

Laparoscopic management of ectopic pregnancies: a comparison between interstitial and “more distal” tubal pregnancies

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Abstract

Background/aims Laparoscopy is an established, safe, and feasible management option for tubal pregnancies, even in women with significant hemoperitoneum. In case of interstitial pregnancy, however, a laparoscopic surgical approach is still a matter of debate. The objective of this study is to evaluate the safety and feasibility of a laparoscopic approach to interstitial pregnancies.

Methods A total of 92 women with ectopic pregnancy who underwent a surgical management from April 2009 to August 2015 were reviewed. Clinical and surgical outcomes of confirmed interstitial pregnancies ($n = 10$) (IP group) were compared with those of “more distal” tubal pregnancies ($n = 79$) (TP group).

Results Although there were no differences between the two groups in gestational age, β -hCG values were significantly higher in the IP group ($p = 0.005$). All patients with IP were treated by laparoscopic wedge resection. The rate of surgical complications ($p = 0.413$) and subsequent MTX treatment ($p = 0.531$) were not significantly different between groups. Operating room (OR) time ($p = 0.007$) was higher in the IP than in the TP group. After stratification for the presence of hemoperitoneum this

difference remained, with patients in the IP group having longer OR time ($p = 0.034$) and additionally higher intraoperative blood loss (EBL) ($p = 0.013$). On the other hand, in the absence of hemoperitoneum no differences between the two groups were observed.

Conclusions In experienced hands, the laparoscopic management of interstitial pregnancies seems to be as safe and feasible as that of other tubal pregnancies. However, it could be technically more challenging, especially in case of hemoperitoneum.

Keywords Ectopic pregnancy · Extrauterine pregnancy · Interstitial pregnancy · Cornual pregnancy · Laparoscopy

Introduction

Ectopic pregnancy mainly occurs in the Fallopian tubes and still remains one of the major causes of maternal mortality worldwide [1]. The fallopian tube is divided into four sections: the interstitium, the isthmus, the ampulla, and the infundibulum, which run proximally to distally and ectopic pregnancy can occur in any of these regions. The interstitial segment which is the most proximal one, traverses the uterine wall and communicates via the tubal ostium with the uterine cavity [2].

Interstitial pregnancy (IP) is a rare subtype of ectopic pregnancy that accounts for 2–4 % of all ectopic pregnancies [3] and because of its location at the junction between uterine and ovarian vessels its rupture can cause severe bleeding. There is a taxonomic confusion with regards to the terms IP, cornual pregnancy, and angular pregnancy. In the literature, IP and cornual pregnancy are often used as synonyms [1]. However, an IP is a pregnancy occurring in the interstitium of the tube, a cornual

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pregnancy occurs in one horn of a bicornuate uterus, or, by extension of meaning, in one lateral half of a septate uterus, whereas an angular pregnancy is an implantation of the embryo just medial to the uterotubal junction, in the lateral angle of the uterine cavity [4–11]. These differences are not only taxonomic but have a clinical implication: IPs are non-viable pregnancies, whereas cornual and angular pregnancies are viable since they can possibly result in a live-born baby [12].

Although the laparoscopic management of tubal pregnancies (TP) is an established, safe, and feasible treatment strategy even in women with significant hemoperitoneum [13], the traditional treatment for IP has been laparotomy, often requiring hysterectomy. A laparoscopic approach has traditionally been avoided due to late diagnosis, fear of uncontrolled bleeding, and the technical difficulty in reconstructing the cornual region. In the last decades the availability of more sensitive β -hCG assays and transvaginal ultrasound (TVUS), which allowed an earlier diagnosis of IP, as well as the advanced techniques in minimally invasive surgery opened new horizons of therapy [8]. We recently described a new technique to treat IP which is efficient and effective [14]. To prove the safety and feasibility of laparoscopy in IP, we compared the surgical outcome of the laparoscopic management of IP with that of other “more distal” TP in a predefined period of time in our University Hospital.

Methods

Our report was prepared according to the “Strengthening the reporting of observational studies in epidemiology” guidelines [15]. A retrospective analysis of all surgically treated extrauterine pregnancies managed at the Department of Obstetrics and Gynecology, University of Bern from April 2009 to August 2015 was performed. The study was IRB approved (Nr: 295/15).

Patients were included in the study if they underwent surgery either directly after diagnosis of IP or TP or subsequently to a failed conservative treatment. Exclusion criterion was completed conservative treatment either with expectant management or with methotrexate (MTX). Patients treated with laparotomy or who had non-tubal extrauterine pregnancies were excluded from the final statistical analysis.

The diagnosis of IP was hypothesized based on the sonographic findings and was confirmed via intraoperative identification of the pregnancy as an asymmetric bulge in one of the uterine angles lateral to the insertion of the round ligament (IP group). If the pregnancy was inserted in the

isthmus, the ampulla, and the infundibulum segments of the salpinx, it was defined as tubal pregnancy (TP group).

Patients with TP were chosen as a control group since the laparoscopic management of TP is undisputed and their surgical outcome can therefore be considered as a standard to which laparoscopic management of IP should be compared.

Demographic and clinical data, TVUS, laboratory exams, indication for surgery, and type of surgery with related outcomes were retrieved from patients’ computer-based medical records, as were data on future pregnancies if available. Shock index (SI) was calculated by dividing pulse rate by the systolic blood pressure as previously described [16]. Serum β -hCG level was measured with cobas-e601 fully automated electrochemiluminescence immunoassay analyzer (Roche, Germany) in the routine diagnostic laboratory.

Hemoperitoneum was quantified based on the reported total blood aspirated immediately after the laparoscopic access and before starting the intervention. Intra-operative blood loss (EBL) was estimated by the surgeons in each case by subtracting the volume of irrigation fluid from the total fluid aspirated during the surgery. Total blood loss was calculated adding the hemoperitoneum quantity and the EBL.

Management

In our institution the management of IP and TP included systemic MTX treatment if β -hCG was lower than 5000 mIU/ml, if severe clinical symptoms and signs were absent and after informed consent of the patient [17, 18]. In most cases of asymptomatic tubal pregnancy and β -hCG lower than 1000 mIU/ml an expectant management was followed [19]. In the other cases or after failure to respond to a second dose of MTX a surgical therapy was indicated.

All surgeries were performed using a standard technique and were video recorded. TP was treated with salpingectomy, salpingostomy or milking technique according to the size of the pregnancy, the damage of the tube, the concomitant blood loss, and the patient’s desire for future pregnancy. In cases of salpingostomy diluted noradrenalin was injected previously in the mesosalpinx, as the use of vasopressin or pitressin is not recommended for this indication in Switzerland.

For all IP a laparoscopic wedge resection as recently described was performed [14]. Briefly, a 1–0 monofilament encircling suture was placed deep into the myometrium around the base of the interstitial pregnancy and diluted noradrenalin was injected circumferentially (Fig. 1). Then, the basis of the ectopic pregnancy was excised with

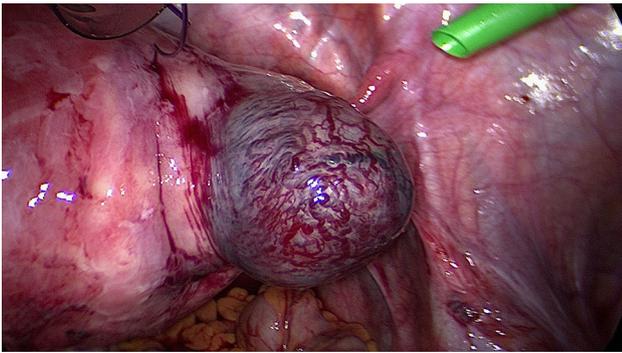


Fig. 1 Encircling suture around the base of the interstitial pregnancy

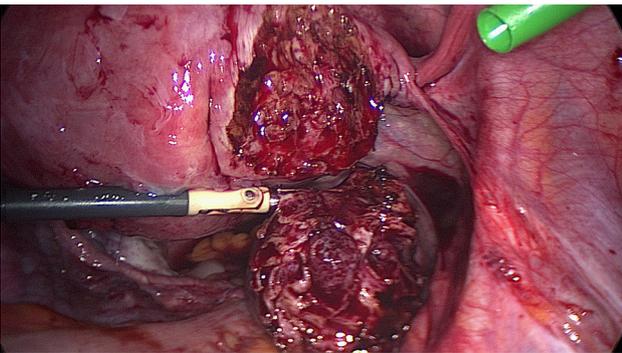


Fig. 2 Excision of interstitial pregnancy

monopolar point diathermy and the embryonal mass including a thin part of myometrium surrounding it resected (Fig. 2). The encircling suture was tied extracorporeally to prevent heavy bleeding. The uterine wound was finally closed with single mattress sutures using a 2–0 braided suture (Fig. 3). The salpinx distal to the ectopic pregnancy was also resected and the removed specimens extracted in an Endobag through the 10 mm port.

Statistical analysis

An available case analysis was performed. Mean values \pm standard deviation (SD) were calculated for continuous variables and percentages for the nominal variables. The variables of patients with IP and TP were analyzed and compared. To compare the two groups, the Student's *t*-test was used for continuous and Fisher's exact test or χ^2 test for nominal variables. Potential factors influencing operating room (OR) time and total blood loss such as age, BMI, previous surgeries, presence of IP, days of pregnancy, β -hCG value, and SI were entered into a multiple regression analysis as independent variables. Categorical data were entered as dummy variables. Statistical analysis was performed using the statistical package StatView (v 5.01.98; SAS Institute Inc, Cary, NC). A *p* value of <0.05 was considered significant.

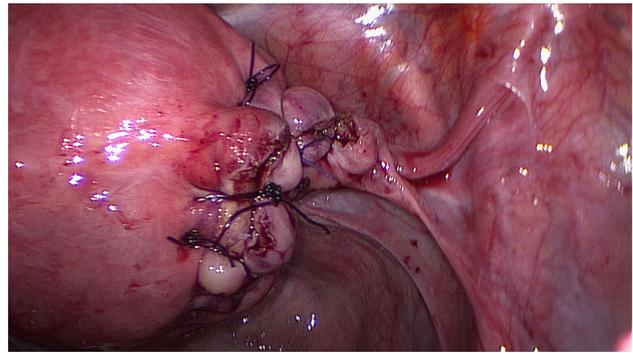


Fig. 3 Uterine wound at the end of the surgery

Results

A total of 92 surgically treated extrauterine pregnancies were identified. All patients except one (99 %) were treated laparoscopically with no need of conversion to laparotomy. One patient (1.1 %) with ruptured tubal pregnancy, stupor state, and a shock index of more than two at admission was treated in the emergency room via emergency laparotomy. Ten (10.9 %), 79 (85.9 %), and 2 (2.2 %) patients had an interstitial (IP group), a tubal (TP group), and an ovarian ectopic pregnancy, respectively. The patient undergoing an emergency laparotomy and the patients with ovarian ectopic pregnancies were excluded leaving 89 cases for statistical analysis.

Sixty-two patients (69.7 %) presented with hemoperitoneum associated with hemodynamic instability and were therefore operated in emergency. Twenty-seven patients (30.3 %) had no hemoperitoneum and were operated either because of severe pain (19 patients), or failure of or refusal to MTX medical treatment (8 patients).

Patients' characteristics as well as clinical and laboratory parameters at admission are reported in Table 1. Data retrieved from patients' computer-based medical records were available for more than 95 % of the examined outcomes. Patients with TP had more often hemoperitoneum as compared to patients with IP but SI and hemoglobin level at admission did not differ among the two groups. Moreover, although there were no differences between the two groups with regards to gestational age, β -hCG values were significantly higher in the IP group ($p = 0.005$). Finally, there were significantly more women with previous ipsilateral salpingectomy in the IP group ($p < 0.0001$).

Women with hemoperitoneum had a higher SI (0.79 ± 0.25 vs. 0.63 ± 0.11 , $p = 0.008$) and a lower hemoglobin at admission (115.53 ± 18.21 vs. 124.22 ± 12.57 g/l, $p = 0.027$) compared to those without. Furthermore, the SI was directly correlated with the volume of hemoperitoneum ($R = 0.639$, $p < 0.0001$).

Table 1 Patient characteristics in the two groups of patients

	IP (<i>n</i> = 10)	TP (<i>n</i> = 79)	<i>p</i>
Age (years)	34.50 ± 6.21	31.72 ± 5.40	0.135
BMI (m/kg ²)	24.91 ± 3.88	23.74 ± 5.06	0.485
Previous pregnancies	2.60 ± 1.58	2.19 ± 1.57	0.439
Previous deliveries	1.00 ± 1.05	0.85 ± 1.03	0.661
Previous ectopic pregnancies	2 (20 %)	8 (10.1 %)	0.352
Previous ipsilateral salpingectomy	4 (40 %)	0 (0 %)	<0.0001
Previous contralateral salpingectomy	1 (10 %)	4 (5.1 %)	0.523
Patients with previous abdominal laparotomies	4 (40 %)	20 (25.3 %)	0.324
Number of laparotomies (range)	(1;1)	(1;3)	0.254
Patients with previous abdominal laparoscopies	3 (30.0 %)	15 (19.0 %)	0.414
Number of laparoscopies (range)	(1;2)	(1;3)	1.000
β HCG (mIU/ml)	27,634 ± 35,198	8998 ± 16,123	0.005
Days of pregnancy	53.25 ± 16.79	46.11 ± 14.70	0.208
Side of ectopic pregnancy			
Right (%)	4 (40 %)	43 (54.4 %)	
Left (%)	6 (60 %)	36 (45.6 %)	0.389
Previous treatment with methotrexate	2 (20.0 %)	16 (20.3 %)	0.985
Hemoperitoneum	4 (40 %)	58 (73.4 %)	0.030
Shock index	0.74 ± 0.19	0.75 ± 0.24	0.904
Hemoglobin (g/l)	121.50 ± 12.11	117.75 ± 17.66	0.516

Data are presented as *n* (%), or mean ± standard deviation of the mean. Significant *p* values are marked bold

IP interstitial pregnancy, TP other tubal pregnancy

Table 2 Variables of clinical interest in the two groups of patients

	IP (<i>n</i> = 10)	TP (<i>n</i> = 79)	<i>p</i>
OR time (min)	115.40 ± 34.16	80.94 ± 37.55	0.007
Without hemoperitoneum (<i>n</i> = 27)	109.00 ± 74.57	74.57 ± 36.74	0.061
With hemoperitoneum (<i>n</i> = 62)	125.00 ± 17.32	83.28 ± 37.89	0.034
EBL (mL)	137.00 ± 178.64	99.30 ± 179.70	0.536
Without hemoperitoneum (<i>n</i> = 27)	83.33 ± 155.13	108.50 ± 123.85	0.683
With hemoperitoneum (<i>n</i> = 62)	217.50 ± 203.04	71.60 ± 99.72	0.012
Number of patients receiving blood transfusions	3/10 (30 %)	13/79 (16.5 %)	0.293
pRBC units received	2.33 ± 1.53	2.00 ± 0.76	0.845
Lowest hemoglobin during recovery (g/l)	91.57 ± 19.48	96.67 ± 17.34	0.464
Length of hospitalization (days)	2.67 ± 1.00	2.39 ± 0.84	0.364
Subsequent MTX treatment <i>n</i> (%)	0/10 (0 %)	3/79 (3.8 %)	0.531

Data are presented as *n* (%), or mean ± standard deviation of the mean. Significant *p* values are marked bold

IP interstitial pregnancy, TP other tubal pregnancy

All patients with IP were treated by laparoscopic wedge resection. In six patients an ipsilateral salpingectomy was performed as well. In the other four patients, who had already undergone a salpingectomy, the tubal remnant was removed. In the TP group 45 (57.0 %) women were treated with salpingectomy, 27 (34.2 %) with salpingostomy, and 7 (8.9 %) with the milking technique, respectively.

OR time was significantly higher in the IP than in the TP group (*p* = 0.007). After stratification for the presence of

hemoperitoneum this difference remains, with patients in the IP group having significantly longer OR time (*p* = 0.034) and additionally higher EBL (*p* = 0.013) as compared to patients in the TP group. On the other hand, in the absence of hemoperitoneum no differences between the two groups were observed (Table 2).

In the multiple regression analysis OR time was found independently related (*p* = 0.029) to the presence of interstitial pregnancy (R² = 0.046), the days of pregnancy

($R^2 = 0.115$), and the β -hCG value ($R^2 = 0.169$). Total blood loss was independently related only to the SI value ($R^2 = 0.322$, $p < 0.0001$).

Four (5.1 %) surgical complications were reported in the TP group: one case of bladder injury caused by a suprapubic trocar and treated with intraoperative suture, one case of postoperative fever treated with antibiotics and two cases of subsequent laparoscopy, 1 and 4 weeks later due to bleeding at the location of the previous salpingostomy, without further complications. Three (11.1 %) of the patients in the TP group treated with salpingostomy presented persistent β -hCG values postoperatively and required subsequent MTX treatment. No complications were observed in the IP group and none required subsequent MTX treatment. The rate of surgical complications ($p = 0.413$) and subsequent MTX treatment ($p = 0.531$) were not significantly different between groups.

Subsequent intrauterine pregnancies were documented in 3 out of 10 (30 %) and in 14 out of 79 (17.7 %) patients in the IP and TP group, respectively. From the three pregnancies in the IP group one resulted in an elective repeat cesarean section at 38 weeks, one in an uneventful spontaneous delivery at 40 weeks and one in a pregnancy termination according to the mother's will. However, data considering this outcome were available only in 31 (39 %) patients.

Discussion

Among 92 women with ectopic pregnancy requiring surgical treatment, all but one have been managed laparoscopically, regardless of their location, amount of hemoperitoneum, and hemodynamic instability. Within this cohort, it was found that in the absence of hemoperitoneum, a laparoscopic approach resulted in similar clinical and surgical outcome in IP and TP. However, in the presence of hemoperitoneum, which is a sign of ruptured ectopic pregnancy, laparoscopic management of IP was characterized by longer OR time and higher EBL. No complications and no need for subsequent methotrexate treatment were observed in the IP group.

The difference in OR time has to be attributed to the higher complexity of the TP surgery but also in part to the intraoperative recruitment of a more experienced surgeon in some of the cases. In the multiple regression analysis OR time was also influenced by gestational age and β -hCG value but not by BMI or previous abdominal surgeries. This is not surprising since the higher the gestational age and β -hCG values are, the higher the risk of rupture and the more complicated the surgery becomes.

Total blood loss was independently related only to SI which in turn was directly correlated with the volume of

hemoperitoneum at the time of diagnosis. This implies that total blood loss should be attributed mainly on the presence of hemoperitoneum and barely on EBL. Moreover, although in cases with hemoperitoneum EBL is significantly higher in the IP than in the TP group, this difference per se is clinically not very important.

Patients with IP were less likely to have hemoperitoneum than patients with TP. Given its peculiar location, it could be supposed that IP causes a hemorrhage only after an erosion of both the wall of the tube and the surrounding myometrium by the trophoblast. This could lead to a reduced rate of hemoperitoneum at very early gestational age and at the same time to heavier bleeding during surgery and after rupture. Moreover, the specific location of IP could facilitate a better growth of the pregnancy thus explaining the higher β -hCG values found compared with TP at the same gestational age.

Patients presenting with IP had previously been subjected to ipsilateral salpingectomy in 40 % of the cases. Prior damage to the fallopian tube secondary to previous pelvic or abdominal surgery, and pelvic infection are known risks for ectopic pregnancy and recurrent IP [20].

No intraoperative or postoperative complications were recorded in the IP group treated with the laparoscopic wedge resection technique and an acceptable rate was recorded in the TP group. The persistent β -hCG rate after salpingostomy (11.1 %) requiring subsequent MTX treatment is similar to previous published data [21]. In the IP group, on the contrary, there was no need for adjuvant medical treatment. The reason for this might be that according to the operation technique described a small amount of myometrium surrounding the IP is resected. Therefore, the trophoblast is always excised in toto.

In our series, IP accounted for 11 % of the ectopic pregnancies treated surgically. This is two to threefold higher than that reported in the literature [3, 22, 23] and is likely related to the fact that our Department is a tertiary referral center where the more complex cases are referred to.

In the largest series on laparoscopic management of interstitial pregnancies, including 53 patients, Ng et al. report mean surgical time of 67 min and mean EBL of 500 ml taking into account that no encircling suture was used [22]. In our series OR time is longer, however, 40 % of the patients with IP presented with hemoperitoneum and some degree of hemodynamic instability as compared to 15 % in the series of Ng et al. Furthermore, all patients in our study underwent a wedge resection as compared to 62 % of the patients reported by Ng et al. Further surgical treatment in this study included cornuostomy and salpingectomy in 24.5 and 13.2 % of the cases, respectively. Altogether, we believe that our patient population represents a population at higher surgical risk given the higher

rate of hemoperitoneum and higher rate of need for wedge resection.

Various preventive measures designed to reduce the blood loss during the removal of an IP are reported, such as injection of diluted vasopressin [22, 24, 25], use of an endoloop [25] and temporary ligation of the uterine arteries [26]. In our institution, the current laparoscopic technique was introduced in 2009 and since then it has been used systematically in every case. A similar technique has also been proposed by Aust et al. and by Cuccinella et al. [27, 28]. The main difference which we consider a specific advantage of our technique is that during the resection the encircling suture is held loose, thus permitting a deeper wedge resection and complete removal of ectopic pregnancy. The suture is tied only after the wedge resection to prevent excessive bleeding. As mentioned above this might be the reason why no persistent β -hCG values were documented in our series on the contrary to 17 % in the series of Ng et al.

In a retrospective analysis Hwuang et al. compared the outcome of patients with IP undergoing wedge resections via laparotomy and laparoscopy in 54 and 34 cases, respectively [29]. Surgical outcomes were comparable among the two groups with mean OR time of 71 and 88 min, EBL of 400 and 500 ml, and transfusion rates of 46 and 38 % for the laparotomy and laparoscopic group, respectively. Our data correlate well with these, confirming the laparoscopic performance in the management of IP, even in case of rupture.

It is unclear whether the risk of uterine rupture after the surgical management of an IP is increased but given the full-thickness nature of the wedge resection a risk similar to that after laparoscopic myomectomy can be presumed. Consequently, some surgeons recommend planned cesarean section. In our and other series uncomplicated spontaneous deliveries have been reported [22]. However, in a subsequent pregnancy, when labor occurs, we recommend to monitor it strictly and to keep a high index of suspicion for uterine rupture.

The major limitations of this study include its retrospective nature and the relatively small sample size. On the other hand, the structured surgical approach to IP, the control group including other “more distal” tubal pregnancies, and the almost complete data availability for each measured outcome represent its strengths. Finally, randomizing patients to laparoscopy versus laparotomy would have provided the most reliable form of scientific evidence to evaluate the safety and feasibility of a laparoscopic approach to IP. However, considering the associated benefits of laparoscopy, a randomization of patients to laparotomy would not have been ethically appropriate in a clinic where laparoscopic management of IP is already the first-choice treatment. In this case, the

comparison of outcomes with a cohort of patients undergoing an established laparoscopic surgery for TP during the same time period represents the only reasonable way to examine the feasibility and safety of a laparoscopic approach to IP.

In conclusion, the laparoscopic management of IP has similar surgical outcomes as compared with that of TP implying that laparoscopic IP surgery could be as safe and feasible as laparoscopic TP surgery. In case of rupture, however, laparoscopic IP management is characterized by longer OR time and higher EBL. We believe that this is more related to the nature of the disease than to the surgical approach. Thus, laparoscopy should be favored for the management of these patients when adequate surgical expertise, along with blood bank and intensive care unit are available.

Compliance with ethical standards

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Conflict of interest The authors KN, AP, GG, BMc, DB, and MDM declare that they have no conflict of interest.

Ethical standards All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study was IRB approved (Nr: 295/15).

Informed consent Since this is a retrospective study no informed consent was obtained from the participants included in the study.

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