Conservative management of nontubal ectopic pregnancies

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Objective: To report successful conservative management of nontubal ectopic pregnancies.
Design: Retrospective case series.
Setting: University tertiary-care hospital.
Patient(s): Sixty-four women with diagnosis of nontubal ectopic pregnancies (cervical, cornual, and cesarean section scar) were treated with minimally invasive procedures.
Intervention(s): Systemic methotrexate alone or combined with ultrasound-guided fetal intracardiac injection of potassium chloride.
Main Outcome Measure(s): Success of the treatment, preservation of the uterus, rate of serious complications, and the need for additional interventions.
Result(s): Conservative treatment was successful in 63 patients with nontubal ectopic pregnancies. One patient had rupture of cornual pregnancy and underwent cornual resection. None of the patients in this case series required hysterectomy. This series included four patients with heterotopic pregnancies, three of whom continued intrauterine pregnancy to term gestation after conservative treatment. Seven patients experienced minimal morbidity that was treated with additional nonsurgical interventions.
Conclusion(s): Conservative management and fertility preservation is feasible in most nontubal ectopic pregnancies. (Fertil Steril 2011;96:1391–5. ©2011 by American Society for Reproductive Medicine.)
Key Words: Cervical ectopic pregnancy, cornual ectopic pregnancy, cesarean section scar pregnancy, conservative management, potassium chloride, methotrexate

Nontubal ectopic pregnancies comprise pregnancies implanted at sites other than the fallopian tube. These ectopic pregnancies may implant in the cervix, cesarean section scar, cornua of the uterus, ovary, or abdominal cavity. Nontubal ectopic pregnancies were considered rare occurrences in the past, but they are becoming more common in recent years. The chief reasons for the rising incidence of these ectopic pregnancies worldwide include increase in pregnancies with assisted reproductive technologies and increase in cesarean section rates. The diagnosis of nontubal ectopic pregnancy is difficult and requires high suspicion and ultrasound expertise. Advances in ultrasound technology and the availability of quantitative β-hCG have made diagnosis of such pregnancies possible at early gestation. In the past the traditional treatment of nontubal ectopic pregnancies has been hysterectomy or extensive cornual resection, which is associated with high morbidity and loss of reproductive function. Conservative management of nontubal ectopic pregnancies is possible now, although there is no universally accepted protocol to effectively treat these ectopic pregnancies. Nevertheless, conservative medical treatment and less-invasive interventions, if successful, should be the preferred treatment in these pregnancies.

Most published information regarding conservative treatment available at present is only pertaining to cervical ectopic pregnancies, and it is mostly in the form of case reports or small case series. Different conservative or minimally invasive treatments for cervical ectopic pregnancies have been reported. Methotrexate, mifepristone, and misoprostol all have been used successfully to terminate and expulse the cervical ectopic gestation. Use of local or systemic methotrexate injections has been the most common treatment modality (1, 2). Other interventions include ultrasound-guided injection of potassium chloride (KCl), curettage and tamponade, amputation of the cervix, cervical cerclage, Foley catheter placement in the cervical canal, internal iliac artery ligation, angiographic uterine artery embolization, intracervical carboprost injection, and needle aspiration of the products (3–5). Alternatively, methotrexate or KCl can be injected directly into the gestational sac or fetus under ultrasound guidance. Methotrexate injection into the cervical ectopic pregnancy along with systemic methotrexate has also been reported to be a successful method (2, 6). Some authors have reported the use of minimally invasive laparoscopic surgery or hysteroscopic excision in management of these pregnancies (7–9). All these conservative management modalities have been reported with a high degree of success and with minimal morbidity.

Reports of successful conservative treatment of nontubal ectopic pregnancies are sparse. In nontubal ectopic pregnancies, early diagnosis is of utmost importance, because conservative treatment is highly successful and morbidity is minimal in early ectopic pregnancy. Conservative treatment is still possible in advanced nontubal
ectopic pregnancies; however, the treatment can be associated with increased morbidity. Advanced pregnancies often require multiple combination treatments over a prolonged period, with attendant higher morbidity. Hemorrhage is one of the significant complications associated with nontubal ectopic pregnancies, and it may require interventions such as tamponade with Foley’s catheter in cases of cervical or cesarean section scar ectopic pregnancy. Other interventions to control acute hemorrhage in nontubal ectopic pregnancy include placement of a cerclage suture for cervical ectopic pregnancy, and embolization of the uterine arteries. The availability and use of these highly successful interventions to control acute hemorrhage in nontubal ectopic pregnancies have drastically reduced the need for hysterectomy. Thus, modern conservative treatment of ectopic pregnancies has overall brought highly successful outcomes with minimal morbidity and preservation of reproductive function.

The objective of this study was to report our experience of the efficacy of the conservative treatment protocol that we follow at our institution in the management of nontubal ectopic pregnancies. The primary outcome in this study was preservation of reproductive function. Secondary outcomes were to determine the incidence of complications and the need for additional treatment in management of these pregnancies.

MATERIALS AND METHODS
We performed a retrospective review of all nontubal ectopic pregnancies diagnosed at our institution between January 1, 2000 and December 31, 2010. The institutional review board of Miller School of Medicine at the University of Miami approved this study. The electronic data of patients with diagnosis of nontubal ectopic pregnancies (cervical, cornual, cesarean section scar, heterotopic), maintained at our center’s Electronic Health Record, were collected and analyzed. The diagnosis of nontubal ectopic pregnancy was made with transvaginal ultrasound examination and serum quantitative \( \beta \)-hCG levels in all cases. All pregnancies were diagnosed by a physician with expertise in gynecologic ultrasound imaging. A cervical pregnancy was diagnosed by the criteria established by Timor-Tritsch et al. (1) and Rasin (10). Figure 1 shows a transvaginal ultrasound image of a cervical ectopic pregnancy. Cesarean section scar pregnancy was diagnosed by the presence of ultrasound features diagnostic of cesarean section scar pregnancy described by Vial et al. and Jurkovich et al. (11, 12). Figure 2 shows a transvaginal ultrasound image of a cesarean section scar ectopic pregnancy. Cornual ectopic pregnancies were diagnosed by the criteria described by Timor-Tritsch et al. (13). Supplemental Figure 1 (available online) shows a transvaginal ultrasound image of a cornual ectopic pregnancy.

All patients were counseled regarding the treatment options at the time of diagnosis. Options included medical management with a minimally invasive approach or surgical treatment, which included conservative surgical resection or hysterectomy.

The treatment protocol used in the conservative medical management of all cases of nontubal ectopic pregnancies included systemic methotrexate injection alone or a combination of systemic methotrexate with fetal intracardiac injection of KCl solution as previously reported by our group in the management of cervical ectopic pregnancies (14). Systemic methotrexate was administered in doses between 50 and 75 mg/m\(^2\) body surface area. All patients in whom a viable fetus was present in the ectopic pregnancy underwent ultrasound-guided injection of 2 mL (2 mEq/mL) KCl into the fetal heart to achieve cardiac asystole. After conservative treatment, all patients were followed by serial \( \beta \)-hCG levels, and if the decline in \( \beta \)-hCG levels was not appropriate (more than 15% over the baseline) after 1 week of initial treatment, then a repeat dose of methotrexate was given. Patients underwent a follow-up transvaginal ultrasound examination only if indicated clinically, such as for symptoms of abdominal pain or significant vaginal bleeding.

RESULTS
During the study period from January 1, 2000 to December 31, 2010, a total of 68 nontubal ectopic pregnancies were diagnosed and
Four patients among the group opted for surgical management: cornual ectopic resection (three cases) and hysterectomy (one case). The remaining 64 nontubal ectopic pregnancies were treated by conservative minimally invasive treatment, and they constitute the study material for this analysis. Of these 64 pregnancies, 29 were cervical, 23 cornual, and 12 were cesarean section scar pregnancies. Only one pregnancy in this series was from IVF, and the remaining pregnancies were the result of spontaneous conception. Two patients (3.1%) had twin gestations in this series, one of which was a cervical ectopic twin pregnancy identified at 7 weeks and the other a cesarean section scar ectopic twin pregnancy identified at 8 weeks, 4 days. Four patients (6.2%) had heterotopic gestations with a combination of cervical and intrauterine pregnancies. All heterotopic pregnancies were identified within the first 7 weeks of pregnancy.

More than half of these patients had a history of previous cesarean section or a history of termination of pregnancy (Table 1). The demographic features and initial laboratory findings in these 64 patients are summarized in Table 1.

The mean gestational age was similar in all the subgroups, with a wide variation in the range of gestational age (Table 1). Initial β-hCG levels also varied extensively among our study patients (Table 1). In half of the cases fetal cardiac activity was detected. Three cervical ectopic pregnancies had spontaneous resolution of

### TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Cervical</th>
<th>Cornual</th>
<th>C/S scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>64 (100)</td>
<td>29 (45.3)</td>
<td>23 (35.9)</td>
<td>12 (18.8)</td>
</tr>
<tr>
<td>Mean age (range) (y)</td>
<td>30.5 (18–42)</td>
<td>34 (22–42)</td>
<td>29.7 (18–40)</td>
<td>27.8 (22–37)</td>
</tr>
<tr>
<td>Median parity (range)</td>
<td>1 (0–6)</td>
<td>1 (0–5)</td>
<td>1 (0–5)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Median gravidity (range)</td>
<td>3 (1–9)</td>
<td>3 (1–7)</td>
<td>3 (1–7)</td>
<td>6 (1–7)</td>
</tr>
<tr>
<td>Fetal cardiac activity</td>
<td>36 (56.2)</td>
<td>19 (65.5)</td>
<td>9 (39.1)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>History of previous C/S</td>
<td>22 (34.4)</td>
<td>6 (20.7)</td>
<td>5 (21.7)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>History of uterine curettage</td>
<td>15 (23.4)</td>
<td>5 (17.2)</td>
<td>6 (26.0)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Mean EGA (range) (wk)</td>
<td>7.7 (5.1–19.5)</td>
<td>7.6 (5.1–19.5)</td>
<td>7.3 (5.6–12.2)</td>
<td>8.1 (6.1–11.6)</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>34 (53.1)</td>
<td>19 (65.5)</td>
<td>9 (39.1)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Mean β-hCG (mIU/mL) at presentation (range)</td>
<td>35,255 (165.5–341,603)</td>
<td>30,879 (165.5–179,900)</td>
<td>12,770 (250–65,257)</td>
<td>62,116 (1,053–341,603)</td>
</tr>
</tbody>
</table>

Note: Values are number (percentage) unless otherwise noted. C/S = cesarean section; EGA = estimated gestational age.
pregnancy. Two cervical ectopic pregnancies, which resulted in spontaneous resolution, had low initial β-hCG levels and a small gestational sac. The third cervical pregnancy that resolved spontaneously was a heterotopic pregnancy with successful continuation of intrauterine pregnancy. Twenty-five patients (40.9%) were treated with systemic methotrexate alone and did not require additional treatment. Thirty-three pregnancies (54%) with fetal cardiac activity needed ultrasound-guided fetal intracardiac KCl injection along with methotrexate. Table 2 summarizes the treatment modality used in each category of ectopic pregnancy. Three heterotopic pregnancies were managed by intracardiac KCl injection alone. Thirty-two patients received single-dose IM methotrexate therapy, and 25 patients received two doses of IM methotrexate therapy. One patient with advanced cervical pregnancy at 19 weeks, 4 days was treated with multiple doses of methotrexate with leucovorin rescue. The methotrexate dosage given to this patient was according to the protocol established for treatment of gestational trophoblastic disease. This patient had prophylactic bilateral uterine artery embolization to avoid serious hemorrhage. This patient required evacuation of the fetal products and cervical curettage 4 weeks after initial treatment. One other second-trimester cervical pregnancy patient also needed removal of the fetal bones and curettage, and in that case evacuation of products of conception was performed 8 weeks after initial treatment.

Seven patients (10.9%) in this series experienced bleeding during or after conservative treatment that required other interventions. Two patients needed embolization to control the hemorrhage. In one case the bleeding was effectively controlled by embolization alone, whereas the other patient with twin cervical ectopic pregnancy who presented with bleeding before treatment required embolization and cervical curettage. One patient experienced chronic hemorrhage and cervical curettage 4 weeks after initial treatment. One other second-trimester cervical pregnancy patient also needed removal of the fetal bones and curettage, and in that case evacuation of products of conception was performed 8 weeks after initial treatment.

Two patients needed embolization to remove the retained fetal bones. In one of them (19 weeks, 4 days gestation) severe hemorrhage occurred even after prophylactic bilateral uterine artery embolization. In both cases the bleeding was effectively controlled by Foley’s catheter tamponade. One patient with cornual ectopic pregnancy needed laparoscopic surgical cornual resection after methotrexate and KCl treatment owing to rupture of the cornual pregnancy 4 days after the methotrexate treatment.

Out of four heterotopic pregnancies, in three patients intrauterine pregnancy successfully continued to term. One patient with heterotopic pregnancy had spontaneous miscarriage of intrauterine pregnancy at 15 weeks of gestation.

Overall we have a limited follow-up on many of these patients at our center because most of them were referred to us for the treatment of ectopic pregnancies only. However, our subsequent enquiry revealed that at least 10 patients in this cohort went on to have successful intrauterine term pregnancies and live births. These included the two patients with second-trimester cervical ectopic pregnancies who underwent successful conservative management.

**DISCUSSION**

We previously reported successful treatment of cervical ectopic pregnancies with minimal morbidity (14) and now extend in this report the use of a similar protocol to other nontubal ectopic pregnancies at our institution. We observed that most nontubal ectopic pregnancies could be managed by minimally invasive treatment with preservation of fertility. Unfamiliarity with these pregnancies among physicians in the community often results in misdiagnosis and less than optimum management. Patients with these unusual pregnancies are generally referred to tertiary centers at a later gestational age. The delay in diagnosis is associated with a higher morbidity and requires additional procedures for management. Identification of these ectopic pregnancies requires diagnostic ultrasonic expertise, but if timely diagnosed they can be managed in conservative manner with minimum morbidity and with preserved fertility.

Ours is a referral center, and despite our extensive community physician outreach, we sometimes see these missed ectopic pregnancies at a later gestational age. Early diagnosis of ectopic gestation for successful conservative treatment cannot be overemphasized. Although conservative management is possible in advanced nontubal ectopic pregnancies, these are then associated with higher morbidity and may require the use of multiple conservative modalities (15). In our series of 64 patients, we had two second-trimester cervical ectopic pregnancies. These two cases had a complicated clinical course requiring the use of multiple treatment modalities (higher doses of methotrexate, uterine artery embolization, removal of fetal products, cervical curettage, tamponade with Foley’s catheter, and prolonged hospitalization) for effective management.

Doubilet et al. (16) reported a case series of 27 patients with pregnancies at unusual location managed conservatively. Potassium chloride injection alone into the ectopic gestational sac or fetus under transvaginal or transabdominal ultrasound guidance was reported to be successful in these nontubal ectopic pregnancies (16). Monteagudo’s group treated 18 cases of live ectopic pregnancies conservatively, which included tubal and nontubal ectopic pregnancies, by either ultrasound-guided KCl or methotrexate injection (3). Both agents were reported to be successful in the resolution of the pregnancies (3). Ours is the largest case series to our knowledge reporting successful conservative management of “nontubal” ectopic pregnancies.

We used the protocol we initially established at our institution for the treatment of cervical ectopic pregnancies to manage all nontubal ectopic pregnancies.
ectopic pregnancies. As we reported previously (14), we observed that systemic methotrexate treatment alone is adequate for effective management of nontubal ectopic pregnancies at early gestations. We believe that when the cardiac activity is present, intracardiac KCl should be injected to achieve cardiac asystole, and that this intervention improves the efficacy of systemic methotrexate treatment. In our experience, such a relatively simplified protocol has helped in guiding other physicians in managing these early-stage pregnancies. Practically all early nontubal pregnancies can be managed skillfully with preservation of the fertility with this protocol. Severe hemorrhage is a potential complication during the conservative management of tubal or nontubal ectopic pregnancies. Therefore, these patients require close clinical monitoring. Access to a facility with angiographic embolization is required in some cases of severe hemorrhage (17). Uterine artery embolization can be combined with conservative medical treatment to prevent or decrease the risk of bleeding. In our series, two patients required emergency embolization to control the bleeding. In one case of advanced cervical pregnancy, we performed prophylactic uterine artery embolization to avoid the expected profuse hemorrhage during the removal of the products of conception. We had a total of three cases with profuse hemorrhage (including the case with prophylactic embolization), and we found that Foley’s catheter tamponade immediately controlled the hemorrhage in all these cases. In one of them, the patient presented to the emergency room with profuse hemorrhage 4 weeks after treatment of cesarean section scar pregnancy. The bleeding was immediately controlled in the emergency room with Foley’s catheter tamponade intervention. The other two patients managed with this modality were with second-trimester cervical ectopic pregnancies. Foley’s catheter is easily available and can be very effective immediately, whereas arterial embolization requires radiologic intervention and may not be available in a timely manner.

An overview of the published literature indicates that there is no standardized protocol for the management of nontubal ectopic pregnancies. On the basis of our experience, we recommend that features such as clinical presentation, gestational age, initial β-hCG levels, and presence or absence of cardiac activity should be the guiding factors in determining the treatment modality. Conservative management of advanced nontubal ectopic pregnancy should be managed at a tertiary-care center with greater experience, facilities for blood transfusion, and expertise for emergency radiologic interventional procedures.

In conclusion, nontubal ectopic pregnancies, which were considered rare in the past, are now becoming more common because of increased use of assisted reproductive technology and increase in cesarean section rates worldwide. A high level of suspicion along with expertise in ultrasound is instrumental to correctly diagnose these pregnancies during the early stages. In all these pregnancies, early diagnosis is the key because conservative treatment in early stages is highly successful with no or minimal morbidity. In fact, management of these early pregnancies by medical treatment and the least invasive interventions can be considered the current standard of care. Advanced pregnancies can be associated with higher morbidity and may require multiple interventions and therefore should be managed at a tertiary-care center with facilities for blood transfusion and emergency radiologic intervention.

REFERENCES

Transvaginal sonogram shows cornual ectopic pregnancy with very thin myometrium at the site of implantation (arrow).