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Review

Ectopic Pregnancy: An Overview

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Abstract

Objectives: Purpose of this narrative review is to compare, the latest findings about ectopic pregnancy (EP) reporting pathogenetic hypothesis, common and uncommon symptoms, diagnostic work-up, treatment alternatives. EP is a pathological condition characterized by an abnormal blastocyst implant at any site apart from uterine cavity. Dealing with pathogenesis we can recognize many factors: hormonal imbalance, post infective or mechanical induced defects of the tube, assisted reproduction techniques. This condition has aroused interest for its capacity to evolve instantly in a life-threatening condition, needing an early diagnosis and an urgent surgical solution. **Mechanism**: A comprehensive literature research of recent articles has been performed. Researches for relevant data were conducted utilizing multiple databases, including PubMed, SCOPUS and Ovid. Searches included combinations of the key terms: tubal pregnancy, cervical pregnancy, cesarean scar pregnancy, 'twin and ectopic pregnancy', 'twin and tubal pregnancy', 'twin heterotopic pregnancy', 'laparoscopy and twin pregnancy', 'laparoscopy and tubal pregnancy', 'surgery and pregnancy', 'surgery and ectopic', 'surgery and twin tubal pregnancy', "methotrexate and twin pregnancy 'cornual pregnancy' ". **Findings in brief**: EP is frequently located in the salpinges but may also occur in many other sites like uterine horns, cervix, ovaries, cesarean scar or in splanchnic organs. Typical signs and symptoms of EP usually consist of pelvic pain, vaginal bleeding or sudden amenorrhea. Beta-human chorionic gonadotropin (b-hCG) dosages are fundamental tools for diagnosis of the early pregnancy whether is normal or not, always considering tubal pregnancy a possible event. Imaging diagnostic tools are described in our review, Ultrasound, Magnetic resonance imaging (MRI), Computed Tomography (CT) are the main options. When the serum b-hCG is positive but at ultrasound examination of pregnancy cannot be found, physician must define this condition as a pregnancy of unknown location (PUL). In this literature-based review we found three therapeutic solutions: expectant, medical or surgical management. Expectant strategy consists of strictly monitoring b-hCG values with no pharmacological or surgical intervention. Methotrexate administration following therapeutic schemes is a cost-effective solution and keeps patient away from surgical risks. Surgery maintains a key role in treatment choice considering that is the only one available in emergency scenario. **Conclusions**: EP is a diagnostic challenge for the physician, therapy choice is a careful and difficult decision that must be always individualized to ensure patient life uppermost and also future fertility desire.

Keywords: ectopic pregnancy; tubal pregnancy; abdominal pregnancy; ultrasound; methotrexate; laparoscopy

1. Introduction

Ectopic pregnancy (EP) is an important cause of several maternal morbidity. 2% of reported pregnancy are EP. Improvements of ultrasound diagnosis and laparoscopic technique in the last 3 decades have allowed amore expectant management and an early diagnosis which often solve the emergency problem. Furthermore, this EP could be managed with double combined approach based on medical therapy and surgical approach. In the surgical management of EP, the benefits of salpingectomy over salpingostomy are uncertain. Although there have been advances in the management of EP, there are still questions to be answered.

2. Pathogenesis

Physiologically, egg cell is fertilized in the ampulla portion of the fallopian tube, subsequently blastocyst travels down the salpinx to the implantation area. Any impinging with the normal function of the fallopian tube during this step can lead to the development of an ectopic pregnancy.

We differentiate between EP that arise in the uterine adnexa and abdominal pregnancies. Embryo transportation to the endometrium usually protects human fallopian tube from ectopic implantation. Hormones have a great influence on tubal muscles causing erroneous transit of the embryo. This transportation involves a substantial change of tubal smooth muscle cells state and mainly a modification of oviductal ciliary beat and muscle contractions. Predominantly in the ampullary-isthmic and utero-tubal junction

of the salpinx, estrogens produce a sphincter-like response while progestins relax these zones. Further studies must investigate even other hormones role. In fact, prostaglandins, catecholamines, oxytocin could have a main role in embryo transport. Ectopic implantation is more frequent when a chromosomal defect which cause abnormal development is present. Inflammation has a key role in this process, that's why pre-existent tubal disease is a major factor for EP development [1,2]. Poole *et al*. [3] found that the most of EP cases are caused by tubal insult after surgery, infection and smoking. A third of the possible causes remain unknown. Risk of EP increases with pelvic infections number, but this factor contributes less to ectopic implant risk than smoking. Between infective agent, chlamydia seems to have a key role like demonstrated in many studies [3,4]. Even assisted reproductive technologies (ARTs) increase the risk. In fact, age, tubal infections, intra-fallopian transfer, fresh embryo-transfers (ETs), day of ET, number of ETs and intrauterine hormonal environment have an impact on EP rate. This rate lowers when frozen embryos are transferred compared with fresh embryo due to the influence of no-medication versus medicated cycle on endometrial receptivity. An interesting explanation for this could be the increased uterine muscles fibers activity in stimulated cycles. This raises in uterine contractility favor embryo migration into the fallopian tubes and decrease uterine implantation rate. Studies has widely demonstrated that larger diameter of the blastocyst lower possibility of migration into the salpinx [5,6]. Like has been reported in our previous studies, twin EP is an occurrence that must be considered especially in patients that undergo to ARTs which can cause bilateral ovulation. We can distinguish twin heterotopic pregnancy, when intrauterine pregnancy coexists with EP; bilateral twin EP, when both tubes are interested, or even unilateral tubal twin EP, this last one is related to previous contralateral salpingectomy. Ectopic pregnancy develops in almost 2% while twin pregnancy counts for 1 every 80 spontaneous pregnancies. Unilateral twin ectopic pregnancy occurs with a frequency of 1/20.000–125.000 pregnancy and 1/200 ectopic pregnancy, rarer than expected [3–5]. Although the trend for ectopic pregnancy has been constantly increasing over the past 30 years, unilateral twin ectopic pregnancies have remained anecdotal, just approximately 106 cases described in literature, of which only 8 cases had a live twin. Some authors explain the twin EP as a mere result of a bilateral ovulation. Just like in singleton EP, fallopian tube is the most common site [7,8]. Among EP risk factors Intrauterine device with progestogen (IUDs) were one of the principal subjects of investigation. Like has been largely demonstrated, IUD use does not increase risk of an abnormal pregnancy implantation. But as Iavazzo *et al*. [9] illustrated in a 2008 review, results are conflicting and if an IUD is inside uterine cavity, possibilities of an EP are higher. In an observation analysis Schultheis *et al*. [10] reported that between copper or medicated IUDs users' risk was significantly lower compared to barrier methods of contraception or no contraception. Some studies have found that EP incidence rate among women using a low-dose hormonal IUD was higher than in women using other types of hormonal contraception [11]. Like demonstrated in a systematic review by Callahan *et al*. [12], progestin-only implant or injectable contraception substantially reduces their risk of pregnancy and, thus, EP. Even combined oral contraceptives (COCs) reducing pregnancy rate lowers EP risk. However, the ability of COCs to reduce the risk of pelvic inflammatory disease may provide a second important mechanism of EP reduction [12–14]. Tubal sterilization highly increases abnormal pregnancy implantation chances; risk is even higher for those who undergo to this procedure by electrocautery and in young women [15]. Finally, we have to remember cornual pregnancy that is one in the rudimentary horn of a unicornuate uterus. Cornual pregnancies are the rarest form of EP at 0.27%. The term is often used interchangeably in the medical literature with interstitial pregnancybut the two are distinct entities. Lastly with the raise of cesarean section we have to focus the attention on 2 different types of CSPs (cesarean scar pregnancy) depending on the depth of the implantation: type 1 progressing toward the uterine cavity and type 2 progressing toward the bladder.

3. Symptoms and Signs of Ectopic Pregnancy

EP can present with many different signs and symptoms depending on blastocyst implantation site. Among sites fallopian tube is the most common accounting for the 98% of cases [1]. Abdominal EPs can arise in almost every organ, from most frequent to least implant site: uterine pouches, omentum, appendix, liver, spleen, retroperitoneum and abdominal wall [3,16]. In addition, to this physician should always contemplate risk of uterine cervical pregnancy in a woman in the first trimester of pregnancy that shows pain and great vaginal blood discharge. EP often is discovered only when dilatation and curettage is performed for a suspect of incomplete abortion, then massive hemorrhage follows and often hysterectomy is practiced to stop uncontrollable bleeding [17]. This condition needs a careful work-up, physician have to evaluate Methotrexate (MTX) pre-treatment and hemorrhage prevention techniques before surgery [18]. Cesarean deliveries are increasing, because cesarean scar pregnancies (CSPs) have become frequent in the last years. This is a particular form of EP that is a real diagnostic challenge for the physician. One quarter of women are asymptomatic indeed, while the remaining presents with bleeding and pain. If this condition is not quickly recognized, CSP can evolve into placenta accreta or uterine rupture [19,20]. Being somehow similar and somehow different, the management of twin ectopic pregnancy can't just mirror the single one. The symptoms of the classic triad of amenorrhea, vaginal bleeding and pelvic pain are all presents in less than half patients Maiorana *et al*. [21] reported a case of a nulliparous

woman with an omental pregnancy. Until bleeding, the only symptoms showed was an 8 weeks long amenorrhea and abdominal tenderness in lower quadrants at physical examination [21]. Patient with rectal EP can show rectal bleeding while hepatic EP, except for the amenorrhea and vaginal bleeding is hardly ever symptomatic [22–24]. Splenic rupture due EP is a very rare event, but it must be recognized considering massive hemoperitoneum [25]. Symptoms of EP may vary depending on the involved structure, remembering that embryo can implant in almost every organ [26]. Typical EP symptoms are pain whether located in the abdomen or in the pelvis, menstrual irregularities or amenorrhea, genital bleeding, breast tenderness, gastrointestinal symptoms, syncope, shoulder tip pain, dysuria, rebound tenderness reaching up to frank peritonism with pallor, tachycardia or bradycardia, abdominal distension, shock [15,27–29]. Even periumbilical ecchymosis (Cullen's sign) was observed [30].

4. Diagnosis

If pregnancy cannot be found inside the uterus in a patient with b-hCG values higher than 2000 mIU/mL, physician must consider this situation very suspicious of EP until surely excluded [31]. Making EP diagnosis can be a real challenge, but transabdominal or, when possible, transvaginal ultrasound (TVUS) is a precious tool that in expert hands can be useful for diagnosis especially in initial workup. Like reported until 6-week pregnancy, tool sensitivity is only 56%. When fetal heartbeat observed at an ectopic implantation by TVUS is evidence of an ectopic pregnancy. A common mistake in TVUS examination is recognizing as hemorrhagic corpus luteum or luteal cyst what in reality is a gestational chamber. For patients who undergo *in vitro* fertilization (IVF) ultrasound detection can be even harder due to intense ovarian activity. Even if intrauterine pregnancy is found adnexa should be always checked, remembering that adnexal masses are not visible until mass size is around 2 cm, measures that are usually reached at 7 weeks of gestation, and that pulsation from embryonic pole is not always found. If high velocity, low resistance is found at Doppler examination, this could be a consequence of developing trophoblast, with increase of flow, in the typical "ring of fire" image. Identification of this is particular pattern in the adnexa increases sensitivity of EP diagnosis to 73% [32,33]. Some authors recommend using 3D ultrasound (US) with the scope of determine EP exact location. This ultrasound tool reproduces uterine coronal plane starting by orthogonal plans. Transparency mode functioning with this methodic provides complete vision of the whole salpinx even of the interstitial portion. This modality is very useful to precisely define EP site, such as angular and cornual pregnancy giving possibility to plan appropriate treatment in a short time [34,35]. Considering that these particular EP subtypes arise in high vascularized zones, a correct pre-surgical staging with ultrasound is fundamental [31,36,37]. 3D examination is also useful for differentiate between interstitial or angular pregnancy, due to a live baby can born [38]. Ultrasound can fail with abdominal pregnancies diagnosis. For these reasons, physician can use other imaging tools to locate pregnancy and, in a surgery-need scenario, make an accurate pre-surgical staging. Magnetic resonance imaging (MRI) and Computed Tomography (CT) have a key-role in confirming diagnosis, especially determining anatomic location and vascular supports excluding or confirming placental accretism. Frequently CT is used as imaging modality of choice in the evaluation of acute abdomen mainly in trauma setting. The pregnancy status should be checked before performing any radiologic imaging procedure. MRI does not provide ionizing radiation, can produce multiplanar imaging, gives great contrast between tissues and fluids. In the need of identification of hemorrhage and air bubbles T2-weighted images are the best choice. Contrast-enhanced imaging plays a main role in determining the presence of bleeding, as shown by extravasation, lesion vascularity and relation of the mass with pelvic vessels [39,40]. The ultrasonographic criteria for cornual pregnancy diagnosis are: an empty uterine cavity, a gestational sac located eccentrically and 1 cm from the most lateral wall of the uterine cavity, and a thin (<5 mm) myometrial layer surrounding the gestational sac. Traditionally, treatment of cornual pregnancy can been surgical and may include hysterectomy or cornual resection by laparotomy or laparoscopy.

Treatment Options

In some cases, the evaluation even combining all the informations, is not discerning: the pregnancy is then classified of unknown location (PUL). Expectant management can be a choice in the PUL scenario. b-hCG is measured every 4–7 days checking for his serum level reduction. If these values don't increase nor decrease, uterine suction can confirm an intrauterine miscarriage by seeing chorionic villi at pathology examination. b-hCG values are dosed the day after procedure and if values do not decrease of at least 15%, medical treatment should be administered. If the serum b-hCG level is not influenced by uterine evacuation, pregnancy could be presumed extrauterine [41].

Another option is the medical management with MTX. This choice can be made once having big suspicion for EP in stable patients, with intact mass, and obviously without absolute contraindications to this drug. Patients managed with MTX therapy must be informed that follow-up surveillance is long and fundamental for good outcome. MTX action consists in inhibiting DNA synthesis and repair due to that the main target are proliferating tissues. MTX absolute contraindications are not EP, anemia whether moderate or severe, white cell or platelets deficiency, MTX allergy, pulmonary disease, peptic ulcer, liver or kidney diseases, breastfeeding, ruptured ectopic pregnancy with consequent hemoperitoneum, not wanting to participate in follow-up. MTX treatment relative con-

traindications are embryonic cardiac activity at ultrasound, high b-hCG levels, EP with more than 4 cm in size, refusal of blood transfusion. With one dose scheme physician administer a single dose of MTX at a dose of 50 mg/m^2 by intramuscular injection on day 1. b-hCG levels are dosed on day 4 and day 7. If these values on day 7 decrease more than 15%, b-hCG levels can be measured weekly until negativization. If decrease is less, a new dose is needed and MTX can be re-administered at the same dosage of the first dose and b-hCG dosage must be repeated. If b-hCG levels remain stable even after two doses, surgical management can be a choice. Two doses scheme treatment is composed by a first MTX dose on day 1 with b-hCG levels check as for single-dose scheme, and by a second dose of 50 mg/m^2 on day 4. A new b-hCG dosage is made on day 7. Many authors have found a significant higher success rate for the two-dose versus the single-dose regimen in women with initial b-hCG levels between 3600 mIU/mL and 5500 mIU/mL. After MTX administration, b-hCG levels are monitored. Medical treatment failure in patients who did not undergo to uterine aspiration, can be explainable by an intrauterine gestation with abnormal development. In these patients, uterine aspiration can be done before MTX administration or surgical procedure, unless there is clear evidence of a tubal EP. Available evidence suggests that medical management does not have a negative impact on fertility or future conception probability, not influencing ovarian reserve [42]. Some authors have even found no difference between surgical or medical approach regarding fertility preservation [43]. MTX administration can be systemic or even local under ultrasound guidance, but in a study by Koch *et al*. [27] has been reported that b-hCG clearance is longer when administered locally.

Surgical procedure is needed when absolute contraindications to medical treatment should be evaluated when there are relative contraindications. Surgery can be the right choice when medical management fails his scope or when there is necessity for a simultaneous surgical procedure, such as tubal occlusion or hydrosalpinx removal when an *in vitro* fertilization is planned. An urgent laparoscopic procedure requires general anesthesia and risks should not be underestimated, while medical treatment implies fewer complications. Conservative surgery is more effective, though more costly than medical management [28]. Surgery is generally performed using laparoscopic salpingectomy or laparoscopic salpingostomy. Laparoscopy is a safe, easy to learn, repeatable choice for treatment even for the hemodynamic shock scenarios. Studies show that achieves faster hemostasis than laparotomy and, therefore, overall procedure time is shorter [27].

Ozcan *et al*. [44] in 2021 have made an interesting metanalysis about surgical approach for this condition. Salpingostomy is strongly recommended for women with infertility risk factors. It seems that, in choosing between salpingectomies vs salpingostomies, outcomes are the same in future EP prevention. Regarding laparoscopic access method there is not a preferred one. Salpingostomy consist of incising tube above pregnancy site and removing EP. This is advised when preserving salpinx for future conceptions is our primary target. Hemostasis should be surgeon primary goal, suturing beyond the essential indeed, has not demonstrated to give better results. First incision is made medially to the maximal bulge and extended just for the length required for easily extrude and remove pregnancy, typically to a maximum of 2 cm. While incising tissue damage reduction is our main goal, using laser, electrosurgery or harmonic scalpel is advised. At this point EP should move out spontaneously from incision, if this does not happen, surgeon can use hydrodissection introducing suction irrigator tip or gently dislocate it out with graspers. Salpingectomy consists of total tubal removal, paying attention to keep EP in its place with the aim of minimizing risk of trophoblastic spill and possible persistent EP. Bipolar graspers should approach the tube at superior margin of the mesosalpinx to circumscribe energy spread in the tissue and keeping as far as possible ovarian blood vessels saving ovarian reserve. Removing entire tube and not just the area with the EP is the best option to decrease future cancer risk and avoid recurrent EP. Fallopian fistula is a late complication of the procedure and is linked to great amount of thermic energy used and too few tubal tissue left. Alternatively, removing too small portion of the tube is equally wrong due to greater risk of a future interstitial EP [44,45]. Another approach consists of a segmental laparoscopic tubal segmental resection followed by end-to-end anastomosis, this procedure seems to give very good results in particular on the aspect of ovarian function preservation [46].

Persisting trophoblastic tissue after surgery consist of an insufficient fall in b-hCG. Like reported in a 2018 review by Astrid Collatz Schyum *et al*. [47] this complication seems to be more frequent in women who undergo to linear salpingostomy. Usually, trophoblastic tissue remains in the salpinx and in some cases, tissue could implant in the peritoneum [47]. Finally we have to remember minimally invasive approach for cesarean scar pregnancy with double step management with MTX followed by curettage or resectoscopic approach, if b-hCG values are persistent and pregnancy adsorption is slowly, eventually anticipated by uterine artery embolization. For abdominal pregnancy in general, image magnification during laparoscopy allows complete removal of placental cotyledons from the peritoneal surface [48], thereby avoiding possible postoperative bleeding, infection, and sepsis resulting from retention of placental remnants. However, given the tenacious adherent decidual tissue in some cases the management with MTX could be a choice rather than removing all the placenta tissue.

5. Conclusions

Early detection of an EP is fundamental for avoiding life-threatening complications. Pelvic ultrasound still the best diagnostic tool for adnexal or peri-uterine pregnancy. Ultrasound detection rate is enhanced when combine with b-hCG serum quantitative dosage. When in need of locating abdominal pregnancy MRI is the best choice, but in the emergency scenario, CT is the fastest option.

Many treatment options are available for treating this condition. Authors feel to say that expectant management is useful in the suspect of an early abortion; medical management is easy to apply if the indications are met, but only with surgery we could manage emergency catastrophic scenarios applying procedures that are highly standardized, repeatable and easy to learn.

Author Contributions

GRD and GM made idea and organize the paper, principal and responsibles. DDG wrote the paper performed research. MS, GT, EC and RC review the paper and provide supervision. MG and EDN provide text correction. LMS wrote data research. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. GT is serving as one of the Editorial Board members of this journal. GRD is serving as one of the Guest editors of this journal. We declare that GT and GRD had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to YHK.

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