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DIAGNOSIS OF TUBAL & NON-TUBAL ECTOPIC PREGNANCIES

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ABSTRACT

Ectopic pregnancy is a potentially life-threatening condition accounting for 1-2% of all pregnancies. The most common region of ectopic implantation is the fallopian tube, although 10% of all ectopic pregnancies implant in the cervical, ovary, and interstitial portion of the fallopian tube, abdominal cavity, or within the cesarean scar region. Diagnosing ectopic pregnancy involves a mixture of clinical symptoms, serological conditions, and ultrasound imaging. Medical management is a safe and efficient option for most of the stable patients. Patients with unsuccessful medical management are managed with laparoscopy or less common laparotomy. Similar to tubal pregnancy, non-tubal ectopic pregnancy can be treated surgically using laparotomy or laparoscopy, or medically with methotrexate. For abdominal and ovary cavity ectopic pregnancy laparotomy is a good approach, while for cervical and cesarean scar ectopic pregnancy, initial clinical treatment with methotrexate, and then suction curettage under ultrasound guidance can fix the problem. Patients with tubal and non-tubal ectopic pregnancies should be counseled well regarding associated anomalies, complications, fertility-preserving interventions, and the requirement of prolonged monitoring specifically those women who chose medical therapies. This review describes the incidence, associated risk factors, diagnosis, and management of tubal and non-tubal ectopic pregnancy. The article also discusses the literature available for ectopic pregnancy recurrence and future fertility situations.

KEYWORDS

Introduction

Ectopic pregnancies refer to the condition when an embryo gets implanted outside the uterine cavity. it can commonly lead to morbidity and mortality in women of reproductive age. The etiology of ectopic pregnancies is still unknown, however, various risk factors have been determined (Shaw et al., 2010). Diagnosing ectopic pregnancy can be difficult. In developed countries, diagnosing ectopic pregnancies relies on combining serum beta-human chorionic gonadotrophin hormone levels and ultrasound scanning techniques (Horne et al., 2010). Ectopic pregnancies are one of the rare clinical conditions that can be managed medically or surgically (Varma and Gupta, 2009). Due to advancements in clinical testing, trans-vaginal ultrasound scans, chemotherapies, and laparoscopy technology, the diagnosis and management of ectopic pregnancy have progressed gradually. In addition, the maternal mortality rate has declined from 3.5 out of 10,000 pregnancies in the 1970s to 2.5 out of 10,000 pregnancies in 1995 (Creanga et al., 2011).

Most commonly, the ectopic pregnancy location is in the fallopian tube with predominance in the ampullary region of the fallopian tube called tubal pregnancy. Moreover, embryo implantation other than the fallopian tube such as in the cervix, ovarian cavity, uterus lining, abdominal cavity, cesarean scar, and interstitial region of the fallopian tubes is referred to as non-tubal ectopic pregnancies. They are uncommon and happen in less than 10% of ectopic pregnancies. Broad signs and symptoms of non-tubal ectopic pregnancies make its diagnosis and treatment difficult, and in some cases, significantly delayed, resulting in a high frequency of morbidity. However, surgical management remains the main step of diagnosis and treatment, there is growing evidence that some of these cases can be managed clinically or by combining both medical and surgical techniques to give good outcomes. The present review article summarizes the prevalence, associated risk factors, diagnosis, and treatment strategies for women with tubal and non-tubal ectopic pregnancies. Also, we will focus on reviewing the existing evidence regarding their future fertility.

Prevalence of Tubal and Non-tubal Ectopic Pregnancy

The total rate of ectopic pregnancy is 1-2% among the general population and 2-5% among patients who have used assisted reproductive technology (ART) (Practice Committee of the American Society for Reproductive Medicine, 2013). However, the mortality frequency has declined over time, ruptured ectopic pregnancies still account for up to 6% of all maternal mortality rates, a review of death in ART-associated ectopic pregnancies similarly reported a mortality rate of 32 deaths per 1 lakh pregnancies (Perkins et al., 2015).

The non-tubal ectopic pregnancies account for less than 10% of overall ectopic pregnancies, however, their incidence has slightly increased in recent years (Barnhart, 2009). Moreover, the non-tubal ectopic pregnancy contributes disproportionately excessively to maternal morbidity and mortality in comparison to tubal ectopic pregnancy. Cervical ectopic pregnancies account for occurring in 1:2500 to 1:20,000 pregnancies (Yankowitz et al., 1990).

The probable incidence of cesarean scar ectopic pregnancies is 1:1800 to 1:2200 pregnancies or 6% of all ectopic pregnancies in females with at least a single C-section delivery (Seow et al., 2004). The interstitial region ectopic pregnancies account for around 4% of overall ectopic pregnancies, however, the associated morbidity is much higher, with mortality rates of 2.5% or 7 times the mortality frequency associated with other ectopic pregnancy regions, majorly due to hemorrhage (Moawad et al., 2010). Pregnancies entrenched within the uterus lining account for an estimated 1% of overall ectopic pregnancies (Kirk et al., 2013), and abdominal pregnancies account for around 1.3% of all ectopic pregnancies (Khan et al., 2006). These have been categorized as primary or secondary abdominal ectopic pregnancy; secondary pregnancies are conceived to be an outcome of extruded fallopian tubes and consequent intra-abdominal implantation (Rana et al., 2013). The major common regions of implantations are in the posteriorly and anteriorly situated pouches of the uterus and the serosa lining of the uterus; retro-peritoneal, bowel, hepatic, and splenic implantations have also been reported (Poole et al., 2012).

Etiology of Tubal Ectopic Pregnancy

The fallopian tube provides a secure environment to enable oocyte transfer, fertilization, and transport of early embryos to the uterus for implantation. Facts suggest that tubal ectopic pregnancies originate from both abnormal embryo transfer and any modification in the tubal environment, which causes abnormal implantation to happen (Shaw et al., 2010).

Transferring oocyte and embryo via the fallopian tube depends on both the contraction of smooth muscles and ciliary muscles beating which are impacted by various factors including hormonal, infectious, and immunological. However, smoking and alcohol drinking have been shown to decrease cilia movement density, and cilia beating rates are affected by hormonal imbalances due to menstrual cycles (Lyons et al., 2006). Studies with fallopian tube epithelial cell samples incubated with nitric oxide and estradiol have shown increased ciliary movement, which may lead to abnormal tubal transfer (Paltieli et al., 2000). Nitric oxide also impacts smooth muscle contraction in the fallopian tube, its expression has been found to differ during the menstrual cycle, with probable implications for ectopic implantations (Al-Azemi et al., 2010). At last, the estradiol-mediated effects through estrogen receptors on genetic regulatory and expression pathways also included in apoptosis and implantation mechanisms might be involved in abnormal tubal functioning and ectopic pregnancies. However, more research studies are required to have a clear understanding of these pathways.

Risk Factors associated with Tubal Ectopic Pregnancy

Around 50% of females diagnosed with tubal ectopic pregnancies have no clear risk factors identified; however, various risk factors are associated with ectopic pregnancy (Barnhart, 2009). These include age, unhealthy lifestyle, prior history of ectopic pregnancy, tubal surgery or damage, previous pelvic infection, and pregnancy achieved by assisted reproduction.

Age is an important risk factor to be considered for ectopic pregnancy, with the highest incidence among females above 35 years of age in both natural pregnancies and those conceived after assisted reproduction techniques (Bouyer et al., 2003). The description for this reflection is not clear; however, age is observed to affect tubal functioning, including delayed oocyte transfer (Bouyer et al., 2003).

History of ectopic pregnancy is a strong risk factor for recurring ectopic pregnancies, with a recurrent frequency of 5-25% among the general population (de Bennetot et al., 2012). Early diagnosis and treatment for ectopic pregnancy, whether clinical or surgical, might result in pathological modifications in tubal movement, ciliary functioning, and uterus contractility (Weigert et al., 2009).

Lifestyle modifications including smoking and drinking alcohol also increase the risk of occurrence of ectopic pregnancies by causing tubal malfunctioning. Tobacco intake may dysregulate the paracrine signals required for controlled embryo transfer and development. In a retrospective study considering 480 IVF cycles, the probability of tubal ectopic pregnancy was 3 times higher among smoking addicts.

Previous history of tubal surgeries including but not limited to tuboplasty, and salpingostomy are considered risk factors for tubal ectopic pregnancy. In parallel, any risks of pelvic adhesions, including appendicitis, endometriosis, or different pelvic surgeries, may malformed the functioning of the fallopian tube (Farquhar, 2005).

A history of pelvic infection or pelvic inflammatory disease is related to an increased risk of consequent ectopic pregnancy. Due to infection from *Chlamydia trachomatis*, the risk of ectopic pregnancy increases, and consequent salpingitis leads to tubal dysfunctioning and abnormal uterus implantation (Farquhar, 2005).

Assisted reproductive techniques pose a risk factor for ectopic pregnancy, as 2-5% of pregnancies from these reproductive technologies are tubal ectopic pregnancies. Major factors influencing this increased risk are the kind of protocol, reproductive health parameters of females, and evaluated embryo transplantation potential (Chang et al., 2010). Any previous history of infertility, even no tubal disease, is related to ectopic pregnancy, with the condition rising with infertility duration. Infertility with tubal factor is connected with a two-fold risk of ectopic pregnancy following the in-vitro fertilization (IVF) cycle (Huang et al., 2014). Various IVF cycle constraints may be connected with an increased risk of ectopic pregnancy. The females undergoing IVF treatment activated with gonadotropin-releasing hormone rather than recombinant human chorionic gonadotropin are at higher risk of ectopic pregnancy. In a review of 470 IVF cycles, gonadotropin agonists are at higher risk of ectopic pregnancy rate. This observation is conjectured due to improper endometrium receptivity following gonadotropin-releasing hormone agonist administration (Sahin et al., 2015).

Risk Factors for Non-tubal Ectopic Pregnancy

The risk factors for ovarian ectopic pregnancy and interstitial ectopic pregnancy are similar to those for tubal pregnancy including a history of previous ectopic pregnancy, pelvic inflammatory disease, and using IVF treatment (Tulandi et al., 2004). Using an intrauterine device may be a risk factor for non-tubal ectopic pregnancy, particularly for ovarian ectopic pregnancy (WHO, 1985). For interstitial implantation, risk factors include previous salpingectomy. Risk factors for other non-tubal ectopic pregnancies are discussed in the following sub-sections.

Cesarean section Ectopic pregnancy

The risk for cesarean scar implantation is not related to the quantity of prior cesarean section deliveries. In addition, it is also not related to single- or double-layer closure of hysterectomy during cesarean section delivery. Cesarean scar implantation may be common for elective signs, which is hypothesized due to improper healing of the lower uterine segment (Maymon et al., 2004).

Abdominal pregnancy

Rik factors for abdominal pregnancy are similar to those discussed above for tubal pregnancy, including using assisted reproductive techniques, endometriosis, and pelvic infections. A twin pregnancy case study with implantation in a broad ligament after IVF treatment reported an abdominal pregnancy. Uterine perforations were suggested as probable cause as embryo transfer was done using stylet instead of standard catheters (Deshpande et al., 1999).

Cervical pregnancy

History of dilation and curettage in previous pregnancies has been associated as a risk factor for cervical ectopic pregnancy and is observed in nearly 70% of maternal cases. IVF treatment has also been proposed as a significant risk factor for its occurrence.

Diagnosis of Tubal and Non-tubal Ectopic Pregnancy

Serum β-human chorionic gonadotropin marker

Diagnosing ectopic pregnancy often starts with a primary diagnosis of pregnancy of an unknown location which is defined as a positive serum β-human chorionic gonadotropin hormone in the nonappearance of ultrasound findings suggestive of intra- or extra-uterine pregnancy. Around 30% of patients with pregnancies of unknown locations will progress into an ongoing intra-uterine pregnancy, while 50-70% will be diagnosed with failed pregnancies (Kirk et al., 2009).

In a normal patient, measuring levels of β-human chorionic gonadotropin hormone is important to clarify pregnancy position and diagnosis. Generated primarily by the syncytiotrophoblast in the placenta, β-human chorionic gonadotropin hormone is measurable in the blood after 14 days of pregnancy until a peak of 10-12 weeks. However, a single measurement of hormone levels is not sufficient to determine pregnancy prognosis, and serial hormone levels commonly regulate early pregnancies. A retrospective review study including 1000 patients with pregnancies with unknown locations suggests a minimum rise in hormone serum level of an intrauterine pregnancy is 35% in two days (Morse et al., 2012). A β-human chorionic gonadotropin hormone level rise less than 35% in two days has a positive predictive value of 96%, a negative predictive value of 69%, and a total precision of 80% in predicting ectopic pregnancy. In comparison, patients diagnosed with failed pregnancies were observed with β-human chorionic gonadotropin hormone level decrease in two days is 35-50%. The hormone level cut-offs are not however flexible, 16% of ectopic pregnancies and 7% of intrauterine pregnancies would be non-categorized using serial β-human chorionic gonadotropin hormone levels. Determining a third β-human chorionic gonadotropin hormone level and primary ultrasound scanning declined the non-classification of intra-uterine pregnancy to 3%. The expected frequencies of β-human chorionic gonadotropin hormone levels increase and decrease for various pregnancies, following assisted reproduction and obese females (Chung et al., 2006). The absolute β-human chorionic gonadotropin hormone levels may be higher in various pregnancies or less in patients with increased body mass index.

Serum Progesterone levels

It has been discovered as a potential serum marker for non-viable pregnancies, including ectopic pregnancies, as progesterone hormone levels have been observed to be declining in ectopic pregnancies in comparison to normal (Rausch et al., 2012). Various studies revealed that a progesterone cut-off of 10 ng/ml as the most precise value to identify spontaneous ectopic pregnancy. In a meta-analysis study including 4678 patients under 14 weeks of gestation with pain or vaginal bleeding, a serum progesterone level of less than 10ng/ml value predicted a non-viable pregnancy with a sensitivity of 66.5% and an accuracy of 96% (Verhaegen et al., 2012). The optimum cut-off value may be higher in women who received fertility treatments, as they have multiple corpus lutea releasing progesterone and also receiving external progesterone. A cut-off value of 30ng/ml, 28-50 days after the last menstrual phase, may be more appropriate in women who have consumed clomiphene citrate, while an ideal cut-off is yet to be decided in patients after IVF treatment (Fernandez et al., 2004).

Serum progesterone levels often misinterpret higher normal pregnancies in comparison to β-human chorionic gonadotropin hormone measurements (Guha et al., 2014). Serum progesterone levels also cannot further differentiate between miscarriages and ectopic pregnancies. However, progesterone levels may highlight women at higher risk of ectopic pregnancies, it is not sufficient in itself to differentiate between intrauterine pregnancies, miscarriages, and

ectopic pregnancies.

Other serum markers

Several studies have determined other serum markers of ectopic pregnancies, concentrating on proteins associated with the placenta, endometrium, corpus luteal functions, angiogenesis, and inflammation. These include Inhibin A generated by corpus uteum; activin A which is pregnancy-associated plasma protein-A and Disintegrin and metalloprotease produced by placenta and vascular endothelial growth factor produced by different cell types and may be upregulated by ectopic pregnancy (Rausch et al. 2012). Different messenger RNAs may also be differentially expressed by ectopic pregnancy.

Ultrasound Imaging for Tubal Ectopic Pregnancy

In females presented with pain and vaginal bleeding, pregnancy location is not usually visualized precisely in the initial ultrasound scan during the presentation; however, diagnosis of ectopic pregnancy is quite possible while following standard guidelines. Determination of gestational sac and fetal pole, with or without heart rate called as "bagel" or "tubal" indication. Doppler flow is highly indicative of ectopic pregnancy. If an unpredictable mass called a "blob" sign moves distinctively from the ovary, the predictive value is more than 90% in symptomatic females with positive serum β-human chorionic gonadotropin hormone level and no intra-uterine pregnancy on trans-vaginal ultrasound imaging (Doubilet, 2014).

Ultrasound Imaging for Non-tubal Ectopic Pregnancy

Ectopic pregnancy identified in anatomical regions other than the fallopian tube can also be determined by ultrasound imaging. The diagnostic features for each non-tubal ectopic pregnancy are deliberated in the following paragraphs.

Ultrasound imaging for interstitial ectopic pregnancy involves a gestational sac of 1 cm lateral to the uterus, with a thin myometrial lining overlying it. Cervical ectopic pregnancy can be determined in ultrasound imaging by an inflated cervix canal including a gestational sac with peripheral Doppler flow beneath a closed cervix internal opening. The sliding organ indication while applying pressure with the transvaginal probe is related to spontaneous abortions and should not be present in cervical ectopic pregnancy.

The diagnostic feature for cesarean scar ectopic pregnancy through ultrasound imaging includes the presence of a gestational sac at the region of the previous hysterectomy lying outside the endometrium. The myometrial lining is visualized as very thin or absent between the gestational sac and urinary bladder. A negative Doppler flow is expected in this case.

Ovarian ectopic pregnancies in an ultrasound imaging reveal a hypo-echogenic region surrounded by a broad echogenic area with peripheral Doppler flow. While applying transvaginal probe pressure, ovarian ectopic pregnancy moves towards the ovary and should be associated with the uterus through ovarian ligaments. These types of ectopic pregnancy are difficult to differentiate from ovary cysts which might have analogous presence and peripheral Doppler flow. Given the hardship of diagnosing it through ultrasound imaging, laparoscopy is needed for a definitive diagnosis.

Abdominal ectopic pregnancy cases are few and diagnostic guidelines through ultrasound imaging are limited. Guidelines involve visualization of the extra-uterine gestational sac, fetus, or placenta with no myometrial lining between the fetus and urinary bladder. This gestational sac will be near the abdomen and may be gathered through bowel loops.

Medical Management of Ectopic Pregnancy

The highly prevalent interventions for managing ectopic pregnancy are medical management with systemic methotrexate and surgical excision of the pregnancy. Methotrexate management of ectopic pregnancy has been observed to be more cost-effective in comparison to surgical management while sustaining equal treatment efficacy and future fertility (Alleyassin et al., 2006).

Methotrexate is a dihydro-folate reductase inhibitor that deforms DNA and RNA precursor formation. It marks quickly dividing cells and in an ectopic pregnancy malforms preliminary trophoblastic tissues. Treatment of ectopic pregnancy through methotrexate was explored in 1982 and the common side effects associated with this treatment include pelvic pain, nausea, headaches, abdominal pain, diarrhea, and skin infections.

Various reports have revealed the efficacy of intramuscular methotrexate for treating ectopic pregnancy; however, success rates are inversely correlated to β-human chorionic gonadotropin hormone levels. In a meta-analysis study including 500 females with ectopic pregnancy treated with a single dose of methotrexate, efficient treatment, described as evasion of surgery, for preliminary β-human chorionic gonadotropin hormone levels between 1000-2000 mIU/ml was 95% in comparison to just 80% in females with initial β-human chorionic gonadotropin hormone levels of 10,000 to 150,000 mIU/ml. Moreover, β-human chorionic gonadotropin hormone levels of more than 5000 mIU/ml prove an efficient treatment instead of methotrexate, with a success rate of 85%.

Surgical Management of Ectopic Pregnancy

Surgical management of ectopic pregnancy is suggested in patients who show less efficiency in medical treatment. The standard surgical intervention was laparotomy until this technique was discovered in 1973 by Shapiro and Adler, since then it has gained wide acceptance (Shapiro et al., 1973).

Three randomized studies have shown the advantage of the laparoscopic technique over laparotomy in particular to decreased blood loss, abdominal pain, bleeding, hospital stay duration, and effective cost. The reproductive consequences, including rates of recurrent ectopic pregnancy and subsequent intrauterine pregnancy, are not predominantly distinct between laparoscopy and laparotomy.
Irrespective of the means of abdominal entry, two approaches to the removal of tubal ectopic pregnancy have been reported: Salpingectomy refers to partly or full removal of the fallopian tube, and salpingostomy refers to the eradication of ectopic pregnancy through an incision of the fallopian tube while leaving behind the tube *in situ*. Salpingectomy is suggested in cases of wide tubal deterioration and ruptured, uncontrollable vaginal bleeding, prior tubal sterilization, or broad tubal ectopic pregnancy. The surgical management for ectopic pregnancy is also deferred by the patient's fallopian tube condition, the patient's forthcoming fertility plans, and the surgeon's comfort or suggestion.

Recurrence of Ectopic pregnancy and future fertility

The probability of recurrence of tubal ectopic pregnancy ranges from 5-25% and it is not impacted by the treatment methods- medical and surgical management. In a randomized controlled study of 450 female patients undergoing surgical management for tubal ectopic pregnancy, the recurrent frequency (5%) was similar after salpingostomy and salpingectomy (Mol et al., 2014).

Another review report included 54 cases of previous interstitial ectopic pregnancy and observed a recurrence frequency of 10% following either medical or surgical management (Siow et al., 2011). In females with a previous history of interstitial ectopic pregnancy, information is limited regarding uterus rupture risk in a consequent intrauterine pregnancy, although uterus rupture has been reported after surgical management.

The frequency of recurrent cesarean scar ectopic pregnancy is inconstant, as great as 25% in smaller cases. Risk factors for recurrence are protruding of the prior cesarean scar into the uterus fold, preliminary visualization with irregular bleeding and pain, prior end of initial cesarean scar ectopic pregnancy, early cesarean delivery at the rural hospital, and thin lower uterine segment.

Data on the risk of recurrent cervical ectopic pregnancy are limited. One recurrence study was observed in a cohort of 35 female patients with previous cervical ectopic pregnancy treated with distinct modalities (Ushakov et al., 1997). Data are limited to comment on recurrence rates in pregnant women with prior ovarian, and abdominal ectopic pregnancies.

Irrespective of the location of ectopic pregnancy, conceiving is not recommended till three months after exposure to methotrexate, however, data is not available in the literature to support this fact. Outcomes of population-based reports of pregnancy consequences after a prior tubal ectopic pregnancy are independent of treatment methods. The frequency of intrauterine pregnancy has shown similar

outcomes following salpingectomy and salpingostomy in various large cohorts (Butts et al., 2003). In addition, in a study of 1064 females with prior tubal ectopic pregnancies struggling with conception, the frequencies of intrauterine pregnancies within two years were similar among salpingectomy (65%), salpingostomy (75%), and medical management (75%) (de Bennetot et al., 2012). After two previous ectopic pregnancies, the rate of consequent intrauterine pregnancy may be as low as 5% (Skjeldestad et al., 1998).

Conclusions

Ectopic pregnancy is a common clinical condition in reproductive medicine and obstetrics. However, tubal pregnancies are more common, ectopic pregnancies can happen throughout the pelvic region and abdominal cavity. The treatment of normal patients is often medical, although patients with ectopic pregnancy outside the fallopian tube may need differential or invasive treatment, including removal of tubal by laparoscopy or laparotomy. In patients with tubal ectopic pregnancy, the probability of intrauterine pregnancy is high, and independent of significant treatment modalities.

Key Points:

- Ectopic pregnancy is a rare condition that can be managed medically or surgically.
- Most commonly occurring is tubal pregnancy if embryo transplantation is in the fallopian tube and non-tubal ectopic pregnancy is embryo transplanting other than the fallopian tube i.e., cervix, interstitial region of the fallopian tube, uterus lining, ovary, abdominal cavity, and cesarean scar.
- Ectopic pregnancy accounts for 1-2% of the general population while non-tubal pregnancy accounts for less than 10% of all ectopic pregnancies.
- Risk factors associated with ectopic pregnancy include age, unhealthy lifestyle, prior history of ectopic pregnancy, tubal surgery or damage, previous pelvic infection, and pregnancy achieved by assisted reproduction.
- Measuring levels of β-human chorionic gonadotropin hormone is important to clarify pregnancy position and diagnosis in patients with ectopic pregnancy.
- Diagnosis of ectopic pregnancy is quite possible through ultrasound imaging while following standard guidelines. Additionally, ectopic pregnancy identified in anatomical regions other than the fallopian tube can be determined by ultrasound imaging.
- The prevalent interventions for managing ectopic pregnancies are medical management with systemic methotrexate and surgical excision of the pregnancy.

REFERENCES

1. Al-Azemi M, Refaat B, Amer S, Ola B, Chapman N, Ledger W. The expression of inducible nitric oxide synthase in the human fallopian tube during the menstrual cycle and in ectopic pregnancy. Fertil Steril. 2010;94:833–40
2. Alleyassin A, Khademia A, Aghahosseini M, Safdarian L, Badenoosh B, Hamed EA. Comparison of success rates in the medical management of ectopic pregnancy with single dose and multi dose administration of methotrexate: a prospective, randomized clinical trial. Fertil Steril. 2006;85:1661–6.
3. Barnhart K. Ectopic pregnancy. N Engl J Med. 2009;361:379–87.
4. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol. 2003;157:185–94.
5. Butts S, Sammel M, Hummel A, Chittams J, Barnhart K. Risk factor and clinical features of recurrent ectopic pregnancy: a case control study. Fertil Steril. 2003;80:1340–4
6. Chang HJ, Suh CS. Ectopic pregnancy after assisted reproductive technology: what are the risk factors? Curr Opin Obstet Gynecol. 2010;22:202–7
7. Chung K, Sammel MD, Coutifaris C, Chalian R, Lin K, Castelbaum AJ, et al. Defining the rise of serum HCG in viable pregnancies achieved through use of IVF. Hum Reprod. 2006;21:823–8.
8. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980–2007. Obstet Gynecol. 2011;117:837–43.
9. de Bennetot M, Rabischong B, Aublet-Cuvelier B, Belard F, Fernandez H, Bouyer J, et al. Fertility after tubal ectopic pregnancy: results of a population-based study. Fertil Steril. 2012;98:1271–6. e1-3
10. Deshpande N, Mathers A, Acharya U. Broad ligament twin pregnancy following in-vitro fertilization. Hum Reprod. 1999;14:852–4.
11. Doubilet PM. Ultrasound evaluation of the first trimester. Radiol Clin North Am. 2014;52:1191–9.
12. Farquhar CM. Ectopic pregnancy. Lancet. 2005;366:583–91.
13. Fernandez H, Gervaise A. Ectopic pregnancies after infertility treatment: modern diagnosis and therapeutic strategy. Hum Reprod Update. 2004;10:503–13. 79.
14. Guha S, Ayim F, Ludlow J, Sayasneh A, Condous G, Kirk E, et al. Triaging pregnancies of unknown location: the performance of protocols based on single serum progesterone or repeated serum hCG levels. Hum Reprod. 2014;29:938–45
15. Horne AW, Duncan WC, Critchley HO. The need for serum biomarker development for diagnosing and excluding tubal ectopic pregnancy. Acta Obstet Gynecol Scand. 2010;89:299–301.
16. Huang B, Hu D, Qian K, Ai J, Li Y, Jin L, et al. Is the frozen embryo transfer cycle associated with a significantly lower incidence of ectopic pregnancy? An analysis of more than 30,000 cycles. Fertil Steril. 2014;102:1345–9.
17. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367:1066–74.
18. Kirk E, Condous G, Bourne T. Pregnancies of unknown location. Best Pract Res Clin Obstet Gynaecol. 2009;23:493–9
19. Kirk E, McDonald K, Rees J, Govind A. Intramural ectopic pregnancy: a case and review of the literature. Eur J Obstet Gynecol Reprod Biol. 2013;168:129–33.
20. Lyons RA, Saridogan E, Djahanbakhch O. The reproductive significance of human Fallopian tube cilia. Hum Reprod Update. 2006;12:363–72.
21. Maymon R, Halperin R, Mendlovic S, Schneider D, Herman A. Ectopic pregnancies in a caesarean scar: review of the medical approach to an iatrogenic complication. Hum Reprod Update. 2004;10:515–23.
22. Moawad NS, Mahajan ST, Moniz MH, Taylor SE, Hurd WW. Current diagnosis and treatment of interstitial pregnancy. Am J Obstet Gynecol. 2010;202:15–29
23. Mol F, van Mello NM, Strandell A, Strandell K, Jurkovic D, Ross J, et al. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. Lancet. 2014;383:1483–9.
24. Morse CB, Sammel MD, Shaunik A, Allen-Taylor L, Oberfoell NL, Takacs P, et al. Performance of human chorionic gonadotropin curves in women at risk for ectopic pregnancy: exceptions to the rules. Fertil Steril. 2012;97:101–6.
25. Paltieli Y, Eibschitz I, Ziskind G, Ohel G, Silbermann M, Weichselbaum A. High progesterone levels and ciliary dysfunction–a possible cause of ectopic pregnancy. J Assist Reprod Genet. 2000;17:103–6
26. Perkins KM, Boulet SL, Kissin DM, Jamieson DJ, National ART Surveillance (NASS) Group. Risk of ectopic pregnancy associated with assisted reproductive technology in the United States, 2001–2011. Obstet Gynecol. 2015;125:70–8.
27. Poole A, Haas D, Magann EF. Early abdominal ectopic pregnancies: a systematic review of the literature. Gynecol Obstet Invest. 2012;74:249–60.
28. Practice Committee of the American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy: a committee opinion. Fertil Steril. 2013;100:638–44
29. Rana P, Kazmi I, Singh R, Afzal M, Al-Abbasi FA, Aseeri A, et al. Ectopic pregnancy: a review. Arch Gynecol Obstet. 2013;288:747–57.
30. Rausch ME, Barnhart KT. Serum biomarkers for detecting ectopic pregnancy. Clin Obstet Gynecol. 2012;55:418–23.
31. Sahin S, Ozay A, Ergin E, Turkgeldi L, Kürüm E, Ozornek H. The risk of ectopic pregnancy following GnRH agonist triggering compared with hCG triggering in GnRH antagonist IVF cycles. Arch Gynecol Obstet. 2015;291:185–91
32. Seow KM, Huang LW, Lin YH, Lin MY, Tsai YL, Hwang JL. Cesarean scar pregnancy: issues in management. Ultrasound Obstet Gynecol. 2004;23:247–53.
33. Shapiro HI, Adler DH. Excision of an ectopic pregnancy through the laparoscope. Am J Obstet Gynecol. 1973;117:290–1
34. Shaw JL, Dey SK, Critchley HO, et al. Current knowledge of the etiology of human tubal ectopic pregnancy. Hum Reprod Update. 2010;16:432–444.
35. Shaw JL, Dey SK, Critchley HO, Horne AW. Current knowledge of the aetiology of human tubal ectopic pregnancy. Hum Reprod Update. 2010;16:432–44
36. Siow A, Ng S. Laparoscopic management of 4 cases of recurrent cornual ectopic pregnancy and review of literature. J Minim Invasive Gynecol. 2011;18:296–302
37. Skjeldestad FE, Hadgu A, Eriksson N. Epidemiology of repeat ectopic pregnancy: a population-based prospective cohort study. Obstet Gynecol. 1998;91:129–35
38. Tulandi T, Al-Jaroudi D. Interstitial pregnancy: results generated from the Society of Reproductive Surgeons Registry. Obstet Gynecol. 2004;103:47–50.
39. Ushakov FB, Elchalal U, Aceman PJ, Schenker JG. Cervical pregnancy: past and future. Obstet Gynecol Surv. 1997;52:45–59
40. Varma R, Gupta J. Tubal ectopic pregnancy. Clin Evid (Online) 2009;2009:1406. pii.
41. Verhaegen J, Gallos ID, van Mello NM, Abdel-Aziz M, Takwoingi Y, Harb H, et al. Accuracy of single progesterone test to predict early pregnancy outcome in women with pain or bleeding: meta-analysis of cohort studies. BMJ. 2012;345, e6077.
42. Weigert M, Gruber D, Pernicka E, Bauer P, Feichtinger W. Previous tubal ectopic pregnancy raises the incidence of repeated ectopic pregnancies in in vitro fertilization-embryo transfer patients. J Assist Reprod Genet. 2009;26:13–7
43. World Health Organization. A multinational case-control study of ectopic pregnancy. The World Health Organization's Special Programme of Research, Development and Research Training in Human Reproduction: Task Force on Intrauterine Devices for Fertility Regulation. Clin Reprod Fertil. 1985;3:131–43
44. Yankowitz J, Leake J, Huggins G, Gazaway P, Gates E. Cervical ectopic pregnancy: review of the literature and report of a case treated by single-dose methotrexate therapy. Obstet Gynecol Surv. 1990;45:405–14.