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COMPARISON OF MANAGEMENT REGIMENS FOLLOWING ULTRASOUND DIAGNOSIS OF NON-TUBAL ECTOPIC PREGNANCIES: A RETROSPECTIVE COHORT STUDY

SHORT TITLE: Management regimens for non-tubal ectopic pregnancies

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ABSTRACT

Objective

To review management options for non-tubal ectopic pregnancies.

Design

Retrospective cohort study.

Setting

Tertiary hospital in Melbourne, Australia.

Population

100 non-tubal pregnancies: 1 abdominal, 32 caesarean scar, 14 cervical, 41 cornual-interstitial, 12 ovarian.

Methods

Cases were classified according to ectopic site. Management categories were medical, surgical, combination or expectant. Use of minimally invasive approaches (ultrasound guided intra-sac injections or selective surgical techniques) was identified. Primary management was considered to be successful if no further unplanned interventions were required.

Main Outcome Measures

Success of primary management and frequency of unplanned interventions

Results

A high rate of success (82%) was demonstrated for all management regimens, with minimal morbidity and no deaths occurring. A high success rate was shown when the primary management regimen was systemic methotrexate or ultrasound guided intra-sac injection (88%). The success rate for primary surgical management was 57%. High success rates were reported for both primary management with ultrasound guided injections or in combination with systemic methotrexate (94%) and for primary management with systemic methotrexate alone (81%). Seventy-five percent of women managed with minimally invasive surgical approaches avoided the need for more extensive surgery, however required longer follow-up and additional interventions.

Conclusion

Minimally invasive approaches were found to be safe and effective treatment for women desiring to conserve fertility. Ultrasound guided intra-sac injection and laparoscopic ectopic removal procedures aimed at preserving reproductive organs should be included as minimally invasive primary management tools in addition to the well-recognised option of systemic methotrexate.

Funding

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TWEETABLE ABSTRACT

Non-tubal ectopics: minimally invasive procedures a safe alternative to surgery in selected cases.

KEYWORDS: ectopic pregnancy, methotrexate, ultrasound, minimally invasive

INTRODUCTION

The incidence of ectopic pregnancy is approximately one to two percent of all pregnancies, with implantation in the fallopian tubes the most common site. Non-tubal ectopic pregnancies are those that implant in sites other than the fallopian tubes and account for less than ten percent of ectopic pregnancies.[1] There has been an increasing incidence of these rare pregnancies, especially caesarean scar ectopic pregnancies.[2] Diagnosis and management of this potentially fatal condition poses a challenge for clinicians as they are frequently diagnosed later than other ectopic pregnancies and are associated with higher morbidity and mortality rates. Serious complications may be immediate or delayed and include life threatening haemorrhage, hysterectomy and death.[3]

The widespread use of transvaginal ultrasound with high resolution probes, accurate and rapid serum beta human chorionic gonadotrophin (β-hCG) assays and establishment of dedicated early pregnancy units have allowed for early diagnosis.[4] This has led to the progression from predominantly radical surgical management to more conservative, fertility sparing approaches

including minimally invasive surgery, medical therapy, ultrasound guided interventions, radiological interventions and even expectant management in selected cases.[3, 5, 6, 7]

Literature in this area predominantly comprises case reports and case series with only a few studies looking into optimal management protocols. Therefore, at present there is a paucity of evidence-based guidelines for the management of these challenging cases.[8, 9]

The objective of this study was to review management of non-tubal ectopic pregnancies in a tertiary referral hospital setting, with a particular focus on the success of various primary treatment modalities, including ultrasound guided intra-sac injection. We aimed to critically appraise the outcomes and guide an evidence-based approach to the management of these difficult conditions and ultimately contribute to development of clinical practice guidelines.

Methods

This is a retrospective audit of non-tubal ectopic pregnancies identified at The Royal Women's Hospital Melbourne, Australia. The hospital is a tertiary referral centre that managed 1811 ectopic pregnancies during the 11 year study period from November 2003 to November 2014. Cases were identified from an Ultrasound Picture Archiving and Communication System (PACS) report, using the search term 'ectopic'. All cases were reviewed and assigned a preliminary classification according to ectopic site based on ultrasound findings.

As a retrospective, anonymised audit project, this study met the criteria for quality assurance activities outlined by the National Health and Medical Research Council.[10]

Data was collected from Ultrasound PACS, electronic clinical reports and review of medical records. We examined demographics, previous pregnancy and gynaecological history, risk factors, clinical presentation, ectopic pregnancy sites, ultrasound and magnetic resonance imaging (MRI) findings, intended primary management and the actual management for these women. Length of inpatient stay and date of discharge from outpatient care were recorded. If the actual management differed from the intended primary management, the reasons for this change were noted. Complications were noted. β-hCG at presentation and maximum β-hCG level were recorded. For medical regimen

cases, the date of β-hCG resolution and ultrasound resolution were recorded. Collection and management of data was done using REDCap.[11]

Following complete investigation, including surgical and imaging findings, all non-tubal ectopic cases were classified according to ectopic site; cornual-interstitial, caesarean scar, ovarian, cervical and abdominal (Figure S1). Heterotopic pregnancies were classified according to the location of the non-tubal pregnancy site.

Ultrasound diagnosis was made on established diagnostic criteria for each of the non-tubal sites.[12-18] We acknowledge that while cornual and interstitial pregnancies are different entities, they have been grouped together as the terms were often used interchangeably. In all cases the diagnosis was confirmed by an experienced ultrasonologist including review of all images at presentation and subsequent ultrasounds. Women were counselled and managed by a team of gynaecologists and ultrasonologists: management options and treatment plans were individualised based on clinical, biochemical, and imaging findings and the desire for conserving fertility.

Treatment modalities included: medical (systemic and / or local intra-sac injection), surgical, combination (combined medical and surgical) or expectant regimens. Minimally invasive approaches included ultrasound guided intra-sac injections (USGI) or surgical techniques that selectively removed the ectopic trophoblastic tissue without permanent or functional loss of organs or structures. Systemic methotrexate doses were calculated as 1mg/kg intramuscular injection (IM). The protocol at our institution for USGI included transabdominal or transvaginal approaches depending on access, performed under local anaesthesia. The gestational sac was aspirated to mechanically disrupt the pregnancy before 50 mg of methotrexate was injected into the sac using an 18G CVS needle, followed by a saline flush; prior injection of 2 mls (30mmol/ml) of KCl was used to achieve asystole when embryonic heart activity was present. Follow-up for cases with medical or expectant management included weekly β-hCG levels. A single dose of systemic methotrexate was added for those cases where B-hCGs plateaued.

The main outcomes of interest were success of the primary management regimen and the frequency of further unplanned interventions. Primary management was considered to be successful if no further different, unplanned interventions were required.

Secondary outcomes were: success of minimally invasive approaches, time interval to discharge from all medical care, time interval to resolution (determined as achieving β-hCG levels <20 IU/l) and time interval to resolution on imaging for medically managed cases.

Frequency of complications for the different treatment regimens are described and statistically compared (odds ratio for all categorical variables and Mann-Whitney U Test for mean time to discharge from medical care).

All independent variables were considered for a binary logistic regression analysis on the likelihood of success for the primary management (1-successful; 0 –unsuccessful). A model was then created including only those characteristics which yielded a significant contribution. The Hosmer and Lemeshow test has been used to test the model for significance. Nagelkerke R2 was used to establish the amount of variance explained by the model.

RESULTS

During the study period 114 non-tubal ectopic pregnancies were diagnosed on ultrasound and managed at our hospital. Nine cases (7.9% of suspected cases) were subsequently excluded as they were found to be tubal ectopic pregnancies at surgery. One case of presumed caesarean scar ectopic who spontaneously miscarried was excluded as the exact pregnancy site was not able to be confirmed. Four cases were excluded as a result of incomplete follow-up, resulting in 100 eligible cases for the study.

Demographics and clinical characteristics

Ectopic site classification following complete investigation included: 1 abdominal, 32 caesarean scar, 14 cervical, 41 cornual-interstitial and 12 ovarian (Figure S2). Two heterotopic pregnancies occurred in the series, one cervical and the other an interstitial ectopic. Selected demographic and clinical characteristics are shown in Table 1.

<Table 1>

Four women had two consecutive non-tubal ectopic pregnancies and one had three during the study period. Each pregnancy was considered an individual case for purposes of the study. The majority of these women had repeat caesarean scar ectopic pregnancies.

Twenty-four women (24%) were asymptomatic and their diagnosis was considered to be an incidental finding; many were diagnosed on routine ultrasound assessment following ART (n=12). Three women conceived spontaneously and were asymptomatic, however presented for early assessment as they had a history of ectopic pregnancy.

The majority of non-tubal ectopics (72%) were diagnosed in the latter part of the study. Table S1 describes trends for ectopic sites during the study period.

Overall Management

Intended primary treatment regimens for these 100 cases were: 2 expectant, 83 medical, 14 surgical and 1 combination regimen. Actual management regimens for these 100 cases were: 1 expectant, 73 medical, 11 surgical and 15 combination regimen. Ninety-one percent of primary treatment regimens utilised minimally invasive approaches.

Management commenced prior to referral to our hospital in a small proportion of cases (n=7).

The primary management plan was successful in 82 (82%) of these 100 pregnancies: 64 had no complications and required no further intervention, 15 cases required additional interventions (systemic methotrexate doses, USGI) and three had unexpected complications arising from the

planned treatment. Table 2 describes the success of management by primary treatment regimen for each ectopic site.

<Table 2>

Approximately two thirds (64%) of cases were managed following exactly the primary plan. The frequency of additional or unplanned interventions was 36%; of these, 16 cases needed a surgical procedure, with the remaining being managed with additional medical or USGI approaches.

Eighteen cases (18%) required a different, unplanned intervention and their primary management plans were considered unsuccessful. Sixteen of these unsuccessful cases (89%) required surgical procedures not included in the primary management plan.

For these 18 cases with unsuccessful management:

- Eight cases required surgery following failed medical treatment for rupture, haemorrhage or persistently elevated β-hCG levels.
- Two were subsequently found to have placental site/trophoblastic tumours and both required hysterectomy.
- Three cases had failed surgical management prior to referral to our hospital.
- Two surgical regimen cases required subsequent systemic methotrexate for persistently elevated β-hCG levels.
- One case thought to be abdominal on imaging was found at surgery to be located in a non-communicating atrophic horn of the uterus requiring a different, unplanned procedure (resection).
- A caesarean scar case, deemed likely to resolve spontaneously (β-hCG at presentation 6 IU/l), was managed expectantly; however required surgical management for persistent bleeding.
- One caesarean scar case with suspected placenta accreta chose to continue with the pregnancy against medical advice, requiring an emergency caesarean-hysterectomy at 24 weeks gestation.

Logistic Regression Analysis

A binary logistic regression model was performed for treatment success. All independent variables were considered for inclusion in the model. Maternal age, maternal BMI, parity, smoking status, trophoblastic mass size and presence of a heartbeat did not yield a significant fit and were therefore not included in the final model. β-hCG at presentation was included in the model but did not make a significant contribution in the prediction of treatment success. According to the Hosmer and Lemeshow test, the final binary logistic regression model was statistically significant: $\chi 2(8) = 19.015$, $p = 0.015$. The model explained 24% of the variance in success of the primary management for ectopic pregnancy and correctly classified 88% of cases. The maximum β-hCG level was significant to the model but did not affect the odds of the outcome for the primary management. Gestational age in days was significant to the model: an increase in the gestational age in days was associated with a reduction of the likelihood of success of the primary management (Table S3).

Systemic methotrexate

Systemic methotrexate was included in the primary management for 75 cases, however was included in the actual management for 83. The mean IM dose for single dose systemic methotrexate was 80mg (range 50 – 100mg; n = 25). The mean total dose for multidose systemic methotrexate was 288mg (range 120 – 602mg; n = 57) and the median number of doses was four (range 2 – 9 doses).

Ultrasound Guided Intra-sac Injection

Forty-two (42%) of the 100 cases had USGI included in their management; 18 cases had intra-sac methotrexate, 22 cases had both KCl and intra-sac methotrexate, and two cases had only intra-sac KCl. The use of this approach peaked in 2012-2014 when it was used in 61% of cases (Table S2).

Ectopic site classification for these 42 cases included: 19 caesarean scar, 6 cervical and 17 cornual-interstitial ectopic pregnancies, including two heterotopic pregnancies.

Most doses of USGI were administered transvaginally (n=25 or 60%). Seventeen cases (40%) had transabdominal administration. The mean dose of methotrexate used for USGI was 38mg (range 7-70 mg).

Of the 42 cases, USGI was included in the primary management for 36 cases. The six remaining cases had USGI following systemic methotrexate for rising β-hCG levels, increasing fetal size or persistent heartbeat. Table 3 compares the success of management for cases with USGI and those managed with systemic methotrexate.

<Table 3>

All eight cases with planned USGI as the primary management were considered to be successful; three of these cases with caesarean scar ectopic pregnancies required a single dose of systemic methotrexate for plateauing β-hCG levels as per protocol.

Of the 28 cases of USGI commenced in conjunction with systemic methotrexate; 22 cases were considered successful and did not require any further intervention, two were considered successful but required further doses of systemic methotrexate for persistent β-hCG levels, two were considered successful but experienced unexpected complications (pneumonia, blood loss requiring transfusion), two cases were considered unsuccessful and further unplanned management was required. One of these unsuccessful cases was a caesarean scar ectopic with rising β-hCG levels: ectopic rupture occurred and emergency uterine wedge resection was performed. The other unsuccessful case was a caesarean scar ectopic requiring total abdominal hysterectomy and salpingectomy for a placental site tumour.

Surgical management

Primary surgical management was planned for 14 women, however was eventually undertaken for 25. Four (29%) of these 14 women were clinically unstable and required urgent surgical procedures. One multigravida aged 47 with an unplanned pregnancy did not wish to preserve fertility and had primary surgical management. Three (22%) had failed surgical procedures performed externally

before referral to the study site. Six (43%) were clinically stable but were considered complex and directed towards primary surgical management.

Subsequent unplanned surgical management was required for 13 women: two women with primary surgical management, 11 women with primary medical or expectant management.

To preserve fertility a minimally invasive surgical approach of selective enucleation or resection of the ectopic trophoblastic tissue was the primary procedure for five cases. Four of these five women required further management:

- Two required systemic methotrexate for plateauing β-hCG levels.
- One ovarian ectopic initially managed externally required salpingo-oophorectomy.
- A primigravida with a ruptured cornual-interstitial pregnancy required multidose systemic methotrexate for rising β-hCG levels and a laparoscopic wedge resection for residual trophoblastic tissue four months after treatment commenced.

Three further cases were successfully treated with minimally invasive surgical procedures as an additional, unplanned treatment: two cornual-interstitial ectopics following multidose systemic methotrexate and one caesarean scar ectopic managed expectantly.

Combined Management

Combined management was planned for only one woman with a cervical heterotopic pregnancy, however was eventually undertaken for 15 cases (n=15%). Ten arose from the primary medical regimen group; the additional four stemmed from the primary surgical regimen group.

Treatment Length

Time to discharge from all medical care, including outpatient follow-up, was known for 94 cases (Table 1). The mean time to discharge for the primary medical regimen group (n=79) was not significantly different to those (n=14) with a primary surgical approach (U = 377.5, p = 0.059).

Complications

Complications according to the different treatment regimens are described in Table 4. Hysterectomy was required for seven women and the clinical details of these particular cases are described in Table S4.

<Table 4>

Subsequent Pregnancies and Fetal Anomalies

In our cohort of 100 cases, 42 women were known to have 52 subsequent pregnancies: 46 intrauterine, six repeat non-tubal ectopics, no tubal ectopics occurred. Three intrauterine pregnancies were affected by a fetal anomaly: one trisomy 15, one absent ductus venosus, one skeletal anomaly.

DISCUSSION

Main Findings

This study reviews the management of women diagnosed with non-tubal pregnancies in different anatomical sites, analysing the efficacy of different treatment regimens.

A high rate of success (82%) is demonstrated for all management regimens, with minimal morbidity and no deaths occurring following the diagnosis of these complex pregnancies.

The primary management in stable women was predominantly conservative, with minimally invasive approaches comprising 90% of cases; 83 women managed medically, two managed expectantly, one with combined USGI and minimally invasive surgical management and four others with minimally invasive surgical procedures.

For women who were clinically unstable or did not wish to preserve fertility, surgical procedures were chosen as primary management (10%).

This study supports the emerging evidence[9, 19] that minimally invasive approaches are safe and effective treatment options for non-tubal ectopic pregnancies in women desiring to conserve fertility. Higher success rates were shown when primary management was systemic or intra-sac injection (88%) when compared with primary surgical management (57%); this result was found to be statistically significant.

This study offers additional insights into the role of USGI and minimally invasive surgical procedures, aimed at preserving reproductive organ structures and function. This series highlights the possibility of including them as tools in addition to the well-recognised option of systemic methotrexate. This is supported by the similarly high success rates reported for primary management with USGI alone or in combination with systemic methotrexate (94%) and for primary management with systemic methotrexate alone (81%). In addition, seventy-five percent of the eight women managed with minimally invasive surgical approaches avoided more extensive surgery; some however, required lengthy follow-up and additional management with systemic methotrexate.

To our knowledge this is the largest case series (n=42) of consecutive non-tubal ectopic pregnancies where USGI has been used as part of the management plan. USGI was shown to play an important role in the management of women with caesarean scar, cervical and cornual-interstitial pregnancies.

We compared the success rates according to anatomical site for all medically managed cases and reported a higher success rate (94%) for cases managed primarily with USGI alone or when used in conjunction with systemic methotrexate as compared to 81% for cases managed with systemic methotrexate alone. The benefit of subsequent USGI for the six failed cases (with persistently elevated β–hCG levels or a growing live fetus) is illustrated by the 100% rate of success. This is in

keeping with observations from other large series (Doubilet et al.[20], Verma et al.[5]), which reported similar rates of successful outcomes .

Forty-two women achieved a subsequent pregnancy following this potentially catastrophic diagnosis and three were affected by a fetal anomaly. The pregnancy diagnosed with skeletal anomaly was conceived 3 weeks following treatment for an ovarian ectopic with systemic methotrexate.

Currently there is no consensus on how long to wait to conceive after the use of methotrexate. At our institution the suggested interval between methotrexate administration and a new pregnancy is four months. In view of the increased possibility of fetal anomalies if conception happens soon after the administration of methotrexate, we recommend these women should undergo detailed early fetal anomaly scans.

Strengths and Limitations

To our knowledge this is one of the largest series of consecutive non-tubal ectopic pregnancies treated predominantly by minimally invasive approaches, including a significant proportion of cases managed with USGI.

Limitations of this study include its retrospective nature and a relatively heterogeneous approach to similar clinical presentations, especially in earlier years where management plans were less well structured.

We acknowledge a potential for selection bias as more unstable or urgent cases may have been directed towards surgical treatment, therefore resulting in relatively poorer outcomes for this treatment regimen group.

It is also valid to observe that the study spans over 11 years, a period in which technological advances have favourably impacted diagnostic and treatment modalities such as ultrasound and laparoscopy.

During this eleven year period we documented an increment in the total number of non-tubal ectopic cases and in particular of caesarean scar ectopics. This rise in frequency was accompanied by a corresponding increase in the choice of USGI as the primary treatment regimen in all ectopic sites.

Unfamiliarity with these infrequent ectopic pregnancies can lead to misdiagnosis and suboptimal management[5]. Twenty-four cases were referred to our hospital after failed treatment, following inability to locate the pregnancy or following failed termination of pregnancy. This contributed to a delay in diagnosis and advancing gestational age increases risks and complexity of care.

Interpretation

Our success rates for the conservative management of non-tubal ectopic pregnancies are in keeping with similar studies. [5, 9]

The cornual-interstitial group (41%) and the caesarean scar ectopic group (32%) were the largest groups in this series. The high incidence reflects the rising caesarean section rates, increasing rates of ART, advances in ultrasound technology and increasing availability of early ultrasound to diagnose these cases.[5, 21] Both these groups were predominantly managed medically with a success rate of 86% and 88% respectively; these results are similar to other series in the literature.[19, 22]

Seven of the 100 women in this series required hysterectomy (7%); within these cases, caesarean scars were the most common ectopic site (n = 5; 71%). Similar rates of hysterectomy are reported in other series including Petersen et al. [23] (6%).

The major criticisms of medical management include lengthy follow-up, prolonged bleeding or haemorrhage, risk of persistent trophoblastic disease and risk of rupture even after β-hCG levels decrease.[19, 22] These criticisms are supported in our study: two cases required hysterectomy following unexpected rupture; lengthy follow-up in cases managed medically (mean time to β-hCG resolution 52 days; mean time to ultrasound resolution 144 days). Four cases had residual lesions

months after resolution of β-hCG, prompting surgical intervention in two, who were subsequently found to have placental site or trophoblastic tumours and required hysterectomy.

CONCLUSION

Non-tubal ectopic pregnancies may be safely treated by minimally invasive procedures in selected cases. USGI and surgical procedures aimed at preserving reproductive organ structures and function should be included as primary management tools in addition to the well-recognised option of systemic methotrexate. These options are relevant for women desiring to conserve fertility. The disadvantages may be the longer resolution times, the risk of residual trophoblastic disease and need for unplanned surgery.

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Study data were collected and managed using REDCap electronic data capture tools hosted at The University of Melbourne[11]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

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Disclosure of interests

None declared. The ICMJE disclosure forms are available as online supporting information.

Contribution to authorship

RPD, JR, CA, GK and KR all contributed to the study design, data collection, analysis, and interpretation. JR, KR and RPD wrote the manuscript. RPD, CA, GK critically reviewed the manuscript for accuracy and intellectual content.

Details of ethics approval

Human Research and Ethics Committee (HREC) approval for a retrospective anonymised audit project that met the criteria for quality assurance activities outlined in the National Health and Medical Research Council guideline 'Ethical Considerations in Quality Assurance and Evaluation Activities'[10] was obtained . Correspondence confirming this was received from The Royal Women's Hospital HREC on 21/10/2014 .

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Table 1: Selected Demographic & Clinical Characteristics of Subjects (n= 100)

Variable	Cases n (%) Mean/Median	Min.	Max.
Median maternal age	34.81	20.10	47.48
Median gravida	3.00	1	13
Median parity	3.00	0	6
History of tubal ectopic pregnancy	10		
History of non-tubal ectopic pregnancy	7		
Previous caesarean section multigravida women (n=79)	36 (46%)		
History of pelvic inflammatory disease (PID)	5		
Infertility	28		
Assisted reproductive techniques	22		
Intrauterine device 'in situ' conception	-		
Previous miscarriages (n=99)*	33 (33.34%)		
Previous surgical termination of pregnancy (n=99)*	29 (29.3%)		
History of other uterine surgery	13		
History of other pelvic or abdominal surgery	23		
History of endometriosis	4		
History of uterine fibroids	6		
History of congenital uterine abnormality	3		
Presentation following unsuccessful termination of pregnancy	6		
Mean gestational age at diagnosis (weeks)	7.38	4.57	11.14
Mean trophoblast mass at diagnosis (largest diameter mm) (n=98)*	25.13	4.30	100.00
Mean fetal CRL† at diagnosis (mm) (n=47)*	9.38	2.00	55.00
Fetal cardiac activity present at diagnosis (n=99)*	32 (32.32%)		
Median β-hCG at presentation IU/l (n=98)*	7 566	6	666 818
Median maximum β-hCG IU/l (n=96)*	10 139	6	666 818
Mean days to resolution of β-hCG (n=78)*	52	4	150
Mean days to resolution on ultrasound (n=18)*	144	7	398
Mean treatment length surgical regimen cases (days to discharge all care) (n=14)	49	6	152
Mean treatment length medical regimen cases (days to discharge all care) (n=79)*	63	4	401

* data not available or applicable for all cases

† crown rump length(CRL)

Table 2: Success of Primary Management by Ectopic Site

Site of ectopic	total cases by site (n)	median gestational age (weeks)	primary management expectant		primary management medical (systemic / local)		primary management surgical	
			n	successful n (%)	n	successful n (%)	n	successful n (%)
Abdominal	1	5.430	-	-	-	-	1	0 (0%)
Caesarean scar	32	6.710	2	0 (0%)	29	25 (86%)	1	1 (100%)
Cervical	14	6.785	-	-	14*	12 (86%)	-	-
Cornual or interstitial	41	7.000	-	-	35†	31 (89%)	6‡	4 (67%)
Ovarian	12	7.215	-	-	6	6 (100%)	6	3 (50%)
Total cases all sites	100		2	0 (0%)	84	74 (88%)§	14	8 (57%)§

* includes the primary combination regimen case with heterotopic intrauterine and cervical ectopic pregnancy that was principally managed with intra-sac injection in combination with a uterine artery coil embolization procedure to prevent complications

† includes 1 heterotopic intrauterine and cornual ectopic pregnancy

‡ includes management of 1 ectopic located in a non-communicating uterine horn; considered unsuccessful as an unplanned extension of the surgical procedure was required.

§ statistically significant difference (p = 0.01 OR= 0.18) between the success rates of the planned management medical regimen group (n=84), and surgical regimen group (n=14) using two sided Fishers exact test.

Table 3: Comparison of Success for Intra-sac and Systemic Medical Management by Ectopic Site

Site of ectopic	total medical management cases by site	primary management ultrasound guided injection with/without systemic methotrexate		primary management systemic methotrexate only		primary management systemic methotrexate with subsequent ultrasound guided injection	
	n	n	successful n (%)	n	successful n (%)	n	successful n (%)
Abdominal	–	–	–	–	–	–	–
Caesarean scar	29	16	14 (88%)	10	8 (80%)	3	3 (100%)
Cervical	14	6*	6 (100%)	8	6 (75%)		
Cornual or interstitial	35	14†	14 (100%)	18	14 (77%)	3	3 (100%)
Ovarian	6	–	–	6	6 (100%)	–	–
Total all sites	84	36	34 (94%)‡	42	34 (81%)‡	6	6 (100%)‡

* heterotopic live intrauterine and live cervical ectopic pregnancy; local injection of methotrexate and KCL to both cervical and intrauterine pregnancies with systemic single dose methotrexate and performed with surgical procedure of uterine artery coils/embolisation.

† includes 1 heterotopic failed intrauterine and live cornual ectopic pregnancy; local injection of methotrexate and KCL to cornual ectopic and systemic multidose methotrexate.

‡ no statistically significant difference (p = 0.177, OR = 3.4) between the success rates of the primary management ultrasound guided injection with/without systemic methotrexate (n=36), and combined primary management systemic methotrexate only and primary management systemic methotrexate with subsequent ultrasound guided injection (n=48) regimens using two-sided Fisher's exact test.

Table 4: Frequency of complications according to treatment regimen and comparison between medical and surgical groups

	total cases (n=100)	primary management medical (n=84)	primary management surgical (n=14)		primary management expectant (n=2)
	n	n (OR = 1)	n	OR (95% CI)	n‡
Hysterectomy	7	5	1	0.82 (0.09-7.62)	1
Rupture during course of treatment	4	3	1†	0.48 (0.05-4.99)	-
Blood transfusion or excessive bleeding requiring treatment	13	10	2	0.81 (0.16-4.16)	1
Admission to ICU or Complex Care	3	1	1	0.16 (0.01-2.66)	1
Unplanned hospital admission	30	25*	5	0.76 (0.23-2.50)	-
Residual trophoblastic lesion or tumour	4	3	1	0.47 (0.05-4.87)	-
Specific surgical complications	2	-	2	-	-
Side effects from systemic methotrexate	25	25	-	-	-

* includes combined management heterotopic case managed with USGI and uterine artery embolization

† ruptured before planned surgery was able to be performed

‡ expectant case numbers too small for a meaningful statistical comparison