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# Non-Tubal Ectopic Pregnancy: Incidence and Diagnosis

*Aliye Nigar Serin and Özer Birge*

## Abstract

Ectopic pregnancies occur at 1-2% of all pregnancies. The most common implantation site is the fallopian tube with 95, and 5% are non-tubal located. The aim of this review is to determine the current state of data about the diagnosis and the treatment of non-tubal ectopic pregnancies. Literature is reviewed concerning cervical, interstitial, cornual, ovarian, Caesarean scar, and abdominal ectopic pregnancies from PubMed databases. Non-tubal ectopic pregnancies are often misdiagnosed and overlooked. Clinical symptoms and ultrasound must be combined to diagnose. Management may involve medical treatment with methotrexate or surgery or a combination according to patient's clinical stability and the location of ectopic pregnancy. Non-tubal ectopic pregnancies are rare but can be a life-threatening condition due to late diagnosis. Early diagnosis and treatment of patients are associated with decreased morbidity and mortality in non-tubal pregnancy and, very importantly, preserve the uterus and subsequent fertility. Increased experiences have led to choose the best way to manage non-tubal pregnancies and develop new techniques.

**Keywords:** non-tubal ectopic pregnancy, methotrexate, cervical, interstitial, cornual, ovarian, caesarean ectopic

## 1. Introduction

An ectopic pregnancy (EP) refers to the implantation of a pregnancy outside of the uterus cavity. The overall rate of EP is 1–2% in the general population and 2–5% among patients who have utilized assisted reproductive technology (ART) [1, 2]. Up to 98% of ectopic pregnancies occur in the fallopian tubes. Non-tubal ectopic pregnancies are rare, accounting for 7–10% of all ectopic pregnancies and occurring outside the uterus and tubes [3, 4], yet are associated with higher morbidity due to their late presentation and diagnostic difficulties [5–8]. There are six main locations for non-tubal ectopic pregnancies that are cervical, interstitial, cornual, ovarian, Cesarean scar, and abdominal. The main risk factors for non-tubal pregnancy include previous ectopic, history of assisted reproduction, pelvic infections, smoking, and the use of the progesterone only pill or intrauterine device [9]. Early diagnosis and treatment of patients are associated with decreased morbidity and mortality in non-tubal pregnancy and, very importantly, preserve the uterus and subsequent fertility.

## 2. Cervical ectopic pregnancy

Cervical pregnancies are rare accounting for less than 1% of all ectopic pregnancies, and the incidence is 1:2500–18,000 [3, 4, 9]. They result due to the risk of trophoblast penetration through the mucosa of cervical wall into the uterine vessels. Cervical ectopics may arise should the blastocyst pass through the uterine cavity and implant into the mucosa of the endocervical canal [10–13]. Almost 70% of cases with subsequent cervical EP have a history of dilation and curettage (D&C) in a previous pregnancy [12, 14]. Also in vitro fertilization (IVF) seems as a risk factor but often jointly with D&C and other possible risk factors; anatomic anomalies (myomas, synechiae), intrauterine device (IUD) use, and diethylstilbestrol exposure, although these are not strong associations, are difficult to isolate as an independent contributor to risk [15].

Vaginal bleeding without pain is the most common presenting symptom but in more advanced pregnancies may be coupled with abdominal pain and urinary problems. Examination findings include an enlarged, globular, or distended cervix, which is often associated with dilatation of the external os [12].

Before 1979, cervical pregnancy was almost always associated with hysterectomy because of out-of-control vaginal bleeding, and the primary diagnosis was made by histological analysis of the hysterectomized uterus [16]. Preoperative diagnosis was rarely possible. After the first ultrasound report of cervical pregnancy was published by Raskin in 1978, transvaginal ultrasonography has become the main diagnostic tool [17]. This put forward more conservative approaches that attempt to limit morbidity and preserve fertility. The majority of patients with a cervical pregnancy are women with low parity; thus, preservation of reproductive function is a priority [12].

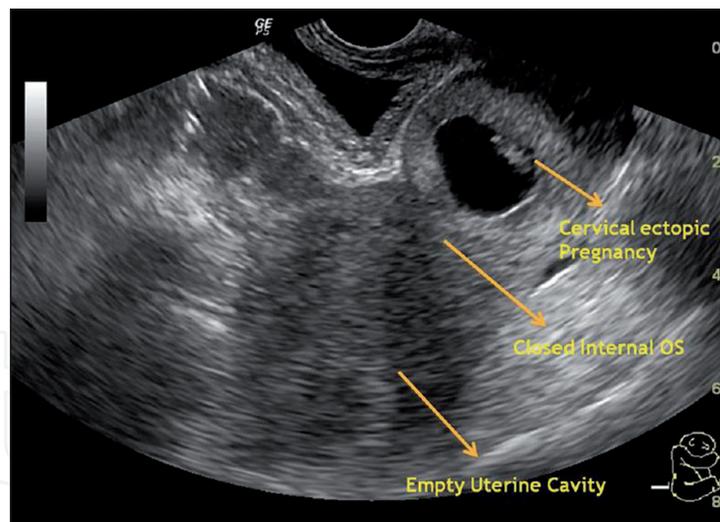
Cervical pregnancy may appear as a hemorrhagic mass, gestational sac, or presence of a fetus (with or without cardiac activity) on TvUSG [10, 12]. Defined sonographic criteria are shown in **Table 1**. A cervical EP is identified on ultrasound by a distended cervical canal containing a gestational sac (**Figure 1**), below a closed internal cervical os [19, 20], misdiagnosed as an intrauterine pregnancy with a low implantation site or a failed pregnancy imminent abortion. The “sliding sign” involves the sliding of the products of conception against the endocervical canal when gentle pressure by the sonographer during transvaginal ultrasound associated with spontaneous abortions in progress and should be absent in a cervical ectopic pregnancy [5, 6, 9].

The treatment for cervical ectopic pregnancy is unclear. If gestation is <12 weeks, with no fetal heart present and lower-serum hCG values, conservative management is most effective in women wishing to preserve fertility [21, 22].

Single- or multiple-dose systemic methotrexate (MTX) efficacy is 91%, reported in a meta-analysis [21]. MTX is more successful in pregnancies <9 weeks and with beta hCG levels <10,000 mIU/mL, CRL <10 mm, and absent fetal cardiac activity [9, 23]. The folic acid antagonist methotrexate is the most widely used systemic chemotherapy.

Anatomical structure	Sonographic appearance
Uterus	Empty
Cervix	Barrel shaped
Gestational sac	Below uterine arteries
Sliding sign	Absent
Doppler blood flow	Around sac

**Table 1.**  
*Sonographic criteria for cervical pregnancy.*



**Figure 1.**  
*Cervical ectopic pregnancy [18].*

In cervical pregnancy with embryonic heart activity, the treatment of choice is local injection of methotrexate or potassium chloride by ultrasound-guided injection [24].

In the treatment of cervical ectopic pregnancy, uterine artery ligation, uterine artery embolization, balloon tamponade, cervical curettage, cerclage, cervical stay sutures, and injection of prostaglandin F<sub>2a</sub> can be combined to control hemorrhage [3, 7, 10, 25].

Medical management must only be suggested if the patient is hemodynamically stable; otherwise, surgical treatment should be attempted as dilatation and evacuation, hysteroscopic resection, and hysterectomy.

### 3. Interstitial ectopic pregnancy

The incidence of interstitial pregnancy is 1–11% of all ectopic pregnancies. It has a high complication and maternal mortality rate, approximately 20% of all deaths caused by ectopic pregnancies [3–5]. The pregnancy implants at the junction of the interstitial part of the fallopian tube and the uterine myometrium. The main risk factor for interstitial implantation is prior ipsilateral salpingectomy; a residual “stump” of tube may form the focus of ectopic pregnancy development [26]. Symptoms are amenorrhea or spotting with or without abdominal pain.

Diagnostic criteria by ultrasound include:

1. Myometrial tissue <5 mm thick surrounded by gestational sac [26] (**Figure 2**).
2. An echogenic line between the gestational sac in the cornua and endometrial cavity named “interstitial line” has a sensitivity of 80% and specificity of 98% [4–6, 28] (**Figure 3**).
3. Empty uterine cavity and gestational sac located in the interstitial portion of the tube, >1 cm far away from cavity [4, 6, 29].

Conservative management may be appropriate in patients who are hemodynamically stable without rupture and with a low or falling beta hCG but carries a risk of uterine rupture due to the weakened myometrial wall [4]. Medical management



**Figure 2.**  
*Empty uterine cavity and gestational sac located in the interstitial portion of the tube, >1 cm far away from cavity [27].*



**Figure 3.**  
*"Interstitial line" [27].*

is to use of methotrexate either given systemically or by local injections. Single- or multiple-dose methotrexate regimens have success rates between 66 and 100% [9]. There is risk of failure due to increased vascularity, higher beta hCGs, and larger gestational sacs, so patient selection must be critical. Using systemic methotrexate in combination with gefitinib (oral epidermal growth factor receptor inhibitor) may be an alternative therapy [30].

Surgical treatment is indicated when medical management failure, according to patient preference, or if there is hemodynamic instability, severe hemorrhage, and/or findings concerning rupture, including pain or imaging evidence of hemoperitoneum. Minimally invasive surgeries are cornuostomy, salpingostomy, and cornual resection for earlier diagnosis. Cornuostomy (entails a linear incision, following the injection of dilute vasopressin at the cornua to minimize blood loss), cornual resection, or salpingostomy is being used for smaller interstitial ectopic pregnancies measuring <3.5 cm [31, 32]. Cornual resection has been recommended for advanced management of more interstitial pregnancies >3.5 cm [33, 34]. Laparotomy and hysterectomy are still the first-line treatment in patients with hemodynamic instability and severe hemorrhage. Selective uterine artery embolization can be used in conjunction with methotrexate in order to reduce hemorrhage, but there

are concerns about the safety and complications of future pregnancies after this technique [35, 36].

#### 4. Cornual ectopic pregnancy

Cornual pregnancies are one of the rare forms of ectopic pregnancy at 0.2–2% and occur in a cornua of a bicornuate uterus, in an rudimentary horn, in a unicornuate uterus, and/or in a septate uterus [37]. Cornual and interstitial pregnancies are often referred to interchangeably, but the following criteria can be used to diagnose cornual pregnancy on ultrasound examination [38]:

1. A single interstitial portion of fallopian tube in the main uterine body.
2. A mobile gestational sac surrounded by myometrium and separate from the uterus.
3. Gestational sac adjoining to the unicornuate uterus with a vascular pedicle.

Methotrexate is generally ineffective due to late diagnosis. Surgery is the main management for cornual ectopic pregnancies that includes myomectomy for an unruptured ectopic, laparoscopic cornuotomy, cornual resection, or excision of the rudimentary horn [4, 39–41]. Laparotomy and hysterectomy may prove necessary due to hemorrhage or large cornual ectopics. Elective Cesarean section is widely recommended in subsequent pregnancies because of risk of uterine rupture.

#### 5. Ovarian ectopic pregnancy

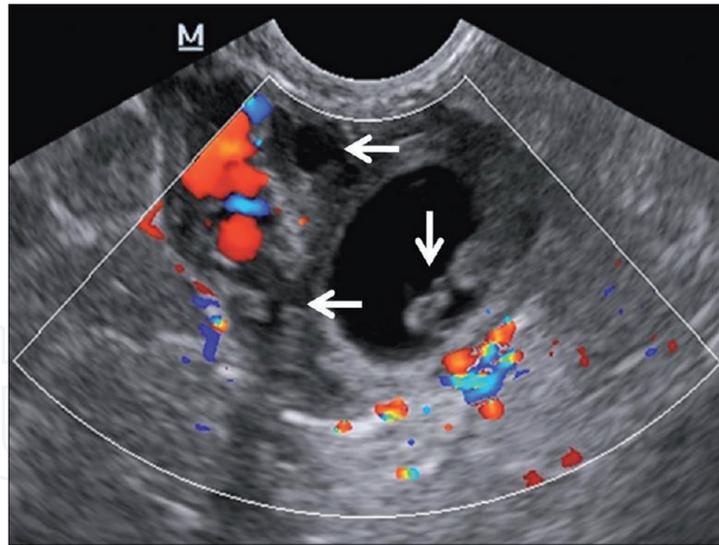
Ovarian ectopic pregnancy accounts for 3% of all ectopic pregnancies [42]. Previous pelvic inflammatory disease, endometriosis, and assisted reproductive technologies seem as risk factors [43–47]. Interference in the release of the ovum from the ruptured follicle, tubal malfunction, and inflammatory thickening of the tunica albuginea are suggested etiologies [48]; however, ovarian ectopic pregnancies have been reported in patients lacking fallopian tubes [49]. Usually symptoms present with abdominal pain and light vaginal spotting. Diagnosis can be difficult to differentiate from a hemorrhagic or corpus luteal cyst or indeed a tubal ectopic.

Diagnostic criteria described by Spiegelberg [50] (**Figure 4**):

1. Completely intact fallopian tubes.
2. Anatomically gestational sac located in the normal position at the ovary.
3. Both ovary and gestational sac connected to the uterus by ovarian ligament.
4. Placental trophoblastic tissue attached to the ovarian cortex.

Also ovarian EPs may be suspected by ultrasound when a hypoechoic area is seen with peripheral Doppler flow surrounded by a wide echogenic ring and may be completely surrounded by ovarian cortex, and a fetal pole is rarely present [38, 43].

Management is most commonly surgical, and little data is available on the medical management of this condition with systemic MTX either single- or



**Figure 4.**  
*Ovarian ectopic pregnancy [51].*

multiple-dose regimens [2]. Fifty milligrams of MTX injections directly into the ovarian EP with transvaginal or laparoscopically have also been reported as a successful management [52, 53]. MTX may also be used in the treatment of persistent trophoblastic tissue after laparoscopy [45]. Partial or total oophorectomy or ovarian wedge resection with laparoscopic surgery has become the standard for management of hemodynamically stable patients [7, 9]. Conservative resection (wedge resection) is performed in patients who want to preserve their fertility.

## 6. Abdominal ectopic pregnancy

The rarest form of ectopic pregnancies is at 0.9–1.4% and relates to implantation at sites throughout the abdomen including omentum; organs such as the liver, spleen, and bowel; large vessels; pelvic cul-de-sac; broad ligament; and pelvic side wall [4, 28, 54–56]. Abdominal ectopic pregnancy can be defined as primary or secondary; when the fimbrial end does not ‘pick up’ the ovulated follicle is primary type, tubal abortion via the fimbria and peritoneal implantation related with secondary abdominal ectopics [4, 28]. Risk factors are similar to tubal ectopic prior history of a medically treated ectopic, previous pelvic inflammatory disease, prior surgery, endometriosis, and assisted conception. Abdominal ectopic pregnancies have been described after ART, specifically after IUI [57], after IVF [58], and after Clomid [59]. Symptoms include abdominal pain, painful fetal movements, vaginal bleeding, nausea, and vomiting. Abdominal X-ray, ultrasound, or diagnostic laparoscopy are used to diagnose, although MRI may be beneficial. In several case reports, diagnosis is only made at Cesarean section [60].

Diagnostic ultrasound criteria have been suggested by Gerli et al. [61]:

1. Absence of an intrauterine gestation sac.
2. Absence of tube and a complex adnexal mass.
3. Gestational cavity surrounded by loops of bowel and separated by peritoneum.
4. Wide mobility similar to fluctuation of the sac with pressure of the transvaginal probe toward the posterior cul-de-sac.

Laparotomy and delivery with removal of the fetus with or without placental tissue are the traditional management [62]. The maternal mortality rate is eight times higher than for any other ectopic pregnancies [63, 64]. Expectant management suggested at rare reports orders to attain a live birth. If abdominal pregnancy is diagnosed after the twentieth week of gestation, expectant management can be considered with close follow-up at a tertiary health care facility. Delivery is recommended at 34 weeks if fetus has no congenital malformations, and placenta which implanted away from upper abdomen is often left in place to avoid the risk for hemorrhage [65, 66]. A few case reports have described subsequent methotrexate treatment and ultrasound-guided injection of potassium chloride [4] or radiological artery embolization to minimize blood loss before leaving placental tissue behind [28, 56, 67–69].

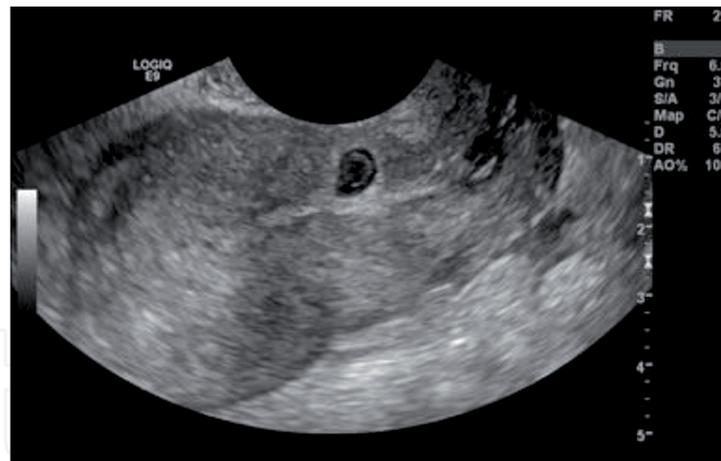
## 7. Cesarean scar pregnancy

Cesarean scar pregnancies are extremely rare, 1:2226 of all pregnancies and 6% of all ectopic pregnancies in women who have undergone at least one previous Cesarean section [4]. Scar pregnancies may be presented with painless vaginal bleeding and also associated with significant rates of uterine rupture and major hemorrhage, uterine rupture, and hypovolemic shock [50]. Risk factors include previous Cesarean, myomectomy, dilatation and curettage, adenomyosis, IVF, and manual removal of the placenta [28, 70]. The suggested theory of pathogenesis is the blastocyst enters a microscopic tract in the uterine scar and implants in the deficient uterine wall. The impact of the number of previous Cesarean sections, the time interval between Cesarean sections, and the rate of scar implantation are unclear [71–73]. With increasing rates of Cesarean section and repeated Cesarean sections, the scar surface area is getting bigger and is increasingly deficient due to fibrosis, poor vascularity, and postoperative healing, thereby leading to higher rates of blastocyst implantation [72]. Although it is suggested to use ultrasound with Doppler, hysteroscopy, and MRI to diagnose and differentiate Cesarean scar from cervical ectopic pregnancies, transvaginal ultrasound is the first-line approach [50].

Ultrasound diagnostic criteria by Jurkovic et al. [74]:

1. An empty uterine cavity without contact with the sac.
2. Gestational sac located anteriorly at the level of the internal os covering the visible or presumed site of the previous lower uterine segment of the prior hysterotomy (**Figure 5**).
3. The myometrium must be very thin (1–3 mm) or absent between the bladder and sac (**Figure 6**).
4. A negative “sliding organ sign” and the presence of peripheral Doppler flow.

There is no definitive consensus of treatment, yet first-trimester termination is recommended to prevent uterine rupture, major hemorrhage, life-threatening complications, and maternal morbidity and preserve future fertility. Term births are associated with hemorrhage and emergent cesarean hysterectomy [74, 77, 78]. Systemic methotrexate can be used in hemodynamically stable patients with an unruptured scar pregnancy, <8 gestation weeks, and a myometrial thickness of <2 mm between the pregnancy and the bladder and more successful if beta hCG level is <5000 IU/L [74]. Local potassium chloride, bilateral uterine artery injection of methotrexate



**Figure 5.**  
*Caesarean scar pregnancy [75].*



**Figure 6.**  
*Myometrial thickness of scar pregnancy [76].*

combined with embolization, and combination of gefitinib and systemic methotrexate have been described [4, 30]. Surgical approaches are uterine curettage, resection or excision with hysteroscopy, laparoscopy or laparotomy. Curettage is an accepted treatment under ultrasound guidance following chemotherapy, but it should not be performed as a first-line treatment because of complication with hemorrhage. Resection allows for revision of the lower uterine segment, which theoretically may reduce risk for recurrence [79]. Hysteroscopic resection is not recommended when the residual myometrium is less than 3 mm, given the risk of anterior wall perforation and bladder injury [80, 81]. Hysterectomy may be required for uterine rupture or more advanced pregnancies [4].

## 8. Conclusion

Non-tubal ectopic pregnancies are rare but can be a life-threatening condition due to late diagnosis. Earlier diagnosis and treatment of patients are associated with decreased morbidity and mortality in non-tubal pregnancy and, very importantly, preserve the uterus and subsequent fertility [28]. Clinicians should have a high index of suspicion in patients presenting with pain and bleeding in pregnancy and take careful note of their previous obstetric and gynecology history to identify key risk factors for ectopic pregnancy. Ultrasound criteria now exist for all non-tubal

ectopic pregnancies, facilitating early diagnosis and giving the patient options for management. It seems reasonable therefore to treat these pregnancies with a combination of local or systemic chemotherapy and/or surgical removal. Increased experiences have led to choose the best way to manage non-tubal pregnancies and develop new techniques.

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