


Management and reproductive counseling in cervical, caesarean scar and interstitial ectopic pregnancies over 11 years: identifying the need for a modern management algorithm

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STUDY QUESTION: Do management strategies (treatment type and order), including provision of reproductive counseling, differ in patients with non-tubal pregnancies?

SUMMARY ANSWER: Medical and surgical treatment strategies varied widely for each type of non-tubal pregnancy and reproductive counseling in this patient population is lacking.

WHAT IS KNOWN ALREADY: Owing to the rarity of non-tubal pregnancies, there is no consensus regarding treatment strategies or protocol. Furthermore, there is limited data on how patients with a non-tubal pregnancy are counseled about future fertility.

STUDY DESIGN, SIZE, DURATION: This is a descriptive retrospective study. Data were collected from January 2006 to December 2017. A total of 50 patients were included in the study.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Patients with an ultrasound diagnosis of a non-tubal ectopic pregnancy (e.g. cervical ectopic pregnancy [CEP], Caesarean scar pregnancy [CSP] or interstitial ectopic pregnancy [IEP]) were included. This study was performed at a university-based institution tertiary referral center. Demographic and clinical characteristics, treatment type and order, reproductive counseling and outcomes were collected. Descriptive statistics were used for analyses.

MAIN RESULTS AND THE ROLE OF CHANCE: Of the 50 patients identified, 13 were CEP (26%), 8 were CSP (16%) and 29 were IEP (58%). Patients with a CSP had a higher parity (median = 3, $P = 0.02$) and number of prior Caesarean deliveries (mean = 2.1, $P < 0.001$). A total of 66% (23/35) of patients expressed a desire for future fertility prior to treatment and only 56% (28/50) of patients received reproductive counseling according to the electronic medical records. Among all non-tubal pregnancies, there were variations in the type and the order of treatments that patients received.

LIMITATIONS, REASONS FOR CAUTION: This study was performed in a tertiary referral center therefore the management strategy could have been influenced by the prior interventions and patient response. The descriptive retrospective design precluded any assumption of causation.

WIDER IMPLICATIONS OF THE FINDINGS: The management for non-tubal pregnancies has wide variations. Reproductive counseling in this patient population is lacking. The findings highlight the need for the development of a treatment algorithm and a reproductive counseling protocol for each non-tubal pregnancy to better standardize treatment strategy.

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Key words: ectopic pregnancy / reproductive decision making / non-tubal pregnancy / implantation / female tract

WHAT DOES THIS MEAN FOR PATIENTS?

Ectopic pregnancies are pregnancies that occur outside the womb and can affect future chances of childbearing. Usually found in the fallopian tubes, they may also occur in other locations within the pelvis as 'non tubal' ectopic pregnancies. These can be treated in a number of ways, but there is no agreement on which is the best option or on how women should be advised about future pregnancy. The authors analysed records from women with non-tubal ectopic pregnancies treated in their own hospital and found a wide variation in treatment. Two thirds of the women were keen to have children but only half received advice about future fertility. Our findings highlight the need to develop a standard way of treating non-tubal pregnancy and providing guidance on how best to try for a family in the future.

Introduction

Ectopic pregnancies account for ~2% of all pregnancies (Prameela and Dev, 2016; American College of Obstetricians and Gynecologists, 2018). Generally, 95% of ectopic pregnancies are found in the fallopian tube but the incidence of non-tubal pregnancies ranges from 5.0% to 8.3% of all ectopic pregnancies (Shen et al., 2014; Prameela and Dev, 2016). Although uncommon, non-tubal pregnancies can be found in the cervical canal, within a Caesarean scar or in the interstitial portion (intramural) that traverses the uterine musculature. The frequency of cervical ectopic pregnancies (CEPs) accounts for <1% of all ectopic pregnancies (Kirk et al., 2006), while Caesarean scar pregnancies (CSPs) and interstitial ectopic pregnancies (IEPs) may represent up to 4.2% (Petersen et al., 2016) and 2–11% of all ectopic pregnancies, respectively (Shen et al., 2014; Petersen et al., 2016).

CEPs are diagnosed usually by a transvaginal ultrasound with trophoblastic invasion into the endocervical tissue and a closed internal cervical os (Zakaria et al., 2011). CSPs are described as pregnancies implanted either entirely within the myometrial defect or manifested with a portion of the trophoblast extending into the myometrial defect, diagnosed by ultrasound or MRI (Zosmer et al., 2015). IEPs are diagnosed when embryo implantation occurs in the uterine interstitium, the area continuously surrounded by the myometrium (Kahramanoglu et al., 2017). Many strategies exist for treatment of non-tubal pregnancies including but not limited to intramuscular methotrexate, potassium chloride intra-amniotic injections, uterine artery embolization, hysteroscopy, laparoscopy, double-balloon catheter, expectant management, internal iliac artery ligation and a hysterectomy. Given the complex nature of non-tubal pregnancies and the many different treatment options that exist, the reasoning for a selected management strategy may depend on surgeon skill/comfort level, overall clinical picture and serum beta-hCG. For example, in a systematic review of CSP literature, there were 31 reported different treatment modalities used, including medical, surgical and radiological treatment and single or a combination of methods (Timor-Tritsch and Monteagudo 2012; Timor-Tritsch et al., 2016).

Due to the rarity of non-tubal pregnancies, there is no consensus regarding treatment strategies or protocol for CEP, CSP or IEP management (Timor-Tritsch and Monteagudo, 2012). Furthermore, there is limited data on how patients with a non-tubal pregnancy are counseled about future fertility; there is insufficient data on safety in regards to a future pregnancy after certain treatment options (i.e. uterine artery embolization; Committee on Gynecologic Practice, 2004). Assessing fertility goals prior to treatment and monitoring pregnancy outcomes following treatment of non-tubal pregnancies can be valuable information when counseling future patients about different treatment options.

Understanding key differences in implemented management strategies and recognizing the importance of pre-treatment reproductive counseling can better inform and guide physicians. The purpose of this study was to investigate the differences in management strategies (treatment types and order) and assess if reproductive counseling was performed in patients with non-tubal pregnancies.

Materials and Methods

The institutional review board approved this descriptive retrospective study analyzing patients at a university-based institution with two tertiary referral centers from January 2006 to December 2017. Non-tubal pregnancies were categorized into three groups: CEP, CSP and IEP. Any patients with an ultrasound diagnosis of a CEP, CSP or IEP were included.

Diagnostic transvaginal ultrasound criteria used for CEP included empty uterine cavity, dilated/barrel shaped cervix, gestational sac within endocervical canal and below the internal os, increased doppler flow around cervix (Shen et al., 2014; Parker and Srinivas, 2016). Criteria used for CSP included no fetal parts in the uterus or cervix without contact with the gestational sac, gestational sac in the anterior isthmic portion covering the scar site or entirely embedded within the myometrium and absence of an interface between the bladder and gestational sac (Shen et al., 2014; Parker and Srinivas, 2016). Criteria used for IEP included empty uterine cavity, interstitial line (i.e. echogenic line between the gestational sac and endometrial cavity) and gestational sac in the intramyometrial portion of the fallopian tube continuously surrounded by the myometrial wall (Shen et al., 2014; Parker and Srinivas, 2016). Patients' demographic data, treatment type and order, desire for future fertility, reproductive counseling performed, complications from treatment and pregnancy outcomes were collected from the electronic medical record (EMR).

Descriptive statistics were used to report all variables of interest. Continuous variables were compared using the ANOVA or Kruskal-Wallis test as appropriate, whereas categorical variables were compared using Fisher exact test. A *P*-value of <0.05 was considered significant. All statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 50 patients identified, 13 were CEP (26%), 8 were CSP (16%) and 29 were IEP (58%). Table 1 presents the demographic characteristics and clinical profile. There was no significant difference in the age at diagnosis, BMI, IVF, tobacco use, prior ectopic pregnancy

Table I Demographic characteristics and clinical profile of the 50 patients in a study of non-tubal pregnancy.

Characteristics	CEPN = 13	IEPN = 29	CSPN = 8	P
Race/ethnicity - n (%)				0.02
White	5 (38.5)	1 (4.0)	4 (50.0)	–
Black	3 (23.1)	14 (56.0)	2 (25.0)	–
Hispanic	3 (23.1)	8 (32.0)	1 (12.5)	–
Other	2 (15.4)	2 (8.0)	1 (12.5)	–
Gravidity - median (IQR)	3 (1–4)	4 (3–5)	4 (3–5)	0.26
Parity - median (IQR)	1 (0–1)	2 (1–3)	3 (2–3.5)	0.02
Gestational age at diagnosis (weeks) - mean (SD)	6.6 (2.0)	7.3 (1.8)	8.4 (2.6)	0.15
Fetal heart tones present - n (%)	8 (61.5)	9 (31.0)	6 (75.0)	0.05
Mean sac diameter visualized - n (%)	9 (69.2)	18 (64.3)	8 (100.0)	0.15
Prior caesarean deliveries – mean (SD)	0.6 (1.4)	0.3 (0.5)	2.1 (0.8)	<0.001

CEP: cervical ectopic pregnancy, CSP: caesarean scar pregnancy, IEP: interstitial ectopic pregnancy, IQR, interquartile range.
Statistical test: Fisher exact test, ANOVA (mean), Kruskal Wallis test (median)

Table II Reproductive counseling that was documented in the EMR.

Fertility data	CEP N = 13	IEP N = 29	CSP N = 8	P
Desired fertility prior treatment (n = 35) - n (%)	6/8 (75.0)	14/22 (63.6)	3/5 (60.0)	0.89
Documented reproductive counseling in EMR - n (%)	4 (30.8)	19 (65.5)	5 (62.5)	0.11
Attempted conception post treatment (n = 30) - n (%)	3/11 (27.3)	3/15 (20.0)	1/4 (25.0)	0.99
Live birth post treatment (n = 30) - n (%)	2/11 (18.2)	2/15 (13.3)	1/4 (25.0)	0.82

EMR: electronic medical record
Statistical test: Fisher exact test

or prior pelvic surgery (dilation and curettage, cold knife cone or loop electrosurgical excision procedure) among the three groups of non-tubal pregnancies. IEP patients were more likely African American, while CSP and CEP were more likely White. Compared to CEP and IEP patients, parity (median = 3, $P = 0.02$) and the number of prior Caesarean deliveries (mean = 2.1, $P < 0.001$) were significantly higher in CSP patients. Overall, 26% of all patients had at least one prior pelvic surgery and the average number of prior ectopic pregnancies was 0.30. A total of 10 patients were referred from outside centers that were correctly diagnosed with a non-tubal pregnancy but no patient was successfully treated prior to arrival. All i.m. methotrexate injections used in this study were single dose (50 mg/m²).

Table II presents the reproductive counseling documented in the EMR. Overall, 56% (28/50) of patients received pre-treatment reproductive counseling. A total of 66% (23/35) of documented patients expressed desire for future fertility prior to treatment. A total of 23% (7/30) attempted conception after resolution of the non-tubal pregnancy, which resulted in five live births (CEP = 2, IEP = 2 and CSP = 1).

Table III presents the types of treatments given. Patients with a CEP were significantly more likely to have a uterine artery embolization, a dilation and curettage or receive a higher number of methotrexate injections. Patients with a CSP were significantly more likely to have a hysterectomy performed. Patients with an IEP were more likely to have a wedge resection.

In patients with a CEP, the majority received multiple different treatments or surgeries in varying orders (Table IV). Among them, four patients received treatment at an outside hospital prior to being transferred to our institution for higher level of care. Five patients experienced complications including hemorrhage requiring blood transfusions, sepsis, persistent beta-hCG, Asherman syndrome and cervical insufficiency.

Similar to CEP, CSP patients also received mixed medical and surgical treatments (Table V). Of the eight CSP patients, two patients received treatment at an outside hospital before being admitted to our institution. All three patients that underwent a hysterectomy were less than 15 weeks gestation and had a hemorrhage requiring a blood transfusion. Of the three patients who received a hysterectomy, one desired future fertility, one had finished childbearing and one had no documentation regarding her desire for future fertility. Two other patients were readmitted to the hospital for further treatment because of an inappropriate decline in their beta-hCG; one patient received methotrexate and the other received an intra-amniotic potassium chloride injection.

Table VI presents various types of surgeries that IEP patients received. Among 29 IEP patients, 4 received a treatment at an outside hospital. A total of 6 patients had a hemorrhage required a blood transfusion, 13 patients were converted from a diagnostic laparoscopy to an exploratory laparotomy, 1 patient was readmitted for a persistent beta-hCG and 1 patient underwent a hysterectomy.

Table III Types of treatments used.

Types of treatments	CEP N = 13	IEP N = 29	CSP N = 8	P
Uterine artery embolization - n (%)	7 (53.8)	0 (0)	2 (25.0)	<0.001
Number of MTX Injections - mean (SD)	1 (0.6)	0.3 (0.5)	0.6 (0.7)	0.0008
KCL intra-amniotic injection - n (%)	3 (23.1)	0 (0)	2 (25.0)	0.01
Suction dilation and curettage - n (%)	5 (38.5)	0 (0)	1 (12.5)	0.001
Hysterectomy - n (%)	1 (7.7)	1 (3.4)	3 (37.5)	0.03
Laparoscopic wedge resection + US - n (%)	–	2 (6.9)	–	–
Laparotomy wedge resection + US - n (%)	–	18 (62.0)	–	–
Laparotomy wedge resection + BS - n (%)	–	2 (6.9)	–	–
Laparotomy wedge resection + USO - n (%)	–	2 (6.9)	–	–
Foley balloon tamponade - n (%)	–	–	1 (12.5)	–

MTX, methotrexate; KCL, potassium chloride;

US, unilateral salpingectomy; BS, bilateral salpingectomy; USO, unilateral salpingoophorectomy

Statistical test: Fisher exact test, ANOVA (mean)

Table IV Order of treatments in patients with CEP.

CEP (N = 13)	
Order of treatments	Number of patients
1: D&C	1
1: KCL*, 2: UAE*, 3: MTX, 4: D&C	1
1: MTX	5
1: MTX, 2: UAE, 3: D&C	1
1: MTX*, 2: KCL*, 3: D&C/intra cervical balloon	1
1: MTX*, 2: MTX*, 3: UAE	1
1: MTX, 2: UAE	1
1: MTX*, 2: UAE, 3: KCL, 4: MTX	1
1: UAE, 2: Hysterectomy (elective)	1

D&C, dilation and curettage; KCL intra-amniotic injection; UAE, uterine artery embolization

*Treatments received at an outside hospital

Table V Order of treatments in patients with CSP.

CSP (N = 8)	
Order of treatments	Number of patients
1: D&C → Hysterectomy/BS (PAS)	1
1: Laparotomy (ectopic not visualized), 2: MTX	1
1: Foley balloon tamponade	1
1: Hysterectomy/BS (PAS)	2
1: MTX*, 2: KCL	1
1: MTX, 2: UAE	1
1: MTX*, 2: UAE, 3: KCL	1

PAS, placenta accreta spectrum; KCL intra-amniotic injection

*Treatments received at an outside hospital

Table VI Order of treatments in patients with an IEP.

IEP (N = 29)	
Order of treatments	Number of patients
1: Hysterectomy	1
1: Laparotomy wedge resection + USO	2
1: Laparotomy wedge resection + US	16
1: Laparotomy wedge resection + BS	2
1: MTX	4
1: MTX*, 2: Laparotomy wedge resection + US	2
1: MTX*, 2: Laparoscopic wedge resection + US	2

*Treatments received at an outside hospital

Discussion

Our study demonstrated that medical and surgical treatment strategies varied widely for each type of non-tubal pregnancy. Furthermore, many of these patients desired future fertility but there was no documentation in the EMR that reproductive counseling was provided to these patients.

Many multiparous patients had a high percentage of Caesarean deliveries and prior ectopic pregnancies. Continued efforts to reduce primary Caesarean deliveries are necessary in preventing repeat Caesarean deliveries and the potential for ectopic pregnancies. From 1996 to 2007, the Caesarean delivery rate in the USA rose by 53% (from 21% to 32%; [Timor-Tritsch and Monteagudo, 2012](#)). After 2007, this rate increased to peak at 32.9% in 2009, then declined to 31.9% in 2016 ([Martin et al., 2018](#)). While the rate of Caesarean deliveries has somewhat declined in recent years, the rate remains high.

Providing every patient with a non-tubal pregnancy with reproductive counseling is important as the information gathered in these discus-

sions can serve as an informative factor when deciding which treatment route to select. In addition, counseling on future pregnancy outcomes relies on previous case reports and literature reviews (Timor-Trisch and Monteagudo, 2012). Standardizing counseling may be beneficial for the patient and physician by means of providing clear, organized information, clarifying expectations and follow-up and addressing implications for future pregnancies.

Many of the treatments that were performed in our study population are consistent with the current literature (Shen *et al.*, 2014). In CEP patients, a few complications occurred in patients with more than one treatment or more technically challenging procedures. A total of 48% of the IEP patients had to be converted because of the clinical situation or surgeon preference. The majority of IEP patients have a laparotomy but laparoscopy can be performed with a surgeon who feels comfortable with this approach (Fylstra, 2012). With CSP, having the appropriate radiologic evidence (i.e. transvaginal ultrasound, MRI) can be vital when deciding which treatment to proceed with, especially when a placenta accreta spectrum is suspected. The success of each treatment could not be measured because of loss to follow up or inadequate charting.

In addition to the treatments or surgeries mentioned in our findings, there are other treatments noted from other studies that may be useful in certain patients. Timor *et al.* (2016) reported using a double-balloon catheter for both CEP and CSP with positive results in a small sample size. Hysteroscopic resection may be possible in appropriate IEP patients (Alalade *et al.*, 2017). Ultrasound-guided surgical evacuation in early CSP patients is another treatment modality to be considered (Jurkovic *et al.*, 2016; Harb *et al.*, 2018).

Prior studies by others that examined different case studies and cohorts to evaluate different treatments for non-tubal pregnancies also observed variations in management strategies applied. For example, Timor-Trisch and Monteagudo (2012) reported that in 184 CSP patients, 31 different treatments were performed. However, given the rare occurrences of non-tubal pregnancies, there is no protocol or algorithm for physicians to follow (Chetty and Elson, 2009; Alalade *et al.*, 2017). Our study helped our institution assess baseline demographics and clinical profiles as well as variations in management strategy over the years and highlighted the need for all patients to be appropriately and proactively counseled about impact on future fertility.

Some limitations in our study included the descriptive retrospective design, which precluded any assumption of causation. Given that our institution is a tertiary referral center, 20% of the patients were transferred for higher level of care but had already received one or more treatments at an outside hospital. Therefore, our management strategy could have been influenced by the prior interventions and patient response. This may have created a more challenging scenario for providers at our institution versus treating a patient from an initial encounter. Loss to follow up occurred with 23 patients (46%), which may be attributed to the tertiary referral center, with some patients residing in distant cities or being uninsured. Also, our institution treats a high volume of patients that requires many providers; 30 different physicians were involved in patient care creating variations in treatment strategies that were likely dependent on physicians' comfort level, experience or surgical ability. In the future, having designated physicians to take care of this patient population may reduce variations in management strategies. The data collected for

desire in future fertility, reproductive counseling, attempting conception and live birth were limited by the retrospective design of the study. Some physicians may have performed reproductive counseling with their patients but failed to provide documentation in the EMR. Some patients were admitted because of a surgical emergency, which may have limited discussion on future fertility. Within the 11-year study period, management options may have changed, which could contribute to observed variations. Future studies are needed to survey patients with non-tubal pregnancies to assess perception and effectiveness of reproductive counseling and treatments being performed.

Despite the limitations, our study had several strengths. To the best of our knowledge, this was one of the first studies to assess desire for future fertility in patients with non-tubal pregnancies and examine if they received reproductive counseling. Having different specialties at our institution allowed for many treatments or surgeries to be performed that may not have been feasible at a community or non-academic-based institution.

Our study demonstrates that the management for non-tubal pregnancies has wide variations. In addition, reproductive counseling in this patient population is lacking. Our findings highlight the need for development of a treatment algorithm and counseling protocol for each type of non-tubal pregnancy in a multidisciplinary fashion to help standardize treatment strategy. This could give physicians a framework when choosing treatment strategies for patients with non-tubal pregnancies.

Authors' roles

J.S.S., S.N., R.P., P.P., P.B., A.J. and A.B. conceptualized the work and designed the study. J.S.S. and S.N. collected data. H.Y.C. performed statistical analysis. J.S.S. reviewed analysis and drafted manuscript. All authors participated in manuscript revision. All authors approved the final version of the article.

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Conflict of interest

The authors have no conflict of interest.

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