

A twelve year analysis of non-tubal ectopic pregnancies: Do the clinical manifestations and risk factor for these rare pregnancies differ from those of tubal pregnancies?

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Abstract The aim of this study was to analyze the characteristics and peculiarity of non-tubal ectopic (NTE) pregnancy presenting to a major district hospital in London, UK. Data were collected between January 2003 and July 2014. There were 850 cases of ectopic pregnancies (798 tubal pregnancies and 53 NTE pregnancies). Forty-seven of the NTE were included in the study. Data were analyzed using IBM SPSS Statistics 20. Pearson's chi-squared analysis was used to compare statistical significance of the data collected; the level of statistical significance at which the null hypothesis was rejected was chosen as 0.05. The 31–40 year age group had the highest incidence (55 % of the cohort). Thirty-seven percent of NTE were primigravida. Most of the women presented at 6–10 weeks gestation (63 %) with abdominal and vaginal bleeding being the most common presentation in 55 % of cases. When compared with tubal ectopic pregnancy, NTE was more likely to present at later gestation of presentation ($p=0.000$), have history of assisted reproduction ($p=0.041$) and more likely to present with diarrhoea, shoulder-tip pain and syncopal attack as well having a significant amount of haemoperitoneum at surgery compared with tubal ectopic pregnancy. NTE pregnancies are likely to present most commonly at 6–10 weeks and therefore clinicians should have a high index of suspicion when treating any pregnant woman at this gestation. The later presentation of NTE pregnancies may relate to the delay in diagnosis of these rarer ectopic

pregnancies; this may be attributed to the clinician having a level of suspicion that is too low, as the incidence of NTE pregnancies is becoming increasingly common. A combination of a thorough history with the presence of specific risk factors such as a history of assisted conception, pelvic surgery and pelvic inflammatory disease and symptoms such as syncope and an abnormal amount of free fluid behind the empty uterus at ultrasound should make the clinician highly suspicious of a NTE or heterotopic pregnancy.

Keywords Ectopic pregnancy · Gynaecology · Gynaecology surgery · Reproductive medicine

Introduction

Extra-uterine zygote implantation accounts for 2 % of all pregnancies [1]. There has been an increase in the rate of ectopic pregnancy (EP) from 0.5 % in 1970 to 2 % in recent times [1]. Between 95 and 97 % of ectopic pregnancies are tubal whilst the remaining 3–5 % are located outside the fallopian tube. Eighty to 90 % of tubal ectopic pregnancies are located in the ampulla of the fallopian tube, 5–12 % in the isthmus and 5–6 % in the fimbrial end.

NTE pregnancies, which can be located in sites such as intramural (within the serosal lining of the uterus), corneal (also called interstitial), in the endocervical canal, intramyometrial (inside an area of adenomyosis), extramural (outside the serosal lining of the uterus), ovarian or abdominal pregnancies only account for 2 % of ectopic pregnancies.

NTE pregnancies which were previously rare have become more common in recent years with the main reasons attributed to assisted reproductive techniques and increase in caesarean section rates [2]. These pregnancies are more likely to result in adverse outcome because of the reported atypical presentation

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[3] and/or lack of recognition by healthcare professionals. Thus, early diagnosis of NTE pregnancy is the key to effective management. This objective however remains extremely challenging despite recent advances in imaging modalities, with advice on diagnosis and management being based on literature reviews of case reports and case series with only small numbers of patients. The aim of this study was to review a large cohort of NTE pregnancies in a London university hospital over a 12-year period.

Methods

Data were collected between January 2003 and July 2014. During this time period, there were 850 cases of ectopic pregnancies (798 tubal pregnancies and 53 NTE pregnancies). Fifty-two out of the 53 NTE pregnancies were managed surgically; six out of the 53 cases had insufficient data for analyses and were therefore excluded leaving 47 cases for inclusion in the study. All patients were clinically assessed with a detailed clinical history and physical examination. Investigations used to aid management include transvaginal ultrasound, urine and serum beta human chorionic gonadotropin (BHCG). All cases included in this study were managed surgically. Data were analysed using IBM SPSS Statistics 20. Pearson's chi-squared analysis was used to compare statistical significance of the data collected. The level of statistical significance at which the null hypothesis was rejected was chosen as 0.05.

Results

Comparison of the different types of NTE pregnancies

Incidence

Of the 53 NTE pregnancies, 47 of the 53 had complete data suitable for analysis. The sites of implantation are listed in Table 1. The mean maternal age on diagnosis was 31.28 years (19–42). The 31–40-year age group has the highest incidence with 55 % of the cohort in this age group.

Risk factors

Of the 47 non-tubal EP, 37 % were primigravida and others reported previous pregnancies, of which only two reported a previous EP. Ten percent of cases had history of previous pelvic surgery. Five women reported a previous history of pelvic inflammatory disease, all of which were diagnosed as cornual EP. Only five women underwent in vitro fertilisation (IVF).

Gestation

Most of the women presented at 6–10 weeks gestation (63 %). Figure 1 shows the distribution of the site of implantation in relation to gestation. Data were missing in one patient.

Clinical presentation

Table 2 shows the varied clinical presentations of women with non-tubal EP, which includes abdominal pain and bleeding per vaginam (PV bleeding) (55 %), abdominal pain only (32 %) and PV bleeding only (4 %).

Comparison of NTE with tubal ectopic pregnancies

The tables below describe the comparison between the tubal and non-tubal ectopic pregnancies.

Baseline characteristics

The above table demonstrates the comparison of the baseline characteristics of women presenting with tubal ectopic pregnancy compared with NTE pregnancy. There is a statistically significant difference at the gestation of presentation of the pregnancy between the tubal and non-tubal ectopics ($p=0.000$)

Risk factors

Table 3 compares the risk factors in both groups. Results show that assisted reproduction confers a statistically significant increased risk of having a non-tubal presentation ($p=0.041$). All the other risk factors analysed were not statistically significant which could be a function of the small numbers.

Clinical presentation

Presentation of ectopic pregnancies whether tubal or NTE pregnancies has similar clinical manifestations as they always present after a short period of amenorrhea and then may present with pain with or without bleeding, shoulder tip pain, cervical excitation and occasionally with a palpable mass. It was noted in our study that there is a differentiation between the way that NTE pregnancies and tubal ectopic pregnancies present (Table 4).

Analysis of clinical presentation shows that tubal ectopic pregnancies present with significantly more pain and bleeding. Alternatively, diarrhoea, shoulder-tip pain and syncopal attack indicate a statistically significant risk of NTE implantation.

The fact that the patient with a NTE pregnancy is more likely to present with shoulder-tip pain and syncopal attack is most likely due to the fact that NTE pregnancies are at a

Table 1 Site of NTE pregnancy versus age at presentation, in percentage

		Site				
		Ovarian	Cornual	Caesarean section	Rudimentary horn	Heterotopic
Age (years)	11–20	5.9 %	3.8 %	0	0	0
	21–30	35.3 %	38.5 %	0	100 %	100 %
	31–40	58.8 %	53.8 %	100 %	0	0
	41–50	0	3.8 %	0	0	0

higher risk of rupturing/creating a haemoperitoneum and therefore cause symptoms associated with peritoneal irritation and hypovolaemia; ovarian pregnancies are very vascular and often present with a haematoperitoneum.

Operative findings

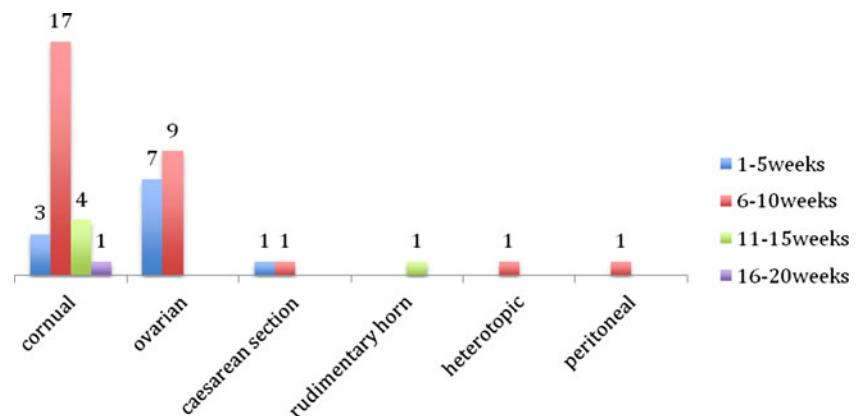
The above results show that tubal and NTE pregnancies differ intraoperatively only in the volume of haemoperitoneum present, with non-tubal implantations having a higher significant amount of haemoperitoneum (Table 5).

Ultrasound scan finding

These results reiterate the difficulty in the diagnosis of the exact site of implantation. There were no statistically significant differences in the scan findings between the two groups.

Interestingly, the caesarean section scar NTE pregnancies had an ultrasound appearance of an empty uterus and cervical canal, with one of these unusual NTE pregnancies having ultrasound features demonstrating an absence of myometrium between the bladder wall and the gestational sac.

The ultrasound findings for cornual pregnancies were rather specific and correlate with literature; the gestational sac had a myometrial mantle surrounding only a portion of it and ‘interstitial lines’ [1] (an echogenic line from the mass to the endometrial echo complex) was noted in 100 % of cornual ectopic pregnancies [4].

Fig. 1 Site of implantation and gestation at presentation of non-tubal EP

In the tubal pregnancies, it was noted that the uterus was empty in 91.1 % of the cases; where the uterus wasn't empty, it was noted that there was ultrasound findings of echogenic material or a normal appearance of a gestational sac (Table 6) (Table 7).

Haemoperitoneum

Again, as described in Table 5, tubal and NTE pregnancies differ intraoperatively only in the amount of haemoperitoneum, with non-tubal implantations having a higher significant amount of haemoperitoneum. Interestingly, the volume of haemoperitoneum more than 800 mls is significantly different between the two groups.

Discussion

Incidence and related factors

The incidence of NTE pregnancy in our study was 6.2 %, which is consistent with that reported in literature which is 4.9 to 10.1 % [5]. The commonest location of NTE pregnancy in our study was the uterine cornua.

Cornual pregnancy, the most common site of NTE pregnancy in our study, accounted for 55 % of extra-tubal pregnancies and 3 % of all ectopic pregnancies; this is higher than other studies, which have reported the incidence of cornual ectopics to be 2.5 % of all ectopic pregnancies [6]. Cornual

Table 2 Clinical presentation of women with NTE pregnancy

Clinical presentation	Site					Total
	Ovary	Cornual	Caesarean section	Rudimentary horn	Heterotropic	
Abdominal pain	8	6	1	0	0	15
PV bleeding	1	1	0	0	0	2
Abdominal pain and PV bleeding	7	17	1	1	0	26
Shoulder tip pain	1	0	0	0	0	1
Asymptomatic	0	1	0	0	1	2
Multiple symptoms	0	1	0	0	0	1
Total	17	26	2	1	1	47

pregnancy, like the other NTE pregnancies in our case series, presented most commonly between 6 to 10 weeks gestation. They were significantly more likely to present later than tubal ectopic pregnancy.

Our case series demonstrates that the most common age groups for all NTE pregnancies are between the ages of 31–40 years with 92 % of tubal pregnancies and 93 % of NTE pregnancies occurring in these age groups. This could indeed be because the older age groups have been exposed to more risk factors such as assisted conception that are associated with extra-uterine pregnancies. However, in up to half of ectopic pregnancies no known risk factors are identified [5], it is unclear whether the similarity in age of presentation of NTE and tubal ectopic is significant as the number of NTE pregnancies analysed was of course lower due to their lower prevalence. However, it should be noted that childbearing at advanced maternal age is becoming increasingly common and the average age of childbearing has increased steadily to 29.5 years of age; this corresponds to a rise in the proportion of women delivering in their 30s and 40s [7]; hence, pregnancy per se is more likely at a more advanced maternal age and therefore could account for ectopic pregnancies being more prevalent in the older age groups. Ectopic pregnancies below the age of 20 years were rare in both tubal and NTE pregnancies (with an incidence of 2 and 4 %, respectively). This is perhaps surprising when it is has recently been acknowledged

that 15–19 year olds have the highest prevalence of sexually transmitted diseases of all the age groups [4]. However, it is recognised that perhaps this age group has not yet been exposed to the other risk factors that are known to increase the likelihood of an extra-uterine pregnancy, such as previous pelvic surgery, infertility, citing of an IUD and previous ectopic pregnancy [2].

Both NTE and tubal ectopic pregnancies were most likely to present between 6 and 10 weeks of gestation with 61 and 68 % of these pregnancies presenting at this gestation, respectively. There was no significance between the two groups irrespective of the gestation at presentation ($p=0.062$; $CI=-1.125-0.027$).

The later presentation of ectopic pregnancies per se and specifically of NTE may relate to the delay in diagnosis of these rarer ectopic pregnancies; this may be attributed to the clinician having a level of suspicion that is too low, as the incidence of NTE pregnancies is becoming increasingly common.

There was only one extra-uterine pregnancy that presented at a gestation of greater than 15 weeks, and this pregnancy was a NTE pregnancy; it was localised to the accessory horn of the uterus. This patient presented haemodynamically unstable and was taken to theatre within 1.5 h of presentation.

Previous research has highlighted many risk factors for ectopic pregnancy including previous ectopic pregnancy,

Table 3 Comparison of baseline characteristics of women with ectopic pregnancy (EP)

	Tubal ectopic	Non tubal ectopic		Mean difference or odds ratio
	Mean \pm SD (<i>n</i>) or % (<i>n</i>)	Mean \pm SD (<i>n</i>) or % (<i>n</i>)	<i>p</i> value	
Age	30.64 \pm 5.784 (793)	31.15 \pm 5.785 (46)	0.558	-0.514
Gestation	6.32 \pm 1.866 (736)	6.87 \pm 2.975 (47)	0.000	-0.55
P0	44.4 % (344)	35.6 % (16)		
P1–P3	51.7 % (401)	57.8 % (26)	0.435	
P4 or more	3.9 % (30)	6.7 % (3)		

Table 4 Comparison of risk factors in both groups

	Tubal ectopic % (n)	Non-tubal ectopic % (n)	p value	Likelihood ratio
Smoking	15.7 % (123)	6.4 % (3)	0.095	3.629
Previous ectopic	11.3 % (89)	4.3 % (2)	0.154	2.845
Previous pelvic surgery	18.8 % (148)	10.6 % (5)	0.180	0.136
Previous miscarriage	23.8 % (187)	36.2 % (17)	0.057	3.404
Previous TOP	18.1 % (143)	21.3 % (10)	0.698	0.280
Assisted reproduction	3.8 % (30)	10.6 % (5)	0.041	3.761
Previous infertility	8.0 % (63)	12.8 % (6)	0.269	1.168
Previous PID	7.6 % (60)	10.6 % (5)	0.573	0.507
PO pill	2.3 % (18)	0 % (0)	0.424	2.109
Post coital pill	1.1 % (8)	0.0 % (0)	0.679	1.050
COC pill	4.2 % (33)	4.3 % (2)	1.000	0
IUCD	1.1 % (9)	2.1 % (1)	1.000	0.300
Mirena coil	0.9 % (7)	0.0 % (0)	1.000	0.815
Condoms	3.9 % (31)	4.3 % (2)	1.000	0.019

pelvic inflammatory disease, previous abdominal surgery, the use of IUD and certain lifestyle factors such as smoking [8]. In our series, it was noted that a history of pelvic inflammatory disease was a significant risk factor for cornual pregnancy with all of the patients that had a history of pelvic inflammatory disease (PID) having a cornual NTE pregnancy unlike other atypical ectopic pregnancies where PID was not a risk factor.

The use of an intrauterine device (IUD) has been reported in literature to be associated with ovarian pregnancy [9] as an IUD is thought to change the pathophysiological environment of the ovary [10]. Although having an IUD in situ does not increase the risk of an ectopic pregnancy per se, a pregnancy with an IUD in situ is more often an ectopic one than a pregnancy with no IUD [7]; our study confirmed that this is more likely to be an NTE ectopic as opposed to a tubal ectopic pregnancy (0.300 likelihood ratio of NTE pregnancy versus tubal pregnancy), there was no specific association with an ovarian pregnancy. There was a statistical association between NTE and assisted conception ($p=0.041$). Our results revealed no statistical significance with smoking, previous ectopic, previous tubal surgery, previous miscarriage, previous

termination of pregnancy and previous pelvic surgery. There was no statistical association with contraception used, i.e. morning after pill, combined oral contraception, progesterone only pill, intrauterine contraceptive device and mirena coil between the two groups, i.e. non-tubal and tubal ectopic.

It is interesting to note that our results only highlight that assisted conception predisposes to NTE pregnancy versus tubal pregnancy. Other risk factors, such as pelvic inflammatory disease, have been documented to have a significant association with NTE pregnancies [3] with up to 44.8 % of NTE pregnancies documented to be associated with PID [3]; the likelihood ratio of tubal versus NTE pregnancies being associated with PID being 0.507.

Our data did not suggest that these previously documented risk factors, such as PID, particularly predispose to a tubal or NTE pregnancy; this may be related to the limited number of positive cases within our data set in the NTE pregnancy group; for example in terms of a previous history of pelvic inflammatory disease, there were only a total of five women with this history recorded (all of which were diagnosed with a cornual ectopic pregnancy).

Table 5 Describes clinical presentation of women with tubal and NTE pregnancies

	Tubal ectopic % (n)	Non-tubal ectopic % (n)	p value	Likelihood ratio
Pain	94.7 % (748)	87.2 % (41)	0.046	3.508
Bleeding	85.6 % (676)	66.0 % (31)	<0.001	10.52
Vomiting	9.1 % (72)	17.0 % (8)	0.118	2.698
Diarrhoea	1.4 % (11)	6.4 % (3)	0.039	4.115
Shoulder tip pain	8.5 % (67)	29.8 % (14)	<0.001	16.176
Syncopal attack	9.9 % (78)	23.4 % (11)	0.012	6.744

Table 6 Illustrates findings at surgery between NTE and tubal ectopic pregnancies

	Tubal ectopic % (n) or mean ± SD	Non-tubal ectopic % (n) or mean ± SD	<i>p</i> value
Presence of hepatic adhesions	7.7 % (58)	14.9 % (7)	0.094
Volume of haemoperitoneum (mls)	440.48+/-726.248	874.89+/-1300.333	0.028
Contralateral pathology	4.2 % (33)	2.7 % (2)	0.0974
Laparotomy	4.2 % (33)	4.3 % (2)	0.595

Italicize entries demonstrates a significant difference

Clinical manifestation

Over half of the patients with NTE pregnancies presented with a combination of abdominal pain and vaginal bleeding. Abdominal pain and vaginal bleeding are the most common presentation of ectopic pregnancy [11]; vaginal bleeding due to a decrease in progesterone levels and abdominal pain due to irritation to the parietal peritoneum.

Our series demonstrated that clinical presentation of extra-uterine pregnancy in both groups (non-tubal and tubal pregnancy) was dominated by complaints of abdominal pain and vaginal bleeding. Abdominal pain was the most common presenting clinical feature in both groups with a significant proportion of tubal and NTE pregnancy presenting with this complaint; however, patients with tubal ectopic pregnancy were more likely to present with abdominal pain ($p=0.046$). Although vaginal bleeding was a common presentation of extra-uterine pregnancies in 66 % of cases, this symptom was more significant in tubal ectopic pregnancies ($p<0.001$). Patients with tubal ectopic pregnancies were significantly more likely to experience shoulder tip pain than those with NTE pregnancies ($p<0.001$). NTE pregnancies were more likely to present with syncope ($p=0.012$) and are more likely to present with a haematoperitoneum ($p=0.028$); the largest in this group of patients being 6000 ml. This could be due to the vascular areas of implantation that these pregnancies implant.

Table 7 Describes a comparison of the ultrasound scan findings between NTE and tubal ectopic pregnancies

	Tubal ectopic	Non-tubal ectopic	<i>p</i> value
	% (n)	% (n)	
Adnexal mass	88.4 % (685)	79.5 % (35)	0.072
Gest sac	20.6 % (160)	22.2 % (10)	0.458
FH present	9.4 % (72)	8.9 % (4)	0.585
PoD fluid	75.6 % (588)	66.7 % (30)	0.123
Empty uterus	91.1 % (707)	100.0 % (47)	0.027

Diarrhoea was also an important symptom in this group of patients ($p=0.039$).

It is postulated that ovarian pregnancy rarely presents with vaginal bleeding [12]; this is indeed confirmed by our cohort with only one ovarian pregnancy noted to have vaginal bleeding on presentation. Instead, due to the highly vascular nature of the ovary, it more commonly presents with shoulder tip pain and circulatory collapse [12]. This was confirmed in our cohort with a significant proportion of NTE pregnancies having presenting symptoms indicative of a haemoperitoneum.

Ultrasonography

Ultrasonography remains the main investigation in the diagnosis of ectopic pregnancy [1]. It is standard practice to offer women transvaginal ultrasound scan across early pregnancy, and emergency transabdominal scans are used in ladies who refuse a transvaginal scan or in cases of haemodynamically compromised [13]. The image modality most frequently used in our study was transvaginal sonography. Our study revealed in cases where patients only had transabdominal scans, it is more likely to diagnose a NTE pregnancy compared with transvaginal scans ($p=0.015$). The use of both scanning modalities does not necessarily improve diagnosis in either group of patients.

Treatment and prognosis

NTE pregnancy has been traditionally diagnosed late and is associated with a high morbidity and mortality [6]. Out of our 47 NTE pregnancies treated within our centre, there was no mortality directly related to these ectopic pregnancies. One of the two cases of caesarean section scar ectopic pregnancy was initially managed medically with methotrexate.

It has been suggested that cornual pregnancies can be managed conservatively, medically, or surgically with the majority being managed by hysterectomy or cornual resection laparoscopically [6]. All of the cornual pregnancies in our study were managed surgically with either a wedge resection or a cornual resection; there was one cornuostomy performed.

Ovarian tissue is rich in vessels, and when an ovary is ruptured severe abdominal haemorrhage, secondary anaemia or shock can occur [5]. As the outcome of an ovarian pregnancy is dangerous, it is no surprise that all of the ovarian ectopic pregnancies were managed surgically in our cohort of patients. Traditionally, an explorative laparotomy was performed, and once the ovarian pregnancy was identified, an oophorectomy or salpingo-oophorectomy was performed, including the removal of the pregnancy. Today, the surgery can often be performed via laparoscopy [10], and in our cohort of patients, 93 % underwent laparoscopic management of their ovarian ectopic pregnancies. The extent of surgery varied

according to the amount of tissue destruction that has occurred. In stable patients, attempts were made to preserve ovarian tissue, and in 12.5 % of patients, surgery only involved the removal of the pregnancy with only a part of the ovary [10]. This was accomplished by an ovarian wedge resection; this has a good prognosis for future fertility and therefore conservative surgical management is advocated

None of our patients presenting with ovarian pregnancies were stable enough to manage medically. Ovarian pregnancies have been successfully treated with methotrexate [14], since it was introduced in the management of ectopic pregnancy in 1988.

The ovarian pregnancies had the most significant morbidity associated with them with a significant number of ovarian pregnancies associated with a haematoperitoneum.

Conclusion

Ectopic pregnancies carry a high morbidity and mortality, and so every clinician should consider them as a differential diagnosis when treating any woman in early pregnancy. The clinician should consider that both tubal and NTE pregnancies are likely to present most commonly at 6–10 weeks and therefore should have a high index of suspicion when treating any pregnant woman at this gestation.

Although NTE pregnancies are hard to diagnose, the combination of a thorough history and the presence of specific risk factors such as a history of pelvic surgery and pelvic inflammatory disease should make the clinician highly suspicious of an NTE pregnancy [1]. Clinical presentation of NTE pregnancies and tubal pregnancies is similar with vaginal bleeding and abdominal pain being the most common presentation [11].

Ultrasound is gold standard for the diagnosis of a pregnancy of unknown location [15], and 85 % of the NTE pregnancies were seen on transvaginal ultrasound, with beta HCG serial measurement being a useful adjunct in the diagnosis of all ectopic pregnancies. Surgery was the most common method of treating NTE pregnancy and is an effective treatment option.

NTE pregnancies need to be considered when investigating and managing any pregnant woman; although they are rare, with the rise in incidence of sexually transmitted infection and indeed in vitro fertilisation, the prevalence of NTE pregnancy will raise. The clinician needs to have a high index of suspicion for these unusual ectopics to reduce the mortality and morbidity associated with these emergency cases.

Compliance with ethical standards This article does not contain any studies with the human participants or animals performed by any of the authors.

Conflict of interest We declare that none of the authors have a conflict of interest.

Authors' contribution Alalade contributed in project development, data collection, data analysis, manuscript writing and editing.

Mayers contributed in data analysis and manuscript writing.

Abdulrahman contributed in data analysis and manuscript writing.

Oliver contributed in data collection and data analysis.

Odejinmi contributed in project development, data collection, manuscript writing and editing.

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