMJ Clin Evid. 2012;2012.
2. Van Mello M, Mol F, Ankum W, Mol BW, Van der Veen F, Hajenius P. Ectopic pregnancy: How the diagnostic and therapeutic management has changed. Fertility and sterility. 2012;98(5):1066-73.
3. Shalev E, Yarom I, Bustan M, Weiner E, Ben-Shlomo I. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy: experience with 840 cases. Fertility and sterility. 1998;69(1):62-5.
4. Kirk E, Papageorghiou AT, Condous G, Tan L, Bora S, Bourne T. The diagnostic effectivness of an intital transvaginal scan in detecting ectopic pregnancy. Human Reproduction. 2007;22:2824-8.
5. Condous G, Kirk E, Lu C, Van Huffel S, Gevaert O, De Moor B, et al. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2005;26(7):770-5.
6. Kim DS, Chung SR, Park MI, Kim YP. Comparative review of diagnostic accuracy in tubal pregnancy: a 14-year survey of 1040 cases. Obstetrics and gynecology. 1987;70(4):547-54.
7. Kadar N. Early recourse to laparoscopy in the management of suspected ectopic pregnancy. Accuracy and morbidity. The Journal of reproductive medicine. 1990;35(12):1153-6.
8. Bourne T, Barnhart K, Benson CB, Brosens J, Van Calster B, Condous G, et al. NICE guidance on ectopic pregnancy and miscarriage restricts access and choice and may be clinically unsafe. Bmj. 2013;346:f197.
9. Mavrelos D, Nicks H, Jamil A, Hoo W, Jauniaux E, Jurkovic D. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2013;42(1):102-7.
10. RCOG. Laparoscopic Management of Tubal Ectopic Pregnancy (Consent Advice No. 8). https://wwwrcogorguk/en/guidelines-research-services/guidelines/consent-advice-8/. 2010.

Figure Caption

Figr-1Figure 1

Flow Diagram of patients' progression through the study



USS findings N (%)	Surgery +ve N (%)	Specimen obtained for histology	Histo pos N (% spec obtained)	Salpingectomy			Salpingotomy			Conservative surgery		
				Histo pos N (%)	Histo neg N(%)	No histo N (%)	Histo pos N (%)	Histo neg N (%)	No histo N (%)	Histo pos N (%)	Histo neg N (%)	No histo N (%)
Embryo + cardiac activity n=154 (16.4)	**154 (100)**	153	152 (99.3)	136 (99.3)	1 (0.7)	0	14 (93.3)	0	1 (6.7)	2 (100)	0	0
Embryo – cardiac activity n= 43 (4.6)	**43 (100)**	43	42 (97.8)	37 (97.4)	1(2.6)	0	4 (100)	0	0	1 (100)	0	0
Gestational sac + yolk sac n=127 (13.5)	**125 (98.4)**	125	117 (93.6)	102 (93.6)	7 (6.4)	0	14 (93.3)	1 (6.70)	0	1 (100)	0	0
Gestational sac, no yolk sac n=200 (21.3)	**197 (98.5)**	197	188 (95.4)	164 (95.9)	7 (4.1)	0	23 (95.8)	1(4.2)	0	1 (50.0)	1(50.0)	0
Solid n=383 (40.7)	**380 (99.2)**	373	350 (94.1)	317 (94.1)	18 (5.3)	1 (0.6)	23 (85.2)	3(11.1)	2 (3.7)	10 (58.8)	2 (11.2)	4 (29.4)
Haemoperitoneum only n=34 (3.6)	**33 (97.0)**	31	29 (93.5)	28 (93.3)	2 (6.7)	0	1 (100)	0	0	0	0	2 (100)
Total 941	**932**	922	878 (95.2)	784 (95.5)	36	1	79 (90.8)	5	3	15 (62.5)	3	6

Table 1: USS findings, surgery and histological outcomes in 932 women with surgical confirmation of a tubal ectopic pregnancy at first surgery

Table 2: Comparison between clinical features, USS findings, surgery and final histological outcomes (n=925)

Clinical, USS or surgical parameter	Positive histology (n=881)	Negative histology (n=44)	Relative risk of negative histology (95% CI)	p
gestational age(days)^	45.0 (21-25)	41.0 (26-104)	-	0.032*
Size of ectopic (mm)^	20.0 (4-88)	15.0 (9-50)	-	0.035*
hCG (IU/l)^	2555 (5-174625)	964 (6-29690)	-	0.000*
Progesterone (nmol/l)^	26.0 (5-191)	28.0 (5-77)	-	0.296
Embryo with cardiac activity	152	1	0.1173 (0.0163 – 0.8457)	0.036*
Gestational ring	350	18	1.0479 (0.5830-1.8835)	0.876
Solid	350	23	1.9145 (1.0743-3.4115)	0.028*
Haemoperitoneum only	29	2	1.3733 (0.3480-5.4184)	0.651
Salpingectomy	787	36	0.558 (0.267-1.167)	0.123
Salpingotomy	79	5	1.279 (0.518-31.57)	0.593
Conservative surgery	15	3	3.675 (1.254-10.772)	0.018*

^median (range), * p<0.05