Non-tubal Ectopic Pregnancies: Overview and Treatment via Local Injection

Andrey V. Dolinko, MD, Roxanne A. Vrees, MD, and Gary N. Frishman, MD
From the Department of Obstetrics and Gynecology, Women and Infant’s Hospital, Providence, Rhode Island (all authors), and Warren Alpert Medical School, Brown University, Providence, Rhode Island (all authors).

ABSTRACT
Ectopic pregnancies account for 1.5% to 2% of all pregnancy in the United States. Of these, approximately 10% implant in nontubal locations, including the abdominal cavity, cervix, ovary, interstitial portion of the fallopian tube, broad ligament, the uterine cornua, or within a cesarean section scar. Because these pregnancies tend to present later than typical tubal pregnancies, they have been associated with greater maternal morbidity and mortality. Advances in ultrasound technology have allowed for earlier diagnosis of nontubal ectopic pregnancies, which in turn has led to the development of novel minimally invasive techniques to manage them. One of these methods involves the local injection of 1 of several agents directly into the ectopic pregnancy. In this article we provide a guide to this technique of local injection, including an overview of the potential agents that can be used, and review the diagnostic and specific ultrasound criteria, other possible treatment options, and overall outcomes for nontubal ectopic pregnancies. Journal of Minimally Invasive Gynecology (2018) 25, 287–296 © 2017 AAGL. All rights reserved.

Keywords: Nontubal ectopic; Cesarean scar ectopic; Ovarian ectopic; Interstitial ectopic; Abdominal ectopic; Cervical ectopic; Heterotopic pregnancy; Local injection

Patient Selection

As for any other surgery or procedure, appropriate patient selection must occur before selection of the best treatment option. The first step in this process is confirming the...
diagnosis of a nontubal ectopic pregnancy. In combination with quantitative β-human chorionic gonadotropin (β-hCG) assays, transvaginal ultrasonography can confirm the absence of an intrauterine pregnancy and the presence of an extra-uterine gestation. Criteria exist for all nontubal ectopic pregnancies, although these are evolving in the era of ultrasound-based diagnosis (see Table 1 and Site-Specific Considerations, below).

Of note, it is imperative that the provider perform real-time ultrasonography to confirm the diagnosis rather than relying solely on a report. For example, there have been cases of patients taken to the operating room with a diagnosis of an interstitial ectopic pregnancy only to find a normally developing intrauterine pregnancy. If ultrasound findings are inconclusive at the time of presentation and the patient is hemodynamically stable, it is reasonable to offer expectant management with close surveillance using repeat ultrasonography and β-hCG levels. This is particularly true in the setting of a desired pregnancy. Alternatively, supplemental imaging using 3-dimensional ultrasound or magnetic resonance imaging can be performed to potentially aid in diagnosis [12].

Once the diagnosis of a nontubal ectopic pregnancy has been confirmed, local injection therapy should be considered in select patients. These include women who desire future fertility, those with heterotopic pregnancies who wish to preserve the intrauterine pregnancy, and patients who wish to avoid systemic therapy or invasive surgical management. These patients must be hemodynamically stable and should display no signs of rupture or impending rupture of the ectopic pregnancy. Furthermore, there must be no contraindications to the agent used for local treatment (see Local Injection Agents, below) [13]. It is imperative that patients opting for local injection therapy have close follow-up to ensure their safety and optimize chances for a successful outcome. Finally, providers must manage patient expectations, because the time between treatment with local injection and resolution of the ectopic mass and β-hCG levels may be several weeks to months. Patients who are unwilling or are unable to commit to such prolonged monitoring should be managed surgically.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Ultrasonic-based criteria for nontubal ectopic pregnancies</strong></td>
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<td>Type of ectopic pregnancy</td>
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| Abdominal pregnancy [6–8] | • Absent intrauterine gestation  
• Absence of a dilated tube and complex adnexal mass  
• Gestational sac, trophoblastic mass, placenta, and/or fetus seen separate from the uterus, tubes, and ovaries  
• Gestational cavity surrounded by loops of bowel and separated by peritoneum  
• Significant mobility/flushation of the sac with pressure of transvaginal probe toward the posterior cul de sac |
| Intraligamentous pregnancy [9] | • Absent intrauterine gestation  
• Gestational sac and/or fetus seen outside and adjacent to the lower part of the side of the uterus |
| Cervical pregnancy [7] | • Absent intrauterine gestation  
• Barrel-shaped cervix  
• Gestational sac or trophoblastic mass below the level of internal cervical os  
• Negative “sliding organ sign”*  
• Peritrophoblastic circulation using color Doppler |
| Cesarean scar pregnancy [7] | • Absent intrauterine gestation  
• Gestational sac located anteriorly at the level of the internal os covering the visible or presumed site of the previous lower uterine segment cesarean section scar  
• Peritrophoblastic circulation on color Doppler  
• Negative “sliding organ sign”* |
| Interstitial pregnancy [7,10] | • Absent intrauterine gestation  
• Eccentrically located gestational sac > 1 cm from endometrial stripe with continuous rim of myometrium measuring < 5–8 mm  
• Interstitial line sign† |
| Cornual pregnancy | • Pregnancy occurring in the horn of an anomalous uterus (e.g., bicornuate or unicornuate uterus) |
| Ovarian pregnancy [7,11] | • Empty uterine cavity  
• Cystic structure with wide echogenic ring on or within ovary  
• Embryo or yolk sac within the cyst is diagnostic  
• Negative “sliding organ sign”* |
| Heterotopic pregnancy | • Both intrauterine pregnancy and a tubal or nontubal ectopic pregnancy |

* Sliding organ sign is the displacement of tissue and/or organs on ultrasound when pressure is applied externally using the transvaginal or transabdominal probe.  
† Interstitial line sign is an echogenic line that runs from the endometrial cavity to the cornual region, abutting the interstitial mass or gestational sac.
Local Injection Agents

Several different agents have been used for local injection of ectopic pregnancies, including methotrexate, KCl, hyperosmolar glucose, and, less commonly, etoposide (Table 2). Of note, all agents are typically injected in a concentrated low-volume solution. Higher volumes run the risk of rupturing the gestational sac with associated hemorrhage (see Technique of Local Injection, below). Although the effect of each agent on rapidly dividing pregnancy tissue is well established, the mechanism of action of local injection therapy remains under debate. Suggested mechanisms include a direct effect of the agent, mechanical disruption of the sac, or, more likely, a combination of the two. Unfortunately, no studies have compared local injection with a specific agent to mechanical disruption alone or in combination with a placebo agent (such as normal saline). Furthermore, because only one study to date has compared two different agents with each other, agent selection should be done on a case-by-case basis. Considerations should include patient characteristics, toxicity profile and contraindications to specific agents, availability and cost, and provider experience.

Table 2

<table>
<thead>
<tr>
<th>Medication/agent</th>
<th>Dosage</th>
<th>Volume*</th>
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</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>1 mg/kg</td>
<td>2–5 mL</td>
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<tr>
<td></td>
<td>50 mg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50–75 mg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.5–100 mg</td>
<td></td>
</tr>
<tr>
<td>KCl</td>
<td>1–2 mEq/mL</td>
<td>1–4 mL</td>
</tr>
<tr>
<td>Hyperosmolar glucose</td>
<td>20%–50% solution</td>
<td>3–5 mL</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50 mg, 100 mg</td>
<td>Not reported</td>
</tr>
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* Volume may vary based on gestational age and amount of fluid in gestational sac.

Methotrexate

Methotrexate, which was first described for the management of an ectopic pregnancy in 1982 [14], functions as a folate antimetabolite by irreversibly binding to and inhibiting dihydrofolate reductase. This leads to the inhibition of DNA synthesis and repair and subsequent cellular replication. Given its mechanism of action, methotrexate interferes with actively proliferating tissues such as a developing embryo. When used systemically, methotrexate is highly effective for pregnancy cessation. With its effect on rapidly dividing cells, systemic methotrexate is potentially associated with related side effects, including dermatitis, stomatitis, conjunctivitis, skin photosensitivity, alopecia, nausea, diarrhea, transient elevation of hepatic aminotransferases, and myelosuppression. Although stomatitis and transient elevation of hepatic aminotransferases can be seen with low doses used for ectopic pregnancies, all side effects are more typically associated with high-dose protocols used for cancer treatment. However, in the interest of safety, absolute medical contraindications include alcohol abuse and chronic liver disease, immunodeficiency, and pre-existing blood dyscrasias.

Local injection of methotrexate may further mitigate these side effects by allowing for higher locally concentrated doses with less systemic absorption. However, because no studies to date have assessed the pharmacokinetics or pharmacodynamics of local methotrexate and resulting circulating levels, this agent should be avoided in patients for whom systemic therapy is contraindicated. Various dosing regimens for local methotrexate have been reported in the literature, including 1 mg/kg, 50 to 75 mg/m², and unadjusted doses of 12.5 to 100 mg, all in 2 to 5 mL of solution; no studies have compared the dosing regimens head-to-head [15–19].

Potassium Chloride

KCl is a cardiotoxic agent that can be used for local injection of pregnancies in which fetal cardiac activity is present. KCl can be safely used in patients who have the above absolute contraindications to methotrexate therapy. It is also particularly useful for heterotopic pregnancies, where isolated local injection into the extraterine pregnancy can avoid the potential systemic side effects and associated toxicity of methotrexate to the desired intrauterine pregnancy [20]. Several doses of KCl have been reported in the literature, ranging between 1 and 4 mL of 1 to 2 mEq/mL KCl solution [19,21–26].

Hyperosmolar Glucose

Hyperosmolar glucose functions as an osmotic agent that leads to cell dehydration and subsequent necrosis of trophoblastic tissue. Similar to KCl, hyperosmolar glucose can be safely used in patients with contraindications to methotrexate and for the injection of the extraterine gestation of a heterotopic pregnancy. Various concentrations ranging from 20% to 50% of hyperosmolar glucose in 3 to 5 mL of solution have been used for local injection [27,28].

Etoposide

Etoposide is a topoisomerase II inhibitor believed to cause DNA strand breaks, leading to arrest of cellular division. It is traditionally used as an antineoplastic agent. However, there have been reports of its successful use for local injection treatment in a limited number of both tubal and nontubal ectopic pregnancies with few side effects alongside preservation of fertility. Reported doses include 50 and 100 mg [29–31].

Technique of Local Injection

Various approaches, including laparoscopic, hysteroscopic, and transabdominal or transvaginal ultrasound guided
techniques, have been used for the local injection of nontubal ectopic pregnancies depending on their exact location [16,32–34]. An ultrasound-guided protocol offers several advantages. First, it offers the patient a minimally invasive approach with potentially lower morbidity, including anesthetic risks. Second, it allows for the real-time confirmation of cessation of fetal cardiac activity if present. Finally, it allows for monitoring for rupture during treatment (although this may be easier to detect and subsequently intervene under laparoscopic or hysteroscopic guidance).

Transvaginal ultrasound–guided local injection requires an ultrasound with a transvaginal probe and color Doppler capability, a long needle and needle guide, and tubing that has been primed with the therapeutic agent of choice. We typically use a 17-gauge 33-cm double-lumen in vitro fertilization needle, although the use of a variety of needles has been reported in the literature. The purpose of a double-lumen needle is to allow aspiration of sac contents and injection of the therapeutic agent through distinct ports without the issues of dead space in the tubing.

Although there is no one standard of care, we prepare and drape the patient in the normal sterile fashion in dorsal lithotomy position. Once adequate anesthesia (typically conscious sedation) is obtained, a sterile, draped transvaginal probe is introduced and the location and characteristics of the ectopic pregnancy reconfirmed. It is of particular importance to identify surrounding vascular structures and to document the presence or absence of fetal cardiac activity using color Doppler. This last step is important for when air bubbles and debris make it difficult to clearly identify cardiac activity at the end of the procedure; cessation of fetal heart activity can be definitively documented by absent color Doppler flow. Finally, the patient should be placed in reverse Trendelenburg position to identify the baseline amount of free fluid, if any, in the pelvis before the invasive procedure.

The needle is then introduced into the gestational sac under direct ultrasound guidance via a needle guide attached to the probe. Any fluid in the gestational sac should be aspirated and the volume noted. Aspiration will help mechanically disrupt the pregnancy and minimize the risk of rupture due to excessive volume when the therapeutic agent is injected. The needle can also be carefully manipulated at this time to further mechanically disrupt the pregnancy and minimize the risk of rupture due to excessive volume when the therapeutic agent is injected. A volume of the agent of choice comparable with that of the fluid aspirate is slowly injected via the previously primed tubing, which helps avoid instilling air into the gestational sac. If fetal cardiac activity is noted at the beginning of the case, intracardiac or intrathoracic injection can be performed. Of note, because the risk of rupture may be highest during this part of the procedure, the provider should be particularly vigilant for any signs of leakage or impending rupture of the ectopic pregnancy because rupture can lead to catastrophic maternal hemorrhage.

After injection the needle should be removed, and the ultrasound should be used to assess the cul de sac with the patient in reverse Trendelenburg position. An assessment of any intraoperative bleeding can be determined by comparing the amount of free fluid with the previously determined baseline assessment. If significant amounts of fluid continue to accumulate, consideration can be given to admission and observation or laparoscopy if concerning. Although controversial, if not contraindicated some physicians also give a dose of systemic methotrexate at this point as a “belts and suspenders” approach.

**Postprocedure Monitoring**

Both during local injection therapy and in the subsequent days to weeks, patients should be monitored for signs and symptoms of rupture and/or hemorrhage. In the absence of data, pelvic rest and avoidance of strenuous exercise are reasonable recommendations. β-hCG levels should be followed to resolution, with testing intervals similar to those used for patients who have undergone either single-dose or multidose systemic methotrexate protocols. For heterotopic cases, monitoring β-hCG levels is unlikely to be helpful given the preservation of the intrauterine pregnancy. Ultrasound can be used to monitor for resolution of the nontubal ectopic mass, although early ultrasounds may misdiagnose treatment failure by demonstrating the presence of free fluid or an enlarging mass [35].

**Site-Specific Considerations**

**Abdominal Pregnancy**

Pregnancies that implant within the abdominal cavity occur in approximately 1 in 8000 pregnancies and make up 1.4% of ectopic pregnancies [36]. Traditionally, a primary abdominal pregnancy has been confirmed using Studdiford’s criteria (Table 3) [23]. These criteria were defined based on the historical management via an open abdominal approach (i.e., laparotomy). Typical ultrasound findings suggestive of an abdominal pregnancy are noted in Table 1.

Although a review of 225 abdominal pregnancies showed that nearly 90% were still managed primarily via surgery, there are reports of abdominal pregnancies managed via less invasive approaches, including laparoscopy, using systemic methotrexate with or without local injection of methotrexate, KCl injection, or selective arterial embolization [23,38,39]. Similar to other gynecologic surgeries, laparoscopic management has been associated with decreased morbidity secondary to shorter surgical times and less blood loss [40]. Adjunctive techniques to further minimize blood loss have also been described, including vasopressin injection at the time of laparoscopic resection [41].

**Intraligamentous Pregnancy**

Broad ligament ectopic pregnancies are particularly rare, with incidence estimated at 1 in 183 900 pregnancies. Intraoperative diagnosis can be made when the pregnancy is noted
Cervical Pregnancy

Pregnancies that implant within the endocervical canal represent between 1 in 2500 and 1 in 18 000 pregnancies [43]. Diagnosis of a cervical pregnancy can be challenging to make. On bimanual exam, one may find a soft cervix that is disproportionately enlarged compared with the uterus. Until recently, ultrasonography was also nondiagnostic, with the differential including an intrauterine pregnancy with low implantation or an impending spontaneous expulsion of an intrauterine pregnancy. Fortunately, clear diagnostic criteria now exist (Table 1), allowing for earlier diagnosis and management.

The late diagnosis of a cervical pregnancy has historically been associated with requirement of a hysterectomy. However, with earlier diagnosis and resulting lower risk of bleeding, conservative management options are now available. Possible fertility-sparing interventions include excision of the trophoblastic tissue from the cervix via dilation and curettage (D&C) or hysteroscopic resection, cervical balloon tamponade to prevent excessive bleeding, systemic methotrexate with or without local injection therapy, and local injection therapy alone [44].

Two case series have demonstrated that local injection therapy alone can be safe and effective using different injection agents. In the first series, authors reported on the local injection of KCl in 38 women with cervical ectopic pregnancies, 22 of which had fetal cardiac activity. Three of those injections were complicated by hemorrhage that was managed with intracervical tamponade and systemic methotrexate with ultimate resolution of the ectopic. Most importantly, 18 of the 21 women who desired future fertility went on to deliver [45]. Another case series reported on 15 women with cervical ectopics managed with local injection of methotrexate. One patient had persistent vaginal bleeding and an enlarging sac requiring uterine artery embolization, and 3 women required a second local injection because of an inadequate decline in β-hCG. Similar to the other case series, 7 of 10 women who desired future fertility had subsequent successful pregnancies [46].

Cesarean Scar Pregnancy

Pregnancies implanting in a cesarean section scar can be diagnosed when trophoblast tissue is noted outside of the uterine cavity at the level of the lower uterine segment with a discontinuity in the anterior wall adjacent to the gestational sac (Fig. 1) [47]. Although originally believed to be quite rare with only 19 cases described between 1978 and 2001 [48], the incidence of cesarean scar ectopic pregnancy is increasing, likely because of the increasing number of cesarean deliveries and improved diagnosis. One study estimated that 1 in 531 women with a prior cesarean will have a cesarean scar ectopic, which may account for up to 4.2% of all ectopics [49]. In addition to prior cesarean, risk factors include prior myomectomy, prior D&C, adenomyosis, and history of manual placental extraction [50,51]. Because of their location and tendency for early invasion of the myometrium, cesarean scar ectopics can lead to catastrophic maternal hemorrhage if not diagnosed promptly.

Table 3

<table>
<thead>
<tr>
<th>Historic criteria for abdominal and ovarian ectopic pregnancies</th>
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<tr>
<td>Studdiford’s criteria for primary abdominal pregnancy (1942) [23]</td>
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<tr>
<td>1. Normal-appearing tubes and ovaries</td>
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<tr>
<td>2. Absence of uteroperitoneal fistula</td>
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<td>3. Pregnancy attached solely to the peritoneal surface</td>
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<td>4. No evidence of secondary implantation after initial primary tubal nidation</td>
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Fig. 1

Cesarean section scar ectopic pregnancy as seen on transvaginal ultrasound. The gestational sac is seen outside of the uterine cavity at the level of the lower uterine segment.
Early diagnosis has enabled the addition of various treatment options, including expectant, medical, and surgical management. Although observation may have a role in cases where the diagnosis is not clear, expectant management is inappropriate in most cases because of the risk of hemorrhage and emergency surgical management. A systematic review identified 4 randomized controlled studies and 48 case series using 14 different modalities for the management of cesarean scar ectopic pregnancy (Table 4). Based on this review, the authors recommended the following 5 modalities for stable patients with nonruptured cesarean section scar ectopic pregnancies: transvaginal resection, laparoscopic resection, uterine artery embolization with D&C and hysteroscopy, uterine artery embolization with D&C alone, or hysteroscopic resection [52].

Additionally, there is also a role for local therapy. Several small cases series have reported the successful use of local methotrexate and/or KCl. In one series, 5 of 7 patients had complete resolution of the pregnancy within 6 to 10 weeks; the other 2 patients developed heavy vaginal bleeding requiring emergent surgical management [53]. In another series, a single injection of local methotrexate was successful in 6 of 8 women, with the other 2 women requiring additional local or systemic methotrexate. Five patients went on to have successful pregnancies; 1 was diagnosed with a recurrent cesarean scar ectopic [54]. In a third case series of 11 patients treated with 50 mg of local methotrexate, treatment failure requiring additional systemic methotrexate was demonstrated in 6 patients, all of whom had β-hCG levels greater than 20,000 mIU/mL [55]. These findings are consistent with local injection in cervical pregnancies, with several studies supporting the combined use of local injection with systemic therapy for successful resolution of cesarean scar pregnancies [56–58].

**Table 4**

<table>
<thead>
<tr>
<th>Reported treatment modalities for cesarean scar pregnancies*</th>
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<tr>
<td>Expectant management</td>
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<tr>
<td>Local methotrexate</td>
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<tr>
<td>Systemic methotrexate</td>
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<tr>
<td>Local + systemic methotrexate</td>
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<tr>
<td>Needle aspiration + methotrexate</td>
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<tr>
<td>Uterine curettage (D&amp;C)</td>
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<tr>
<td>Hysteroscopy</td>
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<tr>
<td>Resection of pregnancy through a transvaginal approach</td>
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<tr>
<td>Laparoscopy</td>
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<tr>
<td>Uterine artery embolization in combination + D&amp;C, without methotrexate</td>
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<tr>
<td>Uterine artery embolization in combination + D&amp;C, with methotrexate</td>
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<tr>
<td>Uterine artery embolization + D&amp;C + hysteroscopy</td>
</tr>
<tr>
<td>Repeated high-intensity focused ultrasound ablation</td>
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<tr>
<td>Repeated high-intensity focused ultrasound ablation + hysteroscopic suction curettage</td>
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* As reviewed by Birch Petersen et al [52].

**Interstitial Pregnancy**

Interstitial pregnancies occur proximal to the isthmic portion of the fallopian tube where the gestational sac is adjacent to the interstitial line and is surrounded by the myometrium of the lateral aspect of the uterine cavity [59]. The interstitial line sign, which consists of visualization of a thin echogenic line from the endometrial cavity to the periphery of the sac in the interstitial area, has been shown to be 80% sensitive and 98% specific for diagnosing this type of ectopic (Fig. 2) [10]. These pregnancies, which are often erroneously interchangeably called cornual pregnancies (see Cornual Pregnancy, below), account for approximately 2.5% of ectopic pregnancies [60]. As with other ectopic pregnancies, a missed diagnosis can lead to catastrophic hemorrhage. Surgical
management has traditionally included either hysterectomy or cornual wedge resection, both of which are detrimental to future fertility. Minimally invasive surgical approaches have been introduced in an attempt to preserve fertility and limit blood loss; techniques reported in the literature include using an endoloop type device, injection of vasopressin, laparoscopic suturing, and hysteroscopic resection [61–65].

Once again, local and systemic medical management techniques have also been used. For stable patients with β-hCG levels at the time of treatment, less than 9000 mIU/mL of methotrexate has been reported as a viable option [66]. Two studies using systemic methotrexate injection alone in 17 patients each reported success rates of 94% and 70.5%, respectively [67,68]. Local injection may be even more effective, with 3 case series of 10 to 14 patients each treated with local methotrexate under ultrasound guidance either via a transabdominal or transvaginal approach reporting success rates of 91% to 100% [34,69,70]. Another study demonstrated success with combined local and systemic injection of methotrexate in a single patient [71]. Although both tubal patency and live births have been reported after treatment of interstitial pregnancies with local injection [71–73], more data are needed to assess the risks of recurrence and subsequent pregnancy complications among all treatment modalities.

**Cornual Pregnancy**

In contrast to interstitial pregnancies, true cornual pregnancies implant within a “horn” of the uterus, whether it be a rudimentary horn of a unicornuate uterus or 1 of the horns of a bicornuate or didelphys uterus. Because these pregnancies account for only 0.27% of all ectopic pregnancies, there has been very limited experience with their management [74]. Nevertheless, a variety of techniques has been reported for managing these rare pregnancies, including local injection, laparoscopic, and open surgical techniques. As with other rare presentations, treatment of cornual pregnancies should be performed by experienced providers.

**Ovarian Pregnancy**

Primary ovarian pregnancies, which account for approximately 3% of ectopic pregnancies, occur when a fertilized ovum implants on the surface of the ovary [60]. No single cause is known, but hypothetical mechanisms include reflux of the fertilized oocyte back into the ovary, interference of the release of the ovum from a follicle, malfunction of the fallopian tubes, and inflammatory thickening of the tunica albuginea [75]. Diagnosis is difficult but can be confirmed via pathologic examination based on the classic criteria suggested by Spiegelberg in 1873 (Table 3) [37,76]. Today, similar to all nontubal ectopics, ultrasound is beginning to play a more prominent role in diagnosis and may lead to changes in the formal definitions of these pregnancies [77]. The definitive finding on ultrasound to confirm the diagnosis of an ovarian pregnancy is the presence of a fetal pole with a fetal heartbeat within the ovary (Fig. 3). More common findings such as a cyst with a wide echogenic ring may be initially misdiagnosed as a corpus luteal cyst [5].

Management of ovarian pregnancies has traditionally been surgical. Laparoscopic approaches include ovarian wedge resection and ovarian pregnancy enucleation. Several case reports have also been published on successful laparoscopic-guided local injection of methotrexate or etoposide [78,79]. In an attempt to preserve fertility, oophorectomy should be used only as a last resort. Medical management of ovarian pregnancies has also been reported, both with systemic and ultrasound-guided local injection of methotrexate [77,80].

**Heterotopic Pregnancy**

Heterotopic pregnancies, which are defined by the presence of an intrauterine pregnancy and a tubal or nontubal ectopic pregnancy concurrently, account for 1 in 4000 of all pregnancies and up to 1 in 100 in vitro fertilization pregnancies [81]. Management of a heterotopic pregnancy revolves around a patient’s desire to preserve the intrauterine pregnancy. For these patients, local injection has been successfully used to terminate the ectopic component of heterotopic pregnancies rather than a more aggressive approach such as laparoscopy [27,82,83]. As described above, agents other than methotrexate should be used in the local injection management of heterotopic pregnancies. Unfortunately, local injection may not be effective for cervical heterotopic pregnancies, with adverse outcomes including miscarriage of the remaining pregnancy, preterm delivery, and maternal hemorrhage [84].

**Conclusion**

Because of their late presentation and challenges in diagnosis, nontubal ectopic pregnancies have traditionally been
associated with significant maternal morbidity and mortality. With improvements in ultrasound technology and the development of clear diagnostic imaging criteria for different types of nontubal ectopic pregnancy, earlier intervention has led to decreased mortality and increased fertility preservation. Earlier diagnosis has also allowed for the advent of minimally invasive management approaches.

As described in this article, in carefully selected patients meeting appropriate criteria, local injection of methotrexate, KCl, hyperosomolar glucose, or etoposide is a viable approach. Patients who desire future fertility and/or wish to avoid more invasive surgery may be particularly appealing candidates. Local injection can be performed under transvaginal or transabdominal ultrasound, hysteroscopic, or laparoscopic guidance. Although these local approaches may mitigate the morbidity associated with open surgical approaches, the risks of massive hemorrhage and need for further surgical intervention persist. As such, providers attempting this technique should have appropriate training and experience and access to emergency services and operating suites.

Furthermore, although numerous case reports and case series have been published on local injection techniques and the associated complications and successes, no studies to date have compared the different agents with each other. Although it would be difficult to perform given the rare nature of each type of nontubal ectopic pregnancy, multicenter randomized controlled studies should be attempted to assist with the selection of appropriate candidates and to compare local therapy, systemic therapy, and surgical options. In the meantime, providers should consider local injection therapy as part of their armamentarium to treat nontubal ectopic pregnancies.

References


