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Review Article

A Review of the Changing Proportions of Unusual Ectopic Pregnancy Sites: Clinico-Pathological Correlates

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Abstract

Objective. Ectopic pregnancy is a major cause of maternal morbidity and mortality. Of great concern is the increasing proportion of unusual sites of these pregnancies. This trend poses the problem of delayed diagnosis and failed timely appropriate management of affected patients. The objective of this study is to review the literature to highlight the challenges inherent in the changing proportions of ectopic pregnancy sites, focusing on the pathophysiology and the management strategies to reduce maternal morbidity. **Methodology.** Using our hospital records, and online search engines, publications on ectopic gestation were selected and reviewed. In addition, the experiences of some of the authors of this paper form parts of the review. The sum total findings of the various ectopic pregnancy sites were carefully studied in order to identify clinical consequences and challenges encountered with the management of cases. **Result/Conclusion.** The conclusion was arrived at by careful analysis of the various unusual ectopic sites and patterns of presentation. These sites included abdominal, ovarian, caesarean scar and cervical pregnancies; and the patterns included heterotopic, bilateral tubal, tubal twin ectopic pregnancies, and caesarean scar-site pregnancy. The increasing incidence of ectopic pregnancy in unusual sites is closely linked to pelvic infections, assisted reproductive technology procedures increasing caesarean section rates and use of intrauterine devices. The authors conclude on the need for a high index of suspicion of implanted blastocysts in these uncommon sites with potential for delayed appropriate treatment and increased morbidity.

Keywords: Ectopic Pregnancy, Unusual Sites, Complexities

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Introduction

In general terms, a pregnancy is designated ectopic when a blastocyst is implanted outside the usual uterine endometrium. The first documented description of an ectopic gestation was by Al-Zahrawl, in the 11th Century. [1] There is increasing interest locally, regionally, and globally in the causes and clinical outcomes of ectopic pregnancies. Scholarly articles on ectopic pregnancies have documented cases of ectopic gestation occurring in varying proportions at different sites that include the peritoneal cavity, the ovaries, within the fallopian tubes, caesarean scar and the cervix. And these occur

in various rare patterns that include abdominal, heterotopic, bilateral tubal, tubal twin, caesarean scar-site, intra-mural (intramyometrial), and cervical ectopic pregnancies. These unusual sites result in increasingly diverse atypical clinical presentations that pose diagnostic challenges, and delayed appropriate treatment with undesirable complications, culminating in severe maternal morbidity with occasional avoidable mortality. These diagnostic challenges and consequent delayed treatment are particularly common in low socio-economic settings that lack effective infrastructural network facilities for uniform primary healthcare services or effective early pregnancy assessment centres.

The scope of this review includes pathophysiology, epidemiology, and the increasing proportion/variability of ectopic pregnancy sites, the accompanying complications, and the clinical approaches to the management of cases.

Epidemiology

The incidence of ectopic pregnancy varies between countries and regions. In South-Eastern Nigeria, Lawani et al. [2] had an incidence of 2.1% during a 10-year study period. In the United States of America (US), the prevalence rate is 1-2%. [3,4] Risk factors in the emergence of ectopic implantation of fertilized ovum include tubal surgery, pelvic inflammatory disease, Kartagener syndrome (ineffective ciliated epithelium), [5] assisted reproductive procedures, hormonal imbalance from contraceptive pills, and smoking. [3][4] The commonest risk factor is previous pelvic infection. [6]

The most common site of ectopic pregnancy is the fallopian tube, accounting for about 95 percent of cases. Chanana et al. [7] record the proportion in incidence of ectopic pregnancy, essentially in agreement with several other authors' publications, as follows: ampullary tubal (70-80%), interstitial tubal (2-4%), cervical (<1%), ovarian (1-3%), Caesarean scar (<1%), secondary abdominal (0.9-1.4%) and heterotopic ectopic pregnancy (1-3%). Intramural (intramyometrial) ectopic pregnancy is probably the rarest (0.0033). [8]

Pathophysiology

Numerous pathologies have been linked to ectopic /gestation. Factors that impede the movement of the ovum or the blastocyst are major contributors to the genesis of ectopic gestation.

Injury to the Fallopian tube in pelvic inflammatory disease results in the formation of scar tissue within the tubal mucosa. Fibrosis of the fallopian tube mucosa is a major factor in the genesis of ectopic gestation. A fibrosed tube is unable to propel the blastocyst, thus preventing its passage to the uterus, resulting in tubal pregnancy. Fibrous peritoneal bands, a late complication of abdominal surgery, will impede the movement of the ovum after ovulation and lead to fertilization occurring outside the oviduct, resulting in ectopic gestation. Although mortality arising from ectopic pregnancy is low, morbidity is high in Nigeria and sub-Saharan Africa.[6] In a 10-year review of 434 ectopic gestation cases, Olamijulo et al recorded 70.8% cases of hypovolemic shock, and a case fatality rate of 1.4%. [6]

In Kartagener Syndrome, [5] there is ciliary dyskinesia, resulting in poor ciliary activity in the fallopian tube and stasis of the ovum or the blastocyst. After ovulation, if fertilization occurs, it is mostly in the ampullary section of the fallopian tube. Thereafter peristaltic movement of the tube enables the embryo to reach the uterine cavity. If the tube has adhesions or ciliary dyskinesia, the embryo will be halted in the tube giving rise to an ectopic gestation. Similarly, adhesions in the pelvis can prevent the released ovum from migrating into the tube. If fertilized outside the tube, the embryo can get implanted in one of several extrauterine sites. These sites include abdominal pregnancy involving mesosalpinx, the broad ligament, the omental bursa, the mesenteries, and any point in the abdominal cavity.

Unusual Ectopic Pregnancy Sites: Clinical Presentation and Management

Abdominal pregnancy is a major consideration in assessing unusual ectopic pregnancy sites. Several cases of abdominal ectopic pregnancies have been reported in the literature. At the Igbinedion University Teaching Hospital, a 19-year-old patient, Para 0^{+1}, presented with sixteen-week amenorrhoea, fever, and features of anaemia. The packed cell volume was 19%. Abdomino-pelvic scan reported an intrauterine pregnancy. However, because of increased abdominal pain and persistent vaginal bleeding, a decision was taken for exploratory laparotomy. At laparotomy, a dead fetus, with the placenta inserted on the omentum, was found (Figure 1). The placenta, along with the fetus, was carefully extracted and adequate haemostasis was secured. The anaemia was corrected. Her recovery was uneventful.

Akunaeziri et al. [9] managed a 27-year-old woman, Para 2, that presented at 32 weeks' gestation, diagnosed by ultrasound as abdominal ectopic pregnancy. The patient had laparotomy at 34 weeks gestation with the delivery of a live baby. The placenta was excised from the uterine fundus.

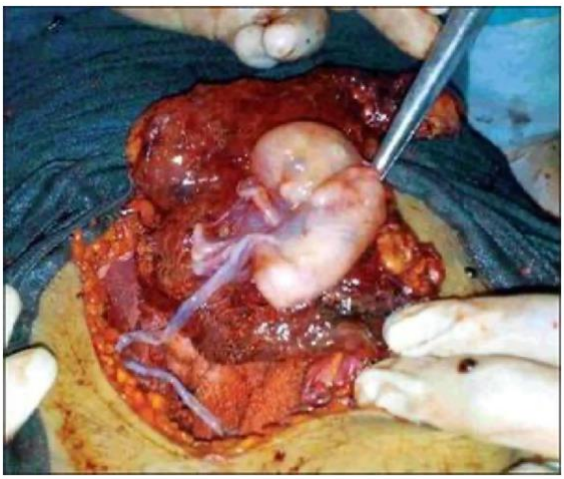

Fig. 1: Abdominal pregnancy with a dead fetus. The placenta is inserted on the omentum

Cases of term abdominal pregnancy have been reported. Mengistu et al. [10] reported a case of a 32-year-old woman, Para 2, at 40 weeks' gestation with symptoms of progressive abdominal pain of four months durations. Abdominal ultrasound confirmed abdominal pregnancy. At laparotomy, a live baby was extracted while hysterectomy was performed because of severe uncontrollable bleeding from the placental site. This shows that placental adhesion to intra-abdominal organs can sometimes cause severe life-threatening haemorrhage.

Chen Y et al. [11] reviewed 17 cases of abdominal ectopic pregnancy from 1989 to 2021. They found an incidence of 0.19% of all ectopic gestations; the median age of women was 34 years. Twelve out of 17 cases were misdiagnosed as tubal pregnancies, reemphasizing the fact that a high index of suspicion is imperative. Ahmed Hajji et al. [12] successfully managed early primary abdominal pregnancy in a 35-year-old woman with laparoscopic resection of a 2cm size gestational ectopic mass.

Ovarian ectopic pregnancy results when a fertilized ovum is retained in the ovary. Clinical presentation is similar to that of an ovarian cystic mass such as vague abdominal discomfort, with a distinguishing feature of amenorrhoea. Hatar Ghasemi Tehrani et al. [13] reported a case of 30-year-old multiparous woman, with two previous caesarean sections, that presented with ruptured ovarian ectopic pregnancy which was managed by wedge resection of the ovary.

Unusual presentations of ***tubal pregnancy*** have been reported. A case of bilateral tubal ectopic pregnancy was reported by Unuigbe et al. from Riyadh, Saudi Arabia. [14] A 23-year-old woman, Para 1, presented with abdominal pain and seven-week amenorrhea. Ultrasound was suggestive of right tubal ectopic pregnancy. At laparotomy, both tubes had swellings.

FIG 2: Histology of specimen from left fallopian tube *with trophoblastic (syncytial and Langerhans') cells.*Hematoxylin and Eosin (200x).[Unuigbe et al]

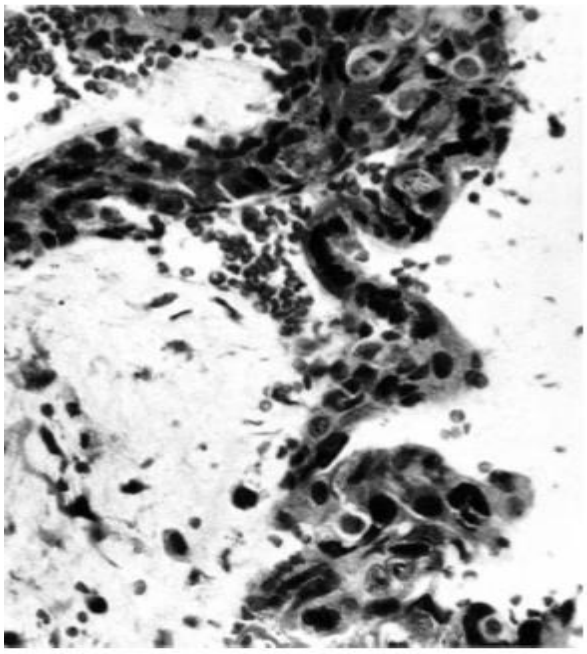

FIG 3. Histology of specimen from right fallopian tube, Chorionic Villi *with trophoblastic (syncytial and Langerhans') cells.*
Haematoxylin and eosin (200x) [Unuigbe et al]

The contents of the right ampullary swelling were expressed through the fimbrial ostium and contents of the left tube were removed with forceps through a linear salpingostomy. Histology of both specimens showed chorionic villi, confirming the diagnosis of ectopic gestation (Figures 2 and 3). Using hystero-salpingography, tubal patency was confirmed six weeks post-surgery. The woman successfully

achieved conception soon after and was delivered by caesarean section twelve months after the laparotomy.

Interstitial tubal ectopic pregnancy occurs when there is implantation of a blastocyst in the intramyometrial segment of the fallopian tube. Brincat et al. **[15]** reviewed 86 articles significantly related to the diagnosis and management of interstitial pregnancies. They concluded that the diagnosis and management of interstitial pregnancy remains challenging, in part due to the rarity of these cases and the paucity of evidence to guide management. They recommend ultrasound's central role as first-line investigation to diagnose interstitial as well as other very rare patterns of ectopic pregnancy. Ultrasound findings of an echogenic interstitial line and abnormal bulging of the myometrial contour are characteristic of interstitial ectopic pregnancy.

Heterotopic pregnancy is a rare but notable type of uncommon pregnancy with implantation of one blastocyst in the endometrium of the uterine cavity and a second blastocyst outside, at the same time. The incidence is 1 in 30,000 of spontaneous pregnancies and 1 in 100 to 1:500 with assisted reproductive technologies. **[3]** A 25-year-old patient, Para 2, was seen at the emergency clinic of Igbinedion University Teaching Hospital with acute abdominal pain and vomiting with eight-week amenorrhoea. Transvaginal ultrasound revealed a six-week viable intrauterine gestation. Further ultrasound examination showed coexisting tubal ectopic pregnancy. Exploratory laparotomy with right salpingectomy was performed with minimal handling of the uterus. The intrauterine pregnancy was carried to term and a caesarean section was performed for transverse lie. A live baby was delivered. Archibong et al. **[16]** from Calabar, Nigeria**,** reported a case of heterotopic pregnancy following induction of ovulation, highlighting the role of ovulation induction as causative factor in heterotopic pregnancy.

Nabiu et al.**[17]** from a six-case report brought to the limelight the diagnostic dilemma usually associated with heterotopic pregnancy. Diagnostic difficulties are not uncommon with heterotopic pregnancies as a result of failed suspicion of a second pregnancy after either an ectopic pregnancy or intrauterine pregnancy has been diagnosed. A high index of suspicion is the key to avoidance of any untoward outcome.

Twin ectopic tubal pregnancy is an unusual pregnancy. Betti et al. [18] reported a case of twin ectopic pregnancy in one fallopian tube. A 31-year-old woman, Para 0^{+1}, had a history of endometriosis and right tubal pregnancy treated with laparoscopic salpingectomy. She presented seven months later with a twin ectopic gestation, diagnosed by ultrasound, involving the contralateral tube. She was successfully treated with methotrexate. Clinical presentation of a twin tubal pregnancy is similar to singleton ectopic gestation except that the β-hCG level tends to be higher than that of a single ectopic pregnancy. [18] Ultrasound detection of two adnexal heartbeats suggests a live twin ectopic pregnancy.

Cervical ectopic pregnancy (CEP) is a rare form of ectopic pregnancy in which the blastocyst implants in the lining of the endocervical canal. It accounts for less than 1% of all ectopic pregnancies. [19] Unuigbe et al. [20] managed a cervical ectopic pregnancy that presented as a missed abortion. The diagnosis was missed at ultrasound examination but made during examination under anaesthesia. The severe haemorrhage that ensued following an attempt at dilatation and curettage, could only be controlled by a total abdominal hysterectomy. The diagnosis was confirmed by histology.

CEP can easily be misdiagnosed as abortion in progress, resulting in subsequent dilatation and curettage with attendant severe haemorrhage and haemodynamic collapse. The need to be circumspect in handling this type of case cannot be overemphasized. The risk factors for cervical ectopic pregnancies include the use of an intrauterine device, repeated endometrial curettage, Asherman's syndrome and in-vitro fertilization.**[2][3]** Tanos et al. [21] managed 12 cases of CEP using hysteroscopic surgery as a sole treatment**.** Of the 12 cases treated, seven were earlier treated unsuccessfully with methotrexate. They also managed eight cases of CEP using a combination of hysteroscopy and uterine artery embolization. At Ile-Ife, Nigeria, [22] a diagnosis of CEP was made by ultrasound on a 30-year-old woman, Para 2, who presented with vaginal bleeding at 11 weeks' gestation. She was conservatively treated with methotrexate. Bukar et al. [23] also successfully managed a patient with CEP, using intramuscular methotrexate.

An early pregnancy transvaginal ultrasound that reveals a gestational sac located below the internal cervical os containing an embryo with fetal echos is characteristic of a cervical pregnancy. However, Magnetic Resonance Imaging (MRI), when available, has superior accuracy in detecting ectopic intra-cervical embryonic tissues with an added value of ruling out caesarean scar pregnancy. [24]

Caesarean scar ectopic pregnancy (CSEP) is a rare form of ectopic pregnancy where the gestational sac,

villi and placenta are wholly or partially inserted in the myometrium of a previous scar. The incidence of 1:2000 [25] has increased over the years because of an increase in Caesarean delivery rates. Early diagnosis is very important to avoid uterine rupture with severe haemorrhage. Ajong et al. [25] presented a case report of ruptured uterus complicating CSEP that was successfully managed by laparotomy with uterine repair. Malhotra et al. [26] successfully managed five cases of caesarean scar ectopic pregnancy with systemic methotrexate. In low-resource countries, patients usually present very late with consequent ruptured uterus followed by severe haemorrhage. [2]

Intramural (intramyometrial) ectopic pregnancy, considered the rarest of ectopic pregnancies, occurs with a risk of 1:30,000 (0-003%). **[7]** The diagnosis is challenging and often requires exploratory laparotomy for confirmation. Consequently, because of late diagnosis, intramural pregnancy quite often requires hysterectomy for life-threatening intraoperative haemorrhage. It requires trans-vaginal ultrasound and MRI to establish early diagnosis and timely surgical intervention to preserve the uterus and future fertility.**[7]**

Discussion

The emergence of unusual implantation sites other than tubal sites is related to the rise in invasive procedures during assisted reproduction. In-vitro fertilization and embryo transfer are leading causes of extra tubal ectopic pregnancy.[6] Invasive procedures such as laparoscopic harvesting of embryos carry the risk of tissue fibrosis during the healing process. Also, intrauterine contraceptive devices prevent implantation of blastocyst in the uterine cavity, thus promoting ectopic pregnancy.

Abdominal pregnancy as a clinical entity is a major challenge worldwide. It accounts for about one percent of ectopic pregnancies. **[5]** It is either primary or secondary as earlier stated. The incidence of primary abdominal ectopic pregnancies varies from 1:10,000 to 1:30,000 **[6].**

Studdiford [27] in 1942 established three criteria for the diagnosis of primary peritoneal pregnancy; the presence of normal tubes and ovaries, no evidence of uteroperitoneal fistula, and the presence of a pregnancy-related sac, exclusively to the peritoneal surface at an early gestational age. Primary omental pregnancy with secondary implantation into the posterior cul-de-sac has been recognized. **[9]** Sometimes the diagnosis can be a dilemma. Clinically, patient can present with foetal mal-presentation, easily palpable foetal parts, and oligohydramnios.

Biochemical analysis, lateral projection sonography and radiography in advanced pregnancy can be helpful. An oxytocin-stimulation test with no effect on the uterus and abnormally high maternal serum α-foeto protein, have been found to be useful. MRI and CT scan can be done in later stages of pregnancy but are not widely available especially in low resource setting. [18]. Treatment is generally by laparotomy. Laparoscopic and ultrasound guided procedures for early presentations have been carried out [10]. Bleeding from the placental insertion site can be life-threatening during laparotomy. The recommendation is to leave the placenta for enzymatic degeneration while monitoring β-hCG levels.[11] From all indications the incidence of abdominal ectopic pregnancy appears to be on the rise. A high index of suspicion is necessary for early diagnosis and treatment to prevent preventable complications.

When a fertilized ovum is retained in the ovary it is termed ovarian ectopic pregnancy. It constitutes about 0.5–3% of all ectopic pregnancies.[14] Clinical presentations as vague abdominal discomfort are like ovarian cystic mass but for the presence of amenorrhoea. Risk factors are like the other forms of ectopic gestations. It is usually differentiated from corpus luteum cyst by a surrounding ring of echogenicity on an ultrasonic scan image.[18] Diagnosis of ovarian ectopic pregnancy must meet Spiegelberg's criteria,[28-30] namely; an intact ipsilateral tube, clearly separate from the ovary; a gestation occupying the normal position of the ovary; a gestational sac connected to uterus by the utero-ovarian ligament; and ovarian tissue in the wall of the sac. Ovarian ectopic gestation usually ends with rupture before the end of first trimester if not detected early. Early detection with a transvaginal ultrasound is the key to prevent disastrous rupture.

The use of assisted reproductive technology such as ovulation stimulation has led to an increase in incidence of ectopic pregnancies. The mechanism is uncertain. However, ovarian follicular production, resulting in high levels of progesterone and estradiol that may affect tubal peristalsis and uterine relaxation, has been implicated. The number of transferred embryos as well as the placement of embryo could also be a factor.[2,3] Literature is replete with publications about assisted reproductive techniques and ectopic pregnancy complication rates. While some studies have reported no increased incidents of ectopic gestations, there are credible reports from the United States [31] on increased rates associated with multiple embryo transfer. Among patients undergoing fresh non-donors IVF-ET procedures, Clayton et al [32] reported an increased risk for ectopic pregnancy among women with tubal factor infertility.

A high index of suspicion for caesarean scar ectopic pregnancy (CSEP) is vital because up to 40% of patients will not present with specific clinical symptoms. Diagnosis is based on transvaginal sonography (TVS) with a positive pregnancy test. The criteria are an empty uterine cavity or a cervical canal with a clearly visible endometrium; a gestational sac or mixed-echo mass located in the anterior isthmus; or in the caesarean scar defect with diminished myometrium between the bladder wall and the scar [26].

There is currently no consensus on the best approach to the management of CSEP. Treatment options include expectant management, especially for the endophytic type in which the pregnancy grows towards the uterine cavity; medical treatment with methotrexate; surgical treatment by laparotomy or by laparoscopic caesarean scar resection. Transvaginal curettage after uterine artery embolization and trans-abdominal ultrasound-guided hysteroscopic curettage can also be done.

The incidence of interstitial tubal ectopic pregnancy is about 2.5% of tubal pregnancy. The timing of rupture could suggest interstitial ectopic tubal gestation as it happens much later than other tubal gestations. Rupture of ectopic tubal pregnancy usually occurs around 6-8 weeks, 8-12 weeks, and 12-16 weeks in isthmic, ampullary and interstitial ectopic gestations respectively. [3] Interstitial ectopic gestation ruptures much later because myometrium can stretch to allow the gestational sac to grow bigger. The gestational sac is in the uterus but outside the endometrial cavity, creating a diagnostic dilemma of differentiating it from normal uterine pregnancy. It is associated with greater degree of haemorrhage when rupture occurs because of the proximity of the gestational sac to the intramyometrial arcuate vasculature.

Early unruptured interstitial ectopic pregnancy can be managed successfully with methotrexate followed with serial β-hCG measurement. Conservative laparoscopic surgery and uterine artery embolization can also be offered. In an emergency associated with severe haemorrhage, conuaectomy or hysterectomy may be the last option.

Conclusion

Although over ninety-five percent of ectopic gestation is in the fallopian tube, the implantation of gestational sac in uncommon sites should be considered a strong possibility at all times. There is need for desired overwhelming insight into the unusual and sometimes dramatic clinical presentations of ectopic pregnancies that occur in unusual sites. High-resolution ultrasonography and MRI, where available, play a key role in the early diagnosis of ectopic pregnancy. [33] These measures are necessary in order to avoid delayed diagnosis and implement timely treatment of patients, thus preventing unpleasant consequences.

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