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GENERAL GYNECOLOGY

# Chronic ectopic pregnancy: case report and systematic review of the literature

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## Abstract

**Background** Chronic ectopic pregnancy (CEP) is a variant of ectopic pregnancy (EP) characterized by low or absent serum human chorionic gonadotropin (hCG) levels, resistance to methotrexate (MTX), and an adnexal mass with fibrosis, necrosis, and blood clots due to repeated and gradual fallopian tube wall disintegration. CEP may complicate the course of patients with EP and is difficult to diagnose.

**Case presentation** The case of a 36-year-old woman with EP, low serum hCG levels, a small echogenic adnexal mass, and resistance to MTX is presented. Salpingectomy was performed and histology demonstrated CEP with fibrosis, necrosis, and a hematocele within degenerated chorionic villi.

**Systematic literature review** In a database search, 19 case reports, 3 case–control studies, and 3 case series describing 399 patients with CEP were identified. Serum hCG was negative in 40/124 cases (32%) with reported levels of serum hCG. The most common presenting symptom was abdominal pain (284/399 [71%]), followed by irregular vaginal bleeding (219/399 [55%]), and fever (20/399 [5%]). 73/399 (18%) women were asymptomatic. An adnexal mass was seen in 144/298 (48%) cases with perioperative ultrasound examination and with a mean largest diameter of 6.8 cm. Data on treatment modalities and outcomes were available for 297 women. Of these, 89% underwent surgery as first-line therapy. Laparoscopy was performed in most cases. MTX was the first-line therapy in a minority of cases. Complete resolution was achieved by first-line therapy in 287/297 (97%) cases. Adverse events were reported in 218 patients with CEP. Among those, adverse events ≥ grade 3 were seen in 186/218 (85%) cases. There was no case of treatment-related mortality.

**Conclusion** CEP is a variant of EP with low or absent trophoblast activity. A prolonged clinical course is typical and surgery is the mainstay of treatment.

**Keywords** Chronic ectopic pregnancy · Pregnancy · Methotrexate · Pregnancy complication · Trophoblast

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## Abbreviations

| | |
|---|---|
| CCSL | Case–control study |
| CEP | Chronic ectopic pregnancy |
| CR | Case report |
| CRP | C-reactive protein |
| CS | Case series |
| CTCAE | Common toxicity criteria for adverse events |
| EP | Ectopic pregnancy |
| hCG | Human chorionic gonadotropin |
| LAP | Laparotomy |
| LSC | Laparoscopy |
| MTX | Methotrexate |
| WBC | White blood cell count |

## Background

Chronic ectopic pregnancy (CEP) is a variant of ectopic pregnancy (EP) characterized by low or absent serum human chorionic gonadotropin (hCG) levels and resistance to methotrexate (MTX). CEP may complicate the course of patients with EP and is difficult to diagnose. It usually has a prolonged and indolent clinical course and may even resolve spontaneously [1]. Histologically, CEP is characterized by a compact adnexal mass with degenerated chorionic villi, necrosis, and multiple blood clots due to repeated small ruptures of the fallopian tube wall. Abramov et al. defined CEP as a pelvic mass with minimal symptoms and a low or absent serum hCG [2]. Bedi et al. defined CEP histologically as an adnexal mass with hematocele, blood clots, and gestational tissue, surrounded by adhesions [3, 4].

The exact incidence of CEP is difficult to assess due to its rarity and varying definitions used in the literature. For example, Cole et al. cite an incidence of 6% of all EP cases [5]. In contrast, Bedi et al. found that 28% (42/149) of EP cases fulfilled the criteria for CEP in a retrospective series with histological assessment [4]. Turan et al. retrospectively investigated the histology of 305 EP cases [6]. In this study, 62/305 cases fulfilled the criteria for CEP resulting in an incidence of 20.3%. Barnhart et al. even reported an incidence of 44% of CEP cases in a retrospective cohort study of 452 patients with EP at the University of Pennsylvania using a clinical definition [7]. Specifically, CEP was defined in this study as an EP with non-acute presentation and delayed diagnosis. In summary, when using the most stringent definitions of CEP based on histopathology, an incidence of up to 20% within the population of patients with EP can be assumed.

Physiologically, CEP is an EP with gradual disintegration of the fallopian tube walls, repeated minor ruptures, and the subsequent development of a pelvic hematocele [4]. Multiple blood clots embedded within degenerated chorionic villi and surrounded by dense adhesions are typical features of CEP [2, 4, 8, 9]. Another physiological aspect of CEP is chronic inflammation. Leukocyte infiltration, abscess formation, and elevated serum markers of chronic inflammation such as C-reactive protein have been reported [5, 10]. In line with this observation, chronic salpingitis isthmica nodosa has been found to be a risk factor of CEP [11, 12].

Ultrasonography may help with establishing a diagnosis of CEP. Abramov et al., for example, proposed aberrant vessels, arteriovenous shunting, and extensive external vascularization as typical ultrasonographic signs of CEP [2]. Turan et al. described a non-homogenous sonographic echo pattern of the adnexal mass and an absence of color Doppler flow within the adnexal mass [6]. The final diagnosis of CEP, however, is usually established after surgery on the basis of histopathology. This includes hemorrhage and blood clots, disintegration of the tubal wall, multiple minor ruptures, and areas of dense fibrosis and necrosis embedded within degenerated and/or avital chorionic villi [2–4].

To increase the awareness of CEP in the gynecologic community and to highlight the clinical characteristics, management, and prognosis of patients with CEP, we report the case of a woman with signs and symptoms of CEP and present a systematic review of the literature with case reports, case series, and retrospective case–control studies describing women with CEP.

## Case report

We report the case of a 36-year-old G2, P0 who presented to the clinic with amenorrhea of 6 weeks, a serum hCG of 4056 mIU/mL, and a dense echogenic adnexal mass of 2 × 3 cm. The uterine cavity was empty with a homogenous endometrium and no gestational sac. The patient was asymptomatic. Based on serum hCG values of 3771 and 5408 mIU/mL after 2 and 4 days, respectively, the diagnosis of EP was established. Subsequently, the patient received one course of i.m. MTX at a dose of 50 mg/m$^2$ body surface area. Due to persistently high serum hCG levels after the first course of MTX, a second and a third course were administered. After the third course of MTX, hCG finally declined over a period of 3 months and then remained at levels of around 20 mIU/mL for a period of 4 weeks. The patient was clinically stable throughout this time. CEP was suspected and the patient underwent laparoscopy. A small 3 × 3 cm compact right mass in the ampullary part of the fallopian tube was identified and right salpingectomy was performed. There were no pelvic adhesions. The histological report confirmed the diagnosis of CEP with areas of necrosis, fibrosis, and blood clots embedded within degenerated chorionic villi. Figure 1 shows a histopathological image of the CEP specimen with the tubal lumen filled with degenerated and avital chorionic villi embedded in blood clots. The postoperative course was uneventful. In this case, the diagnosis of CEP was established by the histopathological report, whereas the clinical course was not typical for CEP. This case thus underlines the difficulty in diagnosing CEP and suggests that there is a considerable overlap of clinical cases with a primarily indolent, chronic course and those with acute EP, later developing chronic features based on late diagnosis, delayed therapy, or MTX resistance.

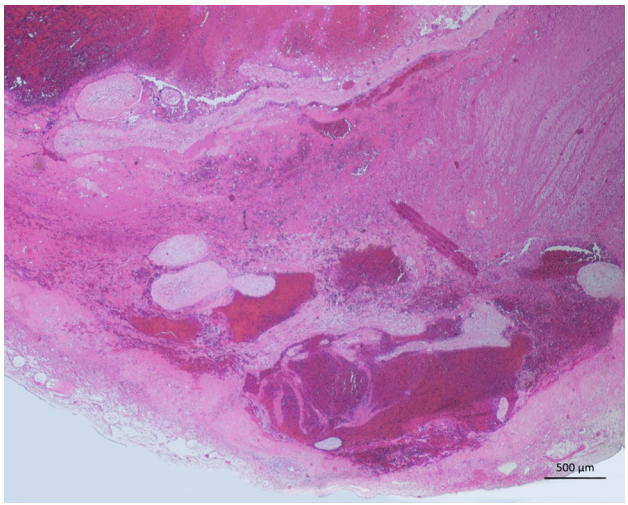


**Fig. 1** Histopathological image of a case of chronic ectopic pregnancy with tubal lumen filled with degenerated chorionic villi, blood clots, and fibrosis. Black bar, 500 µm

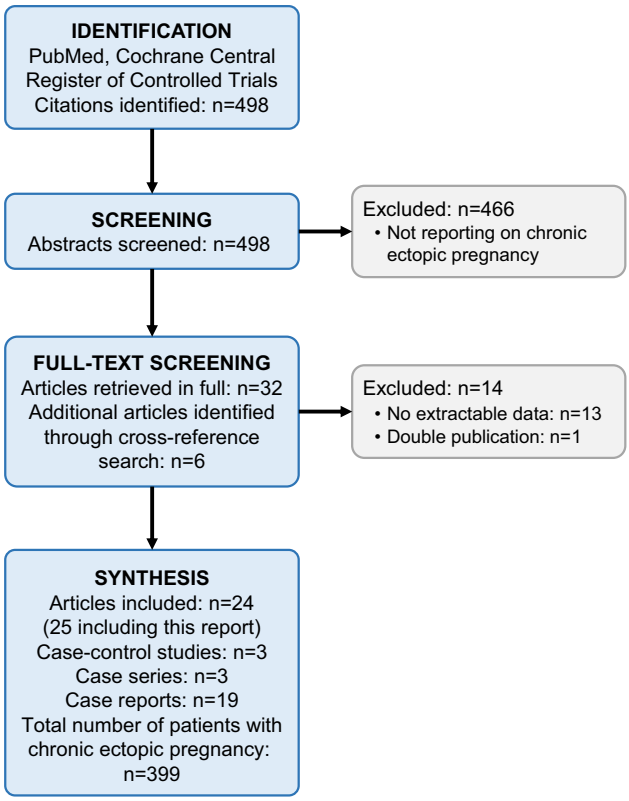


**Fig. 2** Flow diagram of the literature search algorithm

## Literature review

In a systematic literature search of the databases PubMed and Cochrane Central Register of Controlled Trials (search date 27-12-2018) using the search terms chronic[All Fields] AND ("pregnancy, ectopic"[MeSH Terms] OR ("pregnancy"[All Fields] AND "ectopic"[All Fields]) OR "ectopic pregnancy"[All Fields]), 498 citations were identified. After screening all abstracts, 32 citations were selected reporting on patients with CEP [1, 2, 4, 3, 5–7, 9, 8, 10–32], defined for the purpose of this review as chronic clinical presentation of an EP and/or low or absent hCG serum levels and/or a histological diagnosis of CEP based on local histopathological criteria but including at least 3 of the following: chorionic villi, necrosis, fibrosis, tubal rupture, hematocele, and blood clots. The 32 studies were retrieved in full and cross-reference searching was performed identifying a further 6 studies reporting on women with CEP [33–38]. Studies not reporting individual patient data and studies containing no extractable clinical data were excluded [4, 24–35]. One study was excluded because it was a double publication [23]. Therefore, in summary, 24 studies were included and analyzed for this review (25 when including the present case report). Figure 2 shows a flow diagram of the literature search algorithm. Among the 25 studies, we found 19 case reports, 3 case–control studies, and 3 case series describing in summary 399 patients with CEP.

The clinical characteristics of all studies reporting on women with CEP are shown in Table 1. The mean age of affected women was 26.7 years. The mean serum hCG level in those women who had a measurable quantitative serum hCG was 1500 mIU/mL. Serum hCG levels were reported for 124 patients and were negative in 40/124 cases (32%). Inflammation markers were only elevated in a minority of women, i.e., 14/61 (23%). The most common presenting symptom of women with CEP was abdominal pain, diagnosed in 284/399 (71%) of women, followed by irregular vaginal bleeding (219/399; 55%), and fever (20/399; 5%). An asymptomatic presentation was found in only 73/399 (18%) cases. An ultrasonographically visible adnexal mass at the time of the initial diagnosis was described in 144/298 (48%) cases with perioperative ultrasound examination and a mean largest diameter of 6.8 cm (Table 1).

The treatment modalities and outcomes of women with CEP are shown in Table 2. Relevant data were extractable for 297 women. Of these, 89% underwent surgery as first-line therapy with laparoscopy in 172/297 (58%) cases and laparotomy or laparoscopy followed by laparotomy in 92/297 (31%) cases. MTX was the first-line therapy in 33/297 (11%) of cases. Complete resolution was achieved by first-line therapy in 287/297 (97%) cases. In 10 cases (10/297; 3%), second-line treatment was necessary (MTX in 7 cases, laparotomy with adnexectomy in 2 cases, and laparoscopic salpingectomy in 1 case). Adverse events reported in individual studies were graded according to Common Toxicity Criteria for Adverse Events (CTCAE) criteria [39]. Data were available for 218 patients. Severe adverse events ≥ CTCAE grade

**Table 1** Clinical studies describing women with chronic ectopic pregnancy

| References | Year | Study type | Cases | Age (years) | Serum hCG (mIU/mL) | Inflammation marker(s) | Clinical characteristics | Ultrasonographic characteristics |
|---|---|---|---|---|---|---|---|---|
| Tempfer [this] | 2019 | CR | 1 | 36 | 4056 | WBC (9300/μL) | Asymptomatic; infertility history | 2×3 cm adnexal mass |
| Fujita et al. [9] | 2018 | CR | 1 | 41 | Negative | | Asymptomatic | 5.5 cm heterogeneous adnexal mass; prominent vascular flow |
| Kasaven et al. [37] | 2018 | CR | 1 | 27 | Negative | | Bleeding, infertility | No visible lesion |
| O' Neill et al. [38] | 2018 | CR | 1 | 26 | 3951 | | Abdominal pain | 10 cm adnexal mass |
| Vukas-Radulovic [10] | 2017 | CR | 1 | 31 | 412 | CRP (100 g/L) | Moderate abdominal pain, rectal bleeding; intrauterine device in situ | 6×5 cm hypoechoic and anechoic adnexal mass |
| Drakopoulos et al. [8] | 2014 | CR | 1 | 34 | Negative | CRP (0.6 g/L); WBC 9200/μL | Pain; bleeding | 5.6×4.5 cm heterogeneous adnexal mass |
| Nacharaju et al. [13] | 2014 | CR | 1 | 22 | 9.8 | | Asymptomatic | 8×6 cm adnexal mass |
| Harada et al. [14] | 2010 | CR | 1 | 45 | Negative | | Abdominal distension | 8 cm heterogeneous adnexal mass |
| Su et al. [15] | 2009 | CR | 1 | 35 | | | Abdominal pain | 13×11 cm heterogeneous adnexal mass |
| Allen [16] | 2007 | CR | 1 | 31 | | | Asymptomatic | Non-viable fetus in pelvis |
| Di Spiezio Sardo [17] | 2004 | CR | 1 | 28 | Negative | | Asymptomatic; infertility | Incidental finding at laparoscopy; 2 cm adnexal mass |
| Walter et al. [18] | 2004 | CR | 1 | 29 | | | Abdominal pain | – |
| Barnhart et al. [7] | 2003 | CCS | 203 | 28.5 (mean) | 1787 (mean) | | Pain (134/203); bleeding (168/203); asymptomatic (32/203)) | Non-diagnostic (150/203) |
| Brennan et al. [19] | 2000 | CR | 2 | 28; 23 | Negative (2/2) | WBC (13,700/μL) (1/2) | Pain (2/2); | 8.3×6.8 cm adnexal mass (1/2); free fluid (2/2) |
| Curry et al. [11] | 1999 | CR | 1 | 27 | 46 | | Asymptomatic; infertility | |
| Porpora et al. [20] | 1999 | CR | 1 | 30 | Negative | | Pelvic pain | 5 cm adnexal mass |
| Abramov et al. [2] | 1997 | CR | 1 | 36 | Negative | CRP (10 g/L) | Intermittent abdominal pain; adhesions | 5.4×4.6 cm adnexal mass |
| Turan et al. [6] | 1996 | CS | 55 | 28.6 (mean) | 340 (mean; $n=51$); negative ($n=4$) | WBC > 10,000/mL ($n=9$) | Abdominal pain ($n=50$); acute abdomen ($n=6$); fever ($n=7$); asymptomatic ($n=5$) | Complex mass ($n=55$); heterogeneous echo pattern ($n=48$) |
| Dunn et al. [21] | 1995 | CR | 1 | 31 | Negative | | Pain; fever | Hypoechoic adnexal mass |
| Kouam et al. [1] | 1995 | CR | 1 | 26 | | | Asymptomatic | Incidental finding at myomectomy; complete resorption |

**Table 1** (continued)

| References | Year | Study type | Cases | Age (years) | Serum hCG (mIU/mL) | Inflammation marker(s) | Clinical characteristics | Ultrasonographic characteristics |
|---|---|---|---|---|---|---|---|---|
| Bedi et al. [3] | 1984 | CCS | 22 | | Negative (8/22) | | Pain (15/22); bleeding (18/22); fever (2/22); free fluid (4/22); asymptomatic (4/22) | Complex, inhomogeneous adnexal mass (22/22) |
| Cole et al. [5] | 1982 | CS | 50 | 28 (mean) | Negative (10/11) | WBC 9300/μL (mean) | Pain (43/50); fever (10/50); asymptomatic (7/50) | |
| Romer et al. [22] | 1981 | CR | 1 | 20 | Positive (qualitative urine test) | WBC normal | Abdominal pain | 9×6 cm adnexal mass |
| Carty et al. [12] | 1976 | CS | 10 | 28 (mean) | | | Asymptomatic (10/10) | |
| Clark [36] | 1975 | CCS | 39 | | Negative (8/20) | | Pain (31/39); bleeding (30/39); asymptomatic (8/39) | |
| Pooled analysis | | CR ($n=19$); CCS ($n=3$); CS ($n=3$) | 399 | 26.7 (mean) | 1500 mIU/mL (mean); negative in 40/124 cases (32%) | Elevated in 14/61 cases (23%) | Pain (284/399; 71%); bleeding (219/399; 55%); asymptomatic (73/399; 18%); fever (20/399; 5%); history of infertility (3/399; 0.7%) | Adnexal mass (144/298; 48%); largest diameter of the adnexal mass: 6.8 cm (mean) |

*hCG* human chorionic gonadotropin, *CR* case report, *WBC* white blood cell count, *CRP* C-reactive protein, *CCS* case–control study, *CS* case series

**Table 2** Treatment modalities and outcomes of women with chronic ectopic pregnancy

| References | Year | Cases | Treatment modality (first line) | Treatment modality (second line) | Side | Histology | Outcome | Morbidity (CTCAE) | Mortality |
|---|---|---|---|---|---|---|---|---|---|
| Tempfer et al. [this] | 2019 | 1 | MTX | LSC (salpingectomy) | R | Necrosis; fibrosis; hematocele; degenerated villi | Resolution (second line) | 3 | 0 |
| Fujita et al. [9] | 2018 | 1 | LSC (salpingectomy) | | L | Hematoma; degenerated villi; adhesions | Resolution | 3 | 0 |
| Kasaven et al. [37] | 2018 | 1 | LSC (salpingostomy) | | R | Degenerated chorionic villi | Resolution | 3 | 0 |
| O' Neill et al. [38] | 2018 | 1 | LAP (adnexectomy) | | R | Adhesions, chronic inflammation, blood clots, infarcted chorionic villi | Resolution | 3 | 0 |
| Vukas-Radulovic et al. [10] | 2017 | 1 | LSC (adnexectomy) | | R | Adhesions, rectal perforation, chronic inflammation | Resolution | 4 | 0 |
| Drakopoulos et al. [8] | 2014 | 1 | LSC (salpingectomy) | | L | Inflammation; necrosis; degenerated villi | Resolution | 3 | 0 |
| Nacharaju et al. [13] | 2014 | 1 | LSC (salpingectomy) | | L | Chorionic villi | Resolution | 3 | 0 |
| Harada et al. [14] | 2010 | 1 | LSC (salpingectomy) | | R | Necrosis, adhesions | Resolution | 3 | 0 |
| Su et al. [15] | 2009 | 1 | LSC (ovariectomy) | | R | Hemorrhage, necrosis, degenerated chorionic villi | Resolution | 3 | 0 |
| Walter et al. [18] | 2004 | 1 | LSC (salpingectomy) | | R | Necrotic chorionic villi | Resolution | 3 | 0 |
| Barnhart et al. [7] | 2003 | 203 | LSC (138/203); LAP (33/203); MTX (32/203) | MTX (7/203); LAP (2/203) | | | Resolution (second line, $n=9$) | 3 ($n=171$) | 0 |
| Brennan et al. [19] | 2000 | 2 | LSC (2/2; salpingotomy; salpingectomy) | | R, R | | Resolution | | |
| Porpora et al. [20] | 1999 | 1 | LSC (salpingectomy, partial ovariectomy) | | L | Adhesions, blood clots, necrosis, atrophic chorionic villi, fibrinoid material | Resolution | 3 | 0 |
| Abramov et al. [2] | 1997 | 1 | LAP (adnexectomy) | | R | Hematoma; degenerated villi | Resolution | 3 | 0 |
| Turan et al. [6] | 1996 | 55 | LAP (n = 55); salpingectomy (n = 36); adnexectomy (n = 16); adnexectomy + hysterectomy (n = 3); colostomy (n = 2); cystotomy ($n=1$)[a] | | | | Resolution | | 0 |

**Table 2** (continued)

| References | Year | Cases | Treatment modality (first line) | Treatment modality (second line) | Side | Histology | Outcome | Morbidity (CTCAE) | Mortality |
|---|---|---|---|---|---|---|---|---|---|
| Dunn et al. [21] | 1995 | 1 | LSC (salpingectomy) | | L | Fibrosis; degenerated villi | Resolution | 3 | 0 |
| Bedi et al. [3] | 1984 | 22 | LSC (22/22) | | | Blood clots (14/22); adhesions (14/22) | Resolution | | |
| Romer et al. [22] | 1981 | 1 | LAP (adnexectomy) | | R | Adhesions, chronic inflammation | Resolution | 3 | 0 |
| Allen et al. [16] | 2007 | 1 | LAP (corneal resection) | | L | Macerated fetus; cornual pregnancy | Resolution | 3 | 0 |
| Pooled analysis | | 297 | LSC (172/297, 58%); LAP (92/297, 31%); MTX (33/297, 11%) | | R (11/17; 62%) | Adhesions (20/37); hemorrhage (20/37); degenerated chorionic villi (10/37); necrosis (5/37); fibrosis (2/37) | Complete resolution achieved by first-line treatment: 287/297 (97%) | CTCAE 3 (185/218); CTCAE 4 (1/218) | 0% |

*CTCAE* common toxicity criteria for adverse events, *MTX* methotrexate, *LSC* laparoscopy, *LAP* laparotomy, *CR* case report, *CRP* C-reactive protein, *CCS* case–control study, *WBC* white blood cell count, *CS* case series

[a]Multiple therapies in one patient possible

3 were seen in 186/218 cases (CTCAE grade 3 in 185 cases and CTCAE grade 4 in 1 case). In all studies, there was no case of treatment-related mortality (CTCAE grade 5).

Histologically, CEP lesions were extensively characterized in 37 cases. Among them, hemorrhage was seen in 20/37 cases and degenerated chorionic villi in 20/37 cases. Necrosis and fibrosis were seen less often in 5/37 and in 2/37 cases, respectively. Of note, more CEP lesions were right-sided (11/17; 62%).

The largest studies on women with CEP were published by Barnhart et al. with 203 cases [7], Turan et al. with 55 cases [6], Cole et al. in 50 cases [5], and Clark et al. with 39 cases [36].

Barnhart et al. analyzed 452 patients diagnosed with EP and divided this patient population in two groups, i.e., acute EP and CEP. CEP was defined for the purpose of this study as an EP with non-acute presentation and delayed diagnosis. According to this definition, 203 women had CEP. The authors assessed a total of 37 parameters including historic and demographic factors, findings at presentation, and treatment as well as outcome variables. Multivariable analysis demonstrated that women with CEP compared to women with EP were less likely to have received fertility medications and to present with pain. They had lower hCG serum levels at presentation and a lower chance of fallopian tube rupture. The authors suggested that differences in risk factors, clinical presentations, and outcomes of women with CEP reflect differences in trophoblast viability and invasive potential [7].

Turan et al. used stringent histopathological criteria for the diagnosis of CEP, namely chorionic villi in the presence of old blood in the peritoneal cavity, a pelvic hematocele formation, and adhesions between the tube and surrounding organs or omentum [6]. They retrospectively analyzed 62 cases identified over a period of 5 years for an incidence of 20% (62 cases of CEP in a population of 305 cases of EP). Of these 62 cases, 55 had transvaginal ultrasound examination. All 55 cases had a complex adnexal mass and 18/55 had free fluid in the pelvis. In the majority of cases (48/55), there was a non-homogenous echo pattern within the adnexal mass. Thirty women had a color Doppler flow examination, of whom none had color Doppler flow imaging within the mass. There was a negative serum hCG in 4/55 cases. The authors concluded that CEP is not a rare clinical entity and should be considered as a differential diagnosis in all women with EP with supporting evidence given by transvaginal sonography and color Doppler imaging of the adnexal mass.

Cole et al. analyzed 50 cases of CEP in a 3.5-year period [5]. The incidence of CEP in this study was 6% with 50 cases of CEP among 882 cases of EP. The authors state that CEP is characterized by hemodynamic stability, chronicity of symptoms, and a high incidence of false-negative pregnancy tests. In their series, dense adhesions and abscess formation were

additional typical findings at surgery. Surgical procedures included salpingectomy in 20 cases, salpingo-oophorectomy in 17 cases, and hysterectomy and salpingo-oophorectomy in 13 cases. Three patients required additional appendectomy. Substantial intraoperative complications were noted in 2/50 cases with cystotomy and colon perforation in 1 case each.

Clark et al. described 39 cases of CEP in a case–control study of 109 women with EP diagnosed over a period of 5 years [36]. In this study, the most common presenting symptoms besides amenorrhea were abdominal pain (present in 80% of cases) and irregular vaginal bleeding (present in 77% of cases). Less frequent complaints were rectal fullness or diarrhea in 20%, shoulder girdle pain in 12%, syncope in 10%, and dyspareunia in 7% of the cases. A palpable adnexal mass was found in 37% of the cases. Of note, 38% of these patients had last menstrual periods longer than 2 months prior to admission. The authors of this study suggest that CEP results from slow leakage of blood into the abdominal cavity or into the tubal lumen resulting in adhesions, walling off, and hematocele formation. As a result of the slow leakage, the clinical complaints of patients with CEP may spread over a long period of time.

## Discussion

CEP is a form of EP characterized by low or absent serum hCG levels and an adnexal mass with degenerated or avital chorionic villi, fibrosis, necrosis, and blood clots. In a case report and systematic review of the literature, we analyzed the clinical presentations, management, and outcomes of 399 cases of CEP. We found that the most common presenting symptoms were abdominal pain and irregular vaginal bleeding, whereas an asymptomatic presentation was only seen in 18% of cases. Of note, serum hCG was negative in a high proportion of CEP cases, namely in 32%. This is consistent with an inactive or avital trophoblast in women with CEP. At presentation, an adnexal mass was visible by ultrasonography in around half of all the cases, but no distinct morphological pattern of the CEP adnexal masses could be identified. Most authors described the ultrasonographic images of the adnexal masses as inhomogeneous or complex [13, 14, 19]. In line with the low or absent trophoblast activity in women with CEP, some authors described an absence of color Doppler flow imaging within and around the adnexal mass [6]. In our literature review, surgery was the most commonly used first-line management and it was effective in 97% of cases. The morbidity of the management was considerable with CTCAE grade 3/4 seen in 85% of cases. However, in most cases, the surgery itself was the reason for a CTCAE grade 3 classification. Specific intraoperative complications such as cystotomy or colon perforation were rare. These data underline the necessity of recognizing CEP as a potential differential diagnosis of EP with typical characteristics and disease outcomes different from the usual course of disease in EP patients.

CEP has been described in the literature as being resistant to MTX based on the low amount of active chorionic villi and minimal or absent trophoblast activity. However, based on the data in the literature, we cannot confirm this assertion. MTX was only used in 11% of CEP cases as first-line treatment. In these cases, it was mostly effective. Therefore, there are no clinical data demonstrating that MTX is ineffective in women with CEP. There may, however, be an overlap between cases of CEP and cases of EP, which are resistant to MTX. These cases may have a chronic clinical course, but they do not display the histologic features typical for CEP. Specifically, persistent EP is characterized by residual trophoblastic activity with rising or plateauing hCG after initial MTX treatment, whereas CEP is a different entity containing no active trophoblast or degenerated chorionic villi with initially low or absent hCG titers in many cases.

CEP is often described as presenting without clinical symptoms [1, 2, 7]. This is in contrast with the results of our literature review. We found that most women with CEP had clinically recognizable signs and symptoms. Specifically, the most common presenting symptom was abdominal pain in almost three quarters of women. Irregular vaginal bleeding was seen in more than half of all the cases. In fact, an asymptomatic presentation was reported in only 18% of cases. Therefore, CEP is not usually indolent, and abdominal pain and irregular vaginal bleeding must be seen as typical symptoms of both EP and CEP. Clearly, there is no typical clinical symptom of CEP. A suspected diagnosis of CEP may, therefore, only be based on a prolonged clinical course, a low or absent serum hCG level, and finally on the histological examination of the specimen. In accordance with the literature, we found that hemorrhage, degenerated chorionic villi, necrosis, and fibrosis are present in most specimens of CEP.

The most common treatment of CEP documented in the literature is surgery with laparoscopic salpingectomy used as the approach of first choice. This treatment strategy is very effective. In our literature review, we found that 97% of women with CEP were successfully treated with this strategy and only 3% needed a second-line treatment. Therefore, our data support the recommendation to treat women with CEP with laparoscopic salpingectomy.

In conclusion, we found that CEP is a distinct form of EP with low or absent trophoblast activity. It usually has a prolonged clinical course characterized by abdominal pain. An adnexal mass can be identified in most cases. Surgery with laparoscopic salpingectomy is the treatment of first choice. Gynecologists should be aware of CEP as a potential differential diagnosis in any woman with pain, adnexal mass,

or bleeding abnormalities, especially in those with a long history of amenorrhea and clinical complaints.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Consent for publication** Available.

**Availability of data and material** Available.

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