The Comparison Between Extra- amniotic Saline Infusion and Gemeprost As Abortificient In Mid- trimester Silent Miscarriage

By

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Abbreviations

And

Glossary

AP diameter	Anterior- posterior diameter
APL	Anti- phospholoipid syndrome
APTT	Activated partial prothrombin time
ß- hCG	Beta human Gonadotrophin
BPD	Biparietal diameter
DES	Diethylstilboesterol
DIVC	Disseminated intravascular coagulation
EASI	Extra- amniotic saline infusion
ERPOC	Evacuation and removal of product of conception
GSH	Group, screen and hold
Hb	Haemoglobin
IUCD	Intrauterine contraceptive device
PG	Prostaglandin
POC	Product of conception
PT	Prothrombin time
RCOG	Royal College of Obstetrician and Gynaecologists
RCR	Royal College of Radiologists
RR	Risk ratio

SOGC	Society of Obstetricians and Gynaecologists of Canada
WHO	World Health Organisation

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Abstrak

(Versi Bahasa Malaysia)

"Extra- amniotic saline infusion" (EASI) bukanlah satu agen pengguguran yang baru, tetapi sebagaimana yang dilaporkan, ia adalah satu kaedah yang selamat digunakan. Di sebaliknya, Gemeprost merupakan kaedah yang popular dan kerap digunakan tetapi mahal. Pada ketika ini, perbelanjaan rawatan adalah tinggi. Dengan sebab itu, sesetengah hospital mencari alternatif bagi menggugurkan kandungan.

Tatacara kajian: Bermula dari 1hb. Mac 2001 sehingga 28hb. Februari 2002, seramai 91 pesakit "silent miscarriage" telah dipilih secara rawak untuk kedua- dua kaedah pengguguran ini, iaitu kaedah EASI atau Gemeprost. Keberkesanan kedua-dua kaedah ini dibandingkan dari segi kesempurnaan pengguguran, jangkamasa yang diambil untuk mengalami keguguran, jangkamasa berada di hospital, kos rawatan, kesan sampingan dan akhirnya penerimaan pesakit terhadap kaedah tersebut.

Keputusan: Seramai 91 orang pesakit yang mengalami keguguran senyap dimasukkan ke dalam kajian ini, di mana seramai 42 orang pesakit menerima EASI sebagai agen pengeluaran janin dan yang selebihnya menerima gemeprost 1mg sehari. Keberkesanan cara- cara tersebut dari segi kesempurnaan keguguran,

tempoh yang diambil untuk merangsang pengguguran, tempoh berada di hospital, kesan- kesan sampingan yang berlaku dan kos dibandingkan. Sebanyak 54.8% daripada pesakit yang menerima EASI mengalami keguguran sempurna berbanding dengan 59.2% di dalam kumpulan gemeprost.Hitung panjang masa yang diambil oleh EASI untuk menggugurkan kandungan adalah 12.76 jam berbanding dengan 10.24 jam di dalam kumpulan gemeprost. Kedua- dua pemerhatian ini adalah tidak relevan dari segi statistik. Tiada perbezaan didapati dari segi jangkamasa tinggal di hospital dan kesan sampingan yang dialami. Walau bagaimanapun, sepertimana yang dijangkakan, EASI adalah jauh lebih murah berbanding gemeprost bagi setiap pengguguran (RM 69.25 berbanding RM183.30).

Cadangan: Kaedah EASI didapati sama berkesan dengan Gemeprost, dengan itu disarankan kaedah ini digunakan sebagai alternatif kepada Gemeprost untuk pesakit- pesakit terpilih terutamanya mereka yang berada di tempat- tempat di mana masalah kewangan merupakan faktor penting.

Abstract

(English version)

Extra- amniotic saline infusion (EASI) as abortifacient is not new, however it is still a safe abortifacient as quoted in the literatures. Gemeprost on the other hand is a popular abortifacient used widely however at exhorbitant cost. In this day and age when the price of health care is escalating some countries are considering cheaper alternatives. We at Hospital Kota Bharu wished to evaluate EASI as an alternative method of abortifacient.

Methodology: From 1st March 2000 till 28th February 2001, 91 patients were randomly selected to two methods of abortifacient, Gemeprost 1mg daily (which is the standard protocol in HKB) and EASI. Both methods were analysed and compared for effectiveness in terms of completeness of abortion and induction-abortion interval, adverse effects, duration of hospital stay and the cost of treatment and finally the patients' satisfaction of the treatment.

Results: 54.8% of the patients receiving EASI had complete abortion as compared to 59.2% in the gemeprost group. The mean duration of induction- abortion interval was 12.76 hours in the EASI group and 10.24 hours in the gemeprost group. Both of these 2 end- results were not statistically significant. No difference in the duration of hospital stay and side- effects were noted. However, it is noted that using EASI is far

cheaper than gemeprost, being RM 69.25 and RM183.30 respectively. Majority of the patients were satisfied with the treatment, however, 17% of the patients receiving EASI were not satisfied with the treatment, whilst none were noted in the gemeprost group.

Recommendation: EASI is as effective as gemeprost as abortifacient in mid-trimester silent miscarriage provided that the patients were initially explained regarding the expected discmfort. We recommend EASI as an alternative to gemeprost in selected patients especially in places where financial constrain is an important factor.

1. Introduction

WHO estimates that throughout the world, approximately 500 000 women die every year from pregnancy- related causes. A large proportion of these deaths are attributable to complication of abortion.

Spontaneous miscarriage occurs in 10 to 20 % of clinical pregnancy and amounts for 50000 in- patient admissions to hospital in United Kingdom annually. Management has changed little in the last 50 years and is commonly based on tradition rather than evidence- based approach. Until recently, miscarriage has achieved less attention in the medical literature than any other pregnancy- related problem.

Majority of the women with silent miscarriage are referred to the hospital for further assessment and subsequently evacuation of the uterine content. This can be achieved via several methods, which includes surgical uterine evacuation, medical management as well as expectant management. 88% of the referred case will undergo surgical uterine evacuation (Penny G. et al, 2000). In a partially randomized study comparing surgical and medical evacuation, 20% of the female expressed strong preference for medical management. The main reasons given for their choices were "avoidance of general anaesthesia" and the feeling of being "more in control" (Penny et al, 2001).

Gemeprost has long being used as abortifacient (Benette et al, 1990, Lim et al, 1990,Byrne and Onyekwuluje, 1994, Krauss et al, 1994). Being a prostaglandin E_1

analogue, it stimulates uterine contraction thus causing expulsion of the products of conception. The efficacy of gemeprost 1mg given at 3 hourly interval to a maximum of 5 administrations per day has been published (Byrne and Onyekwuluye,1994). Lower dosage of gemeprost had been shown to be as effective as the recommended dose, with lesser side- effects (Thong and Baird, 1992, Armatage and Luckas, M.J.,1996). Based on these data, Hospital Kota Bharu has been using a lower dosage of gemeprost to induce silent miscarriage as the standard abortifacient.

The need for refrigeration and its exhorbitant price has changed gynecologists' perception on this drug. Concern on health economics has inspired the researchers to find alternative for gemeprost. The recent discovery of misoprostol as abortifacient served this purpose. Being in the same group as gemeprost, as effective and at the price of far cheaper than gemeprost, misoprostol now is much accepted. However, its vaginal usage is not guarantied by the manufacturer neither does it licensed by the FDA of United Kingdom (Misoprostol Literature Review, 2001). Due to this, misoprostol is not yet accepted by the administration of Hospital Kota Bharu as abortifacient.

However, whether it is the gemeprost or misoprostol, these drugs are not without side-effects and complications. The manufacturer has clearly documented the caution usage of gemeprost in certain condition like obstructive airway disease, cardiovascular insufficiency, elevated intraocular pressure, cervicitis and vaginitis (Misoprostol Literature Review, 2001). Therefore, alternative, which is much safer should be used in these conditions.

The usage of extra- amniotic saline infusion (EASI) has long been forgotten without any strong and proper reason. It was first introduced in 1974 to induce abortion (Halbrecht. and Blum, 1974) and 100 percent success rate without any complication was reported. This achievement was later repeated by several other authors on cases of silent miscarriages and fetal death (Mahomaed and Jayaguru, 1997, Mawire et al, 1999). As EASI was proven safe and cheap, Hospital Kota Bharu has adopted this method to induce abortion for high risk cases.

This study was designed to compare the effectiveness, side effects, cost and patients' acceptance of EASI and gemeprost. If it is proven that EASI is as comparable to gemeprost, it can be used in place of gemeprost especially where financial constraints are an important factor.

2. Literature review

2.1. Terminology

. The term abortion does not differentiate between spontaneous abortion and induced abortion. Therefore many gynaecologists refer the former as "miscarriage". Abortion and other inappropriate terminology (e.g.: "pregnancy failure", "abnormal pregnancy", etc.) may contribute to the development of negative self- perception in a group of women already feeling a sense of failure and perhaps shame, guilty and insecurity (Chalmers, 1992). In 1997, a Study Group of The Royal College of Obstetricians and Gynaecologists recommended that traditional medical terminology should be changed (for example:"miscarriage" replacing "spontaneous abortion", "incomplete miscarriage" replacing "incomplete abortion" and "silent miscarriage" replacing "missed abortion" (Recommendations from 33rd RCOG Study group, 1997). Alternative terminology for the later include "delayed miscarriage" or "early fetal demise".

2.2.Definition

Familiarity with the local legal definition is mandatory because there is considerable state - to - state variation. In United Kingdom, miscarriage is defined as pregnancy loss occurring before 24 completed weeks of gestation (Llewelyn- Jones et al, 1999). United States of America however, defined it as termination of pregnancy before the 20th gestational week (Gant and Cunningham, 1993). Because of the different definitions of viability in different countries, the World Health Organization (WHO)

has recommended that a fetus is viable when gestational period has reached 22 or more weeks or when the fetus weighs 500 grams or more (Llwelyn- Jones et al, 1999).

Malaysia at the moment is defining it as pregnancy loss occurring before 24 completed weeks of gestation, equivalent to expulsion of fetus weighing 500 gram or less.

2.3. Varieties of miscarriage

For descriptive purposes the miscarriage is classified according to the findings when the women are first examined, but one kind may change into another if the miscarriage process continues. If infection complicates miscarriage, the term septic miscarriage is used. Below are the descriptions of various types of miscarriage:

a) *Threatened Miscarriage*

Threatened Miscarriage refers to intra- uterine bleeding less than 24th week of gestation, with or without uterine contraction, without cervical dilatation, and without expulsion of products of conception. It may or may not be accompanied by mild cramping pain resembling dysmenorrhoea or by low backache. Ultrasound therefore must reveal the fetus to show signs of life (e.g. presence of heart beat or motion). Other causes of bleeding in early pregnancy should be excluded. Of those women who bleed in early pregnancy, only one half or even less actually abort (Recommendations from the 33rd RCOG Study Group, 1997). Bleeding in threatened miscarriage is frequently slight, but it may persist for days or weeks. Unfortunately,

an increased risk of suboptimal pregnancy outcome in the form of prematurity, low birth weight, and perinatal death persists. However, the risk of birth of a malformed infant does not appear significant. It is no longer a normal practice to insist that the women must stay in bed until the bleeding ceased. However, if the women feel more comfortable to be there, she may do so.

b) *Inevitable miscarriage*

Inevitable miscarriage is intra-uterine bleeding less than 24th week of gestation, with continued cervical dilatation but without expulsion of products of conception. Miscarriage is considered inevitable with 2 or more of the following criteria's (Llewelyn- Jones et al, 1999):

i) moderate effacement of the cervix

ii) cervical dilatation more than 3 cm

iii) rupture of membranes

iv) bleeding more than 7 days

v) persistence of cramps despite narcotic analgesia

vi) signs of termination of pregnancy (e.g.: absence of mastalgia)

Inevitable miscarriage may follow signs of threatened miscarriage or more commonly, starts without warning. Soon after the onset of inevitable miscarriage, the miscarriage occurs either completely or incompletely. In most cases, the miscarriage is incomplete.

c) *Incomplete Miscarriage*

Incomplete miscarriage is expulsion of some but not the entire products of conception less than 24th weeks of gestation. The fetus and the placenta are likely to be expelled together in miscarriages occurring before tenth week, but separately thereafter (Gant and Cunningham, 1993). When the placenta in whole or in part is retained in the uterus, bleeding ensues sooner or later to produce signs of incomplete miscarriage. With more advanced gestational age, bleeding may be more profuse and may occasionally be massive to the point of producing profound hypovolaemia. If the placenta is partly separated and partly attached, the splint- like action of the attached portion of the placenta interferes with myometrial contraction in the immediate vicinity. The vessels in the denuded segment of placental site, deprived of constriction provided by contraction and retraction of the myometrium, bleeds profusely.

d) *Complete Miscarriage*

Complete miscarriage is expulsion of all products of conception less than 24th weeks of gestation when the entire conceptus has been expelled, pain ceases, but slight spotting persists for a few days. Ultrasound shows an empty uterus (or one containing less than 10 mm of tissues or blood clots) (Chipchase and James, 1997).

e) *Septic Miscarriage*

Septic miscarriage is less common nowadays, because of better care and fewer "backyard" abortion. Infection complicating either spontaneous or induced miscarriage is usually mild and is localized to the uterus. However septic miscarriage induced by criminal abortion usually involved endogenous organisms, most commonly anaerobic streptococci which may spread to the fallopian tubes, cervix, parametrium or other pelvic cellular tissue and later causing peritonitis.

f) *Silent miscarriage*

Silent miscarriage is death of embryo or fetus less than 24th week of gestation, but the product of conceptus are retained in utero.

If the embryo dies in the early weeks, it is likely to be anembryonic or blighted. In other cases a fetus forms but die. Multiple haemorrhage may occur in the choriodecidual space, which bulge into the empty amniotic sac. This condition is called *carneous mole* (figure 1).

2.4. Incidence of miscarriage

The incidence of spontaneous miscarriage is between 15 and 20% of all clinically diagnosed pregnancies. However, the actual loss maybe as high as 60% of "chemical" pregnancy diagnosed before the first missed period by estimation of the β- HCG (sub- clinical or undiagnosed spontaneous miscarriage) (David et al, 1999).

Figure 1: Carneous mole- a small fetus can also be seen in the center

2.5.Aetiology of miscarriage

The causes of miscarriage may be classified depending on the aetiological defect, which may relate to the fetus, placenta and maternal condition.

a) Fetal causes of spontaneous miscarriage
   i) chromosomal abnormality (eg: trisomy16, 22, 21 and 15)
   ii) structural abnormality (eg: neural tube defect)
b) Abnormalities of implantation
c) Uterine causes of miscarriage
   i) submucosal fibroids
   ii) fusion abnormality of the uterus

iii) cervical incompetence

d) maternal diseases

i) maternal illnesses such as poorly controlled diabetes mellitus, thyroid disease, SLE, Von Willebrand Disease and anti- phospholipids syndrome.

ii) Maternal infection such as syphilis, rubella, herpes simplex, toxoplasmosis and cytomegalovirus infection.

e) Undetermined causes

2.6.Diagnosis and investigations

2.6.1. Estimations of serum ß-hCG

The majority of patients attending the gynaecology ward can be managed using ultrasound scan. However, in some cases, there is difficulty in diagnosing some cases of early pregnancy and early ectopic pregnancy and its potentially serious implications. In such situation, estimation of serum ß- hCG is essential.

2.6.2. Ultrasound diagnosis

Traditionally much reliance was placed on the clinical history and the pelvic examination but these are unreliable, perhaps none more so than menstrual dating. Ultrasound has become the main means of primary categorization. Even though clinical features do provide important additional information, the history and examination can be tailored to the needs of the individual patient according to the scan findings. With the

introduction of transvaginal ultrasound, longitudinal assessment of early pregnancy can be made in terms of viability and growth.

The Joint Working Party of Royal College of Radiologists (RCR) and the Royal College of Obstetric and Gynaecology (RCOG) in 1995 had advised that the documentation of early pregnancy scans should be standardized as shown below:

Table 1: RCR/ RCOG guidelines for ultrasound in early pregnancy (minimal data set).

- Gestational sac number, size and quality
- Presence/ absence of fetal yolk sac
- Fetus number, size (crown- rump length) and cardiac activity
- Intrauterine haematoma
- Adnexal lesion
- Peritoneal fluid

Documentation of an intrauterine pregnancy can be made consistently at the end of 5^{th} menstrual week by identification of the gestational sac within the uterus. This structure is anechoeic, but it has a characteristic highly echogenic border that represents the decidual reaction. Development milestones seen by

transabdominal ultrasound scanning in the first trimester of pregnancy are summarized below:

a) Gestational sac	5 – 6 weeks
b) Fetal pole	6 – 7 weeks
c) Cardiac activity	7 – 8 weeks
d) Somatic activity	8 – 9 weeks
e) Placenta	9 – 10 weeks
f) BPD	12 weeks

Ultrasound plays a major role in maternal assurance, where fetal cardiac activity is seen and is pivotal in the assessment of early pregnancy complication such as vaginal bleeding. However, there are limits to the ultrasound resolution of normal early pregnancy development. Advice by The Joint Working Party of Royal College of Radiologists (RCR) and RCOG produced in 1995 concluded that a diagnosis of miscarriage should not be made if no fetal pole is seen and the gestational sac diameter is less than 20mm, or if the visible fetal pole is less than 5mm, as only 65% of normal embryo will display detectable cardiac activity at this stage. Repeat ultrasound after at least a week is recommended, and if features are unchanged, this is diagnostic of pregnancy loss.

2.7. Treatment of miscarriage

The technique of evacuation of products of conception employed will depend on a number of factors, the most important being the duration of pregnancy and the preference of the gynaecologist carrying out the operation. The duration of pregnancy can be divided according to the gestation, that is:

a) very early abortion

b) 1st trimester abortion

c) 2nd trimester abortion

Removal of products of conception for 2nd trimester pregnancy is more difficult, has a higher complication rate, and may require subsequent curettage under anaesthesia to complete uterine evacuation.

2.7.1. Surgical uterine evacuation for miscarriage

Since the 1800s surgical uterine evacuation has been the standard treatment offered to women who miscarry. This is based on an assumption that retained tissue increases the risk of infection and haemorrhage. However, the introduction of surgical infection occurred at a time when illegal abortion was common and antibiotics were not available. It remains the treatment of choice if bleeding is excessive, if vital signs are unstable or when infected tissue is present in the uterine cavity. Studies suggest that less than 10% of women who miscarry fall into these categories (Ballargh et al,1998).

Sharp/ blunt curettage and suction curettage have been used for delayed miscarriage. Serious complications of surgery include perforation, cervical tears, intra- abdominal trauma, intra- uterine adhesions and haemorrhage.

In all cases where surgery is being considered the need for cervical ripening should be assessed.

2.7.2. Expectant management for miscarriage

Expectant management has been accepted as alternative technique, although it has not replaced surgical evacuation. Observational and controlled trials of expectant management in patients with spontaneous miscarriage versus surgical management showed wide variations in reported efficacy of the expectant management, i.e. 25 to 100 percent (Nielsen and Hahlin, 1995, Chipchase and James, 1997, Hurd et al, 1997, Jurkovic et al, 1998).

Various ultrasound criteria were used to define "retained products" at study entry. Nielsen and Hahlin (1995) included patients with AP tissue diameter of 15-50mm with ultrasound review at 3 days (efficacy 71%). Chipchase and James (1997) included all those with an AP tissue diameter of less than 50mm and reviewed patients clinically on three occasions up to 6 months (efficacy 100%). However, the mean tissue diameter managed expectantly was only 11mm. These would have been defined as "complete miscarriage" by Nielsen and Hahlin (1995) and excluded from his study.

When ultrasound assessment of uterine cavity shows heterogenous shadows with a maximum AP diameter of 15mm or less, genuine retained products are much less likely to be confirmed histologically (Rulin et al, 1993).

2.7.3. Medical management for miscarriage

Although the medical management of miscarriage with herbal remedies was known before the 19th century, only in the last decade of the 20th century has interest in this field been rekindled (Hinshaw, 1997). As well as avoiding complications of surgery, it is also less expensive than surgery (Hughes et al, 1996).

Various efficacy rate for this type of management has been cited. Factors determining the success rate of the treatment include type of miscarriage, gestational age, type, dose and route of administration of the medication and whether ultrasound scan was used to access completeness of abortion.

The available drugs used for medical management of mid- trimester silent miscarriage include anti-progesterone, mifepristone and various types of prostaglandin analogues such as sulprostone, gemeprost and misoprostol.

a) Mifepristone

Mifepristone (RU486) is a 11ß- dimethyl- amino- phenyl derivative of norethidrone. It has a high affinity for progesterone and glucocorticoid receptors (Mahajan and London, 1997). Receptor binding in the placenta is followed by inefficient transcription of progesterone receptors in the deciduas, myometrium and cervix and thus causing termination of the pregnancy.

If used alone, the success rate of mifepristone to cause complete mid-trimester abortion is about 60% to 65% (Sitruk- Ware, 1990, The RU 486 Collaborative Group, 1990). However, its effectiveness increases dramatically to 94 to 96% if used in combination with prostaglandin (eg: gemeprost) (Grimes et al, 1988, Couzinet et al, 1986). It was reported that 5% to 15% of those cases induced with mifepristone need to undergo dilatation and curettage (D&C) to achieve complete abortion (Chan, 1993).

The recommended dose of oral mifepristone is 600mg followed by 1mg of gemeprost given 48 hours later. However, subsequent studies have shown that a lower dose of mifepristone (200mg) is equally effective (Penny et al, 1995, Baird et al, 1995).

Various side effects were reported with the use of mifepristone. Infection mainly involving the pelvic and genital tract was reported to be one of the commonest adverse affect seen (Hill, 1990, Rodger et al, 1987) and was thought to be due to the suppression of immune system brought by this drug (Schulster, 1976). 79.1% of the patients had severe uterine cramps and 80.5% needed strong analgesia (Norman, 1991). Excessive bleeding per vaginum was also noted and this was attributable to the nature of expulsion of the fetus (Hill et al, 1990, WHO, 1990, WHO task force, 1993).

b) Gemeprost

Gemeprost is a Prostaglandin E_1 analogue with the chemical name of 16, 16- dimethyl- trans- delta 2- PGE_1 methyl ester, with the below structure:

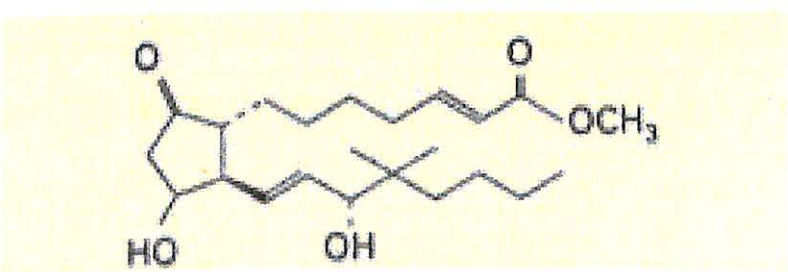

Figure 2: The structure of gemeprost

It has a role for induction of abortion, ripening of the cervix and as a post- partum haemostatic agent. Its role as 2nd trimester abortifacient has been widely published (Krauss et al, 1994, Byrne and Onyekwuluje, 1994, Querido and Haspels, 1990, Cameron et

al, 1987). It stimulates uterine contraction by binding to specific receptors on the myometrial-cell surface. This action results in increased calcium production by the endoplasmic reticulum and, consequently, in uterine contraction causing expulsion of the POC.

Gemeprost was reported to be effective in terms of completeness of abortion in 86% to 91% of the cases of mid- trimester silent miscarriage with the mean induction- abortion interval of 11 to 14 hours (Le Roux et al, 2001, Gemzell- Danielsson and Ostlund, 2000, Wong et al, 1998). The high efficacy is associated with increase adverse effects. In a randomised trial, where 1 mg versus 0.5 mg of Gemeprost at 3 hours interval was compared, the complete miscarriage rate was similar for the 2 groups (98% – 100%), although the incidence of adverse effects were significantly lower in the later group (Rodger et al, 1987). The recommended dosage for gemeprost at the moment is 1 mg given at 3 hours interval for the maximum of 5 administrations in a day.

Cameron et al (1987) reported that 82% of the cases aborted within 24 hours with the mean induction- abortion interval of 881 minutes ± 31 minutes. Querido and Haspels in 1990 showed that 58.9% of their patients aborted after one administration of gemeprost (aborted within 12 hours after the initial insertion). They

considered the method fail if patients still not aborted within 24 hours. 32.1% of them failed to abort despite 5 administrations of gemeprost. Side- effects were noted in 58.9% of the cases but no serious side- effects were encountered.

The known side- effects of gemeprost are as below:

a) vaginal bleeding
b) uterine cramp and pain
c) nausea and vomiting
d) loose stool
e) headache
f) muscle weakness
g) dizziness
h) flushing
i) chills
j) backache
k) chest pain
l) mild pyrexia
m) uterine rupture

Byrne and Onyekluwuje (1994) reported that retained placenta was the commonest side- effect encountered (85%), followed by nausea, diarrhoea and vomiting (25%, 15% and 10% respectively).

Abdominal cramp was seen after 275 minutes of gemeprost

administration in which 79% needed pain relief and 80% of these cases required parenteral opiate. Serious side- effect (uterine rupture) has been reported (Thong et al, 1995, Norman, 1995). This rare complication occurred especially in multiparity and those with previous uterine surgery.

c) Sulprostone

Sulprostone is a Prostaglandin E_2 analogue which has the chemical name of 15- methyl PGF2α. It is 10 times more potent than gemeprost. It is available in an infusion form at the dosage of 1000μg diluted in 500 mls of normal saline given at 10 hours infusion or 500μg by slow infusion over 10 hours (Marpeau et al, 1993). Its effectiveness (expulsion of POC within 24 hours) has been reported to range from 63% to 93% (Biswas and Roy, 1996, Waner et al, 1994, Maria and Matheron, 1994, Marpeau et al, 1993). All abortions were achieved within 24 hours with the mean induction- abortion interval of 14 hours. Minimal side- effects, which include diarrhoea and vomiting, were observed in all cases. Marpeau et al (1993) reported 3 cases, which needed laparotomy for haemorrhagic syndrome and reported a case of uterine rupture with this agent. In April 1991, the first death of medical termination of pregnancy was reported in which a 37year old French woman who was a Para 12 and had 1 previous abortion died of heart attack after injection of sulprostone (Anon, 1991). Since this

incident, extra caution was taken in terminating pregnancy and the safety of medical and surgically induced abortion was compared.

d) Misoprostol

Misoprostol is a prostaglandin E_1 analogue indicated for prevention and treatment of gastric and duodenal ulcer resulting from long- term non- steroidal anti- inflammatory drug use. It is produced by Searle Pharmaceuticals under the product name Cytotec® and is available in most countries. The Obstetrics and gynaecological application for which misoprostol- only regimens are being evaluated include 1st and 2nd trimester abortion, treatment of miscarriage, cervical priming, induction of labour and prevention and treatment of post- partum haemorrhage (SOGC Clinical Practice Guidelines, 2001).

Being a synthetic analogue of prostaglandin E_1, it causes increase in the uterine contractility and therefore causing expulsion of the POC. Among the key advantages of misoprostol as abortifacient is its effectiveness, low cost, stability (tablets have a shelf half life of several years at room temperature), accessibility and its potential to lead to safer reproductive health outcomes than the currently used therapies (Misoprostol Literature Review, 2001). Its uterotonic properties is enhanced if women are pretreated with mifepristone, reflecting the effect of anti- progesterone in increasing sensitivity to prostaglandin. When misoprostol is used in combination with

mifepristone, the vaginal route has been shown to be superior to the oral route (95% versus 87%, respectively) (El-Refaey et al, 1995). The incidence of adverse effects was also reduced in the former group. This is an unlicensed use of misoprostol and should be emphasized to patient prior to its administration (British Medical Society and Royal Phamarceutical Society of Great Britain, 2000).

Medical management of abortion maybe less suitable for those women with heavy vaginal bleeding, anaemia (Hb less than 10 g/dl) or who are pyrexial and who have contraindication to medical therapy (table 2).

Table 2: Contraindications to medical induction of labour

Absolute contraindications:

- Pregnancy more than 63 days
- Suspected ectopic pregnancy
- Adrenal insufficiency
- Long term glucocorticoid therapy
- Haemoglobinopathy or on anti- coagulant therapy
- Anaemia
- Known allergy to mifepristone or prostaglandin
- Smokers over 35 years of age
- Porphyria

Relative contraindications:

- Hypertension
- Severe asthma

2.7.4. Mechanical management for miscarriage

The mechanical methods of abortifacient include foley catheter (with or without extra- amniotic saline infusion), natural dilators (eg: laminaria) and synthetic dilators.

The mechanism of action of this method is by dilating the cervix through mechanical pressure and increase prostaglandin production thus causing expulsion of the POC (Keirse et al, 1983, Boulvain et al, 2000).

For pregnancy around and after the 3rd month, the intrauterine introduction of a urinary catheter or a similar flexible device is the technique used in most places. In Latin America it is called the *sonda*. The introduction of the foreign body causes release of the prostaglandin and induces uterine contraction and expulsion of products of conception 1 to 2 days after insertion of the foreign body.

The variation of the above method is by using extra-amniotic saline infusion. This method was first introduced by Halbrecht and Blum in 1974 as a variation of inducing abortion using intra- or extra- amniotic injection of prostaglandin which has unpleasant side- effect and intra- amniotic

injection of various hypertonic solution which have frequent complications and maybe serious.

A self- retaining bladder catheter ending in a balloon is passed through the cervix, the balloon is inflated with sterile water to hold the catheter in place and an extra- amniotic injection of saline is made continuously using some form of drip or pump, as in figure 3.

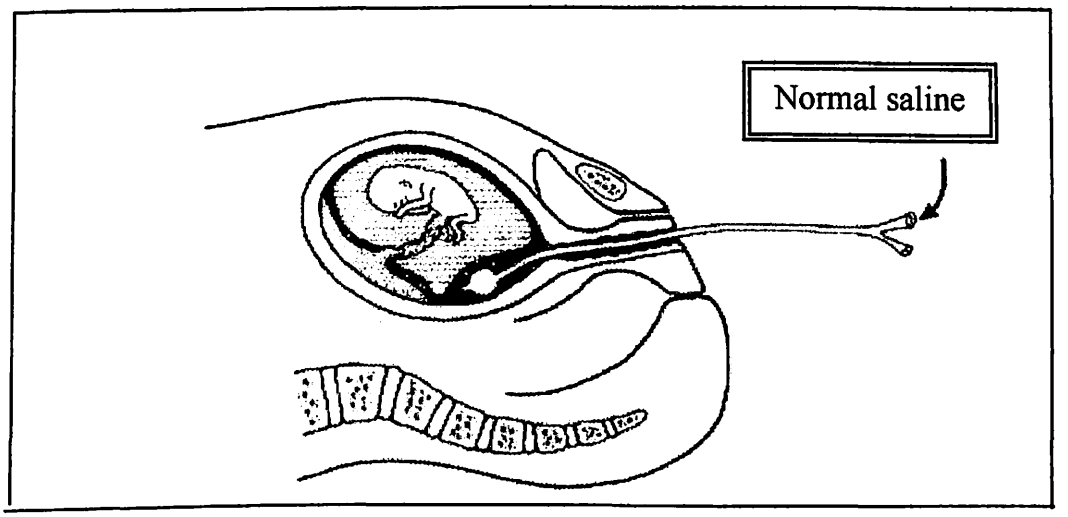

Figure 3: Diagramatic figure showing EASI as abortifacient

The mechanism of abortion with extra- amniotic saline infusion is unclear. It is postulated that the mechanical separation of membrane by instillation of the saline induces a rise in local endogenous prostaglandin, which is responsible for the onset of the uterine contraction. Human studies have measured increased prostaglandin concentrations in amniotic fluid and maternal plasma during balloon- induced cervical ripening. Chandra et al