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REVIEW

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Middle-East obgyn graduate education (MOGGE) foundation practice guidelines: diagnostic approach to pregnancy of unknown location: practice guideline no. 03-O-21

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Abstract

Background: Pregnancy of unknown location (PUL) is a term used to describe failure of visualization of intrauterine or extrauterine gestational sac in a woman with a positive pregnancy test.

Body of the abstract: Ectopic pregnancy (EP) accounts for 1–2 % of all pregnancies. EP contributes to maternal mortality of a known cause by 4% in developed countries. However, case fatality rate may be 10 times higher in low-resource countries. This may be attributed to delayed diagnosis and lack of resources. PUL is a temporary term that may eventually lead to diagnosis of viable intrauterine pregnancy, pregnancy loss, or more seriously, EP.

Conclusion: This guideline appraises current evidence on assessment of PUL and early diagnosis of EP particularly in low-resource settings.

Keywords: Ectopic pregnancy, First trimester, Miscarriage, Early pregnancy loss, Abortion

Introduction/knowledge

Definitions

Pregnancy of unknown location (PUL) refers to inability to confirm either an intrauterine or extrauterine pregnancy despite a positive pregnancy test. Ectopic pregnancy (EP) is a disorder of conception that results from implantation of a fertilized oocyte in an anatomical site that is not physiologically purposed to adopt pregnancy. The term "EP" is used interchangeably with tubal pregnancy "TP" being the most common type of ectopic pregnancy [1]. EP accounts for 1–2% of all pregnancies and incidence has increased with propagation of in-vitro fertilization (IVF) [2]. Some other risk factors of TP are also more prevalent among contemporary population, including smoking, alcohol consumption, initiation of oral contraceptives prior to the age of 16 years, and tubal ligation [3].

Regional challenges

In the USA, EP mortality ratio is extremely low (0.48 per 100,000 live births) and it contributes to maternal mortality of a known cause by only 4% [4, 5]. This low incidence may be attributed to wide use of diagnostic

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protocols in women with pregnancy of unknown location (PUL), and to early laboratory and sonographic screening of women at high risk of EP. On the contrary, case fatality rate of EP in African countries, an example of low-resource countries, is 1–3%, which is 10 times the rate in developed countries [6]. Deficient implementation of PUL protocols, poor compliance to follow-up, and poor documentation and communication of risk factors, that warrant early pregnancy assessment, may lead to delayed diagnosis. Outcomes of delayed diagnosis may be aggravated by poor transportation, limited availability of blood products, and lack of prompt surgical intervention. While the latter factors are more challenging to be corrected, timely diagnosis seems to be more readily achievable in low-resource settings.

Resources and search approach

Our approach started by *defining clinical questions* that need to be addressed both globally and regionally. In this guideline, our question targeted approaches to manage PUL and early diagnosis of EP. A literature search on the latest versions of internationally recognized guidelines, that are representative of global practice, was conducted from January 2000 to January 2020. These guidelines are American College of Obstetricians and Gynecologists (ACOG) practice bulletins 2018 [7], Royal College of Obstetricians and Gynaecologists (RCOG) guidelines 2016 [8], National Institute for Health and Care Excellence (NICE) 2019 [9], and Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines 2018 [10]. The second step involved assigning each clinical question to a panel of 2 researchers. Each panel *reviewed how their question was covered by available guidelines*. This step aims at verifying whether the question was adequately and consistently answered in these guidelines, and to assess references and level of evidence supporting these answers. The third step is to *conduct systematic search of the literature to retrieve newly published studies* that may be related to these clinical questions and correspond to high level of evidence (systematic reviews, meta-analyses, clinical trials, and large cohort studies). Similarly, a literature search was performed to recruit studies that originate primarily in the Middle East or alternatively, in other low-resource countries that may share similar challenges. For this purpose, PUBMED, SCOPUS and Cochrane library were searched for from January 2010 to April 2020, using the following terms: ["ectopic" OR "extrauterine"] AND ["pregnancy" OR "hCG"] OR ["pregnancy of unknown pregnancy"] AND ["management" OR "diagnosis"]. Selection process is detailed in Additional file 1.

The fourth step was to *survey obstetricians in the Middle East* to assess their current practice, needs, and constraints to standard practice. Respondents were obstetricians at different levels of experience, who are involved in either community based or university-based practice with different years of experience. Responses were received through direct reaction to proposed questionnaire and was conducted using multiple choice questions to key practice points in the topic. The fifth and final step was to *appraise available results and recommendations and consider those which provided the highest level of evidence* that was appropriate for low-resource settings.

The level of evidence is classified according to Oxford Centre for Evidence-based Medicine–Levels of Evidence, which stratifies studies depending on their design to level 1 (A to C), level 2 (A to C), level 3 (A and B), level 4, and level 5. Grades of recommendation range from A to D. Level A refers to level 1 studies, level B is consistent with level 2 or 3 studies, level C refers to level 4 studies, while D is consistent with level 5 studies [11]. A KAST approach will be used to present this topic; Knowledge, Assessment, Sharing decision, and Treatment. Treatment in this guideline refers to action/decision-making.

MOGGE take home message: Knowledge		Grade of recommendation
• Case fatality rate of ectopic pregnancy is 10 times higher in developing countries compared to developed countries (systematic review)	IIA	B

Clinical evaluation and diagnosis of EP/assessment

General principles

As stated earlier, timely diagnosis plays a crucial role in determining clinical outcomes of EP, and is a matter of integrating clinical suspicion, and sonographic evaluation with or without serial assessment of serum human chorionic gonadotrophin (hCG). Clinical suspicion is driven primarily by symptoms and, to less extent, by known risk factors. This is particularly important because patients with EP are usually symptomatic by 7 weeks of gestation, which is generally far from routine first ultrasound examination [12]. First ultrasound is typically performed later in the first trimester, approximately between 10 and 12 weeks of gestation, to provide more conclusive information on fetal viability, number of fetuses, gestational age, and nuchal translucency compared to earlier ultrasound [13].

Clinical suspicion should be followed by ultrasound assessment. Failure to visualize an intrauterine sac is an indication of transvaginal ultrasonography, with or without serum hCG level measurement [14].

Clinical presentation of EP

Obstetricians typically suspect EP in any reproductive-aged woman who presents with abdominal pain or vaginal bleeding regardless of contraception status [15, 16]. Suspicion of EP rises significantly in the presence of hemodynamic instability and acute abdominal pain [14]. However, the presence of symptoms typically indicates disruption of EP rather than just diagnosis of EP, and distinctness of clinical diagnosis may be proportional to worsening outcomes. Therefore, outcomes are generally better if EP is detected before it is clinically evident. Ideally, screening of women with known risk factors using pelvic ultrasound and serial β-HCG early in pregnancy would yield the best scenario. Unfortunately, most cases of EP occur without identifiable risk factors [17, 18]. Therefore, women who present with symptoms, regardless of their severity and presence of risk factors, should be evaluated and closely followed-up if intrauterine pregnancy (IUP) is not visualized. Strategies that promote early diagnosis and intervention are known to reduce EP-related mortality [19].

Patient history alone has a limited role in diagnosing EP. A meta-analysis of 14 studies found that while positive likelihood ratio (LR+) of all elements of patient history were less than 1.5, physical examination was highly indicative of EP. The most relevant sign was cervical motion tenderness (LR+ 4.9; 95% CI 1.7–14), followed by an adnexal mass (LR+ 2.4; 95% CI 1.6–3.7), and adnexal tenderness (LR+ 1.9; 95% CI 1.0–3.5) [2].

Role of discriminatory level in diagnosis of EP

The term "discriminatory level or zone" has been used to describe a single hCG level, above which a viable intrauterine pregnancy should be visualized using pelvic ultrasound. Therefore, if this level is reached while no intrauterine sac is visualized, the diagnosis of EP is highly likely [20]. Although the concept has been widely adopted in clinical practice, defining discriminatory level is debatable. Because it is impossible to set a cutoff level that yields no false negative or false positive results, each cutoff level conveys risk of delayed diagnosis versus risk of unnecessary intervention or pregnancy disruption. A prospective study of 569 (10.3%) women with PUL found that sensitivity and specificity of 3 cutoffs of hCG were 21.7% and 87.3% (for 1000 IU/L), 15.2% and 93.4% (for 1500 IU/L), and 10.9% and 95.2% (for 2000 IU/L), respectively [21]. To reach probability of 99% of visualizing gestational sac using an 8 to 9 MHz vaginal transducer, a β-hCG cutoff of 3510 IU/L should be used [22]. On the other side, hCG level at time of diagnosis of EP is disperse (1233 ± 1802 IU/L) and it is likely to be below 3500 when diagnosis is overt [23]. Furthermore, hCG levels vary significantly in twin pregnancy and may be doubled compared to singleton pregnancy [24]. IVF protocols may affect hCG levels in early pregnancy as well [25].

In conclusion, hCG discriminatory level is of limited clinical use and should not be considered as a diagnostic test of EP. ACOG recommends that if discriminatory level is to be considered, a conservative level should be used (3500 IU/L) to avoid disruption of a possible viable pregnancy [7]. However, at such high levels, EP is unlikely to be asymptomatic and therefore, this scenario would not be commonly encountered. Furthermore, the presence of hCG above 3500 IU/L in absence of symptoms and sonographic findings suggestive of EP may be unusual and possibility of multifetal pregnancy should be considered particularly in the presence of risk factors. Therefore, clinical suspicion, aided by accurate estimation of gestational age, sonographic or laboratory information, rather than a discriminatory hCG, would diagnose EP.

Diagnostic role of pelvic sonography

Transvaginal ultrasound (TVUS) is the first assessment tool in women at high risk of EP or who are symptomatic in the first trimester. Given the extremely low incidence of heterotopic pregnancy after spontaneous conception, definite sonographic visualization of IUP should be adequate to rule out EP and omit further assessment [26]. A meta-analysis of 3 studies including symptomatic women in the first trimester who present to the emergency department showed that sensitivity and specificity of TVUS in diagnosing IUP is above 98% and 90%, respectively. Therefore, it is adequate for symptomatic patients to be safely dismissed. However, close observation should continue in symptomatic women who conceive after IVF cycle, where reported incidence of heterotopic pregnancy may reach 0.1–1% [27]. Fortunately, women who conceive following IVF receive early sonographic evaluation compared to women who conceive spontaneously and therefore, heterotopic pregnancy can be timely diagnosed in most situations. In a single retrospective study, sensitivity and specificity of TVUS in diagnosing heterotopic pregnancy was 92.4 and 100%, respectively [28]. On the other side, visualization of an extrauterine gestational sac, characterized by a fetal pole or a yolk sac, is a definite evidence of EP. However, no adnexal abnormalities are reported in up to 35% of patients with EP [29]. In a prospective study of 152 women with EP who underwent TVUS prior to surgery, extrauterine viable and non-viable gestational sac were reported in only 7.3% and 5.9% of patients, respectively [30].

On the contrary, failure to visualize IUP is not adequate to make a conclusion and it leads to a temporary diagnosis of PUL, which triggers a protocol of strict

follow-up. There is a spectrum of sonographic findings that lie between definite IUP and definite EP. A meta-analysis of 31 studies (5,858 women) showed that sensitivity and specificity of a pseudosac in diagnosing EP was 5.5% (95% CI 3.3–9.0%) and 94.2% (95% CI 75.9–98.8%), respectively. Sensitivity and specificity of adnexal mass were 63.5% (95% CI 48.5–76.3%) and 91.4% (95% CI , 83.6–95.7%), and sensitivity and specificity of free fluid were 47.2% (95% CI , 33.2–61.7%) and 92.3% (95% CI , 85.6–96.0%), respectively [31].

In absence of an extrauterine gestational sac, a non-cystic or inhomogeneous mass was the most sensitive sonographic sign of EP; a meta-analysis of 10 diagnostic studies (2216 patients) showed that this sign had sensitivity of 84%, specificity of 98.9%, positive predictive value of 96.3% and negative predictive value of 94.8% [32]. The presence of inhomogeneous mass is the most commonly encountered sonographic sign of EP and is reported in 57.9% prior to surgery, followed by the presence of an adnexal mass with echogenic/tubal ring (20.4%) [30].

These findings convey that TVUS should not be used to rule out EP. Nevertheless, suspicious sonographic findings should raise serious concerns.

MOGGE take home message: Assessment		Grade of recommendation
• Before intrauterine pregnancy is confirmed, clinical assessment of symptomatic women is crucial. Most suspicious signs are cervical motion tenderness, followed by an adnexal mass, and adnexal tenderness	IIA	B
• A single β-hCG (discriminatory level) has a limited role and should not be used as a diagnostic test of EP	IIB	B
• Visualization of intrauterine pregnancy with ultrasound is sufficient to dismiss symptomatic women who conceived spontaneously	IIA	B
• Even with visualization of an intrauterine sac, women who conceived after in-vitro fertilization may still need to be followed-up to rule out heterotopic pregnancy particularly if clinically suspected	IIB	B
• Other than visualization of extrauterine gestational sac, sonographic signs of ectopic pregnancy are associated with low sensitivity and high specificity and should not be used to rule out ectopic pregnancy	IIA	B
• The presence of inhomogeneous mass is the most commonly encountered and most sensitive sonographic sign of EP	IIA	B

Decision-making and patient counselling/sharing decision

Patient counselling

Patients should be encouraged to participate in their plan of care and be offered the necessary information. Symptomatic women with no sonographic evidence of IUP should be carefully counselled on the meaning of PUL. Although only 6–20% of patients PUL are eventually diagnosed with EP, this information should be carefully conveyed to the patient [33]. This percentage means that PUL does not necessarily mean pregnancy loss. However, it raises concerns on a life-threatening condition that should be closely monitored. Each assessment should be carefully reviewed with the patient and test results should be interpreted to her in a timely manner.

Warning symptoms and signs of EP should be reviewed with the patient and she and her family should be provided with contact information of an appropriate and available facility. Phone surveys may be considered. It is important to review patient's current location and availability of assistance to ensure she can get immediate help if needed. It should be made clear to the patient that her general condition could deteriorate abruptly, and she should keep a low threshold of reporting any symptoms.

Shared decisions

If a decision is made to proceed with a diagnostic/therapeutic intervention based on current information, it is crucial to share information on pros and cons of this intervention. If laparoscopy is considered necessary to localize pregnancy, patients should be carefully counselled on anticipated outcomes of this procedure. Although teratogenicity and abortion risks of anesthesia are inconclusive, first trimester surgeries are only considered if deemed necessary because of these concerns [34]. On the other hand, laparoscopy is not a definitive diagnostic tool. Although sensitivity of laparoscopy in diagnosing EP is approximately 100%, specificity of 85% was reported, meaning that a negative laparoscopy does not completely rule out EP [35]. Endometrial aspirate provides the most definitive diagnosis. However, it should not be considered unless the possibility of a viable IUP is very unlikely. Methotrexate may be considered if abnormal pregnancy is highly anticipated [7]. All these situations should be carefully discussed with the patient before a procedure is recommended for diagnosis or management and outcomes of each test or intervention should be explained in priori.

MOGGE take home message: Sharing decision		Grade of recommendation
• Women should be actively involved in the process of management of PUL	IV	D
• Providers should be aware of patient's individualized circumstances including their residence and accessibility of appropriate care	IV	D
• Being invasive does not mean it is conclusive, and patient should be aware that laparoscopy is a diagnostic and therapeutic tool. However, it may miss diagnosis of ectopic pregnancy	IB	A

Management of PUL/treat

Role of gestational age calculation

While it may be superior to discriminatory level, role of gestational age in diagnosis of PUL is usually underestimated. Regardless of number of fetuses, IUP should be visualized using TVUS between 5 and 6 weeks (gestational sac at 5 weeks, yolk sac at 5 + 3 weeks, and fetal heartbeat at 6 weeks). These findings are reproducible and reliable and variation lies within 3–4 days [36]. Therefore, failure to visualize an intrauterine gestational sac beyond a certain gestational age (5 + 3 weeks) should indicate PUL that is concerning of EP. However, this conclusion is limited by unreliability of last menstrual period (LMP) alone in calculating gestational age even with reliable dates. A clinical trial of 104 women, who were assigned to dating verification with first trimester ultrasound, showed that 41.3% of these women had their gestational age revised using crown-rump length (CRL) measurement, meaning that dating discrepancy between LMP and CRL was 5 days or more [37]. A cross-sectional study of 225 women in early pregnancy revealed that mean history-based gestational age was generally 5–9 days less than ultrasound gestational age [38].

Compared to dating with LMP, β-hCG is associated with significant variation per gestational age. A study of 131 women showed that median β-hCG (10th and 90th centile) was 268 (11, 1682), 660 (47–3559), and 1450 (119–5769) mIU/mL at 2, 4, and 6 weeks, respectively [39]. These values substantially overlap with each other and span around traditional discriminatory level even at early gestational ages. Despite the pitfalls of dating with LMP, it may be more useful than a single measurement of serum β-hCG. Although both methods should not be used to diagnose EP, gestational age calculation should be always considered and in the presence of reliable LMP, it may or may not trigger a PUL protocol that comprises close observation and laboratory workup.

To facilitate usage of these reference ranges, an application was created to calculate and interpret change in β-hCG according to change percentage and baseline β-hCG in concordance to this guideline (MOGGE PUL calculator 1.0 ®, https://www.mogge-obgyn.com/mogge-software).

Role of serial β-hCG measurements

Serial β-hCG measurement is the standard tool for assessment and management of PUL. β-hCG follow-up protocols should be triggered by clinical suspicion and accurate estimation of gestational age, if available. Although variation in β-hCG level in early pregnancy is considerable, changes in β-hCG over time is more consistent. Therefore, assessment of 2 β-hCG levels 48 h apart has been widely adopted to assess PUL over a single measurement. However, interpretation of β-hCG change should be carefully made. A rise of β-hCG by 53% and 63% was reported in 99% and 85% of women who were eventually diagnosed with a viable IUP, respectively [40]. Nevertheless, 21% of patients with EP may trend within the same range of normal pregnancy [41]. Accordingly, a rise of β-hCG should be used as good positive and not a good negative test, meaning that failure of β-hCG to rise above 53% is strongly predictive of a non-viable pregnancy (EP or miscarriage), while a rise above 53% should not be used to confirm IUP. Using baseline β-hCG, these recommendations can be refined. If initial β-hCG is at or below 1500 mIU/ml, a rise of at least 49% is anticipated in 99% of women with IUP. A minimal rise of 40% and 33% is anticipated in women with initial β-hCG between 1500 and 3000 and above 3000, respectively [42].

On the other side, in 95% of women with eventual miscarriage, β-hCG declines by 12%, 21%, 24%, 28%, 30%, 31%, and 35% when initial β-hCG is 50, 250, 500, 1000, 1500, 2000, and 5000 mIU/ml, respectively [43]. Again, β-hCG of women with EP may decline below these levels in 8% of cases. Therefore, the test should be used to suspect, rather than to rule out, EP [41]. Sole use of 2 serial β-hCG may be associated with misclassification of 16.8% of EPs and 7.7% of IUPs [44]. A third measurement may reduce misclassification of IUP particularly if β-hCG rise is borderline (between 33 and 49% in 48 h) after clinical judgement is made [42].

Role of initial and follow-up ultrasound

The role of ultrasound extends from preclinical suspicion, diagnosis of symptomatic women, to follow-up of women with known PUL.

Preclinical suspicion refers to sonographic assessment of women at high-risk of EP or pregnancy loss including women with prior history and women who conceive after IVF. In the latter, ultrasound is usually scheduled after

3–4 weeks of embryo transfer, which corresponds to 5–6 weeks by LMP in women who conceive naturally. Therefore, suspicious cases of PUL can be identified early and thereby, EP would be unlikely to be missed. This strategy is not applied to low-risk women even though most cases of EP are not associated with risk factors. Universal implementation of early first-trimester ultrasound may be opposed by cost-effectiveness of performing more than one sonographic examination in the first trimester. Cost-effectiveness and economic studies may vary significantly among different countries. While in western countries, a dating ultrasound may cost $200, ultrasound in many developing countries is performed by the obstetrician, not by a sonographer, and its cost is extremely low compared to western countries [45]. A survey of 650 obstetricians showed that first trimester ultrasound is a part of antenatal visit and is performed with no additional cost by 85% of participants, while 9.9% reported that ultrasound cost is equal to a single visit cost. In Egypt, an example of a low resource country, an obstetric visit costs $12.5 on average. Therefore, cost-effectiveness could be extremely different in low-resource countries. Given the limited availability of accessible tertiary centers, blood banks, and transportation, early universal screening may be justified in these countries. The other drawback of universal screening could be safety of routine sonographic assessment particularly if more than one sonographic assessment would be routinely offered. However, paying attention to safety measures during each examination is more important than number of examinations. First trimester scan is deemed generally safe and there are new clinical trends to expand its use to routine anatomy scan [46]. Expected risks of sonographic examination are related to thermal and mechanical effect of ultrasound waves. Providers should be familiar with safety measures; Doppler examination should be avoided whenever possible, and M-mode should be used to instead to assess fetal hear rate. Keeping thermal index under 0.7 and mechanical index under 1.0. TIs (Thermal index for soft tissue) is the most relevant to first trimester. Examination limited to 10 minutes is ideal particularly if thermal index is between 0.7 and 1.5 [10, 47].

As mentioned earlier, sonographic assessment is crucial in symptomatic women and it may confirm IUP, EP or reveal signs that are suggestive of EP. If pregnancy cannot be located, ultrasound follow-up may facilitate final diagnosis/decision as guided by serial β-hCG results. If β-hCG change is consistent with IUP, ultrasound assessment should be repeated after 7–10 days to confirm this conclusion. It should be also repeated if new symptoms suggestive of miscarriage or EP develop. If β-hCG trend is consistent with pregnancy loss, ultrasound follow-up may not be necessary and β-hCG may be followed-up as long as it trends down appropriately till it is negative [8, 48, 49].

Role of endometrial sampling

In women whose β-hCG is highly suspicious of EP, meaning that it does not meet anticipated trend of IUP or spontaneous pregnancy loss, patients may be offered methotrexate or laparoscopy for definitive management. In these patients, office endometrial sampling may represent a good alternative that may obviate the need for these interventions and promote quicker resolution of pregnancy, compared to methotrexate [50]. The presence of chorionic villi is robust evidence of IUP loss, and no further management is recommended. However, if decidual reaction without chorionic villi is found, β-hCG should be checked 12–24 h post-procedure and be compared to pre-procedure level. If β-hCG does not drop beyond 10–15%, further intervention is warranted. A drop that exceeds 50% is highly indicative of IUP loss, while a drop between 15 and 50% likely reflects IUP loss [51]. However, in both cases, β-hCG should be followed-up till it becomes negative and patients should be counselled on the ongoing risk and be encouraged to report any concerning symptoms [50].

Unfortunately, office endometrial sampling may not be universally available in low-resource countries and delay in histopathological reporting may disrupt clinical benefit of this method. In our survey of 693 obstetricians, 87% reported that office sampling is not available in their workplace. “Dilation and curettage” in surgical suite omits many benefits that would favor endometrial sampling as an alternative to other interventions. Nevertheless, patients should be counselled, and decision should be made based on clinical scenario and patient preference.

MOGGE take home message: Treat		Grade of recommendation
• Pregnancy should be visualized between week 5 and week 6 of gestation	IIB	B
• Discrepancy between dating by last menstrual period and crown-rump length is common, and it may exceed 5 days in approximately 40% of patients. Therefore, interpretation of history-based gestational age should be carefully made	IB	B
• β-hCG is not indicative of gestational age and should not be used for this indication	IIIB	B
• Serial β-hCG is ideally measured 48 h apart. The rise that is consistent with viable intrauterine pregnancy varies according to baseline level	IIIB	B

MOGGE take home message: Treat		Grade of recommendation
• The decline in β-hCG that indicates pregnancy loss is determined by baseline level	**IB**	**A**
• A rise or decline in β-hCG should be used to suspect, rather than, to rule out ectopic pregnancy.	**IIIB**	**B**
• A third β-hCG may reduce risk of misclassification in women with borderline rise (33–49%)	**IIB**	**B**
• Universal screening of abnormal pregnancy at 5–6 weeks may be justified in low-resource countries	**IV**	**D**
• Office endometrial sampling is a good alternative to methotrexate in women with probability of abnormal pregnancy.	**IIIB**	**B**

Further research

It is not clear whether there are any individualized factors that would add to interpretation or decision making, such as age, parity, body mass index, which would be considered in the future to facilitate decision-making. An individualized prediction model using personal factors in addition to other known findings, could be a potential topic to consider in the future.

Supplementary Information

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Additional file 1. Flow chart of literature search (management of pregnancy of unknown location and early diagnosis of ectopic pregnancy)

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Authors' contributions
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