PAIN AND FERTILITY OUTCOMES POST ENDOMETRIOSIS SURGERY AT GROOTE SCHUUR HOSPITAL

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DECLARATION

I, Dr Kita Christian Kalwiba, declare that this research is based on my independent research and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to another University. This work has not been reported or published prior to registration for the MMed degree.

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ABSTRACT

Background

Endometriosis is characterized by the development of endometrial-like tissue outside of the uterus, which results in a persistent inflammatory response. It is an estrogen-dependent chronic disorder and affects millions of women in their reproductive age. The true incidence is not well known but it is around 6% or more.

The clinical presentation of endometriosis varies. Most women will present with secondary dysmenorrhea, dyspareunia, pelvic pain and infertility. Laparoscopy is the gold standard diagnostic tool for endometriosis, with surgical management being the mainstay in the treatment of endometriosis.

Objectives

The primary objective of the study was to determine the effect of surgery on pain and infertility in women with endometriosis. Secondly, to determine the demographics, severity of endometriosis and laparoscopic complications, recurrence of symptoms and need for repeat surgery.

Methodology

To achieve the objectives of this research, the study design was a retrospective study. Seventy-five women with endometriosis who attended the reproductive Medicine Unit at Groote Schuur Hospital in Cape Town from January 2016 to December 2018 were analysed.

Results

The mean age in this cohort was 32 ± 7 years with the mean BMI being 28.2 ± 6.6. Eighty-seven percent were HIV negative and 71% were smokers. The prevalence of endometriosis among women undergoing laparoscopic surgeries was 30.6% over the 3-year period. Chronic pelvic pain was the most common symptoms in 86.6% of patients. Dysmenorrhea was reported in 72.6%, 36.5% had dyspareunia, 50% had heavy menstrual bleeding and 53% had primary or secondary infertility. Chronic pelvic pain and infertility were found in 42.67%. Post laparoscopic surgery, the pain improved in 90%, 82%, 85% and 61% of patients with a P value < 0.05 at 6 weeks, 6 months, 1 year and 2 years, respectively. Thirty percent of women operated primarily for infertility conceived spontaneously within 2 years. Nine point three

percent of patients were reoperated with a mean duration from primary to second surgery of 3 years $\pm$ 1.3. More than six percent (6.6%) had intraoperative complications with two patients having ureteric injury, another two with bowel injuries and one who had vascular injuries.

Conclusion

This study has shown a great improvement in pain post laparoscopic surgery varying from 90% at 6 weeks to 61% at 2 years. About one-third of patients operated on for primarily infertility will conceive spontaneously post endometriosis surgery.

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ABBREVIATIONS

ASRM	American Society of Reproductive Medicine
BMI	Body Mass Index
CA125	Cancer Antigen 125
DIE	Deep infiltrating endometriosis
GSH.	Groote Schuur Hospital
HIV	Human immunodeficiency virus
IVF	In vitro fertilisation
LUNA	Laparoscopic uterosacral nerve ablation
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
RMU	Reproductive Medicine Unit

1. INTRODUCTION

1.1 Background

Endometriosis is characterised by the development of endometrial-like tissue outside of the uterus, which results in a persistent inflammatory response.(1) Endometriosis affects millions of women in the reproductive age group worldwide. It is an oestrogen-dependent chronic disorder with serious socioeconomic impact.

The World Endometriosis Research Foundation Endocost study has shown that the cost arising from women with endometriosis treated in referral centers are substantial, resulting in an economic burden that is at least comparable to the burden of chronic diseases like diabetes mellitus.(2)

Endometriosis has a varied clinical presentation; some women will experience pain and/or infertility, and others no symptoms at all. The diagnosis is based on each woman's history, symptoms and signs, and is corroborated by physical examination and imaging techniques. The diagnosis lacks a biological marker, which makes it more challenging. It is definitively diagnosed by histology taken at laparotomy or laparoscopic procedure. The visual recognition of endometriosis alone is of limited value as it has a high false positive rate.(1)

Laparoscopy is the gold standard for diagnosis. The 'see and treat' approach is preferred, with varied outcomes in terms of pain and fertility.

This is the first study to assess the outcome of post-surgical management of endometriosis in the Reproductive Medicine Unit (RMU) at Groote Schuur Hospital (GSH).

I am unaware of any similar studies done in South Africa.

1.2 Literature review

This chapter will explore a brief literature review in line with the objectives of the current study. Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. It is predominantly found in the pelvis but occasionally in the vagina, caesarean section scar, bladder and rectum. Rare extrapelvic sites include the liver and lungs. Endometriosis differs from adenomyosis, which is the presence of endometrial-like tissue in the myometrium. It is believed to be the second most common reason for surgery in pre-menopausal women.

The true incidence of endometriosis is not well known but some literature reports that up to 6% of women in the reproductive age group are affected. Endometriosis has been reported in 4.1% of asymptomatic women undergoing laparoscopy for tubal ligation.(3) In the United States, population-based data suggests that over four million women of reproductive age have been diagnosed with endometriosis, with six out of ten remaining undiagnosed.(4) The mean age of diagnosis ranges from 25 to 35 years. It is rare in premenarchal girls but may be found in 50-70% of adolescents with chronic pelvic pain or dyspareunia.(5)

Endometriosis, although not a life-threatening disease, is a debilitating condition, seriously affecting the quality of life of women globally. It is not restricted to particular countries or ethnicities. Despite its high prevalence, women continue to experience on average eight years delay in diagnosis. Higher rates of absenteeism and overall work productivity loss increase with the severity of the disease.(6) Endometriosis is also associated with an increased incidence of depression, reduced social activities, an adverse impact on intimate relationships and a negative economic impact. The annual cost of productivity loss varies from country to country, and between developed and developing countries with the annual loss estimated at $208 in Nigeria versus $23712 in Italy.(6) These studies only took absenteeism into consideration.

The pathogenesis of endometriosis is still poorly understood. Two main theories emerge from the etiology hypothesis:

- The most popular theory is implantation of the endometrial cells following retrograde menstruation, proposed by Sampson in 1921.(3,7)
- Coelomic metaplasia of the epithelium theory has also been described, as the pelvic peritoneum is embryologically derived from epithelium of the coelomic wall. It postulates that the peritoneum contains undifferentiated cells able to transform into endometrium cells.(3) This theory was proposed by Robert Meyer in 1919 and supported by Ferguson in 1960.

Other theories include vascular dissemination, direct transplantation and altered immunity. No single theory can explain all cases of ectopic endometrial tissue. A genetic factor is not completely excluded in the pathogenesis of endometriosis. The disease is frequent in certain families.(8) The risk of having endometriosis is eight-fold higher in women with first degree relatives affected.(8)

Iatrogenic endometriosis has also been reported following a gynaecological or obstetrical procedure such as an abdominal delivery with implantation of endometrial cells in the scar.(9,10)

Pain is the most common clinical presentation of endometriosis. Dyschezia and deep dyspareunia are particularly troublesome if there are deposits in the pouch of Douglas. The pain is described as chronic, cyclic, persistent and progressive. The degree of pain does not always correlate with the severity of disease found at surgery.

The second most common presentation associated with endometriosis is infertility, affecting 30-50% of infertile women.(11) It causes fertility through several pathways such as pelvic adhesions, anatomical pelvic distortion, inflammatory changes in the peritoneal fluid that affect sperm motility, and endometriomas that affect ovarian reserve.(12)

No biomarker has been identified to diagnose endometriosis. The development of a biological test with higher sensitivity and specificity is urgently needed; unfortunately, all have fallen short thus far. Cancer Antigen 125 (CA125) has been evaluated in an observational prospective study, with specificity of 93% and sensitivity of 52%.(13) CA125 was significantly more sensitive to the diagnosis of moderate or severe endometriosis compared to minimal disease.(14) Unfortunately, a negative test is unable to rule out endometriosis.

Transvaginal ultrasound is traditionally used to evaluate pathologies of the female intra-pelvic organs. This examination should be extended to the anterior and posterior compartments to identify nodules or sonographic signs of deep infiltrating endometriosis (DIE).(15) This offers the benefit of preoperative planning of a single procedure with a good surgical team with an interest in endometriosis. Transvaginal ultrasound compared to magnetic resonance imaging (MRI) in the diagnosis of DIE has similar accuracy of around 73%.(14) Ultrasound, however, is readily available and cheap.

Laparoscopy is the gold standard diagnostic tool for endometriosis.(5) It offers two advantages: to stage the disease and treat it simultaneously. Diagnostic laparoscopy should be replaced with a ‘see and treat’ approach.(16) It also provides histological evaluation of excised lesions.

Endometriosis is classified in four stages according to the American Society of Reproductive Medicine (ASRM), with stage 1 minimal disease, stage II mild disease, stage III moderate disease and stage IV severe disease.(17)

Medical management of endometriosis consists of adequate analgesia including non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal treatment for suppression of the disease. Hormonal therapy that can be offered consists of combined oral contraceptives, progestogens including the Mirena IUS, anti-progestogen and GnRH agonist. If medical treatment fails after 6 months, the patient should be referred to a clinician with good surgical expertise in the management of endometriosis.(18) The goal of medical therapy is to reduce pain by decreasing inflammation as well as local ovarian hormonal production. Medical treatment is not curative but suppressive, and symptoms will recur after treatment discontinuation.(7) Pharmacological treatment is helpful following surgery and may be effective to limit recurrence and progression of the disease. (16,17)

There is no medical therapy for endometriosis associated with infertility although GnRH agonist suppression for a period of three to six months prior to in vitro fertilisation (IVF) does improve the clinical pregnancy rate.(19)

Surgical management is the mainstay in the treatment of endometriosis. The aim is to restore anatomy, free adhesions and ablate or excise endometriotic lesions. Comparing the two techniques (ablation versus excision) in terms of pain control, they both proved effective, with no statistical difference between the two procedures.(20) Excision of endometriomas by cystectomy is effective, having lower recurrence rates than drainage and coagulation, but may affect ovarian reserve in women wishing to preserve fertility.(16)

Laparoscopic uterosacral nerve ablation (LUNA) does not appear to offer additional benefits. It is also associated with uterine prolapse and transection of the ureter.(21,7)

Presacral neurectomy decreases midline dysmenorrhea (87% reduction),(7) and is also beneficial when combined with excision or ablation of endometriosis. It is, however, a technically challenging procedure with significant risk of bleeding intra-operatively and constipation and urinary retention post-operatively.(21,16)

Few studies have been performed to assess the outcome in terms of pain post laparoscopy. Abbott et al. found an 80% improvement in pain after laparoscopic excisional surgery. Other aspects of quality of life also improved significantly at six months post procedure. Approximately 20% of women did not experience any improvement.(22) Disease progression at the second surgery was demonstrated for women having initial diagnostic laparoscopy only in 45% of cases, with 33% remaining static and 22% improving.(22) In the second cohort of

patients who had diagnostic laparoscopy followed by a second laparoscopy with excision of endometriosis, 83% reported pain improvement post-surgery. In this study 12 patients had fertility issues and 50% conceived during the study period.(22)

Research performed in the United Kingdom by Sutton et al. in 1994 had similar findings at six months post-operative laparoscopy, with 73.7% of patients achieving pain relief with mild and moderate disease. If patients with Stage I disease were included, 62.5% reported pain improvement.(23) Results were the poorest for stage I and the best for stage III when the author analysed the outcome according to the disease stages.

According to an article published by Marcoux et al. in the New England Journal of Medicine in 1997, their randomised control trial compared the effect of operative surgery with either excision or ablation in infertile women with mild or minimal disease with adhesiolysis of peri-adnexal adhesion with diagnostic laparoscopy only. The trial found that laparoscopic surgery increased the probability of pregnancy that lasted more than 20 weeks in the first 36 months by 73%.(24)

A study done by Soriano et al. at the Endometriosis Center and IVF at the University of Tel Aviv in Israel evaluated the fertility outcome of women with severe endometriosis stage III and IV according to the ASRM classification and repeated IVF failure. After laparoscopic surgical management, 42.3% conceived and carried pregnancy to term, 9% conceived spontaneously, and the remainder following IVF. The women who delivered were younger with lower rates of diminished ovarian reserve.(12)

In a similar study performed in Australia at the School of Women's and Children's Health conducted in women with severe disease Stage III and IV after operative laparoscopy, 72% of infertile women became pregnant and 56% had a live birth. The median time to pregnancy was 12 months with 63% achieved by expectant management post-operatively.(11)

1.3 Research question

What is the outcome for women undergoing surgery for endometriosis in the Reproductive Medicine Unit at Groote Schuur Hospital?

1.4 Objectives

The primary objective of the study was to determine the effect of surgery on pain and infertility

in women with endometriosis. Secondly, to determine the demographics, severity of endometriosis and laparoscopic complications, recurrence of symptoms and need for repeat surgery in this cohort.

2. STUDY METHODOLOGY

2.1 Study design

To achieve the objectives of this research, a retrospective study was deemed to be the most fitting study design.

2.2 Study setting

The study was carried out at Groote Schuur Hospital, which is the tertiary referral centre for endometriosis in the Cape Town Metro West area. Endometriosis surgery is performed by the reproductive medicine specialist and fellow in the Reproductive medicine unit. It is a busy unit that runs several clinics: general gynae outpatients, gynae endocrine, infertility, and recurrent pregnancy loss clinics, amongst others. Surgical interventions are performed for patients seen at these clinics, as well as those referred from private and other institutions outside our catchment area which lack the necessary expertise. A multidisciplinary team, involving a surgeon or urologist, is involved when complicated DIE is suspected. With two single slates and two double slates per month, the unit performs close to 300 surgical interventions annually.

2.3 Study population

Women with visual or histological confirmed endometriosis at laparoscopy or laparotomy treated in the RMU from January 2016 to December 2018 formed part of this study and were followed up to two years post-surgery.

Inclusion criteria:

- Women diagnosed with endometriosis who had surgery for infertility
- Women diagnosed with endometriosis who had surgery for chronic pelvic pain
- Women with endometrioma
- Women diagnosed with endometriosis who had repeat laparoscopy surgery during the research time frame

Exclusion criteria:

- Women with chronic pelvic pain not diagnosed with endometriosis at laparoscopy
- Infertile women not diagnosed with endometriosis
- Women diagnosed with non-endometrioma ovarian cyst
- Women diagnosed with endometriosis with no follow up
- Women with pain not specified if indication of surgery was primarily pain
- Women with endometriosis found at laparoscopy or laparotomy in other gynae units

2.4 Data collection and statistical analysis

Patients hospital details, were collected from the operating theatre register. Folder numbers were used to trace the patients medical records(folders). Folders were retrieved for patients' demographics and initial indications for surgery as well as other parameters necessary to our analysis. The data collection tool was anonymous to protect patient confidentiality.

We summarised continuous variables using mean (standard deviation) and categorical variables using count (percent). We compared baseline pain score (ordered categorical variable) and post baseline pain score measurements using Wilcoxon matched-pairs signed rank-test. We presented estimates of time to second surgery since first surgery using the Kaplan-Meier graph. Statistical significance was set at $p< 0.05$.

2.5 Ethics consideration

The data were treated confidentially and were protected. Only the investigative team of this study had access to the data collected. Patient data were kept anonymous at all times during the research. Permission from relevant authorities was obtained before proceeding to the collection of the data. The Provincial Health Research Committee (HREC) and the Chief Executive Officer of GSH were contacted for permission to use patient folders, and permission was granted (Appendix C and B, respectively). Due to the nature of this research, which is a retrospective study, patient consent was not required.

2.6 Budget and budget motivation

Expenses	**Estimated cost**
Stationery, printing and sundries	R1000
Statistician	R4000
Total	R5000

2.7 Reporting of results

The study findings will be made known to the Department of Obstetrics and Gynaecology at Groote Schuur Hospital and all collaborating partners. Presentations will be delivered at relevant departmental and national forums. A manuscript will be prepared for publication. The dissertation will be submitted for examination as an MMed in obstetrics and gynaecology.

3. RESULTS

3.1 Case identification

Eighty-seven folders were identified from the theatre registry as endometriosis cases from January 2016 to December 2018. Of these, 32 had presented in 2016, 21 in 2017 and 34 in 2018. Twelve folders could not be retrieved, therefore 75 patients out of the 87 were included in and analysed for this study. Some of the 75 patient files had missing information regarding some of the variables.

3.2 Demography

The mean age of patients enrolled in this study was 32 ± 7 years with the youngest being 14 and the oldest 51 years old, with a mean body mass index (BMI) of 28 ± 6 kg/m^2. Among the 75 women, 67 (87%) tested negative for the human immunodeficiency virus (HIV), four (5.5%) were HIV positive, and the HIV status of five women (6.8%) was unknown. Of the 75 patients, the smoking history of 64 was documented and nine patients' smoking history was undocumented. Forty-six out of the 64 were smokers.

These demographic characteristics are presented in Table 3.1 and 3.2.

	Min	Mean	Max	SD
Age (years)	14	32	51	± 7,2
BMI kg/m^2	16,5	28,2	44,5	± 6,6

Table 3. 1: Demography of age and BMI

	N	%
HIV	67 (negatives)	87%
Smokers	46	71%

Table 3. 2: Demography of HIV status and smoking

The total number of women who had laparoscopic surgeries in the research time frame was 284, breaking down into 104, 79 and 101 in 2016, 2017 and 2018, respectively. The prevalence of endometriosis in the total number of operative laparoscopies over the three-year period was 30,6% with a yearly prevalence of 30,7% (34/104) in 2016, 26,6% (21/79) in 2017 and 33,7% (34/101) in 2018. The number and prevalence of laparoscopies and endometriosis over three years are presented in Figure 3.1.

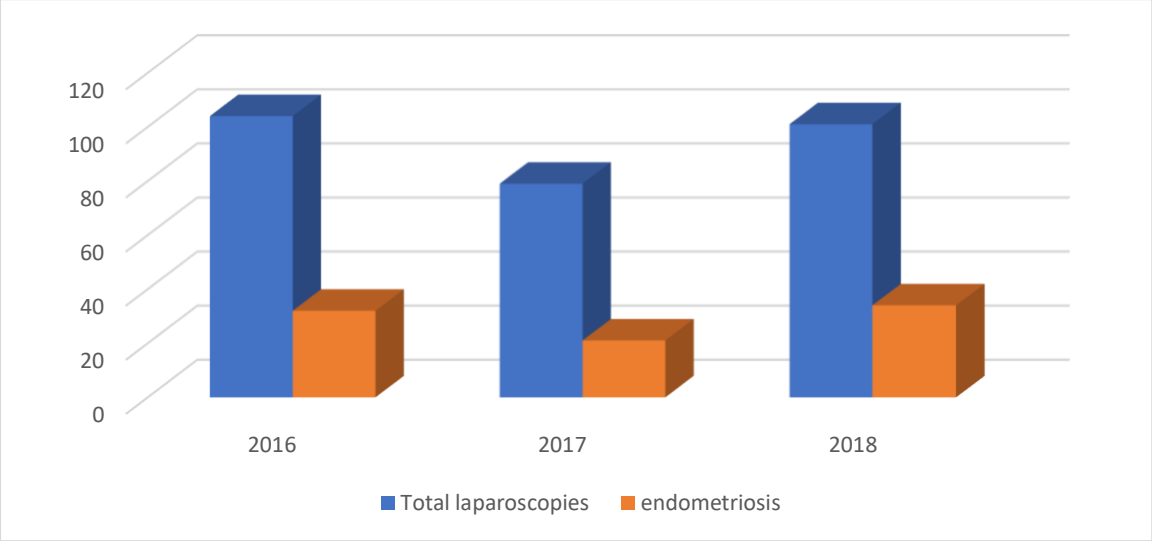

Figure 3. 1: Total laparoscopies and endometriosis

3.3 Clinical presentation

In this cohort, most of the patients, 49 (65,3%), were nulliparous. Fifty-three (72.60%) presented with dysmenorrhea and 65 (86,6%) with chronic pelvic pain. The pain was graded into three categories according to severity namely mild, moderate, and severe.

Of the 75 patients in this research, 47 (62,3%) had severe pain, 14 (18.7%) had moderate pain, four (5,3%) had mild pain and 10 (13,3%) did not have any pain. The mean duration from onset of pain to the diagnosis of endometriosis was 4.3 ± 4 years.

Twenty-seven (36.5%) patients enrolled in the study had dyspareunia and two (2,7%) suffered from dyschezia. Almost half (36/72) presented with heavy menstrual bleeding, it was not clearly stated in three patient files if the patient had heavy menstrual bleeding or not. Among

the 75 patients, 40 (53%) had primary or secondary infertility and 32 (42,67%) presented with both pain and infertility.

The clinical presentation of the participants in this cohort are summarised in Table 3.3 and Figure 3.2.

SYMPTOMS	N	PERCENTAGES %
Pelvic pain	65	86.6%
Dysmenorrhea	53	72.6%
Dyspareunia	27	36.5%
Dyschezia	2	2.7%
Heavy menstrual bleeding	36	50%
Infertility	40	53%
Infertility + Pain	32	42,67%

Table 3. 3: Clinical presentation

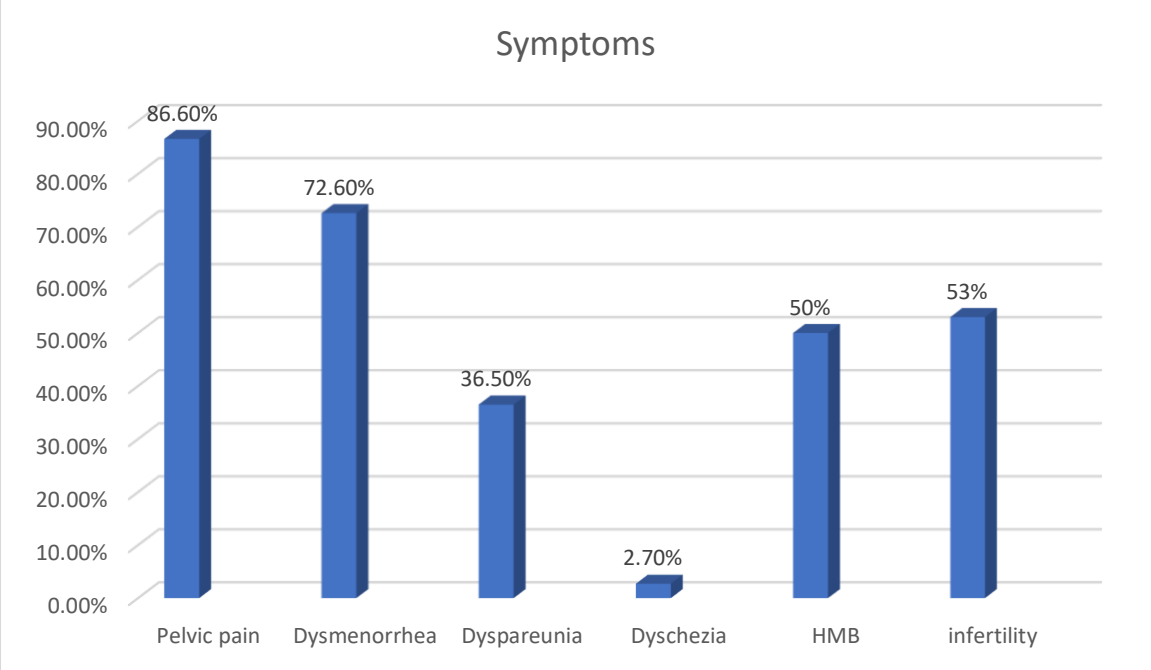

Figure 3. 2: Graphic representation of symptoms

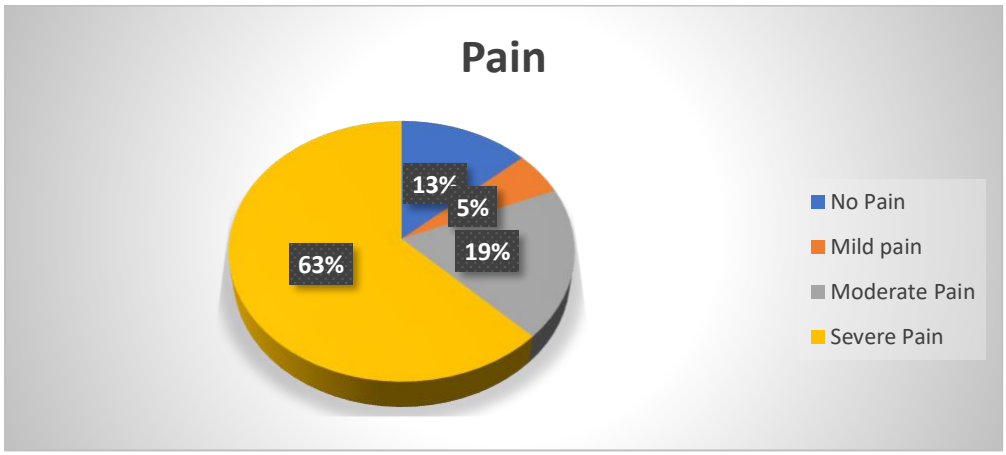

Figure 3. 3: Severity of pain

In this cohort, 24 patients (32,4%) had previous laparoscopic surgery for endometriosis. Ten (13,5%) had had at least one previous caesarean section and 11 (14,6%) had had other abdominal surgeries. Figure 3.4 is a graphic representation of these previous surgeries.

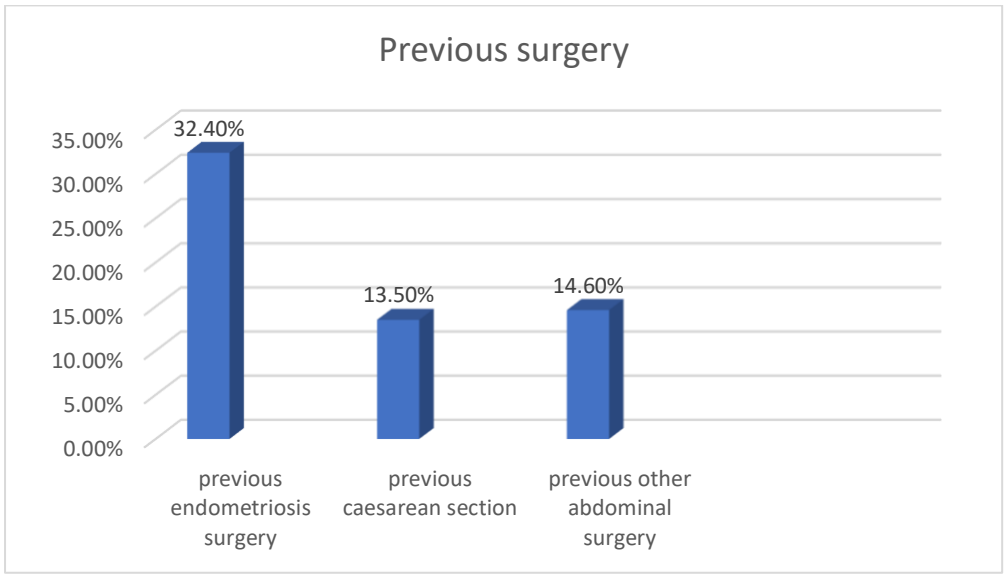

Figure 3. 4: Previous surgeries

3.4. Indications for surgery and intra-operative findings

For the majority of patients, that is 49 patients (65%) the primary indication for surgery was pain and for 26 patients (34,7%) it was infertility. The approach was laparoscopic in 69 (92%), with six (8%) having a laparotomy. The ASRM classification of endometriosis to stage the disease intraoperatively was used and the results were as follows: Twelve patients (16,2%) had Stage 1 endometriosis, 22 patients (29,7%) Stage 2, 14 (18,9%) Stage 3, and 26 patients (35,2%) had Stage 4 endometriosis. Twenty-seven patients (36%) had endometriosis with endometrioma, nine (12%) had unilateral hydrosalpinx and three (4%) had bilateral hydrosalpinges.

The indications for surgery and the intra-operative findings in terms of endometriosis are presented in Figure 3.5 and 3.6.

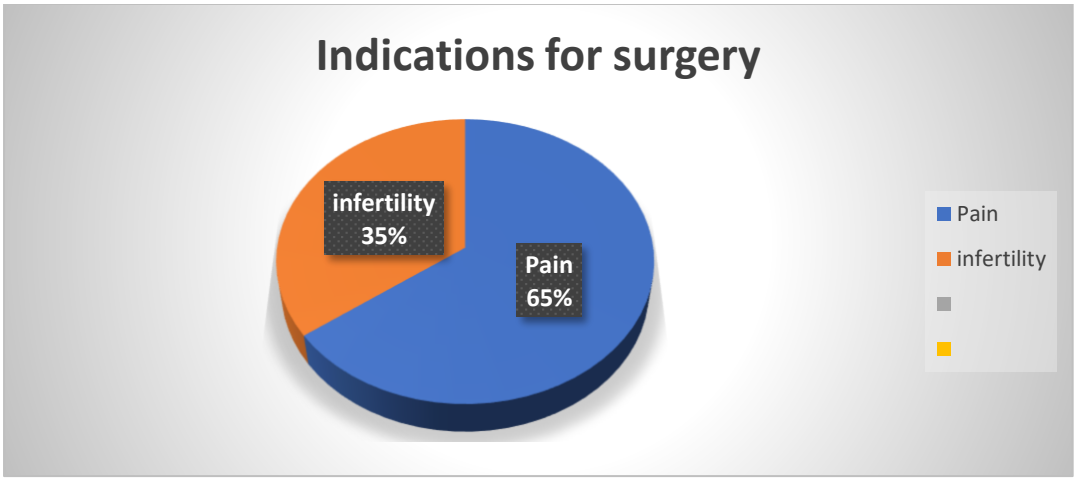

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Figure 3. 5: Indications for surgery

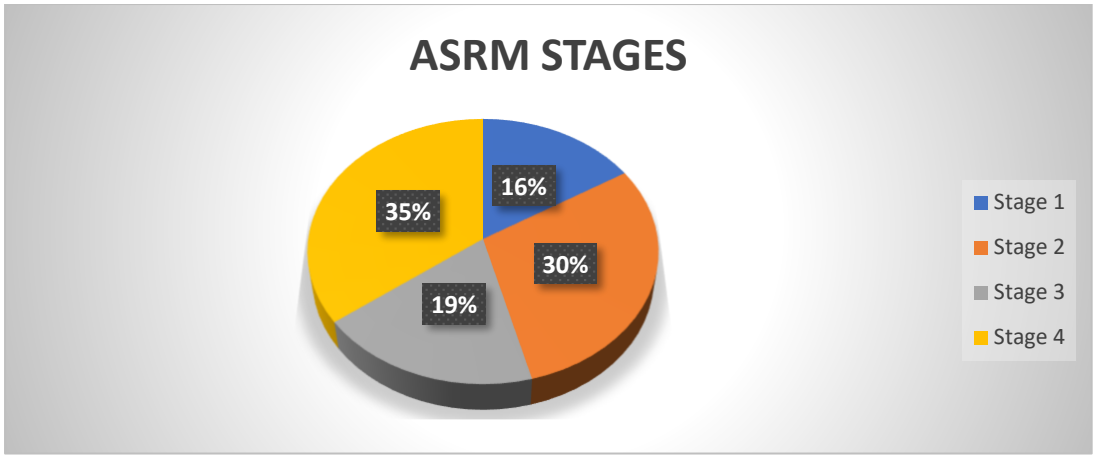

Figure 3. 6: Endometriosis ASRM stages

Most patients, 39 (58.2%, n=67), particularly those primarily operated on for pain, were given hormonal suppression at discharge. Combined oral contraceptives were used in 13 (36%) followed by Mirena in 10 (27,8%), 6 (16,67%) patients used Dienogest, 4 (11,1%) oral provera and the least used GnRH analog (zoladex) in 3 patients (8,3%). And in the last 3 patients the type of hormonal suppression used was undocumented. At 6-months, 1-year and 2-year visits patients continuing with suppression were 29 (59%, n =49), 23 (46%), and 18 (36%).

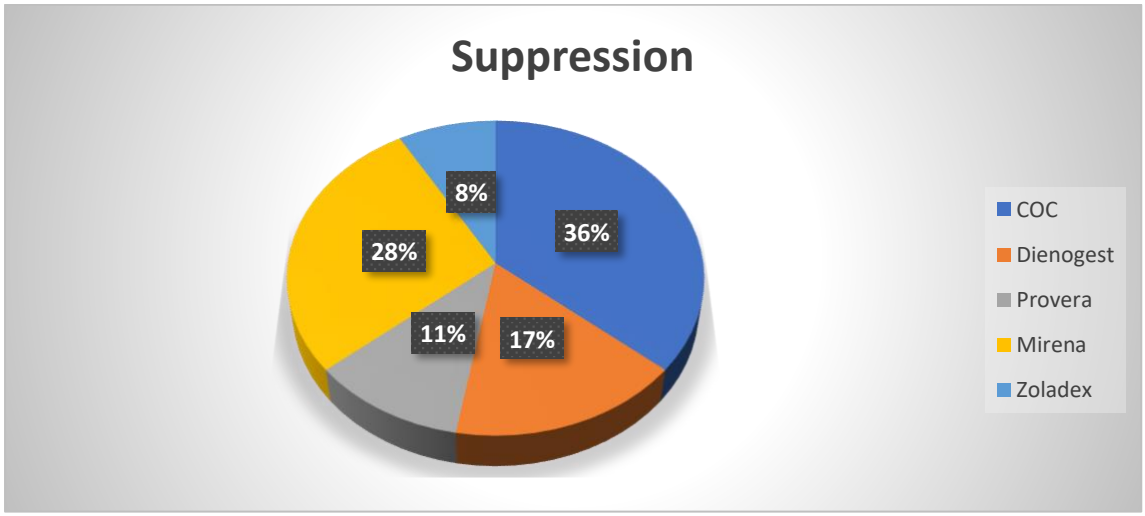

Figure 3.7: Suppression at discharge

3.5 Pain outcomes

With regards to pain improvement from a higher category (severe or moderate) pre surgery to mild or no pain post operatively, the following was found: At six weeks, 36 patients (90% n =40) improved with a P value of < 0.05. Three (7,5%) patients' pain severity remained unchanged. At six months visits, 29 (82% n= 35) with P value < 0.05 were found withfive patients having had their pain unchanged. At one year, 23 (85%) out of 27 reported an improvement in pain with P value < 0.05. Only three (11.1%) patients' pain severity was equal to that of the preoperative category. Finally at two years, 11 (61% n 18 and P value < 0.05) patients reported an improvement in their pain levels.

The pain outcomes as measured at visits over two years are presented in figure 3.7.

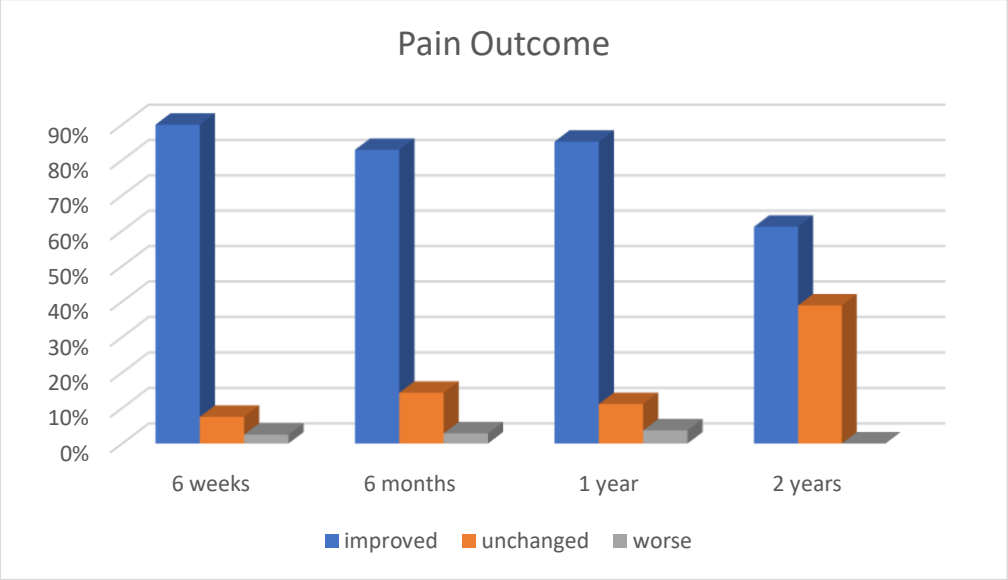

Figure 3. 7: Pain outcomes

3.6 Fertility outcome

Of the 26 patients operated primary for infertility, six patient folders were not retrieved. Among the remaining 20, two (10% n =2) conceived in the first year post-surgery and four (22%) conceived in the second year . A total of six (30%) patients conceived spontaneously within the two years of the follow-up in this study. During the follow-up period, six other patients were offered assisted reproductive techniques, mainly IVF. Four patients had an IVF cycle,

with the following outcomes: One patient had one cycle but did not conceive due to poor ovarian stimulation response; two had two IVF failed cycles and the last one had four unsuccessful IVF cycles. The duration from endometriosis surgery to ovarian stimulation ranged between 7 and 12 months with a mean of 8,5 months.

3.7 Reoperation rate

The study revealed that 7 (9,3%) had repeat surgery from January 2016 to December 2021. The mean duration from primary to the second surgery was three years, with a standard deviation of 1.3 years.

Figure 3.8 shows the surgical curve indicating the duration between surgeries.

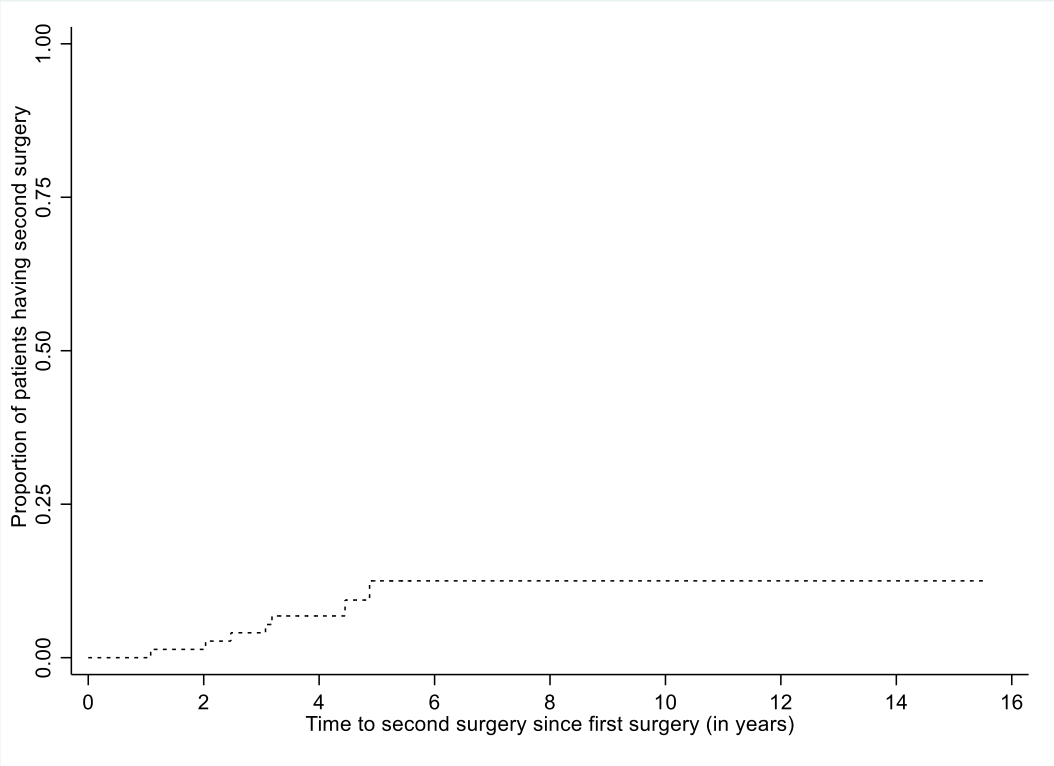

Figure 3. 8: Survival curve

3.8 Complications

Among the 75 patients enrolled in this study who had surgery for endometriosis from January 2016 to December 2018, ten presented with intra-operative injuries. Five (6,6%) patients had an intraoperative injury to the viscera, two had (2,7%) ureteric injury, two had (2,7%) bowel injuries and one (1,3%) patient presented with vascular injury.

Figure 3.9 presents the intra-operative complications suffered by patients who underwent surgery for endometriosis.

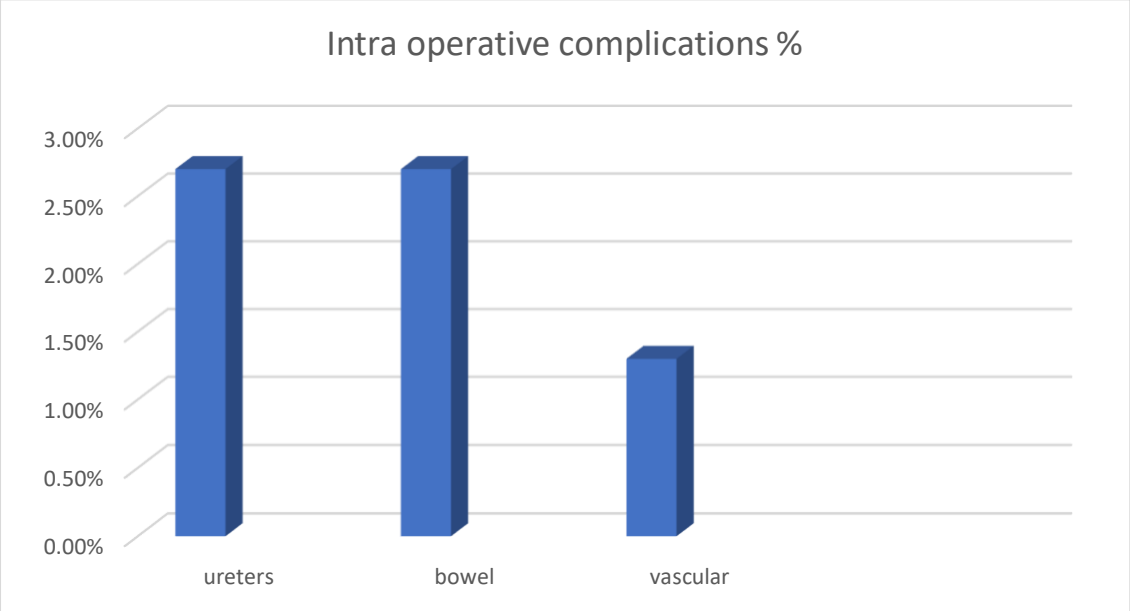

Figure 3. 9: Intra-operative complications

4. DISCUSSION AND CONCLUSION

4.1 Discussion

This study assessed the outcome of post-surgical management of endometriosis and other variables in keeping with our primary and secondary objectives.

Endometriosis is a debilitating disease that negatively impacts the quality of life in the reproductive age group and adolescent girls. The demographic characteristics of the patients in our cohort showed a mean age of 31.7 years, with the youngest patient being 14 years.

The clinical presentation of endometriosis differs but the main symptoms are dysmenorrhea, non-cyclical pelvic pain, dyspareunia and infertility, amongst others.

The findings of this present research concur with other researchers' results. This study revealed that 72,6% participants presented with dysmenorrhea, 86% with chronic pelvic pain, 36.5% with dyspareunia, 50% with heavy menstrual bleeding, and only 2,7% with dyschezia.

A study done by Sinaii et al. analysing the characteristics of 1 000 women with endometriosis revealed that the most common symptoms were dysmenorrhea (79%) and pelvic pain (69%). The authors also found that 48% of women with endometriosis were using more overnight pads, which is generally associated with heavy menstrual bleeding.(25) A 2016 study by Soriano et al. from the endometriosis centre in Tel Aviv shows that dysmenorrhea was present in a large majority of women affected by endometriosis before surgery (87%), followed by dyspareunia at 41%.(12)

The mean duration from onset of symptoms to diagnosis was 4.3 ± 4 years in this study, which corroborates with the finding by Nnoaham et al. that there was a delay in diagnosis of 6.7 years from the beginning of the symptoms.(6)

Laparoscopic surgery for endometriosis, be it excision or ablation of the lesion, significantly improves pain when comparing the pre-operative and post-operative pain scores. In the current study the pain improved 82%, 85% and 61% at 6, 12 and 24 months, respectively. Similar findings were observed in different studies across the world. Nezhat et al., in a paper published in 2019 on how to manage pain associated with endometriosis optimally, revealed that there was a 65% pain improvement at 12 months.(7)

Abbott et al. in their article published in 2004, comparing laparoscopic surgery to a placebo, revealed an improvement in pain in 80% of women after 6 months,(22) showing similar results to our findings. In their second group of patients, they reported an 83% improvement in pain after the second surgery.(22) The improvement rate in this study dropped with lapse of time, with the rate of suppression also decreasing. This is probably due to the disease progression after the stoppage of suppression.

In terms of fertility outcome, this research revealed a high association between infertility and endometriosis, with 53% of participants having either primary or secondary infertility. It also showed that 30% of patients conceived spontaneously after two years of observation: 10% in the first year and 20% in the second year of investigation. The pregnancy rate was increasing over time, and if the observation was longer than 24 months the pregnancy rate could have been higher. Regarding the zero percent pick-up rate after the assisted reproductive technique, it was quite difficult to come to a conclusion as the sample size was very small at only six patients. One patient had a poor response to ovarian stimulation due to poor ovarian reserve. Also, Covid might have impacted negatively on patients' IVF cycle in 2020 as the andrology laboratory at Groote Schuur Hospital was temporarily closed.

A study by Llarenaet al. in 2019 reported that the pregnancy rate after laparoscopic surgical intervention was ranging between 30 to 60% over a period of 12 to 36 months of observation.(26)

Marcoux and al., in their Canadian multicenter study on laparoscopy in infertile women published in 1994, reported a 30.7% increase in the probability of conceiving after the laparoscopic operation.(24)

In a large prospective study by Abbott published in 2017 in the Australian and New Zealand Journal of Obstetrics and Gynecology, women having surgery for endometriosis revealed accumulative pregnancy rates of respectively 36%, 50%, and 67% at 12, 24 and 36 months, respectively.(11)

4.2 Study limitations

The sample size of 75 patients was relatively small and did not allow the statistician to assess the improvement in pain and fertility rate according to the stages of the disease. We were for the same reason also unable to compare the effectiveness of different suppressions formulas used. Race as a variable was not included due to ethical reasons, also because it is no longer captured in a patient's demography at Groote Schuur Hospital. The study findings can therefore not answer to the beliefs of many gynaecologists in terms of the paucity of endometriosis in black women.

4.3 Conclusion

The prevalence of endometriosis, which has a negative impact on the quality of life of affected women in their reproductive years, is most likely higher than what is currently known. It is not only underdiagnosed but there is also a long delay of four to eight years in the diagnosis. Operative laparoscopic surgery is an effective treatment modality for pain associated with endometriosis when done by a skilled surgeon, with an improvement in pain severity of around 80% in the first year post-surgery, as this research has shown. Suppression is paramount in the management of this category of patients. The chance of spontaneous conception was about 30% in our centre over a 2-year period.

4.4 Recommendations

- Patients with symptoms suggestive of endometriosis should be referred to a centre with expertise in endometriosis surgery.
- The reproductive firm should design a pre-operative assessment form for patients highly suspected of having endometriosis. The form should have a good pain scoring system like the analog pain system, and the impact of the pain on the patient's quality of life.
- The endometriosis fertility index, a novel pelvic assessment, should be introduced in the firm to assess patients who need an assisted reproductive technique post-

operatively, as well as those who should be subjected to a longer period of attempting spontaneous conception.

- The reproductive firm should come up with a post-operative follow-up form for patients with confirmed endometriosis. This should include assessment of symptoms; a pain scoring system; assessing an improvement in quality of life; suppression type and reason for discontinuing e.g fertility desire; and fertility desire at each follow-up visit.

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APPENDICES

Appendix A: Data collection sheet

Study identifier n*:

Demographics

Age: DoB: / / Date of surgery / / 20..

HIV status: ☐ positive ☐ negative ☐ unknown

BMI: ☐ ☐ unknown

Smoker: ☐ yes ☐ no

PRESENTATION

Pain: ☐ severe ☐ moderate ☐ mild

Dysmenorrhea: ☐ yes ☐ no

Dyspareunia: ☐ yes ☐ no

Dyschezia: ☐ yes ☐ no

Duration of Pain: ☐ < 1 yr ☐ > 1yr < 5 yr ☐ > 5yr

Heavy Menstrual bleeding: ☐ yes ☐ no

Infertility: ☐ yes ☐ no

Duration of infertility:

Previous surgery endometriosis surgery: ☐ yes ☐ no

Previous caesarean section ☐ yes ☐ no

Previous other abdominal surgery ☐ yes ☐ no

Indication for surgery: ☐ primarily pain ☐ primarily infertility

Approach: laparoscopy ☐ laparotomy ☐

FINDINGS

Stage: ☐ 1 ☐ 2 ☐ 3 ☐ 4

Endometrioma: ☐ yes ☐ no

Hydrosalpinges: ☐ yes ☐ no. If yes, bilateral ☐ unilateral ☐

Co-existing PID: ☐ yes ☐ no

Histology proven: ☐ yes ☐ no

COMPLICATIONS: ☐ yes ☐ no

Bladder injury: ☐ yes ☐ no

Ureter injury: ☐ yes ☐ no

Bowel injury: ☐ yes ☐ no

Vascular injury: ☐ yes ☐ no

Convert to open laparotomy: ☐ yes ☐ no

FOLLOW-UPS

Primary indication for surgery pain

Suppression: ☐ yes ☐ no. If yes: ☐ COC ☐ Dienogest ☐ Provera ☐ Mirena ☐ Other

Pain at 6-week visit: ☐ severe ☐ moderate ☐ mild ☐ no pain

COC ☐Dienogest ☐Provera☐ mirena☐ zoladex☐ other☐

Pain at 6-month visit: ☐ severe ☐ moderate ☐ mild ☐ no pain

COC☐ dienogest☐Provera☐mirena☐zoladex☐other☐

Pain at 1 year visit: ☐ severe ☐ moderate ☐ mild ☐ no pain

COC☐dienogest☐Provera☐mirena☐zoladex☐other☐

Pain at 2-year visit: ☐ severe ☐ moderate ☐ mild ☐ no pain

COC☐dienogest☐Provera☐mirena☐zoladex☐ other☐

The primary indication for surgery infertility

Conceived spontaneously within 6 months: ☐ yes ☐ no

Conceived spontaneously after 6 months to 1 year: ☐ yes ☐ no

Conceived spontaneously after 1 year: ☐ yes ☐ no

Conceived with ART within 6 months: ☐ yes ☐ no

Conceived with ART after 6 months: ☐ yes ☐ no

Number of cycles: ☐ 1 ☐ 2 ☐ 3 ☐ 4

Appendix B: HREC Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 March 2021

HREC REF: 102/2021

Dr K Kadwa
Obstetrics & Gynaecology
H-Floor OMB
Email: khatijak@gmail.com
Student: KICKYKAL@YAHOO.FR

Dear Dr Kadwa

PROJECT TITLE: PAIN AND FERTILITY OUTCOMES POST ENDOMETRIOSIS SURGERY AT GSH-MMED CANDIDATE DR KITA KALWIBA

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 March 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Kita C Kalwiba will also be involved in this study.

Please quote the HREC REF 102/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Appendix C: Extension of HREC approval

HUMAN RESEARCH ETHICS COMMITTEE
08 APR 2022
HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.3.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	14/4/2022

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	28 March 2022		
HREC REF Number	102/2021	Current Ethics Approval was granted until	30 March 2022
Protocol title	Pain and fertility outcomes post endometriosis surgery at GSH		
Principal Investigator	Dr Khatija Kadwa		
Department / Office Internal Mail Address	Obstetrics and Gynecology, H floor, old Building khatijak@gmail.com		
1.1 Does this protocol receive US Federal funding?		☐ Yes	Type equ ☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		
Total number of records or specimens collected, reviewed or stored since last progress report		
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI		Date	28 March 2021

Appendix D: Groote Schuur Hospital approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

Dr K. Kadwa
OBSTETRICS & GYNAECOLOGY

E-mail: khatijak@gmail.com / kickykal@yahoo.fr

Dear Dr Kadwa,

RESEARCH PROJECT: Pain And Fertility Outcomes Post Endometriosis Surgery At Groote Schuur Hospital (MMed Dr Kita Kalwiba)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 March 2022**.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
o) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

p.p. **DR BERNADETTE EICK**
CHIEF OPERATIONAL OFFICER
Date: 28 May 2021

C.C. Mr. L. Naidoo / Dr F. Conrad / Professor L. Denny

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