Iranian Journal of Emergency Medicine . 2023; 10(1): e17

REVIEW ARTICLE

Review of Predisposing Factors of Cervical Ectopic Pregnancy; an Update

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Received: March 2023; Accepted: June 2023; Published online: 29 July 2023

Abstract: Cervical ectopic pregnancies (CEPs) are rare, comprising less than 1% of ectopic pregnancies. On one hand, the abundant blood supply of the cervix and its incompatibility to keep the pregnancy in progress increases the potential for bleeding following CEP, mortality, complications, and infertility in affected women. CEPs are more difficult to diagnose and get identified at later gestational ages. CEP is one of the rarest forms of ectopic pregnancies and most commonly are a consequence of assisted reproductive technology (ART); while definitive risk factors are not fully known. Possible risk factors include cervical and uterine anomalies, previous curettages or cesarean sections, smoking, tubal factor infertility, or in vitro fertilization (IVF) treatment. Our analysis of literature in 200 patient restricted to retrospective case series , showed that a history of previous C-section, uterine curettage or D&C procedures, and a history of using assisted reproductive technology might be some of the potential risk factors. The increasing application of Hegar dilators was hypothesized as the cause of the rise in CEPs. Dilation and curettage (D&C) might also make the subject vulnerable to CEP development in the future. Previous DC history could be a potential predisposing factor that is common among CEP patients. In this review, we critically reviewed these potential risk factors. In conclusion, the risk factors of CEP and their effect on fertility are also not studied properly. The rarity of these cases makes it difficult to predict as well if the risk of their recurrence is elevated.

Keywords: Cervical Ectopic Pregnancy, Cervix, Risk Factor, Ectopic Pregnancy

Cite this article as: Hajmolarezaei E, Khoroushi F, Haddad Nameghi M, Khatami S, Beiglarzadeh A, Panahi M. Review of Predisposing Factors of Cervical Ectopic Pregnancy; an Update. Iranian Jour Emerg Med. 2023; 10(1): e17. https://doi.org/10.22037/ijem.v10i1.40580.

1. Introduction

Ectopic pregnancy (EP), also known as extrauterine pregnancy (EUP), happens when a blastocyst gets implanted somewhere outside the uterine (1). Most cases of EP are blastocyst implantation in the fallopian tube (2-4), where embryo development ceases in most cases. However, embryonic development might lead to severe and critical symptoms in patients. The ovarian (3.2%) and abdominal (1.3%) sites are the next most prevalent implantation sites (5). This is a major source of morbidity and death in women when a tubal rupture happens that is associated with severe intra-abdominal bleeding. Also, if the patient survives, there will be a potential risk of infertility in the future (6-8). As a result, EP is a medical emergency that has to be treated right away (9). Over the last 30 years, the yearly incidence of EP has risen (10). Pregnancy-related fatalities account for 4–10% of all deaths in the Western world (11, 12).

Despite advancements in diagnostic technologies that have enabled earlier detection, EP is still a life-threatening illness. This medical condition is responsible for approximately 75%

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of first-trimester fatalities and 9% of all pregnancy-related deaths (7).

2. Epidemiology

In the United Kingdom, around 10,000 people are diagnosed with EP annually. EP is more common in the UK (11.1/1,000 pregnancies) than in other northern European nations and Australia (13-15). In the United Kingdom, epidemiological data shows that EP rate and its associated mortality have been constant since 1994, where, 0.35 deaths per 1,000 EP cases happened from 2003 to 2005 (16).

According to the Al-Turki study, there is an upward tendency in EP in eastern nations such as Saudi Arabia (17). According to the meta-analysis study by Hasani and et al in 2016, the prevalence of ectopic pregnancy after 2006 was reported as 3.7 per 1000 pregnancies in Iran., which has increased compared to the prevalence of 1.9 EPs in 1000 pregnancies before 2006 (14). To have better insight into the issue, all other types of Eps and their known risk factors are discussed in this review, finally focusing on CEP.

3. Ectopic pregnancy classification

In the majority of tubal ectopic pregnancy instances, the fallopian tube is the main location. 75%–80% of EPs occur in the ampullary section of the fallopian tube in with 10%–15% of cases happen in the isthmic portion, and approximately 5% in the fimbrial end (13). A transvaginal ultrasound (US) uses high-frequency sound waves to create and display images of the inside of the body. Transvaginal sonography (TVS) can identify tubal EP.Transvaginal ultrasound shows changes in the fallopian tubes in favor of ectopic pregnancy. Or fallopian tube with a developing pregnancy. While abdominal ultrasound is relatively accurate and gives complete information about the abdominal organs, this is not the case with the pelvic organs. It is better to use transvaginal ultrasound to check the pelvic organs for any evidence of EP. Transvaginal ultrasound has good diagnostic value in the diagnosis of ectopic pregnancy. Using the index of mass presence in the adnexa with very high sensitivity and then examining the positive Leash sign, which has a high specificity, can be a very good diagnostic combination (15).CEP is uncommon, accounting for only 0.15 percent of all EP (18). Before 1979, a CEP was nearly usually followed by a hysterectomy for uncontrolled vaginal hemorrhage, rendering women infertile (19, 20). According to Hofmann and Timor-criteria, Tritsch's it can be diagnosed by ultrasonography. Doppler investigations of CEP reveal trophoblast patterns (21, 22).

4. Ovarian ectopic pregnancy (OEP)

Ovarian ectopic pregnancy (OEP) has a low incidence and accounts for 0.53% of all ectopic pregnancies which makes it a rare type of EP. OEP is usually diagnosed by a positive biochemical pregnancy test, abdominal pain, and vaginal bleeding (23). Misdiagnosis of ovarian pregnancy is common since in more than 75% of cases, it is misdiagnosed with rupture of the corpus luteum as it is like other miscarriages (23, 24). Ovarian pregnancy is a single event in a healthy woman in other respects without specific clinical, laboratory, and ultrasound signs and is indistinguishable from tubal pregnancies. Laparoscopy also suggests bleeding from the corpus luteum or rupture of the ovarian cyst. The only accurate diagnostic method is sample histology (24-26). Due to the incidence of severe bleeding, medical treatment with MTX is not an option. Most surgeons prefer to conduct a laparotomy in cases of hemoperitoneum. Several studies have documented a few examples of laparoscopic therapy in women with hemoperitoneum (27).

5. Cesarean scar pregnancy

Cesarean section pregnancy is a type of ectopic pregnancy that is located at the site of the previous cesarean section in the myometrium and is a rare but threatening finding (28). Complications include severe hemorrhage and coagulopathy, uterine rupture, and maternal death. Laparoscopy and laparotomy, uterine artery embolization and injection of potassium chloride and methotrexate into the sac of pregnancy are available treatment choices (28, 29). Increasing prevalence of cesarean section (CSP) in the near future following the increased cesarean sections will lead to conditions for miscarriage fatalities, including bleeding, DIC hemorrhage (advanced coagulation disorder), and maternal mortality (30-32); while the etiology of cesarean scar pregnancy is unknown.

6. Interstitial pregnancy (IP)

Interstitial pregnancy (IP) accounts for 5% of all EPs (33). It can be difficult to diagnose , and it necessitates precise ultrasound interpretations. Ultrasound and perhaps laparoscopic examination are used to make the diagnosis (34). The interstitial line connecting the gestational sac and the lateral side of the uterine cavity is seen, then the myometrial mantle is continued around the ectopic sac (21). An ectopic pregnancy in the rudimentary horn of a unicornuate uterus is a genuine cornual ectopic pregnancy (35). In the medical literature, this phrase is frequently used in conjunction with interstitial EP (28, 36). Cornual excision or hysterectomy has been the usual treatment for interstitial pregnancy in the situation of a severely damaged uterus (37). However, effec-

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tive laparoscopic excision of cornual pregnancies has been reported (38). Although laparoscopic intervention is found to be effective and tolerated by patients, it is important to be aware of the risk of urinary tract abnormalities (39, 40).

7. Abdominal ectopic pregnancy

Abdominal EP is an exceedingly rare and severe kind of extrauterine pregnancy that occurs in 1.3 percent of instances and is detected at an incidence of 1:10,000 births (33, 41). Following the embryo's attachment to an abdominal structure, the fetus continues to develop while drawing blood from a potentially large blood supply. Abdominal EP is most commonly seen on the uterine surface, wide ligaments, or ovaries, and also on the liver, spleen, or intestines (14, 41). laparotomy surgery for resection of placental tissue is the standard treatment, whether it has a fetus or not (36, 38). When a woman has any of the aforementioned EP in addition to an intrauterine pregnancy, she is diagnosed with a heterotopic EP (39). It's also more prevalent in IVF, and superovulatory medications are used in fertility therapies (40, 42). In a case with heterotopic EP, high-resolution transvaginal ultrasonography with color Doppler will probably be the most important imaging tool in diagnosing an ectopic pregnancy. Observing an intrauterine sac with or without fetal cardiac activity is sufficient to rule out ectopic pregnancy in the abdomen. Using transvaginal ultrasound, intrauterine pregnancy can be observed from day 24 after fertilization (43).

8. EP risk factors (non-CEP)

Numerous risk factors for ectopic pregnancy have been identified, including a previous history of ectopic pregnancy, pelvic inflammatory disease, and smoking. Other factors such as age, history of abdominal or pelvic surgery, miscarriage, and contraceptive methods such as the use of intrauterine devices (IUDs) and minipills may also play a role. Due to problems such as the small sample size in different communities, and the study method that exists in previous studies, the role of the mentioned factors is not clear. The studies show that several factors are involved in the occurrence of ectopic pregnancy, but the risk is significantly increased in the presence of multiple factors (21, 44, 45). Early diagnosis intervention can significantly reduce complications and mortality. In this review, we critically reviewed these potential risk factors of CEP.

9. CEP pathophysiology

Rubin provided three morphological and histological criteria for determining the presence of cervical pregnancy in a hysterectomy specimen in 1911 (46). An aborting intrauterine pregnancy living in the cervix, as described by Jurkovic et al. in 1996, can be distinguished by detecting the 'Sliding sign' on transvaginal ultrasonography (21). Unlike an implanted cervical pregnancy, the gestational sac of an abortus slips against the endocervical canal when mild pressure is applied to the cervix with the probe. In the event of cervical pregnancy, color Doppler ultrasonography can also show peritrophoblastic blood flow (45).

Historically, CEPs were not getting diagnosed in the early gestational age (45). As cervical tissue is highly vascular, CEP cases might experience severe bleeding in the course of gestational sac development. Massive hemorrhage might necessitate emergency hysterectomy. Emergency hysterectomy is usually always performed in cases of severe and life-threatening bleeding, and sometimes this surgery leads to complications such as hemorrhagic shock or death. Early diagnosis of CEP could help decrease morbidity, as there are medical options that could help physicians preserve the uterus (47).

Cervical pregnancy was identified before 1980 when unexpected bleeding occurred after dilatation and curettage for a supposed incomplete abortion (48). However, nowadays a first-trimester ultrasound examination may identify it. Methotrexate, either with or without intra-amniotic potassium chloride, has made significant progress in ending cervical ectopic pregnancy, particularly when fetal heart beat is detected (20). The intramuscular method is often chosen among the different methotrexate administration techniques. The patient must be hemodynamically stable and follow all of the post-treatment instructions (44).

10. CEP risk factors

We made a literature review in the retrospective case series of CEP, as most studies evaluating CEP are performed in a small sample of patients as this is a rare medical condition. Most studies are focusing on the treatments, and its risk factors were not reported in most papers. Only one paper was found with the primary aim of evaluating the risk factors of CEP. Excluding case reports, we found 11 (table 1) studies that varied in number of cases from 7 to a maximum number of 50 patients in Song et al. (2009) study. Age of patients varied significantly and ranged from 20 to 45. Therefore, we think CEP might not be related to maternal age.

Previous cesarean section as a risk factor was present in about 4 to 95 percent of patients. In the study of Song et al. (2009), 23 patients (95.83%) had a history of previous C-section. Also all 11 patients of the Elmokadem et al. study had the same history of previous C-sections. In total, an average of 35.62% of percent of patients had a history of previous C-section among these 200 CEP cases. 27.08% had a history of uterine curettage or DC procedures. Assisted reproductive technology and IVF were present in an average

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Table 1: literature reviewed retrospective case series studies reporting risk factors

Study	n	age	Previous cesarean section	History of uterine curettage	assisted reproductive technology	tubal ectopic pregnancy	tubal/ cervical manipulation	IUD	Pelvic inflammatory diseases/ History of Sexually Transmitted Diseases	Fibroids /polyp	previous elective abortion	abortions
Verma et al. 2009 (58)	24	34.25	9(37.5%)	12(50%)	NR	NR	NR	NR	NR	NR	NR	NR
Kirk et al. 2006 (59)	7	median 37	1(4.17%)	0(0%)	NR	NR	NR	NR	NR	NR	NR	NR
Murji et al., 2015 (60)	27	median 34	3(12.5%)	8(33.33%)	12(50%)	4(16.67%)	3(12.5%)	NR	NR	NR	NR	NR
Shan et al. 2014 (61)	8	32±7.5	1(4.17%)	5(20.83%)	NR	0(0%)	NR	1(4.17%)	4(16.67%)	NR	NR	NR
Luis et al., 2020 (62)	21	32 (25.3 - 34.3)	5(20.83%)	9(37.5%)	1(4.17%)	1(4.17%)	NR	0(0%)	5(20.83%)	3(12.5%)	NR	NR
Song et al., 2009 (63)	50	33.7	23(95.83%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Elmokadem et al., 2019 (64)	11	26-41	11(45.83%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hu et al. 2016 (65)	19	19	8(33.33%)	NR	NR	NR	NR	NR	NR	NR	16(66.67%)	13(54.17%)
Fylstra et al., 2014 (66)	13	21 to 44	NR	5(20.83%)	NR	NR	3(12.5%)	NR	NR	NR	NR	NR
Ishikawa et al., 2016(67)	11	20 to 39	NR	NR	3(12.5%)	NR	NR	NR	NR	NR	NR	NR
Cruz-Orozco et al;., 2019 (68)	9	29 to 44	3(12.5%)	NR	3(12.5%)	NR	4(16.67%)	NR	NR	4(16.67%)	NR	NR

IUD: Intrauterine device; NR: Not reported;

of 19.79% of subjects. Pelvic inflammatory diseases or a history of sexually transmitted diseases had an 18.75% average prevalence among CEP patients. Other reported predisposing factors were not prevalent enough to be considered as a risk factor.

Cervical pregnancy is a high-risk situation because it might result in an unanticipated life-threatening hemorrhage due to the erosion of the cervical blood arteries, necessitating a hysterectomy to save patient's life. Previous research postulating risk variables for CEP have only been case series due to the rarity of the disease (49-53). Shinagawa et al. proposed a link between a history of DC and CEP as early as 1969 when they found a link between an increase in CEP and an increase in legal abortions in Japan (50). According to the literature, there is no consensus for treatment. Cervical pregnancy is often associated with significant morbidity and devastating effects on future fertility. This can be due to the deep rooting effect of the trophoblast on the cervical walls and the uterine blood supply. 70% of reported cases of CEP required a hysterectomy due to massive blood loss (52). The maternal mortality rate was reported to be 0% to 6% (52-55).

Some authors have suggested some of the possible risk factors, including cervical and uterine anomalies, previous curettages or cesarean sections, smoking, tubal factor infertility, or IVF treatment (56). Although CEP can be asymptomatic, patients usually attend the clinic due to heavy painless vaginal bleeding. Paalman and McElin described the most acceptable clinical criteria for the diagnosis of cervical pregnancy as: 1) painless bleeding from the uterus after a period of amenorrhea, 2) disproportionately enlarged cervix, 3) ovular tissue completely placed in the endocervix, and 4) closed internal os of the uterus with partially open external

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os of the uterus (57). Ushakov et al. established that the diagnostic accuracy of a transvaginal US examination is 87.5% (58). In other cases, MRI can be successfully used as an additional method (59). In the differential diagnoses, cervical pregnancy can be misinterpreted as spontaneous abortion when pregnancy tissue is found within the cervical canal (60). The increasing application of Hegar dilators was hypothesized as the cause of the rise in CEPs. Dilation and curettage (DC) might also make an individual vulnerable to CEP development in future. Although the precise pathophysiology is uncertain, hypothesized causes include cervical traumas caused by fast cervical dilatations and cervical and endometrial lining injuries caused by a sharp curettage (60). Previous DC history could be a potential predisposing factor that is common among CEP patients.

IVF and other assisted reproductive techniques have been linked to an increased incidence of cervical pregnancy in recent years, with the etiology being related to the rapid transport of fertilized ovum into the endocervical canal due to an unreceptive endometrium. Cervical pregnancy occurs in 0.1 percent of in vitro fertilization pregnancies (44).

11. Conclusion

In conclusion, the risk factors of CEP and its effect on fertility are not studied properly. The rarity of these cases makes it difficult to predict if the risk of their recurrence is elevated. As compared to intrauterine or tubal pregnancies, a history of DC appears to be a substantial risk factor for CEP. Despite the increased statistical chance of developing a CEP after a DC, considering the rarity of this disease, the total absolute risk is likely to remain modest.

12. Declarations

12.1. Acknowledgement

Hereby we acknowledge the research vice-chancellor of Mashhad University of medical sciences for their support

12.2. Conflict of interest

All authors declare that they have no relationships or interests that could have direct or potential influence or impart bias on the work.

12.3. Funding and supports

This study did not receive any funding or grants from the company or institution

12.4. Author contributions

Conceived and designed the experiments: EH.MP. Performed the experiments: EH,MH,FKH. Analyzed the data: AB SHKH EH MP. Contributed reagents/materials/analysis tools: AB Wrote the paper: EH MP

12.5. Data Availability Statement

No new data were created or analysis in this study. Data sharing is not applicable to this article.

12.6. Ethics Statement

This article does not contain any studies with the human participant or animal performed by any of the authors.

12.7. Using artificial intelligence chatbots statement

Not used in this article.

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