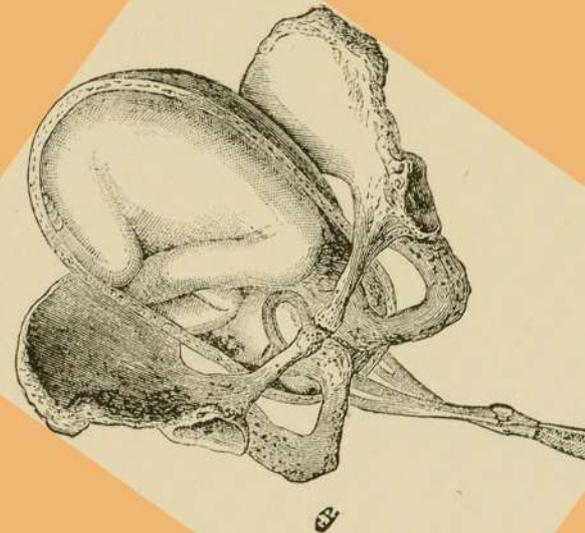
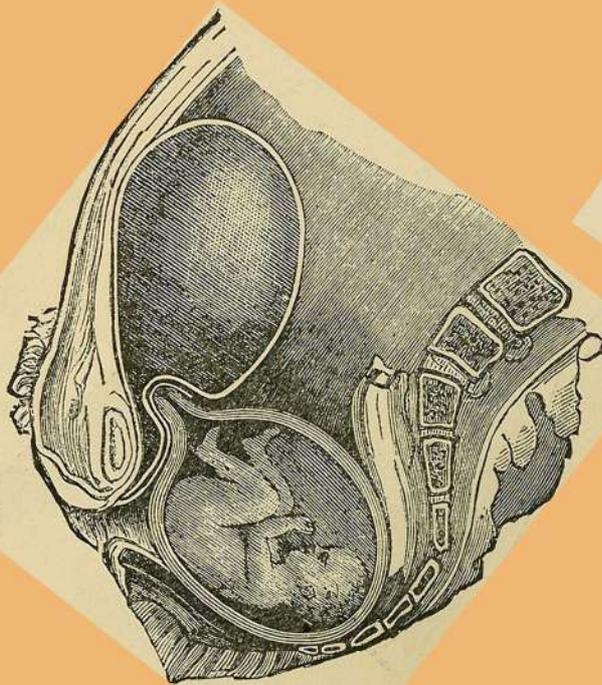


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Original Research

Prevalence of Anaemia among Pregnant Women Attending 82 Division Nigerian Army Hospitals, Enugu

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ABSTRACT

Introduction

Anaemia is the most common hematologic abnormality diagnosed in pregnancy. It continues to be a major health problem in many developing countries and is associated with increased rates of maternal and perinatal morbidity and mortality.

Material and Methods

This is a retrospective study of 400 pregnant women who attended antenatal care at the 82 division Nigerian army hospital, Enugu State, Nigeria. Their antenatal case records were retrieved from the records department and the antenatal records unit of the hospital. All the relevant information were retrieved and analyzed.

Result

Using the World Health Organization (WHO) criterion of packed red cells (PCV) < 33% to define Anaemia in pregnancy, a number of our pregnant women at booking, 184 (46%) were anemic at booking with 152 (38%) being mildly anemic, 24 (4%) moderately anemic, while 8 (2%) pregnant woman presented severe Anaemia.

Conclusion

Anaemia in pregnancy has an unacceptably high prevalence in our pregnant population at booking, and all efforts must be made to correct this widespread problem as early as possible using the most appropriate and expeditious means to avoid preventable calamities.

Keywords

Anaemia; Pregnancy; Antenatal; Mortality.

INTRODUCTION

The World Health Organization (WHO)¹ defined Anaemia as a haematologic condition and a sign of an underlying disorder characterized by a reduction in the number of red blood cells, or a reduction in the concentration of haemoglobin in the blood stream to a level below 10.5 g/dL. Anaemia has also been defined as a reduction below normal in the number of red corpuscles per cubic millimeter, the quantity of haemoglobin and the volume of packed red cells per 100 ml of blood as a result of impaired erythrocyte production or increased erythrocyte loss which leads to impaired tissue perfusion.² The causes of anaemia according to WHO includes the following; pregnancy and child birth, repeated infections (malaria, hookworm), poor feeding due

to socioeconomic factors (poverty and low educational status) and haematologic conditions such as impaired erythrocyte production or increased erythrocyte loss.³ Malaria in pregnancy is one of the predominant causes of anaemia in pregnancy.⁴ Malaria accounted for more than 56% anaemic cases in pregnancy in Nigeria.⁵ Forty per cent of all maternal peri-natal deaths are linked to anaemia. Favourable pregnancy outcomes occur (30%-45%) less often in anaemic mothers and their infants have less than one and a half of normal iron reserves.⁶ Anaemia is a common problem worldwide and poses a great challenge to both health workers and governments due to its attendant consequences on health and socioeconomic indices. These indices reflect the quality of life of citizens of a nation.⁷ Anaemia in pregnancy poses a great danger to both mother and child.⁸ WHO⁹ report estimates that 35% to 80% of

pregnant women in developing countries are anaemic: notably, in Nigeria (60% pregnant women are anaemic), Tanzania (86% pregnant women have iron deficiency anaemia and 1/3 of the anaemic women had malaria), Coastal Kenya (75.6% are anaemic while 9.8% are severely anaemic). Also a WHO study in Guinea during 2000-2006 revealed that 58% of pregnant women who died during child birth were anaemic while a small percentage (18%) of the pregnant women from industrialized countries is anaemic.

In Nigeria, studies carried out by various groups have shown varying results. For instance, a study done by Esike et al¹⁰ at the University Teaching Hospital Abakaliki, Ebonyi State, revealed that anaemia in pregnancy has a prevalence rate of 56% out of a population of 3,400 women who attended antenatal clinic at the hospital that year. The study also revealed that out of the 1,904 (56%) cases of severe anaemia having haemoglobin level less than 10.5 g/dL, 1,850 women responded to treatment with oral and parenteral haematinics while the remaining 54 women required blood transfusion. Unfortunately 2 women developed complications (pre-mature labour and still birth at 2nd and 1st trimester of pregnancy respectively).

MATERIALS AND METHODS

Study Area

This cross-sectional study was carried out in the antenatal clinic of at 82 division Nigerian army hospital, Enugu This is one of military health facility in Enugu State and is situated in the South-East geopolitical zone of Nigeria. Enugu, the capital city, is located in the tropical rain forest belt of Nigeria with an annual temperature of 26.3 °C and average rainfall of 1730 mm annual rainfall of 2430.0 mm. However, there is a dry season from November to April when monthly rainfall is low. The military hospital serves both the military personnel within the barracks and civilian populace and is strategically located within the city center. The hospital can be easily accessed from every part of the city.

Estimation of Sample Size

Average prevalence of anaemia in pregnancy in developing countries including Nigeria is put at 60.0%.^{11,12} The estimate from this study was desired to be within five percent of the actual prevalence with 95 percent confidence level. The sample size was calculated using the Kish Leslie formula for cross-sectional studies.¹³

$$n = \frac{Z^2 Pq}{d^2}$$

Where n is the desired sample size and Z is the standard normal deviate usually set at 1.96, which corresponds to the 95% confidence interval. P is the proportion of pregnant women with anaemia, which is 60.0%. q is complementary proportion equivalent to one minus; that is, 1-0.6 equal to 0.4. d is the degree of accuracy desired (absolute precision), which is 5.0% (0.05).

Thus;

$$n = \frac{(1.96 \times 1.96 \times 0.6(1-0.6))}{0.05^2} \rightarrow \frac{0.92194}{0.0025} \rightarrow 369$$

Hence about 369 subjects were needed for the study. Since follow-up was not needed in the study, attrition rate was not necessary. However, there was a deliberate increase in sampling size to 400.

Inclusion Criteria

Every pregnant woman attending the weekly antenatal clinic of the hospital is recruited into the study.

Exclusion Criteria

Those excluded were pregnant women at their follow-up antenatal visit and those who had received blood transfusions in the index pregnancy or were already receiving treatment for anaemia in pregnancy before their booking visit.

Data Collection

Data were collected over a period of study (September 2016 to May 2017); during that time 400 pregnant women were recruited at their first antenatal visit. The women were interviewed with copies of a structured questionnaire. The following information was recorded: maternal age, parity, gestational age, last child birth, last menstrual period, level of education and occupation of the women and their husband, history of fever in the index pregnancy, presence of any chronic illnesses, and history of vaginal bleeding in present pregnancy.

Packed cell volume (PCV) was done for each woman at the time of recruitment. From each of the recruited woman, 5ml of venous blood was collected from the antecubital vein using plastic disposable syringes into sample bottles containing Ethylenediamine-tetraacetic acid (EDTA).

Packed Cell Volume Estimation

Two capillary tubes labeled for each subject were filled with blood to about 2/3 of the length of each tube and one end of each of these tubes was then sealed with plasticin. This was to ensure that the average of the two values obtained was used for calculation. Several labeled samples were assembled in the centrifuge (haematocrit machine) and spun at 5000 revolutions per minute for 5 minutes. When the machine rotated to a halt, the cover was opened, the capillary tubes removed, and the PCV was read from a Hawksley microhaematocrit reader.

RESULTS AND DISCUSSION

Anaemia and iron deficiency related to pregnancy remain a major health problem especially in Africa. The diagnosis of anaemia dur-

ing booking among pregnant women is essential as it affords one the opportunity to institute interventions to prevent the complication of anaemia especially considering the prevalent high maternal and perinatal morbidity and mortality associated with anaemia in pregnancy in the tropics.¹⁴ Data from the literature in developing countries have reported prevalence of anaemia in pregnancy that ranged from 35.0% to 75.0%.¹⁵

Table 1. The PCV Range of Pregnant Women and their Percentage Occurrence (n=400)

PCV range (%)	Frequency (n)	Percentage (%)
<19	8	2
19-26	152	38
27-33	24	6
≥34	216	54

PCV Ranges: Normal (PCV≥34%), Mild (PCV 33-27%), moderate (PCV 19-26%), and severe (PCV below 19%)¹⁴

Results from the present study showed that the mean age of the women was 28.46±4.81 with a range of 18 to 38 years with a standard error of 0.68. The mean PCV was 33.32±4.51 with a range of 15% to 41%. The severity of Anaemia was classified as follows: mild (PCV 33%-29%), moderate (PCV 19-26%), and severe (PCV below 19%).¹⁴ Results from the tables above shows that of the 400 samples analyzed, 184(46%) were anemic. The finding in our study correlates with the estimated global prevalence rate of Anaemia in pregnancy is in the range of 40%-60%.¹⁶ The prevalence of Anaemia in this study is slightly lower than the 56.0% quoted by WHO for prevalence of anaemia in Africa based on the 1988 data¹⁷ implying that even after 29 years; the situation has only marginally improved. The 46% prevalence of Anaemia reported in this study is slightly higher than the value of 40.4% reported by Dim and Onah¹⁸ working in the same city earlier a decade ago but higher than the 56% reported in 2016 by Esike et al¹⁰ working in nearby Abakaliki all in the same south east region of Nigeria. It is however slightly different from the rate of 35.3% reported by Anorlu et al¹³ working in the south west region, 51.8% reported by Bukar et al¹⁹ working in northern Nigerian, 43.5% reported by Bassi et al²⁰ working in the North Central and 31.8% by Olatunbosun et al²¹ working in the South Region of the country. However, this is not comparable to the cross sectional survey conducted in four Nigerian States (Jigawa, Katsina, Yobe, Zamfara) where the prevalence rate of anaemia was estimated to be 61.2%-88.7%.²² The significant difference in the prevalence rate may be attributed to relatively higher utilization of iron-folic acid supplementation amongst the women in this study. The high prevalence of anaemia in this study is probably related to the low socioeconomic status of the women, which may have impact on their nutritional status and health seeking behavior.^{12,13} When the WHO⁹ criterion for the diagnosis of Anaemia in pregnancy, i.e. hemoglobin <11.0 g/dL (PCV<33%) is applied, 46% of the women were anemic. A range of 35%-75% has been reported for developing countries.^{15,23} The definition of what constitutes Anaemia in pregnancy has been the subject of lively debate for several years. If this definition were to be applied in Nigeria, more than two thirds of women attending antenatal clinics in the country will require to be investigated for Anaemia.¹⁵ In practice, it has been found that a large number of

pregnant Nigerian women with hematocrit values between 30% and 33% get through pregnancy without any apparent ill effects to themselves or their offspring. Thus, in practice, only Anaemia with hematocrit lower than 30% is deemed worthy of further investigation and treatment in this environment (Table 1).¹⁵

While most cases of Anaemia were either mild or moderate, some women still presented with severe Anaemia. Expectedly, of the 184(46%) anemic pregnant women from the present study, 152/184(82.61%) of the anemic pregnant women presented mild Anaemia, which was similar with most reports within the country. The study also showed that 24/184(13.04%) of the anemic women had moderate, while 8/184(4.35%) anemic pregnant woman presented severe Anaemia. This report is a departure from results by Dim CC, et al¹⁸ working in the same city. In their study, they reported 0% rate of severe Anaemia while presenting 90.7% mild Anaemia and 9.8% moderate Anaemia, which was similar with reports by Esike COU, et al¹⁰ working in nearby Abakaliki in the same south east region of Nigeria. The 4.35% of severe Anaemia reported in the study also contradicts other recent studies from southeastern Nigeria^{24,25} and Ibadan, Western Nigeria,²⁶ where no case of severe Anaemia was noted, unlike in Shagamu, Western Nigeria,²⁷ where 0.7% of the anemic pregnant women were severely anemic. This was also higher than the lower than 2.1% by Bukar et al.¹² Reports from Bassi et al²⁰ working in Jos showed that 2% of pregnant women had severe anaemia, which are comparable with those from Bida, Niger state, Nigeria.²⁸⁻³⁰

However, it can be noted that the level of sever anemic pregnant women (4.35%) could be an isolated case as reports from the south east especially from the same Enugu showed no presence of severe Anaemia as reported here. Most severe Anaemia cases where reported mostly in Northern Nigeria.

Mild to moderate Anaemia, although generally well-tolerated, clearly adversely affects the sense of well-being, resulting in fatigue and a decrease in work capacity. Women in sub-Saharan Africa are the “hewers of wood and the drawers of water;” therefore the decreased work capacity as a result of the Anaemia will have economic consequences on the family in particular and on society at large.²⁰

There was a statistically significant association between increasing maternal age and prevalence of anaemia. Women within the age group 36-41 had the lowest mean PCV (31.00±7.00) (Tables 2,3). This finding is however at variance with some other studies that suggested the highest rate of anaemia in teenagers and adolescent.

Table 2. Results of Mean PCV According to Age (n=400)

Age (Years)	Frequency (n)	Mean PCV
18-23	88	33.63±3.17
24-29	128	32.1±5.13
30-35	160	34.00±3.92
36-41	24	31.00±7.00

Table 3. Results of Percentage Age Brackets of Anemic Pregnant Women

Age (Years)	Frequency (n)	% of anemic Pregnant
18-23	32	17.39%
24-29	72	39.13%
30-35	64	34.78%
36-41	16	8.70%

From the present study, it was shown that the number of anemic pregnant women reduced as the women grow older similar to the findings of Dim and Onah, Aimakhu and Olayemi, and Bukar et al.^{18,19,25} However, it is at odd with the finding of Hoque et al³¹ working in Greytown South Africa, and Idowu et al³² working in Abeokuta. It must however be noted that the influence of age is often closely intertwined with that of parity.¹²

RECOMMENDATIONS

During pregnancy, efforts should be geared towards the early detection and treatment of Anaemia before delivery. Also, medical staff managing pregnant women should endeavor to investigate anemic pregnant women further in order to identify the etiology whenever possible, despite commencing the usual treatment with iron and folate. All of these efforts would help to ensure safe motherhood.

CONCLUSION

The prevalence of Anaemia at booking is still high in Enugu. The results suggested that Anaemia predates the pregnancy in the majority of cases. Hence, preconception care, including iron and folic acid supplementation, is advocated to reduce this problem. During pregnancy, efforts should be geared towards the early detection and treatment of Anaemia before delivery. Also, medical staff managing pregnant women should endeavor to investigate anemic pregnant women further in order to identify the etiology whenever possible, despite commencing the usual treatment with iron and folate. All of these efforts would help to ensure safe motherhood.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Brief Research Report

Compliance with Highly Active Antiretroviral Therapy (HAART) does not Prevent Human Papilloma Virus (HPV)-Related Cancers in Women Infected with Human Immunodeficiency Virus (HIV)

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ABSTRACT

Introduction

Cancer is one of the leading causes of death in people with human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS), due to behavioral choices and overlapping risk factors.

Aim

The purpose of this report is to determine the long-term incidence of human papilloma virus (HPV)-associated cancer in women with pre-invasive cervical neoplasia, and compliance with medication and cancer screening recommendations.

Methods

HIV-infected women diagnosed with pre-invasive cervical neoplasia and an HPV-associated malignancy between 1995-2008 were identified. Data collected includes: demographics, HIV treatment/response, malignancy treatment/response, other healthcare utilization, use of health navigators, and compliance.

Results

Seventy one subjects were identified with HIV infection, cervical dysplasia, and at least ten years' follow-up. 17/71 (24%) were identified with an HPV-related malignancy. The mean age of those diagnosed with HPV-related malignancy was 39-years. Malignancies included: Cervix-9, Vulva-7, Anal-4, Vagina-3, Urethra/Bladder-2, Oropharyngeal-3. Eight also had *in-situ* neoplasms: Cervix-4, Vulva-3, Oropharyngeal-1. Four subjects had 3 separate malignancies, and two others had 2 malignancies. Compliance with HAART correlated strongly with immunocompetence, response to therapy, use of patient navigators, and survival. Sixty out of seventy one (84.5%) subjects underwent screening mammography, 57/71 (80.3%) underwent colonoscopy, and 67/71 (94.3%) underwent pap smear testing. Compliance with screening compared favorably with the general population, and overall survival was similar.

Discussion and Conclusion

The long-term incidence and mortality from cancer in women with HIV and cervical dysplasia appears to be comparable to that seen in the general population, with the possible exception of oropharyngeal cancers. Compliance with cancer screening recommendations appears to be higher than in the general population. This suggests that structured primary care programs for HIV-infected women are effective in prevention/early diagnosis of cancer. Standardized screening programs for oropharyngeal cancers should be considered in this population.

Keywords

Human immunodeficiency virus (HIV); Cancer; Human papilloma virus(HPV); Women; AIDS; Highly active anti-retroviral therapy (HAART).

INTRODUCTION

Cancer is one of the leading causes of death in people with human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS).^{1,2} With the introduction of highly active anti-retroviral therapy (HAART) in the mid-1990s, the overall incidence and mortality of cancer has decreased in this population, largely due to striking declines in AIDS-defining cancers such as Kaposi sarcoma and non-Hodgkin lymphoma.³ However, the incidence of invasive cervical carcinoma, (also an AIDS-defining cancer) has been relatively stable; while a number of non-AIDS defining cancers have increased in incidence (presumably due to the increasing numbers and age of HIV-infected individuals) and now constitute the majority of cancers in this population.^{4,5} Factors suspected to contribute to increased cancer incidence in HIV-infected persons include HIV viremia, immune deficiency, oncogenic virus co-infection, and lifestyle exposures (e.g. tobacco, alcohol).^{6,7,8} In particular, among individuals with AIDS, a statistically significant elevated risk of human papilloma virus (HPV)-associated cancers has been reported, with the level of risk strongly correlated with increased levels of immune suppression.⁹

Although HIV-associated malignancies have been extensively analyzed and reported, the data on cancers in women, with the exception of invasive cervical cancer, has been relatively limited due to an overall paucity of women in study populations.¹⁰ Further, many of these studies involved populations with multiple additional risk factors for cancer in addition to HIV infection, such as intravenous drug users or men who have sex with men.¹¹ In contrast to earlier reports, which typically included relatively few HIV-infected women, as well as a relatively short follow-up, the

goal of this study is to determine the incidence and outcomes of HPV-related genital and non-genital tract malignancies in HIV-infected women with a diagnosis of pre-invasive cervical neoplasia (dysplasia) and at least a 10-year follow-up. Further, as screening programs have been shown to be very effective in reducing the incidence of invasive cervical cancer in HIV-infected women,¹² the secondary goal of this study is to evaluate the degree of compliance with cancer screening recommendations in this cohort.

METHODS

As part of a facility-based quality improvement (QI) program, all HIV-infected women diagnosed with an HPV-associated malignancy between 1995-2008 were identified. Data sources included standard medical records, tumor registries, and clinical research trial records. Data collected includes: demographics, HIV treatment/response, malignancy treatment/response, other healthcare utilization, use of health navigators, and compliance. The data was analyzed using standard statistical tests, and the study was determined to be exempt from Institutional Review Board (IRB) review.

RESULTS

Seventy one subjects were identified with HIV infection, cervical dysplasia, and at least ten years' follow-up data from a large, inner-city academic institution in New Orleans, Louisiana, USA. Seventeen out of seventy one (24%) were identified with an human papilloma virus (HPV)-related malignancy. The mean age of those diagnosed with HPV-related malignancy was 39-years and all were African-American. Invasive malignancies included: Cervix-9, Vulva-7, Anal-4, Vagina-3, Urethra/Bladder-2, Oropharyngeal-3. Eight

Table 1. Characteristics of HIV-Infected Women with Cervical Dyplasia and at Least one HPV-Associated Malignancy

Subjects	Age	Cervix	Vulva	Anal	Vagina	Urethra/ bladder	Oropharyngeal	Cervix IS	Vulva IS	Oro IS	HAART Compliance	CD4>200	Patient navigator	Survival
1	45	x	x				x							27
2	52		x					x			x	x	x	N/A
3	50	x		x			x		x					19
4	34	x	x							x	x	x	x	N/A
5	30			x				x			x	x	x	N/A
6	35	x				x								21
7	37				x			x			x	x	x	N/A
8	51	x	x		x									9
9	29				x						x	x	x	N/A
10	45		x								x	x	x	N/A
11	38	x					x		x		x			13
12	33	x									x	x	x	N/A
13	60			x				x			x	x	x	N/A
14	32	x	x			x					x	x	x	N/A
15	30										x	x	x	N/A
16	36	x		x					x		x	x	x	28
17	28		x											18

IS=In-Situ; Survival in months; N/A=living at time of this analysis

additional subjects had *in-situ* neoplasms which included: Cervix-4, Vulva-3, Oropharyngeal-1. Four subjects had 3 separate malignancies, and two others had 2 malignancies correlated strongly with survival. Compliance with HAART correlated strongly with immunocompetence, (as measured by CD4>200/ μ L) response to anti-malignancy therapy, and survival. Further, compliance correlated strongly with the use of patient advocate/navigators (Table 1).

Thirty five out of seventy one (49%) participated in federally-sponsored clinical trials, including AIDS Clinical Trial Group (ACTG) 200, ACTG 293, Southwest Oncology Group (SWOG) 8797, Gynecologic Oncology Group (GOG) 154, and GOG 155. Sixty out of seventy one (84.5%) subjects underwent screening mammography, 57/71 (80.3%) underwent colonoscopy, and 67/71 (94.3%) underwent pap smear testing, all in accordance with American Cancer Society (ACS) guidelines. The level of compliance with guideline-based screening compared very favorably with that seen in the general population of New Orleans and Louisiana, USA, and overall survival at 5-years was similar.¹³

DISCUSSION

In this cohort, the long-term incidence and mortality from HPV-associated cancers in HIV-infected women with a history of cervical dysplasia was comparable to that seen in women with cervical dysplasia in the general population of this area. This appears to be in contrast with previous reports, which found an increased risk of both AIDS-defining and non-AIDS defining cancers in similar populations.¹⁴ It seems clear from these findings that while the use of HAART can reduce the risk of HPV-associated cancers in this group to at least that of the general population, it does not prevent those cancers, and therefore active screening remains important, even in those HIV-infected individuals who remain compliant with their medications. A possible explanation for these findings include strong compliance with HAART as seen here, which is known to be protective for both AIDS-defining and non-AIDS defining cancers. Another explanation could be the increased level of compliance with cancer screening recommendations in this group. While HIV-infected patients with cervical dysplasia are at risk for HPV-associated cancers, that risk does not seem to exceed that seen in the general population of this area, which has long been among the highest in the US.¹⁵ This apparent success in cancer screening is likely due to the work of a well-organized and (relatively) well-funded clinic system for HIV-infected individuals in the New Orleans Metropolitan area. This system has been in existence for over 25-years, makes extensive use of patient advocate/navigators, and has been credited with dramatic improvements in multiple health outcomes.¹⁶ This suggests that communities where HIV infection is common will benefit from organized primary care delivery systems, with emphasis on adherence to HAART.

Another possible explanation for the findings reported here is that the baseline characteristics of this group differ from those in prior studies. This study population, while limited in size, was exclusively female and appeared to have both similar levels of personal risk factors and similar demographics to the general population of the area. Prior studies of cancer risks in HIV-infected persons typically comprised a cohort that was predominantly

male and included many additional known risk factors for cancer, including high rates of intravenous drug use, alcohol use, smoking, and infection with known cancer-causing viruses such as Hepatitis B and C viruses, (HBV and HCV) in addition to HPV.¹⁷

It is well-known that HIV-infected women from the pre-HAART era demonstrated an elevated risk for and mortality from cervical abnormalities and dysplasia.¹⁸ A study by Ellerbrock et al, reported that 1 in 5 HIV-infected women without previous evidence of cervical dysplasia developed biopsy-confirmed cervical squamous intraepithelial lesions.¹⁹ In addition, HIV-infected women with a greater level of immune suppression have an increased risk of persistent HPV infection and progression to cervical dysplasia.²⁰ Interestingly, a separate study showed that the incidence of cervical dysplasia in HPV-negative, cytology-negative HIV-infected women with CD4 counts greater than 500/ μ L was comparable to that in HIV-negative women.²¹ Massad et al found that while the risk for an abnormal Pap test was greater in HIV-infected women than seronegative women, once an HIV-infected woman develops an abnormality, her risk for high grade cervical dysplasia was only marginally greater than that of seronegative women.²² Of importance for patient care, another study of HIV seropositive women from 1994-2001 from the same investigators found the risk of invasive cervical cancer to be indistinguishable from that of the general population when the HIV seropositive women were enrolled in a program of cervical cancer screening and prevention.^{23,24}

An intriguing finding from the current study is that the long-term incidence of oropharyngeal cancers may be higher than expected. This may be partially explained as a reflection of the overall increase in oral HPV infection and oropharyngeal cancers in recent years.²⁵ However, understanding of the pathophysiology of HPV is incomplete, and may differ in the female genital tract compared to the oropharyngeal tract. Consistent with this, a study by Beachler, et al, found an elevated prevalence of oral HPV in HIV-infected persons after controlling for differences in cigarette smoking and sexual behavior.²⁶ This unexpected number of oropharyngeal cancers in HIV-infected persons suggests that standardized screening programs for oropharyngeal cancers should be considered.

Compliance with cancer screening recommendations in this study group appeared to be higher than in the general population. Although there is limited data on certain cancers in HIV-infected women, prior studies have indicated benefits of screening these patients for cervical cancer, anal cancer, breast cancer, and hepatocellular carcinoma.²⁷ Currently there is insufficient evidence to recommend lung cancer screening for HIV-infected women without other risk factors such as smoking. Although the incidence of lung cancer is elevated in HIV patients, it has also been reported that they have a greater cumulative pack-year smoking history.²⁸

CONCLUSION

The long-term incidence and mortality from cancer in women with HIV and cervical dysplasia appears to be comparable to that seen in the general population, with the possible exception of oropharyngeal

ryngeal cancers. Compliance with cancer screening recommendations appears to be higher than in the general population. This suggests that structured primary care programs for HIV-infected women are effective in prevention/early diagnosis of cancer. Standardized screening programs for oropharyngeal cancers should be considered in this population.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Original Research

A Study to Explore the Impact of Endometriosis in the United Kingdom: A Qualitative Content Analysis

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ABSTRACT

Objective

To gain insight into the areas that impact women with endometriosis.

Design

A qualitative content analysis of an online survey.

Setting

Online questionnaire *via* Endometriosis UK.

Population

Women diagnosed with endometriosis of any age range.

Methods

Free-text online questionnaire through Endometriosis UK completed by women. Results were analysed using NVivo version 9, qualitative analysis software. The software creates links between common words (codes), and these links allow data to be placed in nodes (called themes) which are then developed into categories. Content analysis was used to understand this data.

Main outcome measures

Impact of endometriosis on women's lives.

Results

In total, 1872 questionnaires were returned but not everyone was able to identify ten separate features that affected them. As such, 1872 women provided at least one area that affected them, 1800 provided two areas, 1770 provided three areas and 1600 provided four areas. The results show that the main areas of concern for these women were pain (53%), heavy menstrual bleeding (11%), low mood (8%) and the perceived lack of understanding displayed by other people (7%). Other important factors were fertility concerns, impact on employment, problems with the medical team and uncertainty. These then impacted on their daily life whereby some women felt "guilty" for not 'being a normal mother'. A key term that resonated was that endometriosis is an "invisible disease".

Conclusion

This analysis provides us with insight into the complex psycho-social factors that interact with bio-physical symptoms. Further research is required in sub-population groups such as teenagers and ethnic minority women to explore any differences in impact and how care can be guided accordingly.

Keywords

Endometriosis; Impact; Qualitative methods; Quantitative methods; Online survey.

BACKGROUND

Endometriosis is a disease in which endometrial glands and/or stroma are found in areas outside of the endometrium including the ovaries, bowel and pelvis.¹ As a result, women experience a myriad of symptoms including pelvic pain, menorrhagia and dyspareunia.¹ Endometriosis is also associated with infertility.¹ Endometriosis affects 1.5 million women in the United Kingdom and can have a host of physical, psychological and social sequelae.² The average time to diagnose endometriosis is approximately 7.5-years in the United Kingdom.³

A mixed-methods approach to research is quite commonly used. Qualitative research is a term used to cover a wide range of approaches and methods. A pragmatic definition is that “qualitative research is a naturalistic, interpretative approach concerned with understanding the meanings that people attach to actions, decisions, beliefs, values and the like within their social world.”⁴

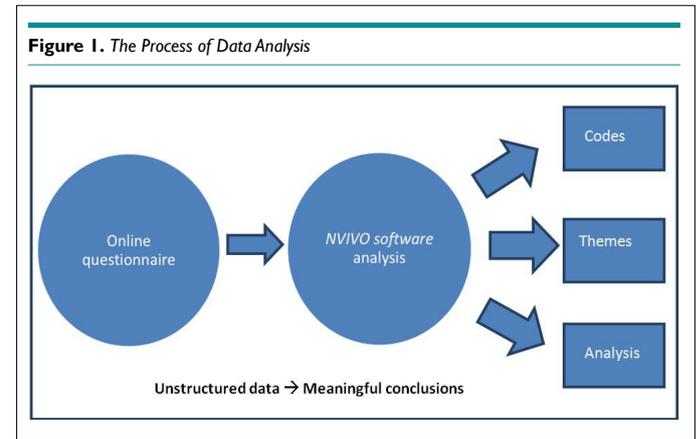
Qualitative research is based on personal experience and has a role in obtaining detailed information on why people behave the way they do and the impact of various life experiences. Data are generally obtained through structured or semi-structured interviews, focus groups or observations.⁴ Approaches taken to qualitatively analyse data include grounded theory (to generate a theory), phenomenology (to understand lived experience and how individuals make sense of this experience) and content analysis.^{3,4} The different types of content analysis include conventional, directed and summative approaches.⁵ With conventional content analysis, categories are created from the text, summative content analysis involves counting key words and then analysing it and directed content analysis involves using a theory to guide which codes will be created.⁵ The ultimate aim of qualitative research is to obtain meaning from how people view the world and why people behave in the manner they do as well as how people feel within certain contexts.⁶ As the data was collected through an online questionnaire, content analysis was deemed to be the most appropriate method of analysing the data.

Using the Cochrane database, we found that there are a limited number of studies exploring the impact of endometriosis on women in the United Kingdom.⁷⁻¹⁰ The objective of this study was to gain insight into the main factors that impact the lives of women with endometriosis using mixed methods in order to further improve their clinical care. This mixed methods approach involved the administration of an online questionnaire and subsequent analysis *via* qualitative content analysis.

METHODS

Endometriosis UK charity collects information *via* a periodic online questionnaire to assess the experiences of their members with diagnosis and management of their condition. The final question in their questionnaire was, ‘Which aspects of endometriosis have the greatest impact on your life?’ with up to ten unprompted free text responses allowed. The webpage also re-iterated that all responses from the questionnaire will be kept confidential.

These results were collated onto a Microsoft Excel file and the data was analysed qualitatively using the software NVivo version 9 (Figure 1). Through this software, the data was uploaded and manually formatted according to text size, font and layout in order for Nvivo to auto-analyse the data.



NVivo is a software that allows unstructured data, usually in the form of free text (for instance, patient interview scripts), to be qualitatively coded to generate meaningful conclusions.¹¹ The software creates links between common words (codes), and these links allow data to be placed in categories (also known as themes).¹¹ The researcher is then able to interpret the themes according to their area of research interest. Importantly, the results from Nvivo can be stored in various formats including audio, text memos and other graphical displays. This method of analysis allows subtle detail to be generated. Content analysis was used to analyse the data for common codes and themes, whilst the quantitative aspect involved gaining insight into the frequency of code and theme occurrence.

RESULTS

In total 1872 participants responded to the questionnaire. Participant demographics are described in Table 1.

Table 1. The Participant Demographics

Ethnicity	Caucasian	72%
	Asian	5%
	Other	23%
Age range	16-20	22%
	21-30	31%
	31-40	24%
	41-50	20%
	51-60	3%
Location	England	71%
	Wales	8%
	Scotland	20%
	Northern Ireland	1%

One thousand, eight hundred and seventy-two women

Figure 2. Number of Women Reporting 1, 2, 3 and 4 Areas of the Impact that Endometriosis had on Them

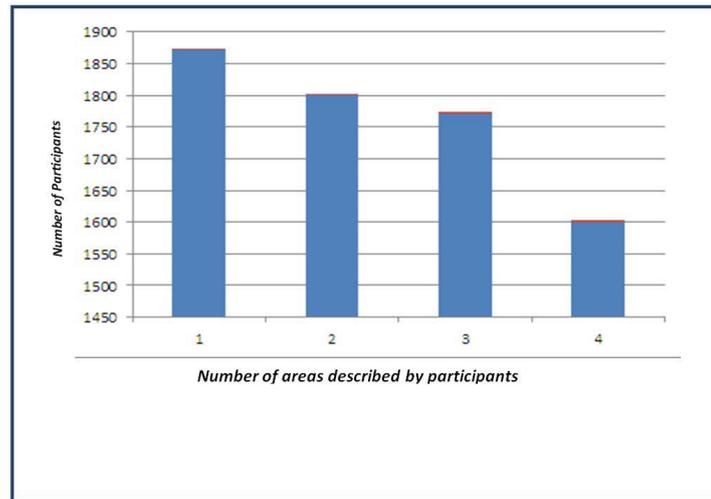
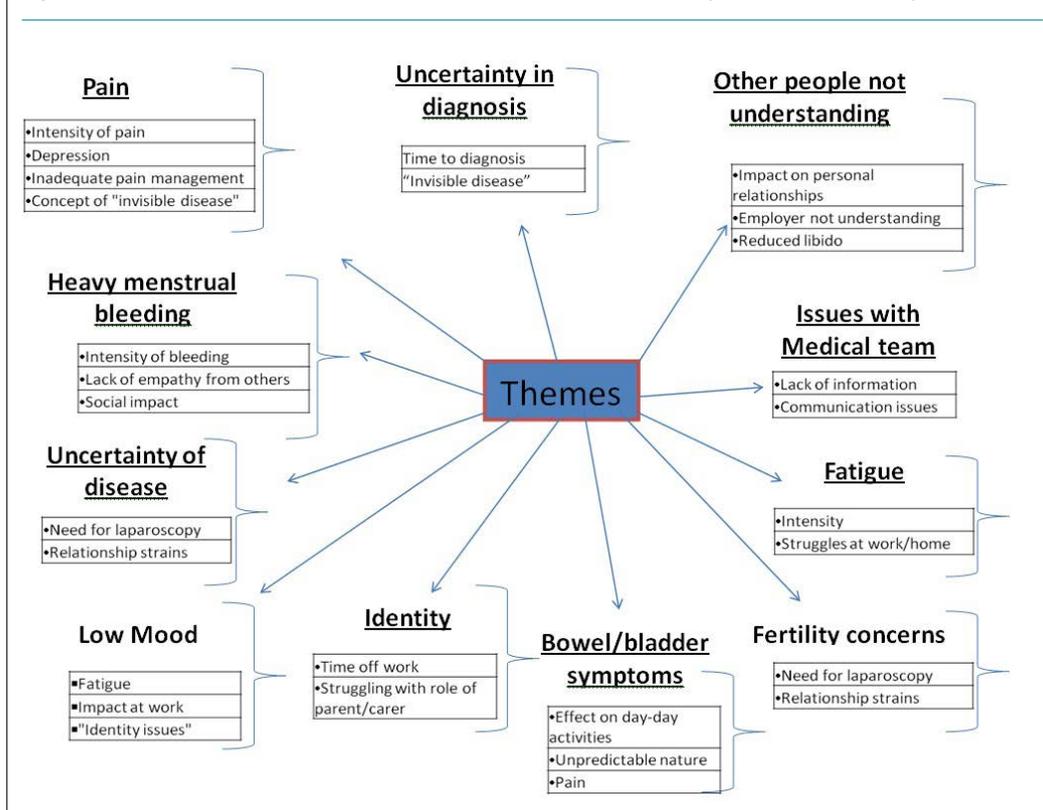


Figure 3. The Main Areas of Endometriosis that Affected Women the Most as Derived from Analysis of the Questionnaire Responses



responded to the questionnaire, but not all provided ten features that affected them. One thousand, eight hundred and seventy-two women provided at least one area that affected them, 1800 provided two areas, 1770 provided three areas and 1600 provided four areas (Figure 2). After the fourth set of impact, no new information was gathered from the software analysis of the data and therefore this was not included in this analysis. Based on 1872 replies, the top four concerns that women described were pain, heavy menstrual bleeding, fatigue and “other people not understanding” (Figure 3).

employment, future fertility concerns, fatigue, and apparent lack of support (from clinical teams and personal support). The main areas described in depth by women will be explained below in further detail. Although the findings from this analysis are portrayed as various sub-headings, the reality is that all these factors are a representation of the complex interaction between them. Extracts from the questionnaire are included in quotation marks within this study.

Other areas that concerned women included impact on

The findings from the study are represented as quotes taken directly from the questionnaire responses and discussed

within in this study.

Pain

The analysis found that 995/1872 women (53%) stated that pain was the single most important issue that affected them. The impact of pain was described as “severe” “crippling” or “unpredictable”. Women felt that “other people” – partner’s, family members, friends and employers, were not able to always “appreciate the intensity of pain”. Women then went on to describe the intensity of the pain and how this impacted their day-to-day activities. Some respondents became “house bound” and “isolated”, which impacted on their social functioning. Approximately twenty percent of the women, who described pain as their main concern, went on to state that “depression” was the second greatest effect on their life. The majority of women said that pain management alone was inadequate treatment, mainly due to the side effects from the analgesia itself. A number of women went in to describe their illness as “invisible” because “other people” were not able to appreciate the intensity of the pain they experienced.

– *“Pain during menstruation stopped me doing normal things, at school, work and at home”.*

– *“Severe Pain. Because it’s taken 24-years for a surgeon to finally operate on me, I’ve been in horrendous pain on a daily basis. I’m currently taking 180mg of morphine per day. I hope my open surgery later this year will hugely improve my health”.*

– *“Crippling pain meant I could not look after my son without help from my parents”.*

Heavy Menstrual Bleeding

Eleven percent (201/1800) of the women stated that heavy menstrual bleeding was the second most important issue that concerned them. Menstruation was described as “flooding” and “unpredictable”. A number of women, who described heavy menstrual bleeding as affecting them the most, also explained that “other people” are not able to visualise the disease process and they felt the need to constantly justify their symptoms to other people. Some women found that if they described their symptom of heavy menstruation to women who do not suffer from endometriosis, then the extent of the understanding and empathy offered from them was limited.

Those women, who were unfortunate to experience heavy menstruation as well as irregular menstrual cycles, explained that this had a significant and “catastrophic” effect on their social lives; for instance women were not able to make concrete plans with friends, felt scared in case of “leaking” and were constantly cancelling pre-arranged plans.

– *“Constant flooding means I have to get to the toilet quickly and so this restricts my employment choices”.*

Low Mood

Eight percent (142/1770) of the women stated that low mood was

the third most important area that affected them. They explained that low mood also made them feel more fatigued, which had a significant impact on day to day activities such as shopping, maintaining family demands and socialising with friends and family. A number of the women explained that their fatigue caused performance issues at work and sadly, a few women even stopped working as a result. The extent of the fatigue was described as “unpredictable”.

- Due to fatigue and low mood, women were not able to spend quality time with children or family; and as a result, a proportion of women said this made them feel “guilty” They felt that their fatigue meant they were unable to take on the role of “a normal mother” and therefore also felt “guilty”. Ultimately, they described significant issues with their own identity as a result of this complex interaction.

– *“I felt no-one believed me, I felt very alone, and at times I’ve been depressed-I thought I wouldn’t live past 30”.*

– *“Solitude and loneliness. I have, very rarely, been able to leave the house, because of pain and other side effects, since August 2013. I’ve lost contact with a lot of people. I’ve had to cancel so many meetings last minute due to pain and this has pushed people away”.*

Other People Not Understanding

Seven percent (117/1600) of the women explained that the apparent lack of understanding from other people (partners, family, friends and employers) was the fourth area that impacted them the most.

Due to the chronic nature of the disease process and regularly experiencing various symptoms, women felt that their partners were not always able to appreciate or understand the symptoms they were going through. Some of those women, who opted to discuss their illness further with employers, found that, the employer did not always understand the impact this was having on them. One woman explained “my employer said, is your tummy pain not like a normal period pain?” and another woman described the words used by a female employer as “just get on with the pain, you will be fine”. Interestingly, some women explained that “male employers were more understanding” and female employers were less understanding because there was an expectation from them to “just get on and deal with it”. Another important area was that many women had significantly reduced libido (many did not expect this) and felt their partners also struggled to understand the impact of this.

– *“I also find that people tell me that “it’s just period problems” or “it’ll go with a baby”. They are both totally dismissive reactions. Added to which, who suggests have a baby?! What if I didn’t want to/ couldn’t afford it etc?”*

– *“My entire secondary school education was disrupted – a social worker was brought in and laughed at me whenever I tried to explain I was off school frequently due to bad periods”*

Other areas of focus that women provided insight into are described below:

Conflicts with the medical team: A minority of women felt that information about their care between primary care and secondary care could be better communicated.

- Some women explained that post diagnostic laparoscopy; they would have preferred to have written information on endometriosis as well as any complications to be aware of from the procedure.
- Women felt there were constant referrals between various specialties including gynaecology and general surgeons before a formal diagnosis was made.
- A number of women said instead of a diagnostic laparoscopy, they also would have preferred to have surgical management at the same time for endometriosis, if appropriate.

- *“I feel like I’m on a constant merry go round of referrals. Despite having a resurgence of symptoms, the latest gynaecologist has now told me it could be gastrointestinal and has referred me elsewhere. This is despite my history”.*

- *“Frustration that Doctors don’t understand impact”.*

Fertility worries and concerns with intimacy: There were significant concerns about future fertility and endometriosis. Women were not only worried about their chances of becoming pregnant but were also worried if *In-Vitro* Fertilisation (IVF) would be available to them or not.

- *“Not being able to have children because of having to have a hysterectomy”.*

- *“Lack of sexual contact. Unfortunately, my husband and I have been unable to carry out full sex for the past 5-years. I hate myself for this. I’m very lucky to have a very supportive husband. I fear if I don’t get better soon he will get fed up with me. He says that will never happen. Fingers crossed my surgery works this year”.*

Impact on work: A few women explained that they were made redundant from their job due to “time off sick” and as a result had financial implications. Although the impact on employment is also described in the “other people not understanding section”. It is also important to note that some women felt very embarrassed to talk about endometriosis with their employer and some felt that some female employers perceived endometriosis “as not an illness”.

- *“My job involves me standing for most of the day and dealing with people 1 on 1. Very difficult and embarrassing when in pain, and having to stop what you’re doing/saying”.*

Uncertainty: Women described that they struggled to explain their symptoms and disease process to other people. Many went on to describe the uncertainty they faced during diagnosis as they had “many laparoscopies before diagnosis”. The uncertainty of

the disease patterns (for instance sudden abdominal pain, irregular heavy menstruation) meant that women often cancelled social plans at short notice and overtime, felt isolated. A large number of women described endometriosis as an “invisible disease”.

- *“Its invisible so people not aware... Unless bloated then they ask if you are pregnant?”.*

Main findings: Women described pain; heavy menstrual bleeding, fatigue and “other people not understanding” as the top four concerns that impacted them. Other areas of concern to women included impact on employment, future fertility concerns, fatigue and apparent lack of support from either clinical teams or from personal relationships. A number of women described endometriosis as an “invisible disease” in addition to having worries about the disease process uncertainty and “feeling guilty” for not being able to “be a normal mother”.

DISCUSSION

To our knowledge, this is the first ever reported mixed-methods endometriosis study involving over 1800 participants whereby the data was collected online. The high number of participants allowed us to draw conclusions that are meaningful and robust. In the analysis of the results we could thus prove that the most common areas of concern that affected women with endometriosis who responded were pain, heavy menstrual bleeding, low mood and the perceived lack of understanding displayed by other people. Other areas that affected women included fertility concerns, impact on employment, problems with the medical team and uncertainty.

Pain was the most reported factor that impacted women with endometriosis. Women described this pain to varying intensities. A key term that resonated from the results was when women described endometriosis as an “invisible disease”. Content analysis showed that women said this for a number of reasons; namely due to other people not being able to appreciate the extent of pain suffered by these women. With freely available pharmacological and non-pharmacological analgesia, why are so many women with endometriosis still in pain? One suggestion to help tackle this issue could be to provide women with a holistic summary of the various methods to control pain, including alternative therapies, analgesia and hormonal therapies. In addition, having joint clinics between gynaecologists and anaesthetists specialising in chronic pain control are likely to be of use to women.^{10,11}

Women also went on to describe that their symptoms had a significant impact on employment and that many women felt “embarrassed” to discuss their symptoms with a trusted employer. There is limited research in this area. Whilst there are patient and public educational resources on endometriosis created by Endometriosis UK and the Royal College of Obstetricians and gynaecologists (RCOG), not all women were aware of these resources. During clinical encounters, patients should be directed to these resources as they will also be able to direct their employers to such resources, should they wish.

The perceived lack of support, especially from partners,

was also made obvious by women in their answers. Women often felt “guilty” for “burdening” their partners with the symptoms they experience from endometriosis. Interestingly, some women explained that their partners struggled to cope with the sexual health implications from the disease (for instance, women experienced reduced libido). With the consent of the patient, involvement of partners in clinical consultations may also help address such issues. There are a number of local support networks around the country, including those provided through Endometriosis UK; however, there are still areas in the UK lacking such groups. This would certainly be an area of further focus.

Education forms a major part in raising awareness of endometriosis. Whilst menstrual well-being will be taught as part of the national curriculum in England by 2020, there is still scope to improve awareness in medical education. The findings from this study provide insight into the communication challenges women faced with their healthcare practitioners; developing this as part of communication skills teaching at medical school would be useful.

Women have described here how the social isolation and fatigue impacting upon day to day life had led to potential identity issues. Some women described feeling “guilty” as a result of not being able to spend quality time with their children. Again, self-identity and how this is impacted through the psycho-social sequelae of endometriosis is an area that does not appear to have been studied in great detail before. Our study has provided insight into the guilt some women with endometriosis have experienced and how this has influenced their self-identity. This is important as it will have an influence on how women cope with their symptoms.

A systematic review by Young et al analysed eighteen qualitative research papers and concluded that further studies were required to assess the impact of infertility due to endometriosis and impact of the social exclusion.¹² An Australian qualitative study Moradi et al involved thirty-five women with endometriosis in semi-structured group discussions found that endometriosis had an impact negatively on women in all aspects of their lives, but more research was required on the impact in teenagers.⁷

The results from this analysis clearly provide us with an insight into the complex psycho-social factors that interact with bio-physical symptoms. There are still very limited qualitative studies exploring the impact of endometriosis on women’s lives, particularly in the United Kingdom.

This study underpins the important of understanding patient experiences in endometriosis. It raises a number of important research and ethical issues.

CONCLUSION

Further research is required in sub-population groups to include teenagers, ethnic minority women, post-menopausal women and those from varying socio-economic classes as all these groups may have differing sequelae and may benefit from tailored services.

We feel that this study is mandatory reading material for

all that care for women with endometriosis. It provides valuable insight into the physical and psychosocial effects of this disease from women unconstrained by investigator bias and restrictive drop/tick box surveys. It is the first of its kind in the UK; it highlights what women really think as it represents the voices of thousands of women with the disease.

STRENGTHS AND LIMITATIONS

This study highlights how useful the internet can be to obtain rich and detailed information from women suffering from endometriosis. There was no researcher bias and women were given the opportunity to write free flow text in the questionnaire.

This study did not involve direct face to face participant contact and therefore as researchers were unable to ask women further questions about their symptoms or impact.

FUNDING

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ETHICS APPROVAL

Ethical approval was obtained from the ethics committee at the University of East Anglia on July 13, 2017. Reference 2016/2017-87.

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CONFLICTS OF INTEREST

Dr. Morris reports grants and personal fees from Gedeon Richter, personal fees from Pfizer, personal fees from Chugai Pharma, outside the submitted work; and Trustee, Royal College of Obstetricians and Gynaecologists (RCOG) Trustee, British Menopause Society. Dr. Simpson reports grants and personal fees from Gedeon Richter, personal fees from Chugai Pharma, outside the submitted work;

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APPENDIX

Below is the Raw Data in a Tabulated Form

Table 1. The Number One Feature that Affects Women with Endometriosis (Pain)

Reason Number 1	Total Number	Percentage
Pain	995	53%
Impact on work	176	9%
Fertility worries	147	8%
Fatigue	97	
Heavy bleeding	84	
Pain during sex	60	
Tiredness	50	
Day to day activities	49	
Cannot understand disease	40	
Having to take analgesia	28	
Problems with medical team	23	
Low mood	21	
Impact on school	17	
Relationship impact	16	
Bowel symptoms	15	
Menstrual cycle disturbance	11	
Bloating	10	
Miscarriage	7	
Not feeling "normal"	6	
Fainting	4	
Infertility requiring IVF	4	
Not sure	4	
Had to have an operation	3	
Nausea	2	
Not had much impact	2	
Migraine	1	
Total	1872	

Table 2. The Second Most Common Feature that Affects Women with Endometriosis (Heavy Menstrual Bleeding)

Reason Number 2	Total Number	Percentage
Pain	362	20%
Heavy bleeding	201	11%
Fatigue	144	8%
Impact on work	143	
Fertility worries	108	
Tiredness	100	
Day to day activities	97	
Low mood	90	
Pain during sex	84	
Bowel symptoms	63	
Relationship impact	53	
Cannot understand disease	48	
Menstrual cycle disturbance	43	
Bloating	39	
Lack of support	39	
Problems with medical team	36	
Having to take analgesia	34	
Nausea	25	
Sleep impact	19	
Had to have an operation	15	
Impact on school	12	
Hormonal treatment needed	8	
Fainting	7	
Fertility worries	7	
Infertility requiring IVF	5	
Migraine	5	
Not feeling "normal"	5	
Embarrassed	4	
Miscarriage	3	
Not had much impact	1	
Not sure	0	
Total	1800	

Table 3. The Third Most Common Feature that Affects Women with Endometriosis (Low Mood)

Reason Number 3	Total Number	Percentage
Pain	210	12%
Day to day activities	148	8%
Impact on work	142	8%
Low mood	142	8%
Lack of support	124	
Fertility worries	111	
Heavy bleeding	110	
Pain during sex	104	
Fatigue	94	
Tiredness	92	
Relationship impact	88	
Bowel symptoms	84	
Bloating	56	
Having to take analgesia	39	
Menstrual cycle disturbance	37	
Problems with medical team	37	
Cannot understand disease	34	
Nausea	26	
Hormonal treatment needed	17	
Had to have an operation	12	
Sleep impact	10	
Fainting	9	
Migraine	8	
Impact on school	7	
Not feeling "normal"	7	
Embarrassed	6	
Follow up appointments	6	
Weight issues	5	
Miscarriage	2	
Acne	2	
Isolating	1	
Infertility requiring IVF	0	
Not had much impact	0	
Not sure	0	
Total	1770	

Table 4. The Fourth Most Common Feature that Affects Women with Endometriosis (Low Mood)

Reason number 4	Total Number	Percentage
Low mood	164	
Pain	157	10%
Work impact	125	10%
Other people not understanding	117	8%
Tiredness	96	7%
Bowel/Bladder issues	86	
Day to day impact	86	
Heavy bleeding	84	
Infertility	79	
Issues with medical team	76	
Issues with sexual intercourse	71	
Unpredictable disease process	63	
Pain after sex	54	
Side effect of drugs	54	
Social life impact	46	
Nausea	43	
Bloating	42	
Relationship impact	32	
Surgery	22	
Others not believing you	15	
Sleep problems	15	
Isolated	11	
Headache	9	
Weight gain	9	
Embarrassed	7	
School impact	7	
No cure	7	
Stress	5	
Financial worries	4	
Guilt	4	
Having to attend appointments	4	
Acne	2	
Disease taking over life	2	
Fear of hysterectomy	1	
Miscarriage	1	
Total	1600	

Original Research**Robot Assisted Comprehensive Surgical Staging for Endometrial Cancer: A Validation Study**

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Corresponding author*Nitin A. Wadhwa, DO**Catholic Health Services, Long Island, 1000 Montauk Highway West Islip, NY 11795, USA; E-mail: Nitin.Wadhwa@chsli.org**Article information****Received:** September 23rd, 2019; **Revised:** October 27th, 2019; **Accepted:** October 29th, 2019; **Published:** November 19th, 2019**Cite this article**Wadhwa NA, Mauricio D, Eisner I, Wadhwa RK, Singhal P. Robot assisted comprehensive surgical staging for endometrial cancer: A validation study. *Gynecol Obstet Res Open J.* 2019; 6(1): 20-26. doi: [10.17140/GOROJ-6-151](https://doi.org/10.17140/GOROJ-6-151)**ABSTRACT****Objective**

The study sought to evaluate the historical surgical-pathological trends in Gynecologic Oncology Group (GOG) 33 in a cohort of patients who underwent robot-assisted staging of uterine carcinomas.

Materials and Methods

This is a retrospective study from June 2016 through December 2018 at Catholic Health Services Hospitals in Long Island (CHS-LI), NY, USA. All patients underwent robotic surgical staging with hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Fifty patients were included, and patients were separated into cohorts with endometrioid or non-endometrioid histology for analysis. Patients were staged using the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification.

Results

For all patients undergoing surgical staging, the rate of pelvic and para-aortic nodal metastases occurred at 10% and 8%, respectively. Sixty percent of the grade 1 endometrioid tumors had less than 50% myometrial invasion. No patients had positive para-aortic lymph nodes in the absence of pelvic node involvement. High-risk histologies were associated with nodal disease thirteen percent of the time. A correlation between increasing depth of invasion and positive lymph nodes was demonstrated. Increasing grade of tumors was correlated with the frequency of nodal metastasis. Intraperitoneal spread was highly correlated to metastatic lymph nodes. Deep invasion was positively correlated with nodal disease.

Conclusion

The results of this study validate the trends previously known from GOG 33 in a population undergoing robot-assisted surgical staging for uterine carcinomas.

Keywords

Gynecologic Oncology Group (GOG) 33; Robotic; Surgery; Uterine cancer; Lymph nodes; Trends.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States, afflicting approximately 61,380 annually.¹ It is well-known today that most clinical stage I endometrial carcinomas are limited to the uterus, but 20% have occult metastatic disease on final pathology after surgical staging.² Prior to 1988, endometrial adenocarcinomas were clinically staged diseases, primarily relying upon physical examination and radiological evidence. A landmark trial by the Gynecologic Oncology Group

(GOG), known as GOG 33, was conducted in 1987 and paved the way for the adoption of surgical staging for all endometrial carcinoma. The study prospectively examined patients with clinical stage 1 carcinoma of the endometrium and evaluated the surgical-pathologic behaviors of these tumors. The results were remarkable that 22% of patients assumed to have stage 1 uterine confined disease were found to have extrauterine spread at the time of surgery with microscopic pelvic and/or para-aortic metastases in 11% of women.³ After the results of this study were published, the International Federation of Gynecology and Obstetrics (FIGO) soon

thereafter reclassified endometrial carcinomas as a surgically staged disease.

The patients in GOG 33 underwent abdominal surgical staging, including hysterectomy with pelvic and para-aortic lymphadenectomy. Since the publication of the study, minimally invasive techniques have become the standard of care for the comprehensive surgical staging of endometrial carcinomas.^{4,5} In gynecologic surgery, the 1990s were notable for the advancement of laparoscopic techniques, as well as for the development of more advanced surgical equipment. Multi-institutional clinical trials followed to compare laparotomy and laparoscopy. For example, in 2009, the GOG LAP 2 study was the most prominent prospective trial to compare these techniques during surgical staging procedures. Laparoscopy was found to be feasible, safe, and equivalent in nodal counts, and resulted in fewer complications and shorter hospital stays.⁵

Since abdominal staging has become largely replaced with laparoscopy, robotic surgery is increasingly utilized within gynecologic oncology. For example, the FIRES trial published in 2017 investigated the diagnostic accuracy of sentinel lymph nodes in uterine cancer using robotic surgery. The results of the trial showed a high sensitivity (97.2%), and a low false negative rate (3%) with the use of robotic surgery.⁶ Advantages of robotic surgery include improved visualization with three dimensional (3D) optics, greater dexterity with wristed instruments, and more comfortable ergonomics. The authors of this study sought to evaluate the historical surgical-pathological trends in GOG 33 in a cohort of patients with uterine carcinomas who underwent robot-assisted staging of uterine carcinomas. Subset analyses were performed based upon histology and high-risk factors.

MATERIALS AND METHODS

This study is a retrospective, institutional review board (IRB)-exempt analysis from June 2016 through December 2018. Subjects included were women who underwent surgical staging of endometrial cancer at Good Samaritan Hospital in West Islip (GSHWI), NY, USA which is part of the Catholic Health Services Hospitals in Long Island (CHSLI), NY, USA. Sixty-five patients were identified during this time period. Fifteen patients were excluded for a variety of reasons, such as the inability to perform a complete surgical staging or the necessity to convert to a laparotomy.

Fifty patients with carcinoma of the endometrium were evaluated who had undergone a robot-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and para-aortic lymphadenectomy. No patient was excluded if lymphadenectomy was performed, irrespective of the number of lymph nodes removed.

As performed in GOG 33, the surgical pathologic findings of these patients were evaluated. Additionally, two cohorts were developed, dependent upon the uterine histology, and subgroup analyses were separately performed. Thirty-five patients with endometrioid endometrial adenocarcinoma were grouped together, as were fifteen patients with high-risk histologies. For the purposes of this study, the high-risk histologies included uterine serous, clear cell, carcinosarcoma, and undifferentiated adenocarcinomas. The FIGO stage was classified according to the 2009 guidelines.

Surgical Procedures

A robot-assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy was performed. In the pelvis, the bilateral retroperitoneal spaces were opened and the lymph bearing tissues were removed. The anatomic boundaries included the deep circumflex iliac vein distally; the midpoint of the common iliac artery proximally; the genitofemoral nerve laterally and the superior vesical artery medially. The obturator nerve served as the posterior boundary. If a suspicious node was identified in any area, it was removed. The peritoneum over the aorta and vena cava was opened. The fat pad above the inferior mesenteric artery extending to the proximity of the renal vessels was removed *in toto*. Peritoneal cytology was obtained at the conclusion of the lymphadenectomy.

Descriptive analyses were performed to determine the significance of each factor to the frequency of positive pelvic and paraaortic nodes. The findings of this study were compared to the results in GOG 33.

RESULTS

Overall, with all uterine histologies combined, our results were significant for a pelvic and para-aortic nodal metastases rate of 10% and 8%, respectively. Four percent (4%) had spread to the adnexa, and 2% had other extrauterine metastases at the time of surgery.

Table 1.1. Descriptive Statistics for Scale Variables of Interest

	Age (Years)	Height (in)	Weight (kg)	BMI	Stay (hrs)	OR Time (min)	Tumor Size (cm)	Uterine Weight (gm)
n	50	50	50	50	48	48	45	50
Missing	0	0	0	0	2	2	5	0
Mean	63.50	76.00	81.82	31.84	28.21	172.9	2.909	96.62
Median	61.50	64.00	80.75	31.86	25.00	173.0	2.600	82.50
SD	11.17	32.97	19.91	7.638	14.85	60.38	1.916	99.55
Range	43.00	110.0	97.80	33.80	72.00	347.0	9.500	475.0
Minimum	46.00	60.00	45.50	18.80	0.000	50.00	0.000	0.000
Maximum	89.00	170.0	143.3	52.60	72.00	397.0	9.500	475.0

Table 1.2. Descriptive Statistics

	n	Percent	
Smoking History	Yes	22	44.0
	No	28	56.0
Diabetes Mellitus	Yes	10	20.0
	No	40	80.0
Hypertension	Yes	29	58.0
	No	21	42.0
Hyperlipidemia	Yes	14	28.0
	No	36	72.0

When analyzed as distinct cohorts, the results in the endometrioid and high-risk subgroups were different. Patients with endometrioid uterine histologies had a rate of metastasis of 9% to the pelvic lymph nodes, 6% to the para-aortic nodes, 3% to the adnexa, and 3% had other extrauterine metastases at the time of surgery. In the high-risk cohort, our results found that 13% of patients had pelvic

nodal metastases, 13% had para-aortic lymphadenopathy, 7% had spread to the adnexa, and 0% had other extrauterine metastases at the time of surgery.

The distribution of the study parameters are detailed in Table 1. There were more patients with endometrioid adenocar-

Table 2: Surgical-Pathologic Findings

Surgical-Pathologic Findings of Endometrioid Adenocarcinomas		
	Patients	Percentage
Stage		
IA	22	63%
IB	8	23%
II	1	3%
IIIA	1	3%
IIIB	0	0%
IIIC1	1	3%
IIIC2	1	3%
IVA	0	0%
IVB	1	3%
Histology		
Endometrioid Adenocarcinoma	35	100%
Grade		
1 Well	20	57%
2 Moderate	10	29%
3 Poor	5	14%
Myometrial Invasion		
Endometrium only	11	31%
Inner 1/3	8	23%
Middle 1/2	8	23%
Deep 1/3	8	23%
Peritoneal Cytology		
Positive	6	17%
Negative	22	63%
Not Collected	5	14%
Indeterminate	2	6%
Adnexa Involvement		
Positive	1	3%
Negative	34	97%
Pelvic Node Metastasis		
Positive	3	9%
Negative	32	91%
Aortic Node Metastasis		
Positive	2	6%
Negative	33	94%
Other Extrauterine Metastasis		
Positive	1	3%
Negative	34	97%
Capillary-Like Space Involvement		
Positive	6	17%
Negative	29	83%

Surgical-Pathologic Findings of Non-Endometrioid Adenocarcinomas		
	Patients	Percentage
Stage		
IA	8	53%
IB	3	20%
II	1	7%
IIIA	1	7%
IIIB	0	0%
IIIC1	0	0%
IIIC2	2	13%
IVA	0	0%
IVB	0	0%
Histology		
MMMT/Carcinosarcoma	2	13%
Clear Cell	5	33%
Serous	6	40%
Undifferentiated	2	13%
Grade		
1 Well	0	0%
2 Moderate	0	0%
3 Poor	15	100%
Myometrial Invasion		
Endometrium only	5	33%
Inner 1/3	5	33%
Middle 1/2	3	20%
Deep 1/3	2	13%
Peritoneal Cytology		
Positive	7	47%
Negative	7	47%
Not Collected	1	7%
Indeterminate	0	0%
Adnexa Involvement		
Positive	1	7%
Negative	14	93%
Pelvic Node Metastasis		
Positive	2	13%
Negative	13	87%
Aortic Node Metastasis		
Positive	2	13%
Negative	13	87%
Other Extrauterine Metastasis		
Positive	0	0%
Negative	15	100%
Capillary-Like Space Involvement		
Positive	2	13%
Negative	13	87%

cinoma. Thirty five patients (70%) had endometrioid histology, and fifteen (30%) had a high-risk histology. Well-differentiated and poorly-differentiated tumors were evenly present as 20 patients (40%) had well differentiated tumors, and 20 patients (40%) had poorly differentiated tumors. Forty-two percent (42%) of patients had tumors with middle and deep myometrial invasion (greater than 50% myometrial invasion). Twenty-six percent (26%) of patients had positive cytology. Sixteen percent (16%) of patients had tumors with lymphovascular space invasion (Table 2).

Most endometrioid tumors were grade 1 and confined to the endometrium. Sixty percent (60%) of the grade 1 endometrioid tumors were present within the endometrium or superficial myometrium. Sixty-six percent (66%) of the high-risk histology tumors were present within the endometrium or superficial myometrium (Table 3).

Table 3: Histologic Grade and Depth of Invasion

Histologic Grade and Depth of Invasion in Endometrioid Adenocarcinomas				
Depth	G1	G2	G3	Total
Endometrium Only	8 (40%)	2 (22%)	1 (17%)	11 (31%)
Superficial	4 (20%)	1 (11%)	3 (50%)	8 (23%)
Middle	5 (25%)	2 (22%)	1 (17%)	8 (23%)
Deep	3 (15%)	4 (44%)	1 (17%)	8 (23%)
Total	20 (100%)	9 (100%)	6 (100%)	35 (100%)

Histologic Grade and Depth of Invasion in Non-Endometrioid Adenocarcinomas				
Depth	G1	G2	G3	Total
Endometrium Only	0	0	5 (33%)	5 (33%)
Superficial	0	0	5 (33%)	5 (33%)
Middle	0	0	3 (20%)	3 (20%)
Deep	0	0	2 (13%)	2 (13%)
Total	0	0	15 (100%)	15 (100%)

Five patients (10%) had metastasis to the pelvic and/or to the para-aortic lymph nodes. Four patients (8%) had nodal metastasis to both pelvic and para-aortic lymph nodes. Zero patients had positive para-aortic lymph nodes in the absence of pelvic node involvement. Eighty percent of patients who had positive pelvic lymph nodes also had positive para-aortic lymph nodes (Table 4).

Table 4: Relationship of Positive Pelvic Nodes to Aortic Nodes

Relationship of Positive Pelvic Nodes to Aortic Nodes in Endometrioid Adenocarcinomas				
Pelvic	Aortic			Total
	Negative	Positive	Total	
Negative	32 (91%)	0 (0%)	32 (91%)	
Positive	1 (3%)	2 (6%)	3 (9%)	
Total	33 (94%)	2 (6%)	35 (100%)	

Relationship of Positive Pelvic Nodes to Aortic Nodes in Non-Endometrioid Adenocarcinomas			
Pelvic	Aortic		
	Negative	Positive	Total
Negative	13 (87%)	0 (0%)	13 (87%)
Positive	0 (0%)	2 (13%)	2 (13%)
Total	13 (87%)	2 (13%)	15 (100%)

Differing histologic cell types were related to pelvic lymph nodes metastasis. Clear cell and undifferentiated histologies were associated with positive pelvic and para-aortic lymph nodes 29% of the time. Any non-endometrioid histology was associated with nodal disease 13% of the time (n=2). Endometrioid adenocarcinoma affected pelvic and para-aortic lymph nodes 9% of the time (n=3).

Grade of the tumors was correlated with the frequency of nodal metastasis. No grade 1 tumors had any positive lymph

Table 5. Frequency of Nodal Metastasis Among Risk Factors

Risk Factor	N	Pelvic		Aortic	
		Number	Percentage	Number	Percentage
Histology					
MMMT/ Carcinosarcoma	2	0	0%		
Clear Cell	5	1	20%	1	20%
Serous	6	0	0%	0	0%
Undifferentiated	2	1	50%	1	50%
Endometrioid Adenocarcinoma	35	3	9%	2	6%
Grade					
1 Well	20	0	0%	0	0%
2 Moderate	10	1	10%	1	10%
3 Poor	20	4	20%	3	15%
Myometrial Invasion					
Endometrium only	16	0	0%	0	0%
Inner 1/3	13	0	0%	0	0%
Middle 1/3	11	2	18%	1	9%
Deep 1/3	10	3	30%	3	30%
Peritoneal Cytology					
Positive	13	2	15%	2	15%
Negative	29	1	3%	0	0%
Not Collected	6	1	17%	1	17%
Indeterminate	2	1	50%	1	50%
Adnexa Involvement					
Positive	2	0	0%	0	0%
Negative	48	5	10%	4	8%
Other Extrauterine Metastasis					
Positive	1	1	100%	1	100%
Negative	49	4	8%	3	6%
Capillary-Like Space Involvement					
Positive	8	3	38%	3	38%
Negative	42	2	5%	1	2%

nodes. Four patients with grade 3 tumors had positive lymph nodes (20%). The same trend was present for para-aortic lymph nodes (Tables 5 and 6).

Table 6: Grade, Depth of Invasion, and Pelvic Node Metastasis

Grade, Depth of Invasion, and Pelvic Node Metastasis of Endometrioid Adenocarcinomas			
Depth of Invasion	Grade		
	G1 N=20	G2 N=9	G3 N=6
Endometrium Only N=11	0 (0%)	0 (0%)	0 (0%)
Inner N=8	0 (0%)	0 (0%)	0 (0%)
Middle N=8	0 (0%)	0 (0%)	1 (100%)
Deep N=8	0 (0%)	1 (25%)	1 (100%)

Grade, Depth of Invasion, and Pelvic Node Metastasis of Non-Endometrioid Adenocarcinomas			
Depth of Invasion	Grade		
	G1 N=0	G2 N=0	G3 N=15
Endometrium Only N=5	0 (0%)	0 (0%)	0 (0%)
Inner N=5	0 (0%)	0 (0%)	0 (0%)
Middle N=3	0 (0%)	0 (0%)	1 (33%)
Deep N=2	0 (0%)	0 (0%)	1 (50%)

A correlation between increasing depth of invasion and positive lymph nodes was demonstrated. No patients with tumor confined to the endometrium or inner myometrium (less than 50% myometrial invasion) had nodal metastasis. 23% of patients with pelvic node disease and 25% of patients with para-aortic disease had tumors with at least 50% myometrial invasion.

Thirteen patients (26%) had positive cytology. Those with non-endometrioid histologies had positive cytology 47% of the time, compared to 17% with patients with endometrioid adenocarcinoma. Overall, 15% of patients with positive cytology also had positive lymph nodes. All patients in this study with positive washings were affected with pelvic and para-aortic nodal disease.

Adnexal involvement was present in 2 patients (4%). Regardless of histology, adnexal involvement was not related to nodal disease.

Intraperitoneal spread was highly correlated to metastasis to the pelvic and para-aortic lymph nodes. In the one patient with intraperitoneal spread, both the pelvic and para-aortic nodes were affected. However, the absence of intraperitoneal spread does not exclude nodal disease. In 49 patients with negative intraperitoneal

spread, 4 patients (8%) were affected by positive nodal disease. This trend was seen in endometrioid adenocarcinoma tumors and high-risk tumors.

Lymphovascular space invasion (LVSI) was present in 17% and 13% of endometrioid and high-risk tumor histologies, respectively. Non-endometrioid tumors affected by LVSI had positive pelvic and para-aortic lymph nodes 50% of the time. Endometrioid adenocarcinoma with LVSI was seen to have positive pelvic and para-aortic lymph nodes in thirty-three percent of cases.

Grade and depth of invasion were evaluated in the correlation of nodal disease. Even though both are risk factors, depth of invasion is more influential. Deep invasion of any histology of tumor was correlated with nodal disease. No patients with superficial invasion were affected by positive lymph nodes. All five patients with nodal disease were noted to have at least 50% myometrial invasion (Tables 6 and 7).

Table 7: Grade, Depth of Invasion, and Aortic Node Metastasis

Grade, Depth of Invasion, and Aortic Node Metastasis of Endometrioid Adenocarcinomas			
Depth of Invasion	Grade		
	G1 N=20	G2 N=9	G3 N=6
Endometrium Only N=11	0 (0%)	0 (0%)	0 (0%)
Inner N=8	0 (0%)	0 (0%)	0 (0%)
Middle N=8	0 (0%)	0 (0%)	0 (0%)
Deep N=8	0 (0%)	1 (20%)	1 (100%)

Grade, Depth of Invasion, and Aortic Node Metastasis of Non-Endometrioid Adenocarcinomas			
Depth of Invasion	Grade		
	G1 N=0	G2 N=0	G3 N=15
Endometrium Only N=5	0 (0%)	0 (0%)	0 (0%)
Inner N=5	0 (0%)	0 (0%)	0 (0%)
Middle N=3	0 (0%)	0 (0%)	1 (33%)
Deep N=2	0 (0%)	0 (0%)	1 (50%)

DISCUSSION AND CONCLUSION

GOG 33 was a landmark trial to instill the reform for uterine cancers to become a surgically staged disease. Our primary objective was to compare the trends from GOG 33 to the surgical-pathologic trends noted in this retrospective study of patients who underwent robot-assisted laparoscopic staging of uterine cancers. The two cohorts of patients analyzed were those with endometrial

endometrioid adenocarcinomas and those with non-endometrioid uterine adenocarcinomas.

Overall, several trends noted in our data paralleled the findings from GOG 33 regarding the frequency of nodal involvement and depth of tumor invasion. As expected, the non-endometrioid cohort contained high-risk uterine subtypes, and this group demonstrated an increased rate for metastatic spread outside of the uterus with involvement of the adnexa, pelvic, and para-aortic lymph nodes. All uterine subtypes also showed a positive correlation between lack of tumor differentiation and an increased incidence of lymph node spread. None of the patients with well-differentiated tumors were noted to have nodal spread. Conversely, all of the patients with pelvic or para-aortic lymph node metastasis were seen to have poorly differentiated grades of tumor, regardless of histology. There was one patient with a moderately differentiated tumor grade who had spread to the pelvic and para-aortic lymph nodes. Lastly, all of the patients with positive pelvic and para-aortic nodal metastases had greater than 50% myometrial invasion.

Our results show two important differences between GOG 33 and other contemporary trials. The results from GOG 33 show a 2% rate of isolated positive para-aortic nodes without pelvic nodal involvement. In a contemporary trial from 2008, Mariani et al describe a 16% isolated positive para-aortic rate in those patients with deeply invasive, high grade tumors.⁷ Our study, on the other hand, shows a 0% isolated positive para-aortic lymph node rate with robot-assisted surgery, in both endometrioid and non-endometrioid tumors. We show that all patients with positive para-aortic lymph nodes also had positive pelvic lymph nodes.

A second difference between our results and GOG 33 is the concomitant rate of positive aortic nodes when the pelvic nodes harbor metastatic disease. GOG 33 showed approximately one-third of aortic nodes will be positive with pelvic nodal disease.³ Instead, our results show a higher rate with 80% aortic involvement. It is possible that our study is underpowered to make the same observations as previous studies. Another explanation may be that the magnification present during robotic surgery allows the surgeon to better visualize enlarged lymph nodes, leading to their removal, with fewer reported instances of isolated para-aortic tumor spread. Further studies with robot-assisted surgical staging are needed to evaluate this possibility.

Our data is significant in that it parallels the results of previous landmark studies, providing further validation for robot-assisted laparoscopic surgical staging of endometrial carcinoma. Previous research has evaluated conventional laparoscopic surgical staging. The GOG LAP 2 trial compared conventional laparoscopy to laparotomy and demonstrated decreased hospital inpatient stays and blood loss with low rates of recurrence.⁸ Additionally, other publications have compared the outcomes of robotic surgery to conventional laparoscopy. Corrado et al examined the surgical and oncological outcomes in robotic surgical staging in obese patients with endometrial cancer. The authors demonstrated the safety, feasibility, and reproducibility of robotic surgical staging.⁹

Nieto et al examined the rates of robotic-assisted procedures, as well as survival, in non-endometrioid endometrial cancers. The authors report that 75% of all minimally invasive surgeries were performed robotically without adversely impacting survival.¹⁰ Additional studies have evaluated other outcomes, such as blood loss, nodal counts, and post-operative complications in laparoscopic surgical staging.^{11,12}

Despite the work previously performed from the above studies, no other study has evaluated the surgical-pathological trends in robot-assisted surgical staging for uterine cancers as did GOG 33. In summary, the results of this study validate the trends previously known from GOG 33, in a population undergoing robot-assisted surgical staging for uterine carcinomas.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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