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EVALUATING PRACTICE TREND CHANGES IN LAPAROSCOPIC SURGICAL MANAGEMENT OF ECTOPIC PREGNANCY AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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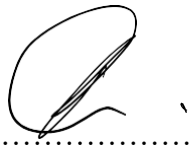
UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of the Master of Medicine in the branch of Obstetrics and Gynaecology.

Johannesburg, 2021

DECLARATION

I, Gugulethu Mbele, declare that the research reported in this work is completely my own. It is submitted to the Faculty of Health Sciences for the degree of Master of Medicine in Obstetrics and Gynaecology, at the University of Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination at this, or any other university.



……

(Signature of candidate)

25 February 21
…..... day of……20…, in…… Wits Medical School Parktown

DEDICATION

This work is dedicated to my late mother, Thandi Pride Mngomezulu. COVID has taken a lot from us, including you. Our memories are what I choose to hold onto. Thank you for all your teachings. I will love you forever, and I promise to make you proud.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the following people:

1. My wonderful supervisor, Dr. Langanani Mbodi, for his dedicated assistance with every aspect of the study and continued support, his love of teaching and for what he does was evident throughout. Thank you for being so patient with me and never giving up on me.
2. Zanele Kubheka, for assisting me with data analysis.

ABSTRACT

Background

Ectopic pregnancy is, by definition, a pregnancy in which implantation of a fertilized oocyte occurs outside the uterus. Globally, a ruptured ectopic pregnancy is the root of maternal mortality in early pregnancy (1). Ectopic pregnancies also increase the risk of infertility as well as subsequent ectopic pregnancies. Laparoscopic surgical approach has been shown to be better in terms of outcome to laparotomy and, therefore, should be gold-standard in the diagnosis and treatment of ectopic pregnancies in gynecological departments (2,3,4). Laparoscopy has been used for many years now, for the diagnosis of ectopic pregnancy, more so in first world countries, it is now being used habitually in the surgical treatment of ectopic pregnancy (5). The use of laparoscopic surgery globally is variable, with high-income countries using laparoscopy routinely and more commonly than low to middle-income countries (6). However, there seems to be expansion and growth in the use of laparoscopy as a diagnostic and treatment modality for ectopic pregnancy, even in low to middle-income countries (7). Most institutions bargain about the overall cost-effectiveness of laparoscopy. The rate of laparoscopic surgery was low in our center, and this led to the issue of a directive that made it compulsory for all surgeries for ectopic pregnancy if meeting criteria, to reduce the number of open surgeries for ectopic pregnancy.

Methods

This was a comparative, period-based, retrospective study using medical record review at Charlotte Maxeke Johannesburg Academic Hospital in Parktown, Johannesburg. This study included all patients admitted with ectopic pregnancy who were managed surgically and medically and those who met the criteria for laparoscopic surgery. In the study, we compared the trend in management for the time period January 2013 to December 2015 and January 2016 to December 2018, a period following a directive that all ectopic pregnancies should be laparoscopically managed if meeting criteria with regard to the use of laparoscopy for ectopic pregnancy. Both intraoperative and postoperative complications were followed up. The duration of the hospital stay was also anlaysed. The software of choice was STATA. It was

used for the analysis of data, and quantitative methods were employed in data analysis, and significance was conceded as 5%.

Results

A total of 255 women were retrospectively recruited for the study. Of which, 15 were excluded due to missing files and some patients having absconded or signed refusal of hospital treatment (RHT). The remaining files that met the criteria were 240 with 120 in each group (control/pre-MIS directive and study group/post-MIS directive). The mean age for the entire study population was 29.3 years (SD±4.65). The median parity and gravidity were not statistically different in both groups, with an overall median parity of 1(ranges 0-4) and gravidity of 3(ranges1-6). The groups also had similar characteristics in terms of co-morbid diseases and past surgical history. HIV infection being present in 31(12,9%) of the women. With 35(14,6%) of the patients having had previous abdomino-pelvic surgery.

In the study group, 107 (89,2%) of the patients were hemodynamically stable, of which 6(5,6%) had normal findings, and 101(94,4%) patients presented with pallor and abdominal pain. Only 13(10.8%) patients in the study group presented with hemodynamic instability. In the control group, only 14(11,7%) patients were recorded as meeting criteria for laparoscopic surgery, 106(88,3%) patients were said to not meet criteria for laparoscopy. With the advancement in technology, more and more surgeons are opting for minimally invasive gynecological surgery. Specialists in training are also being encouraged to assess patients that present to the emergency department as either meeting the criteria for laparoscopy or not, based on their individual clinical presentation. In the study group, there was a slight increase in the number of patients being identified as meeting criteria for laparoscopic surgery, with 21(17,5%) patients were identified as meeting criteria and 91(75,8%) were identified as not meeting criteria. There was no statistically significant difference in the number of patients treated medically for ectopic pregnancy in the two groups. Generally, the goal for medical treatment with Methotrexate is early diagnosis before the ectopic ruptures. Medical management also requires the patient to have normal biochemistry in terms of blood results as there is always a risk of toxicity if incorrectly used. Registrars are often met with turmoil when having to make this decision on their own, hence the reluctance to use Methotrexate over the years.

In the study group,21(17,5%) of the patients had laparoscopic surgery, 95 (79,2%) had open laparotomies. This shows a remarkable increase in the number of laparoscopic procedures for

ectopic pregnancies being performed. There seems to also be an increase in the number of registrar lead cases, with 17(80,9%) of the laparoscopic surgeries that were performed by registrars and 4(19,4%) were performed by consultants. Implementation of a Pro-Laparoscopy directive has had a great impact in the work and training of Registrars.

There were no notable differences in the duration of hospital stay between the control and the study group. Perhaps clinicians were following a routine practice of discharging patients after a certain predetermined period.

Conclusion

Patients are now likely to have laparoscopic surgery provided they meet the criteria for laparoscopy since the enforcement of the protocol. Registrars are leaning more towards laparoscopic surgery as the treatment of choice since the issued directive that prescribed that it is compulsory for patients who meet the criteria to be operated on laparoscopically. This is evidence that with good and directed protocols, support, and mobilisation of resources, performance of MIS can improve in our centre. This study also confirms that minimally invasive surgery overall reduces morbidity and mortality as compared to open surgery, even in centres with limited resources such as ours. There is a need for a prospective study to explore the reasons or challenges contributing to slow progress in adopting MIS technique for all ectopic pregnancies.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynaecologists
AKI	Acute Kidney Injury
ART	Assisted Reproductive Therapy
B- HCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
CEO	Chief Executive Officer
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DNA	Deoxyribonucleic acid
ED	Emergency Department
EP	Ectopic Pregnancy
ESRD	End Stage Renal Disease
GDoH	Gauteng Department of Health
HIV	Human Immunodeficiency Virus
HPL	Human Placental Lactogen
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IU	International Units
IUP	Intra-uterine pregnancy
KDIGO	Kidney Disease Improving Global Outcomes
LESS	Laparoscopic-endoscopic Single-site Surgery
LIF	Leukemia Inhibiting Factor
LMIC	Low Middle-Income Countries

MIS	Minimal Invasive Surgery
MIGS	Minimally Invasive Gynaecological Surgery
NICE	National Institute for Health and Care Excellence
NHLS	National Health Laparotomy Services
OL	Operative laparoscopy
PAPP-A	Pregnancy Associated Plasma Protein-A
PID	Pelvic Inflammatory Disease
PUL	Pregnancy of Unknown Location
RCOG	Royal College of Obstetricians and Gynaecologists
RHT	Refusal of Hospital Treatment
RMMCH	Rahima Moosa Mother and Child hospital
SOP	Standard Operating Procedure
SILS	Single Incision Laparoscopy
SP1	Serum Specific protein-1
UK	United Kingdom
URO-GYNAE	Urogynaecology Division of Obstetrics and Gynaecology

CHAPTER 1

1.1 INTRODUCTION

“Laparoscopy requires a different skill set than open surgery. Surgeons typically view patients from the outside in. When a laparoscopic camera is inserted, they see patients from the inside out.”-M Cenk Cavusoglu

Laparoscopy is a surgical procedure in which a fiber-optic instrument is inserted through the abdominal wall to view the organs in the abdomen and pelvis. With developing technology and laparoscopic equipment, gynaecologists are now able to diagnose and treat different types of conditions, including ectopic pregnancies, endometriosis, and ovarian masses (8). Laparoscopy is used as a diagnostic tool in the management of ectopic pregnancy and is now the preferred surgical option for the excision of ectopic pregnancies. Salpingectomy is associated with better overall outcome, but the preservation of the fallopian tube at salpingostomy is also a probable option when wishing to preserve fertility (5). If the contralateral tube is healthy, salpingectomy is often favoured over salpingostomy. In 2005, Ghezzi et al. treated a total of ten (10) ectopic pregnancies with a single-port technique. Typically, two trocars are needed for laparoscopic salpingectomy, and it has now been shown that the one-port technique is a feasible and safe approach for ectopic pregnancies (9). In LMICs, cost remains a huge barrier for access to good healthcare for a significant population (6). Cost is often seen as a major barrier in the integration of Laparoscopy in resource-poor clinical settings. Increasing knowledge and improving training for doctors will enhance the overall efficacy of a health institution and improve service delivery to patients (10). In seven (7) randomized control trials based in low-income countries, surgeons crudely believe that the direct primary trocar insertion method is as safe as other methods (11). Nevertheless, none of these randomized control trials are strong enough to detect dissimilarities in complications.

1.2 LITERATURE REVIEW

1.2.1 Prevalence

There is currently not enough data and research showing the incidence and prevalence of ectopic pregnancies in developing countries. The incidence of ectopic pregnancies is 1-2% of all reported pregnancies in developed countries. The true incidence in developing countries is unknown; however, it is said to be much higher than in developed countries. The reason for this is, some cases of ectopic pregnancies are not documented or reported in developing countries (12). Often there are no identifiable risk factors. However, in industrialized countries, some of the risk factors include any potential cause of tubal damage, more commonly a pelvic infection with chlamydia trachomatis or pelvic surgery, a previous ectopic pregnancy and fertility treatment using assisted reproductive therapy (ART) should be considered as risk factors for ectopic pregnancy (13). In developing countries, there has been a great association between Pelvic Inflammatory Disease (PID) and the risk of ectopic pregnancy (4,5). Case-control studies have explored and reported organisms such as Chlamydia trachomatis and Neisseria gonorrhoea being common pathogens in the aetiology of ectopic pregnancy (13).

1.2.2 Diagnosis

1.2.2.1 History

Early detection is associated with better outcomes in ectopic pregnancy. Recent advances in technology have led to a reduction in mortality of at least 50% since the 1980s (14). Thorough history taking is important in identifying those at risk and those who may potentially need lifesaving procedures. Patients with an ectopic pregnancy can present with an array of symptoms. This can help identify those who are stable and un-ruptured from those that are hemodynamically unstable and ruptured. Commonly, patients with an un-ruptured ectopic pregnancy present with 1st trimester bleeding and abdominal pain. These symptoms are non-specific, in the sense that they do occur in intrauterine pregnancies and spontaneous

miscarriages (14). On general enquiry the presence of risk factors with a history of vaginal bleeding after a period of amenorrhea may raise clinical suspicion for the diagnosis of an ectopic pregnancy (13). The severity of symptoms should also be ascertained on history taking. There is potential room to treat a select group of patients expectantly, provided they are haemodynamically stable.

1.2.2.2 Physical examination

Physical examination is vital in establishing haemodynamic status of the patient. When performing the examination, it is important to have the patient as relaxed as possible. The aim is to detect signs of peritonism, such as rebound tenderness, guarding, and cervical motion tenderness (15,16,17). These indicate a possibility of hemoperitoneum. Visual inspection of the cervical os for product of conception can assist in differentiating between an incomplete abortion and an ectopic pregnancy. Pathological evaluation of the tissue retrieved from the vagina is critical in avoiding misdiagnosing a decidual cast as products of conception (14). Abdominal pain associated with a fall in haematocrit is indicative of a slow rupture. A collapse related to sever lower abdominal pain is often characteristic of an acute rupture (18). Sharp shoulder pain may be a sign of blood accumulating below the diaphragm (18). Cullens sign is an oedematous blueish discolouration of the skin around the umbilicus (19). It was named after Thomas Stephen Cullen (1869-1953), a gynaecologist, who first described the sign in a ruptured ectopic pregnancy in 1916 (18).

1.2.2.3 Imaging

In early pregnancy, the imaging modality of choice is ultrasonography. Ideally, both transabdominal and transvaginal evaluation should be offered. However, this may not always be possible, especially in resource-poor countries. Transvaginal ultrasonography provides a more detailed assessment of the structures owing to its closer proximity to pelvic organs. This is important in patients without an identifiable intrauterine pregnancy (IUP) (20). High-definition probes have revolutionized the assessment and examination of patients presenting to the Emergency Department (ED) with an early pregnancy loss. The positive identification of a non-cystic adnexal mass with an empty uterus has a sensitivity of 84-90% and a specificity of 94-99% for the diagnosis of an ectopic gestation (2). Often it is difficult to visualize an ectopic pregnancy. Therefore, ultrasound is used to identify and confirm the site

and viability of a pregnancy. In a normal pregnancy, the gestational sac generally is visible on ultrasound five to six weeks after the last menstrual period (18). Tubal ectopic pregnancy may also be an echogenic ring around the adnexa. The tubal ring sign is the second most common sign of ectopic pregnancy and has a 95% positive predictive value (20). Imaging with Colour Doppler often shows a hyper-vascular circumferential ring (15, 20).

Additional sonographic findings associated with ectopic pregnancy are; presence of free fluid in the Pouch of Douglas in patients with a positive pregnancy test and empty uterus has a specificity and sensitivity of 69% and 63%, respectively, for ectopic pregnancy (20). False positives do occur because other pelvic pathologies such as ovarian cysts, tumours, and inflammatory processes do often sometimes resemble an ectopic pregnancy. An ectopic pregnancy can be missed if the ectopic is small or if it is concealed by bowel or in cases of dual pathology where uterine anomalies such as fibroids coexist (2).

It is also recommended that ultrasounds be performed or directly supervised and reviewed by appropriately qualified healthcare professionals with training in and experience in diagnosing ectopic pregnancies (17).

1.2.2.4 Serum B-h*CG concentrations*

Human chorionic gonadotropin (hCG) is a polypeptide hormone produced by syncytiotrophoblastic cells of the placenta during pregnancy. It consists of an alpha and beta subunit. In the presence of hCG , the corpus luteum produces progesterone to sustain the pregnancy. Trends and changes in serum B-hCG are typically used to predict the outcome of a pregnancy of unknown location (PUL) or confirmation of a failing pregnancy (2). With a combination of high-resolution ultrasound and the use of assays sensitive to hCG, a great proportion of ectopic pregnancies can be detected early (21). Kadar and Romero described serial changes on the basis of a small sample of 20 women using an 85% confidence interval. They're study demonstrated that in a normal viable pregnancy, the minimal rate of increase in quantitative B-hCG is 66% in 48 hours. A recent study of 287 participants who presented with lower abdominal pain or bleeding, the minimum rise in B-hCG for a viable intrauterine pregnancy (IUP) was 24% at 24 hours and 53% at 48 hours (2). Seeber et al. produced data with a 99% CI that suggested a more conforming minimum rise of 35% over 48 hours(22).

Currently, most gynaecological clinical units use a minimum value between 50% and 66% as an acceptable increase in 48-hour for normal viable intrauterine pregnancy (2).

Ectopic pregnancy is suspected if transvaginal ultrasound does not show an IUP and the B-hCG is above 1500mIU/m (21). The assays that measure the alpha subunit hCG are available within several minutes to two hours; however, their sensitivity varies from 30 to 94% (18).

Impeding Factors:

There are various reasons that could explain a hCG test (serum or urine) being an incorrect report. False-positive hCG often has detrimental consequences. Commonly, a false-positive result leads to unnecessary medical care and/or irreversible surgical procedures. Coequally, False negatives may result in a delay in diagnostic and interventional evaluation. Below are potential causes of false results (23).

Serum False Positives:

- Endogenous production of hCG (hCG -secreting tumors, of the reproductive and gastro-intestinal system including hepato-biliary tumours) (24).
- Heterophile antibodies (25).
- Rheumatoid factor.
- IgA deficiency.
- Chronic renal failure.
- Transfusion of hCG containing blood product.
- Exogenous administration of hCG.(25).

Serum False Negatives

- Premature measurement soon after conception.
- "Hook effect" occurs when hCG levels are markedly elevated. Typically, at about 500,000 mIU/mL. The excess hCG molecules lead to saturation of both the tracer and the antibodies separately. This leads to failure of wedging of the tracer-hCG antibody required for the measurement. The outcome of this is disintegration of all complexes, giving a false-negative result. Laboratories should be informed to perform dilution prior to testing if gestational trophoblastic disease is suspected (23).

1.2.2.5 Serum progesterone and other biomarkers.

It has been shown that ectopic pregnancy is linked to abnormal corpus luteal function. This is evidenced by low serum levels of progesterone, estradiol, and 17-hydroxyprogesterone (26). Studies have demonstrated serum progesterone is higher in normal pregnancies and in comparison to B-hCG, serum levels remain relatively steady in the first two weeks of gestation (24). Low serum progesterone, in the absence of clinical and ultrasonographic evidence of a miscarriage, is highly suggestive of an ectopic pregnancy (26). Stromal cells and trophoblastic tissue produce other placental hormones which include leukemia inhibiting factor (LIF), serum specific protein-1 (SP1), human placental lactogen (HLP), and pregnancy-associated plasma protein-A (PAPP-A). The biological function of these proteins is unclear, but they are a direct reflection of the biosynthetic capacity of the decidualized endometrium (24). A few studies have also demonstrated that these serum proteins are markedly reduced in ectopic pregnancies (2,21,24,27,28). Sjöberg measured serum PAPP-A concentrations in 164 patients that presented to gynaecologic emergency services: 124 of these women had ectopic pregnancy (EP), and 40 had intrauterine miscarriages (24). They compared the serum PAPP-A levels in 136 women with normal IUP with serum levels of 460 women who weren't pregnant. Serum PAPP-A levels were lower in the EP and intrauterine miscarriage groups compared to the normal pregnancy group; levels were imperceptible in 82% of the EP group and 55% of the intrauterine miscarriage group. Thus, the probability that a pregnant patient with undetectable PAPP-A levels has an EP was calculated to be 30%; the probability of an intrauterine failing pregnancy was calculated to be 29%. Even though PAPP-A levels are lower in individuals with ectopic pregnancies and intrauterine failing pregnancies compared to those with normal pregnancies, PAPP-A measurements cannot be used to discriminate between EP and intrauterine miscarriage(24).

1.2.3 Management of an Ectopic pregnancy

It is important to know that an ectopic pregnancy is a gynaecological emergency. It can have catastrophic sequelae if not attended to promptly with precision. Women presenting with an ectopic pregnancy need immediate treatment. If shock ensues, immediate resuscitation with intravenous fluid and blood product is warranted. However the clinical presentation of

ectopic pregnancies can vary from a life threatening condition to a more benign condition for which non-surgical treatment modalities being readily available, such systemic treatment with Methotrexate or even expectant management (29). Expectant management is a type of management approach in which treatment is not administered, with the aim of seeing whether the condition will resolve naturally (30).

1.2.3.1 Expectant Management

Expectant management may not always be ideal, especially in a poor resource setting where there is limited access to hospital and surgical treatment. A certain percentage of ectopic pregnancies do resolve spontaneously (31). Rates of success between 47% and 82% have been reported, depending mostly on the patient's initial status (2). Typically, it is those which are un-ruptured with a B-hCG of < 1000miu/ml. Watchful waiting is a valid and viable option, but criteria need to be stringent as not all patients will be able to comply with conditions of follow up. In a large prospective study done by Korhenon et al., they looked at 118 patients with ectopic pregnancies treated expectantly, and they reported a 65% success rate. They found that success rates of expectant management were directly proportional to serum B-hCG levels. Success rates of serum B-hCG levels <200, <500 and >1000miu/ml were 98%, 73% and 25% respectively (32). In the overall analysis, they found that if serum B-hCG level is less than 1000miu/ml, expectant management is successful in 88% of patients. Unfortunately, B-hCG alone is not a good enough marker to reliably predict and identify the subset of women with ectopic pregnancies that will spontaneously resolve (31).

1.2.3.2 Medical Management

Historically, the management of ectopic pregnancy was limited to surgery. With evolving medical treatment, Methotrexate has become the drug of choice. Methotrexate is a folic acid analogue that works by inhibiting dihydrofolate reductase and therefore preventing the synthesis of DNA. Medical management has been found to be as equally effective as surgical treatment, especially when taking into consideration future fertility (29). Currently, there are three treatment regimens for Methotrexate: one dose, two-dose regime, and lastly, the fixed multi-dose regime (33). However, the most practical and efficient method of administration of Methotrexate is the single intramuscular injection, the dosage being 50mg/m² (4). This is mostly to minimize side effects, improve patient compliance, and to reduce the overall cost (29).

National Institute for Health and Care Excellence (NICE) suggests Methotrexate should be offered to patients who meet the following criteria (30):

- No significant pain.
- An unruptured ectopic with an adnexal mass <35mm in diameter with no visible heartbeat.
- No intrauterine pregnancy.
- No blood dyscrasias, renal or hepatic dysfunction.

These patients should have access to transport and be able to follow up. The patient must be well informed, willing, and able to comply with following up regime. Methotrexate treatment is successful in 78% to 96% of patients (21).

Srivichai et al. performed a study on 106 patients, and they found a success rate of 90.6% in 96 out of the 106 patients who were successfully treated with Methotrexate even though four of the treated patients required a second dose of Methotrexate (29). Treatment success with Methotrexate is described to be a decrease in serum B-hCG level by >15% between day 4 and day 7. Complete resolution is seen in 75% of cases, 15% of cases will need a second dose after 7 days, and lastly, 10 % may still require surgery (34). Signs of success are based on both clinical and biochemical parameters being a haemodynamically stable patient with no symptoms of rupture or significant intraabdominal haemorrhage with decreasing serum B-hCG titres. The only hindrance that may arise from medical management with Methotrexate would be poor patient follow up with lack of documentation (there is often also poor counselling with regards to identifying warning signs). Patients are also not advised adequately regarding contraception and future fertility (33).

1.2.3.3 Surgical Management

Surgical excision or removal of the ectopic pregnancy can be performed laparoscopically or by open laparotomy. The options involved in both these techniques are salpingectomy and salpingostomy (31). Salpingectomy involves the removal of the part of the fallopian tube involved. It is recommended when there are no future fertility desires (4) and if there is recurrent ectopic pregnancy in the affected tube, due to aetiology of ectopic pregnancy as well as haemorrhage (35). Salpingostomy is a technique in which an incision is made on the tubal wall, trophoblastic tissue is removed, and the tube is flushed. This technique involves leaving the affected fallopian tube behind (36). In patients who wish to conserve future

fertility, salpingostomy is preferred (14). Salpingostomy is, however, associated with the recurrence of ectopic pregnancy in the same fallopian tube. Open laparotomy should be reserved for haemodynamically unstable patients with extensive intraperitoneal bleed and intravascular compromise. Several systematic reviews have investigated reproductive consequences following the salpingectomy and salpingostomy in patients with a healthy contralateral tube. These studies conclude that the possibility of successive intrauterine pregnancy is not increased after salpingostomy compared with salpingectomy (37,38,39). Additionally, conservative surgical techniques expose women to a reduced risk of tubal haemorrhage in the immediate postoperative period and the probable need for further treatment of persistent trophoblast, which is associated with recurrence of symptoms (35,40,41). This contributes to current guidelines stating that the operative method of choice, where there is a healthy contralateral tube, is laparoscopic salpingectomy (2,4,34,42).

1.2.4 Laparoscopic surgery

Laparoscopy has been demonstrated to be of higher ranking than laparotomy; therefore, it has been gold-standard for the treatment of ectopic pregnancy (5,34). Almost all gynaecological/surgical procedures can be performed using minimally invasive surgery. The rise in the employment of this type of operative procedure can be attributed to patients desiring better cosmesis, reduced pain and swift postoperative recovery time (10). In poor socio-economic regions, the adoption of minimally invasive surgery has not been easy.

Laparoscopy is a surgical technique that entails operating in the abdominal cavity through small incisions (usually 0.5-1.5 cm) as opposed to the larger incisions needed in laparotomy. Laparoscopic surgery utilizes images displayed on-screen monitors to magnify the surgical elements. It fits in largely with the broader field of endoscopy (43). One of the most notable advances in laparoscopic surgery is the introduction of single-incision laparoscopic surgery (SILS). When compared to the conventional laparoscopy that is commonly performed by using a total of three to five small incisions (5–20 mm each), SILS is performed by using a single small incision of the umbilicus (44). In general, there is limited data concerning the use of SILS in gynaecological surgery.

1.2.4.1. Operative technique

Under general anaesthesia, the patient is placed in dorsal lithotomy with both arms against the sides of the patient, fastened to arm boards. After cleaning and draping the patient, the bladder is emptied, and a uterine manipulator is inserted into the uterus through the cervix. A small incision is made through the umbilicus or preferred point of entry. This is usually 2-2,5cm in size. The abdominal cavity may be entered through direct vision or via a Veress needle. The Laparoscopic surgery entry, when done blindly, is often associated with greater morbidity and mortality (45). Upon entry, the abdomen is then insufflated using CO2 gas. Two assistants are often required, one that stands to the right of the surgeon, controlling and manipulating the scope, whilst the second assistant stands between the patients' legs with the uterine manipulator. The lap-scope camera can be a 30 degree or zero-degree lens. Graspers and manipulators are used to move pelvic organs away from the organ being examined. Once the ectopic pregnancy is identified a Ligasure® or electrosurgical resector is used to grasp and with the aid of diathermy, coagulate and cut off the ectopic tissue achieving haemostasis. In cases where the ectopic pregnancy is ruptured, suction and washout can be done using warm saline. Then with the aid of an Endobag®/endoscopic bag, the ectopic tissue is retrieved from the abdominal cavity. The subcutaneous tissue is then closed using Vicryl® 3-0 suture or Steri-strips® (11).

One of the most challenging steps in performing laparoscopic surgery is the method used for access and entry into the abdominal cavity. There is still no consensus as to which method is optimal (45). In patients who are suspected of having extensive adhesions secondary to prior abdominal surgery, Palmer suggested the insertion of the Veress needle 3 cm below the left subcostal border in the midclavicular line (46). This technique can be used in the obese as well as the wasted patient. In patients with prominent sacral promontory and android pelvis, the surgeon should be mindful of the great vessels that lie 1 cm to 2 cm beneath the umbilicus, and in obese women, the umbilicus is shifted caudally to the aortic bifurcation. When compared, both the open and closed entry techniques for gaining access into the peritoneal cavity are safe, but the Veress needle method has the advantage of less time taken to enter the abdominal cavity as compared to the open method (45).

A Cochrane Database of Systematic Reviews revealed that there is insufficient evidence to show whether there are differences between groups in the rate of failed entry, vascular or visceral injury, or in other major complications with the use of an open-entry compared to a closed-entry technique (47). The open laparoscopy or Hasson's technique is fundamentally a mini laparotomy. A small incision is made transversely or longitudinally at the umbilicus.

The proposed benefits are the prevention of gas embolism from preperitoneal insufflation and the likelihood of visceral and major vascular injury (46).

1.2.5 Role of laparoscopic surgery in resource poor setting

In as much as minimally invasive laparoscopic surgery has its proven benefits, it also has its limitations. It is said to reduce overall morbidity and mortality as some of its benefits. Limitations of Laparoscopic surgery are even further pronounced in poor resource settings. In general, laparoscopy requires more technical skill from the surgeon. It requires more operative time and a longer training period to enable the acquisition of sufficient skill to improve outcomes, compared with open surgery (48). In sub-Saharan Africa, a few factors have been identified as limitations, such as an overall lack of human and material resources, a need for technological support, and challenges with the training of junior staff (49). A study was conducted in the Bayelsa state of Nigeria to assess the knowledge, practices, and challenges of laparoscopy amongst doctors to create awareness on this paradigm shift to laparoscopy to improve patient operative outcome. They recruited about 170 doctors in surgical disciplines. They found that the greater proportion (61%) of the doctors demonstrated low knowledge of laparoscopy compared to 7.1% of doctors that conveyed high knowledge. The remainder (31.8%) of doctors expressed average knowledge. 22 (12.9%) doctors had documented training in laparoscopy, and of this, only 3 (13.6%) had performed a laparoscopy on their own. Participants identified an increase in the cost of laparoscopic appliances, the limited number of skilled support staff, agreeability of procedure to patients, cognizance among doctors, overall opposition to change, increase in the learning curve, and lack of reliable electricity supply as challenges to the use and practice of laparoscopy in Bayelsa state (10).

1.2.6 Maternal outcomes in laparoscopic surgery

Benefits of minimally invasive surgery over conventional abdominal surgery are well established and include reduced recovery time, reduction in post-operative pain, and thus reduced need for pain control, short hospital stays, and faster return to premorbid status (50).

Aesthetics is also proving to be an important factor. There is better cosmesis with laparoscopic surgery (49,50).

A systematic Cochrane review of 35 randomized control trials that compared laparoscopic salpingostomy with the open laparotomy technique found evidence in keeping with earlier findings. They reported that laparoscopic salpingostomy resulted in notably shorter operating time (73 vs 88 min), less perioperative blood loss (79 vs 195 ml), shorter period of hospital stays (1-2 vs 3-5 days), reduced recuperating time and thus overall reduction in costs (3). However, laparoscopic salpingostomy did have a poorer success rate compared to the open laparotomy technique in the evacuation of trophoblastic tissue leading to higher persistent trophoblastic disease in the laparoscopic surgery group (3). Several studies have investigated maternal outcomes post laparoscopic surgery for ectopic pregnancy, but a great deal of attention needs to be placed on investigating long term outcomes of fertility and recurrent extra-uterine pregnancy, health-related quality of life, and treatment preferences when performing laparoscopic surgery (22).

Laparoscopy is a secure and constructive procedure in experienced hands, and it reduces morbidity to the patient, even in cornual or ruptured ectopic pregnancy. Laparoscopy provides direct visualization and access to the diseased fallopian tube, as well as the healthy tube and the abdomino-pelvic cavity; it provides panoramic visibility and may well assist in providing future fertility planning and management.

1.3 PROBLEM STATEMENT

Laparoscopic surgery is a global topic of discussion, especially in surgical disciplines in medicine. Institutions have had to devise appropriate protocols that are suitable for their patient profiles. In low resource centers where there is a shortage of admission beds and theatre time (compared to equipment availability) and also, a lack of staff (compared to the number of patients seen), an attainable surgical approach should be sought. This approach should expedite theatre time and decrease the rate of operative complications, thus condensing the length of hospital stay with minimal maternal morbidity.

The Charlotte Maxeke Johannesburg Hospital Gynaecology Division of Obstetrics & Gynaecology has had a fully equipped laparoscopic machine, including consumables, for more than 10 years. The use of laparoscopy, in general, has been low owing to the long learning curve, and hence the use of this equipment in an ectopic pregnancy has also been low. In the past 4 years (2016-2020), there has been emphasis and directive to encourage gynaecologists to opt for a laparoscopic method in those patients who meet the criteria and to support registrars during their intake days during the day and night. It is expected that there should be a positive change in the use of laparoscopy compared to the two years preceding this period. Evaluating changes in trends will help to inform the department as to which surgical techniques to retain and which to change. Factors such as a change in morbidity, rates of conversion to open surgery, and increased demand for training registrars will also inform decision making.

CHAPTER 2

2.1. OBJECTIVES OF STUDY

Primary objective

- To determine if there is change in trend in the use of laparoscopy for ectopic pregnancy when comparing the time periods 1st January 2013- 31st December 2015 and 1st January 2016- 31st December 2018.

Secondary objectives

- Compare the clinical characteristics of patients between these two-time periods.
- To describe the outcome of patients managed with laparoscopic surgery for ectopic pregnancy compared to those managed with open surgery in the two arms.

2.2. RESEARCH METHODS

2.2.1 Study setting

The study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the gynaecology unit of the Department of Obstetrics and Gynaecology. CMJAH is an accredited academic hospital, situated in Parktown Johannesburg. It is also the main teaching hospital for the University of the Witwatersrand, faculty of Health Sciences. The hospital also serves as a referral hospital for several hospitals in its referral chain.

2.2.2 Study design

This was a single center comparative quantitative retrospective study. The study involved analysis of the clinical history and presentation including analysis of clinical findings, surgical techniques, and maternal outcome from patient files.

2.2.3 Sample size

All patients admitted with ectopic pregnancy who were managed medically and surgically. CMJAH admission ward admits at least 3 patients per call, who are diagnosed with ectopic pregnancy and almost all of these are managed surgically. Our study sample was 240 patients in total. We had 120 patients in each arm.

2.2.4 Data Collection

Data was collected retrospectively from patients' records using a data collection sheet (Annexure 1). No patients were interviewed either directly or through a questionnaire. Any laboratory report relevant to the study was retrieved from the files and if not found, it was searched on the NHLS TrakCare® online system. The clinical characteristics of patients, their presentation, initial planned and final management, complications, and outcome were recorded as reflected in their file. Any missing information was managed as "unknown". To isolate/identify the cohort that should have been managed laparoscopically, the RCOG/NICE Guidelines on criteria for laparoscopic surgery was used. No patients or doctors were interviewed.

2.2.4.1 Data collection categories

i. Patient demographics.
ii. Clinical presentation.
iii. Diagnosis and criteria for laparoscopy.
iv. Surgical procedure.
v. Adverse outcomes.
vi. Duration of hospital stay.

2.2.5 Data analysis

Data from previous patient records was captured using RedCap® and exported to Microsoft excel program, sorted, cleaned and coded. Quantitative methods of data analysis were used.

The statistics analysis software used was a STATA® 13. Continuous data variables were tested for normality. Where applicable, the data were presented as means and standard deviations. Categorical data variables were presented as proportions and frequencies. The Chi-squared test was used to assess the relationship between categorical variables. A 95% confidence interval was used during analysis of all data.

2.2.6 Ethical Considerations

Permission to conduct research was requested from the CEO of CMJAH as well as the Clinical Head of the Department of Obstetrics and Gynaecology and was granted. The research protocol was subjected to the assessment of the Assessor Committee of the Obstetrics and Gynaecology Postgraduate Assessor Committee. Application to the Human Research Ethics committee (HREC) of the University of Witwatersrand was made in July 2019 and approval was granted in October 2019 with clearance certificate number M190712.

2.2.7 Funding

All costs of travel, printing, and telephone calls were borne by the researcher. There was no external funding or sponsorship for the project.

CHAPTER 3

RESULTS

A total of 255 women were recruited for the study. Three patients signed refusal of hospital treatment form (RHT), and 1 from the control group was recorded as absconded. Eleven files had missing data and were therefore precluded. The remaining files were 240, making 120 patients in both the control and study group. The control arm was limited to 120 patients to obtain an equal number for comparison with a similar number in the study group. There were also 3 patients in the control group that were treated medically using Methotrexate. In the study group, 4 patients were also treated with Methotrexate. The data from these seven participants were used to create a survival curve but was excluded from the final morbidity and mortality analysis. There were therefore 233 patients included in the final analysis, which included those treated medically.

3.1 Maternal demographics and baseline parameters

The patient demographics were as listed in table 3.1. The mean age of patients in the whole group was 29.3 years, with a standard deviation of 4.65. This was equivalent in both groups. There was no statistical significance difference in the ages. Most patients seen at Charlotte Maxeke Johannesburg Academic Hospital have always been mostly those of African descent. There was no significant change between the two groups, with 90,8% of patients in the control group who were Black in comparison to 93,3% in the study group. Of significance is the increase in the number of foreign national patients. In the control group, 40% of patients seen were foreign nationals in comparison to 51,7% in the study group. The study group showed that 77,5% of patients were single in terms of their relationship status compared to 37,5% in the control group. Parity and gravidity were not different in both groups. Patients in both groups also had similar frequencies in terms of co-morbidities and past surgical history. In the control group, 31 patients had reported comorbidity. Twenty-eight (28) (90,3%) of these patients were HIV positive. One patient (0,3%) had thyroid disease. One (0,3%) had sickle cell disease, and one (0,3%) was an asthmatic. In the control group, 47 (39,2%)

patients previously had normal vaginal deliveries, 9 (19,1%) of these women had miscarriages, and 2 (4,3%) had previous ectopic pregnancies. Of these patients, 7 (14,9%) had a caesarian section and 9 (19,1%) had an exploratory laparotomy.

In comparison to the study group, 36 (30%) had comorbidities reported. Three (3) (8%) were HIV positive. Two (5,6%) had Hypertension. Sixty-two (62) (51,2%) had normal vaginal deliveries. Sixteen (16) (25,8%) of these women had previous miscarriages, and one (1,6%) had a previous ectopic pregnancy. Six (6) (9,7%) previous had termination of pregnancy (TOP) for social reasons.

Table 3.1 Comparison of patients' demographics

Variable	Control Mean Median (range) n=120 (%)	P value	Study Mean n=120 (%)	P value
Age	29.9 (19-41)	<0.01	28.7(20-39)	0.0143
Race				
• Black	109(90,8)		112(93,3)	
• Caucasian	11(9,12)		8(6.67)	
Ethnicity				
• South African	72(60,0)		58(48,3)	
• Foreign nationals	48(40,0)		62(51,7)	
BMI	23.8(18,5-26,6)		26.7(21,8-29,9)	
Marital status				
• Single	45(37,5)		93(77,5)	
• Married	75(62,5)		27(22,5)	
Parity	1(0-4)	0.053	1(0-4)	0.086
Gravidity	3(1-6)	<0.01	3(1-8)	<0.01
Co morbidities	31(25,8)		36(30,0)	<0.01
Past obstetric history	89(74,2)		99(82,5)	<0.01
Past surgical history	16(13,3)		19(15,8)	<0.01

3.2 Clinical presentation

Table 3.2 compares clinical presentation in the two groups. When patients presented, they had an average duration of symptoms for mean 2 days with a standard deviation of 1,856. This was of statistical significance with a p-value<001. The mean number of days from symptoms to admission was 1 day (SD±1,419) and the mean number of days from day of admission to surgery was 0 days. Most patients were operated on the day of their admission. On average, patients that underwent laparoscopic surgery had to wait 1-2 days before procedure was done (p<0,01).

In terms of haemodynamic status, in the control group, 73,3% of patients were hemodynamically stable of which 6 (5%) patients had normal findings and 82 (68,3%) patients were pale and had abdominal tenderness. There were 26,7% patients in the control group who were assessed as being in shock at the time of presentation. In the study group, 89,2% of the patients were hemodynamically stable of which 6 (5%) had normal findings and 101 (84,2%) patients presented with pallor and abdominal pain. Only 13(10,8%) patients in the study group presented with haemodynamic instability.

Table 3.2 Clinical presentation of patients with ectopic pregnancy

	Control Mean Median (range) n=120 (%)	p-value	Study Mean n=120 (%)	p- value
Duration of symptoms (days)	2(1-10)	<0.01	2(1-5)	<0.01
Symptoms to admission(days)	1(1-8)	<0.01	1(1-3)	<0.01
Admission to surgery(days)	0(0-3)	<0.01	0(0-2)	<0.01
Haemodynamically stable				
• Normal examination findings	6(5)		6(5)	
• Pale + Tender abdomen	82(68,3)		101(84,2)	
Haemodynamically unstable				
• Shocked	32(26,7)		13(10,8)	

3.3 Biochemical markers

Table 3.3 Haemotological and biochemical changes associated with an ectopic pregnancy.

	Control Mean Median (range) n=120	p-value	Study Mean Median(range) n=120	p-value
B-hcg (mIU/ml)	16057 (411-115408)	<0.01	14297 (52-99757)	<0.01
Haemoglobin (g/dL)	9,7(5-14,4)	<0.01	10,5(5,2-14,9)	<0.01
Urea(mg/dL)	3,7 (1,8-8,6)	<0.01	3,3 (1-7,6)	0.026
Creatinine (mg/dL)	56,3 (33-127)	<0.01	62,1(27-139)	<0.01
pH	7,37 (6.9-7.5)	<0.01	7,38 (7,2-7,52)	0.084
Base excess	-5,0 (-12- -8)	0.1059	-3,8 (-18-+7,1)	0.0195
Lactate	2,7	<0.01	1,3	<0.01

The mean serum quantitative *B*-hCG at which patients presented was 16057 (SD±28226) and 14297mIU/ml (SD±22297) in the control and study groups respectively. In the control group, mean haemoglobin was 9,7g/dL (SD±2.52). Patients also had normal renal function with 28 (23,3%) patients who had creatinine levels > 90micromoles per litre. On blood gas sampling mean pH was 7,37 (SD±0.11), mean Base excess of -5,0 (SD±2.83) and mean lactate of 2,7 (SD±5.41). In the study group mean Haemoglobin level was 10,5g/dL (SD±2.48) and 117 patients had normal renal functions with the exception of three (2,5%) that presented with an Acute kidney Injury. Blood gas sampling was mostly along normal limits which may mean patients are presenting earlier or rather being referred timeously.

Table 3.4 Ultrasound image findings in early ectopic pregnancy

	Control Mean n=120 (%)	P value	Study Mean n=120	P value
Normal	4(3,3)		1(0,8)	
Free fluid	2(1,7)		1(0,8)	<0.01
Adnexal mass	33(27,5)		3(2,5)	
Uterus empty	27(22,5)		30(25)	
Free fluid+ empty uterus	50(41,7)	<0,01	27(22,5)	
Free fluid +adnexal mass + uterus empty	4(3,3)		56(46,7)	<0,01

Table 3.4 shows the ultrasound findings commonly identified at diagnosis of an ectopic pregnancy. In the control group, the most frequently used features for the diagnosis of ectopic pregnancy were the presence of free fluid and an empty uterus. There were 50 (41,7%) cases who were diagnosed based on the above-mentioned ultrasound features ($p<0,01$). The presence of an adnexal mass alone was used in 27,5% of cases, and only 4 (3,3%) cases had all the three features suggestive of ectopic pregnancy, which are an empty uterus, free fluid, and an adnexal mass. In the study group, 46,7% of the cases were diagnosed using all three features. There were 30 (25%) cases that were diagnosed based on a positive pregnancy test and an empty uterus on ultrasound alone.

35 Diagnosis and criteria for laparoscopy

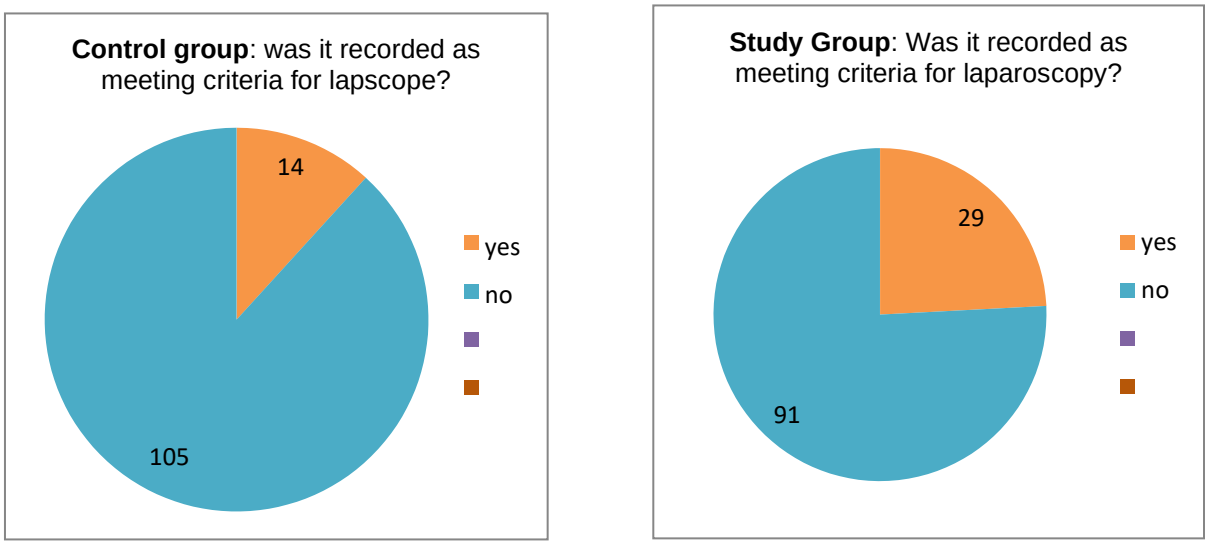


Figure 3.1 Distribution of patients meeting criteria for laparoscopic surgery.

The above two pie charts compare number of patients recorded as meeting criteria for laparoscopy. In the control group, only 14 (11,7%) patients were recorded as meeting criteria for laparoscopic surgery and 106 (88,3%) patients did not meet criteria for laparoscopy. In the study group there was a slight increase in the number of patients being identified and recorded as meeting criteria for laparoscopic surgery with 21(17,5%) patients who were identified as meeting criteria and 91(75,8%) were identified as not meeting criteria.

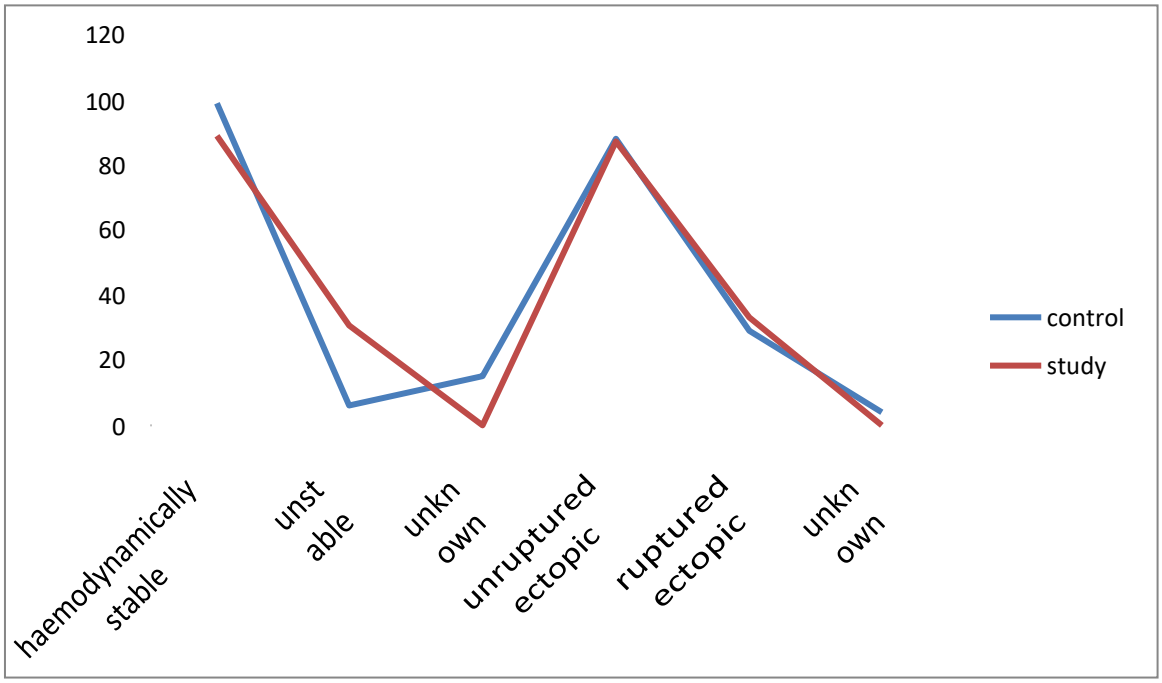


Figure 3.2 Distribution of haemodynamic stability in patients with an ectopic pregnancy.

The line graph above indicates that most of the patients were assessed as being haemodynamically stable and un-ruptured and thus meeting eligibility criteria for laparoscopic surgery in both groups. In the control group, 99 (82,5%) patients were said to be haemodynamically stable, even though 88 (73,3%) of them had ruptured ectopic pregnancies, and 29(24,2%) were un-ruptured. There were three (3) (2,5%) who were documented as unknown although suspected to have been ruptured. Three (3) (2,5%) of these patients were also managed medically using Methotrexate. This reveals that more patients met the criteria for laparoscopy but were incorrectly classified. In the study group, 89 (74,2%) patients were reported to be haemodynamically stable and 31(25,8%) patients were reported to be unstable. This was of statistical significance with a p-value=0,010. There were 87 (72,5%) of these patients who were found to have ruptured ectopic pregnancies and 33 (27,5%) were not ruptured. Four (4) (3,3%) of the un-ruptured patients who were managed medically with Methotrexate.

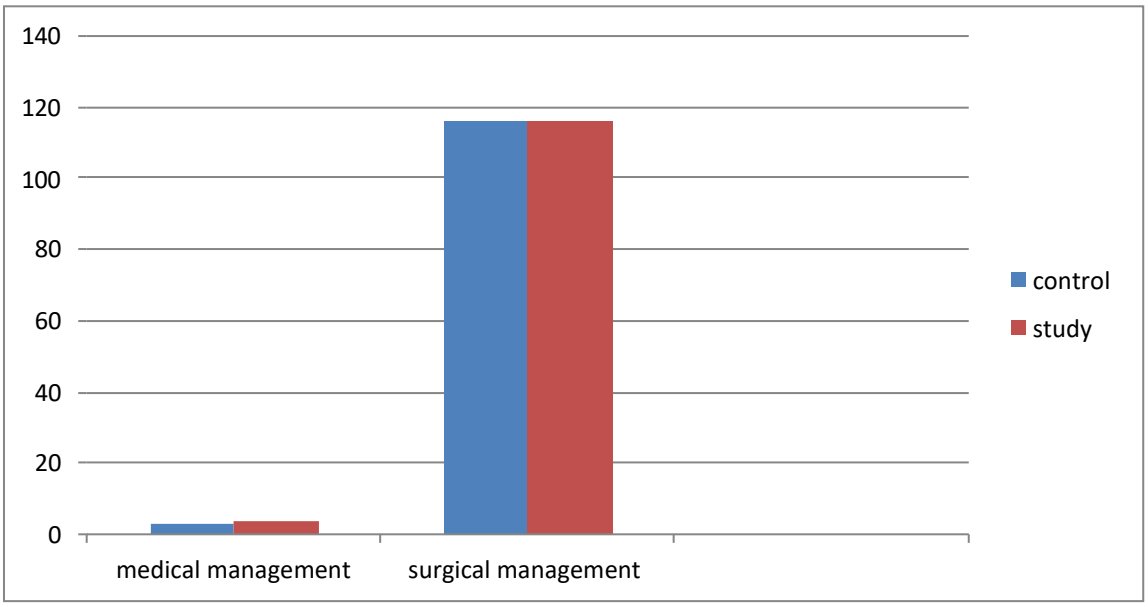


Figure 3.3 Comparison of Medical vs Surgical management of ectopic pregnancy.

There was no significant change in the numbers of patients treated medically in the two groups. In the control group, 3 (2,5%) patients were treated with methotrexate and 4 (3,3%) in the study group as previously stated above (p-value<0,01).

3.6 Surgical procedures

Table 3.5 Comparison of operative intervention and experience/skills level of primary surgeon

	Control n=120 (%)	p-value	Study n=120(%)	p-value
Laparoscopy	7 (5,8%)	<0,01	21(17,5)	<0,01
Registrar	1(14,3%)		17(80,9%)	<0.01
Consultant	6(85,7%)		4(19,1%)	<0.01
Conversion to open laparotomy	0(0%)		1(4,8%)	<0.01
Laparotomy	110(91,7)		95(79,2)	<0,01

In the control group, 7 (5,8%) patients who met the criteria had laparoscopic surgery and 6 (85,7%) of these cases were done by the consultant. There was only 1 (14,3%) case that was done by the registrar. There were no conversions to open laparotomy on those patients who were taken for laparoscopic surgery. There were 110 (91,7%) cases that had laparotomies done from the control group. In the study group, 21 (17,5%) of the patients had laparoscopic surgery and 95 (79,2%) had open laparotomies. This shows a remarkable increase in the number of laparoscopic procedures for ectopic pregnancies being performed. There seems to also be an increase in the number of registrar lead cases with 17 (80,9%%) of the laparoscopic surgeries being performed by registrars and 4 (19,1%) performed by consultants. There was, however, 1 (4,8%) conversion to open laparotomy, due to visceral injury.

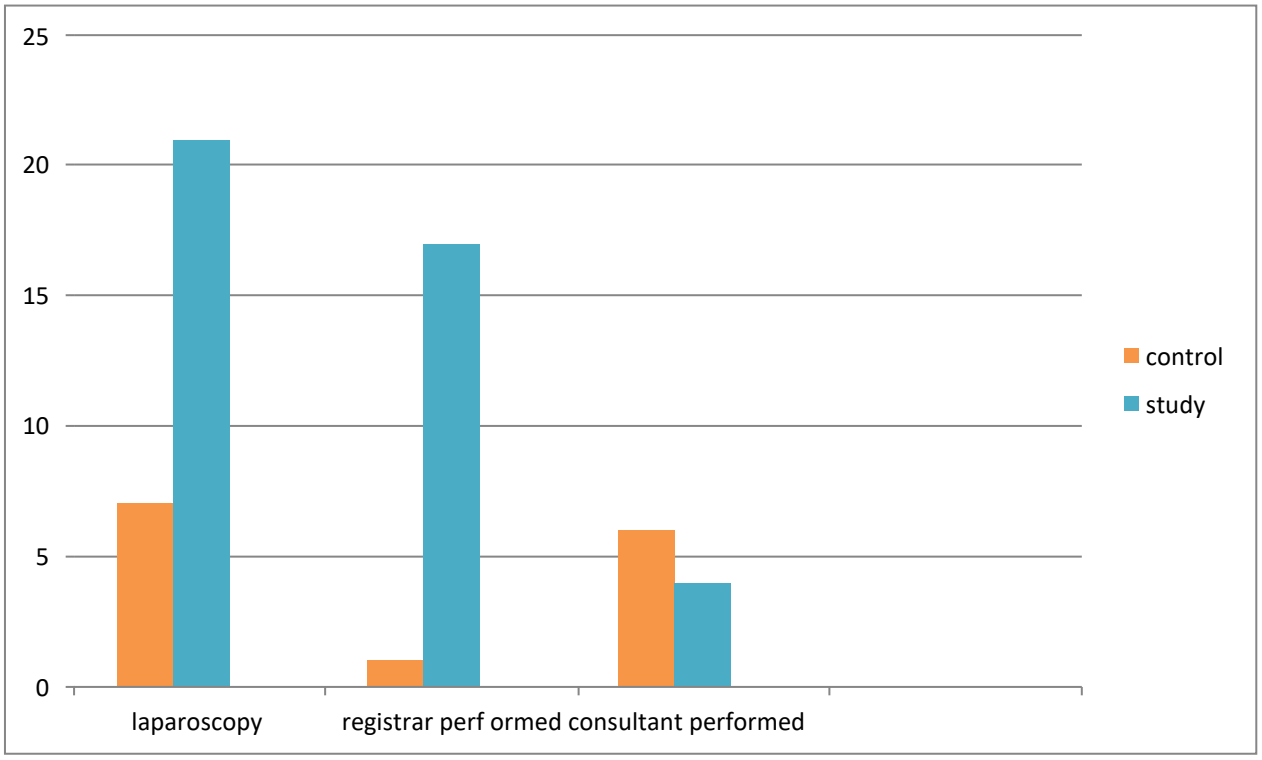


Figure 3.4 Recorded number of registrar lead vs consultant lead laparoscopic surgery for ectopic pregnancy.

This graph (figure 3.4) shows significant differences in the number of laparoscopic surgeries and differences between registrar and consult performed laparoscopic surgeries. This may

indicate an improved in teaching and uptake laparoscopic skills from a registrar point of view.

Table 3.6 Complications and other adverse outcomes recorded intra-operatively and post-operatively.

	Control n=120(%)	Study n=120(%)	p- value
Blood transfusion	47(39,2)	25(20,8)	<0.01
Negative lap	1(0,8)	4(3,3)	<0.01
Bladder/bowel injuries	1(0,8)	2(1,7)	
Admission to critical care unit	9(7,5)	3(2,5)	<0.01
Haemorrhage	22(18,3)	2(1,7)	<0.01
Sepsis	0	0	
Paralytic ileus	0	0	
Pulmonary complications	0	1	
Relook laparotomy	1(0,8)	0	

The rates of complications and adverse outcomes were similar between the control and study groups in terms of the need for blood transfusion, negative findings at operation, visceral injury, and admission to critical care unit. Neither of the two groups reported sepsis, paralytic ileus, thrombo-embolic phenomenon, and pulmonary complications. There was 1 (0,8%) case where a patient in the control group required a relook laparotomy due to a diagnosis of missed bladder injury. There were 47 (39,2%) patients in the control group who required a blood transfusion, and most of these patients, 13 (27,7%) had presented late with symptomatic anaemia. However, 22 (18,3%) of the patients required blood transfusion due to intraoperative blood loss. This was mostly due to delays in a patient getting to the theatre and operative difficulties experienced by the surgeon, such as difficulty achieving haemostasis after identification of ectopic pregnancy. There were 9 (7,5%) patients admitted to a critical

care unit (ICU) for ventilatory support. Only 20,8% of patients in the study group required blood transfusion. There were 2 (1,7%) patients in this group who were complicated by haemorrhage, and 1 (0,8%) patient developed pulmonary oedema requiring prolonged intubation. The 3 (2,5%) patients subsequently required admission in a critical care unit for support.

3.8 Duration of hospital stay.

There were no significant differences in the duration of hospital stay between the control and the study group. There were 93 (77,5%) patients in the control group who stayed in hospital for period between 2 and 3 days. Five (5) (4,2%) of the patients that were discharged after 1 day of hospital admission were those that had laparoscopic surgery performed. There were 17 (14,2%) patients who were hospitalized for period between 4 and 5 days. There were 2 (1,7%) patients in this group who had prolonged stay and were discharged after 6 days. One of them had a relook laparotomy and the other had prolonged stay in ICU. In the study group only 1(0,8%) patient stayed for longer than 6 days. This patient had prolonged intubation due to pulmonary complications secondary to receiving a massive blood transfusion.

Table 3.7 Comparison of duration of hospital stay.

Number of days	Control	p-value	Study	p-value
1 day	5	0,0355	6	0,0417
2-3 days	93	0,019	98	<0,01
4-5 days	17	0,0571	11	<0,01
>6 days	2	0,0455	1	0,0395

CHAPTER 4

DISCUSSION

The main aim of this study was to identify if there was an increase in trend in the use of a laparoscopic surgical intervention for ectopic pregnancy after the directive was issued, and this was observed over the course of 4 years. This study showed that there was indeed a significant increase in the number of cases of ectopic pregnancy being performed by laparoscopic surgery and, more so, these procedures being performed by registrars. Most of the findings in our area are in keeping with the current literature on laparoscopy for ectopic pregnancy, as well as upraise topics for further studies needed to optimize and improve on patient management.

4.1 Maternal Demographics

There was minimal heterogeneity between the characteristics of the patients in the control and study groups. The mean maternal age of all the patients collectively in the study (n=240) of 29.25 years and the mean age of 29 years in each group was in keeping with other studies where the average age was between 26-30 years old (1,16). Many patients being of African descent in both groups is likely biased towards the population that the hospital serves being predominantly of African descent, and hence it should be interpreted with caution. However, ectopic pregnancy has been found to be statistically higher in women of African descent than Caucasian, with 92.05% of the patients in the study (n=240) who were black (51). The consistency in a disparity between black-white ectopic pregnancy is remarkable. Perhaps this is most likely due to higher rates of infections such as chlamydia in black women compared to white women. A contributory factor to this may be a possible delay in the diagnosis and treatment of sexually transmitted infections, causing injury and damage to the fallopian tubes

(51). Low socio-economic status is an important additional factor in the black group (1). However, the finding of race disparity must be interpreted with caution as this centre now serves majority of black patients compared to pre-1994 era.

The findings of the median parity of one in each group and the median gravidity of 3 were not in keeping with most literature. It was previously thought that ectopic pregnancy is a disease of the multiparous as it tends to occur at an older age (52). This was not the case with our study. Ectopic pregnancy has been found by some researchers to occur at first pregnancy without any given history of risk factors. This may be due to mis-shaped fallopian tubes with undiagnosed anomalies, previously untreated PID and endometriosis (52).

Both the control and study groups reported an increase in mean BMI (23.8 and 26.7, respectively). Obesity is becoming a global pandemic associated with an increase in non-communicable diseases (53). Our study showed a significant increase in the mean BMI in the two groups. There was also an association between the increase in BMI and the incidence of comorbidities.

Several studies have shown previous pelvic surgery to be a risk factor for ectopic pregnancy (54,55,56). However, this was not the case in our study. Only 35 patients of the 240 patients had previous abdominopelvic surgery, making a 14,6% of the total study population. Two (5,7%) of these patients had previously had laparotomy for ectopic pregnancy and 18 (51,4) patients, the surgery was a previous caesarean section. Previous studies have shown previous caesarean section to be a risk factor for ectopic pregnancy (54,56). Ranji et al. found that the common risk factors noted were previous caesarean (31.5%), treatment for infertility (31.5%), and eighteen (15%) patients did not have any risk factors (16). In our study population, none of the patients had conceived using Assisted Reproductive Therapy (ART).

4.2 Clinical Presentation and biochemical markers

The mean duration of symptoms of two days for both groups and admission to surgery of 0 days was of statistical significance (p value<0,01). However, it was noted that even though the majority of patients had surgery on the day of admission, patients that had laparoscopic surgery were most likely to wait 1-2 days for surgery. This was most likely attributed to theatre time constraints such as unstable emergency patients being prioritized, anaesthetists not being agreeable to performing laparoscopic surgery after hours, and lastly, due to lack of

or malfunctions of available laparoscopic equipment. Currently, there is no available data in the literature on the exact incidence of problems with technical equipment.

Because of the great deal of symptoms that can occur with ectopic pregnancy, it has been sometimes dubbed “The great masquerade”. The classic triad of symptoms-abdominal pain, amenorrhea, and abnormal vaginal bleeding-is not always present, and ectopic pregnancies often are misdiagnosed (18).

The late presentation of the patients in our study could be attributed to a lack of understanding of the severity and urgency of an ectopic pregnancy being a gynaecological emergency. Access to emergency facilities remains a constraint in some communities. With ongoing patient education, communities can be uplifted on having better health-seeking behaviour. At the primary care level, healthcare workers are also encouraged to be able to pick up danger signs and to refer unstable patients promptly. However, the current reality is that patients are not accessing emergency services as readily as they should in South Africa. Mothers sometimes die giving birth in taxis, and children are dying in ambulances at times. The root of this issue is mainly structural and capacity problems. Some provinces still do not have at least half of the required number of emergency ambulance services per community served.

The level of B-hCG is an important indicator of a tubal ectopic pregnancy for the discriminatory zone. Alterations of some haematological and biochemical parameters are often used as an accessory to the diagnosis in ectopic pregnancy but may still be indifferent from such seen in normal pregnancy (57). In our study, no significant differences in biochemistry and haematology were observed between the two groups. Haemoglobin levels were often used as a marker of haemodynamic stability, and it influenced the surgeon’s choice of management approach. The use of haemoglobin levels alone was insufficient to distinguish those who had ruptured from those who had not.

According to the Kidney Disease: Improving Global Outcomes (KDIGO) classification, Acute Kidney Injury by definition is any of the following: a rise in serum creatinine by ≥0.3 mg/dl (≥26.5 umol/l) within 48 hours; or an increase in serum creatinine ≥1.5 times baseline, which assumed to have occurred within the prior 7 days; or a Urine output volume < 0.5 ml/kg/h for 6 hours (58). In pregnancy, normal physiological renal changes occur, such as increased renal blood flow leading to glomerular hyperfiltration accompanied by a lower serum creatinine level. Values considered normal in the non-pregnant state may be abnormal

during pregnancy (59). Major bleeding from a ruptured ectopic pregnancy may lead to an acute kidney injury. Depending on the severity, it may cause irreversible damage to the renal parenchyma. In our study, one patient had haemorrhage complicated by an acute kidney injury requiring a massive blood transfusion and haemodialysis. However, the incidence of dialysis-requiring Acute Kidney Injury (AKI) in our study cannot represent the true incidence in the total population and, therefore, should be interpreted with caution.

4.3 Ultrasound findings

Ultrasound (US) evaluation is crucial in the diagnostic algorithm of an ectopic pregnancy. Early identification and diagnosis is associated with better maternal outcome and reduces morbidity and mortality by preventing complications(20). It is important to carefully examine patients clinically and to thoroughly study ultrasound images for successful diagnosis and management of gynaecological conditions(60).

The presence of a gestational sac outside of the uterine cavity in the adnexal region, distinctly separate from the ovary is highly suggestive of an ectopic pregnancy. Fluid in the Pouch of Douglas is an additional feature. When ultrasound findings are not diagnostic of an ectopic pregnancy, the examiner should use their own clinical discretion(15).

Better ultrasound machines with higher resonance on transvaginal probes may well be the reason why 46,7% of the cases, in the study group, were diagnosed using all three features for an ectopic pregnancy. Ultimately, an ultrasound probe is as good as the hands it is in. Improvement of the quality of transvaginal ultrasound scan can be done by simulation training for junior doctors and registrars. Le louis et al. found that Simulation-based training improved the quality of pelvic US images in general practice residents assessed after 2 months of experience in gynaecology compared to clinical training alone (60). Ultrasound courses and skill-based assessment is therefore of significant benefit in the training and curriculum of specialists in training.

4.4 Diagnosis and criteria for Laparoscopy

Literature reviews show that although laparoscopic salpingectomy is recommended for treatment of ectopic pregnancy, it is not always indicated (4,32,39). A select group of

patients, who met the criteria for laparoscopy, were treated medically with Methotrexate successfully. In our study, there was no significant difference between the two groups, there wasn't an increase or a decrease in the number of patients treated with methotrexate. None of the patients treated with Methotrexate were admitted to hospital, this finding is in keeping with other studies that reported that medical management of ectopic pregnancy is associated with shorter duration of hospital stay (16,17). Difficulties in follow-up/poor compliance in our population may be the reason for some junior registrars being apprehensive to medical treatment for certain patients.

There was no clear guideline as to which eligibility criteria for laparoscopic management was used in the study population. Patients were said to meet criteria if they were haemodynamically stable and sonographic findings showed an un-ruptured ectopic pregnancy. The description of such patients is often difficult as the majority of patients presented with lower abdominal pain, some with localized peritonism, but with no features suggestive of haemoperitoneum on ultrasound.

Our study showed a significant increase in the number of cases of ectopic pregnancy being treated laparoscopically. In the study group, 21 (17,5%) patients had laparoscopic surgery performed. This is more than a 50% increase compared to previous years (control group). What was even more impressive was that more of these surgeries are being performed by registrars. In the 21 cases that were performed laparoscopically, 81% were registrar lead surgeries. This shows an increasing trend in laparoscopic surgery for ectopic pregnancy in this facility.

4.5 Maternal outcome and duration of hospital stay.

Patients that presented earlier and therefore diagnosed sooner had a reduction in complications. Mortality associated with an ectopic pregnancy has significantly declined in developing countries in the past 15 years (61,62). In this study, there was a statistically significant difference in the number of patients requiring blood transfusions, intraoperatively and post-operatively. Patients that were managed with traditional open surgery often required blood transfusion when compared to those managed laparoscopically.

The Saving Mothers report 2011-2014 reported a significant reduction in deaths due to non-pregnancy related infections, but deaths due to obstetric haemorrhage remains unchanged

(62). In our study, there was overall, 47 (39,1%) and 25 (20,8%) patients who required a blood transfusion in the control and study group, respectively. Forty-five patients (18,8%) out of the (240) total study population were admitted in a shocked condition requiring a massive blood transfusion (4 units PRC: 4 units FFP: 1 megaunit Platelets), 12 (5%) patients required admission to an intensive care unit, there were no reported deaths from complications related to ectopic pregnancy and its management. Laparoscopic surgery will not prevent bleeding and laparotomy surgery does not cause blood loss that requires blood transfusion. It is the disease process and stage of presentation that determines need for transfusion and mode of surgery.

Studies have suggested that laparoscopy incurs less blood loss, a shorter duration of operating time, hospital stay and recovery time when compared to laparotomy (31,32). A shorter duration of operating time was not always the case in our study. The average duration for laparoscopic surgery for an ectopic pregnancy was 90-120 minutes. Teaching in laparoscopy remains paramount. Longer operating times is a characteristic of the procedure and not necessarily operator dependent (7). In our study, operating time was appreciably longer for laparoscopic surgery compared with laparotomy. The learning curve for laparoscopic surgery is noted.

The recovery period was significantly shorter in patients who had laparoscopy compared to those who had laparotomy. However, considering the waiting time for laparoscopy, the total duration of hospital stay/admission days remained unchanged in both groups. A randomized trial in Pretoria done by Snyman et al. found that the period to recovery in the laparoscopy group was remarkably shorter. Many patients in that study regarded themselves as fully recovered within a week from the day of the operation compared with <50.0% in the laparotomy group, where the greater proportion of patients regarded themselves as fully recovered after two weeks (7). In our study, we cannot confirm or confute this finding as patients were not followed up past the point of discharge

CHAPTER 5

CONCLUSION

The study has shown that there are indeed changing trends in laparoscopic surgical management for ectopic pregnancies. There are undoubtedly great prospects in laparoscopic training, given the opportunity and adequate resources. Women need to be offered the best treatment wherever possible, to reduce morbidity and mortality.

It is of paramount importance to educate women on better health-seeking behaviors as early presentation often results in prompt intervention and, therefore, better overall outcomes. Over time, it has been proven that minimally invasive surgery is indeed effective. There is no doubt that our patients will benefit from such surgical interventions. Soon, with technological advancement, national training programs will be established.

Enforcement of the protocol for MIS for ectopic pregnancy indeed increase the rate of procedures performed laparoscopically without increasing in morbidity on these patients. This also enhance the teaching of specialists in training.

CHAPTER 6

RECOMMENDATIONS

1) All pregnant women presenting with signs and symptoms in keeping with an ectopic pregnancy should be referred to a hospital with access to an operating theatre and blood bank with blood product.
2) There should be ongoing gynaecology ultrasound training/courses for medical officers and registrars with availability of a Point-of-Care ultrasound in emergency departments.
3) All patients that meet criteria for medical management with Methotrexate should be treated; accordingly, however, there should be a strict follow up programme.
4) Gynaecology emergency units should be moving closer to universal SOPs that support laparoscopy as the gold standard for management of ectopic pregnancies.

CHAPTER 7

7.1 LIMITATIONS

Our study design was retrospective, therefore, prone to recall bias or misclassification bias. It was difficult to measure certain key statistics; other risk factors that may have been present were not measured.

Although the findings of this research are validated and can be considered reliable, it must be noted that data collection commenced just when the government lockdown regulations due to the COVID-19 pandemic were brought into order, and renovations were undergoing at the records department.

Lastly, we did not investigate the actual reasons for not doing laparoscopy, such as availability of equipment or availability of consultants to assist in the cases. This may be misinterpreted as a poor change in practise trends even though registrars and clinicians wanted to perform laparoscopic surgery but could not be due to the abovementioned constraints.

Due to nature of the functioning of this public healthcare center, it was not possible to calculate an estimate of the costs saved by performing a laparoscopy as opposed to open surgery.

7.2 STRENGTH OF THE STUDY

This study was conducted at one of the largest hospitals in Johannesburg with a large study population for the study type. These patients are a representation of the population we serve.

As this is a retrospective study, it can be used as the initial study generating hypotheses to be studied further by larger, more expensive prospective studies.

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APPENDIX A: Data Collection Sheet

Study/Control [ ] #

Group:	Control (1st Jan 2013-31 December 2015)		Study (1st Jan 2016-31st December 2018	

Patient Demographics

Age: _____

Duration of onset of symptoms (days):_____Symptoms to admission (days): _____

Admission to surgery (days):___

LNMP:_____Parity:_____Gravidity: _____

Past medical history: _____

Past Obstetric/gynaecological history: _____

Past surgical history:_____

Clinical case presentation

Examination findings	Well		Pale		Clammy	
	Shocked		Confused		Tender abdomen	
	Palpable mass		Normal findings			
	Heart rate		Respiratory rate		Blood pressure	
Biochemical findings	Quanti B-hcg		Haemoglobin		Hct	
	Urea		Creatinine			
Blood gas	pH		BE		Lactate	
Ultrasound findings	Free fluid		Adnexal Mass		Empty uterus	

Diagnosis & Criteria for Laparoscopy

Was it recorded as meeting criteria for laparoscopy? (According to NICE guidelines)	Yes		No		
clinical findings					
Hemodynamic stable (if ruptured)		Unruptured		Not amenable for medical management	

Surgical procedure

Laparoscopy					Laparotomy						
Registrar		Consultant			Registrar		Consultant				
Duration	< 1hour		>1hour		Duration	<1hour		>1hour			
Blood transfusion	Yes		No		Blood transfusion	yes		No			
Conversion into open laparotomy	Yes		No								
Post op HC/ICU	Yes		No		Post op HC/ICU	yes		No			
Complications					Complications						
• Haemorrhage					• Haemorrhage						
• Sepsis					• Sepsis						
• Paralytic ileus					• Paralytic ileus						
• Pulmonary complica					• Pulmonary complica						
Duration of hospital stay		1 day	2-3days	4 -5 5days	6 and more						

APPENDIX B: Department of Obstetrics & Gynaecology Approval Letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Office of the Head of Department: Obstetrics and Gynaecology
Enquiries: Prof. L. Chauke

Tel: 011 488-3179
Fax:011 643-2522

05 June 2019

Ms G. Bogoshi
CEO
Charlotte Maxeke Johannesburg Academic Hospital
Parktown
Johannesburg

Dear CEO

Re: Request to conduct research titled:

Permission to obtain: Evaluation practice trend changes in laparoscopic surgical management of ectopic pregnancy at Charlotte Maxeke Johannesburg Academic Hospital.
Dr Gugulethe Mbele.

The above matter refers. I have looked at the protocol and **satisfied to recommend** that she be granted permission to conduct the study as proposed. The candidate has also satisfied the requirements of the Wits Human Research Committee.

Thank you

Prof. H. L. Chauke
Chief Specialist and Clinical Head
Department of Obstetrics and Gynaecology
Charlotte Maxeke Johannesburg Hospital and the University of the Witwatersrand

APPENDIX C: Hospital Approval Letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gautemg.gov.za
28 October 2019

GP_201908_020

Dear Dr. G. Mbele

STUDY TITLE: Evaluating Practice Trend Changes in Laparoscopic Surgical Management of Ectopic Pregnancy at Charlotte Maxeke Johannesburg Academic Hospital

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~**not supported**~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 29/10/2019

Approved/**not approved**

Ms. G. Bogoshi
Chief Executive Officer
Date: 29.10.2019

APPENDIX D: National Health and Laboratory Services Approval letter

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

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Dr Y Perner MBBCh (Witwatersrand) FCPath (SA); MMed (Witwatersrand)

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

August 20, 2019

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Gugulethu Mbele with her research entitled "Evaluating practice trend changes in laparoscopic surgical management of ectopic pregnancy at Charlotte Maxeke Johannesburg Academic Hospital".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Mbele will be in contact with the Department of Anatomical Pathology in respect of this.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

APPENDIX E: Ethics Approval Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Gugulethu Mbele

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190712

NAME: (Principal Investigator)	Dr Gugulethu Mbele
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Evaluating practice trend changes in laparoscopic surgical management of ectopic pregnancy at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	26/07/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Langanani Mbodi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/10/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore be due in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 25/02/2021

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix F: Plagiarism Declaration



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

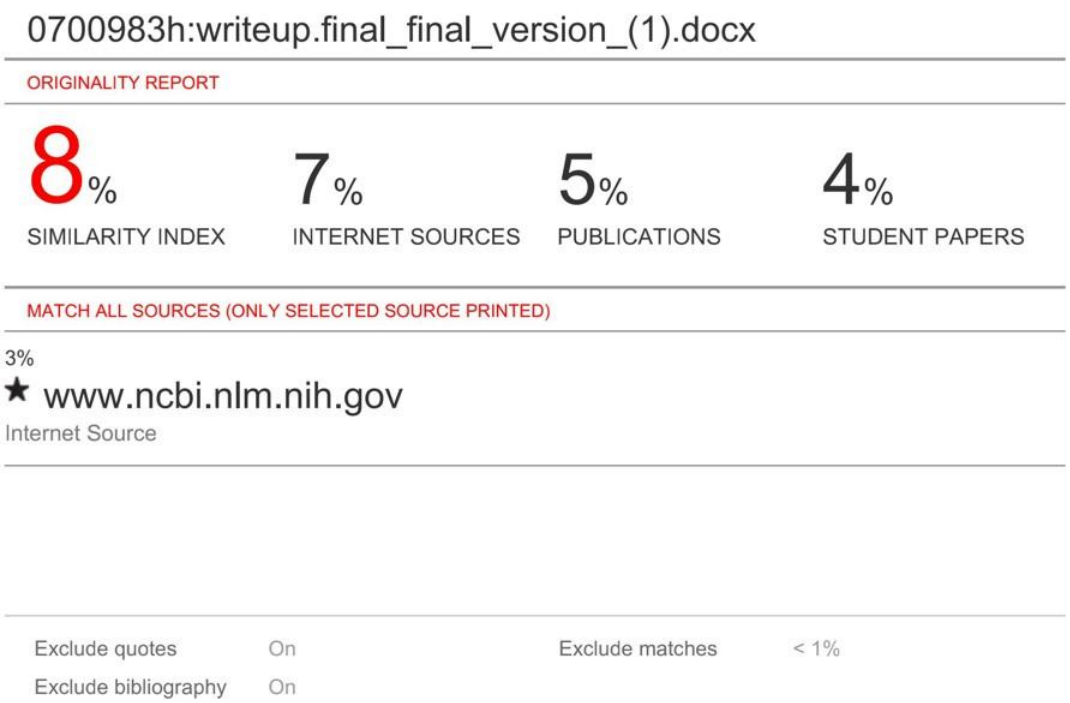
I Gugulethu Mbele (Student number: 0700983h) am a student registered for the degree of Masters of Medicine in Obstetrics and Gynaecology in the academic year 2018.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 25/2/2018

Appendix G: Turn-It-In Report



0700983h:writeup.final_final_version_(1).docx

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