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Elective uterine artery embolization prior to laparoscopic resection of interstitial pregnancy: two cases and literature review

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Abstract

Background: Interstitial pregnancies (IP) can be treated medically or surgically. The most common complication remains hemorrhage. The risk of that may be reduced by elective uterine artery embolization (UAE) prior to surgery, which we applied in two consecutive cases with high vascularization on ultrasound. We also reviewed larger series ($n \geq 10$) on medical as well as surgical management of IP on success and complication rates and reviewed the entire literature on UAE.

Results: A gravida 5 (two ectopic pregnancies treated by salpingectomy) para 1 (cesarean section complicated by a niche, earlier repaired) presented with an asymptomatic IP. Primary treatment consisted of systemic methotrexate (MTX). Because of raising β-hCG and persisting heart activity 1 week later, she was referred for surgery (β-hCG = 59,000 IU/L; CRL = 10.5 mm). Another gravida 5 para 3 presented with an asymptomatic evolutive IP on dating ultrasound. Because of the size (CRL = 24.5 mm), thin overlaying myometrium, and high β-hCG (121,758 IU/L), we opted for primary surgery. Both IPs were highly vascularized with high flow rates. To prevent bleeding, a bilateral UAE was performed. The surgery was nearly bloodless.
In the literature, a wide range of treatment regimens for IP is reported. Larger series report a success rate of 76% for primary systemic MTX, 88% for primary local medical treatment, and 94% for primary surgery. It was not possible to determine reliable hemorrhage or rupture rates following MTX administration. As to laparoscopic surgery, the blood transfusion rate for bleeding was 9% while the conversion rate for hemorrhage was 2%. The use of UAE to reduce the risk for hemorrhage before ($n = 2$) or after ($n = 19$) MTX administration was reported in 21 cases. This failed in two cases (90% success rate), and one patient required transfusion (5%). Two cases treated with UAE and primary surgery were reported, yet the exact indication for embolization was not elaborated. Alternative hemostatic techniques during surgical management have been proposed to reduce blood loss and operating time, yet individual outcomes were not identifiable.

Conclusion: We report on the use of elective UAE prior to laparoscopic resection of IP, because of signs of strong vascularization on ultrasound. This strategy coincided with a nearly bloodless operation. Literature review suggests that this is one of the effective methods to reduce blood loss intra-operatively.

Keywords: Ectopic pregnancy, Interstitial pregnancy, Embolization, Laparoscopy, Cornual resection, Cornuostomy

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Background

Ectopic pregnancy (EP) is any type of pregnancy in which the fertilized ovum implants outside the uterine cavity. The vast majority of EPs are situated in the fallopian tube, typically in the ampullary region (70%), less likely in the isthmic (12%), fimbrial (11%), or interstitial part (2–4%). Other uncommon locations include ovarian (1–3%), abdominal (< 1%), cervical (< 1%), rudimentary horn (< 0.5%), and cesarean scar pregnancies (1–3%) [1–4].

In 1989, EPs occurred at an estimated prevalence of 1–2% worldwide. This is two to three times higher than in 1970 [5]. The increase is presumably related to an increased prevalence of risk factors directly or indirectly leading to decreased tubal passage. The prevalence has since not significantly changed [6, 7].

Pregnancies that are situated in the interstitial portion of the fallopian tube are referred to as *interstitial* [8, 9]. The intramural or interstitial part of the tube is approximately 0.7 mm wide and 1–2 cm long, often with a tortuous course [8]. Interstitial pregnancies (IPs) are also referred to as "cornual," though some reserve this entity to pregnancies located within a rudimentary horn of an abnormal uterine cavity [8, 9]. While the generic risk factors displayed in Table 1 may also apply, specific risk factors to this type of EP are previous ipsilateral or bilateral salpingectomy, previous EP, in vitro fertilization, and tubal damage from previous EP [8]. Historically, the mortality rate of this condition was around 2.5%, which is approximately seven times higher than that of EPs in general. It is assumed that this can be explained by the greater expansion capacity at this location, the richer vascularization of the area, eventually leading to life-threatening hemorrhage when rupture occurs [8].

There is to our knowledge no consensus on the best treatment modality of IP. Herein, we provide a literature review which we did on the occasion of treating two patients with uterine artery embolization (UAE) immediately prior surgical treatment, because of an anticipated high risk for bleeding.

Two cases

A 28-year-old gravida 5 para 1 was referred for a second opinion on an evolutive IP. She had a history of a primary cesarean section for vasa previa, a spontaneous first trimester miscarriage, two EPs treated by salpingectomy, and a hysteroscopic cesarean scar niche repair. The latter niche repair was done because of ultrasound signs of fluid in the niche before starting in vitro fertilization (IVF) treatment. On hysteroscopy, blood and debris were confirmed and a repair was performed 4 months prior to the index event (IP). Control hysteroscopy 1 month after the procedure showed normal findings. The index pregnancy was by IVF. On early scan at 6 + 6 weeks, an IP was suspected. We confirmed this at 7 + 1 weeks to be a left IP with a gestational sac of 19 × 20 mm, CRL of 6.8 mm, β-hCG of 38,000 IU/L, and heart activity. There was no abdominal fluid. The referring center opted for a single-dose methotrexate (MTX) protocol (75 mg; 50 mg/m^2). She presented on day one post-injection with stinging and cramping abdominal pain, yet without hemodynamic impact or peritoneal signs. On day six post-injection, she was referred because of raising β-hCG and persisting heart activity, spotting, along with intermittent abdominal pain. Figure 1 displays the ultrasound, β-hCG, and hemoglobin findings over the reporting period. We decided to proceed with surgical intervention yet opted for prior bilateral UAE during the same general

Table 1 Risk factors of ectopic pregnancy [19–23]

Highly increased risk (OR = 4–40)	Moderately increased risk (OR = 2–20)
Previous tubal surgery	Infertility
Documented tubal pathology	Previous genital infections
History of EP	Multiple sexual partners
In-utero exposure to DES	
Use of IUD [22, 23]	
Minimally increased risk (OR = 1-4)	Other risk factors
Previous pelvic/abdominal surgery	Age (> 35–40 years)
Cigarette smoking	Assisted reproductive technologies
Vaginal douching	Anatomical uterine abnormality
Early age at first intercourse	Non-Caucasian
	Prior spontaneous or medically induced abortion

OR odds ratio, *EP* ectopic pregnancy, *DES* diethylstilbestrol, *IUD* intra-uterine device

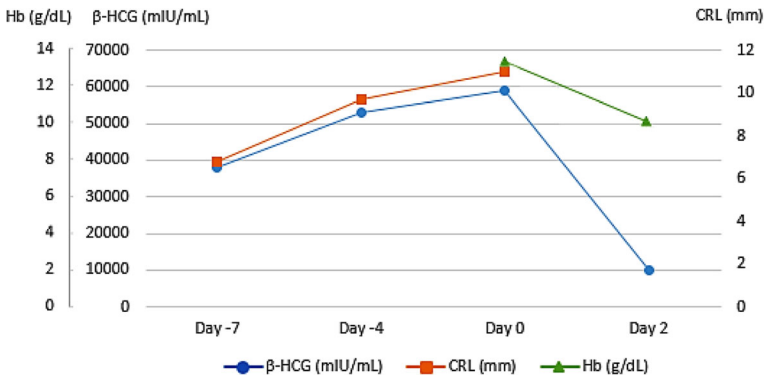

Fig. 1 Case 1: clinical, biochemical and ultrasound findings (day 0 = day of surgery)

anesthesia to reduce the risk for hemorrhage based on the apparent high vascularization around the pregnancy. Access was gained through the right femoral artery with catheterization of the left internal iliac artery followed by selective catheterization of the left uterine artery. Polyvinyl particles (Contour 250-350, Boston Scientific, Diegem, Belgium) were injected under 3D angiography control. The same procedure was followed on the contralateral side. Then, a laparoscopic cornual resection was performed and the uterine defect was closed in two layers using Vicryl 2-0 (Fig. 2). Blood loss was negligible, yet operating time was 140 min. Histopathology confirmed an IP. She was discharged on day two, and β-hCG became unmeasurable 4 weeks later. She had a withdrawal bleeding 3 weeks after the operation and had another period 5 weeks later. A waiting period of at least 6 months [10, 11] was advised to allow maximal healing of the uterus. She conceived 8 months after the IP in the first IVF cycle. She presented again with right fossa pain at 5 + 3 weeks, yet ultrasound confirmed an intracavitary position without any signs of IP.

A 32-year-old gravida 5 para 3 spontaneously conceived. She was referred because on elective dating ultrasound at 9 + 2 weeks a right evolutive IP was found. She had a history of a spontaneous first trimester miscarriage and three uncomplicated term vaginal deliveries. On ultrasound, the surrounding myometrium was 2.2 mm which was strongly vascularized (Fig. 3). Because of the size (CRL = 24.5 mm), the thin myometrial layer, and a β-hCG of 121,758 IU/L, we advocated immediate surgery, yet because of the vascularization we first offered bilateral UAE. Polyvinyl particles (Contour 355-500, Boston Scientific; Embosphere 500-700 and 700-900, Merit Medical, Brussels, Belgium) and spongostan plugs (Ethicon, Diegem, Belgium) were used (Fig. 4). On laparoscopy, a 6-cm pregnancy in the right uterine horn was observed. The pregnancy was removed by cornuostomy, and the myometrial defect was sutured in three layers (first V-loc 2-0, second and third Vicryl 2-0). Blood loss was negligible, and operating time was 180 min. Two months later she still had some brown vaginal discharge. Ultrasound showed normal findings with a strong proliferative endometrium along with a corpus luteum on the left ovary and a normal looking scar at the resection site. β-hCG was 3.2 IU/L.

Both patients explicitly consented to have their history being reported in the literature.

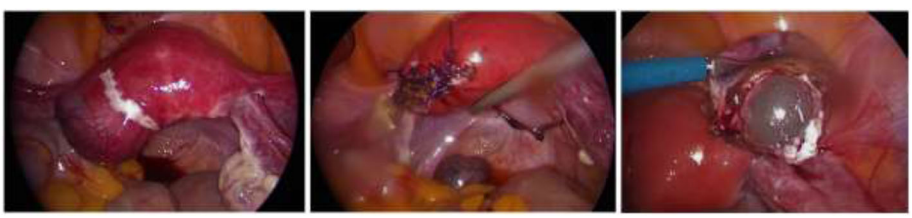

Fig. 2 Case 1: Left: left interstitial pregnancy, preventive coagulation around insertion line. Middle: status post cornual resection and closure of uterine defect with gestational sac in the pouch of Douglas. Right: gestational sac bulging out of resection piece

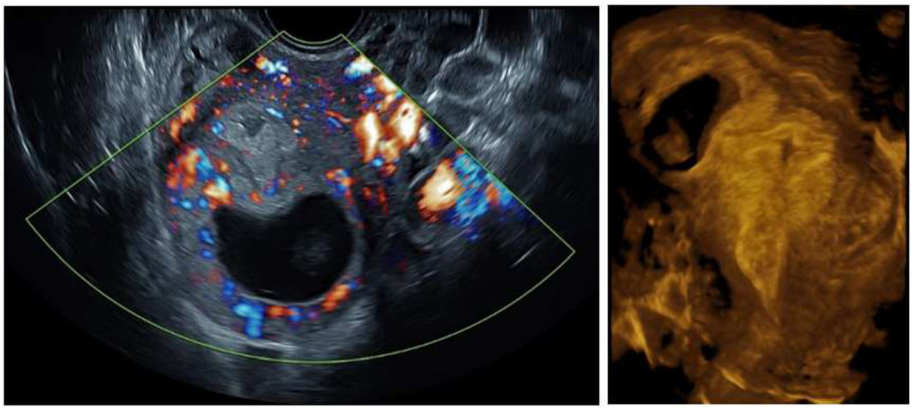

Fig. 3 Case 2: interstitial pregnancy on ultrasound: Left: 2D image showing high flow in the thin surrounding myometrium. Right: 3D rendered image showing the interstitial localization

Methods

For the literature review, we searched the PubMed on this matter, published until February 2018, using the following key terms "Pregnancy, Interstitial"[-Mesh], "Therapeutics"[Mesh], "Interstitial Pregnancy," and "Pregnancy Treatment" (953 papers). Sources of relevant articles in the references were screened as well (> 100 papers). All English-, French-, Dutch- and German-language articles were retrieved and screened on title and abstract for relevance (Appendix 1, 2, 3, 4, 5, and 6). Articles in which the location of the EP was unclear or in which the outcome was not clearly specified or objectively measured were excluded. We empirically decided to further discuss outcomes of series with 10 patients or more as to have reasonable denominators for calculating overall outcomes. The only exception to that was Table 4, which displays the entire published experience with UAE. There was not a single series with ≥ 10 patients treated with UAE.

Results

There is considerable experience with primary systemic medical therapy in asymptomatic hemodynamically stable patients with IP. Table 2 summarizes studies describing ten or more patients with IP treated by primary *systemic* MTX. Dosing and regimen of MTX are inconsistent, and success rates are typically over 70%, except in one series [12]. In case of failure (persisting β-hCG leading to additional treatment), surgery was offered, except in one series by Hiersch et al., where second-line local MTX was combined with UAE. Out of five patients, two still required surgery as a third step. Tanaka et al. described 33 cases treated with a very consistent scheme of slowly intravenously injected, yet a fixed dose MTX. The success rate was 94%; two patients required surgery. The opposite was true in the experience of Kim et al. (n = 30) administering intramuscular MTX, yet with an inconsistent dosing regimen. Sixteen (53%) required additional surgery.

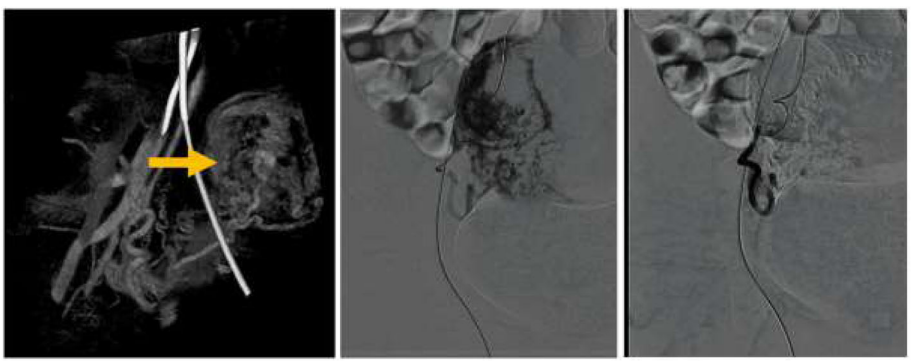

Fig. 4 Case 2: Left: 3D CT angiography after contrast injection in the right iliac artery visualizing the right interstitial pregnancy (arrow). Middle: before embolization of the right uterine artery. Right: after embolization of the right uterine artery

Table 2 Primary systemic MTX treatment of interstitial pregnancy

Author	*N*	Initial β-hCG	Systemic MTX treatment	Hospital stay	Negative β-hCG	Success
Jermy et al. [24]	17	32–31,381	50 mg/m^2 IM	0–40	3–13	16/17
Hiersch et al. [25]	14	15,764	1 mg/kg/d IM on day 1, 3, 5, 7	N/A	N/A	9/14
	3	< 2500	50 mg/m^2 IM	1	N/A	3/3
Tanaka et al. [26]	33	230–106,634	100 mg IV + 200 mg IV	1–4	3–19	31/33
Kim et al. [12]	5	375–102,970	1 mg/kg/d IM on day 1, 3, 5, 7	N/A	N/A	14/30
	24		50 mg/m^2 IM	N/A	N/A	
	1		100 mg IV in bolus followed by 200 mg IV	N/A	N/A	

N number of cases, *β-hCG* mIU/ml, *MTX* methotrexate, *IM* intramuscular, *IV* intravenous, *hospital stay* days, *negative β-hCG* weeks

Local injection of MTX, potassium chloride (KCL), etoposide, and actinomycin D under laparoscopic, ultrasound, or hysteroscopic guidance have all been reported as effective (Table 3 and Appendix 2). These injections are usually given into the gestational sac, occasionally in the surrounding myometrium or locally intra-arterial. These are invasive procedures, compared to systemic MTX. Benifla et al. used MTX for IP locations and KCl for heterotopic presentations, out of concerns for teratogenicity. Of the three eutopic pregnancies associated to a heterotopic location, two were eventually lost. Further details on outcomes are missing. The calculated success rate was 88%. Treatment failures were not offered a second MTX injection, yet successfully managed by surgery.

Table 4 displays reports on patients managed with *selective UAE* combined with any administration regimen of MTX. The actual indication for *secondary* UAE was refusal of surgery (Ophir et al., Yang et al.; each $n = 1$) or not mentioned (Deruelle et al., Tamarit et al., Berretta et al., Hiersch et al.). *Primary* UAE combined with MTX was either part of a standard protocol ($n = 9$; Krissi et al.) or because of the suspicion of increased risk for hemorrhage ($n = 1$; Valsky et al.). The paper does however not mention how that increased risk was estimated. Table 4 also includes two cases managed by UAE followed immediately by planned surgery (either laparoscopic or hysteroscopic). The argument for UAE was made based on increased vascularization on 3D CT angiography. In one of those two cases, a subsequent spontaneous conception and cesarean delivery of a healthy baby at 37 weeks was reported. Overall success rate in all the series in this table is 91%.

Table 5 displays the experience with *primary* surgery, typically by minimally invasive access. Success rate was 94%; transfusion need was 9%. Primary laparotomy was performed for tubal rupture, in case of severe adhesions (Tulandi et al.) or because of surgeon's preference (Hwang et al.). Conversions were because of significant hematoperitoneum or because of uncontrolled bleeding perioperatively ($n = 7$; 2%).

Discussion

Today the diagnosis of EP is usually made by ultrasound. In high-risk patients or countries where access to early ultrasound is easy, the diagnosis can be made *prior* to the development of symptoms. This allows careful planning of management. We surgically managed two cases of IP, which both were initially asymptomatic. One had typical risk factors and the other one did not. One had prior MTX therapy, and the second one had a very high β-hCG level. Both the ultrasound examination raised the suspicion of a highly vascularized lesion. Therefore, we decided to perform primarily bilateral UAE and surgery in the same anesthesia. This is different than the cases managed in Table 4. Though it is impossible to prove that UAE reduces the risk for hemorrhage, it seems that our surgery in both cases was nearly bloodless. Treatment was apparently also effective given that β-hCG levels fell as expected.

When systematically searching the literature, a gap of knowledge is identified on the use of UAE or in a broader perspective, the management of IP. This is probably because of the rarity of the condition. The data around do neither allow a proper meta-analysis, so that we limited ourselves to summarize the findings in somewhat larger series for each management option. There is quite some experience with primary medical therapy in asymptomatic hemodynamically stable patients. In analogy to other ectopic locations [13], the variability of MTX administration protocols is wide, including systemic single shot (either promptly or slowly infused), repetitive doses, and local administration [13]. Medical therapy has also been combined with UAE, mostly successful, yet Hiersch et al. reports on two cases where second line local MTX treatment combined with UAE failed. In those, we would guess the patient would have had more benefit of surgery.

Table 3 Primary local medical treatment of interstitial pregnancy

Author	*N*	Initial β-hCG	Local medical treatment	Hospital stay	Negative β-hCG	Complications	Success
Benifla et al. [27]	2	16,000–43,000	MTX 1 mg/kg + SMTX	3	6 (1/2)	Bleeding 1/2	1/2
	6	360–10,000	MTX 1 mg/kg	3	1–3	–	6/6
	3[a]	15,000–25,205	KCL 2 mEq in 2 ml volume	3	[a]	Miscarriage 2/3	3/3
Cassik et al. [28]	23	102–69,820	MTX 25 mg	N/A	3–14	–	21/23
Framarino et al. [29]	14	2800–3200	MTX 25 mg	N/A	Max. 8	–	14/14

N number of cases, *β-hCG* mIU/ml, *(S)MTX* (systemic) methotrexate, *KCL* potassium chloride, *hospital stay* days, *negative β-hCG* weeks
[a]Heterotopic pregnancy

Our literature review learns that the most frequent complication of surgery is hemorrhage, either with or without transfusion. The overall transfusion rate in IP is not judgeable since no reference to that outcome was made in any of the medically treated cases. However, 9% of laparoscopically managed IPs required blood transfusion. Therefore, it seems logical to take measures to reduce that risk. Surgically, one can use prophylactic coagulation by electrosurgery or ligation of the feeding artery, yet this may compromise viability of the tissue. Alternatively, vasoconstrictors have been described to reduce blood loss and operating time, yet they may have their own side effects and have only been reported to be effective for IPs with an average β-hCG of 10,000–25,000 IU/L [8, 14, 15]. Conversely, these are very cheap agents.

Modern invasive radiologic techniques are becoming increasingly popular, and those services become more widely accessible even in a semi-acute setting. Embolization techniques have found their place in modern obstetrics and gynecology. The experience with uterine myomas is meanwhile very large, and subsequent conception seems to be possible and relatively safe [16]. Torre et al. described an insignificant change in fertility rate and ovarian reserve after UAE for uterine fibroids in women with no other infertility factors [16]. Krissi et al. reported on the subsequent fertility after MTX administration with UAE in the treatment IP. Out of five women who tried to conceive, four did so, and three delivered successfully. Disadvantages of UAE are the higher cost in comparison to vasopressin, the longer duration of anesthesia, the more complicated logistics, and the additional local morbidity (e.g. ischemic pain, Asherman syndrome) [17, 18].

Conclusions

We report on the use of elective UAE prior to laparoscopic resection of IP, which coincided with a nearly bloodless operation. A literature search shows a wide variety of treatment options, yet most cases seem to be following the typical approach to EP. The overall success rate of surgical treatment of IP is higher than that of medical treatment. When performing laparoscopy, good hemostatic techniques are recommended since the operation takes place in a strongly vascularized region [8, 14, 15]. Our experience with two cases of UAE is yet another approach. It seems safe and reliable and does not preclude future conception.

Table 4 Primary and secondary treatment of interstitial pregnancy with elective UAE

Author	*N*	Initial β-hCG	Initial treatment	β-hCG pre- UAE	Treatment	Hospital stay	Negative β-hCG	Complications	Success
Valsky et al. [30]	1	11,695	–	–	MTX + UAE	N/A	5	–	1/1
Takeda et al. [31]	1	95,365	–	–	UAE + CR	8	6	–	1/1
Krissi et al. [32]	9	1667–46,923	–	–	UAE + S/LMTX	13	8	–	9/9
Takeda et al. [33]	1	44,917	–	–	UAE + TE + SMTX	N/A	13	–	1/1
Ophir et al. [34]	1	33,689	SMTX	51,098	UAE	7	8	–	1/1
Deruelle et al. [35]	1	17,785	SMTX	20,458	UAE	6	10	–	1/1
Yang et al. [17]	1	29,454	SMTX	35,654	UAE	6	4	–	1/1
Tamarit et al. [36]	2	4394–8970	SMTX	8689–10,164	UAE + LMTX	1	10	–	2/2
Berretta et al. [37]	1	49,997	SMTX	59,494	UAE	11	10	–	1/1
Hiersch et al. [25]	5	15,383	SMTX	N/A	UAE + LMTX	N/A	N/A	Transfusion 1/5 Rupture 2/5	3/5

N number of cases, *β-hCG* mIU/ml, *S/LMTX* systemic/local methotrexate, *UAE* uterine artery embolization, *CR* cornual resection (laparoscopic), *TE* transcervical evacuation (under laparoscopic guidance), *hospital stay* days, *negative β-hCG* weeks

Table 5 Primary surgical treatment of interstitial pregnancy

Author	*N*	Initial β-hCG	Surgical treatment	Duration	Rupture	Hospital stay	Negative β-hCG	Complications	Success
Moon et al. [38]	3	1320–24,700	Laparoscopic CS°	52	No	N/A	N/A	–	3/3
	18	28.5–305,100	Laparoscopic CS°°	U:28; R:82	3/18	N/A	N/A	–	17/18
	3	4469–13,000	Laparoscopic CS°°°	35	No	N/A	N/A	–	3/3
Tulandi et al. [39]	13	11,471	Laparotomic CR	N/A	9/13	N/A	N/A	Transfusion 7/13	13/13
	8	2087	Laparoscopic CR	N/A	5/11	N/A	N/A	Transfusion 2/11	7/8
	3	2087	Laparoscopic CS	N/A	5/11	N/A	N/A	Transfusion 2/11	3/3
MacRae et al. [40]	3	3150–38,000	Laparoscopic CS	N/A	1/3	2	N/A	–	3/3
	8	0–21,352	Laparoscopic CR	N/A	3/8	2	N/A	Conversion: 1/8	7/8
Ng et al. [41]	53	N/A	Laparoscopic CS if IP 1–2 cm° Laparoscopic CR if IP ≥ 3 cm°	67 (mean)	8/53	2	3	Conversion: 1/53 Transfusion: 8/53	44/53
Moon et al. [14]	20	177–39,508	Laparoscopic CS°	N/A	2/20	N/A	N/A	–	19/20
Hwang et al. [42]	54	12,741	Laparotomic CR	71	19/54	6	N/A	Transfusion 25/54	54/54
	34	12,905	Laparoscopic CR	81	8/34	5	N/A	Transfusion 13/34	34/34
Cai et al. [43]	15	N/A	Laparoscopic CS°	30–80	N/A	2–5	2–5	–	15/15
	7	3000–32,000	TE, LG and HG	45–90	No	N/A	2–5	Perforation: 2/7	5/7
Zuo et al. [44]	16	14,696	Laparoscopic CR	25–120	No	3–4	N/A	Rupture: 1/16	16/16
Ahn et al. [45]	6	17,797–69,303	TE, UG	N/A	N/A	2–8	N/A	–	5/6
	9	20,319–50,271	Laparoscopic CR	N/A	N/A	4–7	N/A	Transfusion: 1/9	9/9
Douysset et al. [46]	13	369–45,780	Laparoscopic CR	N/A	9/18	5	N/A	Transfusion: 4/18	11/13
	5	369–45,780	Laparoscopic CS	N/A	9/18	5	N/A	Transfusion: 4/18	4/5
Watanabe et al. [47]	12	998–55,820	Laparoscopic CS°	61–160	2/12	N/A	N/A	–	12/12
	1	69	Laparoscopic CS°	N/A	Yes	N/A	N/A	–	1/1
Kim et al. [11]	13*	N/A	Laparoscopic CR	40–145	2/13	2–7	N/A	Rupture 1/11 Transfusion: 2/13 Miscarriage: 1/13	13/13
Nikodijevic et al. [48]	13	16,687	Laparoscopic CR	N/A	N/A	N/A	4–8	Conversion: 5/13 Transfusion: 4/13	13/13
Nirgianakis et al. [49]	10	27,634	Laparoscopic CR~	115	N/A	3	N/A	Transfusion: 3/10	10/10
Wang et al. [50]	38	25,150	Laparoscopic CS°	71	11/38	3	N/A	–	35/38
Lee et al. [51]	53	575–64,831	Laparoscopic CR	77	N/A	N/A	N/A	–	49/53
	22	1454–62,422	Laparoscopic CS· °	59	N/A	N/A	N/A	–	21/22

N number of cases, *β-hCG* mIU/ml, *CR* cornual resection, *CS* cornuostomy, *IP* interstitial pregnancy, *TE* transcervical evacuation, *HG* under hysteroscopic guidance, *LG* under laparoscopic guidance, *R* ruptured, *UR* unruptured, *duration* minutes, *hospital stay* days, *negative β-hCG* weeks

Hemostatic technique: °vasopressin, °°endoloop, °°°encircling suture, *heterotopic pregnancy

Appendix 1

Table 6 Primary systemic MTX treatment of interstitial pregnancy

Author	N	Initial β-hCG	Systemic MTX treatment	Hospital stay	Negative β-hCG	Complications	Success
Tanaka et al. [52]	1	64,000	30 mg IM day 0 + 15 mg/d IM 5 days, 3 cycles	N/A	3	Liver function ↓	1/1
Benifla et al. [27]	2	364–5340	15 mg/d IM for 5 days	3	3 (1/2)	–	1/2
	2	430–450	1 mg/kg/d IM for 4 days	3	3–6	–	2/2
Hajenius et al. [53]	8	410–81,000	1 mg/kg/d IM on day 1, 3, 5, 7	N/A	7–21	–	8/8
Galimberti and Jones [54]	1	7072	50 mg/m^2 IM	N/A	N/A	–	0/1
Bernardini et al. [55]	1	12,470	100 mg IM	N/A	14	–	1/1
Fisch et al. [56]	1	102,000	50 mg/m^2 IM on day 1, 3, 5, 7	11	7	–	0/1
Sagiv et al. [57]	1	28,166	2 × 75 mg IM	4	N/A	–	0/1
Lalchandani et al. [58]	1	12,338	400 mg/w IV for 8 weeks	N/A	8	–	1/1
Verity et al. [59]	1	1060	2 × 75 mg IM	N/A	7	–	1/1
	1	5560	2 × 50 mg/m^2 IM, 48 h apart	N/A	8–9	–	1/1
	1	3510	1 mg/kg IM, 2 doses	N/A	4	–	1/1
	1	9070	1 mg/kg IM, 1 dose	–	6–7	–	1/1
Advincula and Senapati [60]	1	62,889	N/A	N/A	N/A	N/A	0/1
Jermy et al. [24]	17	32–31,381	50 mg/m^2 IM°	0–40	3–13	–	16/17
Ophir et al. [34]	1	33,689	50 mg/m^2 IM°	7	8	–	0/1
Reid and Buddha [61]	1	4680	50 mg/m^2 IM	N/A	7	–	1/1
Rodriguez et al. [62]	7	1592–75,868	50 mg/m^2 IM°	N/A	2–15	–	7/7
Tulandi et al. [39]	4	2627–6739	50 mg/m^2 IM	N/A	7 (2/4)	–	2/4
Cassik et al. [28]	5	793–41,150	2 × 50 mg/m^2 IM, 48 h apart	N/A	3–7	Obstipation 2/5 Neuropathy 1/5 Mild ↓ liver 1/5	4/5
Deruelle et al. [35]	1	17,785	2 × 1 mg/kg IM	6	10	–	0/1
Klemm et al. [63]	3	11,743–22,134	1 mg/kg/d IV on day 1, 3, 5, 7; 2 cycles	N/A	N/A	–	3/3
Araujo et al. [64]	1	4815	50 mg IM	N/A	N/A	–	0/1
Yang et al. [17]	1	29,454	1 mg/kg IM	6	4	–	0/1
Fujioka et al. [65]	1	11,430	50 mg/m^2 IM	N/A	N/A	–	0/1
Api and Api [66]	1	11,706	1 mg/kg IM	1	1	–	0/1
Günenç et al. [67]	1	8314	2 × 1 mg/kg IM	N/A	N/A	–	0/1
Tamarit et al. [36]	2	4394–8970	2 × 50 mg IM	1	10	–	0/2
Kato et al. [68]	1	90,000	50 mg/m^2 IM	N/A	N/A	–	0/1
Lee et al. [69]	1	3029	4 × 1 mg/kg IM	3	N/A	–	0/1
Gomez et al. [70]	2	3724–4116	70–75 mg + oral Mifepristone	2	5–7	–	2/2
Monia et al. [71]	3	3000–111,633	1–4× IM	N/A	2–6 (2/3)	–	2/3
Szylit et al. [72]	1	21,281	2 × 50 mg/m^2 IM, 48 h apart	N/A	N/A	–	0/1
Ahn et al. [45]	1	4478	Multiple doses	4	N/A	–	1/1
Berretta et al. [37]	1	49,997	2 × 80 mg IM	11	N/A	–	0/1
Sagiv et al. [73]	4	4304–28,166	50 mg/m^2 IM°	N/A	N/A	–	1/4
Surbone et al. [74]	3	2974–15,022	1 mg/kg IM	N/A	N/A	–	2/3
Fritz et al. [75]	1	8200	50 mg/m^2 IM	N/A	N/A	–	0/1
Hiersch et al. [25]	14	15,764	1 mg/kg/d IM on day 1, 3, 5, 7	N/A	N/A	–	9/14
	3	< 2500	50 mg/m^2 IM	1	N/A	–	3/3
Horne et al. [76]	5	2458–9730	50 mg/m^2 IM°	N/A	10	–	5/5
Meddeb et al. [77]	1	6320	Single dose	N/A	N/A	PTD	0/1
Corioni et al. [78]	1	8681	1 mg/kg IM	11	9	–	1/1
Kim et al. [79]	1	35,890	Every 2 days for 4 weeks	N/A	17	Pseudocyst	1/1

Table 6 Primary systemic MTX treatment of interstitial pregnancy *(Continued)*

Author	N	Initial β-hCG	Systemic MTX treatment	Hospital stay	Negative β-hCG	Complications	Success
Singh et al. [80]	1	89,000	1 mg/kg IM, 3 doses	21	12	–	1/1
Tanaka et al. [26]	33	230–106,634	100 mg IV in bolus followed by 200 mg IV	1–4	3–19	–	31/33
Nikodijevic et al. [48]	2	19,563	N/A	N/A	4	–	3/3
Kahramanoglu et al. [81]	1	1263	50 mg/m^2 IM	7	6	–	1/1
Kim et al. [12]	5	375–102,970	1 mg/kg/d IM on day 1, 3, 5, 7	N/A	N/A	N/A	14/30
	24		50 mg/m^2 IM	N/A	N/A	N/A	
	1		100 mg IV in bolus followed by 200 mg IV	N/A	N/A	N/A	

N number of cases, *β-hCG* mIU/ml, *MTX* methotrexate, *IM* intramuscular, *IV* intravenous, *hospital stay* days, *negative β-hCG* weeks, *PTD* persistent trophoblastic disease
°With a second injection, if β-hCG decrease is less than 15% from days 4 to 7

Appendix 2

Table 7 Primary local medical treatment of interstitial pregnancy

Author	N	Initial β-hCG	Local medical treatment	Hospital stay	Negative β-hCG	Complications	Success
Timor-Tritsch et al. [82]	1*	14,100	KCL 0.5 ml of 2 mEq/ml cornual	N/A	6 (*)	Miscarriage	1/1
	1	1400	MTX 25 mg cornual	4	5	–	1/1
Benifla et al. [27]	2	16,000–43,000	MTX 1 mg/kg intrasaccular, UG[1]	3 (1/2)	6 (1/2)	Bleeding 1/2	1/2
	6	360–10,000	MTX 1 mg/kg intrasaccular, UG/LG	3	1–3	–	6/6
	3*	15,000–25,205	KCL 2 mEq in 2 ml volume intrasaccular	3	*	Miscarriage 2/3	3/3
Baker et al. [83]	1*	18,423	MTX 12.5 mg with 1 ml of 20% KCL	0	*	–	1/1
Wilkinson et al. [84]	1	10,500	MTX 40 mg	N/A	N/A	–	1/1
Lin et al. [85]	1	3256	MTX 50 mg with diluted vasopressin	2	2	–	1/1
Oyawoye et al. [86]	1*	78,685	MTX	N/A	*	–	1/1
Verity et al. [59]	1	5780	MTX 50 mg, LG[2]	N/A	9	–	1/1
	1	5578	MTX 50 mg, LG	N/A	4	–	1/1
Tulandi et al. [39]	2	2627–6739	MTX, LG	N/A	7 (1/2)	–	1/2
	2		MTX	N/A	7	–	2/2
Cassik et al. [28]	23	102–69,820	MTX 25 mg, UG[3]	N/A	3–14	–	21/23
Chou et al. [87]	1	6413	KCL 2.5 mEq, UG	N/A	12	–	1/1
Narang and Kalu [88]	2	3700–40,000	MTX 50 mg/m^2	N/A	N/A	–	2/2
Andrés et al. [89]	3	6193–21,999	MTX 50 mg intrasaccular, UG[4]	1	4–10	Leukopenia 1/3	2/3
Monia et al. [71]	2	7909–64,000	MTX 20–40 mg[5]	N/A	2	–	2/2
	1	8400	MTX 60 mg	N/A	4	–	1/1
Surbone et al. [74]	6	2974–15,022	MTX 1 mg/kg	N/A	N/A	–	5/6
Swank et al. [90]	1	90,504	MTX 50 mg[5]	7	7	–	1/1
Douysset et al. [46]	2	369–45,780	N/A	N/A	N/A	–	2/2
Framarino et al. [29]	14	2800–3200	MTX 25 mg	N/A	Max. 8	–	14/14
Yu et al. [91]	4*	N/A	MTX 1 mg/kg	N/A	N/A	–	4/4
Maçães et al. [92]	1	2776	MTX 25 mg with 2 mEq KCL	N/A	8	–	1/1
Leggieri et al. [93]	1	5055	MTX 25 mg	4	3	–	1/1
Nikodijevic et al. [48]	3	19,563	MTX[5]	N/A	4	–	2/2
	1		MTX	N/A	N/A	N/A	0/1
Kim et al. [12]	2	2292–59,090	MTX 1 mg/kg	N/A	N/A	N/A	7/8
	6		MTX 1 mg/kg[5]	N/A	N/A	N/A	

N number of cases, *β-hCG* mIU/ml, *KCL* potassium chloride, *MTX* methotrexate, *UG* under ultrasound guidance, *LG* under laparoscopic guidance, *hospital stay* days, *negative β-hCG* weeks
*Heterotopic pregnancy: 1: MTX 1 mg/kg/d IM 3 days after, 2: MTX 50 mg IM on days 2 and 4, 3: in viable pregnancies + KCL intracardially (5/23), 4 MTX 50 mg/m^{2}IM (2/3 patients), 5: systemic MTX

Appendix 3

Table 8 Secondary/tertiary systemic/local medical treatment of interstitial treatment

Author	*N*	Initial β-hCG	Initial treatment	Medical treatment	Hospital stay	Negative β-hCG	Complications	Success
Fisch et al. [56]	1	102,000	SMTX	MTX 50 mg intrasaccular	11	7	–	1/1
Moon et al. [38]	1	47,200	Laparoscopic CS	MTX	N/A	N/A	N/A	1/1
Tulandi et al. [39]	1	2086	Laparoscopic CR	MTX	N/A	N/A	N/A	1/1
Takeda et al. [94]	1	16,100	Laparoscopic CS	MTX	30	N/A	N/A	1/1
Araujo et al. [64]	1	4815	SMTX	LMTX (50 mg), UG	N/A	N/A	–	1/1
Fujioka et al. [65]	1	11,430	SMTX	Dactinomycin 12 μg/kg IV	N/A	N/A	–	1/1
MacRae et al. [40]	1	7237	Laparoscopic CR	SMTX	N/A	N/A	N/A	1/1
Ng et al. [41]	9	N/A	Laparoscopy	SMTX	N/A	N/A	N/A	9/9
Sahoo et al. [95]	1	12,000	Laparoscopy	SMTX	N/A	N/A	–	1/1
Moon et al. [14]	1	9836	Laparoscopic CS	SMTX	N/A	N/A	N/A	1/1
Kato et al. [68]	1	90,000	SMTX	LMTX (25 mg)	N/A	6	–	1/1
Surbone et al. [74]	1	N/A	LMTX	SMTX	N/A	N/A	N/A	0/1
Douysset et al. [46]	2	N/A	Laparoscopic CR	MTX	N/A	N/A	N/A	2/2
	1	N/A	Laparoscopic CS	MTX	N/A	N/A	N/A	1/1
Poon et al. [96]	2	3658–89,968	Expectant	LMTX	N/A	N/A	N/A	2/2
Wang et al. [50]	1	N/A	Laparoscopic CS	MTX 20 mg IM for 5 days	N/A	4	–	1/1
Lee et al. [51]	5	N/A	Laparoscopy	MTX multiple dose regimen	N/A	N/A	–	5/5

N number of cases, *β-hCG* mIU/ml, *(S/L)MTX* (systemic/local) methotrexate, *CR* cornual resection, *CS* cornuostomy, *IM* intramuscular, *IV* intravenous, *UG* under ultrasound guidance, *hospital stay* days, *negative β-hCG* weeks

Appendix 4

Table 9 Primary surgical treatment of interstitial pregnancy

Author	*N*	Initial β-hCG	Surgical treatment	Operating time	Rupture	Hospital stay	Negative β-hCG	Complications	Success
Steadman [97]	1	N/A	Resection of GT	N/A	Yes	7	N/A	Transfusion	1/1
Bickerstaff [98]	1	N/A	CR	N/A	N/A	N/A	N/A	–	1/1
Farabow et al. [99]	1	N/A	Laparotomic CR	N/A	Yes	N/A	N/A	Transfusion	1/1
Iuchtman and Grunstein [100]	2	N/A	Laparotomic resection of GT	N/A	Yes	8	N/A	N/A	2/2
Hill et al. [101]	1	N/A	Laparoscopic resection of GT°	N/A	No	2	4–5	–	1/1
Reich et al. [102]	1	16,300	Laparoscopic CR	N/A	Yes	2	3	Transfusion	1/1
de Boer et al. [103]	1	N/A	Laparotomic CS	N/A	No	N/A	N/A	–	1/1
Pelosi [104]	1	N/A	Laparoscopic CR	45	N/A	1	N/A	–	1/1
Laury [105]	1	2450	Laparoscopic CS	N/A	No	0	N/A	–	1/1
Sherer et al. [106]	1*	N/A	Laparoscopic CR	N/A	Yes	3	*	Transfusion	1/1
Tulandi et al. [107]	4	4700–14,500	Laparoscopic CR°	N/A	No	N/A	N/A	–	5/5
	1	8000	Laparoscopic SS°	N/A	No	N/A	N/A	–	1/1
Woodland et al. [108]	1	11,061	Laparoscopic CR°	N/A	No	1	N/A	–	1/1
Katz and Lurie [109]	1	6300	Laparoscopic CS°	N/A	No	N/A	N/A	–	1/1
Grobman and Milad [110]	1	32,827	Laparoscopic CS°	N/A	No	N/A	6	–	1/1
Kasum et al. [111]	1*	5450	Laparoscopic resection of GT	N/A	Yes	N/A	*	–	1/1
Crvenkoviæ et al. [112]	1	8800	Laparoscopic CR°	60	No	4	2	–	1/1
Rahimi [113]	1	3672	Laparoscopic CS°	N/A	No	1	2	–	1/1
Moon et al. [38]	3	28.5–305,100	Laparoscopic CS°	52	No	N/A	N/A	–	3/3
	18		Laparoscopic CS°°	U:28; R:82	3/18	N/A	N/A	–	17/18
	3		Laparoscopic CS°°°	35	No	N/A	N/A	–	3/3
Vicino et al. [114]	1	21,800	Laparoscopic CR	N/A	No	N/A	2	–	1/1
Ayoubi et al. [115]	1*	N/A	Laparotomic resection of GT	N/A	Yes	N/A	*	–	1/1
Dumesic et al. [116]	1*	N/A	Laparotomic CR	N/A	Yes	N/A	N/A	Transfusion Miscarriage	1/1
Kun and Tung [117]	1	N/A	Laparotomic resection of GT	N/A	Yes	6	N/A	–	1/1
Osuga et al. [118]	3	14,352–19,457	Laparoscopic CR	N/A	N/A	N/A	N/A	–	3/3
Sagiv et al. [57]	1	N/A	Laparoscopic CS	N/A	Yes	1	N/A	Transfusion	1/1
DeWitt and Abbott [119]	1	N/A	CR	N/A	Yes	3	N/A	Transfusion	1/1
Sills et al. [120]	1*	N/A	Laparoscopic CS	< 60	No	3	*		1/1
Chang et al. [121]	1*	63,300	Laparotomic resection of GT	N/A	N/A	N/A	*	–	1/1
Habek et al. [122]	2	N/A	Laparotomic hysterectomy	N/A	Yes	8	N/A	Transfusion 1/2	2/2
Izquierdo et al. [123]	1	2500	CR	N/A	N/A	3	N/A	–	1/1
Katz et al. [124]	2	3467–9800	TE, LG and HG	N/A	No	N/A	N/A	–	2/2

Table 9 Primary surgical treatment of interstitial pregnancy *(Continued)*

Author	*N*	Initial β-hCG	Surgical treatment	Operating time	Rupture	Hospital stay	Negative β-hCG	Complications	Success
Yoo et al. [125]	4	39,245	Laparoscopic CS°	54	No	2	4	–	4/4
Gezer and Mutlu [126]	1	N/A	Laparoscopic CS	N/A	No	1	N/A	–	1/1
Grimbizis et al. [127]	1	821	Laparoscopic CR	N/A	Yes	1	3	–	1/1
Lee et al. [128]	1	45,000	Laparotomic CS	N/A	No	7	N/A	–	1/1
Savvidou et al. [129]	1	27,724	Laparoscopic resection of GT	N/A	Yes	4	3	Transfusion Conversion	1/1
Thakur et al. [130]	2	3356–17,735	TE, LG and UG	N/A	No	2	N/A	–	2/2
	2		TE, LG and UG	N/A	No	N/A	N/A	–	2/2
Tulandi et al. [39]	13	11,471	Laparotomic CR	N/A	9/13	N/A	N/A	Transfusion 7/13	13/13
	8	2087	Laparoscopic CR	N/A	5/11	N/A	N/A	Transfusion 2/11	7/8
	3		Laparoscopic CS	N/A	5/11	N/A	N/A	Transfusion 2/11	3/3
Zhang et al. [131]	3	8593–16,820	TE, LG	< 18	No	3 (max)	4	–	3/3
Huang et al. [132]	4	39,933–74,551	Laparoscopic CS	N/A	No	N/A	4	–	4/4
Kumakiri et al. [133]	1	9460	Laparoscopic CR°	84	No	2	4	–	1/1
Ross et al. [134]	2	23,480–45,780	TE, UG[1]	N/A	No	2	4–8	–	2/2
Takeda et al. [94]	2	4250–15,500	Laparoscopic CR	44–98	Yes	6–11	N/A	Transfusion 2/2	2/2
	1	16,100	Laparoscopic CS	75	Yes	30	N/A	Transfusion	0/1
Ko et al. [135]	1	1356	Laparoscopic resection of GT	N/A	No	1	1	–	1/1
Lee et al. [136]	1	N/A	Laparotomic CS	N/A	No	3	N/A	–	1/1
Oliver et al. [137]	5	14,874	TE, LG and UG	N/A	No	N/A	N/A	–	5/5
Lialios et al. [138]	1*	N/A	Laparoscopic CR	N/A	Yes	2	*	–	1/1
Qin et al. [139]	1*	N/A	Laparoscopic CR°°	N/A	No	N/A	*	–	1/1
Sherer et al. [140]	1	N/A	Laparotomic resection of GT	N/A	Yes	3	N/A	–	1/1
Casadio et al. [141]	1	9383	Laparoscopic CR	40	No	2	5	–	1/1
Cheng et al. [142]	1	59,959	Laparoscopic CS	N/A	No	6	5	–	1/1
Choi et al. [143]	8	3400–74,060	Laparoscopic CS°	35–80	No	N/A	2–5	–	8/8
Duong et al. [144]	1	N/A	Laparotomic resection of GT	N/A	Yes	7	N/A	Transfusion	1/1
MacRae et al. [40]	3	3150–38,000	Laparoscopic CS	N/A	1/3	2	N/A	–	3/3
	8	0–21,352	Laparoscopic CR	N/A	3/8	2	N/A	Conversion 1/8	7/8
Ng et al. [41]	53	N/A	Laparoscopic CS if IP 1–2 cm°; Laparoscopic CR if IP 3 cm or more°	67 (mean)	8/53	2	3	Conversion 1/53 Transfusion 8/53	44/53
Pluchino et al. [145]	1	N/A	Laparoscopic CS	N/A	Yes	2	N/A	–	1/1
Moon et al. [14]	20	177–39,508	Laparoscopic CS°	N/A	2/20	N/A	N/A	–	19/20
Pan et al. [146]	1	79,194	Bilateral CR (bilateral IP)	N/A	No	10	N/A	–	1/1
Pistofidis et al. [147]	1	18,900	Laparoscopic resection of GT	N/A	Yes	2	N/A	–	1/1
Tinelli et al. [148]	3	7600–12,500	Laparoscopic CS	45 (mean)	1/3	1	2	–	3/3

Table 9 Primary surgical treatment of interstitial pregnancy *(Continued)*

Author	*N*	Initial β-hCG	Surgical treatment	Operating time	Rupture	Hospital stay	Negative β-hCG	Complications	Success
Vignali et al. [149]	3	431–3252	Laparoscopic CR	36–60	No	1	N/A	–	3/3
Walid et al. [150]	1	N/A	Laparoscopic resection of GT°	N/A	N/A	N/A	N/A	–	1/1
Yan [151]	1	3600	Laparoscopic resection of GT°	60	No	N/A	N/A	–	1/1
Aust et al. [152]	1*	N/A	Laparoscopic CR	N/A	No	0	*	Miscarriage	1/1
Cerviño et al. [153]	1	20,940	TE, UG[2]	N/A	No	N/A	5	–	1/1
Chachan et al. [154]	1*	N/A	Laparoscopic CS	N/A	No	1	*	–	1/1
Hwang et al. [42]	54	12,741	Laparotomic CR	71	19/54	6	N/A	Transfusion 25/54	54/54
	34	12,905	Laparoscopic CR	81	8/34	5	N/A	Transfusion 13/34 Bowel injury 1/34	34/34
Lazard et al. [155]	2	4900–14,720	Laparoscopic CR	25–35	No	2–3	2–3	–	2/2
Lodhi et al. [156]	1	6041	Laparoscopic CR	N/A	No	2	N/A	–	1/1
	1	N/A	Laparoscopic CR	N/A	Yes	2	N/A	Transfusion	1/1
Yamamoto et al. [157]	1	N/A	Laparoscopic CR°	N/A	No	1	N/A	–	1/1
Ahsan Akhtar et al. [158]	1	16,740	Laparoscopic CR	25	No	1	3	–	1/1
Cai et al. [43]	15	N/A	Laparoscopic CS°	30–80	N/A	2–5	2–5	–	15/15
	7	3000–32,000	TE, LG, and HG	45–90	No	N/A	2–5	Perforation 2/7	5/7
Cucinella et al. [159]	5	1286–20,680	Laparoscopic CR°°°°	31–46	No	N/A	3–4	–	5/5
Garavaglia et al. [160]	1	2173	Laparoscopic CS	N/A	N/A	N/A	N/A	–	1/1
Muglu et al. [161]	1	N/A	Laparoscopic resection of GT	N/A	N/A	N/A	N/A	–	1/1
Rheinboldt et al. [162]	1	7787	Laparoscopic CR	N/A	N/A	N/A	N/A	–	1/1
Zuo et al. [44]	16	14,696	Laparoscopic CR	25–120	No	3–4	N/A	Rupture 1/16	16/16
Ahn et al. [45]	6	17,797–69,303	TE, UG	N/A	No	2–8	N/A	–	5/6
	9	20,319–50,271	Laparoscopic CR	N/A	N/A	4–7	N/A	Transfusion 1/9	9/9
MacKenna et al. [163]	1	5820	Laparoscopic CR°	N/A	No	1	2	–	1/1
Mooij and Van Dillen [164]	1	N/A	Laparotomic resection of GT	N/A	N/A	N/A	N/A	N/A	1/1
Sagiv et al. [73]	3	3282–13,260	Laparoscopic CR	N/A	N/A	N/A	N/A	–	3/3
	2	21,930–88,270	Laparoscopic CS	N/A	N/A	N/A	N/A	–	2/2
Surbone et al. [74]	2	2974–15,022	Laparoscopic CR	N/A	N/A	N/A	N/A	Conversion 1/2	2/2
Warda et al. [165]	1	N/A	Laparoscopic CS°	N/A	No	N/A	N/A	–	1/1
Wright et al. [166]	3	1455–27,052	TE, UG[1]	N/A	No	N/A	6–12	–	3/3
Zhang and Yuan [167]	2	2808–14,030	Laparoscopic CR°	45–95	No	6–7	< 1	–	2/2
Chandran [168]	1	N/A	Laparotomic CR	N/A	No	5	N/A	–	1/1
Douysset et al. [46]	13	369–45,780	Laparoscopic CR	N/A	9/18	5	N/A	Transfusion 4/18	11/13
	5		Laparoscopic CS	N/A	9/18	5	N/A	Transfusion 4/18	4/5
Garretto et al. [169]	1	26,476	Laparoscopic CR	N/A	No	1	N/A	–	1/1
Manea et al. [11]	2	2238–8915	Laparoscopic resection of GT	N/A	Yes	N/A	N/A	–	2/2

Table 9 Primary surgical treatment of interstitial pregnancy *(Continued)*

Author	*N*	Initial β-hCG	Surgical treatment	Operating time	Rupture	Hospital stay	Negative β-hCG	Complications	Success
	1	6892	Laparoscopic CR~	N/A	Yes	N/A	N/A	–	1/1
Nezhat et al. [170]	1	N/A	TE°, UG + LG	N/A	No	1	5	–	1/1
Wang et al. [171]	8	636–13,310	Laparoscopic CS°	40–100	No	2	N/A	–	8/8
	1	N/A	Laparoscopic CS°	N/A	No	2	N/A	–	1/1
Warda et al. [172]	4	N/A	Laparoscopic CS°	N/A	No	N/A	N/A	–	4/4
Watanabe et al. [47]	12	998–55,820	Laparoscopic CS· °	61–160	2/12	N/A	N/A	–	12/12
	1	69	Laparoscopic CS°	N/A	Yes	N/A	N/A	–	1/1
Yu et al. [91]	4*	N/A	Laparotomic resection of GT	N/A	N/A	N/A	*	Miscarriage 1/4	4/4
Ansari et al. [173]	1	65,000	Laparoscopic CS°	78	No	0	12	–	1/1
Afifi et al. [174]	2	3890–17,445	Laparoscopic CS°, °°°°°	55–65	1/2	1	1–2	–	2/2
Faioli et al. [10]	3	10,119–18,765	Laparoscopic CR	28	No	N/A	3	–	3/3
Grindler et al. [175]	1	39,745	TE, UG	N/A	No	0	N/A	–	1/1
Jeon et al. [176]	9*	N/A	Laparotomy	N/A	N/A	N/A	N/A	N/A	9/9
Kim et al. [177]	13*	N/A	Laparoscopic CR	40–145	2/13	2–7	N/A	Rupture 1/11 Transfusion 2/13 Miscarriage 1/13	13/13
Mallick et al. [178]	2	2304–14,480	Laparoscopic CS	N/A	1/2	0	N/A	–	2/2
	2	N/A	Laparoscopic CS	N/A	No	1	N/A	–	2/2
Nikodijevic et al. [48]	13	16,687	Laparoscopic CR	N/A	N/A	N/A	4–8	Conversion 5/13 Transfusion 4/13	13/13
Nirgianakis et al. [49]	10	27,634	Laparoscopic CR~	115	N/A	3	N/A	Transfusion 3/10	10/10
Said [179]	4	N/A	Laparoscopic resection of GT~	40–60	N/A	2	N/A	–	4/4
	1*	N/A	Laparoscopic resection of GT	N/A	Yes	N/A	*	–	1/1
Wang et al. [50]	38	25,150	Laparoscopic CS°	71	11/38	3	N/A	–	35/38
Xu et al. [180]	1	N/A	Resection of GT	N/A	Yes	N/A	N/A	Transfusion	1/1
Kahramanoglu et al. [81]	1	> 10,000	Laparotomic resection of GT	N/A	Yes	3	N/A	Transfusion	1/1
	1	9277	TE, UG	N/A	No	0	4	–	1/1
	1	N/A	TE, LG	N/A	No	1	1	–	1/1
Lee et al. [51]	53	575–64,831	Laparoscopic CR[3]	77	N/A	N/A	N/A	–	49/53
	22	1454–62,422	Laparoscopic CS· °	59	N/A	N/A	N/A	–	21/22

N number of cases, *β-hCG* mIU/ml, *CR* cornual resection, *CS* cornuostomy, *TE* transcervical evacuation, *SS* salpingostomy, *GT* gestational tissue, *R* ruptured, *U* unruptured, *UG* under ultrasound guidance, *LG* under laparoscopic guidance, *HG* under hysteroscopic guidance, *IP* interstitial pregnancy, *operating time* minutes, *hospital stay* days, *negative β-hCG* weeks

*Heterotopic pregnancy, hemostatic technique: °vasopressin, °°endoloop, °°°encircling suture, °°°°"Purse-string" suture, °°°°°stitch at the uterine fundus and in the mesosalpinx, ~local injection of diluted adrenaline (1/4)—1: MTX 50 mg/m^2 IM; 2: MTX 1 mg/kg IM; 3: +/− postoperative prophylactic MTX

Appendix 5

Table 10 Secondary/tertiary surgical treatment of interstitial pregnancy

Author	N	Initial β-hCG	Initial treatment	Surgical treatment	Operating time	Rupture	Hospital stay	Negative β-hCG	Complication	Success
Benifla et al. [27]	1	5340	SMTX	Laparotomic CR	N/A	N/A	N/A	N/A	N/A	1/1
	1	43,000	LMTX	Laparotomic CR	N/A	Yes	N/A	N/A	N/A	1/1
Galimberti and Jones [54]	1	7072	SMTX	Laparotomy	N/A	N/A	N/A	N/A	–	1/1
Hamada et al. [181]	1	8000	Expectant	Laparotomic HE	N/A	No	N/A	N/A	–	1/1
Sungurtekin and Uyar [182]	1	31,737	SMTX	Laparotomy	N/A	No	N/A	N/A	–	1/1
Bremner et al. [183]	1	92	Expectant	Laparoscopic CS	N/A	No	0	N/A	Ileus	1/1
Sagiv et al. [57]	1	28,166	SMTX	Laparoscopic CS	N/A	Yes	4	N/A	–	1/1
Advincula et al. [60]	1	62,889	SMTX	Laparotomic CR	N/A	N/A	N/A	N/A	–	1/1
Coric et al. [184]	1	1770	Expectant + aspiration	Laparoscopic CR	60	No	5	N/A	–	1/1
Jermy et al. [24]	1	> 10,000	SMTX	Laparotomy	N/A	No	N/A	N/A	–	1/1
Tulandi et al. [39]	2	2627–6739	SMTX	Laparoscopy	N/A	No	N/A	N/A	N/A	2/2
	1		LMTX	Laparotomy	N/A	No	N/A	N/A	N/A	1/1
Cassik et al. [28]	1	41,150	SMTX	Laparotomic CR	N/A	N/A	N/A	N/A	N/A	1/1
	2	102–69,820	LMTX	N/A	N/A	N/A	N/A	N/A	N/A	2/2
Api and Api [66]	1	18,654	SMTX	Laparoscopic CS	N/A	No	1	1	–	1/1
Günenç et al. [67]	1	8314	SMTX	Laparoscopic CS	N/A	No	N/A	5	–	1/1
Lee et al. [69]	1	14,273	SMTX	Laparoscopic CR	90	No	3	N/A	–	1/1
Lodhi et al. [156]	1	19,714	MTX	Laparoscopic CR	N/A	No	2	N/A	–	1/1
Andrés et al. [89]	1	6193	LMTX	Laparoscopy	N/A	Yes	N/A	N/A	–	1/1
Monia et al. [71]	1	94,000	SMTX	Laparoscopic CR	N/A	N/A	N/A	N/A	–	1/1
Szylit et al. [72]	1	21,281	SMTX	Laparoscopic CR	N/A	N/A	2	N/A	–	1/1
Sagiv et al. [73]	2	4304–4987	SMTX	Laparoscopic CR	N/A	N/A	N/A	N/A	–	2/2
	1	28,166	SMTX	Laparoscopic CS	N/A	N/A	N/A	N/A	–	1/1
Surbone et al. [74]	1	N/A	SMTX	Laparoscopic CS	N/A	N/A	N/A	N/A	N/A	1/1
	1	N/A	L/SMTX	Laparoscopic CS	N/A	N/A	N/A	N/A	N/A	1/1
Fritz et al. [75]	1	8200	SMTX	TE, LG	N/A	No	0	3	–	1/1
Hiersch et al. [25]	2	15,383	SLMTX + UAE	N/A	N/A	Yes	N/A	N/A	–	2/2
Meddeb et al. [77]	1	6320	SMTX	Laparoscopic CR	N/A	No	N/A	N/A	PTD	1/1
Tanaka et al. [26]	2	8500–63,000	SMTX	N/A	N/A	Yes	N/A	N/A	–	2/2
Nikodijevic et al. [48]	1	19,563	LMTX	N/A	N/A	No	N/A	N/A	–	1/1
Wang et al. [50]	2	176-N/A	Surgery	Repeat laparoscopy	N/A	Scar	Day 3	3–4	–	2/2

N number of cases, *β-hCG* mIU/ml, *(S/L)MTX* (systemic/local) methotrexate, *UAE* uterine artery embolization, *CR* cornual resection, *CS* cornuostomy, *HE* hysterectomy, *operating time* minutes, *hospital stay* days, *negative β-hCG* weeks, *PTD* persistent trophoblastic disease

Appendix 6

Table 11 Recurrent interstitial pregnancy and its treatment

Author	N	β-hCG	Treatment 1st IP	Success	β-hCG	Treatment 2nd IP	Success	β-hCG	Treatment 3rd IP	Success
Sungurtekin and Uyar [182]	1	32	SMTX	1/1	31,737	SMTX	0/1	–	–	–
Sagiv et al. [57]	1	15,400	LMTX	1/1	2577	Laparoscopic CS°	1/1	–	–	–
Vilos [185]	1	12,000	Laparoscopic CR	1/1	4700	Laparoscopic CR	1/1	–	–	–
Sahoo et al. [95]	1	N/A	Laparotomy	1/1	N/A	Laparoscopy	0/1	N/A	Laparoscopic CR	1/1
Siow and Ng [186]	2	N/A	Laparoscopic CS	2/2	N/A	Laparoscopic CR	2/2	–	–	–
	1	N/A	Laparoscopy	1/1	N/A	Laparoscopic CR	1/1	–	–	–
	1	N/A	Laparoscopic CR	1/1	N/A	Laparoscopic CR	1/1	N/A	Laparoscopic CR	1/1

N number of cases, *β-hCG* mIU/ml, *IP* interstitial pregnancy, *S/LMTX* systemic/local methotrexate, *CR* cornual resection, *CS* cornuostomy
Hemostatic technique: °vasopressin

Abbreviations
EP: Ectopic pregnancy; IP: Interstitial pregnancy; IVF: In vitro fertilization; KCL: Potassium chloride; MTX: Methotrexate; UAE: Uterine artery embolization

Availability of data and materials
Search results and supplementary tables are available on line. The dataset is available with the primary author.

Authors' contributions
IV, FD, PJB, DT, AVH, SAC, ASVR, LVDH, SG, CT, and JDP did the clinical management of the patients involved. IV and FD did the data collection. IV and JDP did the data analysis. All authors contributed to the manuscript writing and read and approved the final manuscript.

Authors' information
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Ethics approval and consent to participate
Both patients explicitly consented to have their history being part of a case report. This study is approved by the Education-Support Committee of The University of Leuven (OBC MP001948). The Education-Support Committee (OBC) evaluates master's thesis projects as mandated by the Research Ethics Committee of the KU/UZ Leuven.

Competing interests
The authors declare that they no competing interests.

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