

NON-TUBAL ECTOPIC PREGNANCIES IN AHMADU BELLO UNIVERSITY TEACHING HOSPITAL, ZARIA, NIGERIA: A CASE SERIES AND REVIEW OF LITERATURE

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Abstract:

Background: Non-tubal ectopic pregnancy (NTEP) is a rare, often misdiagnosed condition associated with higher maternal morbidity and mortality compared to tubal pregnancy. The incidence of NTEP is increasing with the advent of assisted reproductive techniques and increasing rates of delivery by caesarean section.

Objectives: To review the incidence, types, risk factors, clinical presentation, perioperative management, and outcomes of NTEP at Ahmadu Bello University Teaching Hospital, Zaria.

Methods: Case-notes with the diagnosis of ectopic pregnancy seen between September 2010 and September 2019 were retrieved from the medical records department. Relevant demographic and clinical information were extracted and coded. The coded data were entered and analyzed using SPSS 21. The level of statistical significance was set at <0.05 . Fischer exact test was used to determine any non-random associations between two categorical variables.

Results: NTEP accounted for 4.4% (9/205) of ectopic pregnancies (EP) managed. Abdominal, ovarian, and interstitial pregnancies accounted for 44.4%, 33.3%, and 22.2% of cases respectively. The commonest risk factor was previous pelvic infection (44.4%). Assisted conception and previous EP were each found in only 11.1%. The odds ratio of having an abdominal pregnancy with low parity was $OR=0.5$ (CI: 0.03-8.95) whilst that with interstitial pregnancy was $OR=2.5$ (CI: 0.10-62.60), but this was not statistically significant. Less than 50% presented with the classic triad of EP, and abdominal pain was the commonest presenting complaint. Accurate pre-operative diagnosis using ultrasound was made in only 22.2% of cases. There was no maternal death but two fetal losses occurred in the advanced abdominal pregnancies.

Conclusion: NTEP is often misdiagnosed with 2-D ultrasound. Clinicians should maintain a high index of suspicion especially in women with risk factors for EP.

KEYWORDS: non-tubal pregnancy, ectopic pregnancy, risk factors, maternal morbidity, Nigeria

INTRODUCTION

Non-tubal ectopic pregnancy (NTEP) refers to a pregnancy that implants outside the uterine cavity and fallopian tube.¹ NTEP can be located in the abdomen, cervix, surgical caesarean section scar, ovary, or interstitial portion of the tube.²⁻⁴ NTEP accounts for 5 – 12.7% of ectopic pregnancies (EP).⁵⁻⁷

The risk factors for NTEP are similar to those of tubal EP except for ipsilateral salpingectomy which is a documented risk factor unique to interstitial pregnancy.⁸ They include pelvic infections, previous ectopic pregnancy, use of in vitro fertilization, tubal surgeries including tubal sterilization procedures, smoking, and use of intrauterine contraceptive devices.⁹ The incidence of NTEP is rising due to increasing use of assisted reproductive techniques and increasing rates of caesarean section.¹⁰

The clinical features are often similar to those of tubal EP, whereby patients present with history of missed period, abdominal pain, and vaginal bleeding.¹¹ In addition, it can manifest with haemodynamic instability or with unexplained acute abdomen. Ultrasonography remains the main modality of diagnosis supported by clinical features.¹² However, laparotomy is still of great use in many centres where advanced technologies are sparse.

The management of NTEP may be expectant, medical, surgical, or a combination of these modalities as dictated by the location of the NTEP, patient's clinical condition, availability of advanced technology, and surgeon's experience.¹²

NTEP rarely occurs and it is often overlooked, thus diagnosed late with consequent increase in the risk of maternal morbidity and mortality.¹² A high index of suspicion is therefore needed for early diagnosis to be made, in order to reduce the incidence of adverse outcomes. We therefore set out to review the incidence, types, clinical presentation, perioperative

management and outcomes of NTEP at Ahmadu Bello University Teaching Hospital, Zaria

METHODOLOGY

This was a retrospective study and case-notes of all women with the diagnosis of NTEP between September 2010 and September 2019 were retrieved from the medical records department. Relevant demographic and clinical information were extracted from the case-notes and coded. The coded data were entered and analyzed using IBM SPSS Statistics V21.0. The level of significance was set at <0.05. Fischer exact test was used to determine any non-random associations between two categorical variables. NTEP was defined as an ectopic pregnancy on a site other than the isthmic, ampullary, or fimbrial part of the tube.

RESULTS

There was a total of 205 cases of ectopic pregnancy during the study period, nine of which were NTEP with an incidence of 4.4%. The types of NTEP recorded were abdominal pregnancies (4/9, 44.4%), ovarian pregnancies (3/9, 33.3%), and interstitial pregnancies (2/9, 22.2%). The mean age of women with NTEP was 30.3 ± 4.7 years with the highest incidence among women aged 30-34 years. Only 33.3% of them had tertiary level of education and 44.4% were gainfully employed. The majority of the women were of low parity. Assisted reproductive technique (ART) and previous history of ectopic pregnancy were each reported in only 11.1% of cases. These are shown in Table 1. The types, presentation, risk factors and management are as summarized in Table 2.

Table 1: Socio-demographic characteristics and reproductive profile of women with NTEP

Socio-demographics	Number (%) n = 9	Reproductive profile	Number (%) n = 9
Age (years)		No. of deliveries	
20-24	1(11.1)	0-1	3(33.3)
25-29	2(22.2)	2-4	4(44.4)
30-34	5(55.6)	=5	2(22.2)
35-39	0(0.0)		
40-44	1(11.1)		
Tribe		No. of children alive	
Hausa	6(66.7)	0-2	7(77.8)
'Others'	3(33.3)	>2	2(22.2)
Religion		No. of miscarriage	
Islam	7(77.8)	0	5(55.6)
Christianity	2(22.2)	=1	4(44.4)
Highest educational level		No. of previous ectopic gestation	
Secondary	6(66.7)	0	8(88.9)
Tertiary	3(33.3)	=1	1(11.1)
Gainfully employed		Conception in index pregnancy	
Yes	4(44.4)	Spontaneous	8(88.9)
No	5(55.6)	Assisted	1(11.1)
Place of residence			
Semi-urban	7(77.8)		
Urban	2(22.2)		

Case	Age (years)	Parity	GA at presentation (weeks)	Type of NTEP	Presenting complaint(s)	Risk factor(s)	Ultrasound diagnosis	Type of surgery	Blood loss (ml)	Length of hospital stay (days)
1	23	2 ⁺⁰	5	Abdominal	Vaginal bleeding, Lower abdominal pain	Pelvic infection	Right tubal ectopic gestation	Laparotomy and excision of gestational sac	400	3
2	27	0 ⁺³	5	Ovarian	Vaginal bleeding, Lower abdominal pain	Previous ectopic pregnancy, pelvic infection, pelvic surgery	Right ovarian gestation	Laparotomy and right oophorectomy	600	6
3	28	2 ⁺⁰	6	Ovarian	Amenorrhoea, Vaginal bleeding	Current Implanon use	Right tubal ectopic gestation	Laparotomy and right ovarian resection	800	9
4	30	0 ⁺⁰	24	Abdominal	Amenorrhoea, Lower abdominal pain, Vaginal bleeding	None identified	Partial mole	Exploratory laparotomy, removal of abdominal pregnancy and left salpingo-oophorectomy	2000	12

5	30	3 ⁺	9	Ovarian	Amenorrhoea, Vaginal bleeding, Lower abdominal pain	Use of 50mg of <i>Clomiphene</i> <i>citrate</i> for 10 days	Left ovarian gestation	Laparotomy and left oophorecto my	1500	5
6	30	6 ⁺	30	Abdominal	Amenorrhoea, Lower abdominal pain	None identified	Intrauterine fetal death	Laparotomy with removal of abdominal pregnancy	400	26
7	30	2 ⁺	6	Abdominal	Vaginal bleeding	Pelvic surgery, previous pelvic infection	Right tubal ectopic gestation	Exploratory laparotomy	300	5
8	31	0 ⁺	6	Interstitial	Amenorrhoea, Vaginal bleeding, Lower abdominal pain	Pelvic infection	Right tubal ectopic gestation	Right salpingecto my with cornual resection	3500	6
9	40	8 ⁺	6	Interstitial	Vaginal bleeding, Lower abdominal pain	None identified	Left tubal ectopic gestation	Left salpingecto my with cornual resection	1300	8

Table 2: Summary of NTEP cases

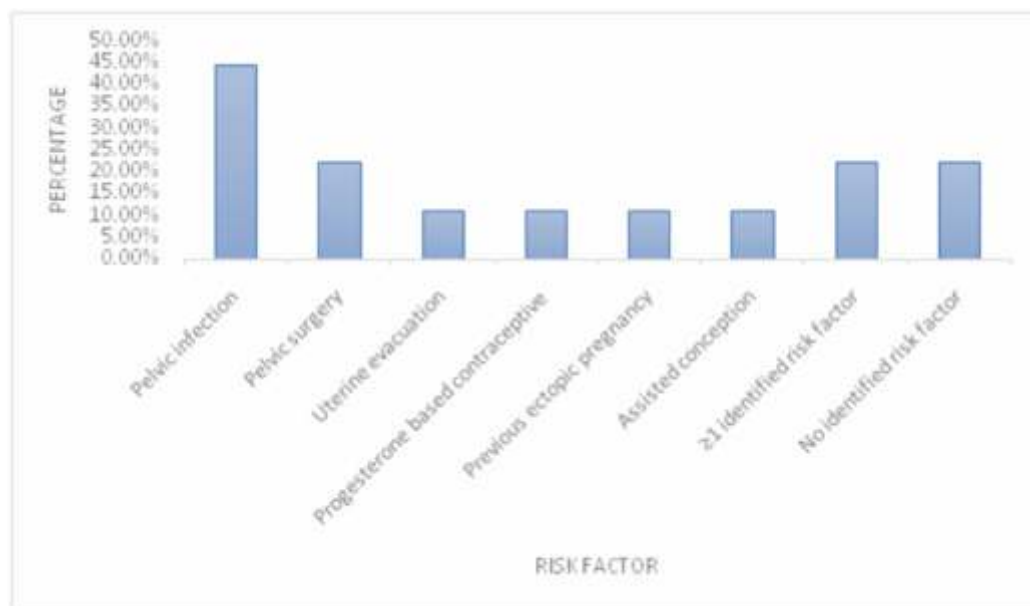


Figure 1: Risk factors in women with NTEP

The most common risk factor identified was previous pelvic infection. Pelvic surgery was reported in only 22.2% of cases. For the three ovarian pregnancies; ART with ovulation induction using 50mg of *Clomiphene citrate* for 10 days, prior ectopic gestations (tubal and ovarian), and current use of Implanon were found to be risk factors. Only 22.2% of cases had no identifiable risk factor. See Figure 1.

The odds ratio of having an abdominal pregnancy with low parity was (OR=0.5; CI 0.03-8.95) whilst that of an interstitial pregnancy with low parity was (OR=2.5; CI 0.10-62.60) but this was not statistically significant as shown in Table 3.

Table 3: Association of parity and NTEP

Parity	Type of NTEP		p-value	Odds ratio	Confidence interval	
	Ovarian n (%)	Non-ovarian n (%)			Upper limit	Lower limit
0-1	1 (11.1)	2 (22.2)	1.00	1.00	0.05	18.91
≥2	2 (22.2)	4 (22.4)		1.00		
	Abdominal	Non-abdominal				
	n (%)	n (%)				
0-1	1 (11.1)	2 (22.2)	0.64	0.5	0.03	18.06
≥2	3 (33.3)	3 (33.3)		1.00		
	Interstitial	Non-interstitial				
	n (%)	n (%)				
0-1	1 (11.1)	2 (22.2)	0.57	2.5	0.10	62.60
≥2	1 (22.2)	5 (55.6)		1.00		

The gestational age (GA) at diagnosis of NTEP ranged between 5 – 30 weeks with a median of 6 weeks. All the ovarian pregnancies presented before eight weeks with a mean GA of 5.3 weeks. The abdominal pregnancies presented at variable GA up to 30 weeks. There were two cases of primary and two cases of secondary abdominal pregnancies. All the interstitial pregnancies presented at 6 weeks' gestation.

Only one-third of the patients presented with the classic triad of amenorrhoea, vaginal bleeding, and abdominal pain. However, abdominal pain was the commonest presenting feature seen in 77.8% of patients (7/9). Though

absence of menses was reported in 55.6% (5/9), all the patients had a positive serum pregnancy test. Accurate pre-operative diagnosis was made in only 22.2% (2/9) of cases, all of which were ovarian pregnancies. Initial differential diagnoses considered included tubal pregnancies (5/9), partial mole (1/9), and intrauterine fetal death (1/9). All the cases had laparotomy. Two-thirds (6 of 9 cases) of the surgeries were performed by senior residents and median intra-operative blood loss was 800mls. The median duration of hospital stay was 6 days (range was 3-26 days). These are shown in Tables 4 and 5.

Table 4: Clinical presentation of NTEP

Symptoms	Frequency (%)
Classic triad*	3(33.3)
Vaginal bleeding only	1(11.1)
Vaginal bleeding and abdominal pain only	3 (33.3)
Amenorrhoea and abdominal pain only	1 (11.1)
Amenorrhoea and vaginal bleeding	1(11.1)

*Classic triad- Amenorrhoea, vaginal bleeding and abdominal pain

Table 5: Peri-operative details of NTEP

Cadre of Surgeon	
Junior resident	1(11.1%)
Senior resident	6(66.7%)
Consultant	2(22.2%)
Cadre of Anaesthetist	
Junior resident	2(22.2%)
Senior resident	7(77.8%)
Consultant	0(0.0)
Mean intraoperative blood loss (mls)	
Abdominal	775
Ovarian	1133
Interstitial	2400

The commonest early post-operative complication was anaemia (Figure 2). There was no maternal death but two fetal deaths occurred in the advanced cases of abdominal pregnancies.

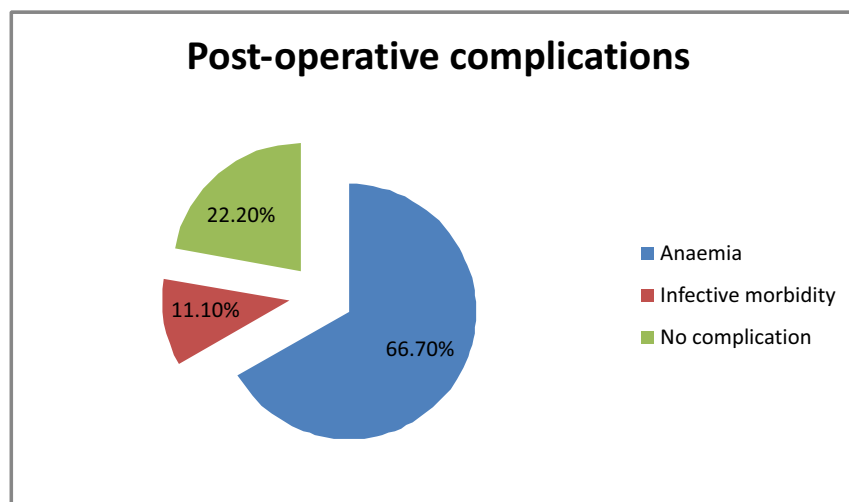


Figure 2: Early post-operative complications in women with NTEP

DISCUSSION:

NTEP accounts for less than 10% of total EP though the overall incidence has recently increased. Cervical pregnancy accounts for less than 1%; caesarean scar pregnancy 6%; interstitial pregnancy 4%; abdominal pregnancy 1.3% and ovarian pregnancy accounts for 0.5% of all EP.¹ The incidence of ovarian pregnancy is increased to 3% of EP among intrauterine device users.¹³ The

incidence of NTEP we found was lower than that reported by other researchers.⁵⁻⁸ It was however similar to findings by Alalade et al¹⁴ and Kirk et al¹⁵. The commonest site of the NTEP in this study was abdominal pregnancy (4 of 9 cases) which differs from findings by Onwuhafua et al⁸ two decades ago in the same centre who found cornual pregnancy to be the commonest NTEP. This also contrasts with findings in other climes that reported

abdominal pregnancy to be the least common NTEP.¹⁰ Igwegbe et al¹⁶ and Lawani et al¹⁷ reported ovarian and interstitial pregnancies to be the commonest NTEP respectively.

The high incidence of NTEP in women aged greater than 30 years is similar to findings in other studies.^{6,14} This finding lends credence to the fact that advancing age has been implicated as a risk factor for ectopic pregnancies (both spontaneous and following ART).¹ Age has also been theorized to affect tubal function, including a delay of oocyte transport.⁶ Thus, with childbearing becoming more common at advanced maternal ages, all of which predispose to the risks of pelvic infections, infertility, and assisted reproductive techniques⁹, EP is increasingly diagnosed.

The majority of the cases occurred in women of low parity which is consistent with findings from other studies in Nigeria.^{7,18} The low percentage of women with tertiary education and gainful employment suggests that these women are likely of low socio-economic status. A low socioeconomic status that is prevalent in developing countries predisposes women to contract sexually transmitted infections and exposure to unsafe abortion; which are known risk factors for EP in general.⁷

Overall, risk factors for NTEP are similar to those for tubal pregnancy. These include the previous history of EP, pelvic infection, in vitro fertilization, and the use of intrauterine device.¹ In this study, the commonest risk factor for NTEP was a previous pelvic infection and this is consistent with findings of Alalade et al.¹⁴ Though ipsilateral salpingectomy is a documented risk factor for interstitial ectopic pregnancy, this was not demonstrated in this study.^{1,6} The ovarian pregnancies in this series had risk factors of ovulation induction with Clomiphene citrate, prior multiple ectopic gestations, and current use of progesterone

implant (Implanon®). This contrasts with reports in the literature where intrauterine devices are a significant risk factor in ovarian pregnancies.^{13, 19, 20} Assisted reproductive techniques have been associated with higher rates of NTEP when compared to other ectopic pregnancies.^{1,21} Though one of the patients with ovarian pregnancy had prolonged use of Clomiphene citrate for 10 days, Dasari et al¹⁹ had reported ovarian pregnancy in a patient who had ovulation induction with clomiphene citrate for five days. A minority of our patients had no identifiable risk factor for NTEP; which is not unusual as some cases of ectopic gestations may not have an identifiable risk factor.⁷

Abdominal pain was the commonest presenting feature and this is consistent with findings from other studies.^{14, 18} Absence of menses was reported in more than half of the patients, but all of them had a positive serum pregnancy test. The classic triad of amenorrhoea, vaginal bleeding, and abdominal pain was seen in only 3 of the 9 cases in this series. This reflects the varied clinical presentation of NTEP thus, a high index of suspicion is needed in order to make an accurate diagnosis.¹

Abdominal pregnancy is largely due to secondary implantation with the primary sites being the tube or ovary. Rare reports of abdominal pregnancy occurring after hysterectomy exist, likely due to the presence of a fistula in the vaginal vault or cervical canal.¹³ Abdominal pregnancy can present with exaggerated pregnancy symptoms, increased fetal movements, and easily palpable fetal parts at later gestation. Diagnosis of abdominal pregnancy is largely clinical with the finding of intact tubes and ovaries without evidence of recent injury; absence of utero-peritoneal fistula and presence of a pregnancy related to the peritoneal surface.¹³ The abdominal pregnancies in this series presented at variable

gestational ages with half of them presenting at ≥ 24 weeks' gestation. This is not an unusual finding as abdominal pregnancies frequently progress to late gestations beyond 20 weeks.^{20,21} All interstitial pregnancies in this series ruptured early (six weeks' gestation) which contrasts with the traditional notion of the surrounding myometrium supporting the pregnancy till later gestational age before it ruptures, but supports the findings of other researchers.^{21,22}

Advances in ultrasonography have improved the detection rates of all ectopic gestations with transvaginal scans having superior detection rates.^{6,10,24} Ultrasound criteria for the diagnosis of interstitial pregnancy are empty uterine cavity; a gestational sac of at least 1cm lateral to the edge of the uterine cavity, a ≤ 5 mm layer of overlying myometrium surrounding the sac and the presence of an interstitial line (an echogenic line between the gestational sac and endometrial cavity).²⁶ Ovarian pregnancy is usually suspected when there is a hypoechogenic area seen surrounded by a wide echogenic ring with peripheral doppler flow; may be surrounded by ovarian cortex and the ovarian pregnancy moves with the ovary when pressure is applied with a transvaginal probe. However, ovarian pregnancy can be difficult to differentiate from some ovarian cysts due to similar ultrasonographic features.¹ Few ultrasound guidelines exist for the diagnosis of abdominal pregnancy; it is however suspected when an extra-uterine gestational sac or fetus and/or placenta is visualized without intervening myometrium seen between the fetus and urinary bladder.¹ All the cases in this series had trans-abdominal ultrasonography, without doppler challenge, and this may account for some of the misdiagnoses. Accurate pre-operative diagnosis using 2D-ultrasound was made in only two-thirds of the ovarian pregnancies. More than half of the NTEP cases were misdiagnosed as tubal ectopic pregnancies despite the availability of ultrasonography in our centre. The other pre-

operative diagnoses in two advanced abdominal pregnancies were partial mole and intrauterine fetal death. This is largely a result of a low level of suspicion at ultrasonography and non-availability of 3D ultrasonography which could have presented clearer imaging thus aiding accurate diagnosis. Evaluation by magnetic resonance imaging (MRI), which is associated with higher detection rates, is currently not readily available in our practice.

The management of NTEP depends on the symptoms at presentation, the location, the size of the gestational sac, and the presence of fetal heart.¹³ Traditionally, NTEP is managed by open surgery, however with early diagnosis now feasible due to advances in ultrasonography, minimal access techniques, adoption of medical and conservative treatments are now possible.²⁷ Surgery is the primary treatment for ovarian, interstitial, and abdominal pregnancies.⁴ All the cases in this series were managed through laparotomy and surgical excision of the pregnancy. This is the main management modality in our centre largely due to late presentation of patients and haemodynamic instability from ruptured gestational sac. These two are significant reasons for non-application of minimal access options for management of EPs in general, despite the unavailability of such technology in our practice as of the time of this review. Open surgical management has been associated with increased morbidity and potential loss of fertility.¹⁰

A dearth of data exists in the medical management of ovarian pregnancy thus treatment is largely surgical. Laparoscopic surgery is the standard approach in haemodynamically stable patients with ovarian pregnancy.¹³

Medical management using systemic or local methotrexate administration is cost-effective whilst maintaining similar success rates and fertility preservation, but is associated with longer hospital stay and risk of rupture.^{6,10,28}

Ultrasound-guided intra-sac injection of Potassium chloride (KCl) or hyperosmolar Glucose and uterine artery embolization has also been reported with success.²⁰ This could not be offered to any of the patients in our series because the majority had ruptured ectopic gestations. Abdominal pregnancy is also largely treated surgically irrespective of gestational age at diagnosis. This is because pregnancy continuation is associated with catastrophic haemorrhage, increased fetal malformation, and perinatal mortality. However, pregnancy continuation for a few weeks to enable fetal lung maturation can only be justified in a few exceptional cases such as those presenting at 30 weeks.¹³ This option could not be offered to the two patients with advanced abdominal pregnancies in this series as fetal demise had already occurred at presentation. The surgical treatment of abdominal pregnancy aims to remove the gestational sac, fetus, placenta, and membranes where possible. However, leaving behind a placenta attached to a vital organ is advocated to prevent catastrophic haemorrhage.¹³ The retained placenta can be allowed to undergo autolysis. Embolization of the retained placenta and/or use of systemic methotrexate or mifepristone can be employed to hasten the resolution of the retained placenta.¹ Reported complications of these include secondary haemorrhage, intestinal obstruction, and infection.

Haemorrhage is a significant contributor to mortality in NTEP. We found a median operative blood loss of 800mls and the commonest postoperative complication encountered was anaemia, but there was no maternal death in our series. The two cases of fetal losses occurred in the advanced abdominal pregnancies and are similar to finding by Huang et al who reported stillbirth at 33 weeks' gestation. Most cases of abdominal ectopic rarely reach term.²⁹

Recurrence risk is not associated with treatment modality.¹ The recurrence rate for interstitial pregnancy is 9.4%.¹ Recurrence of ovarian ectopic

pregnancy was not reported in a 15-year review of women surgically treated for ovarian pregnancy.³⁰

Abdominal pregnancy was the commonest NTEP in our study. NTEP is often misdiagnosed due to low index of suspicion, despite the use of ultrasonography. Thus, clinicians and radiologists should maintain a high index of suspicion especially in women with risk factors for EP.

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