No. 414, May 2021

Guideline No. 414: Management of Pregnancy of Unknown Location and Tubal and Nontubal Ectopic Pregnancies

(En français: Prise en charge des grossesses de localisation indéterminée et des grossesses ectopiques tubaires et non tubaires)

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

This clinical practice guideline was prepared by the authors and overseen by the SOGC Clinical Practice Gynaecology Committee. It was reviewed by the SOGC Diagnostic Imaging Committee and approved by the Guideline Management and Oversight Committee and the Board of the SOGC.

Authors
Leslie Po, MD, MScHQ, Toronto, ON
Jacqueline Thomas, MD, MSc, Toronto, ON
Kelsey Mills, MD, MSc, Victoria, BC
Andrew Zakhari, MD, Toronto, ON
Togas Tulandi, MD, MHCM, Montréal, QC
Mira Shuman, MD, MScCH, Toronto, ON
Andrea Page, MD, MScHQ, Toronto, ON

J Obstet Gynaecol Can 2021;43(5):614–630

https://doi.org/10.1016/j.jogc.2021.01.002

Clinical Practice Gynaecology Committee (2019): Olga Bougie, Annette Bullen, Innie Chen, Devon Evans, Susan Goldstein, Joann James, Sari Kives, Ally Murji, Jessica Papillon-Smith, Leslie Po, Elizabeth Randle, David Rittenberg (co-chair), Jackie Thurston, Wendy Wolfman, Grace Yeung, Paul Yong (co-chair), and Andrew Zakhari

Weeks Gestation Notation: The authors follow the World Health Organization's notation on gestational age: the first day of the last menstrual period is day 0 (of week 0); therefore, days 0 to 6 correspond to completed week 0, days 7 to 13 correspond to completed week 1, etc.

Disclosures: Statements were received from all authors. No relationships or activities were disclosed. All authors have indicated that they meet the journal's requirements for authorship.

Keywords: pregnancy, ectopic; pregnancy, tubal; pregnancy, interstitial; algorithm

Corresponding author: Leslie Po, leslie.po@sunnybrook.ca

KEY MESSAGES

1. Ectopic pregnancies can be life-threatening.
2. Health care providers have the responsibility to make the diagnosis and facilitate patients' informed decision-making about expectant, medical, and surgical treatment options.
3. This guideline is not a substitute for clinical judgement, knowledge, and expertise, and variation from this guideline must take into account individual circumstances.

ABSTRACT

Objective: To provide an evidence-based algorithm to guide the diagnosis and management of pregnancy of unknown location and tubal and nontubal ectopic pregnancy.

Target Population: All patients of reproductive age.

Benefits, Harms, and Costs: The implementation of this guideline aims to benefit patients with positive β-human chorionic gonadotropin results and provide physicians with a standard algorithm for expectant, medical, and surgical treatment of pregnancy of unknown location and tubal pregnancy and nontubal ectopic pregnancies.

Evidence: The following search terms were entered into PubMed/Medline and Cochrane in 2018: cesarean section, chorionic gonadotropin, beta subunit, human/blood, fallopian tubes/surgery, female, fertility, humans, infertility, laparoscopy, methotrexate, methotrexate/administration & dosage, methotrexate/therapeutic use, pregnancy (abdominal, angular, cervix, cornual, ectopic, ectopic/diagnosis, ectopic/diagnostic imaging, ectopic/drug therapy, ectopic/epidemiology, ectopic/mortality, ectopic/surgery, heterotopic, interstitial, isthmo-cervical, ovarian, tubal, unknown location), recurrence, risk factors, salpingectomy, salpingostomy, tubal pregnancy, ultrasonography, doppler ultrasonography, and prenatal. Articles included were randomized controlled trials, meta-analyses, systematic reviews, observational studies, and case reports. Additional publications were identified from the bibliographies of these articles. Only English-language articles were reviewed.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. See online Appendix A (Tables A1 for definitions and A2 for interpretations of strong and weak recommendations).

Intended Audience: Obstetrician–gynaecologists, family physicians, emergency physicians, midwives, registered nurses, nurse practitioners, medical students, and residents and fellows.

SUMMARY STATEMENTS (GRADE ratings in parentheses):

1. Ectopic pregnancies account for the majority of first-trimester maternal deaths (*high*).
2. Tubal pregnancies account for the majority of ectopic pregnancies (*high*).
3. Pregnancy of unknown location is a transient state in the diagnostic process, leading to a final diagnosis of viable or nonviable intrauterine pregnancy, ectopic pregnancy, or persistent pregnancy of unknown location (*high*).
4. Management protocols for pregnancy of unknown location are predictive and not diagnostic. They are formulated to risk stratify pregnancy of unknown location as either high or low risk for ectopic pregnancy (*high*).
5. Methotrexate is a safe and effective treatment for carefully selected tubal and nontubal ectopic pregnancies (*high*).
6. Expectant management of a tubal pregnancy can eliminate medication-related and surgical risks in carefully selected patients. However, expectant management can result in serious morbidity if it fails (*low*).
7. There is no evidence to recommend conservative, tube-sparing salpingotomy over salpingectomy in the surgical management of the majority of tubal pregnancies (*moderate*).
8. Ultrasound diagnosis of nontubal ectopic pregnancy requires experienced sonographers and radiologists (*moderate*).
9. Providers should have a high index of suspicion for cervical ectopic pregnancy because severe outcomes often occur with delayed diagnosis and management (*low*).
10. Women who will be undergoing treatment for a cervical pregnancy should be counselled about the risk of hemorrhage and the possible need for hysterectomy (*low*).
11. The terms *interstitial* and *cornual* pregnancy are used interchangeably in the literature (*low*).
12. Abdominal pregnancies are associated with high rates of maternal mortality owing to the high risk of catastrophic hemorrhage (*low*).
13. Laparoscopy is often required for definitive diagnosis of ovarian pregnancy (*very low*).
14. Spontaneous heterotopic pregnancies are rare (*low*).

RECOMMENDATIONS (GRADE ratings in parentheses):

1. We recommend the use of risk models (e.g., the M6 model) to stratify pregnancy of unknown location as either high or low risk for ectopic pregnancy to guide treatment decisions (*strong, moderate*).

Tubal Pregnancies

2. Clinicians can consider expectant management and very close follow-up in carefully selected patients with early, asymptomatic tubal pregnancies (*conditional, low*).
3. If a patient meets the criteria for medical management of a tubal pregnancy, we suggest the single- or double-dose methotrexate protocol (*conditional, moderate*).
4. If feasible, clinicians should use a minimally invasive approach in the surgical management of tubal pregnancy (*strong, high*).
5. Consider both patient and surgeon factors when deciding between salpingectomy and salpingotomy; there is no evidence to recommend conservative, tube-sparing salpingotomy over salpingectomy when the contralateral fallopian tube is normal (*conditional, low*).

Cesarean Scar Pregnancies

6. Clinicians should consider medical management with multidose and/or local methotrexate as a safe and effective treatment in appropriately selected women with a cesarean scar pregnancy (*conditional, moderate*).
7. Clinicians should consider treating type I cesarean scar pregnancies surgically with hysteroscopy (*conditional, low*).
8. Clinicians should consider treating type II cesarean scar pregnancies surgically with laparoscopy (*conditional, low*).

Cervical Pregnancies

9. In appropriately selected cervical pregnancies, clinicians should offer medical management over surgical management with dilatation and curettage (*conditional, low*).

Interstitial/Cornual Pregnancies

10. Clinicians should offer conservative medical management with multidose and/or local methotrexate for interstitial or cornual pregnancies in appropriately selected patients (*conditional, moderate*).
11. If surgery is required, clinicians may perform either laparoscopic cornuotomy or cornual wedge resection because both procedures have comparable results (*conditional, low*).

Abdominal Pregnancies

12. Clinicians may choose either laparotomy or laparoscopy to excise an abdominal pregnancy (*conditional, low*).

Ovarian Pregnancies

13. Clinicians may offer conservative medical management of ovarian pregnancies with methotrexate in appropriately selected patients (*conditional, low*).
14. Clinicians can perform laparoscopic ovarian wedge resection rather than oophorectomy for ovarian ectopic pregnancies, if clinically appropriate (*conditional, low*).

Heterotopic Pregnancies

15. Clinicians should not offer systemic methotrexate in the presence of a desired intrauterine pregnancy (*conditional, moderate*).
16. We suggest surgical excision of the ectopic pregnancy in cases of heterotopic pregnancy. If the intrauterine pregnancy is not desired, we conditionally recommend adding dilatation and curettage to the surgical procedure to evacuate the uterine cavity (*conditional, moderate*).

INTRODUCTION

Ectopic pregnancy occurs when a developing blastocyst implants at any site other than the uterine cavity. Ectopic pregnancy is most commonly found in the fallopian tube but may also occur in the cornua of the uterus, cervix, ovary, or abdominal cavity or in a cesarean scar (Table).[1] The total incidence is difficult to determine because ectopic pregnancy is no longer managed strictly in an inpatient setting, and multiple encounters for management of a single ectopic pregnancy are common. An estimated 1% to 2% of pregnancies are ectopic, but they account for 75% of maternal deaths in the first trimester and 9% to 13% of all pregnancy-related deaths.[2] In patients consulting for medical abortion (MA), the estimated risk of ectopic pregnancy is considerably lower than in the general population at 0.7 per 10 000 MAs.[3] Clinical signs and symptoms of ectopic pregnancy include abdominal pain and/or vaginal bleeding, as well as an absent menstrual period in a reproductive-aged female.

Diagnosis in early pregnancy can be straightforward if ultrasound definitively identifies either an intrauterine pregnancy (IUP) or ectopic pregnancy. The Society of Obstetricians and Gynaecologists of Canada "Guideline No. 337: Ultrasound Evaluation of First Trimester Complications of Pregnancy" provides evidence-based guidelines for ultrasound and β-human chorionic gonadotropin (β-hCG) cut-offs for the diagnosis of normal and abnormal early pregnancies, including tubal pregnancy.[4] When a pregnancy cannot be located on ultrasound but the β-hCG result is positive, patients are classified as having a pregnancy of unknown location (PUL).

PUL is not a diagnosis in itself but rather a transient state used to classify a patient at risk for ectopic pregnancy. The reported rate of PUL among women attending early pregnancy assessment units varies from 5% to 42%; however, the generally accepted incidence of PUL is about 15% in women undergoing transvaginal ultrasound early in the first trimester.[5,6] Management of a PUL requires close follow-up with repeated diagnostic testing until a definitive diagnosis of either a viable or nonviable pregnancy is reached.

ABBREVIATIONS

β-hCG	β-human chorionic gonadotropin
IUP	Intrauterine pregnancy
MA	Medical abortion
PUL	Pregnancy of unknown location

Table. Sites of ectopic pregnancy

Site of pregnancy	Incidence
Fallopian tube	98%
Hysterotomy/cesarean scar	1 in 2000
Abdominal	1 in 5000
Ovarian	1 in 7000
Cervix	Rare
Rudimentary horn	Rare

SUMMARY STATEMENTS 1, 2, and 3

This guideline was developed to provide guidance in the management of PUL and tubal and nontubal ectopic pregnancies.

MANAGEMENT OF PREGNANCY OF UNKNOWN LOCATION

PUL is a transient state in which β-hCG is positive but a transvaginal ultrasound fails to find either an intrauterine or extrauterine pregnancy. PUL is not a final diagnosis; it is a classification that indicates a patient is at risk for ectopic pregnancy.

The possible pregnancy outcomes for women initially classified as having a PUL are as follows:

1. IUP (34%–40%)[7]
   a. Viable IUP
   b. Nonviable
2. Failed PUL (44%–69%)[7] occurs when serum β-hCG levels fall without intervention, and the location of the pregnancy is never confirmed.
3. Persistent PUL (2%)[7] is defined as a sustained elevation in serial serum β-hCG with no pregnancy visualized on transvaginal ultrasound. This is not a final diagnosis but rather a classification of PUL. Outcomes are dependent on intervention and include a non-visualized ectopic pregnancy (if β-hCG levels continue to rise after uterine evacuation), treated persistent PUL (resolution of β-hCG levels with medical management without confirmation of location of pregnancy), resolution of persistent PUL (either spontaneous or after uterine evacuation, with no evidence of chorionic villi on pathology), or confirmation of IUP (pathology confirmation of chorionic villi after uterine evacuation).[8] In patients with persistently elevated β-hCG levels, rare non–pregnancy-related diagnoses that may cause

elevated β-hCG should be considered, including ovarian cysts (e.g., teratomas), gestational trophoblastic disease, and nongynaecologic sources of elevated β-hCG (e.g., pituitary secretion).

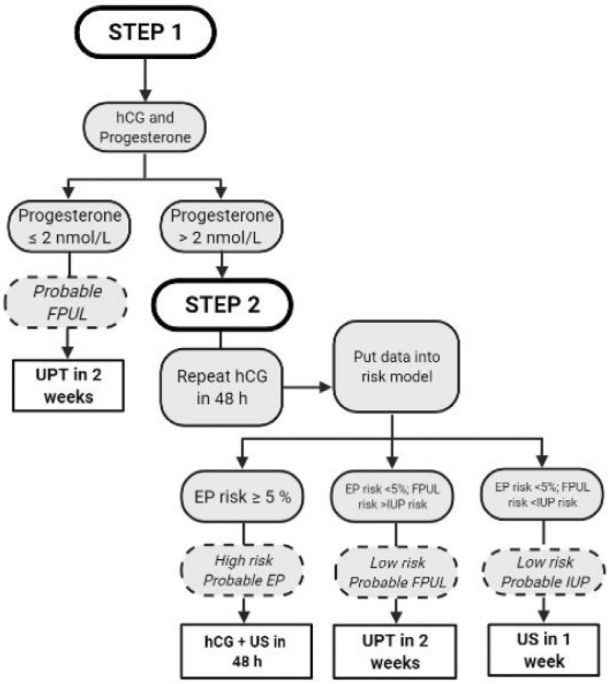
4. Ectopic pregnancy (8%–14%)[7]

Before a final diagnosis can be reached, patients require multiple visits, frequent testing, and consistent follow-up until the location and viability of the pregnancy are determined and definitive management is performed. An expectant approach to PUL is considered safe; however, clinicians are often uncomfortable because the risk of a missed ectopic pregnancy poses a significant risk to the patient's health. Conversely, treatment of a PUL with medical or surgical therapy before a final diagnosis is reached may cause spontaneous abortion or teratogenesis of a viable, desired pregnancy.

There are several published protocols for the management of PUL. Some focus primarily on differentiating PULs by their risk of being an ectopic pregnancy, whereas others focus on determining whether the PUL is viable (e.g., failed ectopic pregnancy or IUP). Patients considered at high risk for ectopic pregnancy require frequent monitoring to avoid a missed diagnosis, which carries significant risk of morbidity and mortality. A variety of evaluation strategies for PUL have been described, including measurements of single β-hCG cut-off levels, the β-hCG ratio (β-hCG at 48 hours/β-hCG at 0 hours), single progesterone cut-off levels, both β-hCG and progesterone levels, and logistic regression models that use combinations of the aforementioned.[5]

A systematic review and meta-analysis of diagnostic protocols for the management of PUL demonstrated that the M4 model was the best available method for predicting the outcome of ectopic pregnancy.[9] Initial serum β-hCG and the 48-hour β-hCG ratio were used to measure the primary outcome, which was an accurate predictor of ectopic pregnancy (high risk) as opposed to either a failed PUL or an IUP (low risk). The sensitivity of the M4 model, given an underlying 5% risk of ectopic pregnancy, is 0.82, and the specificity is 0.80.[10] The M4 has now been replaced by the M6 model, which has been validated in over 3000 patients.[11] The M6 model performs slightly better than the M4 because the M6 included more ectopic pregnancies in its development dataset and includes progesterone levels in its algorithm. See Figure for the algorithm demonstrating the M6 model for PUL. It can be downloaded at http://www.earlypregnancycare.co.uk/. The algorithm can still be used as a prediction model without a serum progesterone level.

Figure. Algorithm for managing pregnancy of unknown location using the M6 regression model. Adapted from Bobdiwala et al. (2019)[11]. Figure created in BioRender.com



EP: ectopic pregnancy; FPUL: failed PUL; hCG: human chorionic gonadotropin; IUP: intrauterine pregnancy; UPT: urine pregnancy test; US: ultrasound examination.

SUMMARY STATEMENT 4 and RECOMMENDATION 1

APPROACH TO MANAGEMENT OF TUBAL AND NONTUBAL ECTOPIC PREGNANCIES

Once ectopic pregnancy, either tubal or nontubal, has been diagnosed on ultrasound, options for management include active surveillance until spontaneous resolution, medical therapy, procedural treatments, surgery, or a combination of treatments.

MANAGEMENT OF TUBAL PREGNANCIES

Expectant Management

Tubal pregnancies are rarely managed expectantly owing to uncertainty around appropriate patient selection, the efficacy and safety of an expectant approach, and medicolegal concerns. There is limited evidence to support expectant management. Spontaneous resolution rates for unruptured asymptomatic tubal pregnancies range from 30% to 70%, depending on the patient selection criteria used in the included studies.[12–16] Although expectant management

avoids the potential risks associated with medical or surgical treatment, failure is associated with severe patient harm.

There is no consensus on the clinical criteria that accurately predict the success of expectant management; however, expectant management may be appropriate for a small number of carefully selected patients with early asymptomatic ectopic pregnancies (Box 1). A strong correlation between initial β-hCG level and the likelihood of spontaneous resolution of an ectopic pregnancy has been repeatedly demonstrated.[12–16] Spontaneous resolution occurred in 96% of patients with an initial β-hCG <175 IU/L.[12] With an initial β-hCG >2000 IU/L, expectant management failed in 93.3% of patients.[15] The spontaneous resolution rate was 66% when the initial β-hCG was 175–1500 IU/L, serum progesterone was low (<10 nmol/L), and gestational age was under 42 days.[12] The likelihood of spontaneous resolution decreases significantly when the initial β-hCG is >1000 IU/L with an odds ratio (OR) for failure of 6.2 (95% confidence interval [CI] 1.76–22) and a relative risk (RR) of 3.6 (95% CI 1.6–8; $P = 0.002$).[13] A cut-off value of 1000 IU/L for initial β-hCG was shown to offer an acceptable trade-off between sensitivity and specificity for spontaneous resolution.[16] The change in β-hCG levels during short-term follow-up assessment (2–7 days) is also clinically important in predicting the chance of spontaneous resolution.[14,16] When β-hCG spontaneously decreased on repeat assessment, 88.8% of cases spontaneously resolved without further treatment, whereas only 51.6% resolved without treatment when β-hCG increased.[14]

MEDICAL MANAGEMENT

Unruptured tubal pregnancy may be treated medically using methotrexate, a folic acid antagonist that inhibits dihydrofolate reductase, resulting in impaired DNA synthesis in rapidly dividing cells. The initial treatment protocol was adapted from protocols designed for gestational trophoblastic disease and used a fixed multidose schedule in which methotrexate 1 mg/kg is given via intramuscular (IM) injection on alternating days with leucovorin rescue. Although effective, the fixed multidose protocol is time and resource intensive, requiring multiple follow-ups and doses of IM medication. Interest in reducing this burden produced 2 alternative protocols: a single IM dose of methotrexate (50 mg/m^2) or 2 IM doses of methotrexate (50 mg/m^2) given at a fixed interval. See Box 2 for various methotrexate dosing regimens.

In carefully selected patients, medical management with methotrexate has outcomes comparable to surgical management in terms of success, complications, and subsequent fertility.[17–20] Early studies using multidose methotrexate protocols in the management of tubal pregnancy showed very high rates of resolution without surgery (85%–94.4% of women).[21–27] The success rate of methotrexate treatment is 70% to 90% for the single-dose protocol,[28–30] 80% to 90% for the double-dose protocol,[30–32] and 89% to 96% for the multidose protocol.[21,28,29] Randomized trials directly comparing surgical treatment and methotrexate for unruptured ectopic pregnancy have not shown significant differences in success rates, ipsilateral tubal patency rates (55%–59%), or subsequent spontaneous conception rates (62%–73%).[17–20] However, despite the demonstrated success of methotrexate in the treatment of ectopic pregnancy, randomized trials have also highlighted the need for careful patient selection because subsets of patients, particularly those with higher initial β-hCG levels, have been shown to be at increased risk of methotrexate treatment failure.[33]

Box 1. Criteria for expectant management of tubal pregnancy

Criteria	Consider expectant management	Consider active treatment
Symptoms	Asymptomatic	Any symptoms
Initial β-hCG	<1000 IU/L	≥1000 IU/L
Change in β-hCG in 48 h	Decreasing (≥15%–20%)	Plateau *or* increase
Adnexal appearance on US	No significant hematosalpinx *and* no fetal heart rate	Large hematosalpinx *or* detectable fetal heart rate
Free fluid on US	No significant free fluid	Hemoperitoneum
Patient characteristics	• Agreeable to participation in close follow-up • Understands and accepts potential risks of failure • Counselled on signs and symptoms requiring emergency care • Can access emergency care	• Barriers to understanding diagnosis or risks • Potential barriers to participating in follow-up • Poor access to emergency care • Requests active treatment

β-hCG: β-human chorionic gonadotropin; US: ultrasound.

Box 2. Methotrexate (MTX) dosing and regimens

	Single-dose protocol	Double-dose protocol	Multidose protocol
Day 1	• Serum β-hCG level • Give MTX 50 mg/m^2 IM	• Serum β-hCG level • Give MTX 50 mg/m^2 IM	• Serum β-hCG level • Give MTX 1 mg/kg IM
Day 2			Give folinic acid 0.1 mg/kg IM
Day 3			• Serum β-hCG level • If ≥15% drop from day 1, stop protocol and follow β-hCG level weekly until negative • If <15% drop from day 1, give second dose MTX 1 mg/kg IM
Day 4	Serum β-hCG level	• Serum β-hCG level • Give second dose MTX 50 mg/m^2 IM	Give folinic acid 0.1 mg/kg IM if second dose MTX given on day 3
Day 5			• Serum β-hCG level • If ≥15% drop from day 3, stop protocol and follow β-hCG level weekly until negative • If <15% drop from day 3, give third dose MTX 1 mg/kg IM
Day 6			Give folinic acid 0.1 mg/kg IM if third dose of MTX given on day 5
Day 7	• Serum β-hCG level • If ≥15% drop from day 4, stop protocol and follow β-hCG level weekly until negative • If <15% drop from day 4, give second dose MTX 50 mg/m^2 IM	• Serum β-hCG level • If ≥15% drop from day 4, stop protocol and follow β-hCG level weekly until negative. • If <15% drop from day 4, give third dose MTX 50 mg/m^2 IM	• Serum β-hCG level • If ≥15% drop from day 5, stop protocol and follow β-hCG level weekly until negative • If <15% drop from day 5, give fourth dose MTX 1 mg/kg IM
Day 8			Give folinic acid 0.1 mg/kg IM if fourth dose of MTX given on day 7
Day 9			• Serum β-hCG level • If ≥15% drop from day 7, stop protocol and follow β-hCG level weekly until negative • If <15% drop from day 7, stop protocol and consider surgery
Day 10	If given second dose of MTX on day 7, serum β-hCG level	• If given third dose of MTX, serum β-hCG level • If ≥15% drop from day 7, stop protocol and follow β-hCG level weekly until negative • If <15% drop from day 7, give fourth dose MTX 50 mg/m^2 IM	
Day 14	• Serum β-hCG level • If <15% drop from previous measurement, consider surgery	• Serum β-hCG level • If <15% drop from previous measurement, consider surgery	
Criteria for failure of protocol	• Development of symptoms of possible tubal rupture • Failure to achieve ≥15% decrease in serum β-hCG after 2 doses MTX	• Development of symptoms of possible tubal rupture. • Failure to achieve ≥15% decrease in serum β-hCG after 4 doses MTX	• Development of symptoms of possible tubal rupture • Failure to achieve ≥15% decrease in serum β-hCG after 4 doses MTX

β-hCG: β-human chorionic gonadotropin; IM: intramuscular.

Patients must be carefully selected for medical management to maximize the chance of success and minimize the risk of complications. Patients selected for methotrexate treatment must be clinically stable without signs of acute intraperitoneal bleeding or tubal rupture, must not be experiencing significant abdominal pain, must be able to understand the proposed treatment, must accept the potential risk of failure, must be able to access to emergency care, and must agree to follow-up to monitor response to therapy. In addition, they must not have any absolute contraindications to methotrexate that make administration of the drug dangerous. Absolute contraindications include the following: clinically significant renal or liver disease, blood dyscrasias or bone marrow suppression, pulmonary fibrosis, peptic ulcer disease, immunosuppression, chronic infections, a concurrent IUP, or breastfeeding.

Although absolute contraindications to methotrexate are well defined, consensus has not been reached on the

relative contraindications to methotrexate that predict the risk of treatment failure. In multiple studies, initial β-hCG level is the most predictive factor for overall success, with higher pretreatment serum β-hCG levels strongly and positively correlated with treatment failure.[34] Despite this relationship, consensus on an appropriate cut-off value for initial β-hCG has not been reached. Treatment failure rates substantially and significantly increase when initial β-hCG levels are >5000 IU/L (14.29% failure) compared with 2000−4999 IU/L (3.77% failure) (OR 5.45; 95% CI 3.04−9.78).[35] The ultrasound appearance of ectopic pregnancy also correlates with treatment success.[34] The presence of a visible embryo, yolk sac, fetal cardiac activity, significant pelvic free fluid or larger hematosalpinx, or a gestational sac is a significant risk factor for treatment failure.[28,34,36]

Ultrasound features that increase the likelihood of methotrexate treatment failure may be divided into two categories. The first group includes normal markers of early gestational development, such as a visualized yolk sac, embryo, or fetal cardiac activity. These markers of normal development correlate with a "healthy" ectopic pregnancy with an increased resistance to interruption by methotrexate, leading to an increased risk of treatment failure.[36−38] In an ectopic pregnancy with a visualized yolk sac, methotrexate treatment failed in 21.9% of patients (vs. 7.4% of patients without a visualized yolk sac; $P = 0.0003$).[36] The presence of a visible embryo also significantly increased the risk of treatment failure; 44% of ectopic pregnancies with a visible embryo were successfully treated with methotrexate, compared with 79% without a visible embryo (OR 24; 95% CI 2.1−269; $P = 0.01$).[37,38] Detectable fetal cardiac activity is also correlated with decreased treatment success, with a fetal heart rate present in 30% of failed treatments compared with 12% of successful treatments ($P = 0.01$).[34,39]

The second group of ultrasound findings associated with increased risk of methotrexate treatment failure comprises markers of evolving or potential tubal rupture owing to intraperitoneal hemorrhage secondary to tubal damage. Markers include a large volume of pelvic free fluid or hemoperitoneum and increasing adnexal mass size.[40,41] Significant pre−methotrexate treatment hemoperitoneum increases the likelihood that the patient will require subsequent surgical treatment (OR 5.1; 95% CI 1.74−15.14) and was present in 62.5% of treatment failures compared with 24.6% of successful treatments ($P = 0.001$).[41] Adnexal mass size is also strongly correlated with treatment outcome, with larger adnexal masses (>3.5 cm) being associated with an increased risk of failure (OR 6.78; 95% CI 3.18−8.22).[40] See Box 3 for patient selection criteria for methotrexate treatment of tubal pregnancy.

There has been considerable interest in determining which methotrexate protocol offers the best balance of treatment success, adverse effects, resource use, and time to resolution in patients deemed to be good candidates for methotrexate treatment. Meta-analysis of multidose versus single-dose methotrexate randomized trial data shows a nonsignificant increase in the odds of success with a multidose protocol. However, a significant increase in the odds of adverse effects and no significant difference in the length of follow-up needed to reach resolution suggests no overall benefit of the multidose protocol.[42] Randomized comparisons of the single- and double-dose protocols also failed to show significant differences in success; however, the double-dose protocol was associated with a faster time to resolution, thereby shortening the length of follow-up required (31.9 vs. 21.7 days; $P = 0.025$).[43] Adverse effects reported were slightly, but not significantly, greater with the double-dose protocol, and patient satisfaction was comparable.[43] Meta-analysis of pooled data showed a small but significant increase in the odds of treatment success with a double- versus single-dose protocol (OR 1.84; 95% CI 1.13−3.00), particularly in the subgroup with larger adnexal mass size or initial β-hCG >5000 IU/L.[44] The double-dose protocol resulted in a 1 week shorter follow-up but had 1.53 times the rate of reported adverse effects, suggesting a possible advantage of the double-dose over the single-dose protocol in selected cases.[44]

Methotrexate is teratogenic or lethal in all animal embryos on which it has been tested. In human embryos, it has been associated with central nervous system abnormalities, including open neural tube defects, hydrocephalus, and anencephaly, as well as skeletal abnormalities, facial and limb malformations, and growth retardation. Neither the minimum dose of methotrexate required to cause teratogenesis nor the critical period of developmental exposure to methotrexate has been definitively determined.[45] The half-life of methotrexate is reported to be 8−15 hours; however, methotrexate metabolites may persist for weeks in the kidneys and up to 116 days in the liver.[45,46] Although there is insufficient evidence to recommend the use of post-methotrexate contraception, it may be prudent for women to delay attempts to conceive for 12 weeks or more after methotrexate treatment to allow for maximum clearance.[47] A retrospective review involving 226 women who conceived after a methotrexate-treated ectopic pregnancy showed no difference in pregnancy outcomes and complications, including pregnancy loss or major malformations, in pregnancies conceived within the 6 months

Box 3. Selection criteria for medical management of tubal pregnancy

Criteria	Consider MTX	Use MTX with caution	Use MTX with extreme caution
Vital signs	Normal	–	Abnormal
Abdominal pain	None	Mild/transient	Significant or persistent
β-hCG	<1500 IU/L	1500–5000 IU/L	>5000 IU/L
Adnexal mass size	<35 mm	–	≥35 mm
Appearance	Empty gestational sac or heterogeneous mass	Yolk sac with or without fetal pole	Fetal heart rate seen
Free fluid on ultrasound	None/minimal	Simple and/or confined to pelvis	Echogenic or large
Ability to follow up	No identified barriers, agreeable to follow-up	Potential barriers: language, social, geographic	Unable or unwilling to follow up
Labs	Normal CBC, Cr, ALT	• Mild anemia or thrombocytopenia • Slight elevation in ALT or Cr (no more than 2 times upper limit of normal)	Significant abnormalities in any of CBC, Cr, or ALT
Patient medical history	Healthy	• Mild anemia or thrombocytopenia • Refuses blood transfusion	• Infection (TB, HIV) • Immunosuppression • Breastfeeding • Liver or renal disease • Bone marrow suppression • Blood dyscrasias • Pulmonary fibrosis • GI or oral ulcers • Heterotopic pregnancy
β-hCG change in 48 h pretreatment (if available)	<20% increase in 48 h	>50% increase in 48 h	Rapidly increasing (mirroring IUP)
Suggested action	Consider single or double dose MTX protocol	• Requires individual consideration of risks and benefits of MTX vs. surgery; increased risk of failure of MTX treatment	• Strongly consider operative management • High risk for MTX failure or adverse reaction to MTX

β-hCG: β-human chorionic gonadotropin; ALT: alanine aminotransferase; CBC: complete blood count; Cr: creatinine; GI: gastrointestinal; HIV: human immunodeficiency virus; IUP: intrauterine pregnancy; MTX: methotrexate; TB: tuberculosis.

immediately following treatment.[48] A retrospective logistic regression analysis that included 314 pregnancies conceived shortly after methotrexate treatment of an ectopic pregnancy showed no evidence of increased risk of fetal malformations or adverse pregnancy outcomes (OR 1.003; 95% CI 0.98–1.02) and concluded that conception within the first 6 months after methotrexate treatment for ectopic pregnancy is safe.[49] There is no evidence regarding the use of high-dose folic acid to reduce the risk of malformations or complications in subsequent pregnancies.[46]

SURGICAL MANAGEMENT

Surgical management of tubal pregnancy should be undertaken when patients either decline or do not meet the criteria for safe expectant or medical management. Surgery may be approached by either laparoscopy or laparotomy, depending on patient factors and the availability of local expertise and resources. Whenever feasible, a minimally invasive approach should be chosen. There is scant and conflicting evidence for the superiority of conservative fallopian tube–sparing surgery (salpingotomy) over salpingectomy.[50–52] In practice, the choice between salpingotomy and salpingectomy is influenced by both patient and surgeon factors, including the patient's age, desire for future fertility, and surgical and obstetrical history; the condition of both the affected and contralateral fallopian tube; and the surgeon's experience and preference (Box 4).

It has been hypothesized that conservation of the fallopian tube, where possible, may improve future fertility. However, two multicentre randomized trials failed to demonstrate any significant benefit over 24–36 months of postoperative follow-up when the contralateral fallopian tube appeared healthy at the time of surgery.[50,52] A meta-

Box 4. Comparison of salpingotomy and salpingectomy in the surgical management of tubal pregnancy

	Salpingotomy	Salpingectomy
Benefits	• May ↑ future fertility in women with contralateral tube damage, pelvic disease • No evidence of fertility benefit when healthy-appearing contralateral tube present	• ↓ risk of persistent ectopic requiring postoperative treatment • Possible ↓ risk of recurrent ectopic
Disadvantages	• Requires follow-up of β-hCG after surgery to ensure resolution of ectopic pregnancy • ↑ risk of persistent ectopic needing postoperative treatment • Possible ↑ risk recurrent ectopic	• Possible ↓ fertility in women with damaged contralateral tube or pelvic adhesions.

β-hCG: β-human chorionic gonadotropin.

analysis showed no statistically significant difference in the subsequent IUP rate between salpingotomy and salpingectomy when controlling for potentially confounding factors.[51] Salpingotomy was associated with a potentially higher risk of recurrent ectopic pregnancy (RR 2.27; 95% CI 1.12−4.58; $P = 0.02$) in the meta-analysis of the cohort study group, but this effect was not seen in the meta-analysis of the randomized studies (RR 1.04; 95% CI 0.89−1.21; $P = 0.61$).[51] In addition, persistent ectopic pregnancy requiring postoperative treatment occurred significantly more often in the salpingotomy group (7%) than in the salpingectomy group (<1%) (RR 15.0; 95% CI 2.0−113.4).[50]

Although salpingotomy did not confer any significant fertility benefit with a healthy-appearing contralateral tube, the condition of the contralateral tube at the time of surgery is an important factor influencing the likelihood of subsequent pregnancy.[53] Subsequent pregnancy rates were significantly higher with a healthy contralateral tube regardless of the procedure performed.[53] In contrast, the subsequent pregnancy rate was significantly lower with salpingectomy when at least one fertility-reducing factor (contralateral tube damage, adhesions) was identified at the time of surgery (40% vs. 75%; $P < 0.05$). This finding suggests that conserving the affected tube, where possible, may be beneficial for patients with pelvic disease.[53]

SUMMARY STATEMENTS 5, 6, and 7 and RECOMMENDATIONS 2, 3, 4, and 5

DIAGNOSIS AND MANAGEMENT OF NONTUBAL ECTOPIC PREGNANCIES

Ultrasound diagnosis of nontubal ectopic pregnancy can be challenging and requires experienced sonographers who can identify atypical and rare locations of a gestational sac. See Box 5 for the diagnostic criteria for a nontubal ectopic pregnancy. Management of nontubal ectopic pregnancy can present a significant surgical challenge and high risk of hemorrhage. Referral of the patient to a tertiary care centre with surgical expertise should be considered.

There is limited evidence for the management of nontubal ectopic pregnancies. Owing to the rarity of some of these ectopic pregnancy types, the majority of the published evidence is of low quality and includes small trials, retrospective observational studies, and case reports or series. Both systemic and local treatments have been described, with some reports of additional adjunct therapies. There is no consensus on the criteria that should guide patient selection for medical versus surgical management or on optimal dosing protocols for medical therapy. The types of surgery performed are site-dependent and dictated by local expertise and resources as well as patient characteristics. Box 6 summarizes the treatment options described in the literature for nontubal ectopic pregnancies. Refer to Box 2 for details of systemic methotrexate dosing regimens.

Cesarean Scar Pregnancy

There are two types of cesarean scar pregnancy.[54] Type I, endogenous-type cesarean scar pregnancy, is characterized by progression of the pregnancy to the cervico-isthmic space or uterine cavity, and type II, exogenous-type cesarean scar pregnancy, is characterized by deep invasion of the cesarean scar defect and progression towards the bladder and abdominal cavity. Type I can result in a viable pregnancy and can, in select cases and with proper counselling, be treated expectantly. Type II may be complicated by uterine rupture and bleeding early in pregnancy. Many cesarean scar pregnancies are believed to progress to placenta accreta spectrum disorders. A systematic review and meta-analysis of the outcome of expectantly managed cesarean

Box 5. Ultrasonographic diagnostic criteria for nontubal ectopic pregnancies

Location of pregnancy	Ultrasound diagnostic criteria
Ovarian	Spiegelberg's criteria[106]: (1) Ipsilateral tube must be intact (2) Gestational sac must occupy a position in ovary (3) Ovary must be connected to uterus by ovarian ligament (4) Ovarian tissue seen in sac wall on pathology
Cesarean scar	(1) Pregnancy located in the anterior uterine isthmus (2) Empty uterine cavity with no contact with the gestational sac (3) Empty cervical canal (4) Discontinuity in the anterior myometrium (or absence of myometrium between the gestational sac and bladder) (5) No suspicious adnexal masses or free fluid
Interstitial or cornual	Timor-Tritsch Criteria[107]: (1) Empty uterine cavity (2) Gestational sac >1 cm from the lateral edge of the uterine cavity (3) Thin (<5 mm) myometrial layer surrounding gestational sac Interstitial line sign[107] (echogenic line in cornual region of uterus from gestational mass to endometrium)
Cervical	• Gestational sac implanted within endocervical canal • Ballooned-out cervix containing a gestational sac with closed internal os[108] • Sliding organ sign: If movement of gestational sac is seen when pressure is applied with the transvaginal probe, it is associated with spontaneous abortion; it should be absent in a cervical ectopic[109]

scar pregnancy showed that 90.3% patients with a viable pregnancy were subsequently diagnosed with invasive placenta.[55] The majority of patients with a cesarean scar pregnancy without fetal cardiac activity had an uncomplicated miscarriage. However, this review did not distinguish between types of cesarean scar pregnancy. Another case series of 10 patients with a type I cesarean scar pregnancy showed that all patients were diagnosed with an invasive placenta by the second trimester.[56]

There are very limited data on the management of cesarean scar pregnancy (primarily case reports), with no consensus on the optimal approach. Treatment of cesarean scar pregnancy with medical or surgical therapy or a combination of the two, with or without adjunct treatments, has been described.

Systemic methotrexate was found to be effective when the serum β-hCG level was <12 000 mU/mL (OR 5.68; 95% CI 1.37−23.48) with no embryonic cardiac activity and with a gestational age under 8 weeks.[57] Type II cesarean scar pregnancy has been successfully treated with multidose systemic methotrexate; however, a small retrospective case series showed that 50% of patients required further surgical intervention.[58] Methotrexate locally injected into the gestational sac has also been advocated in the treatment of cesarean scar pregnancy.[59]

When surgery is being considered, the appropriate surgical approach is dependent on the type of cesarean scar pregnancy, patient status, surgeon experience, and local resources. Type I cesarean scar pregnancy can be treated by hysteroscopy, whereas type II may be better approached with laparoscopy or laparotomy, which allows for concurrent repair of the cesarean scar defect and removal of the pregnancy.[58]

Adjunct treatments include selective uterine artery embolization or pre-procedural treatment with methotrexate, especially in a cesarean scar pregnancy with a gestational age of 8 weeks or over.[58,60]

Cervical Pregnancy

Women presenting with a cervical pregnancy have a significant risk of hemorrhage owing to trophoblastic invasion of the cervix in close proximity to the uterine vessels. Options for management include expectant surveillance, medical therapy, procedural treatments, surgical management, or a combined approach.

Cases involving multidose methotrexate regimens for the management of cervical pregnancy have been frequently reported in the literature, and many of these cases are managed in the inpatient setting (see Box 4 for dosing regimen). In a series of 52 cervical ectopic pregnancies, serum βhCG levels ≥10 000 mIU/mL, a gestational age of 9 weeks or over, presence of fetal cardiac activity, and a crown−rump length >10 mm were factors associated with a lower rate of methotrexate treatment success.[61]

Box 6. Frequently described treatment options for nontubal ectopic pregnancies[a]

Site of pregnancy	Systemic MTX	Local treatment	Possible concomitant procedures	Surgical options
Abdominal	Multidose	—	—	• Laparoscopy/laparotomy excision of pregnancy • Laparotomy and delivery (if viable fetus)
Cesarean scar	• Single dose • Multidose	Intra-sac MTX (50 mg/m^2 or 1–2 mL of 25-mg/mL solution)[59]	Uterine artery embolization	• Suction curettage • Hysteroscopic excision with or without ultrasound or laparoscopic guidance • Laparoscopic wedge resection
Cervical	Multidose	Intra-sac MTX (50 mg/m^2 or 1–2 mL of 25-mg/mL solution)[62,103]	Embolization (uterine or cervical arteries)	• Suction curettage
Interstitial or cornual	• Single dose • Multidose	Intra-sac MTX (1 mg/kg or 1–2 mL of 25-mg/mL solution)[70,103]	—	• Laparoscopic cornuotomy • Laparoscopic wedge resection with or without ipsilateral salpingectomy
Ovarian	Single dose	—	—	• Laparoscopic ovarian wedge resection • Laparoscopic oophorectomy

[a] A multimodal approach frequently is reported in the literature. However, this is largely based on case reports and small case series. There is insufficient evidence to recommend one treatment modality over another. Other treatment modalities have also been described—these are the more frequently reported treatment regimens. Local treatment with MTX is performed under ultrasound or laparoscopic guidance. If fetal cardiac activity is noted, intracardiac injection of potassium chloride can be given. There is no consensus on dosage, but reported doses range from 0.5–5 mL of 2 mEq potassium chloride. Some cases also report aspirating 1–3 mL from the gestational sac before local treatment to reduce the theoretical risk of ectopic pregnancy rupture.[61,103]

MTX: methotrexate.

Ultrasound-guided intra-amniotic and intrachorionic methotrexate injection (50 mg/m^2) have also been used in conjunction with intracardiac injection of potassium chloride if fetal cardiac activity was seen.[62] Arterial embolization with occlusion of the cervical and uterine vessels has also been used in tandem with either subsequent surgery (dilation and curettage) or concomitant systemic methotrexate.[63] Arterial embolization alone has been used in some cases to avoid the risks associated with systemic methotrexate. Arterial embolization also requires a shorter hospital stay. There are limited case reports but no studies assessing fertility and future pregnancy outcomes after embolization for ectopic pregnancy. However, failure of the procedure, hemorrhage, and technical inability to perform the procedure in all centres are important limitations to its use.

Interstitial (or Cornual) Pregnancy

In the literature, the terms *interstitial pregnancy* and *cornual pregnancy* are often used synonymously. However, by strict definition, they are different entities. An interstitial pregnancy occurs in the interstitial or proximal portion of the tube within the muscular wall of the uterus lateral to the round ligament. In contrast, a cornual pregnancy implants in the bicornuate horn of the uterus and is considered an IUP. Because reports in the literature use these terms interchangeably and given the rarity of these pregnancies, there are no large trials or consensus on optimal management.

Successful medical management of interstitial pregnancy with systemic methotrexate was first reported using a multidose regimen.[64] Local methotrexate with intrasac or intramyometrial injection under ultrasound, hysteroscopic, or laparoscopic guidance has been reported.[65–67] Adjunct potassium chloride intracardiac injection when fetal cardiac activity is identified has also been reported.[68,69] Overall, success rates for methotrexate administered systemically, locally, or in combination range from 55.3% to 94%.[70] As in other types of ectopic pregnancy, initial β-hCG level is likely correlated to the success of medical therapy. Using pooled results for systemic and local treatments, no failures with medical management were seen when the initial β-hCG level was lower than 9000 IU/L.[71] Gestational age, size, pelvic pain, and mode of treatment did not appear to influence treatment success. However, a later study showed that local methotrexate was more effective than systemic

methotrexate, with success rates of 87.5% and 46.7%, respectively.[70]

Surgical options for interstitial pregnancy include laparoscopic or open cornuotomy or cornual resection. A retrospective comparison of both procedures performed laparoscopically showed a shorter mean operating time with cornuotomy but no difference in complication rates or persistence of pregnancy.[72] Future pregnancy risks after surgery for interstitial pregnancy include uterine rupture and uterine scar dehiscence (30%) or recurrent interstitial or cornual pregnancy.

Abdominal Pregnancy

Abdominal pregnancies account for about 1.3% of all ectopic pregnancies but carry a nearly 8-fold increased risk of maternal death compared with tubal pregnancies.[73] There are published reports of abdominal pregnancies implanting on the liver,[74] spleen,[75] diaphragm,[76] bowel,[77] cul-de-sac,[78] and abdominal wall,[79] as well as retroperitoneally on the inferior vena cava[80] and aorta.[81] Abdominal pregnancies have even been reported after total hysterectomy.[82] Early abdominal pregnancy may be difficult to diagnose. It should be suspected if there is a positive β-hCG test with an empty uterus and an absence of myometrial tissue between the pregnancy and maternal bladder.[83] Later in pregnancy, physical examination typically reveals a displaced, closed, and uneffaced cervix; an unusual fetal lie; and a small uterus. Failure to produce contractions with prostaglandins or oxytocin should also raise suspicions for an extrauterine pregnancy. In cases of advanced abdominal pregnancy, patients may present with abdominal pain and malaise, occasionally with hypovolemic shock, or rarely with rectal bleeding.[84]

Some early abdominal pregnancies are likely managed medically with methotrexate as a PUL with no establishment of a definitive pregnancy site. A case report described an unsuccessful attempt at treating a confirmed abdominal pregnancy with methotrexate; the patient required laparoscopic excision.[85] Although infrequent, reports of fetal survival, some at term, have been reported.[86–89] However, given the risk of hemorrhage, abdominal pregnancies are typically managed surgically, either with laparoscopy or laparotomy, at the time of diagnosis.[90] At the time of surgery, managing the placenta requires an individualized approach; life-threatening hemorrhage from the placental bed can occur if proper control of the vascular supply cannot be achieved. Successful tying off of the umbilical cord close to the placental insertion, followed by expectant management (with or without methotrexate), has been described in the literature. Preoperative embolization of feeding vessels has also been proposed to mitigate the risk of excessive bleeding.[91,92] The risks of significant bleeding with attempted placental removal must be balanced against the complications associated with leaving the placenta in situ, including the risk of severe sepsis, delayed hemorrhage, and the need for repeat surgery. A multidisciplinary approach involving other surgical specialties (e.g., general or vascular surgery) may be warranted, depending on the location of the ectopic pregnancy.

Ovarian Pregnancy

Distinguishing ovarian from tubal pregnancies by ultrasound can be challenging, and laparoscopy is often required for definitive diagnosis. The majority of the literature on ovarian pregnancies is composed of case reports or series involving the most frequent therapeutic intervention, ovarian wedge resection, and, more rarely, oophorectomy.[93,94] A review of medically managed ovarian ectopic pregnancies published in 2008 reported a 60% success rate (5 patients) with IM methotrexate administration.[95]

Heterotopic Pregnancy

The simultaneous presence of an intrauterine and extrauterine pregnancy occurs infrequently, with a reported rate of 1 in 30 000 spontaneous pregnancies and 1 in 1111 pregnancies conceived with assisted reproductive technology.[96,97] The fallopian tube remains the most common site of ectopic pregnancy, although reports of concurrent pregnancies in the cornua, cervix, cesarean scar, and abdominal cavity have all been described.[98–102] Tubal heterotopic pregnancies are most frequently managed surgically with salpingectomy. Although systemic methotrexate is contraindicated in the presence of a viable and desired IUP, successful targeted treatment of the ectopic pregnancy with intracardiac injection of potassium chloride has been described in the management of heterotopic pregnancies involving all ectopic locations.[103] Management should be tailored to the clinical scenarios and patient's preference. Close follow-up of the IUP is recommended because there is an increased risk of loss of the IUP with the ectopic pregnancy.[104,105]

SUMMARY STATEMENTS 8, 9, 10, 11, 12, 13 and 14 and RECOMMENDATIONS 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16

CONCLUSION

In patients with a positive β-hCG and an ultrasound that fails to find a normally developing IUP, careful follow-up must be arranged with the goal of making a definitive

diagnosis of an IUP (viable or not), ectopic pregnancy, or persistent PUL. When an ectopic pregnancy is identified or strongly suspected, effective treatment and careful follow-up are essential to reduce the risk of serious maternal morbidity or mortality. Successful treatment of ectopic pregnancy may be expectant, medical, or surgical, or it may involve a combination of several approaches, depending on the location of the pregnancy, initial β-hCG level, ultrasound findings, and patient characteristics. Available resources and expertise should also be carefully considered in deciding on a plan of management for any ectopic pregnancy. The decision aids and treatment algorithms provided in this guideline are based on the best available evidence. As further studies become available, recommendations and best practices may change.

GUIDELINE TOOLKIT

SOGC members can visit the Guideline Resource Kit webpage on sogc.org for complementary tools and resources and to participate in accredited continuing professional development activities.

REFERENCES

1. Bouyer J, Coste J, Fernandez H, et al. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. Hum Reprod 2002;17:3224–30.
2. Gaskins AJ, Missmer SA, Rich-Edwards JW, et al. Demographic, lifestyle, and reproductive risk factors for ectopic pregnancy. Fertil Steril 2018;110:1328–37.
3. Cleland K, Creinin MD, Nucatola D, et al. Significant adverse events and outcomes after medical abortion. Obstet Gynecol 2013;121:166–71.
4. Van den Hof MC, Smithies M, Nevo O, et al. No. 375-clinical practice guideline on the use of first trimester ultrasound. J Obstet Gynaecol Can 2019;41:388–95.
5. Kirk E, Bottomley C, Bourne T. Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. Hum Reprod Update 2014;20:250–61.
6. Cordina M, Schramm-Gajraj K, Ross JA, et al. Introduction of a single visit protocol in the management of selected patients with pregnancy of unknown location: a prospective study. BJOG 2011;118:693–7.
7. Reid S, Condous G. Is there a need to definitively diagnose the location of a pregnancy of unknown location? The case for "no". Fertil Steril 2012;98:1085–90.
8. Barnhart K, van Mello NM, Bourne T, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. Fertil Steril 2011;95:857–66.
9. Bobdiwala S, Guha S, Van Calster B, et al. The clinical performance of the M4 decision support model to triage women with a pregnancy of unknown location as at low or high risk of complications. Hum Reprod 2016;31:1425–35.
10. Bobdiwala S, Saso S, Verbakel JY, et al. Diagnostic protocols for the management of pregnancy of unknown location: a systematic review and meta-analysis. BJOG 2019;126:190–8.
11. Bobdiwala S, Christodoulou E, Farren J, et al. Triaging women with a pregnancy of unknown location using a two-step triage protocol including the M6 model: a clinical implementation study. Ultrasound Obstet Gynecol 2020;55:105–14.
12. Elson J, Tailor A, Banerjee S, et al. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. Ultrasound Obstet Gynecol 2004;23:552–6.
13. Jurkovic D, Memtsa M, Sawyer E, et al. Single-dose systemic methotrexate vs expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial. Ultrasound Obstet Gynecol 2017;49:171–6.
14. Mavrelos D, Nicks H, Jamil A, et al. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. Ultrasound Obstet Gynecol 2013;42:102–7.
15. Shalev E, Peleg D, Tsabari A, et al. Spontaneous resolution of ectopic tubal pregnancy: natural history. Fertil Steril 1995;63:15–9.
16. Trio D, Strobelt N, Picciolo C, et al. Prognostic factors for successful expectant management of ectopic pregnancy. Fertil Steril 1995;63:469–72.
17. Hajenius PJ, Engelsbel S, Mol BWJ, et al. Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. Lancet 1997;350:774–9.
18. Krag Moeller LB, Moeller C, Thomsen SG, et al. Success and spontaneous pregnancy rates following systemic methotrexate versus laparoscopic surgery for tubal pregnancies: a randomized trial. Acta Obstet Gynecol Scand 2009;88:1331–7.
19. Saraj AJ, Wilcox JG, Najmabadi S, et al. Resolution of hormonal markers of ectopic gestation: a randomized trial comparing single-dose intramuscular methotrexate with salpingostomy. Obstet Gynecol 1998;92:989–94.
20. Fernandez H, Yves Vincent SC, et al. Randomized trial of conservative laparoscopic treatment and methotrexate administration in ectopic pregnancy and subsequent fertility. Hum Reprod 1998;13:3239–43.
21. Stovall TG, Ling FW, Buster JE. Outpatient chemotherapy of unruptured ectopic pregnancy. Fertil Steril 1989;51:435–8.
22. Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 1993;168(6 Pt 1):1759–62. discussion 1762−5.
23. Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstet Gynecol 1991;77:754–7.
24. Stovall TG, Ling FW, Gray LA, et al. Methotrexate treatment of unruptured ectopic pregnancy: a report of 100 cases. Obstet Gynecol 1991;77:749–53.
25. Rodi IA, Sauer MV, Gorrill MJ, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. Fertil Steril 1986;46:811–3.
26. Sauer MV, Gorrill MJ, Rodi IA, et al. Nonsurgical management of unruptured ectopic pregnancy: an extended clinical trial. Fertil Steril 1987;48:752–5.
27. Henry MA, Gentry WL. Single injection of methotrexate for treatment of ectopic pregnancies. Am J Obstet Gynecol 1994;171:1584–7.
28. Barnhart K. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. Obstet Gynecol 2003;101:778–84.
29. Guvendag Guven ES, Dilbaz S, Dilbaz B, et al. Comparison of single and multiple dose methotrexate therapy for unruptured tubal ectopic

pregnancy: a prospective randomized study. Acta Obstet Gynecol Scand 2010;89:889–95.

30. Saadati N, Najafian M, Masihi S, et al. Comparison of two different protocols of methotrexate therapy in medical management of ectopic pregnancy. Iran Red Crescent Med J 2015;17:e20147.

31. Gungorduk K, Asicioglu O, Yildirim G, et al. Comparison of single-dose and two-dose methotrexate protocols for the treatment of unruptured ectopic pregnancy. J Obstet Gynaecol 2011;31:330–4.

32. Hamed HO, Ahmed SR, Alghasham AA. Comparison of double- and single-dose methotrexate protocols for treatment of ectopic pregnancy. Int J Gynaecol Obstet 2012;116:67–71.

33. Sowter MC, Farquhar CM, Petrie KJ, et al. A randomised trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy. BJOG 2001;108:192–203.

34. Lipscomb GH, McCord ML, Stovall TG, et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999;341:1974–8.

35. Menon S, Colins J, Barnhart KT. Establishing a human chorionic gonadotropin cutoff to guide methotrexate treatment of ectopic pregnancy: a systematic review. Fertil Steril 2007;87:481–4.

36. Lipscomb GH, Gomez IG, Givens VM, et al. Yolk sac on transvaginal ultrasound as a prognostic indicator in the treatment of ectopic pregnancy with single-dose methotrexate. Am J Obstet Gynecol 2009;200. 338 e331–4.

37. Dilbaz S, Caliskan E, Dilbaz B, Degirmenci O, Haberal A. Predictors of methotrexate treatment failure in ectopic pregnancy. J Reprod Med 2006;51:87–93.

38. Chong W, Fridman D, Rotenberg O, et al. Factors predicting the success rate of a single dose of systemic methotrexate for the treatment of ectopic pregnancy. J Minim Invasive Gynecol 2015;22(6S):S89–90.

39. Lipscomb GH, Bran D, McCord ML, et al. Analysis of three hundred fifteen ectopic pregnancies treated with single-dose methotrexate. Am J Obstet Gynecol 1998;178:1354–8.

40. Kimiaei P, Khani Z, Marefian A, et al. The importance of gestational sac size of ectopic pregnancy in response to single-dose methotrexate. ISRN Obstet Gynecol 2013;2013:269425.

41. Gnisci A, Stefani L, Bottin P, et al. Predictive value of hemoperitoneum for outcome of methotrexate treatment in ectopic pregnancy: an observational comparative study. Ultrasound Obstet Gynecol 2014;43:698–701.

42. Yang C, Cai J, Geng Y, et al. Multiple-dose and double-dose versus single-dose administration of methotrexate for the treatment of ectopic pregnancy: a systematic review and meta-analysis. Reprod Biomed Online 2017;34:383–91.

43. Song T, Kim MK, Kim ML, et al. Single-dose versus two-dose administration of methotrexate for the treatment of ectopic pregnancy: a randomized controlled trial. Human Reprod 2016;31:332–8.

44. Alur-Gupta S, Cooney LG, Senapati S, et al. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. Am J Obstet Gynecol 2019;221. 95−108.e2.

45. Donnenfeld AE, Pastuszak A, Noah JS, et al. Methotrexate exposure prior to and during pregnancy. Teratology 1994;49:79–81.

46. Hackmon R, Sakaguchi S, Koren G. Effect of methotrexate treatment of ectopic pregnancy on subsequent pregnancy. Can Fam Physician 2011;57:37–9.

47. Brazerol WF, Grover S, Donnenfeld AE. Unexplained elevated maternal serum alpha-fetoprotein levels and perinatal outcome in an urban clinic population. Am J Obstet Gynecol 1994;171:1030–5.

48. Svirsky R, Ben-Ami I, Berkovitch M, et al. Outcomes of conception subsequent to methotrexate treatment for an unruptured ectopic pregnancy. Int J Gynaecol Obstet 2017;139:170–3.

49. Svirsky R, Rozovski U, Vaknin Z, et al. The safety of conception occurring shortly after methotrexate treatment of an ectopic pregnancy. Reprod Toxicol 2009;27:85–7.

50. Mol F, van Mello NM, Strandell A, et al. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. Lancet 2014;383 (9927):1483–9.

51. Cheng X, Tian X, Yan Z, et al. Comparison of the fertility outcome of salpingotomy and salpingectomy in women with tubal pregnancy: a systematic review and meta-analysis. PloS One 2016;11: e0152343.

52. Fernandez H, Capmas P, Lucot JP, et al. Fertility after ectopic pregnancy: the DEMETER randomized trial. Hum Reprod 2013;28:1247–53.

53. Becker S, Solomayer E, Hornung R, et al. Optimal treatment for patients with ectopic pregnancies and a history of fertility-reducing factors. Arch Gynecol Obstet 2011;283:41–5.

54. Vial Y, Petignat P, Hohlfeld P. Pregnancy in a cesarean scar. Ultrasound Obstet Gynecol 2000;16:592–3.

55. Cali G, Timor-Tritsch IE, Palacios-Jaraquemada J, et al. Outcome of Cesarean scar pregnancy managed expectantly: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018;51:169–75.

56. Timor-Tritsch IE, Monteagudo A, Cali G, et al. Cesarean scar pregnancy is a precursor of morbidly adherent placenta. Ultrasound Obstet Gynecol 2014;44:346–53.

57. Bodur S, Ozdamar O, Kilic S, et al. The efficacy of the systemic methotrexate treatment in caesarean scar ectopic pregnancy: a quantitative review of English literature. J Obstet Gynaecol 2015;35:290–6.

58. Papillon-Smith J, Sobel ML, Niles KM, et al. Surgical management algorithm for caesarean scar pregnancy. J Obstet Gynaecol Can 2017;39:619–26.

59. Cok T, Kalayci H, Ozdemir H, et al. Transvaginal ultrasound-guided local methotrexate administration as the first-line treatment for cesarean scar pregnancy: follow-up of 18 cases. J Obstet Gynaecol Res 2015;41:803–8.

60. Gao L, Huang Z, Gao J, et al. Uterine artery embolization followed by dilation and curettage within 24 hours compared with systemic methotrexate for cesarean scar pregnancy. Int J Gynaecol Obstet 2014;127:147–51.

61. Hung TH, Shau WY, Hsieh TT, et al. Prognostic factors for an unsatisfactory primary methotrexate treatment of cervical pregnancy: a quantitative review. Hum Reprod 1998;13:2636–42.

62. Jeng C-J, Ko M-L, Shen J. Transvaginal ultrasound-guided treatment of cervical pregnancy. Obstet Gynecol 2007;109:1076–82.

63. Chen H, Yang S, Fu J, et al. Outcomes of bilateral uterine artery chemoembolization in combination with surgical evacuation or systemic methotrexate for cervical pregnancy. J Minim Invasive Gynecol 2015;22:1029–35.

64. Tanaka K, Baartz D, Khoo SK. Management of interstitial ectopic pregnancy with intravenous methotrexate: an extended study of a standardised regimen. Aust N Z J Obstet Gynaecol 2015;55:176–80.

65. Lin Y-S, Chen C-L, Yuan C-C, et al. Successful rescue of an early interstitial pregnancy after failed systemic methotrexate treatment: a case report. J Reprod Med 2007;52:332–4.

66. Sagiv R, Golan A, Arbel-Alon S, et al. Three conservative approaches to treatment of interstitial pregnancy. J Am Assoc Gynecol Laparosc 2001;8:154–8.

67. Leggieri C, Guasina F, Casadio P, et al. Hysteroscopic methotrexate injection under ultrasonographic guidance for interstitial pregnancy. J Minim Invasive Gynecol 2016;23:1195–9.

68. Verma U, English D, Brookfield K. Conservative management of nontubal ectopic pregnancies. Fertil Steril 2011;96. 1391−5.e1391.

69. Tasdemir M, Tasdemir S. Minimally invasive treatment of live ectopic pregnancy. Clin Exp Obstet Gynecol 1997;24:92.

70. Kim MJ, Cha JH, Bae HS, et al. Therapeutic outcomes of methotrexate injection in unruptured interstitial pregnancy. Obstet Gynecol Sci 2017;60:571–8.

71. Cassik P, Ofili-Yebovi D, Yazbek J, et al. Factors influencing the success of conservative treatment of interstitial pregnancy. Ultrasound Obstet Gynecol 2005;26:279–82.

72. Lee MH, Im SY, Kim MK, et al. Comparison of laparoscopic cornual resection and cornuotomy for interstitial pregnancy. J Minim Invasive Gynecol 2017;24:397–401.

73. Atrash HK, Friede A, Hogue C. Abdominal pregnancy in the United States: frequency and maternal mortality. Obstet Gynecol 1987;69(3 Pt 1):333–7.

74. Hietala S, Andersson M, Emdin S. Ectopic pregnancy in the liver. Report of a case and angiographic findings. Acta Chir Scand 1983;149:633–5.

75. Nichols C, Koong D, Faulkner K, et al. A hepatic ectopic pregnancy treated with direct methotrexate injection. Aust N Z J Obstet Gynaecol 1995;35:221–3.

76. Fishman DA, Padilla LA, Joob A, et al. Ectopic pregnancy causing hemothorax managed by thoracoscopy and actinomycin D. Obstet Gynecol 1998;91:837–8.

77. Ganeshselvi P, Cherian D, Champ S, et al. Primary abdominal pregnancy implanted on the sigmoid colon. J Obstet Gynaecol 2003;23:667.

78. Shaw SW, Hsu JJ, Chueh HY, et al. Management of primary abdominal pregnancy: twelve years of experience in a medical centre. Acta Obstet Gynecol Scand 2007;86:1058–62.

79. Rahaman J, Berkowitz R, Mitty H, et al. Minimally invasive management of an advanced abdominal pregnancy. Obstet Gynecol 2004;103(5 Pt 2): 1064–8.

80. Bae S-U, Kim C-N, Kim K-H, et al. Laparoscopic treatment of early retroperitoneal abdominal pregnancy implanted on inferior vena cava. Surg Laparosc Endosc Percutan Tech 2009;19:e156–8.

81. Mitra AG, LeQuire MH. Minimally invasive management of 14.5-week abdominal pregnancy without laparotomy: a novel approach using percutaneous sonographically guided feticide and systemic methotrexate. J Ultrasound Med 2003;22:709–14.

82. Arora V. Abdominal pregnancy following total hysterectomy. Int Surg 1983;68:253–5.

83. Varma R, Mascarenhas L, James D. Successful outcome of advanced abdominal pregnancy with exclusive omental insertion. Ultrasound Obstet Gynecol 2003;21:192–4.

84. Poole A, Haas D, Magann EF. Early abdominal ectopic pregnancies: a systematic review of the literature. Gynecol Obstet Invest 2012;74:249–60.

85. Zinger M, Rosenfeld D. Failed treatment of abdominal pregnancy with methotrexate. A case report. J Reprod Med 2001;46:392–4.

86. Roberts RV, Dickinson JE, Leung Y, et al. Advanced abdominal pregnancy: still an occurrence in modern medicine. Aust N Z J Obstet Gynaecol 2005;45:518–21.

87. Baffoe P, Fofie C, Gandau B. Term abdominal pregnancy with healthy newborn: a case report. Ghana Med J 2011;45(2).

88. Badria L, Amarin Z, Jaradat A, et al. Full-term viable abdominal pregnancy: a case report and review. Arch Gynecol Obstet 2003;268: 340–2.

89. Dubinsky TJ, Guerra F, Gormaz G, et al. Fetal survival in abdominal pregnancy: a review of 11 cases. J Clin Ultrasound 1996;24:513–7.

90. Gerli S, Rossetti D, Baiocchi G, et al. Early ultrasonographic diagnosis and laparoscopic treatment of abdominal pregnancy. Eur J Obstet Gynecol Reprod Biol 2004;113:103–5.

91. Oki T, Baba Y, Yoshinaga M, et al. Super-selective arterial embolization for uncontrolled bleeding in abdominal pregnancy. Obstet Gynecol 2008;112:427–9.

92. Demendi C, Langmár Z, Bánhidy F, et al. Successful operative management of an intact second trimester abdominal pregnancy with additional preoperative selective catheter embolization and postoperative methotrexate therapy. Med Sci Monit 2011;17:CS53.

93. Raziel A, Schachter M, Mordechai E, et al. Ovarian pregnancy—a 12-year experience of 19 cases in one institution. Eur J Obstet Gynecol Reprod Biol 2004;114:92–6.

94. Odejinmi F, Rizzuto M, Macrae R, et al. Diagnosis and laparoscopic management of 12 consecutive cases of ovarian pregnancy and review of literature. J Minim Invasive Gynecol 2009;16:354–9.

95. Su W-H, Cheung S-M, Chang S-P, et al. Is ovarian pregnancy a medical illness? Methotrexate treatment failure and rescue by laparoscopic removal. Taiwan J Obstet Gynecol 2008;47:471–3.

96. Reece EA, Petrie RH, Sirmans MF, et al. Combined intrauterine and extrauterine gestations: a review. Am J Obstet Gynecol 1983;146: 323–30.

97. Perkins KM, Boulet SL, Kissin DM, et al. Risk of ectopic pregnancy associated with assisted reproductive technology in the United States, 2001−2011. Obstet Gynecol 2015;125:70.

98. Hutchinson M, Chan C. Laparoscopic management of ruptured heterotopic pregnancy after intrauterine insemination. CMAJ 2016;188 (17-18):E525–7.

99. Na ED, Jung I, Choi DH, et al. The risk factors of miscarriage and obstetrical outcomes of intrauterine normal pregnancy following heterotopic pregnancy management. Medicine 2018;97(37).

100. Barrenetxea G, Barinaga-Rementeria L, de Larruzea AL, et al. Heterotopic pregnancy: two cases and a comparative review. Fertil Steril 2007;87. 417. e9−15.

101. Vetter MH, Andrzejewski J, Murnane A, et al. Surgical management of a heterotopic cesarean scar pregnancy with preservation of an intrauterine pregnancy. Obstet Gynecol 2016;128:613–6.

102. Okunowo AA, Okunade KS, Adefemi AK, et al. A successfully managed spontaneous heterotopic pregnancy diagnosed in the second trimester of pregnancy. Niger Postgrad Med J 2016;23:101.

103. Monteagudo A, Minior V, Stephenson C, et al. Non-surgical management of live ectopic pregnancy with ultrasound-guided local injection: a case series. Ultrasound Obstet Gynecol 2005;25:282–8.

104. Clayton HB, Schieve LA, Peterson HB, et al. A comparison of heterotopic and intrauterine-only pregnancy outcomes after assisted reproductive technologies in the United States from 1999 to 2002. Fertil Steril 2007;87:303–9.

105. Talbot K, Simpson R, Price N, et al. Heterotopic pregnancy. J Obstet Gynaecol 2011;31:7–12.

106. Spiegelberg O. Casuistry in ovarian pregnancy. Arch Gynecol Surv 1978;13:73–9.

107. Timor-Tritsch IE, Monteagudo A, Matera C, et al. Sonographic evolution of cornual pregnancies treated without surgery. Obstet Gynecol 1992;79:1044–9.

108. Singh S. Diagnosis and management of cervical ectopic pregnancy. J Hum Reprod Sci 2013;6:273–6.

109. Jurkovic D, Hacket E, Campbell S. Diagnosis and treatment of early cervical pregnancy: a review and a report of two cases treated conservatively. Ultrasound Obstet Gynecol 1996;8:373–80.

APPENDIX A

Tables A1 and A2

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

Grade	Definition
Strength of recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional [a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Do not interpret conditional recommendations to mean weak evidence or uncertainty of the recommendation.Adapted from GRADE Handbook (2013), Table 5.1.

Table A2. Implications of Strong and Conditional recommendations, by guideline user

Perspective	Strong Recommendation • "We recommend that. . ." • "We recommend to not. . ."	Conditional (Weak) Recommendation • "We suggest. . ." • "We suggest to not. . ."
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policymakers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1.