UNIVERSITY OF KWAZULU-NATAL

A DESCRIPTIVE ANALYSIS OF PATIENTS PRESENTING WITH ECTOPIC PREGNANCIES AT KING EDWARD VIII HOSPITAL, DURBAN.

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A thesis submitted to the Faculty of Medicine, University of KwaZulu-Natal, Durban, in fulfilment of the requirements for the degree of Master of Medicine.

DECLARATION

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ABBREVIATIONS

1. EP - Ectopic pregnancy.
2. U.K. - United Kingdom.
3. CEMD - Confidential Enquiry into Maternal Death.
4. RCOG - Royal College of Obstetricians and Gynaecologists.
5. IVF - In vitro fertilization.
6. ETT – Embryo transfer techniques.
7. HCG – Human chorionic gonadotropin.
8. IU/ℓ - International units per litre.
9. TVS – Transvaginal ultrasonography.
10. PAPP-A – Pregnancy associated plasma protein A.
11. C.I – Confidence interval.
12. R.R – Relative risk.
13. Vs. – Versus.

ABSTRACT

OBJECTIVE:

To describe the patient profile, clinical features, risk factors, management options and complications in women with ectopic pregnancy.

DESIGN:

Descriptive study.

PLACE AND DURATION OF STUDY:

King Edward VIII Hospital, Congella, Durban from July 2005 – June 2006.

MATERIALS AND METHODS:

130 case notes of women with the final diagnosis with ectopic pregnancy were examined retrospectively. Data was retrieved through a structured proforma. The variables studied included age, parity, signs and symptoms, treatment, management, complications and associated maternal morbidity and mortality.

RESULTS:

One hundred and twenty women diagnosed with ectopic pregnancy were included in this study. Ten patients were excluded due to failure to obtain clinical records.

Women's ages ranged from 17-40 years with 32 patients (26.7%) being nulliparous and 88 patients (73.3%) between parity 1-4. Twelve patients (10%) had a history of previous ectopic pregnancy.

The commonest presenting symptom was abdominal pain in 106 (88.3%) patients whereas amenorrhoea and vaginal bleeding were found in 88 (73.3%) and 84 (70%) patients respectively.

The most common physical sign was tenderness: Adnexal tenderness in 99 (82.5%) and pelvic tenderness in 91 (75.8%) of women.

Fourteen women (11.7%) presented to the gynaecological outpatient's department in acute shock with a blood pressure < 90/60 mmHg.

The commonest ultrasound findings were the presence of an adnexal mass and an empty uterus in 82 (68.3%) and 80 (66.7%) women respectively.

The most frequent risk factors were previous genital infection in 34 patients (28.3%) and multiple sexual partners in 32 patients (26.7%).

One hundred and eleven 92.4%) women were managed by laparotomy: One hundred and four (87.4%) women via emergency laparotomy and 6 women (5%) had an elective laparotomy.

One patient (0.8%) had a diagnostic laparoscopy which was converted to laparotomy.

Only 8 patients (6.7%) were managed laparoscopically.

Surgical treatment consisted of salpingectomy 101/120 (84.9%) and salpingotomy in 4 (3.4%) patients.

Post- operation complications were minimal however the one maternal death was probably due to a pulmonary embolus.

CONCLUSION:

Risk factors may not always be present, hence ectopic pregnancy should be suspected in every women of reproductive age who present with unexplained abdominal pain, amenorrhoea and vaginal bleeding. Most women presented with ruptured ectopic pregnancies at King Edward VIII Hospital warranting emergency laparotomy.

CHAPTER 1: INTRODUCTION

Ectopic pregnancy is a life threatening condition that every practicing obstetrician and gynaecologist encounters in his or her practice. Ectopic pregnancy has become an epidemic, and its immediate and delayed sequaelae must not be underestimated.

The diagnosis of ectopic pregnancy continues to be a problem in modern gynaecological practice. Sporadic cases of missed diagnosis continue to occur, sometimes leading to grave consequences. Many diagnostic algorithms have been proposed for early detection and to improve accuracy of diagnosis over the last decade (Koh and Yeo, 2005). However, many gynaecologists are not prepared to subject their patients to a stepwise diagnostic algorithm for the ill-informed impression that it is unnecessarily wasting time before definite treatment (Koh and Yeo, 2005). Its implementation increases the immediate cost and provokes anxiety with longer hospital stay, and the patient may default to go to another doctor. These have to be weighed against the potentially disastrous consequences of missing the diagnosis of ectopic pregnancy, as well as the medico-legal consequences.

An ectopic pregnancy occurs when the developing blastocyst implants either outside the uterus (fallopian tube: ampullary 79.6%; isthmic 12.3%; fimbrial 6.2%, ovary 0.15% and abdominal cavity 1.4%) or in an abnormal position within the uterus (cornua 1.9%, cervix 0.15%) (Odendaal et al., 2001). Entrapment at the developing blastocyst en route to the uterine cavity explains the high percentage (98.3%) of ectopic pregnancies occurring in the fallopian tubes.

A ruptured ectopic pregnancy is a medical emergency, therefore it is imperative to diagnose the unruptured ectopic pregnancy such that timeous intervention will prevent morbidity and mortality. In order to diagnose the unruptured ectopic pregnancy, one has to suspect the diagnosis. The introduction of “Early Pregnancy Assessment Units“ (RCOG Guideline Number 25, October 2006), has rapidly improved the management of early pregnancy complications, facilitated by the use of transvaginalsonography and rapid immunoassay of serum human chorionic gonadotropin (HCG) and serum progesterone.

CHAPTER 2:

2.1 EPIDEMIOLOGY

Although advances in earlier diagnosis have led to decreased case-fatality rates, and conservative laparoscopic treatments have enabled improved outcomes, ectopic pregnancy remains a major cause of maternal mortality and accounts for a sizable proportion of infertility and ectopic recurrence (Condous, 2004).

Over the last 25 years, as the morbidity and associated mortality of ectopic pregnancy have substantially decreased, the incidence has progressively increased (Condous, 2004). The incidence of ectopic pregnancy in the United Kingdom (U.K.) has remained stable in recent years (11.1/1000 pregnancies) with nearly 32 000 ectopic pregnancies diagnosed in the U.K. within a 3 year period (Lewis and Drife, 1999). The fourth leading cause of direct maternal death in the United Kingdom in the Confidential Enquiry into Maternal Death period 1997-1999 was ectopic pregnancy, accounting for 80% of first trimester deaths (Lewis and Drife, 1999). There were 13 deaths resulting from ectopic pregnancy accounting for 12% of total maternal deaths (Lewis and Drife, 1999).

Substandard care was responsible for 65% of these deaths and the most common problem was failure to suspect on ectopic pregnancy (Lewis and Drife, 1999).

According to the Sixth report of the Confidential Enquiry into Maternal and Child Health, Why Mothers Die?, there were 11 deaths from ectopic pregnancies: 7 located in the extrauterine tube and 4 located in the interstitial portion of the tube (cornual pregnancies) (Lewis and Drife, 1999).

Cornual pregnancies account for approximately 2% of ectopic pregnancies and are said to have a high mortality rate between 2.0 – 2.5% (Lewis and Drife, 1999). Ultrasound is successful in around 70% at cases but there are well-recognized diagnostic difficulties. In none of the cases reported was the diagnosis made before rupture. Haemorrhage can be severe because the pregnancies are either more developed than extrauterine tubal pregnancies and because of the large blood supply to the uterus (Lewis and Drife, 1999).

According to the Seventh Report of the Confidential Enquiry into Maternal Death (2003-2005), there were ten deaths from ruptured ectopic pregnancies.

Epidemiologists often describe ectopic pregnancy in terms of overall rates rather than absolute numbers. Underestimation of this rate results from the sizable percentage of spontaneous miscarriages or chemical pregnancies that may actually represent self-resolving ectopic gestations. Generally, ectopic pregnancies are quoted in terms of number per reported pregnancies.

In South Africa, for the triennium 2002-2004, there were 161 early pregnancy deaths during 2002-2004 (National Department of Health, 2006). Ectopic pregnancy attributed to 47 of these deaths, a 74% increase on the 27 deaths reported during 1999-2001. It is not clear whether the increase in ectopic pregnancy deaths in this triennium is real or the result of improved reporting (National Department of Health, 2006).

Maternal death assessors considered 64% of ectopic deaths to be “clearly avoidable”. The most frequent avoidable factors as were diagnostic problems (31%) and resuscitatory failure in hypovolaemic shock (36%).

The rise and fall in ectopic pregnancy rates could be explained in part by the increasing rates of chlamydia infection followed by the effect of prevention and the change in the use of intrauterine devices in developed countries (Diamond et al., 1991).

Further, infertility moderately increases the risk of ectopic pregnancy. There is greater availability of assisted reproductive technology, surgery performed to correct the tubal factor in infertility and widespread use of ovulation induction agents have all been incriminated (Diamond et al., 1991).

Reproductive performance following an ectopic pregnancy is adversely affected with a reported repeat ectopic rate of 10-27% and subsequent fertility rates of 45-60% (RCOG Guideline Number 21, May 2004).

2.2 BACKGROUND

Historically, clinicians managed ectopic pregnancy by excision via laparotomy. The first successful surgical treatment of salpingectomy was described in 1883 by Tait (quoted by Flystra, 1998).

Since then the traditional surgical approach to ectopic pregnancy has been salpingectomy by laparotomy. Conservative surgical treatment of ectopic pregnancy (salpingotomy) in an attempt to preserve the affected fallopian tube is thought to be first performed by Prochownick in 1913 (quoted by Diamond et al., 1991). The first reported salpingotomy was by Stromme in 1953 (quoted by Flystra, 1998). In 1973, Shapiro and Adler reported the first laparoscopic salpingectomy for ectopic pregnancy (quoted by Garry, 1996), while Bruhat reported the first salpingotomy in 1978.

Today the availability of monoclonal β-HCG, high resolution transvaginal scan and laparoscopy has made it possible to make early diagnosis in many cases before rupture. This improved capability, makes a laparoscopic approach feasible and facilitates conservative surgery, particularly in those wishing to conceive again.

Treatment options for ectopic pregnancies are :

i) Surgery e.g. salpingectomy or salpingotomy performed either laparoscopically or by open surgery.

ii) Medical treatment, with a variety of drugs, which can be administered systemically and / or locally by various routes.

iii) Expectant management.

As a consequence, the clinical presentation of ectopic pregnancy has changed from a life threatening disease necessitating emergency surgery to a more benign condition in sometimes even asymptomatic patients.

CHAPTER 3:

3.1 AETIOLOGY

Aetiological factors include :

i) Anatomic alterations.

ii) Inherent defects in the fertilized ovum.

iii) Hormonal imbalance

i) Anatomic alterations

Disruption or damage to the mucosal portion of the fimbria or fallopian tube will prevent normal embryo transport. This accounts for about 50% at all ectopic pregnancies (Diamond et al., 1991). Tubal damage is most commonly due to scarring from infection, inflammation and surgery. Denudation of tubal epithelium disrupts the normally synchronized function of the tubal cilia, particularly within the ampullary portion of the tube, where fertilization and early embryo cleavage normally occur. Intraluminal adhesions or diverticulae at any point along the tube may interfere with normal pre-embryo transport mechanisms.

ii) Inherent Defects in the fertilized eggs

It has been suggested that an increased risk of ectopic pregnancy may reflect instances of either premature ovulation, immature eggs (with denser, less motile cumulus-corona complexes) or delayed-ovulation, post-mature eggs with tendency to implant before arrival in the uterus.

iii) Hormonal Imbalance

Estrogen increases smooth muscle activity and muscular tone in the isthmus of the fallopian tube and may facilitate the retention of a fertilized ovum in the ampullary portion of the tube for a few days.

Progesterone decreases smooth muscle activity, particularly tubal peristalsis. In the luteal phase, progesterone facilitates ovum migration towards the uterus. This may explain the increased incidence of ectopic pregnancy in cycles stimulated with human menopausal gonadotropin and when pregnancy occurs with a progesterone containing intrauterine device in place. Therefore, the transport of the fertilized ovum through the fallopian tube and implantation within the endometrial cavity may require an optimum ratio of estrogen and progesterone (Diamond et al., 1991).

3.2 PATHOGENESIS AND RISK FACTORS

High risk factors include:

i) Tubal surgery including sterilization

ii) Previous ectopic pregnancy

iii) Use of intrauterine device

iv) Documented tubal pathology from pelvic inflammatory disease and adhesions from previous surgery

v) In-utero exposure to diethylstilboestrol

Ectopic pregnancy commonly occurs in patients with impaired tubal function.

Surgically visualized tubal pathology, commonly the result of pelvic infection, endometriosis or previous surgery is the strongest risk factor. Pelvic infection, including gonorrhoea, serologically confirmed chlamydia infection and pelvic inflammatory disease are less significant in a developed setting. In a developing setting the aetiological influence of sexually transmitted diseases, which has recently been compounded by the HIV epidemic, impairs tubal function leading to dramatically increased incidence (Sperling et al., 1991). The risk of ectopic pregnancy increases with the episodes of pelvic infection (Hillis et al., 1997).

Tubal sterilization effectively prevents pregnancy. If pregnancy does occur, ectopic pregnancy should be strongly suspected and excluded. Risks appear highest after electrocoagulation procedures, possibly resulting from tubal recanalisation or formation of an uteroperitoneal fistula (Mc Caussland et al., 1980).

The risk of ectopic pregnancy after sterilization is increased nine-fold, and is especially high for those sterilized by electro-cautery and in women younger than 30 years (Skejeldestad et al., 1988). A third of pregnancies that arise after sterilization are ectopic (Furlong, 2002).

Petersen et al., (1997), reported that 32.9% of pregnancies occurring after prior tubal sterilization were ectopic in location. The greater risk occurred in patients who underwent laparoscopic tubal bipolar cautery, resulting in an overall ectopic pregnancy risk of 17.1 per 1000 procedures, but 31.9 per 1000 procedures when biopolar cautery was used before age of 30 (Kendrick et al. 1997). This is in contrast to a low rate of 1.5 ectopic pregnancies per 1000 procedures, after postpartum bilateral partial salpingectomy at any age (Peterson et al., 1997).

Ectopic pregnancy after tubal sterilization was also more common in black women and in women with a history of pelvic inflammatory disease before the sterilization procedure (Peterson et al., 1997). A third of pregnancies that arise after sterilization are ectopic (Furlong,2002)

The risk is increased in patients who have had ectopic pregnancy previously, and increases further in proportion to the number of previous ectopic pregnancies. Risk of recurrence decreases with subsequent intrauterine pregnancies after the initial ectopic pregnancy (Skejeldestad et al., 1998).

A woman who is not pregnant and is using a non progesterone-containing intra-uterine device is at risk of developing an ectopic pregnancy as a non-pregnant woman not using an intrauterine device. However, because an intrauterine device prevents intra-uterine more effectively than it prevents extrauterine implantation, a pregnancy occurring with an intrauterine device is more often an ectopic pregnancy.

There maybe a slight increased risk for the future development of ectopic pregnancy in past intrauterine device users, and that risk may increase with the duration of use (Furlong et al., 2002).

<u>Moderate risk factors include</u>:

i) Fertility

ii) Previous genital infection

iii) Multiple sexual partners

Assisted reproduction techniques increase the risk of ectopic pregnancy two-fold to 4% (Strandell et al., 1999). The raised likelihood of tubal disease and need for surgery in this population are obvious confounders. It has been shown that tubal factor infertility and previous myomectomy account for 85% of ectopic pregnancies in women who receive fertility treatment (Strandell et al,1999)

Embryo transfer with retrograde embryo migration into diseased tubes is also a reason for the higher incidence seen among those undergoing in-vitro fertilization (Nazari et al., 1993).

Agents that induce ovulation may increase risks through the effect of hormone fluctuations on tubal function.

Low risk factors include:

i) Cigarette smoking

ii) Vaginal douching

Only a slight increased risk was reported in women who smoked, douched and began coitus at an early age.

Kendrick et al.,(1997), reported a strong association between ectopic pregnancy and vaginal douching in black women (adjusted odds ratio = 3.8), but could not distinguish douching as an independent factor from being an agent promoting a pre-existing infection by forcing non-sterile fluid and organisms into the fallopian tube .

CHAPTER 4:

4.1 DIAGNOSTIC EVALUATION

i) A proper history and physical examination remain the foundation for initiating an appropriate workup that will result in the accurate and timely diagnosis of an ectopic pregnancy. A third of women have no clinical signs and 9% have no symptoms of ectopic pregnancy (Tay et al., 2000).

Typical trend of symptoms includes bleeding and abdominal pain after a period of amenorrhoea.

ii) Identification of risk factors can raise the index of suspicion and lend significance to otherwise minor physical finding.

iii) Serum-β-HCG measurements - a single measurement of β-hCG in practice will not be diagnostic in the majority of cases. An understanding of the pattern of serum β-hCG levels in early normal pregnancy is important. At any given time, the serum level of β-hCG is determined by the rate of trophoblastic secretion and renal clearance. Given normal renal function, β-hCG is cleared from the serum with a half life of about 24 hours (Pittaway et al., 1985).

In normal intrauterine pregnancies there should be a 66% rise over the baseline valve over 48 hour (Kader et al., 1981). Using this well known algorithm is not without its pitfalls, as approximately 13% of ectopic and 15% of normal intrauterine pregnancies may exhibit declining, a plateau or erratic and unpredictable β-hCG rises (Long et al., 1994).

Normal intrauterine pregnancies tend to double their β-hCG titres every 2.3 days between conception and 7 weeks of gestation. If the appropriate doubling time is not achieved or if

the serum concentration of β-hCG plateaus, the pregnancy is either an ectopic or a non viable intrauterine pregnancy (Kader et al., 1981).

Kadar et al. (1981) have suggested that non viable intrauterine pregnancies show a more rapid fall in serum β-hCG levels than ectopic pregnancies.

Hormonal results should not be taken in isolation and the clinical assessment and subsequent ultrasound finding are essential to the ongoing management.

Since vaginal ultrasound can detect an intrauterine pregnancy about a week earlier than that of an abdominal scan, β-hCG levels above 1000 IU/L in the absence of an intrauterine sac indicates the need for laparoscopy (Cacciatore et al., 1990).

The absence of an intrauterine gestational sac and a β-hCG titre between 1000-1500 IU/L has been shown to be highly predictive of an ectopic pregnancy (Cacciatore et al., 1990).

iv) Serum Progesterone - serum progesterone levels have been suggested as useful markers of ectopic pregnancy, however a systematic review of the accuracy of a single progesterone measurement concluded that although the progesterone concentration could identify women at risk of ectopic pregnancy, its clinical usefulness is limited because of its discriminative capacity to diagnose ectopic pregnancy with certainty (Mol et al., 1998 a).

Serum progesterone levels are not gestational age dependent, remain relatively constant during the first trimester of normal and abnormal pregnancies and do not correlate with hCG levels (Fylstra, 1998).

Although an absolute cut-off has not been determined, a progesterone level <10 ng/mL is generally not compatible with a viable pregnancy. However, a progesterone level >20 ng/mL is usually consistent with a normal pregnancy (Fylstra, 1998).

McCord et al.(1996), in their study of using a single serum progesterone value as a screen for ectopic pregnancy, reported that only 0.16% of patients with a progesterone < 5 ng/mL (2/1279 patients) eventually were found to have a normal pregnancy and these two patients had rising hCG levels. These authors also recommended a progesterone cut-off of 17.5 ng/mL below which ectopic should be considered (McCord et al., 1996).

v) Biochemical Markers - the ideal marker for ectopic pregnancy would be specific for tubal damage or present early after endometrial implantation. Various markers have been assessed but none are sufficiently sensitive or specific for the diagnosis of ectopic pregnancy (Diamond et al., 1991).

vi) Ultrasound - Shalev et al., (1998) state that the diagnosis of ectopic should not be based on an inability to visualize an intrauterine pregnancy, but rather on the positive visualization of an adnexal mass using transvaginal sonography. If an ectopic pregnancy is present, one should visualize between 87-93% of ectopic pregnancies using transvaginal sonography (Shalev et al., 1998). If a pregnancy cannot be seen, then it is a pregnancy of unknown location ~ 10% at which are ectopic pregnancies (Condous et al., 2004).

The appearances of ectopic pregnancies on transvaginal sonography are highly variable. Classically, they are described as the “bagel sign” with a hyper echoic ring around the gestational sac in the adnexal region, but more often they are seem as a small inhomogeneous mass next to the ovary - “blob sign” (Lerner and Monteagudo, 1995).

A meta analysis (pooled data from 10 published studies) by Brown and Doubilet (1994) has shown that the most appropriate transvaginal criterion on which to diagnose ectopic pregnancy

is any non cystic adnexal mass. This leads to a positive predictive value of 96.3%, negative predictive value 94.8%, specificity 98.9% and sensitivity 84.9% (Brown and Doubilet, 1994). The dimensions of the ectopic should be described, as should the presence of an embryo with or without a heartbeat.

Haematoceles have a characteristic appearance, and the amount of bleeding that has occurred should be commented upon by looking for fluid or blood in the pouch of Douglas. This should not be confused with serous fluid as the appearance of blood and clots are different.

The corpus luteum is a useful guide when looking for an ectopic pregnancy, as it will be on the ipsilateral side in over 85% of cases (Jurkovic et al., 1992).

The so called “pseudosac” is controversial. This is a misnomer and probably represents a fluid collection or debris in the cavity (Condous et al., 2004). This sign is largely based on historical data and relates to the use of transabdominal ultrasonography. Using high resolution vaginal probes, misinterpretation is less likely.

4.2 TREATMENT

Treatment options for tubal ectopic pregnancies are :

i) Surgery e.g. salpingectomy or salpingotomy either performed laparoscopically or by open surgery.

ii) Medical treatment, with a variety of drugs that can be administered systemically and / or by various routes.

iii) Expectant management

LAPAROSCOPY VERSUS LAPAROTOMY

Laparoscopic surgery is considered by many to be the “gold standard” for surgical treatment if the patient is haemodynamically stable (Vermesh et al.,1989). Advances in laparoscopic surgery have enabled a laparoscopic approach in the majority of patients with tubal ectopic pregnancy.

The laparoscopic approach results in less haemorrhage (blood loss), lower analgesic requirement, shorter hospital stay, quicker post operative recovery time and reduce costs considerably (Vermesh et al., 1989; Gray,1995). Nevertheless, there will always be a place for laparotomy in those women who are haemodynamically unstable.

The subsequent intrauterine pregnancy rate was 61% after laparoscopic surgery compared to 52% after laparotomy, while the recurrent ectopic pregnancy rate was lower after laparoscopy (8%) than after laparotomy (14.4%) (Vermesh et al., 1989).

Laparoscopic surgery has been compared with open surgery in 228 women in 3 randomised controlled trials. There was no difference in overall tubal pregnancy rates (RR 0.89; 95% CI 0.74 -1.1) (Vermesh et al., 1989; Lundorff et al., 1991; Gray et al., 1995).

In women who desired future fertility (n = 145), the subsequent intrauterine pregnancy rates where similar (RR 1.2; 95% CI 0.88 -1.15) and there was a trends towards lower repeat ectopic pregnancy rates if the laparoscopic approach was used. (RR 0.43; 95% CI 0.15 – 1.2) (Vermesh et al., 1989; Lundorff et al., 1991; Murphy et al.,1992; Gray et al., 1995).

MINILAPAROTOMY VERSUS LAPAROTOMY

In a study, involving 60 women with an ectopic pregnancy (Sharma et al, 2003) revealed that post-operative complications: paralytic ileus (10% vs. 27%) and wound infection (3% vs. 17%) were significantly less in the minilaparotomy group than in the conventional laparotomy group. Also the duration of hospital stay (3.4 days vs. 6.9 days) was shorter in the minilaparotomy group.

SALPINGECTOMY OR SALPINGOTOMY

There has been considerable debate about whether salpingectomy or salpingotomy should be done at the time of surgery for an ectopic pregnancy.

The possible advantages of removing the tube completely include almost entirely eliminating the risk of persistent trophoblast and that of subsequent ectopic pregnancy, whereas the possible advantage of conserving the fallopian tube is that future fertility is preserved. The reported failure rate after conservative treatment ranges from 3 - 29%, whereas there is practically no failure after radical treatment (< 0.5%) (Murphy et al., 1992).

The decision to perform a salpingectomy or salpingotomy will depend on the size of the ectopic pregnancy, damage to the tube and the health of the contralateral tube (Ramphal and Moodley, 2006).

A number of systemic reviews have examined reproductive outcomes following the management of tubal pregnancy with either salpingotomy or salpingectomy.

There are no randomized controlled trials comparing outcome and assessing future fertility with either form of treatment.

There are four recent cohort studies that specifically compare laparoscopic conservative and radical treatment of ectopic pregnancy.

Silva et al.(1993) examined reproductive outcomes prospectively in 143 women undergoing laparoscopic salpingectomy (55.9%) or laparoscopic salpingotomy (36.4%) (Silva et al., 1993). The intrauterine pregnancy rates were similar when comparing the 2 groups (60% vs. 54% RR 1.11 95% CI 0.74-1.68) but there was a trend towards higher subsequent ectopic pregnancy in the salpingotomy group (18% vs 8% RR 2.38 95% CI 0.57-10.01) (Silva et al., 1993).

Job-Spira et al. (1998), in a study of 125 women, performed a multivariate analysis on reproductive outcomes following ectopic pregnancy (Job-Spira et al., 1998). They demonstrated a trend towards improved subsequent intrauterine pregnancy rates with conservative surgery (hazard ratio 1.22 95% CI 0.68 – 2.20).

The cumulative pregnancy rates at 1 year were 72.4% after conservative and 56.3% after radical surgery (Job-Spira et al., 1998).

In a study by Mol et al.,(1998 b) a cohort of 185 women, the fecundity rate when comparing laparoscopic salpingotomy to salpingectomy during the 18 month following period was 1.4 (95% CI 0.68 – 2.7) for a women with a healthy contralateral tube and 3.1 (95% CI 0.76-12.0) for women with contra-lateral tubal disease.

The 3 year cumulative pregnancy rate was 62% after salpingotomy and 38% after salpingectomy (Mol et al., 1998 b).

Bangsgaard et al., found pregnancy rates higher with salpingotomy. The cumulative pregnancy rate after 7 years was 89% following salpingotomy and 66% following salpingectomy ($p < 0.05$) (Bangsgaard et al., 2003).

The hazard ratio for intrauterine pregnancy following salpingectomy was 0.63 (95% CI 0.42-0.40) when compared to salpingotomy (Bangsgaard et al., 2003).

Conservative surgery should be performed when there is evidence of previous tubal infection at the time of laparoscopy, as this confers the best chance for future fertility. In women with no past history of tubal surgery or infertility and those whose contra-lateral tube is normal, the fertility results after laparoscopic salpingectomy are comparable to those observed after conservative laparoscopic treatment.

Therefore in the presence of a healthy contra-lateral tube, neither salpingostomy nor salpingectomy offers any advantage with respect to future infertility. However, in those who desire future fertility, salpingostomy should be considered as the primary treatment option for tubal pregnancy in the presence of disease in the contra-lateral tube.

The patient must be made aware that there is an approximately 20% risk of recurrent ectopic pregnancy. If conception has not occurred after 18 months following salpingotomy, it is unlikely to occur and in vitro-fertilization should be recommended (Ramphal and Moodley, 2006).

Persistent ectopic pregnancy after laparoscopic salpingotomy varies between 4 - 15% (Fernandez and Gerviase, 2004). Therefore, β-hCG concentration should be followed until they are undetectable.

4.3 MEDICAL MANAGEMENT

Medical treatment with methotrexate is an effective means of treating pregnancy without the risks associated with surgery.

Early diagnosis has made medical therapy of ectopic pregnancy an option. Systemic and local administration of drugs has been introduced in selected patients with an unruptured tubal ectopic pregnancy without active bleeding. Agents that have been used include hyperosmolar glucose, urea, cytotoxic agents like methotrexate, prostaglandins and mifepristone.

Methotrexate is a folic acid antagonist that inactivates dihydrofolate reductase, resulting in the depletion of tetrahydrofolate, a cofactor essential for deoxyribonucleic acid and ribonucleic acid synthesis. The goal of medical management with methotrexate is to selectively kill the cytotrophoblast. The body will then spontaneously resorb the remaining products of conception and blood clots that constitute the ectopic pregnancy.

Leucovorin, a folinic acid, has been used as a “rescue” medication that allows for higher methotrexate dose administration by preventing some of the otherwise prohibitive adverse effects. Leucovorin enter cells via a carrier-mediated system and does not require reduction by dihydrofolate reductase for conversion to active folate cofactors, preventing some of the adverse effects of methotrexate.

Methotrexate maybe administered orally, intramuscularly, intrathecally or by continuous infusion. It maybe used as primary treatment, treatment of persistent ectopic after salpingotomy, prophylaxis for suggested persistent products of conception after conservative surgery and in some cases of unusually located ectopic pregnancies.

Currently there are 2 commonly used protocols for the administration of methotrexate in the treatment of ectopic pregnancy.

i) The fixed multiple dose of regimen is derived from the treatment of gestational trophoblast disease described by Bagshawe (1989) and Goldstein (1976) (quoted by Hajenius et al., 2007) . The regimen of Bagshawe comprise a total of 4 injections of methotrexate 50 mg IM alternated with folinic acid 6 mg IM 30 hours after each methotrexate injection with a rest period of 6 days. The therapeutic protocol of Goldstein comprises of total of 4 injections of methotrexate 1mg/kg IM alternated with folinic acid 0.1mg/kg IM 24 hours after each methotrexate injection.

ii) Alternately, methotrexate can be administered using a “single dose” method (quoted by Hajenius et al., 2007). In 1989, Stovall individualized the methotrexate dosage to improve patient compliance, to minimize side effects and to reduce overall costs, which ultimately led to a single dose regimen of 50 mg/m^2 body surface area given intramuscularly without folinic acid (Stovall et al., 1993)

Each protocol has been demonstrated to have good success rates in uncontrolled independent case series.

Large uncontrolled studies involving single dose methotrexate have reported that 15% of patients will require more than 1 dose of methotrexate and less than 10% of patients treated with this regimen will require surgical intervention. Also 7% of patients will experience tubal rupture during follow up (Lipscomb et al., 1994).

SIGNS OF TREATMENT FAILURE / TUBAL RUPTURE

[ACOG Practice Bulletin 3, 1998 - Medical management of tubal pregnancy] – quoted by Bester and Heard, 2000.

i) Significantly worsening abdominal pain, regardless of change in β-hCG levels.

ii) Haemodynamic instability.

iii) Levels of β-hCG do not decline by at least 15% between day 4 and day 7 post injection.

iv) Increasing or a plateau β-hCG levels after the first week of treatment.

Systematically the efficacy and prevalence of side-effects of the “single” dose and “multidose” regimen were compared (Barnhart et al., 2000)

The overall success rate of women treated with methotrexate for an ectopic pregnancy was 89%. The single dose was much more commonly used. The use of single dose was associated with a significantly greater chance of failed medical management than the use of multidose in both crude (OR 1.71) and adjusted analysis (OR 4.74).

The single dose regimen was associated with fewer side effects (OR 0.4).

COMPLICATION OF METHOTREXATE

The major adverse effects include liver function, stomatitis, gastro-enteritis and bone marrow suppression. Haemorrhage enteritis of the intestinal tract leads to nausea, vomiting, stomatitis, elevated liver enzymes, weight loss and blood diarrhoea.

Destruction of bone marrow precursors puts patients at risk of developing thrombocytopaenia, reticulacytopaenia, lymphopaenia and granulocytopaenia. Thrombocytopaenia predisposes patients to life-threatening haemorrhage and lymphopaenia and granulocytopaenia that predispose patients to systemic infections.

There is also the potential for nephrotoxicity, interstitial pneumonitis, alopecia dermatitis and an anaphylactic reaction.

33-60% of patients may experience an increase in abdominal pain 6-7 days after receiving methotrexate. The pain is often referred to as separation pain as it is believed to result from tubal abortion or haematoma formation with distension at the fallopian tube (Seeber et al., 2006).

Revised criteria for medical therapy with methotrexate

(ACOG Practice bulletin. Medical management of tubal pregnancy) (Number 3, December 1998). (ACOG Consensus Committee Opinions).

Indications for methotrexate use

1. Haemodynamically stable with no signs of tubal rupture.
2. Diagnosis without laparoscopy.
3. No contra-indications to methotrexate.
4. Ectopic mass ≤ 3.5cm.
5. No fetal cardiac activity
6. Peak β-hCG < 15000 mIU / ml
7. Informed consent and able to follow-up

Absolute contra-Indications

1. Haemodynamic instability.
2. Medical disease including liver, gastro-intestinal, renal, pulmonary, pre-existing haematological, severe immuno-deficiency and history of alcoholism.
3. Patient refuses medical therapy.

Relative Contra-Indications

1. Gestational sac > 3.5cm.
2. Positive fetal cardiac motion.

Predictors of Successful Methotrexate Treatment (Lipscomb et al., 1994).

1. Serum β-hCG concentration is inversely associated with success - this is the most predictive.

   Tawfiq et al., (2000) found that treatment failure occurred in 65% of cases when the β-hCG was > 4000 IU/l compared with 3.5% when the level was < 4000 IU/l
2. Progesterone level.
3. Size and volume of gestational mass.
4. Presence / absence of cardiac activity.
5. Presence / absence of free peritoneal blood.

Two recent RCTs compared systemic methotrexate therapy with laparoscopic surgery.

i) **Methotrexate (1mg / kg) versus Conservative laparoscopy surgery**

(Saraj et al., 1998)

78% success rate for methotrexate compared to 92% for laparoscopic surgery.

Methotrexate group	16% required an additional dose 5% required surgery during follow up period
Laparoscopic group	8% persistent trophoblastic tissue

ii) **Methotrexate (50 mg / m^2) versus Conservative laparoscopic surgery**

(Souter et al., 2001)

65 % success rate for single dose methotrexate compared to

93% for laparoscopic surgery (95% Cl 10 – 47%) P < 0.05

Methotrexate group	26% required an additional dose 18% required surgery
Laparoscopic group	2% persistent trophoblastic tissue

Other efforts to attain maximal efficacy while minimizing or eliminating adverse effects resulted in various protocols for local medical treatment administered into the gestational sac transvaginally under sonographic or under laparoscopic guidance. Since the main advantage of medical therapy is its non-invasiveness, intramuscular methotrexate is more practical and less operator dependent than local injection via laparoscopy or ultrasound into the sac. The use of transvaginal treatment techniques requires a high degree of training and skill, and one would not recommend their use, especially in the light of the evidence suggesting that single dose methotrexate is just as effective. To evaluate treatment response after medical treatment, close serum β-hCG monitoring is mandatory to detect impending failure and inadequately declining serum hCG concentrations.

A review of 24 studies found a surgical intervention rate of 9% when methotrexate was injected locally into the gestational sac (either laparoscopically / ultrasound guidance) and a rate of 3.2% in the systemically treated group.

Reproductive outcome after a previously treated ectopic pregnancy appears to be similar, whether the treatment method had been methotrexate or conservative surgery. Intrauterine pregnancy rates seen are comparable in both those groups, with a possible slightly lower risk of recurrent ectopic seen in a medically treated group (Fernandez et al., 1998).

The use of mifepristone as an adjunct treatment to methotrexate for ectopic pregnancy showed no benefit of the combined regimen over methotrexate alone (Rozenburg et al., 2003).
The time to resolve the unruptured ectopic was also significantly faster in the group who received combination mifepristone and methotrexate (Gazvani et al., 1998).

Overall, it would appear that if strict criteria are fulfilled, medical management is a reasonable alternative but costs, longer hospitalization, prolonged follow-up and patient choice need to be considered.

Comparative studies

1. Systemic methotrexate in a single dose versus laparoscopic salpingostomy

(Sowter MC, Farquhar CM, Petrie KJ et al, 1998)

Systemic methotrexate (50mg/m² / 1 mg/kg im) less successful than
Laparoscopic salpingostomy (RR 0,82 95% CI 0,72-0,94)

2.Single versus multiple dose systemic methotrexate

(Alleyassin A, Khademi A, Aghahosseini et al, 2006)

Prospective, randomized controlled clinical trial
No significant difference in treatment success (RR 0,99 CI 0,89-1,1)

3. Systemic methotrexate in combination with mifepristone

(Rozenberg P, Chevret S, Camus E et al, 2003)

Randomized clinical trial comparing methotrexate-mefiprisone versus methotrexate-placebo

Showed methotrexate (50mg/m²) was less successful in the elimination of tubal pregnancy than when mefiprisone 600mg was added
(RR 0,84, 95% CI 0,71-1,0)

4.4 EXPECTANT MANAGEMENT

Expectant management has been advocated, based on the knowledge that the natural course of many early ectopic pregnancies is a self limiting process, ultimately resulting in tubal abortion or reabsorption.

In a select group of women, expectant management of ectopic pregnancy is an option. Ylostalo et al.(1991), managed 15% of their ectopic pregnancy expectantly and observed spontaneous resolution in 64.6%. An analysis of 10 prospective studies with a total of 347 patients managed expectantly, demonstrated 69.2% of ectopic pregnancies resolved spontaneously (quoted by Ramphal and Moodley, 2006)

Favourable factors include:

i) Low initial β-hCG level (1000 – 2000 IU/L).

ii) Haemoperitoneum < 50 mls.

iii) Tubal mass < 2 cm.

iv) Absence of recognizable fetal parts on ultrasound.

v) Absence of clinical symptoms.

Such management requires very close follow up and is reserved for selected cases, with after hour's emergency backup in the event of clinical deterioration.

Royal College of Obstetricians and Gynaecological Guideline include:

i) Follow up twice weekly with serial hCG measurements (ideally less than 50% of initial β-hCG level within 7 days).

ii) Weekly transvaginal examinations - reduction in the size of the adnexal mass by 7 days, thereafter, weekly hCG and transvaginal ultrasound examinations are advised until serum β-hCG levels are less than 20 IU/l.

2 randomized control trials have been published on expectant management for ectopic pregnancy.

1.Prostaglandin versus expectant management in early tubal pregnancy (Egarter c, Kiss H & Husslein P, 1991)

23 patients with unruptured ectopic pregnancy and serum hcg <2500 IU/l

Expectant management was significantly less successful than prostaglandin therapy (RR 0,12 95% CI 0,02-0,81)

2. Low dose oral methotrexate with expectant management of ectopic pregnancy (Korhonen J, Stenman U & Ylostalo P, 1996)

Double blind, placebo controlled trial
Oral methotrexate 2,5mg/d during 5 days was prescribed:

- 60 haemodynamically stable women
- tubal ectopic pregnancy < 4cm with no fetal heart activity
- serum hcg < 5000IU/l

Success rates of 77% was observed in both groups (RR1,0 95% CI 0,76-1,3)

CHAPTER 5: JUSTIFICATION FOR STUDY

Pelvic infections, including Gonorrhoea, serologically confirmed Chlamydia infection and pelvic inflammatory disease are common conditions in Southern Africa. Our patients come from a poorer socioeconomic background and therefore may be at greater risk for pelvic inflammatory disease. Pelvic inflammatory disease together with multiple sexual partners are moderate risk factors for ectopic pregnancy. Laparoscopy is regarded as the final decisive test in suspected ectopic pregnancy. The new non invasive diagnostic methods of transvaginal sonography and serum human chorionic gonadotrophin monitoring now challenge this pivotal role of laparoscopy. There are a few studies auditing ectopic pregnancy in Southern Africa. The clinical management of patients are still problematic. A significant number of deaths are encountered with difficulty in diagnosing ectopic pregnancy. Also the conception rate and reproductive performance following ectopic pregnancy is poor. The decision to carry out this audit was to allow as an appraisal of clinical practice and to identify areas of potential improvement.

CHAPTER 6: MATERIAL AND METHODS

Systemic audit is now considered to be a hallmark of good clinical practice. It allows critical evaluation of current standards of patient care leads to improvement in clinical practice.

Our study involved a descriptive analysis of the management of ectopic pregnancy at a Durban teaching hospital over a period of 1 year.

130 case notes, including anaesthetic and theatre notes of patients presenting to King Edward VIII Hospital, Durban during the period 1 July 2005 to 30 June 2006 with the final diagnosis of ectopic pregnancy were examined retrospectively and management was assessed.

Permission to audit all patient clinical files was obtained from the Head of Department of Obstetrics and Gynaecology at King Edward VIII Hospital. King Edward VIII Hospital is a teaching hospital and serves as a referral hospital for smaller as well as district hospitals. The study protocol was reviewed and ethical approval was obtained (reference number E306/05). All data was collected on a structured data form (annexure) and was analysed using descriptive statistics. Information regarding patient profile, risk factors, presenting symptoms and signs, physical examination, ultrasound finding, type of treatment, level of experience of clinician / surgeon, complication rates, length of hospital stay and associated maternal morbidity and mortality were studied.

Treatment was grouped into medical or surgical.

Surgical treatment was grouped into 5 categories:

i) Emergency laparotomy

ii) Elective laparotomy

iii) Emergency laparoscopy

iv) Elective laparoscopy

v) Laparoscopy followed by laparotomy

Laparoscopic surgical management

Laparoscopy was performed in only haemodynamically stable patients using 2 or more puncture techniques. The type of laparoscopic surgery depended on the consultant. Laparoscopic salpingotomy was performed by making a linear incision using a needle point diathermy on the anti-mesenteric boarder of the tube at the maximum distension of the ectopic. The trophoblastic tissue was removed with tissue forceps followed by irrigation of the tube with saline.

Laparoscopic salpingectomy was performed either by:

i) Placing 2 endoloops around the ectopic which is then excised and retrieved using a retrieval bag (endobag)

ii) Using electrocoagulation, excision and retrieval using a retrieval bag or directly using tissue forceps.

Laparotomy

Laparotomy was performed through a Pfannestiel incision unless the patient had a prior sub umbilical midline incision which was excised and laparotomy performed.

The standard management of ectopic pregnancy at King Edward VIII Hospital depends on the haemodynamic status of the patient and whether the ectopic pregnancy has ruptured or not. All patients are initially resuscitated in the gynaecological outpatient department. Patients who present in hypovolaemic shock are transferred immediately to theatre and resuscitation is ongoing.

In all patients intravenous access is first obtained and baseline investigations include:

- A full blood count
- Urea and electrolytes
- Blood compacting for type and screen
- Rhesus antigen testing
- Urine pregnancy test
- Gynaecological pelvic ultrasound (depending on the stability of the patient)

Patients diagnosed with unruptured ectopic pregnancies are operated on electively.

Statistical data is presented in the form of graphs and tables.

Continuous variables such as age are presented as median and range.

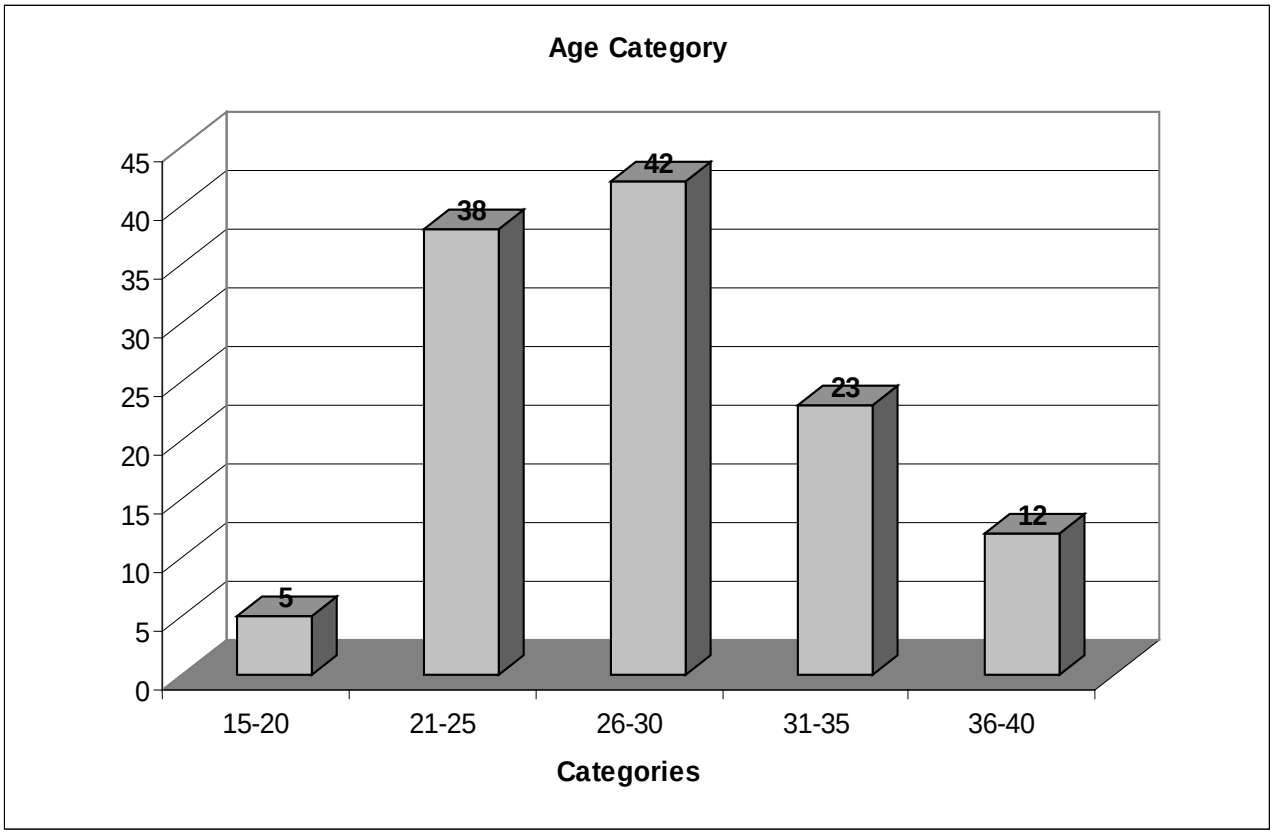
Categorical variables are given a number (percentage).

CHAPTER 7: RESULTS

10 patients were excluded from the study due to failure to obtain correct clinical records or inability to complete structured data form due to missing information and records.

The patients ranged in ages from 17 to 40 years, with a mean of 28 years.

This is represented in Graph 1.



Graph 1: Age categories of the study population

32 patients (26.7%) were nulliparous and 88 patients (73.3%) were between parity 1-4. There were no patients in the category parity 5 and greater (grandmultiparity).

57 patients (47.5%) gave a history of trying to conceive.

12 patients (10%) had a history of previous ectopic gestation.

Signs and symptoms of ectopic pregnancy.

Values are given as n (%). N = 120

Table 1: Patient's symptoms

Symptoms	Number	Percentage
Abdominal pain	**106**	**88.3%**
Amenorrhoea	**88**	**73.3%**
Vaginal bleeding	**84**	**70.0%**
Syncope	**52**	**43.3%**
Shoulder tip pain	**29**	**24.2%**
Fever	**6**	**5.0%**

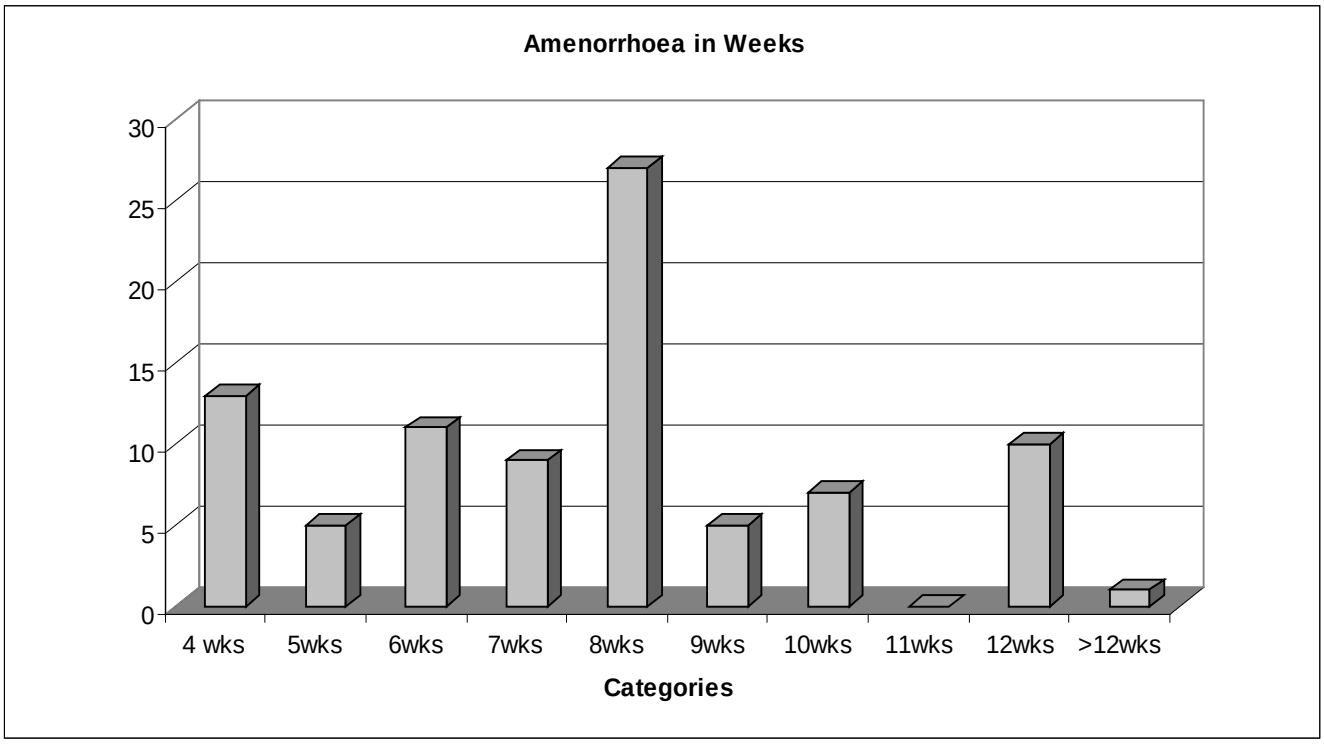
Table 2: Patient's signs

Signs	Number	Percentage
Abdominal tenderness	**26**	**21.7%**
Pelvic tenderness	**91**	**75.8%**
Adnexal tenderness	**99**	**82.5%**
Adnexal mass	**28**	**23.3%**

Abdominal pain occurred in 106 patients (88.3%) whereas amenorrhoea and vaginal bleeding were present in 88 (73.3%) and 84 (70%) patients respectively.

The modus regarding duration of amenorrhoea was 8 weeks.

The period of amenorrhoea varied from 4½ weeks to 14 weeks, but in 32 (26.7%) patients there was no history of a missed period. The greatest duration of amenorrhoea, prior to presenting to hospital, was 8 weeks which occurred in 27 (22.5%) patients. This is represented in Graph 2.



Graph 2: Period of amenorrhoea of the study population

Syncope was present in 52 (43.3%) patients and shoulder tip pain in 29 (24.2%) patients. Only 6 (5%) patients complained of fever.

Among the physical signs, abdominal tenderness was present in 26 (21.7%) patients, pelvic tenderness 91 (75.8%) and adnexal tenderness was found in 94 (82.5%).

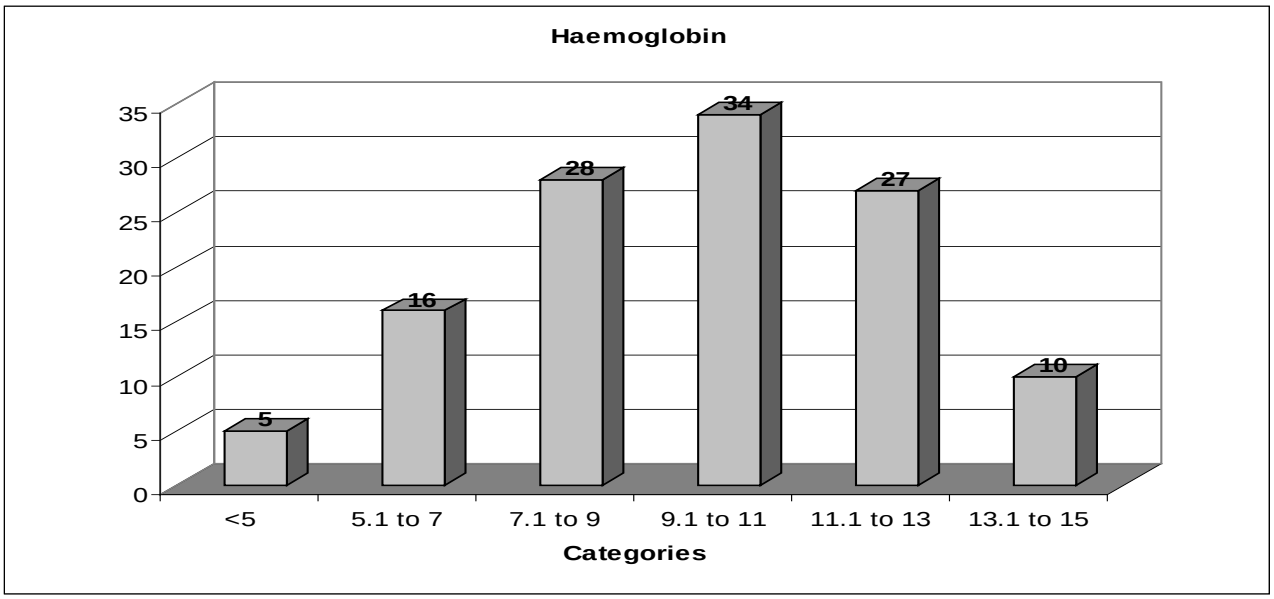
In only 28 (23.3%) patients was an adnexal mass appreciable.

Laboratory tests

The urinary pregnancy test was performed in 119 patients. The test was not performed in 1 patient because the patient was admitted to hospital as an acute surgical emergency and taken to the operating theatre only to diagnose an ectopic gestation intra-operatively. 116 patients had a positive test and 3 patients had a negative test.

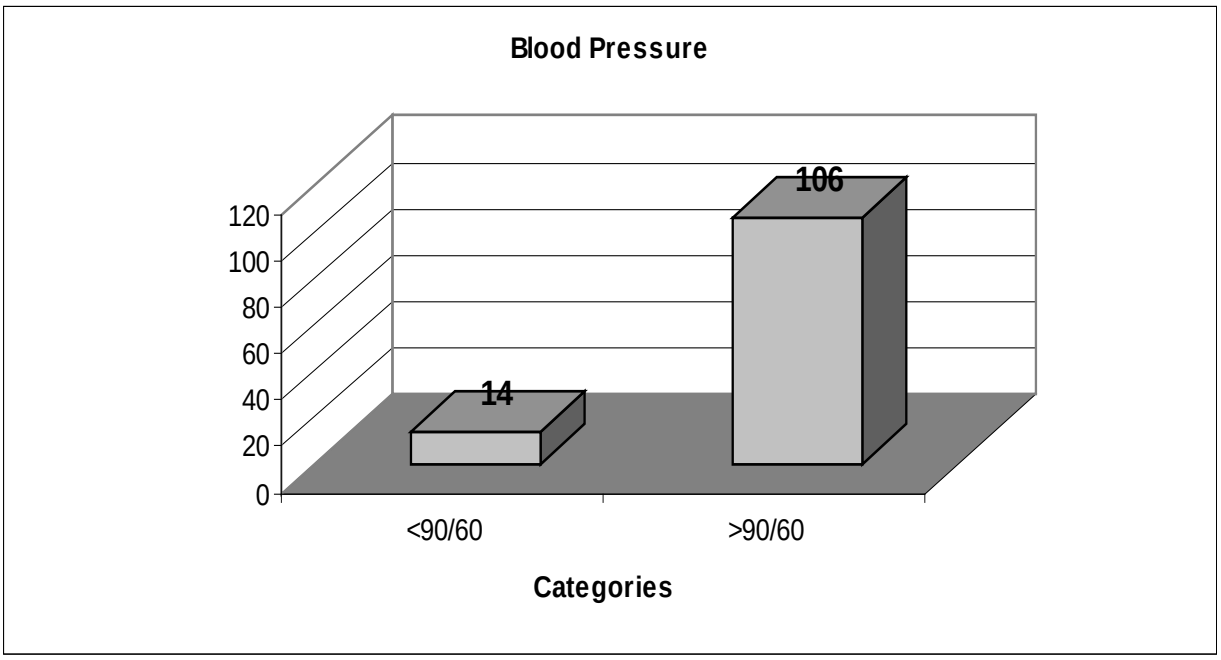
6 patients (5%) were rhesus negative.

Severe anaemia, haemoglobin less than 7 g/dl due to low red cell mass, represented 21 patients (17.5%). Haemoglobin values are represented in Graph 3.



Graph 3: Haemoglobin values of the study population

Vital signs:14 patients (11.7%) presented to the gynaecology outpatient room in acute shock with a blood pressure < 90/60mmHg. These patients required resuscitation and immediate transfer to the operating theatre. Blood pressure recordings are represented in Graph 4.



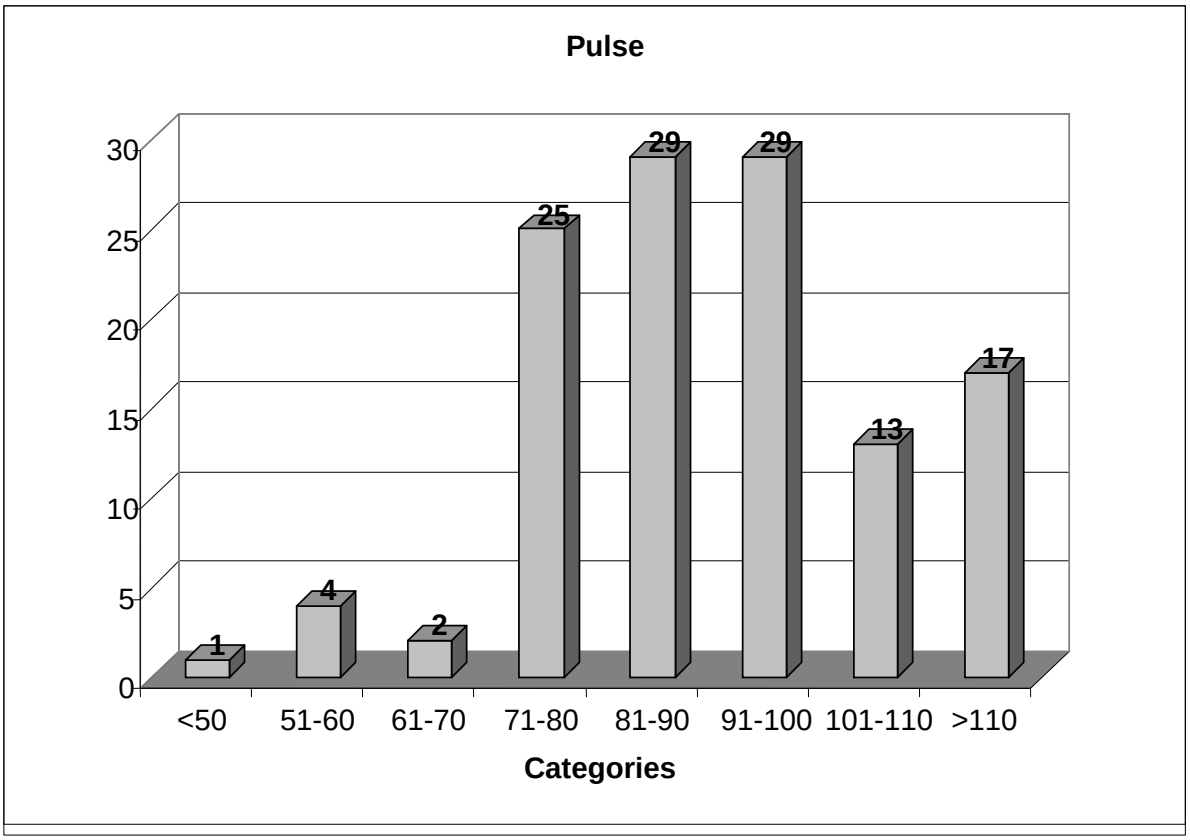
Graph 4: Blood pressure reading of the study population

17 patients (14.1%) were found to have a pulse > 110 beats/minute.

Pulse rate recordings are represented in Graph 5.

5 patients (4.1%) patients had a temperature > 38.0ºC

Graph 5: Pulse rate recording of the study population



Ultrasound:

A readily available ultrasound service ensured that all patients could have an ultrasound on the same day or by the next working day.

75 patients (62.2%) had a pelvic ultrasound performed.

26 patients (21.7%) had a transvaginal ultrasound performed.

Table 3: Ultrasound findings of the study population

ULTRASOUND FINDINGS	TOTAL NUMBER	PERCENTAGE %
Adnexal mass	**82**	**68.3%**
Empty uterus	**80**	**66.7%**
Fluid in pouch of Douglas	**60**	**50.0%**
Presence of fetal heart pulsation	**14**	**11.7%**
Pseudogestational sac	**12**	**10%**

Risk Factors:

RISK FACTOR	TOTAL NUMBER	PERCENTAGE%
Previous sterilization	**1**	**0.83%**
Previous ectopic	**12**	**10.0%**
Previous genital infection	**34**	**28.3%**
Multiple sexual partners	**32**	**26.7%**
Previous abdominal / pelvic surgery	**25**	**20.8%**
Cigarette smoking	**5**	**4.2%**
Vaginal douching	**2**	**1.7%**

Women diagnosed with ectopic pregnancy can be divided into:

Acute ectopic pregnancy

Sub-acute ectopic pregnancy (Magara RA, Trew GH, 1997)

Gynaecology. Churchill Livingston)

Classification according to the type of ectopic included 106 patients (88.3%) with acute presentation, 14 patients (11,7%) with sub-acute presentation.

87 patients (72.5%) presented with ruptured ectopic pregnancies whilst 33 patients (27.5%) presented with unruptured ectopic pregnancies.

119 patients (99.2%) were treated surgically whilst only 1 (0.8%) patient was treated medically. The patient treated medically was diagnosed as having an unruptured ectopic pregnancy and was treated with systemic methotrexate.

The result of this audit shows that 111 patients (92.4%) are managed via laparotomy in our unit.

104 patients (87.4%) - managed via emergency laparotomy.

6 patients (5%) - managed via elective laparotomy.

1 patient (0.8%) - had a diagnostic laparoscopy which was converted to laparotomy.

Only 8 patients (6.7%) were managed laparoscopically in our unit.

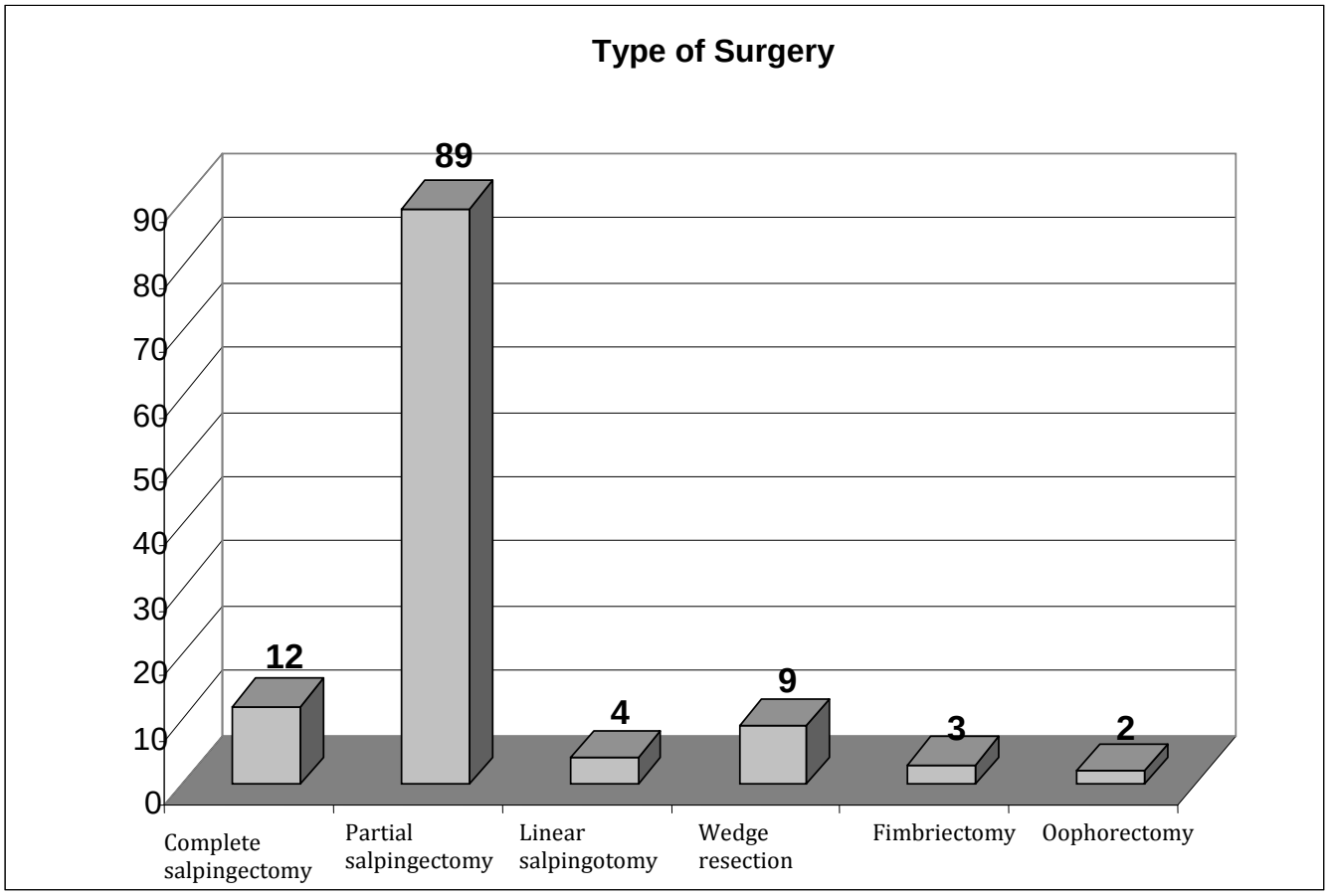
In our audit 101/120 (84.9%) patients had salpingectomy performed.

Only 4 (3.4%) of patients had a salpingotomy performed.

Other types of surgery included:

1. Wedge resection : 9 (7.6%)
2. Fimbriectomy : 3 (2.5%)
3. Oophorectomy : 2 (1.7%)

The type of surgery performed is represented in Graph 6.

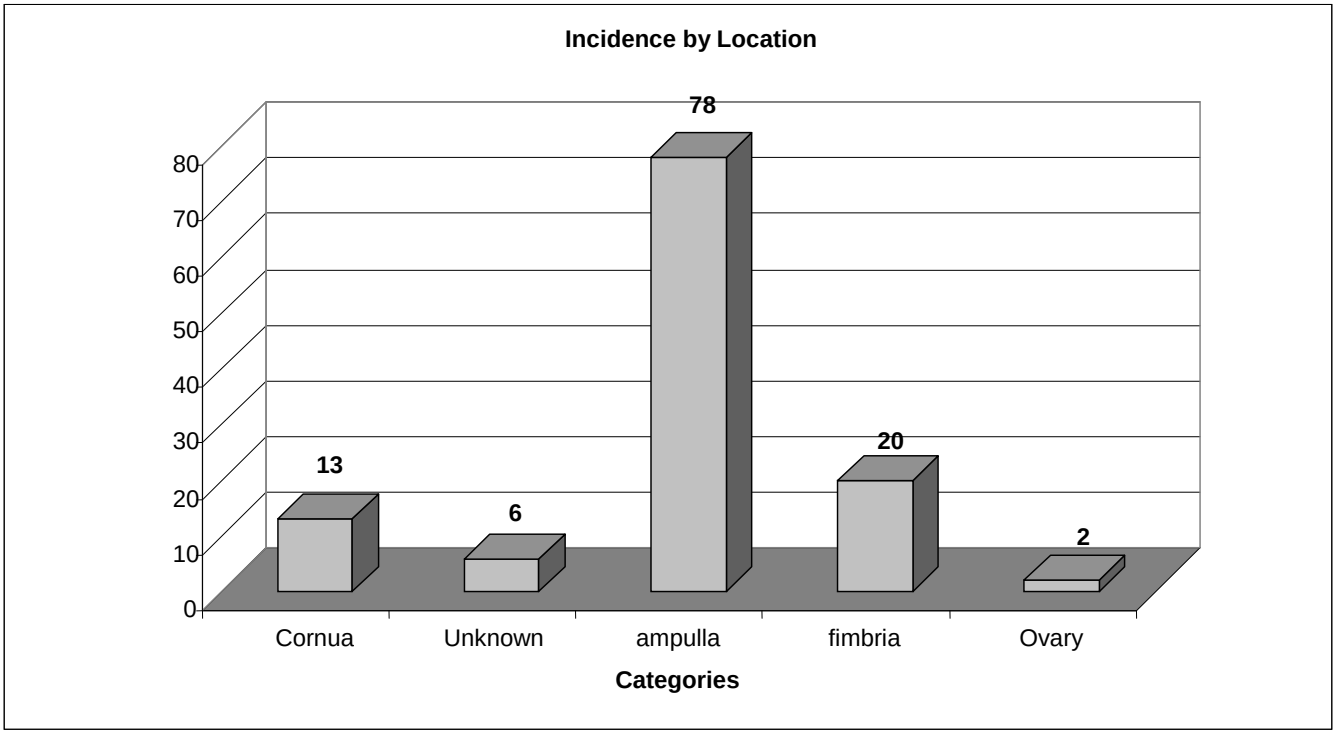


Graph 6: Type of surgery performed in the study population

The location of the ectopic pregnancies are shown in Table 4 and Graph 7.

Table 4: Location of ectopic pregnancies (n= 120)

LOCATION	NUMBERS	PERCENTAGE %
Ampullary	**78**	**65.0%**
Fimbria	**20**	**16.67%**
Cornua	**13**	**10.83%**
Tubal:location not specified	**7**	**5.83%**
Ovary	**2**	**1.67%**



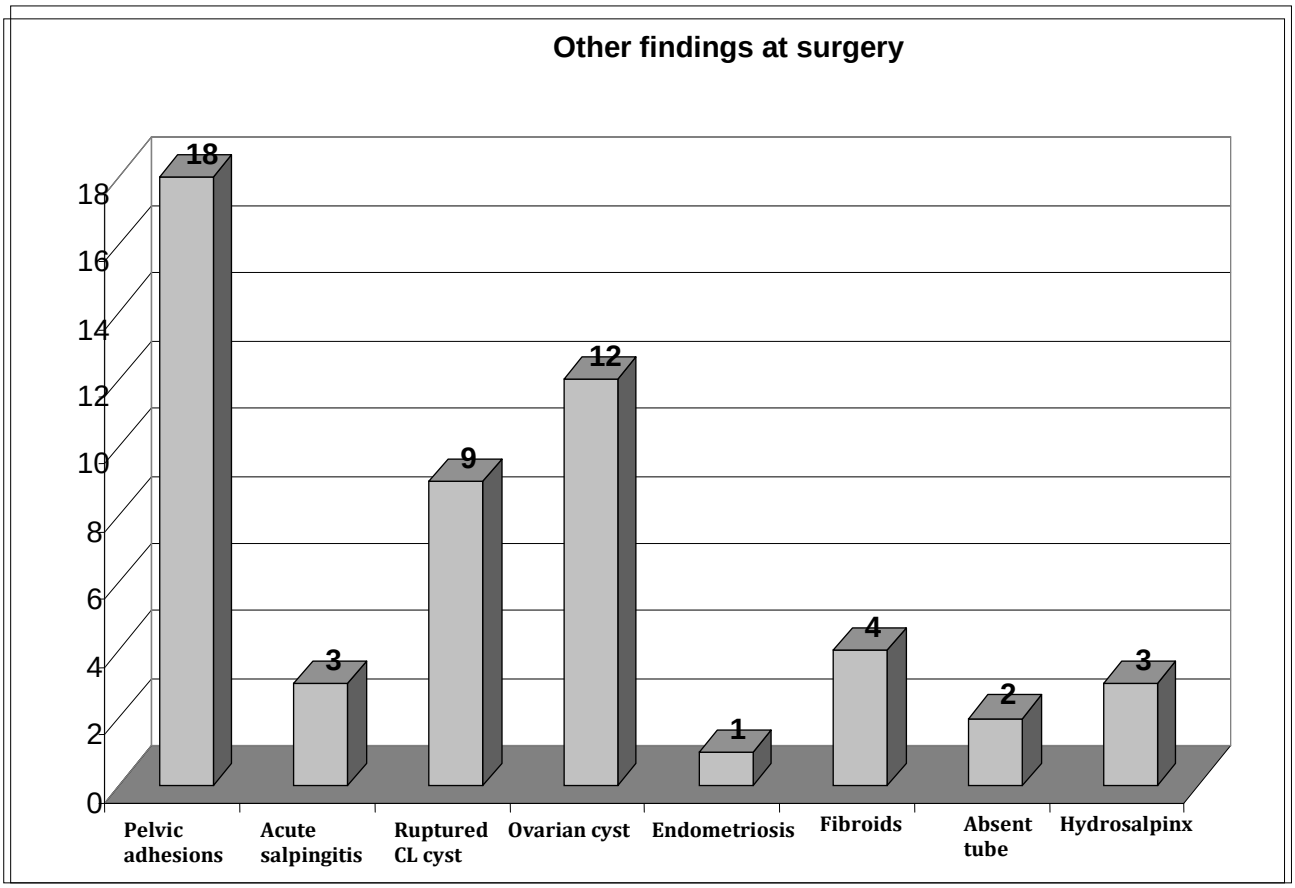
Graph 7: Location of ectopic pregnancy in the study population

The most frequent finding at surgery included pelvic adhesions and ovarian cysts.

Findings at surgery are represented in Table 5 and Graph 8.

Table 5: Findings at surgery

FINDING AT SURGERY	NUMBER	PERCENTAGE %
Pelvic adhesions	18	15%
Ovarian cysts	12	10%
Ruptured corpus luteal cyst	9	7.5%
Fibroids	4	3.3%
Hydrosalpinx	3	2.8%
Acute salpingitis	3	2.8%
Absent tube	2	1.7%
Endometriosis	1	0.8%



Graph 8: Other findings at surgery in the study population

96/120 patients (80%) were operated by registrars alone with assistance provided from medical students or medical interns.

Consultants performed 8.3% of surgery (10/120 patients).

Registrars together with consultants performed 11.7% of surgery (14/120 patients).

In only 4/120 cases (3.4%) registrars' experienced difficulty and consultant help was requested.

One patient sustained an intra-operative bowel injury (jejunal perforation). A surgeon was consulted and the bowel was re-anastomized.

Majority of the surgery (66.4%) was performed within 6 hours.

Duration of operation is represented in Table 6.

Table 6: Duration of operation

TYPE OF OPERATION	MEAN	RANGE
Immediate laparotomy	**49.5 min**	**20-120 min**
Elective laparotomy	**60.2 min**	**20 -88 min**
Laparoscopy	**88.1 min**	**45-150 min**
Conversion to laparotomy	**-**	**-**

In the diagnostic laparoscopy group which needed conversion to laparotomy, there was only 1 patient. The operating time in this case was 90 minutes.

In 8/119 patients (6.7%) an abdominal drain (205 tube drain) was inserted intraperitoneally. Only 1 patient (0.8%) had a corrugated wound drain, below the skin, inserted. In 96/119 (80.7%) patients, a peritoneal lavage with normal saline was performed.

Overall 62/120 patients (51.7%) required blood transfusions and 6/120 (5%) patients required massive transfusions. 58/120 patients (48.3%) did not required blood transfusions. Table 7 represents quantity of blood transfusion.

Table 7: Quantity of blood transfusion

TRANSFUSION TYPE	QUANTITY	NUMBER	PERCENTAGE %
Minor	**1-2 units**	**22**	**18.3%**
Moderate	**3-4 units**	**34**	**28.3%**
Major	**5 + units**	**6**	**5.0%**

POST OPERATIVE COMPLICATIONS:

Chest infection	3 (2.5%)
Intensive care admission	4 (3.4%)
Wound infection	2 (1.7%)
Repeat laparotomy	2 (1.7%)
Maternal death	1 (0.8%)

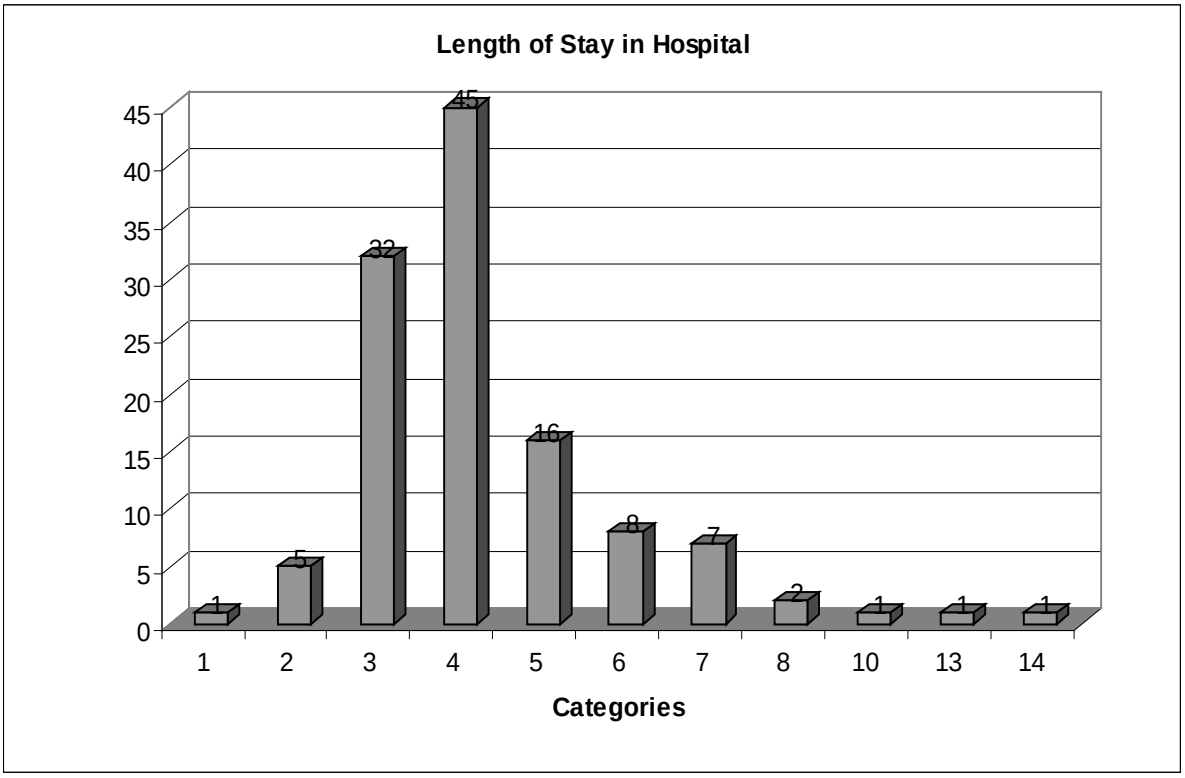
Repeat laparotomy was performed due to:

- Bleeding from the inferior epigastric artery
- Suspicion of intra abdominal sepsis

Length of stay ranged from 2-14 days.

Majority of patients were discharged between 3-5 days (78.2%).

This is represented in Graph 9.



Graph 9: Length of hospital stay in the study population

107/119 patients were discharged home.

12/120 patients were discharged back to the base hospital or to Clairwood Hospital.

CHAPTER 8: DISCUSSION

Ectopic pregnancy is common among first trimester complications. Although the vast majority of patients still undergo surgical management, medical therapy with methotrexate is still evolving as first line standard practice for unruptured ectopic pregnancy.

Current diagnostic algorithms have been optimally refined. Further diagnostic efficiency will be obtainable through more advanced imaging techniques.

The medical literature reporting the treatment of ectopic pregnancy includes mostly observational data with very few randomized trials comparing treatment options. Assessment of treatment reports is difficult because of selection bias and a paucity of accurate follow-up data on future pregnancy outcomes.

This study was undertaken in view of the fact that majority of our patients are brought in as emergencies with ruptured ectopic pregnancies and some patients were in a haemodynamically unstable condition.

The epidemiological characteristics, symptoms and findings on physical examination of the patients in this series of ectopic pregnancies are similar to those found in other series of ectopic pregnancy. Lack of consistency in the clinical presentation is an important reason for failing to suspect an ectopic pregnancy.

In our study the most consistent single presenting symptom was abdominal pain in 88.3% of patients. History of amenorrhoea and vaginal bleeding were present in 73.3% and 70% of patients respectively. The most common physical sign was adnexal tenderness in 82.5% patients. Abdominal tenderness was found in 21.3% patients, pelvic tenderness 75.8% and an

adnexal mass was appreciable in only 23.3% patients. This emphasizes the fact that none of the physical signs are specific for ectopic pregnancy.

According to a study by Tay (Tay et al, 2000), abdominal pain was present in 97% of patients and vaginal bleeding in only 79% of patients. Abdominal tenderness was reported in 91% and adnexal tenderness in only 59% of patients. A study from Nigeria also reported that abdominal pain, amenorrhoea and irregular vaginal bleeding were found in 82.6%, 77.5% and 73.7% of ectopic pregnancies respectively (Gharoro and Igbafe, 2002).

In our series, the commonest risk factor was previous genital infection and multiple sexual partners. Pelvic inflammatory disease has been shown to be a risk factor for ectopic pregnancy. Gonococcal infection and multiple sexual partners have been reported to be correlated with the occurrence of ectopic pregnancies. A study by Bunyavejchevin et al., reported that multiple sexual partners, pelvic inflammatory disease, smoking and infertility were the main risk factors of ectopic pregnancy in Thai women (Bunyavejchevin et al, 2003) However we did not study the relationship with pelvic inflammatory disease as our patients were not screened for Gonorrhoea, Chlamydia trachomatis and Human Immunodeficiency Virus. A close association between ectopic pregnancy and infertility does exist. This was not found in our study. Previous ectopic pregnancy was a risk factor in 10% of patients and tubal surgery (reversal of tubal ligation) in 1 patient. According to a meta-analysis by Mol et al.(1996) of risk factors for ectopic pregnancy, a strong association has been reported between ectopic pregnancy and those risk factors, affecting the fallopian tube that is previous ectopic, tubal surgery, tubal ligation, tubal pathology and in utero diethylstilbestrol. A significant number had no risk factors in their past history indicating that an absence of risk factors does not rule out ectopic pregnancy.

In our study, no evidence of HIV testing was found in the records. This is surprising in that, the HIV pandemic is the highest in the province of KwaZulu-Natal and the opportunity should be taken to offer all patients who attend or are admitted to hospital HIV testing. In patients with ectopic pregnancy who are haemodynamically unstable, the offer for testing can be done prior to discharge from hospital.

Six patients were rhesus negative. Anti-D immunoglobulin at a dose of 50 microgram's was given to all non sensitised patients who were rhesus negative with an ectopic pregnancy.

The last decade has witnessed an increasing number of ectopic pregnancies been managed laparoscopically because of the perceived advantages over laparotomy, including reduced cost, reduced postoperative opiate requirement, shorter hospital stay and early return to work (quoted by Hajenius et al, 2007).Traditionally the treatment of choice for ectopic pregnancy has been salpingectomy. Conservative surgery is more likely to be performed if laparoscopic surgery is performed. Conservative surgery would depend on other factors, such as the state of the affected tube, site of the ectopic pregnancy, whether the ectopic pregnancy is ruptured or not and on the patients desire for future fertility.

Laparoscopy is regarded as the decisive diagnostic test in suspected ectopic pregnancy. After its introduction in gynaecology, the procedure had a major impact on management of patients at risk; it short-circuited the problem of prolonged hospitalization for observation and the risk of performing a superfluous laparotomy.

This audit shows that only 6.7% of ectopic pregnancies are managed laparoscopically. Not all patients will be suitable for laparoscopic surgery and cardiovascular shock remains a contraindication to laparoscopy. The goal is, therefore, to make an early diagnosis before the

ectopic ruptures. Our audit revealed a rupture rate of 72.5 %. Among the reasons given for this slow uptake of laparoscopic surgery is the need for further training among registrars, unpredictability of operating time since we have only one dedicated daytime emergency theatre which is shared by all surgical disciplines and the high rate of ruptured ectopic pregnancies.

Adequate training in minimal access surgery is a prerequisite to minimize complications and all registrars should be competent in laparoscopic surgery for ectopic pregnancy.

Medical management of only one patient occurred using the “single dose” regimen. This patient presented with a 2 x 2 cm right sided adnexal mass and a β-HCG value of 173 mIU/ML. She also gave a history of sustaining a left salpingectomy during 2005 for a ruptured ectopic pregnancy. Her risk factors included being a smoker and previous pelvic infection.

Clinicians continue to miss the diagnosis of ectopic pregnancy despite an abundance of literature and guidelines on the management of ectopic pregnancies in the literature. It cannot be over-emphasized that a high index of suspicion is required to consider pregnancy complication in any reproductive women with atypical vaginal bleeding or lower abdominal pain. There is no single cost effective test to improve the diagnosis of ectopic pregnancy. 6 patients were initially misdiagnosed as having threatened miscarriage, only later to present to the gynaecology outpatient department as ruptured ectopic pregnancies.

There was one maternal death, suspected to be from a pulmonary embolus within the one year audit period; however there was considerable short term morbidity. 14 patients were admitted in a condition of shock. 62 patients required blood transfusions and 6 patients required massive blood transfusions (5 units of pack cell transfusion and greater). Deaths from ectopic pregnancy are not unknown. The 7th report on Confidential Enquiries into Maternal Deaths in

the U.K. state that there were 10 deaths due to ectopic pregnancy and the Saving Mothers report 2002 - 2004 found that there were 47 deaths mainly due to hypovolaemic shock (National Department of Health, 2006).

Four patients required intensive care unit admission for ventilator support secondarily to metabolic acidosis from acute blood loss and haemorrhagic shock. Recommendations are that patients in haemorrhagic shock following rupture of ectopic pregnancy need to be transferred promptly to operating theatre and the transfer must not be delayed by attempts to re-establish a normal circulating volume. Time interval between admission and surgery is a crucial factor in saving the life of the patient in shock. In our audit majority of the surgery was performed within 6 hours.

CHAPTER 9: RECOMMENDATIONS

A substantial improvement in the quality of care of women with ectopic pregnancy is needed.

Our targets should include:

a) Because of the high incidence of tubal ruptures, community education is required to inform women to attend health facilities as early as possible once they have symptoms. The establishment of early pregnancy units may also result in early diagnosis and prevent morbidity.
b) High rate of sonographic diagnosis of ectopic pregnancy. Sonagraphic equipment should be available in all gynaecological emergency units and staff appropriately trained to use and interpret the images.
c) Acceptable rates of tubal conservation. Registrars should be trained to perform conservative surgery.
d) Acceptable rates of laparoscopic surgery in carefully selected patients by improving the level of training of junior doctors in laparoscopic surgery and proving the necessary equipment and facilities.

Short term surveillance of ectopic pregnancy may need to be done in a highly integrated health delivery system where complete ascertainment of cases in a defined population provides the coverage and detail to estimate the ectopic pregnancy rate accurately.

Randomised, controlled trials to assess the benefits and harms of expectant management, medical management and surgery need to be performed. These studies should include long term outcomes of fertility and repeat ectopic pregnancy, health related quality of life, treatment preferences and cost effectiveness analysis.

CHAPTER 10:

ANNEXURE

DATA SHEET

PROFILE OF PATIENTS PRESENTING WITH AN ECTOPIC PREGNANCY ATTENDING

KING EDWARD VIII HOSPITAL, IN DURBAN

PATIENT PROFILE

AGE		[___/___]
PARITY		[____]
TRYING TO CONCEIVE	**Yes = 1; No = 2**	[____]
HAD FERTILITY TREATMENT	**Yes = 1; No = 2**	[____]
PAST OBSTETERIC HISTORY:		
Miscarriage	= 1	
TOP	= 2	
NVD	= 3	[____]
C/S	= 4	
Previous ectopic gestation	= 5	
Gestational trophoblastic disease	= 6	
Heterotrophic pregnancy	= 7	

PRESENTING SYMPTOMS **Yes = 1; No = 2**

Abdominal pain	[____]
Amenorrhoea	[____]
Period of amenorrhoea (weeks)	[____/____]
Vaginal bleeding	[____]
Dizziness / fainting	[____]

Pregnancy symptoms [____]

Passage of tissue [____]

Shoulder tip pain [____]

PRESENTING SIGNS **Yes = 1; No = 2**

Abdominal tenderness [____]

Pelvic tenderness [____]

Adnexal tenderness [____]

Adnexal mass [____]

Uterine enlargement [____]

Orthostatic change [____]

Fever [____]

INVESTIGATIONS

Rhesus **Positive = 1; Negative = 2** [____]

Haemoglobin [____/____]

Urine β-hCG **Positive = 1; Negative = 2** [____]

Serum β-hCG [____/____]

Blood pressure **Systolic** [_____]

Diastolic [_____]

Pulse [____/____]

Temperature [____/____]

Ultrasound finding:

- pelvic / transvaginal **Yes = 1; No = 2** [____]
- Pseudo gestational sac **Yes = 1; No = 2** [____]
- Adnexal mass **Yes = 1; No = 2** [____]

- Size of mass (cm) [____] x [____]
- Fetal heart **Yes = 1; No = 2** [____]
- Fluid in Pouch of Douglas **Yes = 1; No = 2** [____]
- Empty uterus **Yes = 1; No = 2** [____]

RISK FACTORS

High risk:

Tubal surgery **Yes = 1; No = 2** [____]

Sterilization **Yes = 1; No = 2** [____]

Previous ectopic pregnancy **Yes = 1; No = 2** [____]

Intrauterine contraceptive device use **Yes = 1; No = 2** [____]

Documented tubal pathology **Yes = 1; No = 2** [____]

Moderate risk:

Infertility

- Fertility treatment : ovulation induction **Yes = 1; No = 2** [____]
- IVF = 1
- GIFT = 2
- ZIFT = 3 [____]
- Embryo transfer = 4
- Previous genital infection **Yes = 1; No = 2** [____]
- Multiple sexual partner **Yes = 1; No = 2** [____]

Slight risk:

Previous pelvic / abdominal surgery **Yes = 1; No = 2** [____]

Cigarette smoking **Yes = 1; No = 2** [____]

Vaginal douching **Yes = 1; No = 2** [____]

TYPE OF ECTOPIC

Acute ectopic	= 1	
Chronic ectopic	= 2	
Acute on chronic ectopic	= 3	[____]
Suspected ectopic	= 4	
Misdiagnosis	= 5	

TREATMENT

Medical:	**Yes = 1; No = 2**	
Systematic methotrexate		[____]
Local injection of methotrexate under u/s guidance		[____]
Local injection of methotrexate via laparoscopy		[____]
Surgical:	**Yes = 1; No = 2**	
Emergency laparotomy		[____]
Elective laparotomy		[____]
Emergency laparoscopy		[____]
Elective laparoscopy		[____]
Diagnostic laparoscopy converted to laparotomy		[____]
Type of surgery:	**Yes = 1; No = 2**	
Complete salpingectomy		[____]
Partial salpingectomy		[____]
Linear salpingotomy		[____]
Linear salpingotomy		[____]
Wedge resection		[____]

Incidence by location:

Implantation in the fallopian tube:

- o interstitium / cornua = 1
- o isthmus = 2
- o ampulla = 3 [____]
- o fimbria = 4

Implantation outside the Fallopian Tube

- o ovary = 1
- o cervix = 2
- o abdominal = 3 [____]
- o ligamentous = 4

Other finding at surgery

- ◆ pelvic adhesions = 1
- ◆ acute salpingo – oophoritis = 2
- ◆ ruptured corpus luteal cyst = 3 [____]
- ◆ ovarian cyst = 4
- ◆ endometriosis = 5
- ◆ fibroids = 6

Level of experience of surgeon

- ◆ Intern with supervision = 1
- ◆ Medical officer = 2 [____]
- ◆ Registrar = 3
- ◆ Consultant = 4

Time diagnosis made: [__/__h__/__]

Time of commencement of operation: [__/__h__/__]

AT SURGERY

Difficulties at operation	**Yes = 1; No = 2**	[____]
Duration of operation (minutes)		[___/___/___]
Usage of abdominal drain	**Yes = 1; No = 2**	[____]
Usage of wound drain	**Yes = 1; No = 2**	[____]
Peritoneal lavage performed	**Yes = 1; No = 2**	[____]

COMPLICATIONS

Blood loss

- major ≥ 5 units transfused = 1
- moderate 3-4 units = 2 [____]
- minor 1-2 units = 3

Gaseous distension ≥ 48 hours post-operation	**Yes = 1; No = 2**	[____]
Chest infection post-operative	**Yes = 1; No = 2**	[____]
Repeat laparotomy	**Yes = 1; No = 2**	[____]
Wound infection	**Yes = 1; No = 2**	[____]
ICU admission	**Yes = 1; No = 2**	[____]
Maternal deaths	**Yes = 1; No = 2**	[____]

Length of hospital stay (days) [____/____]

If discharged:

Home	= 1	
Clairwood Hospital	= 2	[____]
Other hospital	= 3	

Specify_____

CHAPTER 11: REFERENCES

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