We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Non-tubal Ectopic Pregnancy: Diagnosis and Management

Adebayo A. Adeniyi and Christopher A. Enakpene

Abstract

Ectopic pregnancy is the leading cause of maternal mortality in the first trimester, and prompt diagnosis and intervention are essential to ameliorate its associated complications. A majority of ectopic pregnancies are tubal, but extra-tubal pregnancy may pose more challenges in diagnosis and treatment. Early diagnosis of extra-tubal pregnancies requires high index of suspicion using transvaginal ultrasound and at times complemented with the help of magnetic resonance imaging. Similar to tubal pregnancy, extra-tubal ectopic pregnancies can be treated using surgical approach via laparotomy versus laparoscopy, or medical intervention with methotrexate, potassium chloride and most recently, mifepristone and epidermal growth factor inhibitor (gefitinib). For abdominal and ovarian ectopic pregnancies, the best surgical approach is via laparotomy or laparoscopy, while for cervical ectopic pregnancy and cesarean scar pregnancy (CSP), initial medical treatment with methotrexate, then suction curettage under ultrasound guidance, or hysteroscopic resection can suffice. All patients with extra-tubal pregnancy should be well counseled about the associated complications, fertility preserving intervention, and need for prolong monitoring especially those that choose medical therapy.

Keywords: cervical, ovarian, abdominal, cesarean section scar, interstitial, pregnancy, medical, surgical, treatment

1. Introduction

Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the normal endometrial lining of the uterine cavity, and it accounts for 1–2% of all pregnancies [1, 2]. The true incidence of ectopic pregnancy is unknown but it accounts for 18% of women seen in the emergency room for first trimester vaginal bleeding, or abdominal pain, or both [3]. Moreover, ruptured ectopic pregnancies are responsible for 2.7% of all pregnancy-related deaths, and it is the leading cause of hemorrhage-related mortality [4]. About 95% of ectopic pregnancies occur in the oviduct or the Fallopian tube, while the remaining 5% occur in different locations such as the cervix, ovary, abdominal cavity and previous uterine scar especially cesarean section scar [5]. There have also been reported cases of ectopic pregnancy in unusual locations such as the intrahepatic ectopic pregnancy.

2. Etiology and risk factors

The risk factors for tubal ectopic pregnancy are well known, and this include poorly treated pelvic inflammatory disease (PID) mostly due to chlamydia and gonorrhea, history of ectopic pregnancy, tubal surgeries including tubal sterilization procedure, pelvic surgery and congenital anomalies of the Mullerian duct such as abnormally long fallopian tubes, unicornuate or bicornuate uterus. Other risk factors include infertility, smoking, use of intrauterine contraceptive device (Levonorgestrel impregnated or Copper IUD), and utero exposure to diethylstilbestrol. While the causes of extra-tubal pregnancy are less defined, it is clear that assisted reproductive techniques have contributed significantly to the incidence of all ectopic pregnancies especially the extra-tubal pregnancies [6].

3. Ovarian pregnancy

Ovarian ectopic is also a rare variant of extra-tubal ectopic pregnancy. It accounts for about 0.5% of all ectopic pregnancies [7]. The incidence of ovarian ectopic pregnancy after natural conception ranges from 1 in 2000 to 1 in 60,000 deliveries and accounts for 3% of all ectopic pregnancies among intrauterine devices users [7]. Most ovarian ectopic pregnancy (OEP) will rupture before the end of the first trimester, but few cases that progressed to term have been reported.

Risk factors for ovarian ectopic pregnancy:

1. Embryo migration related to the presence of certain conditions that cause fallopian tube epithelial damage that alters tubal motility [8].

2. A hindrance in the release of the ovum from the ruptured follicle [9].

3. Inflammatory thickening of the tunica albuginea [10].

4. IUD insertion is the most significant risk factor for primary OEP in 57–90% of the cases [8, 9]. This is because IUD provider protection for intrauterine implantation, but it does not prevent ovarian implantation [11].

Criteria for diagnosis of ovarian pregnancy as described by Spiegelberg in 1878:

1. Fallopian tube on the ipsilateral (affected) side must be intact.

2. The gestational sac must occupy the normal anatomical position of the ovary in the ovarian fossa (see **Figure 1**) [12].

3. The gestational sac is connected to the uterus by the ovarian ligament.

4. Ovarian tissue must be found on the wall of ectopic pregnancy on histological examination [13].

3.1 Treatment

The classical management of ovarian pregnancies is surgical. Early bleeding for small lesson has been managed by ovarian wedge section or cystectomy [14]. With larger lesions, ovariectomy is most often performed and this can be performed via laparotomy or laparoscopy which can be used to excise the gestational sac, to perform laser ablation or use of bipolar electrocoagulation. Methotrexate has been used successfully to treat unruptured ovarian ectopic [15].

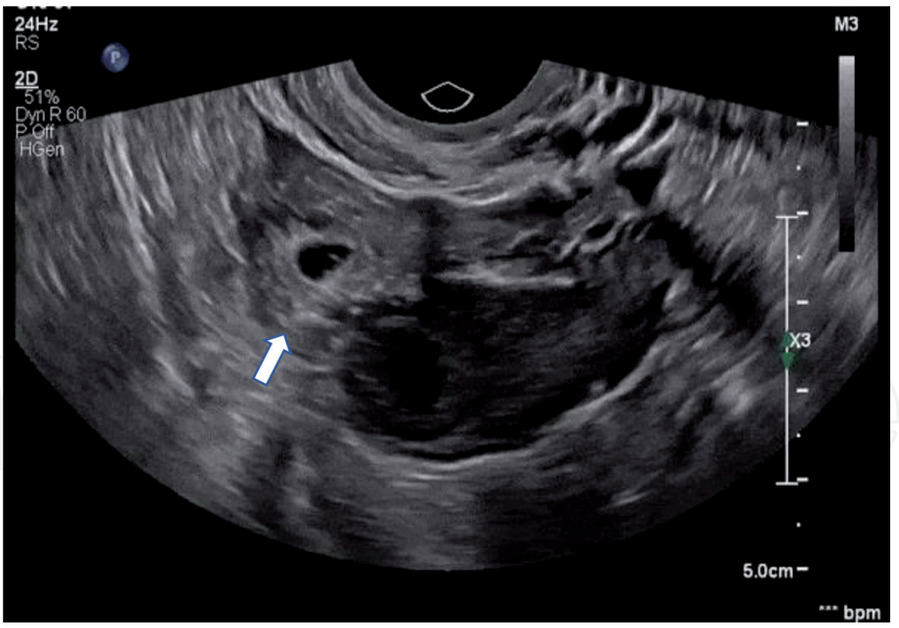

Figure 1.
Ovarian ectopic pregnancy. Transvaginal ultrasound showing a gestational sac located within the ovarian stroma (white arrow) [12].

4. Abdominal pregnancy

Abdominal pregnancy is almost always due to secondary implantation, with the primary sites being the tube, ovary or even the uterus. The conceptus result from tubal abortion into the peritoneal cavity or escapes through a rent in the uterine scar [16]. However, there have been reports of rare pseudo-abdominal pregnancies where women have abdominal pregnancy after hysterectomy with intact ovaries. This is most likely to have occurred via a fistula in the vaginal cuff in fertile women following total hysterectomy or via cervical canal following supracervical hysterectomy. The average incidence is above 1 in 3000 pregnancies. With the used of ART, the incidence is found rising [17]. Primary implantation of the fertilized ovum on the peritoneum is so rare that its existence is questionable.

4.1 Diagnosis

The diagnostic criteria of abdominal pregnancy as described by Studdiford in 1942:

1. Both the tubes and ovaries are normal without evidence of recent injury.

2. Absence of utero-peritoneal fistula.

3. Presence of a pregnancy related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation following primary nidation in the tube [18].

Apart from symptoms of lower abdominal pain and amenorrhea, symptoms of normal uterine pregnancy are often exaggerated such as nausea, vomiting, constipation and increased fetal movements. The fetal parts are felt easily and persistent abdominal attitude and position of the fetus on repeated examination is quite common. While abdominal high position the fetus is commonly found in intraperitoneal pregnancy, though the fetus may be lying low in intraligamentary pregnancy. The cervix is not typically soft and is usually displaced

depending upon the position of the sac. Investigations done in case of suspected abdominal ectopic pregnancy include abdominopelvic ultrasound which shows absence of uterine wall around the fetus with close approximation to maternal abdominal wall and visualization of the uterus separately. Magnetic resonance imaging (MRI) can confirm the diagnosis and may be very accurate. Computed Tomography (CT) is diagnostic and superior to MRI [19]. CT has the risk of radiation. Lateral X-ray on standing position shows superimposition of fetal shadow with the maternal spine shadow.

4.2 Treatment

Once the diagnosis is made the opinion is almost crystallized in favor of urgent laparotomy irrespective of period of gestation. The risks of continuation of pregnancy are; catastrophic hemorrhage, fetal death, increased fetal malformation and increased neonatal loss [20]. Thus, continuation of pregnancy for few weeks hoping the baby to become mature enough to survive can only be justified in exceptional circumstances such as a case where the pregnancy continued up to 30 weeks and eventually resulted in a live born baby [21]. The patient and her relatives should be informed about the eventuality. During the period, the patient should be in the hospital. The ideal surgery is to remove the entire sac, fetus, the placenta and the membranes. This may be achieved if the placenta is attached to a removable organ like uterus or broad ligament. However, if the placenta is attached to vital organs, it is better to take the fetus and leave behind the placenta and the sac after tying and cutting the umbilical cord close to the placental attachment. In such a situation, placental activity is to be monitored by quantitative serum βHCG level and ultrasound. Complete resorption of the placenta occurs through aseptic autolysis. Complications include secondary hemorrhage, intestinal obstruction and infection.

5. Other types of non-tubal pregnancy

The most notable of other extra-tubal ectopic pregnancy are cervical pregnancy, cesarean section scar pregnancy (CSP), interstitial pregnancy and also a recently reported case of intrahepatic pregnancy.

6. Cervical pregnancy

Cervical ectopic pregnancies (CEP) probably the rarest of all ectopic pregnancies and it occurs in about 1:16,000 pregnancies, with implantation occurring in the cervical canal at or below the internal cervical os (see **Figures 2** and **3**) [7, 12, 22–24]. The etiology and risk factors for cervical ectopic pregnancy are similar to those enumerated above, but previous overzealous uterine curettage with associated Asherman syndrome and in-vitro fertilization are probably the most important risk factors. Previous cesarean section has also been implicated as a possible risk factor.

The condition is commonly confused with cervical abortion. In cervical pregnancy, the bleeding is painless and the uterine body lies above the distended cervix. Intractable bleeding following evacuation or expulsion of the products brings about suspicion. The morbidity and mortality are high because of profuse hemorrhage due to paucity of smooth muscles in the cervix, hence unable to contract to stop this bleeding.

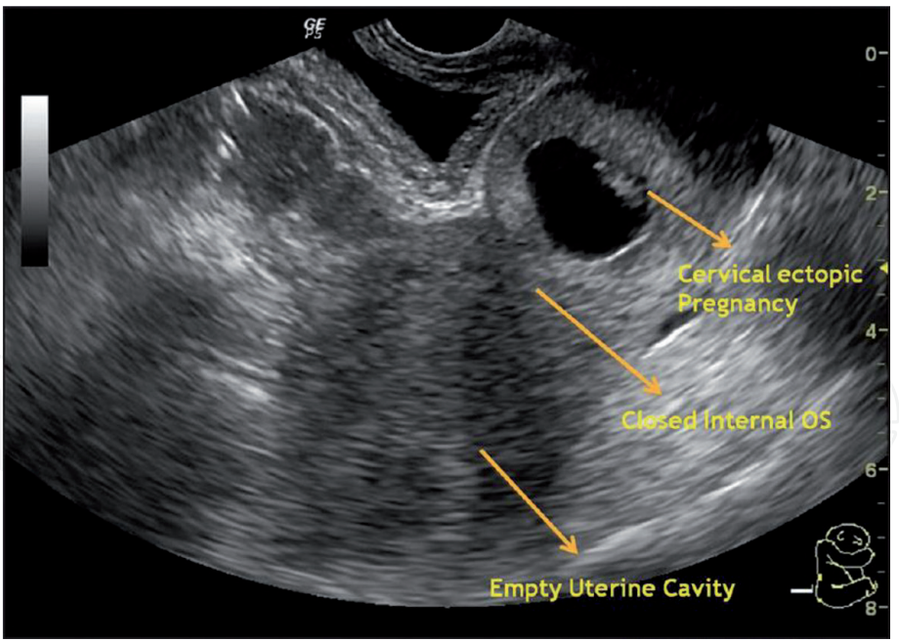

Figure 2.
Early cervical ectopic pregnancy with embryonic pole. Transvaginal ultrasound shows: (1) an empty and normal uterine cavity and (2) a cervical ectopic pregnancy with gestational sac and an embryonic pole (arrows) [23].

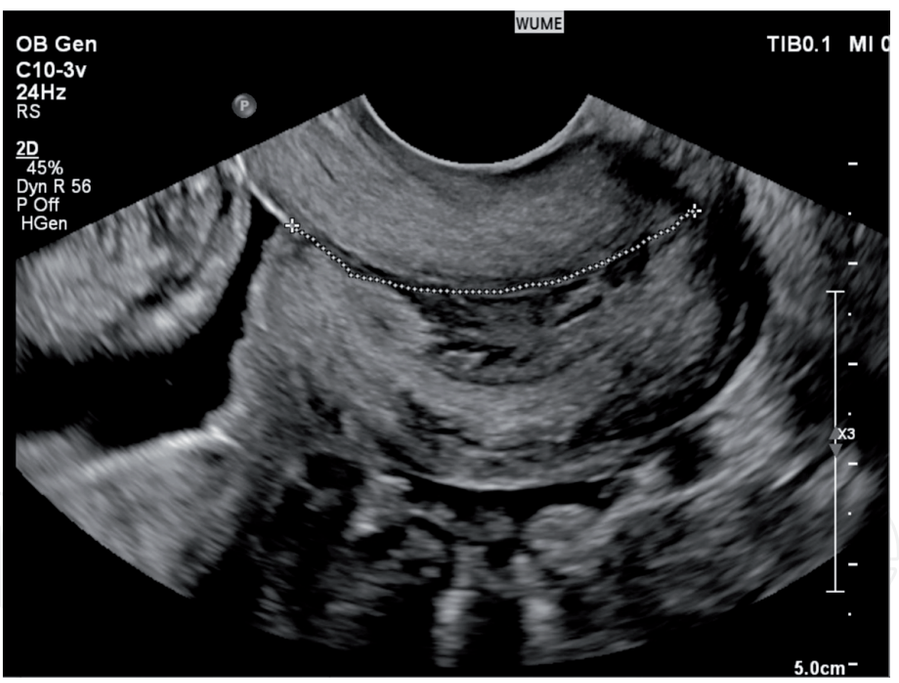

Figure 3.
Cervical ectopic pregnancy with no definite gestational sac. Transvaginal ultrasound showing an organized area with no definite gestational sac located within the posterior cervical stroma (white arrow) [24].

6.1 Diagnosis

Many criteria have been proposed for the diagnosis of ectopic pregnancy which include mostly the anatomical and histological criteria described by Rubin in 1911 but later modified in 1983, the more practical criteria by Paalman and McElin and finally, the sonographic criteria by Raskin et al.

The (Rubin, 1983) anatomical and histological criteria for cervical pregnancy include

1. Cervical gland must be opposite the placental attachment.

2. The placenta attachment to the cervix must be situated below the entrance of the uterine vessels or below the peritoneal reflections of the anterior or posterior surface of the uterus.

3. The fetal elements must be absent from the corpus uteri.

Rubin criteria require a hysterectomy specimen to satisfy these criteria.
Clinical diagnostic criteria as described by Paalman and McElin (1959)

1. Uterine bleeding without cramping pain following a period of amenorrhea.

2. Soft, enlarged cervix equal or larger than the fundus, (the "hourglass" appearance of uterus).

3. Products of conception entirely confined within and firmly attached endocervix.

4. A closed/ snug internal cervical os.

5. A partially opened external os.

Raskin (1978) proposed ultrasound diagnostic features but later modified by Timor-Tritsch et al.

1. Cervical enlargement.

2. Uterine enlargement.

3. Diffused intrauterine echoes.

4. Absence of intrauterine pregnancy.

5. Empty uterus or absence of gestational sac or embryo.

6. The entire product of conception (placenta and chorionic villi) must be located below the internal os and the cervical canal must be dilated and barrel shaped.

Jurkovic (1996) criteria were introduced to distinguish primary cervical ectopic pregnancy from an aborting intra-uterine pregnancy:

1. The "sliding sign" seen on transvaginal examination must be absent.

2. The demonstration of peri-trophoblastic blood flow to the fetus by color Doppler flow must be present.

7. Cesarean scar ectopic pregnancy

Cesarean scar pregnancy (CSP) accounts for 0.04–0.05 of all pregnancies [1]. The prenatal diagnosis of CSP is by the presence of gestational sac at the site of the previous uterine incision and the presence of an empty uterine cavity and cervix, as well as thin myometrium adjacent to the bladder (see **Figure 4**) [25, 26]. Cesarean

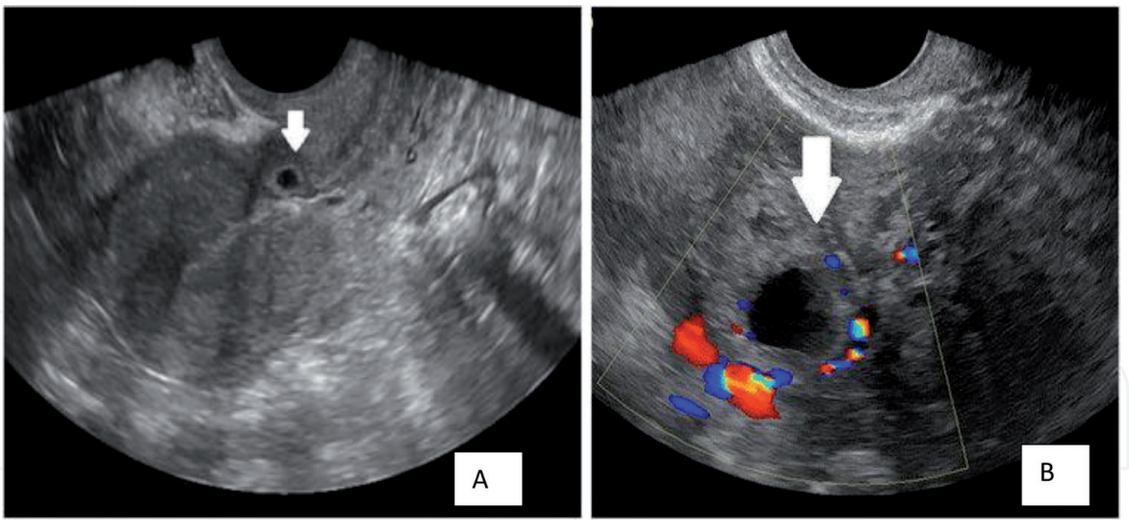

Figure 4.
Cesarean section scar ectopic pregnancy. Transvaginal ultrasound with 2-D and power Doppler showing: (1) normal uterine cavity and endometrium, (2) gestational sac in the cesarean section scar anteriorly, and (3) the vasculature around the gestational sac (white arrows) [25]. (A) shows cesarean ectopic pregnancy on a gray-scale ultrasound, and (B) shows the same pregnancy on color Doppler showing ring of fire of vessels around the gestational sac.

scar pregnancy can be classified based on the degree of invasion of amniotic sac into the myometrium, gestational age at diagnosis, presence of positive fetal heart beats and myometrial thickness of the lower uterine segment. The management of these rarer forms of ectopic pregnancy is just evolving.

Diagnostic criteria of cesarean scar ectopic pregnancy:

1. Empty uterus with clearly visualized endometrium.

2. Empty cervical canal.

3. Gestational sac within the anterior portion of the lower uterine segment at the presumed site of the cesarean scar.

4. Thinned or absent myometrium below the gestational sac and bladder (< 5 mm in two-thirds of cases) [27].

8. Cornual pregnancy

One of the most intriguing of ectopic pregnancies is the cornual or interstitial pregnancy, though not strictly extra-tubal pregnancy. It is neither located in the normal endometrial cavity nor in the normal fallopian tubes, but in the proximal portion of the tube and within the musculature of the uterus. The discussion on extra-tubal pregnancy cannot be complete without pointing out the implications of late diagnosis or misdiagnosis of cornual pregnancy; a potentially dangerous ectopic pregnancy. Often times, it can be mistaking for an intrauterine pregnancy thereby continuing till late first trimester, about 10–12 weeks of gestation. When it ruptures, it can result in rapid catastrophic hemorrhage because of the involvement of the well-vascularized muscular myometrium, and can cause significant maternal morbidity or mortality.

Diagnostic criteria of cornual ectopic pregnancy, 1992 [28]:

1. An empty uterine cavity.

2. A chorionic sac found separated (> 1 cm) from the lateral edge of the uterine cavity.

3. A thin (< 5 mm) myometrial layer surrounding the chorionic sac.

9. Diagnosis of non-tubal ectopic pregnancies

9.1 Pregnancy of unknown location (PUL)

Usually, the absence of intrauterine pregnancy, adnexal mass or abnormally rising serum beta hCG without evidence of intrauterine gestation are not always a confirmation of ectopic pregnancy. In the absence of any ultrasound evidence of visible pregnancy, the terminology of pregnancy of unknown location (PUL) is use. The prevalence of PUL is between 8 and 31% and it can be influenced by the quality of ultrasonography in the given unit, and the experience of the ultrasonographer [29, 30]. Even when PUL is being suspected, there is usually no place for diagnostic suction and curettage to determine the location of the pregnancy because this will disrupt a potential intrauterine pregnancy. Sometimes, some cases of PUL may evolve into ectopic pregnancy; tubal or non-tubal that may cause life threatening complications.

9.2 Ectopic pregnancies

Transvaginal ultrasound (TVUS) is the first line tool and the gold standard diagnostic apparatus of ectopic pregnancy. Ectopic pregnancy is usually diagnosed on TVUS as the presence of a mass with hyperechoic ring around the gestational sac ("bagel sign") or a gestational sac with a fetal pole with or without cardiac activity. The sensitivity and specificity of TVUS in detecting ectopic pregnancy are 90.9 and 99.9%, respectively, with positive and negative predict values of 93.5 and 99.8%, respectively. Another ultrasound feature of ectopic pregnancy is the trilaminar pattern of endometrial thickness with sensitivity of 38% and specificity of 94% for detecting ectopic pregnancy [31]. Magnetic resonance imaging is useful as a troubleshooting tool when ultrasound is equivocal or inconclusive before intervention or therapy [27]. Sagittal, coronal, and transverse sections of T1- and T2-weighted magnetic resonance imaging sequences can be used to show the gestational sac embedded in the anterior lower uterine segment, better evaluate pelvic anatomy, improve intra-operative orientation, and assess the possibility of myometrial invasion and bladder involvement [27, 32, 33]. Magnetic resonance imaging can also be used to measure the volume of the lesion so as to help assess whether methotrexate will be indicated and to predicts its success as medical intervention [27].

10. Management of non-tubal pregnancy

The management of extra-tubal ectopic pregnancy depends on the location, size of the gestational sac, presence of fetal heart beats and symptoms at presentation. The definitive management of extra-tubal ectopic pregnancy involves surgical extermination of the gestational sac via laparotomy, laparoscopy, hysteroscopy or suctional curettage under ultrasound guidance. Another advantage of surgical extermination is that there is confirmation of ectopic pregnancy by histological evidence of the presence of villi within the stroma of the affected structure.

Preservative procedures such as placement of cerclage; a pulse-string suture or cervical plugging have been proposed as adjunct treatment for cervical ectopic

pregnancy. Methotrexates therapy either systemic and /or local injections directly into the gestational sac or intracardiac potassium chloride injection have also been used especially when there is associated embryonic cardiac activity. Uterine artery embolization with Gelfoam has also been used successfully to control hemorrhage. However, hysterectomy is often required to control intractable bleeding. Occasionally, there may be no need for intervention due to declining serum beta hCG levels in asymptomatic patients; however, these patients are usually closely monitored to ensure spontaneous resolution of the pregnancy.

11. Medical management

11.1 Methotrexate

Methotrexate is a chemotherapeutic anti-metabolite that affects rapidly dividing cells, and it is use in the treatment of cancers and connective tissues disorders such as rheumatoid arthritis. The use of Methotrexate in the medical management of ectopic pregnancy has to be thoroughly given serious consideration to avoid inadvertent administration in patient with intrauterine pregnancy. Hence, careful selection of appropriate candidate for Methotrexate treatment to improve success rate is advised. In most instances, Methotrexate should only be given to patients with confirmed or presumed ectopic pregnancy who are hemodynamically stable with an unruptured gestational sac. The success rate is also dependent on the level of serum beta hCG because single-dose systemic Methotrexate had approximately 90% success rate if the initial serum hCG level is less than 5000 mIU/ml [34].

The indications and contraindications of Methotrexate should be reviewed before every use. For some extra-tubal pregnancies like CSP and cervical pregnancies, use of Methotrexate may be considered as the first and only option before surgical intervention to minimize catastrophic hemorrhage. The higher the level of serum beta hCG, the more likely the failure rate of using methotrexate in medical management of all ectopic pregnancies. In view of this, some experts have recommended use of two-dose or multiple-dose regimens for such patients if they are not surgical candidates and medical management is warranted. Lipscomb et al. demonstrated that a high serum hCG level is the most important factor associated with failure of treatment with single-dose MTX protocol among women with tubal ectopic pregnancy [35].

Contraindications to methotrexate therapy [36, 37].

Absolute contraindications

1. Pregnancy of unknown location of only one evaluation.

2. Peptic ulcer disease.

3. Intrauterine pregnancy.

4. Sensitivity to methotrexate.

5. Breastfeeding.

6. Suspected tubal rupture.

7. Immunodeficiency.

8. Active pulmonary disease.

9. Unwilling or unable to return for follow up visits.

Relative contraindications

1. Gestational sac >3.5 cm.

2. Embryonic cardiac motion.

3. Hepatic, renal, or hematologic dysfunction.

4. Serum beta hCG > 5000 mIU/ml.

11.2 Pre-treatment evaluation

Blood type, serum hCG (to be used as "Day 1" level).

Safety labs: full blood counts, complete metabolic panel consisting of AST/ALT, BUN/Cr, also to be repeated prior to additional MTX dosing.

11.3 Systemic methotrexate treatment protocol

Systemic methotrexate is usually given as a single-dose or two-dose or fixed multi-dose regimens. The single-dose regimen of 50 mg of methotrexate per body surface area (BSA, m^2) is usually given only on the first day, then followed by serial monitoring of serum hCG on days 4 and 7. There is the possibility of repeating the same dose on days 7 and 11 if there is less than 15% drop in the levels of hCG between days 4 and 7 or between days 7 and 11. The two-dose regimen also uses 50 mg of methotrexate per BSA (m^2) and it is predetermined to be given on days 1 and 4, then followed by serial serum hCG levels on days 4 and 7 or 11. There is also a possibility of repeating the same dose on days 7 and 11 if the drop in serum hCG levels between days 4 and 7 or days 7 and 11 are less than 15% respectively [36, 37].

The fixed multi-dose regimen uses 1 mg of methotrexate per kilogram body weight for a total of four doses given on alternate days; on the first, third, fifth, and seventh days while Folinic acid rescue is given on the second, fourth, sixth, and eighth days. This regimen requires serial serum hCG monitoring on the days of methotrexate injections until there is more than 15% drop from the previous level. Thereafter, continue weekly to every 4 weeks monitoring until the serum hCG levels is less than 5 mIU/ml [36, 37].

Methotrexate can also be injected locally into the gestational sac or in the fetal intracardiac space to enhance resolution of the pregnancy. This is usually done under ultrasound guidance and it is given in combination with systemic injection in various dosing regimens. Timor-Tritsch et al. suggested using a fixed dose of 75 mg of methotrexate; 25 mg intracardiac injection, 25 mg inside the gestational sac while the remaining 25 mg is given intramuscularly (**Table 1**).

11.4 Adjuvant medical treatments and other interventions

Give anti-D immunoglobulin injection if patient is rhesus negative.

Advise patient to discontinue folic acid supplementation during MTX treatment.

Avoid pelvic exams and sexual intercourse during treatment period.

Caution patients: to reduce gastrointestinal side-effects, avoid alcohol and non-steroidal anti- inflammatory drugs (NSAIDs).

Avoid prolonged exposure to sun due to sun hypersensitivity while on MTX.

Single-dose regimen	
Days	**Activities performed**
1	MTX 50 mg/m^2 IM injection.
4 and 7	Measure hCG levels, a rise may be seen on Day 4 compared to baseline Day 1.
If ≥15% drop from Days 4 to 7, continue to follow weekly until hCG < 5 mIU/ml. If <15% drop from Days 4 to 7, repeat MTX 50 mg/m^2, repeat serum hCG on Day 11.	
Two-dose regimen	
Days	**Activities performed**
1	MTX 50 mg/m^2 IM injection.
4	MTX 50 mg/m^2 IM injection and serum hCG level.
7	Serum hCG level, if ≥15% from Days 4 to 7, continue weekly until hCG < mIU/ml.
If <15% drop from Days 4 to 7, repeat MTX 50 mg/m^2 and check hCG on Day 11; if ≥15% drop from Days 7 to 11, continue to follow up weekly until hCG < 5 mIU/ml. If <15% drop from Days 7 to 11, repeat MTX 50 mg/m^2 and check hCG on Day 14; if ≥15% drop from Days 11 to 14, continue to follow weekly until hCG < 5 mIU/ml.	
Fixed multi-dose regimen	
Days	**Activities performed**
1, 3, 5, 7	MTX 1 mg/kg body weight.
2, 4, 6, 8	Folinic acid 0.1 mg/kg body weight.
Measure serum levels of hCG on MTX dose days; continue dosing until hCG decreases ≥15% from previous measurement. Follow hCG until <5 mIU/ml.	

MTX, methotrexate; hCG, human chorionic gonadotropin; IM, intramuscular.

Table 1.
Different regimens of systemic methotrexate.

Avoid new conception until serum hCG is undetectable.
Combination of systemic and local injection of methotrexate.
Timor-Tritsch recommendation of combined local and systemic injection:

A. 25 mg intragestational sac.

B. 25 mg into the placental site as the needle is being withdrawn.

C. 25 mg intramuscular prior to patient discharge from the hospital.

University of Illinois at Chicago protocol (unpublished):

A. Half dose of 50 mg/m2 BSA injected into the intragestational sac.

B. The remaining half dose of MTX is injected intramuscularly.

11.5 Potassium chloride

In the presence of cardiac activity, intracardiac injection of potassium chloride with 2 mEq/L under ultrasound guidance, and repeat until there is no longer

cardiac activity. It usually requires 2–3 ml injections for the procedure. Potassium chloride can be used as a stand-alone treatment intervention in ectopic pregnancy or in combination with any of the methotrexate injection regimens. In a study of 18 ectopic pregnancies with active embryonic cardiac activity, mean serum beta hCG levels of 33,412 IU/L and mean gestational age of 6 weeks and 6 days, 10 were assigned to KCL injection in the gestational sac while 8 were in the methotrexate group. There was no difference in time to resolution of ectopic pregnancies between those injected with KCL and those with methotrexate [38]. Verma et al. in a three-case series of women with concurrent injection of local KCL and systemic injection of methotrexate, they demonstrated that complete resolution of ectopic pregnancy was achieved and surgery avoided in all 3 cases [39].

11.6 Newer treatment combinations

The use of selective progesterone reception modulator (Mifepristone) as an adjuvant for medical therapy has been tried. In a randomized trial by Rozenberg et al., there was no benefit from the systematic addition of mifepristone except in women with progesterone level of 10 ng/L or more [40]. However, in a larger study involving 72 patients; 30 with combined methotrexate-mifepristone and 42 with methotrexate alone by Perdu et al., the failure rate was lower in the combined group, 1/30 (33.3%) compared to 11/42 (26.2%) in the methotrexate alone group [41]. Use of epidermal growth factor receptor inhibition in combination with methotrexate has been tried in an in vitro experiment and it showed inhibition of growth of placental cells. These results were confirmed in vivo in mouse models, and it revealed faster rate of fetal resorption when the two drugs were combined [42]. In a phase 1 nonrandomized open label study involving 12 women with ectopic pregnancy and 71 controls, the median level of serum beta hCG by day 7 and the time of pregnancy resolution were significantly lower in the combined methotrexate and epidermal growth factor receptor blocker (gefitinib) compared with methotrexate alone group [43]. Hence, the future goal of medical management of extra-tubal ectopic pregnancies should be combination therapy ab initio with various methotrexate regimen.

12. Surgical management of non-tubal pregnancy

To ensure complete removal of a tubal ectopic pregnancy, a British surgeon, Robert Lawson Tait performed a laparotomy with ligation of ruptured tube and board ligament in April 1883. By the 1920s, laparotomy and ligation of the bleeding vessels with removal of the affected tube had become the standard of care, and it remained so until the late 1970s, when operative laparoscopy and salpingectomy replaced laparotomy and salpingectomy. For CSPs, nearly 50% of clinically diagnosed cases miscarriage during the first trimester but most of them will require additional surgical intervention to stop bleeding [44]. Surgical management of any ectopic pregnancy is associated with a high success rate; low complication rate and short post-treatment follow up [19]. In a national cohort study in the UK by Hart et al. of 102 cases of CSP, the success rates of expectant, medical and surgical management were 43% (9/21), 46% (7/15) and 96% (54/56), respectively. The complication rates were 15/21 (71%) with expectant, 9/15 (60%) with medical and 20/56 (36%) with surgical management. Discharge from care (median number of days) was 82 (range 37–174) with expectant, 21 (range 10–31) with medical and 11 (range 4–49) with surgical management [45].

12.1 Suction curettage

This surgical intervention has been used to treat appropriately selected suitable patients with cervical ectopic or cesarean scar ectopic pregnancies. It is usually done under transabdominal or transrectal ultrasound guidance to ensure direct visualization of the pregnancy sac during the procedure. This procedure has been used for cervical ectopic pregnancy (CEP) and CSP despite the fear of potential catastrophic hemorrhage that may warrant emergency hysterectomy or may result in significant maternal morbidity and mortality. When suction curettage is being considered as a treatment option, you also need to plan for possible use of adjuvant interventions to reduce excessive blood loss. Adjuvant methods that have used so far include but not limited to intracervical balloon tamponade, angiographic embolization, cervical cerclage, ligation of uterine arteries or local hysteroscopic endocervical resection of the gestational sac with local use of different substances. Among these, arterial embolization has gained more recognition than any other interventions to decrease potentially dangerous massive hemorrhage thought to be associated with suction curettage of CSP or cervical ectopic pregnancy. However, there have been reports of suction curettage used successfully to evacuate CEP or CSP with minimal complications. In a study by Jurkovic et al. of 232 women with CSP, suction curettage was an effective method for the treatment of 191 pregnancies implanted into the lower uterine segment cesarean section scar because of the 116 women who had a follow up visit, only 7 (6.0%), 95% CI 1.7–10.3% required a repeat surgical procedure for retained products of conception. It was associated with a low risk of blood transfusion and hysterectomy. Of the 191 women, 9 (4.7%) required blood transfusion, 95% CI 1.7–7.7, and 1 (0.5%) women had life-saving hysterectomy due to uncontrollable intraoperative hemorrhage [46].

12.2 Wedge resection

Wedge resection of gestational sac can be used for many extra-tubal pregnancies such as CSP, ovarian or cornual pregnancies. There have been multiple case reports on the safety and effectiveness of wedge resection of CSP via laparotomy. Wedge resection should be considered when the diagnosis is made early, there is no involvement of vital contiguous structures and need for preservation of fertility. In a case report by Vial et al. of 28 years old G3P2002 at 6 weeks gestation, wedge resection of the gestational mass via a Pfannenstiel incision resulted in complete resolution of the pregnancy and subsequent full-term pregnancy delivered by cesarean section [47]. Traditionally, wedge resections of the gestational sac or hysterectomy via laparotomy is the treatment of choice of interstitial or cornual or angular pregnancy. However, laparoscopic cornuotomy is the removal of ectopic pregnancy tissue with preservation of uterine architecture. This increases incidence of persistent and recurrent interstitial pregnancy, but can potentially maintain patient fertility and decrease risk of future uterine rupture. Patients with cornual resection are often delivered at 36–37 weeks of gestation via cesarean section in subsequent pregnancies because of their increased risk of uterine scar rupture. In a study of 29 patients by Liao et al., the incidence of subsequent uterine rupture and dehiscence was 30% [48]. However, there is still controversy in regards to the recommended surgical technique to treat interstitial pregnancies; cornual resection and cornuectomy are both important considerations.

A small ovarian ectopic pregnancy (OEP) or early bleeding can be treated with wedge resection or cystectomy with the intention to preserve some of the affected ovarian tissues. There have been anecdotal case reports of the

effectiveness of wedge resection in the treatment of OEP. A case report by Kraemer et al. showed a 29-year-old G1P0 at 8 weeks gestation with confirmed ovarian pregnancy and she was managed by laparoscopic wedge resection of the OEP. She subsequent was pregnant with a normal intrauterine pregnancy 6 months after her surgery [49].

12.3 Laparotomy/laparoscopy in extra-tubal pregnancy

Directly visualization of the pregnancy via laparotomy or laparoscopy may be helpful in the definitive diagnosis of OEP and abdominal pregnancy. Surgical management of either of the two pregnancies is influenced by the size of the lesion, the proximity or attachment to vital organs, associated symptoms and the patient's desire for future fertility [46]. Small OEP are usually treated conservatively with wedge resection, enucleation, cystectomy, or trophoblast curettage with electrocoagulation or hemostatic suture to preserve fertility. However, large OEP may require oophorectomy when there are no apparent normal ovarian tissues left [47].

12.4 Adjuvant surgical interventions

The use of adjuvant interventions is to accelerate the efficacy of primary treatment or to minimize potential life-threatening complications. Intracervical balloon tamponade or cervical cerclage have been used during cervical curettage for cervical ectopic pregnancy to decrease bleeding. Direct ultrasound-guidance is helpful for all extra-tubal pregnancy to enable injection of methotrexate or KCL or hyperosmolar glucose into the gestational sac. Misoprostol and Methergine are uterotonic agents that cause vasoconstriction, thereby reducing the amount of blood loss during surgical intervention. Careful and appropriate use of these adjuvant treatments can improve successful outcome of primary treatment of extra-tubal pregnancy.

13. Conclusion

Ectopic pregnancy is the leading cause of first trimester maternal mortality, and it is mostly located in the fallopian tubes. When it is located outside the tubes, the need for high index of suspicious and prompt intervention is advised because the more advanced extra-tubal pregnancies can result in catastrophic hemorrhage or maternal death. Different surgical techniques that are unique to individual type of ectopic pregnancy, the use of methotrexate and combination therapy have all demonstrated proven benefits for the treatment of extra-tubal pregnancy.

Author details

Adebayo A. Adeniyi[1,2] and Christopher A. Enakpene[3]*

1 Afe Babalola University, Ado Ekiti, Ekiti State, Nigeria

2 Federal Medical Center, Ido Ekiti, Ekiti State, Nigeria

3 Texas Tech University Health Sciences Center, School of Medicine, Permian Basin, Texas, USA

*Address all correspondence to: christopher.a.enakpene@ttuhsc.edu

References

[1] Rota M, Haberman S, Levgur M. Cesarean scar ectopic pregnancies, etiology, diagnosis and management. Obstetrics and Gynecology. 2006;**107**:1373-1381

[2] Kwawukume EY, Idrisa A, Ekele BA. Ectopic pregnancy In: Kwawukume EY, Emuveyan EE, editros. Comprehensive Obstetrics in the Tropics 2nd Edition. Accra-North Ghana: Assemblies of God Literature Centre Limited; 2015. pp. 282-287

[3] Barnhart KT, Sammel MD, Gracia CR, Chittams J, Hummel AC, Shaunik A. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertility and Sterility. 2006;**86**:36-43

[4] Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sites of ectopic pregnancy: A 10-year population-based study of 1800 cases. Human Reproduction. 2002;**17**:3224-3230

[5] Ann-Marie S, Samantha MD. Early pregnancy risks. In: Alan HD, Nathan L, editors. Current Obstetric & Gynecologic Diagnosis & Treatment. 11th ed. New York: McGraw-Hill; 2013. pp. 687-700

[6] Cepni I, Ocal P, Erkan S, Erzik B. Conservative treatment of cervical ectopic pregnancy with transvaginal ultrasound-guided aspiration and single-dose methotrexate. Fertility and Sterility. 2004;**81**:1130-1132

[7] Odejimi F, Rizzuto MI, MacRae R, Olowu O, Hussain M. Diagnosis and laparoscopic management of 12 consecutive cases of ovarian pregnancy and review of literature. Journal of Minimally Invasive Gynecology. 2009;**16**(3):354-359

[8] Mathur SK, Parmar P, Gupta P, Kumar M, Gilotra M, Bhatia Y. Ruptured primary ovarian ectopic pregnancy: Case report and review of the literature. Journal of Gynecologic Surgery. 2015;**31**(6):354-356

[9] Melcer Y, Maymon R, Vaknin Z, et al. Primary ovarian ectopic pregnancy: Still a medical challenge. The Journal of Reproductive Medicine. 2016;**61**(1-2):58-62

[10] Birge O, Erkan MM, Ozbey EG, Arslan D. Medical management of an ovarian ectopic pregnancy: A case report. Journal of Medical Case Reports. 2015;**9**(290):1-4

[11] Goyal LD, Tondon R, Goel P, Sehgal A. Ovarian ectopic pregnancy: A 10 years' experience and review of literature. Iranian Journal of Reproductive Medicine. 2014;**12**(12):825-830

[12] Huber WJ, Frishman GN. Ovarian ectopic pregnancy. In: Tulandi T, editor. Ectopic Pregnancy. Cham: Springer; 2015. pp. 93-99

[13] Hosni MM, Herath RP, Mumtaz R. Diagnostic and therapeutic dilemmas of cervical ectopic pregnancy. Obstetrical & Gynecological Survey. 2014;**69**(5):261-276

[14] Cunningham FG, Leveno KJ, Bloom SI, Hauth JC, Rouse DJ, Spong CY. Williams obstetrics. In: Ectopic Pregnancy. 23rd ed. New York City, USA: McGraw Hill Professional; 2010. p. 251

[15] Agonistini A, Blanc K, Ronda I. Prognostic value of human chorionic gonadotropin changes after methotrexate for ectopic pregnancy. Fertility and Sterility. 2007;**88**(2):504-506

[16] Ayinde OA, Aimakhu CO, Adeyanju OA, Omigbodun AO. Abdominal pregnancy at university

college hospital, Ibadan; a ten-year review. African Journal of Reproductive Health. 2005;**9**(1):123-127

[17] Zhang J, Sheng Q. Full term abdominal pregnancy: A case report and review of literature. Gynecologic and Obstetric Investigation. 2008;**65**(2):139-141

[18] Studdiford WE. Primary peritoneal pregnancy. American Journal of Obstetrics and Gynecology. 1942;**44**:487-491

[19] Karat LS. Viable abdominal pregnancy. The Journal of Obstetrics and Gynecology of India. 2007;**57**(2):169-170

[20] Stevens CA. Malformations and deformations in abdominal pregnancy. American Journal of Medical Genetics. 1993;**47**(8):1189-1195

[21] Baffoe P, Fofie C, Gandau BN. Term abdominal pregnancy with healthy newborn: A case report. Ghana Medical Journal. 2011;**45**(2):81-83

[22] Shrestha A, Chawla CD. Ruptured primary ovarian pregnancy: A rare case report. Kathmandu University Medical Journal. 2012;**10**:76-77

[23] Ching H-C, Chiu T's-H, Hsieh T's-T's, Lo L-M. Early cervical ectopic pregnancy: A case report and review of literature. Journal of Medical Ultrasound. 2014;**22**(2):117-119

[24] Singh S. Diagnosis and management of cervical ectopic pregnancy. Journal of Human Reproductive Sciences. 2013;**6**(4):273-276

[25] Panelli DM, Phillips CH, Brady PC. Incidence, diagnosis and management of tubal and nontubal ectopic pregnancies: A review. Fertility Research and Practice. 2015;**1**:15

[26] D'Antonio F, Palacios-Jaraquemada J, Lim PS, Forlani F, Lanzone A, Timor-Tritsch I, et al. Counseling in fetal medicine: Evidence-based to clinical answers to clinical questions on morbidly adherent placenta. Ultrasound in Obstetrics & Gynecology. 2016;**47**:290-301

[27] Ash A, Smith A, Maxwell D. 2wn location. Human Reproduction. 2006;**21**(10):2706-2710

[28] Arleo EK, DeFilippis EM. Cornual, interstitial, angular pregnancies: Clarifying the terms and a review of the literature. Clinical Imaging. 2014;**38**:763-770

[29] Condous G, Kirk E, Lu C, et al. There is no role for uterine curettage in the contemporary diagnostic workup of women with a pregnancy of unknown location. Human Reproduction. 2006;**21**(10):2706-2710

[30] Hahlin M, Thorburn J, Bryman I. The expectant management of early pregnancies of uncertain site. Human Reproduction. 1995;**10**:1223-1227

[31] Hammoud AO, Hammoud I, Bujold E, et al. The role of sonographic endometrial patterns and endometrial thickness in the differential diagnosis of ectopic pregnancy. American Journal of Obstetrics and Gynecology. 2005;**192**:1370-1375

[32] Rosen T. Placenta accreta and cesarean scar pregnancy: Overlooked costs of the rising cesarean section rate. Clinics in Perinatology. 2008;**35**:519-529

[33] Maymon R, Halperin R, Mendlovic S, Schneider D, Herman A. Ectopic pregnancies in a caesarean scar: Review of the medical approach to an iatrogenic complication. Human Reproduction Update. 2004;**10**:515-523

[34] Stovall TG, Ling FW, Gray LA. Single-dose methotrexate treatment of ectopic pregnancy. Obstetrics and Gynecology. 1991;**77**:754-757

[35] Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. The New England Journal of Medicine. 1999;**341**:1974-1978

[36] Protocol of Gynecological Service, University of Alabama at Birmingham, December 2011

[37] Barnhart KT, Franasiak JM. American College of Obstetrician and Gynecologist Practice Bulletin Number 193. Tubal ectopic pregnancy. Obstetrics and Gynecology. 2018;**121**(3):e91-e103

[38] Monteagudo A, Minior VK, Stephenson C, Monda S, Timor-Tritsch IE. Non-surgical management of live ectopic pregnancy with ultrasound-guided local injection: A case series. Ultrasound in Obstetrics & Gynecology. 2005;**25**(3):282-288

[39] Verma U, Jacques E. Conservative management of live tubal pregnancies by ultrasound-guided potassium chloride injection and systematic methotrexate treatment. Journal of Clinical Ultrasound. 2005;**33**(9):460-463

[40] Rozenberg P, Chevrets S, Camus E, De Tayrac R, Garbin O, de Poncheville L, et al. Medical treatment of ectopic pregnancies: A randomized clinical trial comparing methotrexate-mifepristone and methotrexate – Placebo. Human Reproduction. 2003;**18**:1802-1808

[41] Perdu M, Camus E, Rozenberg P, Goffinet F, Chastang C, Philippe HJ, et al. Treating ectopic pregnancy with combination of mifepristone and methotrexate: A phase II nonrandomised study. American Journal of Obstetrics and Gynecology. 1998;**179**(3 pt 1):640-643

[42] Nilsson UW, Johns TG, Wilmann T, Kaitu'u-Lino T, Whitehead C, Dimitriadis E, et al. Effects of gefitinib, an epidermal growth factor receptor inhibitor, on human placental cell growth. Obstetrics and Gynecology. 2013;**122**(4):737-744

[43] Skubisz MM, Horne AW, Johns TG, Nilsson UW, Duncan WC, Wallace EM, et al. Combination gefitnib and methotrexate compared with methotrexate alone to treat ectopic pregnancy. Obstetrics and Gynecology. 2013;**122**(4):745-751

[44] Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First-trimester diagnosis and management of pregnancies implanted into the lower uterine segment cesarean section scar. Ultrasound in Obstetrics & Gynecology. 2003;**21**:220-227

[45] Harb HM, Knight M, Bottomley C, Overton C, Tobias A, Gallos ID, et al. Caesarean scar pregnancy in the UK: A national cohort study. BJOG. 2018;**125**:1663-1670

[46] Jurkovic D, Knez J, Appiah A, Farahani L, Mavrelos D, Ross JA. Surgical treatment of cesarean scar ectopic pregnancy: Efficacy and safety of ultrasound-guided suction curettage. Ultrasound in Obstetrics & Gynecology. 2016;**47**(4):511-517

[47] Vial Y, Petignat P, Hohlfeld P. Pregnancy in a cesarean scar. Ultrasound in Obstetrics & Gynecology. 2000;**16**(6):595-593

[48] Liao CY, Tse J, Sung SY, Chen SH, Tsui WH. Cornual wedge resection for interstitial pregnancy and postoperative outcome. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;**57**(3):342-345

[49] Kraemer B, Kraemer E, Guengoer E, Juhasz-Boess I, Solomayer EF, Wallwiener D, et al. Ovarian ectopic pregnancy; diagnosis, treatment to Carnegie stage 16 and review based on clinical case. Fertility and Sterility. 2009;**9**:393.e13-393.e15