

Adjunctive use of methotrexate in the management of advanced abdominal pregnancy: a case report and literature review

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Abstract

Abdominal pregnancy still represents an enigma because of the diagnostic conundrum precluding early intervention. Newer diagnostic techniques, especially Magnetic Resonance Imaging which removes much of the confusion surrounding abdominal pregnancy, are yet to be readily available in developing economies. The really vexed issue surrounding advanced abdominal pregnancy revolves around the best way to deal with the placenta which could partially or totally separate anytime before term leading to torrential haemorrhage and increased maternal morbidity and mortality. Case report presented is the adjunctive use of methotrexate to aid the autolysis of the placenta left in situ after laparotomy in a 22-year old Nigerian nullipara with advanced abdominal pregnancy. Methotrexate, by aiding in the earlier involution of the placenta, may be important in improving the rate of early recovery of patients and reducing the morbidity and mortality associated with advanced abdominal pregnancy.

Keywords: Abdominal Pregnancy, Advanced Abdominal Pregnancy, Placental Autolysis, Methotrexate

INTRODUCTION

An abdominal pregnancy, an extremely rare and serious form of extrauterine gestation (Yildizhan et al, 2008), occurs when the pregnancy is implanted in the peritoneal cavity outside the fallopian tubes or ovary and not located in the broad ligament. It accounts for almost 1% of ectopic pregnancies (Ludwig et al, 1999) which may be present in 1-2% of live births in developed countries and as high as 4% of pregnancies involving assisted reproductive technology. Advanced abdominal pregnancy is defined as a pregnancy that has progressed beyond 20 weeks of gestation in which the foetus is growing and developing in the mother's abdominal cavity or the foetus shows signs of having been in the mother's abdominal cavity (Nunyalulendho and Einterz, 2006; Masukume, 2014). Worldwide, the incidence is about 1 per 10,000 pregnancies (Alto, 1990; Kun et al, 2000) but this may be 34 per 100,000 pregnancies in Nigeria (Sunday-Adeoye et al, 2011) probably due to the increased incidence of

pelvic inflammatory disease (Maas and Stabber, 1975). Abdominal pregnancy is associated with increased perinatal and maternal mortality, 90 times the rate for normal delivery and 7 times the rate for ectopic pregnancy in general (Atrash et al, 1987; Nnadi et al, 2012). The increased maternal mortality which may be as high as 50% (Nnadi et al, 2012; Alto, 1990) is due to massive haemorrhage from partial or total placental separation (Ang et al, 2000) which can occur at any time during pregnancy. The placenta can be attached to the uterine wall, bowel, mesentery, liver, spleen, bladder and ligaments. Other complications include shock, toxemia, anaemia, pulmonary embolism, coagulopathy or disseminated intravascular coagulation and infection.

The greatest risk factors for abdominal pregnancy are the same as for ectopic pregnancy (Sivalingam et al, 2011) and include previous ectopic pregnancy, previous tubal surgery or sterilization, diethylstilboestrol exposure

in utero, documented tubal pathology and use of intrauterine contraceptive device. The greater risk factors include previous genital infection, pelvic inflammatory disease, infertility (in vitro fertilization) and multiple sexual partners. The lesser risk factors include previous pelvic or abdominal surgery, cigarette smoking, vaginal douching and age of first sexual intercourse < 18 years.

Secondary abdominal pregnancy, which commonly results from a tubal abortion, is more common than primary abdominal pregnancy and according to Studdiford (1942), the following conditions meet the criteria for a primary abdominal pregnancy: 1) normal tubes and ovaries, 2) absence of uteroplacental fistula, 3) attachment exclusively to a peritoneal surface early enough in gestation to eliminate the likelihood of secondary implantation. The placenta sits on the intra-abdominal organs, generally the bowel and mesentery, or the the peritoneum and has sufficient blood supply.

The presenting signs and symptoms may include abdominal pain (80-100%), amenorrhea (75-95%), vaginal bleeding (50-80%), dizziness or fainting (20-30%), urge to defecate (5-15%), pregnancy symptoms (10-25%), abdominal tenderness (80-95%), adnexal tenderness (75-90%) and adnexal mass (50%). Severe lower abdominal pain is one of the most consistent findings in abdominal pregnancy (Onan et al, 2005). Vaginal bleeding may occur in 50% of cases (Hallat and Grove, 1985). The cornerstone of diagnosis remains vigilance and critical assessment of these signs and symptoms (Aliyu and Ashimi, 2013).

Diagnostic evaluation

Women with moderate or high-risk factors for extra-uterine pregnancy and those who conceive after in vitro fertilization (IVF) should be evaluated for ectopic gestation as soon as the first missed menses. Identification of intra-uterine pregnancy does not always exclude extra-uterine pregnancy. In heterotopic pregnancy, extra-uterine pregnancy co-exists with intra-uterine pregnancy (Personal Communication, 2014). For example, pregnancies conceived with Assisted Reproductive Technology may be more likely to have heterotopic pregnancies and, here, the incidence of extra-uterine pregnancy may be as high as 1/100 pregnancies.

Transvaginal ultrasound (TVS) is most useful for identifying intra-uterine gestation. Gestation sac is visible at 4.5 to 5 weeks and foetal parts and cardiac activity are first detected at 5.5 to 6 weeks. Extra-uterine pregnancy will be visualized in only 16 to 30% of cases. Findings on ultrasound examination, especially trans-abdominal ultrasound, are sometimes questionable being dependent on the examiner's experience and quality of ultrasound (Yildizhan et al, 2009). Classic ultrasound finding is the absence of myometrial tissue between bladder and

pregnancy. In some cases, diagnosis is not made until laparotomy (Molinaro and Barnhart, 2007).

Absence of intra-uterine gestation sac and beta-human chorionic gonadotropin (b-hCG) concentration above 2,000 iu/L strongly suggests extra-uterine pregnancy. Serum hCG ratios and logistic regression models appear to be better than an absolute single serum hCG level. Majority of cases of ectopic pregnancy will have serial serum hCG levels that increase more slowly than would be expected with an intra-uterine pregnancy or decrease more slowly than would be expected with a failing pregnancy of unknown location (PUL).

Progesterone concentrations are higher in intra-uterine than ectopic pregnancies. Progesterone measurements are useful only to confirm diagnostic impressions already obtained by hCG measurements and transvaginal sonography.

Accurate localization of the placenta pre-operatively can minimize blood loss during surgery by aiding in avoiding incision into the placenta (Martin et al, 1988). Magnetic Resonance Imaging (MRI) provides additional information for patients who need precise diagnosing, such as the precise anatomic relationships of foetal tissues. Non-contrast MRI using T2-weighted imaging is a sensitive, specific and accurate method for evaluating ectopic pregnancy (Yoshigi et al, 2006) but this may not be easily available especially in the developing economies.

Other methods of diagnostic evaluation includes laparoscopy and culdocentesis. Paracentesis abdominis may also help confirm intra-peritoneal haemorrhage. Laparoscopic treatment is used for early abdominal pregnancy (Pisarka et al, 1998). It should be noted that, even, a plain abdominal radiograph may be helpful. It may, in lateral view, reveal over-lapping of maternal spine by foetal parts and maternal intestinal shadows may intermingle with foetal parts in the antero-posterior view (Kassim, 2007).

The use of methotrexate as adjunct in management

The cell-cycle specific antimetabolite, methotrexate, is a folic acid antagonist that binds to the active catalytic site of dihydrofolate reductase thereby interfering with the synthesis of the reduced form that accepts one-carbon units. It thus inhibits the synthesis of DNA, RNA and proteins (Katzung, 2004), especially in actively proliferating cells such as foetal cells and malignant cells. It is rapidly excreted unchanged by the kidneys and up to 90% of an oral dose is excreted in the urine within 12 hours. Folinic acid (leucovorin or citrovorum factor) is used to protect normal cells from methotrexate toxicity which may include mucositis (stomatitis, gastritis, diarrhea), dermatitis, bone marrow depression (with leucopenia and thrombocytopenia), hepatic dysfunction,

pleuritis, reversible alopecia, photosensitivity and pulmonary fibrosis. Methotrexate, even at extremely low doses, can be fatal in patients with renal insufficiency (Kelly et al, 2006). Methotrexate, 50mg/m² or 1mg/kg, either as single-dose or multi-dose protocol, may now be used at all levels of management of ectopic gestation. It is now employed in the medical treatment of ectopic gestation when the gestation sac (ectopic embryonic mass) is less than 3.5 cm. Systemic methotrexate administration resolves ectopic pregnancy in 87% to 95% of cases, maintains tubal patency in 75% to 81%, and results in subsequent successful pregnancy in about 58% to 61% of patients (Ramakrishnan and Scheid, 2006; Gervaise et al, 2004). Pre-operative systemic methotrexate may be used as adjunct to subsequent laparotomy for removal of the foetus and placenta because this approach minimizes blood loss (Gupta et al, 2009) and it is an alternative to pre-operative selective embolisation. Parenteral methotrexate given post-operatively will destroy trophoblastic tissue and accelerate the involution (autolysis) of placenta which normally takes 4 months (France and Jackson, 1980). The combination of methotrexate with the epidermal growth factor receptor antagonist, gefitinib, is a future option (Skubisz et al, 2013). Of all tissues, the placenta expresses the highest levels of epidermal growth factor receptor (Nilsson et al, 2013). The contraindications to the use of methotrexate may include availability of the patient for follow-up, breast-feeding, overt or laboratory evidence of immunodeficiency, alcoholism, liver disease, renal disease or other chronic disease. Others include pre-existing blood dyscrasias, known sensitivity to methotrexate, acute pulmonary disease, peptic ulcer disease. Ectopic embryonic mass > 3.5 cm and embryonic cardiac motility are relative contraindications.

Case Report

A 22-year old jobless nullipara, Miss A. M., presented at Oseghale Oriaifo Medical Centre, Idumebo-Ekpoma, on 14-4-2014 with a 4-month history of amenorrhoea and a 5-day history of lower abdominal pains. She had a gynaecologic history of previous laparotomy for perforated uterus in another part of the country. On examination, she was healthy-looking, not clinically pale and afebrile. The blood pressure was normal at 110 mm/Hg. The lower abdomen felt doughy on palpation with minimal tenderness. On per vaginam examination, it was difficult to properly define a fundal height and there was some adnexal tenderness. PCV was 23%. Abdominal paracentesis was done and it revealed significant intra-peritoneal haemorrhage though the transabdominal ultrasound examination failed to detect a gestation sac separate from the uterus.

She was referred to Irrua Specialist Teaching Hospital's department of Obstetrics and Gynaecology on 15-4-2014 for management. While here, the transvaginal

ultrasound finding was still equivocal. PCV on admission was 22%; WBC count was 8,100/mm³; platelet count was 263,000/mm³. Repeat paracentesis abdominis revealed significant blood which did not clot. In view of this plus the fact the patient was getting haemodynamically unstable with falling blood pressure, exploratory laparotomy was undertaken.

Laparotomy revealed Grade IV pelvic adhesions (frozen pelvis), a macerated male foetus (22 weeks, 6 days gestational age) of weight 0.6 Kg and foul-smelling dark liquor. The placenta was found attached to pelvis/pelvic side-wall on the left. The left ovary was visualized but the right ovary, right and left fallopian tubes were not visualized. Uterus was visualized bound down by adhesions and covered by placenta.

Intramuscular methotrexate (1 mg/kg) was given on days 1, 3, 5 and 7 while leucovorin (0.1 mg/kg) was given on days 2, 4, 6 and 8 (Ramakrishnan and Scheid, 2006). This regimen may lessen the risk of adverse effects which were minimal in this patient. Antibiotics administered were ciprofloxacin, metronidazole and doxycycline. Patient had 4 units of screened and cross-matched blood. Recovery was uneventful. Before discharge for follow-up on 15-5-2014, PCV was 40%, WBC count was 8,600/mm³ and platelet count was 386,000/mm³.

DISCUSSION

Case report illustrates a case of advanced abdominal pregnancy where ultrasound diagnosis was not definitive (Yildizhan et al, 2009) making laparotomy diagnosis imperative (Molinaro and Barnhart, 2007). Abdominal pregnancy remains an enigmatic disease with diagnostic failures even in the best of hands and more so in poor resource settings (Aliyu and Ashimi, 2013; Gaither, 2007). It may be more common in developing countries such as Nigeria (Maas and Stabber, 1995). Recent use of progesterone-only pills and intra-uterine devices with a history of surgery, pelvic inflammatory disease, sexually-transmitted diseases and allergy increase the risk of ectopic pregnancy (Yildizhan et al, 2009). This patient had previous difficult pelvic surgery and the resultant severe pelvic adhesions must have not only increased the risk of the abdominal pregnancy but also helped to hamper better ultrasound resolution. Whether the abdominal pregnancy was primary or secondary could not be determined because of the late stage of presentation.

In this case, placenta was left in situ in order to prevent unnecessary blood loss because removal of the placenta should only be done when the blood supply can be identified and careful ligation performed (Hallat and Grove, 1985). On this contentious issue of how to deal with the placenta, it is now generally advocated that patients should be individualized. The placenta should be

removed only if it is safe to do so, otherwise the patient should be followed for possible complications (Nunyalulendho and Einterz, 2012).

The adjunctive use of methotrexate (combined with leucovorin) to aid placental autolysis could probably have contributed to the uneventful recovery in this patient. By contrast, Mbura and Mgaya (1986) had reported 100% mortality when placentas were not removed. In this patient, the regimen of methotrexate employed did not adversely impact haematologic parameters.

In conclusion, post-operative or post-infective pelvic adhesions remain a risk factor for abdominal pregnancy in Nigeria. Post-operative methotrexate is an agent that accelerates placental autolysis and may contribute to decreasing post-operative morbidity and mortality.

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