

## RESEARCH ARTICLE

# Management of Unusual Not Scar Ectopic Pregnancy: A Multicentre Retrospective Case Series

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**Abstract: Background:** Management of unusual not scar ectopic pregnancies (UNSEPs) is an unexplored clinical field because of their low incidence and lack of guidelines.

**Objective:** To report the clinical presentation, the first- and second-line treatment and outcomes of UNSEPs.

**Methods:** We retrospectively collected patients treated for UNSEP (namely cervical, interstitial, ovarian, angular, abdominal, cornual and intramural), their baseline characteristics, risk factors, symptoms, diagnostic pathway and the type of first-line treatment (medical, surgical or combined). We further collected treatment failures and the type of second-line treatment. We assessed treatment outcomes, time to serum beta human chorionic gonadotropin ( $\beta$ -hCG) level negativity, length of recovery, follow up and return to a normal menstrual cycle.

**Results:** From 2009 to 2019, we collected 79 cases. Of them, 27 (34%), 23 (29%), 12 (15%), 8 (10%), 6 (8%) and 3 (4%) were cervical, interstitial, ovarian, angular, abdominal and cornual, respectively. Forty women (50.6%) were submitted to medical treatment, mostly methotrexate based; conversely, 36 patients (45.6%) underwent surgery and only 3 women (3.8%) received a combined treatment. The success of first-line treatment rate, regardless of UNSEP location, was 53% and 89% for medical and surgical treatment, respectively. Treatment failures (21 patients) were submitted to second-line treatment, respectively 47.6% and 52.4% to medical and surgical approach. Of interest, cervical pregnancies achieved the lowest rate of first-line medical treatment success (22%) and received more frequently (69%) a subsequent surgical approach with no hysterectomy. Interstitial pregnancies were submitted to surgery mostly for a matter of urgency (71%), otherwise, they were treated with a medical approach both at first- and second-line treatment. Ovarian pregnancies were treated with ovariectomy in 44% of the cases submitted to surgery. Angular pregnancies underwent surgery more often, while all the abdominal pregnancies underwent endoscopic or open surgery. Cornual pregnancies received cornuostomy in 75% of the cases. Overall, the need for blood transfusion was 23.1% among the patients submitted to surgery. The median length of hospitalisation was shorter for women submitted to surgical first-line treatment (5 vs. 10 days;  $p = 0.002$ ). In case of first-line medical treatment and in case of failure, we found an increase of 3 days (CI95% 0.6-5.5;  $p = 0.01$ ) and of 3.6 days (CI95% 0.89-6.30;  $p = 0.01$ ) in the length of hospitalisation, respectively. Negative  $\beta$ -HCG levels were obtained earlier in the surgical group (median 25 vs. 51 days;  $p = 0.001$ ), as well as the return to normal menstrual cycle (median 31 vs. 67 days;  $p < 0.000$ ). Post-treatment follow-up, regardless of the failure of first-line treatment was shorter in the surgical group (median 32 versus 68 days;  $p = 0.003$ ).

**Conclusion:** Cervical pregnancies were successfully managed with a surgical approach without hysterectomy, and hence, we suggest avoiding medical treatment. No consensus emerged for other UNSEPs. Ovarian, angular and interstitial pregnancies are burdened by a non-conservative approach on the utero-ovarian structures. The surgical approach led to shorter recovery, earlier  $\beta$ -hCG negativity and shorter follow-up, even though there is an increased risk for blood transfusion.

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## 1. INTRODUCTION

Ectopic pregnancies (EPs) account for 1-2% of all pregnancies and are still the principal cause of mortality of the first trimester. About 95% of EPs occur in the Fallopian tube and there is a robust evidence regarding risk factors and a solid consensus about the diagnosis, treatment and follow up in the daily clinical practice [1].

The remaining 5% of EPs occurs in different locations, especially on the previous uterine cesarean scar, but also in other more atypical locations making up a group of various clinical situations definable as unusual not scar ectopic pregnancies (UNSEPs), including cervical, ovarian, interstitial, angular, cornual, intramural and abdominal pregnancies [2-4].

The management of UNSEPs still poses more challenges because they are often diagnosed later than other EPs and are associated with even higher morbidity and mortality rates [5-8]. No agreement is available in the literature regarding specific risk factors, option of treatment and outcomes. A high index of suspicion on ultrasound with high-resolution probes or other technique of imaging and accurate serum beta human chorionic gonadotropin ( $\beta$ -hCG) assays are warranted to fetch a proper diagnosis [9, 10]. The widespread diffusion of these techniques led to a transition from a radical surgical approach to a more conservative and fertility-sparing management, including medical therapy, minimally invasive surgery, ultrasound-guided interventions, radiological interventions and expectant management [11-13].

The aim of this multicenter case series is to report the treatment and outcomes for UNSEPs and contribute to the current literature.

## 2. MATERIALS AND METHODS

This is a retrospective multicenter study including patients from nine academic hospitals (Spedali Civili, Brescia, Italy; Ospedale della Donna e del Bambino, AOUI Verona, Italy; Policlinico di Modena, Italy; Policlinico Sant'Orsola-Malpighi, Bologna, Italy; IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; Centre for High Risk Pregnancy and Fetal Care, Chieti, Italy; CHU Saint-Pierre, Belgium; Institute for Maternal and Child Health, IRCCS, Burlo Garofalo, Trieste; Policlinico Universitario A. Gemelli, IRCCS, Roma, Italy). From the internal databases, we identified patients diagnosed with EP between 2009-2019. Retrospective observational studies involving the collection of anonymized existing data derived from an audit have been considered, by the local IRB, exempt from the requirement of any approval. Patients with a diagnosis of caesarean scar pregnancy, or with isthmus or ampullary tubal pregnancy, were excluded. Patient diagnosed with the pregnancy of unknown location, namely having positive urine pregnancy test without visualisation of any clear trophoblastic mass at imaging [10], were excluded from the analysis. We collected the baseline characteristics (age, BMI, weeks of amenorrhoea), obstetric history and exposure to known risk factors for ectopic pregnancy, such as current smoking, use of intrauterine device (IUD), previous pelvic surgery, history of

endometriosis or pelvic inflammatory disease (PID) and the use of assisted reproductive technique (ART). We collected the details of the diagnostic pathway (fetching data of the EP such as maximum diameter of trophoblastic mass in millimetres, presence of an embryo with cardiac activity, presence of free fluid in the pelvis or abdomen) and the type of first- and second-line treatment. We fetch the successful rates of treatment, the outcomes, the treatment duration in days and the return to normal menstrual cycle. We collected serum  $\beta$ -hCG levels at diagnosis and the interval up to their negativization. If surgically treated, all ectopic pregnancy sites were histologically confirmed; otherwise, we considered imaging-based diagnosis using ultrasound and/or MRI findings.

### 2.1. Unusual Not Scar Ectopic Pregnancy (UNSEP) Classification

According to the most accepted definitions, we classified UNSEPs into seven categories, as follows:

- [1] Cervical pregnancy (CP); the site of implantation was the endocervical canal and/or myometrium below the level of the internal os [11].
- [2] Interstitial pregnancy (IP); the pregnancy was identified in the interstitial portion of the fallopian tube. These pregnancies are factually tubal, but they are historically considered as separate entities, with a higher risk of serious complications requiring different surgical approaches. In this condition, the trophoblastic mass is clearly separate from an empty uterine cavity, and it is surrounded by myometrium [14]. The distance between chorionic sac and lateral edge of the uterine cavity, along with the thickness of myometrium surrounding the gestational sac, and the presence of the "interstitial line sign" were further retrieved from the ultrasound reports [1].
- [3] Ovarian pregnancy (OP); the pregnancy was partially or completely located within the ovarian parenchyma [15].
- [4] Angular pregnancy (AnP); the site of implantation was the lateral angle of a normally-shaped uterine cavity, just medial to the utero-tubal junction. The implantation site of these pregnancies is intrauterine, entirely surrounded by endometrium, but they were historically considered as a separate entity due to their eccentric location, potentially causing asymmetric uterine enlargement and subsequent complications [4]. However, current literature on angular pregnancies is sparse and not homogeneous, and the term is often used as a synonym of cornual and interstitial pregnancies. Moreover, some authors [16] demonstrated a low rate of major complications in patients with angular pregnancy. There is actually no consensus about the clinical utility of distinguishing this kind of pregnancy from other "normally-implanted" intrauterine pregnancies. While awaiting shared guidelines and classifications, we, however, maintained this term.

- [5] Abdominal pregnancy (AbP); the implantation site was found in the peritoneal cavity (excluding tubal or ovarian sites) [2].
- [6] Cornual pregnancy (COP); the implantation site was located in one horn of a septate or bicorporeal uterus, or in a rudimentary horn. Therefore, it was possible to define a pregnancy as cornual only in the presence of a congenital Müllerian anomaly, not surgically treated [17]. Using the ESHRE/ESGE classification terminology, established by the CONUTA working group in 2013, anomalies associated with possible cornual embryo implantation include class U2 (septate) and U3 (bicorporeal) uterus, but also class U4 (unilateral formed) and U5 (aplastic) uterus if a rudimentary horn is present [18]. Some authors consider as true cornual EP only those implanted in a rudimentary horn; however, given the rarity of this condition, we decided to consider the first, more inclusive, definition [1].
- [7] Intramural pregnancy (InP); the pregnancy is located within the uterus, but it invades myometrium of the

uterine corpus above the line of internal cervical os, going beyond the endometrial-myometrial junction [19]. These pregnancies are extremely rare and described after uterine surgery or in a context of adenomyosis.

We summarized the pathognomonic ultrasound characteristics for each type of the aforementioned EPs in Table 1 [1, 3, 4, 9, 13, 15, 17, 21-26].

### 2.2. Statistical Analysis

We performed statistical descriptive analysis and compared baseline characteristics using univariate analysis, between the different EP sites. We used Pearson's chi-squared, Fisher's tests and Mann-Whitney test as appropriate. To further investigate the differences in length of hospitalisation, time to  $\beta$ -hCG negativity, length of follow-up and return to the normal menstrual cycle, we performed a multivariate linear regression model based on first-line treatment modality and the need for second-line treatment. All analyses were performed using SPSS IBM 23.

**Table 1. Ultrasound criteria for the diagnosis of UNSEPs.**

Site of EP	Transvaginal Ultrasound Features
<b>Cervical</b> [9, 13, 21]	<p><b>To diagnose cervical ectopic pregnancy:</b></p> <ul style="list-style-type: none"> <li>- empty uterine cavity</li> <li>- GS/trophoblastic mass below the level of internal cervical os</li> <li>- cervix is usually enlarged with dilated cervical canal (barrel-shaped cervix)</li> <li>- hourglass appearance of the uterus.</li> </ul> <p><b>To distinguish primary cervical ectopic pregnancy from incomplete abortion of an intra-uterine pregnancy:</b></p> <ul style="list-style-type: none"> <li>- peri-trophoblastic blood flow using color Doppler</li> <li>- negative "sliding organ sign" on transvaginal examination (sliding of GS/trophoblastic mass against the endocervical canal under gentle pressure by the probe during transvaginal ultrasound)</li> <li>- no change in position and shape of the GS on seriate images</li> </ul>
<b>Interstitial</b> [1, 15, 23]	<ul style="list-style-type: none"> <li>- Empty uterine cavity</li> <li>- GS/trophoblastic mass in the intra-myometrial portion of the tube: &gt;1 cm from the lateral edge of endometrial cavity, completely surrounded by myometrium (&lt;5-8 mm thick)</li> <li>- "interstitial line sign": echogenic line connecting the endometrial stripe to the interstitial gestational sac</li> </ul>
<b>Ovarian</b> [2, 8, 16]	<ul style="list-style-type: none"> <li>- Empty uterine cavity</li> <li>- ovarian cyst with a thick echogenic outer ring and high peripheral vascularity on the surface or in the ovarian parenchyma; usually ipsilateral to the corpus luteum</li> <li>- negative "sliding organ sign" (ectopic pregnancy does not separate from the ovary when gentle pressure is applied with the probe);</li> </ul>
<b>Angular</b> [4, 8, 18]	<ul style="list-style-type: none"> <li>- No Mullerian anomalies of the uterus</li> <li>- site of implantation in the lateral edge of the uterine cavity, medial to the utero-tubal junction</li> <li>- GS/trophoblastic mass completely surrounded by endometrium: "double sac sign"</li> <li>- no more than 1 cm of myometrial thickness from the gestational sac to the outer border of the uterus</li> <li>- lack of "interstitial line sign"</li> </ul>
<b>Abdominal</b> [22, 25]	<ul style="list-style-type: none"> <li>- Empty uterine cavity</li> <li>- No evidence of a dilated Fallopian tube or an adnexal mass</li> <li>- GS, trophoblastic mass and/or fetus seen in an unusual location (POD, vesicouterine pouch) or surrounded by bowel loops</li> <li>- significant mobility of the mass/fluctuation of the sac under pressure of the US probe (seen particularly in case of POD site)</li> </ul>
<b>Cornual</b> [5-16]	<p><b>Rudimentary horn pregnancy:</b></p> <ul style="list-style-type: none"> <li>- visualization of a single interstitial portion of Fallopian tube in the main unicornuate uterine body</li> <li>- GS/trophoblastic mass seen mobile and separate from the unicornuate cavity and completely surrounded by myometrium</li> <li>- vascular pedicle adjoining the gestational sac to the unicornuate uterus</li> </ul>
<b>Intramural</b> [26]	<ul style="list-style-type: none"> <li>- GS/trophoblastic mass is completely surrounded by myometrium and separate from the endometrial cavity and fallopian tubes</li> </ul>

GS: gestational sac; US: ultrasound; POD: pouch of Douglas.

Table 2. Baseline characteristics of the patients.

-	All Patients n = 79
Age, Median (IQR)	34 (19-47)
BMI, Median (IQR)	25 (18-38)
Smoking, n (%)	13 (16.4%)
Infertility, n (%)	20 (25.3%)
Gravidity, Median (Range)	2 (0-9)
Parity, Median (Range)	1 (0-7)
Mullerian anomaly, n (%)	8 (10%)
Endometriosis	4 (5%)
Pelvic surgery, n (%)	38 (48.1%)
Prior CS, n (%)	19 (24%)
Previous PID, n (%)	1 (1.3%)
Previous EP, n (%)	15 (19%)
Current ART, n (%)	12 (15.2%)
IUD in place, n (%)	2 (2.6%)
UNSEP sites	
Cervical	27 (34.2%)
Interstitial	23 (29.1%)
Ovarian	12 (15.2%)
Angular	8 (10.1%)
Abdominal	6 (7.6%)
Cornual	3 (3.8%)
Intramural	-

BMI: body mass index; CS: cesarean section; PID: pelvic inflammatory disease; EP: ectopic pregnancy; ART: assisted reproductive technology; IUD: intra uterine device; UNSEP: unusual not scar ectopic pregnancy.

Table 3. Characteristics at diagnosis according to ectopic pregnancy site.

-	All patients n = 79	Cervical n = 27	Interstitial n = 23	Ovarian n = 12	Angular n = 8	Abdominal n = 6	Cornual n = 3
Amenorrhea in weeks, median (range)	7 (5-17)	7 (6-12)	7 (5-17)	7 (5-9)	8+5 (7-13)	7+5 (7-17)	5 (5-6)
Symptoms							
Mild bleeding	40 (50.6%)	15 (55.5%)	11 (47.8%)	8 (66.7%)	3 (37.5%)	2 (33.3%)	1 (33.3%)
Pain	28 (35.4%)	6 (22.2%)	12 (52.2%)	6 (50%)	2 (25%)	1 (16.7%)	2 (66.7%)
Severe bleeding	9 (11.4%)	5 (18.5%)	1 (4.3%)	-	1 (12.5%)	1 (16.7%)	1 (33.3%)
Diagnostic pathway							
Ultrasound 2D	72 (91.1%)	26 (96.3%)	21 (91.3%)	11 (91.7%)	8 (100%)	4 (66.7%)	2 (66.7%)
Ultrasound 3D	13 (16.5%)	2 (7.4%)	9 (39.1%)	1 (8.3%)	-	-	1 (33.3%)
MRI	2 (2.5%)	-	1 (4.3%)	-	-	1 (16.7%)	-
Incidental at surgery	3 (3.98)	1 (3.7%)	1 (4.3%)	-	-	1 (16.7%)	-
Gestational sac, n (%)	63 (79.7%)	24 (88.9%)	19 (82.6%)	7 (58.3%)	8 (100%)	3 (50%)	2 (66.7%)
Throfolastic mass diameter in mm, median (IQR)	25 (17-37)	17 (8-55)	25 (14-51)	25 (16-37)	40 (25-60)	30 (25-40)*	12 (5-22)
Visualized embryo, n (%)	40 (50.6%)	18 (66.7%)	11 (47.8%)	4 (33.3%)	6 (75%)	-	1 (33.3%)
Embryo cardiac activity, n (%)	26 (32.9%)	14 (52%)	5 (21.7%)	1 (8.3%)	5 (62.5%)	-	1 (33.3%)
Free pelvic fluid, n (%)	17 (21.5%)	1 (3.7%)	6 (26.1%)	9 (75%)	2 (25%)	5 (83.3%)	-
Free abdominal fluid, n (%)	11 (13.9%)	-	2 (8.7%)	3 (25%)	1 (12.5%)	5 (83.3%)	-
Hb levels (g/dL), median (IQR)	11.75 (10.9-13.0)	11.7 (10.9-12.8)	12.9 (11.5-13.5)	11.5 (10.9-12.8)	11.4 (9.8-12.5)	9.4 (9.4-12.7)	13.9 (11.7-14)
b-hCG level at diagnosis, median (IQR)	13857 (5089-27861)	25576 (7058-56087)	7604 (2102-18380)	5931 (1523-16373)	26878 (9142-38735)	16886 (7179-17950)	10075 (5331-27861)

b-hCG: beta human chorionic gonadotropin; Hb: haemoglobin; IQR: interquartile range.

### 3. RESULTS

We found 79 patients treated for UNSEPs from 2010 to 2019. Of them, 27 (34%), 23 (29%), 12 (15%), 8 (10%), 6 (8%) and 3 (4%) were cervical, interstitial, ovarian, angular, abdominal and cornual, respectively. No intramural pregnancies were found. The characteristics of the patients are listed in Table 2. We noted a high prevalence of patients with previous pelvic surgery (48.1%), prior caesarean section (24%) and history of infertility (25.3%). Median amenorrhoea was 7+0 weeks (interquartile range, IQR 5-17), while median serum levels of gonadotropin at diagnosis were 13.857 UI/mL (5.089-27.861). The most common diagnostic tool was classical transvaginal ultrasound (TU) scan (91%), while 3D reconstruction was mostly used for interstitial pregnancy (39%). Rarely, the diagnosis was incidental during surgery (4%). Further diagnostic details are described in Table 3.

As first-line treatment, the medical option was adopted in 40 (50.6%) cases, surgical pathway in 36 (45.6%) cases and only three (3.8%) patients were submitted for combined medical and surgical treatment (Table 3). Globally, first line treatment achieved a successful outcome in most of the cases (73.4%) and failure was more frequent for medical option, with a success rate of 53%, regardless of the location of UNSEP. The matter of urgency was registered in 23 patients (29.1%), all submitted to surgical management, mostly because of pelvic pain and severe bleeding. Only 3 patients (respectively one with a cervical pregnancy and two patients with interstitial pregnancies) were treated with systemic methotrexate as outpatient; of these, the latter is a woman with an interstitial pregnancy at 17 weeks of amenorrhoea but with tiny levels of serum  $\beta$ -hCG levels (148 UI/mL) and asymptomatic.

First-line treatments and surgical outcomes details are available in Tables 4 and 5, respectively.

**Table 4. Treatment modalities according to ectopic pregnancy site.**

	All Patients n = 79	Cervical n = 27	Interstitial n = 23	Ovarian n = 12	Angular n = 8	Abdominal n = 6	Cornual n = 3
<b>Matter of urgency, n (%)</b>	23 (29.1%)	3 (11.1%)	5 (21.7%)	8 (66.7%)	1 (12.5%)	-	-
<b>First line medical treatment, n (%)</b>	<b>40 (50.6%)</b>	<b>18 (66.7%)</b>	<b>15 (65.2%)</b>	<b>3 (25%)</b>	<b>3 (37.5%)</b>	-	<b>1 (33.3%)</b>
Systemic MTX	20 (50%)	5 (27.8%)	9 (60%)	3 (100%)	2 (66.7%)	-	1 (33.3%)
Systemic MTX and KCL	4 (10%)	4 (22.2%)	-	-	-	-	-
Local MTX	5 (12.5%)	2 (11.1%)	3 (20%)	-	-	-	-
Local MTCX and KCL	3 (7.5%)	3 (16.7%)	-	-	-	-	-
Local KCL	1 (2.5%)	1 (5.6%)	-	-	-	-	-
Systemic MTX and PGE	2 (5%)	-	2 (13.3)	-	-	-	-
UAE	4 (10%)	2 (11.1%)	1 (6.7%)	-	1 (12.5%)	-	-
PGE only	1 (2.5%)	1 (5.6%)	-	-	-	-	-
<b>First line surgical treatment, n (%)</b>	<b>36 (45.6%)</b>	<b>7 (25.9%)</b>	<b>7 (30.4%)</b>	<b>9 (75%)</b>	<b>5 (62.5%)</b>	<b>6 (100%)</b>	<b>2 (66.7%)</b>
D&C	5 (13.9%)	4 (57.1%)	-	-	1 (20%)	-	-
Hysteroscopy +/- D&C	2 (5.6%)	2 (28.6%)	-	-	-	-	-
Laparoscopy	23 (63.9%)	-	5 (71.4%)	9 (100%)	3 (60%)	4 (66.7%)	2 (100%)
Laparotomy	5 (13.9%)	-	2 (28.6%)	-	1 (20%)	2 (33.3%)	-
Hysterectomy	1 (2.8%)	1 (14.3%)	-	-	-	-	-
<b>First line combined treatment, n (%)</b>	<b>3 (3.8%)</b>	<b>2 (7.4%)</b>	<b>1 (4.3%)</b>	-	-	-	-
PGE/MTX and Hysteroscopy	3 (3.8%)	2 (3.7%)	1 (4.3%)	-	-	-	-
<b>Second line treatment, n (%)</b>	<b>21 (26.6%)</b>	<b>16 (59.3%)</b>	<b>4 (17.4%)</b>	-	<b>1 (12.5%)</b>	-	-
Medical	10 (12.7%)	5 (18.5%)	4 (17.4%)	-	1 (12.5%)	-	-
Surgical	11 (13.9%)	11 (40.7%)	-	-	-	-	-

MTX: methotrexate; PGE: prostaglandin; KCL: potassium chloride; UAE: uterine artery embolization; D&C: dilation and curettage.

**Table 5. Surgical outcome according to UNSEP site (including combined first line treatment).**

	All Patients n = 39	Cervical n = 9	Interstitial n = 6	Ovarian n = 9	Angular n = 6	Abdominal n = 6	Cornual n = 2
<b>Estimated blood loss in millilitres, median (IQR)</b>	225 (46-675)	75 (5-3100)	45 (10-1700)	300 (45-600)	600 (50-3500)	1300 (200-3800)	150 (100-200)
<b>Delta Hb post*, median (IQR)</b>	1.25 (0.15-3.2)	1.3 (0.1-3.2)	1.25 (0.5-3.3)	2.0 (0.1-3.6)	1.5 (0.6-2.5)	2.7 (2.0-5.5)	na
<b>Blood transfusion, n (%)</b>	9 (23.1%)	3 (33.3%)	2 (33.3%)	-	1 (16.7%)	3 (50%)	-

\*: before transfusion.

IQR: interquartile range; Hb: haemoglobin; na: not available.

Cervical pregnancies (CPs) were diagnosed at median amenorrhea of 7 weeks (6-12) and the most common symptom was mild (vaginal) bleeding (56%). Patients with CPs underwent a prior cesarean section more frequently when compared to remaining UNSEPs (18% versus 38.5%;  $p = 0.04$ ). No association with ART ( $p = 0.38$ ), presence of IUD ( $p = 0.42$ ) and previous pelvic surgery ( $p = 0.59$ ) was noted. Medical treatment was the method of choice in CP (67%) but had the highest rate of failure (88%). Conversely, surgical treatment with dilation and curettage (D&C) or hysteroscopy guided resection with or without a subsequent D&C was uneventful in the majority of cases (71%). Among the CPs submitted to second-line treatment ( $n = 16$ ), most of them underwent a surgical approach (69%). A couple of cases treated with successful hysteroscopic removal of CP were treated, respectively with misoprostol and local methotrexate administration before surgery.

Interstitial pregnancies (IPs) were managed successfully with a medical approach in most of the cases (73%); worth mentioning among the IPs submitted to surgery, that 71% of them had criteria for a matter of urgency (massive bleeding). Of interest, mean  $\beta$ -hCG serum levels were 17.922 (CI95% -33514 to -2330;  $p = 0.03$ ) lower when compared to other UNSEPs. Further, all the patients with IPs, failing medical treatment were subsequently treated with a favourable outcome with a further medical approach. We did not find association with known risk factors, as pelvic inflammatory disease ( $p = 0.125$ ) and use of ART ( $p = 0.52$ ).

Ovarian pregnancies (OPs) were all managed successfully with either medical or surgical first-line treatment, and none of them required a further second-line approach. No specific risk factors were identified. Nonetheless, among the OPs submitted to surgery, we found 4 patients (44%) who underwent at least unilateral ovariectomy. Of interest, no difference was noted in the mean age of patients who underwent ovariectomy and those who did not ( $p = 0.24$ ).

Only in one woman with angular pregnancy (AnP) the first-line medical treatment failed, even though a successful outcome was achieved with a further medical approach. Nonetheless, the majority of AnPs were managed surgically, with either D&C or a more invasive laparoscopic or laparotomic uterine wedge resection.

Abdominal pregnancies (AbPs) were all treated with a surgical approach, mostly with laparoscopic access. We had three AbPs located in the pelvis, one omental pregnancy and one hepatic pregnancy; one AbP was located in an unspecified abdominal site. The hepatic pregnancy was completely managed laparoscopically, confirming the feasibility of complex surgery in the hepatic area if conducted by a skilled gynaecologist [26].

Cornual pregnancies (COPs) were extremely rare, and they were managed with cornuostomy in 75% of the cases, while the remaining one underwent successful medical treatment.

Overall, surgical treatment was mostly uneventful and resolutive, even though we noted a 23% prevalence rate of

blood transfusion (Table 5). Notably, the median drop of haemoglobin was similar for OPs and AbPs, but no blood transfusion was performed for OPs; this is probably due to the easier possibility to control the bleeding with ovariectomy in OPs, while bleeding control might be more challenge for AbPs. Moreover, CPs received blood transfusion in 33.3% of cases, but none of these patients underwent a subsequent hysterectomy.

Median duration of recovery (from the first day of treatment up to the day of discharge) was 5 days (IQR 3-11), with a shorter recovery for the patients submitted to surgical treatment, regardless site of UNSEP (median 5 versus 10 days;  $p = 0.002$ ). Negative  $\beta$ -hCG serum levels were obtained earlier in the surgical group (median 25 vs. 51 days;  $p = 0.001$ ), as well as the return to normal menstrual cycle (median 31 vs. 67 days;  $p < 0.000$ ). Notably, the post-treatment follow-up, regardless the failure of first line treatment, was shorter in the surgical group (median 32 versus 68 days;  $p = 0.003$ ). A multivariate linear regression to predict the length of hospitalisation, including the type of first line treatment (medical versus surgery) and the need of second line treatment demonstrated an increase of 3 days for medical treatment (CI95% 0.6-5.5;  $p = 0.01$ ) and an increase in 3.6 days (CI 95% 0.89-6.30;  $p = 0.01$ ) in case of the further second line treatment.

#### 4. DISCUSSION

The management of UNSEPs remains an inadequately explored clinical field due to the rarity of their presentations. We present a synopsis of the management highlighted by our personal case series, comparing with the literature. UNSEPs incidence is extremely low, but they can be life-threatening events if not promptly recognised and treated. In our series, conducted across nine hospital in the last ten years, the most common site of implantation of UNSEP is the cervix, followed by the interstitial part of the tube and the ovary. Less than ten cases were instead observed for angular abdominal and cornual pregnancies.

The incidence of CPs is less than 1% and it ranges from 1/1000 to 1/18.000 of all the EPs. Usually, they are associated with caesarean section, presence of IUD, repeated endometrial surgery and with the adoption of ART [27], while very rarely they occur in the tubal stump after bilateral salpingectomy [28, 29], however, in our case series, we found that only caesarean section is a risk factor for CPs. TU scan was used as an elective imaging tool (96.3%) as supported by literature; it allows an early diagnosis with colour Doppler study of peri-trophoblastic blood flow showing an accuracy of 100% [11]. Usually, the endocervix is eroded by trophoblast and the pregnancy develops in the fibrous cervical wall owing to the most common symptom of vaginal bleeding, that can be followed by uncontrolled haemorrhage. In our case series, we found more than half CPs with vaginal bleeding (55.5%) and near one quarter with severe bleeding (18.5%). Serum levels of  $\beta$ -hCG in CP are often below the normal value due to poor blood supply and in our case series, mean  $\beta$ -hCG serum levels were lower when

compared to other UNSEPs. Usually, in the first trimester, a conservative method was historically adopted for CPs, because of the relatively small invasion of trophoblastic tissue in the cervix, and notably, vaginal bleeding may still occur after conservative treatments. In our investigation, we found that medical options for CPs suffered a very high rate of failure; in fact, finally, 74% of these women required a surgical attempt with D&C, hysteroscopy or both [30], including one case of elective hysterectomy. Recent evidence enforces the transvaginal surgical approach for these types of pregnancy, especially if they are early diagnosed, thus the development of surgical instruments and approaches can be a shifting paradigm [31, 32].

The incidence of IPs ranges from 2% to 4% of all EPs and the interchangeable use of terminology (angular and cornual) in literature created few problems in the reported incidence. The classic symptoms of EP, namely amenorrhoea, vaginal bleeding and pain, can usually happen, but in the case of unruptured IPs, the symptoms may not arise and they can remain asymptomatic for several weeks before the rupture of the tubal segment [7]. IPs can present with rupture in approximately 20-50% of the cases [33]. In our case series, 22% of the IPs were submitted to surgical approach in view of the bleeding and, interestingly, only one patient presented with massive bleeding. Conversely, we found an IP with very low levels of  $\beta$ -hCG at 17 weeks of amenorrhoea that was successfully managed with medical treatment. In this case, the outpatient management was successful and uneventful thanks to an intensive ultrasound follow-up and  $\beta$ -hCG measurement. In literature, ultrasound parameters have a specificity of 88–93%, but a sensitivity of only 40%; however, the presence of an “interstitial line sign” has been reported to be 80% sensitive and 98% specific for diagnosis [3]. Three-dimensional ultrasound images reconstruction and MRI allow for accurate early diagnosis of interstitial pregnancy if suspected on classic TU scan [3].

OPs occur in 1/2100 to 1/60.000 pregnancies and account for 1% to 3% of EPs. OP seems to be a casual event without association to a history of infertility or previous EP and in our case series, we failed to identify relevant associated risk factors. Further, the preoperative diagnosis of this pregnancy is not easy, because OPs are characterised by a poor clinical symptomatology and a difficult ultrasound diagnosis [15], often mimicking tubal EP. The surgical approach was the preferred first-line treatment in our study, in fact, these patients were not asymptomatic at the presentation. Unfortunately, surgical management of OPs included ovariectomy in a considerable quote of women, suggesting the possibility to consider a medical approach in case of asymptomatic presentation, since fertility outcomes can be detrimental [34].

AnPs are characterised by the abnormal position of the blastocyst, on the corner of the uterine cavity and methotrexate rationale is based on the promotion of detachment of the trophoblast. These pregnancies can bring to a spontaneous rupture of the uterus due to over distension in 25-50% of cases, hence, they are considered a potential life-threatening

event [35] and similar to IPs, they can present symptoms later than other UNSEPs. We submitted to surgery the majority of the patients that finally underwent a wedge resection of the utero-ovarian structures, as most of the reports available in the literature [6]. A conservative approach using medical therapy is possible when the diagnosis is early, while only rarely expectant management can be attempted in case an ultrasound diagnosis is not satisfactory [36].

AbPs are a rare, life-threatening condition and they can be primarily located in the peritoneal cavity or secondary to a ruptured EP or tubal abortion CIT. Maternal mortality is 7.7 higher when compared to other EPs, and it is estimated to range from 2% to 30% [37]. Diagnosis of AbP follows the Studdiford's criteria and advanced AbPs with a healthy fetus, surviving up to term is extremely rare [5]. In the past, it has been reported that even when combined with clinical judgement, ultrasound only detects half of the early AbPs [36]. To our knowledge, no recent case series reports an affordable US accuracy in this condition, even though some authors state that ultrasound scan remains the first choice for preoperative diagnosis of AbP, identifying a role for MRI or diagnostic laparoscopy only in undetermined cases [33]. Failing to diagnose an AbP can have serious outcomes, in fact, surgical promptly approach is warranted. Nonetheless, minimally invasive surgery, in cases of diagnostic uncertainty can be invaluable, as in one of the cases of our case series, where an EP was located in the liver surface.

#### 4.1. Strength and Limitation

Our case series of UNSEPs is one of the largest available in the literature, with analysis of first-line treatment, related outcomes and subsequent second-line treatment.

Among the limitations, this is a retrospective case series and may not reflect, given the long observational period, all the UNSEPs managed at each centre. Further, a personal conviction of the physician and different experiences may lead to different treatment pathways for similar patients.

#### CONCLUSION

CPs were successfully managed with a surgical approach, mostly as D&C and hysteroscopy; of interest, none of these women undergo hysterectomy for concomitant surgical complication, and hence, we suggest avoiding medical treatment, even though there is an increased risk for blood transfusion. No consensus emerged for other UNSEPs, unless for AbPs that were straightforward submitted to surgery. Ovarian, angular and interstitial pregnancies suffered non-conservative approach on the utero-ovarian structures, and hence thorough counselling about a possible detrimental effect on fertility is suggested before elective surgery.

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All clinical investigations are conducted according to the Declaration of Helsinki principles. Retrospective observational studies involving the collection of anonymized existing

data have been considered by the local IRB exempt from the requirement of ethical approval.

#### HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

#### CONSENT FOR PUBLICATION

Not applicable.

#### AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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#### CONFLICT OF INTEREST

The author declare no conflict of interest, financial or otherwise.

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