Review of Literature
REVIEW OF LITERATURE:

The controversy on the issue of induced abortions is well recognised. In recent years, it has reached critical dimensions. It is felt that it should be the right of each woman to take a decision on her pregnancy, based upon correct information.

Abortion has earned much popularity in the last decade because of its greater safety and large impact on population control. The world-wide trend towards liberalisation of abortion laws has continued in the last four years, thus bringing changes in Canada, Czechoslovakia, Hungary, The Soviet Union and Vietnam. Forty per cent of the world's people now live in countries where induced abortion is permitted on request and twenty five per cent in countries where it is allowed only if the women's life is in danger (Hanshaw, 1990).

PROBLEM STATEMENT

(a) WORLD: The number of pregnancies terminated yearly by induced abortions throughout the world is not definitely known because of inadequate data, under-registration of abortions and generally unreliable estimates of illegal abortions. It is estimated that 40-60 million abortions are performed in the world each year including 33 million legal procedures. This implies a
world-wide abortion rate of 37-55 per 1,000 women aged 15-44 years and a ratio of 24-32 abortions per 100 known pregnancies (Tietze and Henshaw, 1986).

(b) INDIA: Since legalisation of abortion in India, deliberate induction of abortion by a registered medical practitioner in the interest of mother's health and life is protected under the MTP Act 1971-75. In India, 518,600 pregnancies have been terminated legally in 1983-84, accounting for an abortion rate of 3.3 and abortion ratio of about 2 : 1. But, illegally induced abortions are estimated to have numbered 4-6 millions giving an abortion rate of 36-55 and an abortion ratio of 13-20 per 100 estimated pregnancies per year (Chaudhuri, 1988). Since the inception of the programme in India, in April 1972, over 6.38 million terminations were effected up to March 1989 under the MTP Act (Ministry of Health and Family Welfare, Govt. of India, 1990).

As a result of increased awareness created by the implementation of the MTP Act in India, more and more women are seeking legal abortions.

The use of pharmacological agents for the termination of early pregnancy is preferred over any surgical procedure due to
risks involved in instrumental evacuation. The ideal drug for this purpose should be safe, highly effective and easy to administer. Prostaglandins can be used to terminate pregnancies at any stage of gestation. However, when they are used to terminate pregnancies between 7-12 weeks; the induction-abortion time is significantly prolonged and the doses required produce unacceptable side effects.

During the second trimester between 13-20 weeks pregnancy when the foetus develops rapidly, the uterus is generally quiescent and unresponsive. At this stage, abortion is physically and psychologically more traumatic than the termination of early pregnancy or menstrual induction.

Different methods have been used to provoke abortion since time immemorial:

(i) extra-ovular metureurus.

(ii) introduction of laminaria bougres.

(iii) extra-ovular instillation of hypertonic saline, ethacridine lactate alone or in combination with syntocinon (Cohen, 1846).

(iv) Prostaglandins (PGF₂ and PGF₂α) and their synthetic analogues using intravenous, extra-amniotic, intra-amniotic or intra-vaginal routes of administration.
Continuous intravenous infusion of prostaglandin for termination of pregnancy was first successfully tried by Karim and Filshie (1970). Following this, several authors have reported a success rate ranging from 60-93%. Disadvantages of this route has been the high incidence of nausea, vomiting, diarrhoea and phlebitis at the site of infection. More recently, however, considerable interest has been directed towards other routes of administration.

Since the first systemic study of the prostaglandins by Kurzork and Lieb in 1930, many stimulating researches are being done on prostaglandins all round the world. Prostaglandins have revolutionised the management of pregnancy termination. They are considered to be the method of choice for second trimester abortions. They appear to have high efficacy and less side effects. The efficacy can be further enhanced and side effects further reduced when prostaglandins are administered in combination with some other method.

PROSTAGLANDINS

Term was coined by Von Euler (1935). Prostaglandins are naturally occurring substances of family of polyunsaturated 20 carbon fatty acids containing a cyclopentane ring and two
aliphatic side chains. Chemically derivative of hypothetical prostanoic acid.

Prostaglandins are divided into groups A, B, C, D, E, F, G, H and I which are subdivided according to degrees of unsaturation of side chains and a suffix denoting the number of double bond (e.g. PGE_1, PGE_2, PGE_3). When stereoisomerism exists its nature is shown by additional subscripts alpha or beta (PGF_{2\alpha} and PGF_{2\beta}). Only alpha isomer occur naturally.

BIOSYNTHESIS

In the body prostaglandins are derived from ercose (tri/litre/pento) enoic acids. Thus called eicosonoids. In human tissue, the fatty acids released from membrane lipids in largest quantity is 5, 8, 11, 14 eicosa tetanoic acid (arachidonic acid). During prostaglandins synthesis, two of the four double bonds of arachidonic acid get saturated in process of cyclization, leaving two double bonds inside chain. Thus subscript 2 prostaglandins are most important in man e.g. PGE_2, PGF_{2\alpha}, TxA_2 and PGI_2.

Eicosonoids are most universally distributed autocoid in the body. Practically every cell and tissue is capable of synthesizing one or more types of prostaglandins. Endogenous
prostaglandins are known to be involved in regulation of female reproductive processes. Pickles and co-workers have identified the presence of prostaglandins in menstrual fluid, endometrium and in blood during menses (Elington et al. 1963; Pickles et al. 1965, 1967) while Karim, Devlin and Hiller identified the presence of E and F prostaglandins in the umbilical cord, amniotic fluid, decidua and in venous blood during spontaneous labour and abortion (Karim, 1966, 1967, 1968; Karim and Devlin, 1967; Karim and Hiller, 1970).

Arachidonic acid is a typical polyunsaturated fatty acid present in cells in esterified form, hence the liberation of glycerophospholipids of arachidonic acid is a key event in biosynthesis of prostaglandins and is thought to be the rate limiting step in this process (Samuelsson, 1978).

DEGRADATION

First step in prostaglandins metabolism - These are catalysed by 15 hydroxy prostaglandins dehydrogenase (PGDH) into biologically inactive 15 ketoderivatives, which are rapidly converted to the 13, 14 dehydroxy-15-keto derivatives the major circulating forms (Vonkeman et al. 1969).
Degradation occurs rapidly in most tissues but fastest in the lungs. Plasma half life in few seconds to few minutes (Sameulsson, 1978). Elimination of biologically active prostaglandins is compared by beta and omega oxidations. The products formed are excreted in urine.

Pharmacologically to make the compound stable for therapeutic purposes such as induction of abortion, the 15-OH group of PGF$_{2\alpha}$ is replaced by 15-CH$_3$ group; and this compound 15-methyl-PGF$_{2\alpha}$, hence is not metabolised by 15-hydroxy prostaglandins dehydrogenase.

**DISTRIBUTION OF PROSTAGLANDINS IN HUMAN REPRODUCTIVE ORGANS AND FLUID**

Recent and more definite studies have shown that the distribution of prostaglandins is not restricted to the male accessory glands (prostate) or their secretions as reported earlier but prostaglandins have ubiquitous distribution in the female reproductive organs and fluids also. With increasing research, evidence has accumulated that prostaglandins are active throughout the reproductive system.
PROSTAGLANDINS SYNTHESIS IN THE BODY

DIET ESSENTIAL FATTY ACIDS

MEMBRANE PHOSPHOLIPID

PHOSPHOLIPASE A - ACTIVATION

ARACHIDONIC ACID

CHEMICAL AND MECHANICAL STIMULI

METABOLISED BY 3 MAJOR PATHWAYS

EPoxyGENASES → LEUCOTRIENES

- PROSTAGLANDIN SYNTHETASE CYCLO-OXYGENASE
- BY INCORPORATING TWO O₂ MOL. CYCLO-OXYGENASE CONVERT ARACHIDONIC ACID INTO

PG-G₂

INHIBITED BY NSAIDS LIKE ASPIRIN

PG-H₂

LOOSES TWO MOLECULES OF O₂ AND CHANGES TO

ISOMERASE

PGE₂

PG-D₂

PGF₂α

TX-A₂

PROSTACYCLINE SYNTHETASE

PG-I₂
By the late 1970s prostaglandins were known to be involved in hypothalamic and pituitary hormone releases, ovulation, development of corpus luteum, uterine contractions in labour and spontaneous abortions, ejaculation and sperm transport.

The types of prostaglandins in relation to the source as found by various workers are given in Table I.

<table>
<thead>
<tr>
<th>Source</th>
<th>Types of PGs</th>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Reproductive Tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal blood during preg; labour and spontaneous abortion</td>
<td>$E_2, F_{2a}$</td>
<td>Karim, 1968; Karim &amp; Hiller, 1970</td>
</tr>
<tr>
<td>Amniotic fluid in gestation and labour</td>
<td>$PGF_{2a}, PGF_{1a}$</td>
<td>Karim and Devlin, 1967</td>
</tr>
<tr>
<td>Umbilical and placental blood vessels</td>
<td>$PGF_2, PGE_1$</td>
<td>Karim, 1967a</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>$PGE, PGF$</td>
<td></td>
</tr>
<tr>
<td>Menstrual blood and endometrium</td>
<td>$PGF_{2a}$</td>
<td>Ogra et al. 1974</td>
</tr>
<tr>
<td></td>
<td>$PGF_2, PGF_2$</td>
<td>Pickles and Hall, 1963; Downie et al 1974.</td>
</tr>
<tr>
<td>Male Reproductive Tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminal fluid</td>
<td>$E_1, E_2, E_3, F_1$</td>
<td>Hamberg &amp; Samuelsson, 1966;</td>
</tr>
<tr>
<td></td>
<td>$A_1, A_2, E_1, E_2$</td>
<td></td>
</tr>
</tbody>
</table>
MECHANISM OF ACTION ON UTERINE MUSCLE

Exact mechanism is not clear. Different workers are of the views:

1. Act by Calcium Displacement Mechanism:
   - Prostaglandins interact with specific receptors localized in plasma membrane cells. In uterine muscle, the prostaglandin bind to the \( E_2 \) adrenergic receptors.
   - PGE and PGF inhibit action of adenylate cyclase and decrease cyclic AMP, which in turn increase intra-cellular ionic calcium to actomyosin complex and in this way triggers myometrial contraction (Mary E. Cursten, 1972).

2. Prostaglandins act indirectly through the release of oxytocin. Gillepsie et al. (1972) have shown an increase of oxytocin level in prostaglandin induced abortions.

3. According to Csapo and Pulkkinen, it is the reduction in progesterone supply due to constriction of uterine and placental blood vessels, thus making the myometrium receptive to prostaglandins (Csapo and Pulkkinen, 1979).

4. Prostaglandins appear to induce abortion primarily through uterine contractions. These are probably stimulated both directly by the exogenous prostaglandins and indirectly by
enhanced release of endogenous prostaglandin. There is an increase in uterine muscle tone, followed gradually by regular contractions which physically dislodges the conceptus from the uterine wall.

(5) Prostaglandins are also involved in leuteolysis and inhibit the ability of corpus luteum to secrete the female hormone progesterone which is necessary for maintenance of pregnancy, thus causing abortion.

PROSTODIN

Prostodin is a synthetic analogue of naturally occurring prostaglandin $F_{20}$. Chemically it is tromethamine salt of $15(S)$-15methyl PGF$_{20}$. The generic name is carboprost tromethamine.

The process of abortion by use of PGs is similar to labour at term. There is a latent phase during which the cervix dilates, softens and effaces to facilitate the passage of products of conception. This is followed by an active phase during which the products are expelled through the dilated cervical canal.

The primigravidae take 3-5 hours longer for expulsion. This is mainly due to longer latent phase-analogous to labour. Adequate uterine contraction (3-5 per 10 min.) with the tone returning to baseline is necessary for expulsion of products of
15(S)-15-METHYL PGF₂α (TROMETHAMINE SALT)
conception. On the other hand, contractions superimposed with high basal tone may lead to rupture of uterus, especially in absence of cervical dilatation. The incidence of incomplete abortion is higher during early second trimester than during late second trimester.

CONTRA-INDICATION FOR USE OF PROSTODIN

Prostodin is contra-indicated in the patients with following medical conditions:

(a) Hypersensitive to prostodin
(b) Asthma, allergic bronchitis
(c) Epilepsy
(d) Renal impairment
(e) Cardiovascular diseases
(f) Hepatic diseases
(g) Grand multipara
(i) Scarred-uterus-previous hysterotomy/cesarean section

(i) Other relative contra-indications include large uterine myomata, major congenital anomalies of the uterus, failed saline inductions and purulent cervicitis or vaginitis.
Ethacridine lactate
PHARMACOLOGY OF ETHACRIDINE LACTATE

Ethacridine lactate also known as "Acerenol lactate", "Lacto-actridine", "Aethacridinum-Lacticum", "Rivanolum" in 6-9, diamino, 2-oxyethyl-acridine lactate with a chemical composition of $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3\text{H}_2\text{O}_3\text{H}_2\text{ONH}_2\text{HOOC-CH(OH)CH}_3$ in the following configuration

It is a yellow dye with antiseptic action. In 0.05 to 0.2% solution, it has been widely used as an antiseptic agent for skin and mucous membrane, 0.1% Rivanol, injection intravenously was found to be quite safe and was used in this concentration for many infectious diseases. It has been also used internally as urinary tract disinfectant. Absorption or intravasation of the drug is without any danger.

MODE OF ACTION

The oxytocic effect of Rivanol and other basic dyes in human uterine muscle is well documented. Saperika (1934) investigated the effect of Rivanol on the uterus and showed that it stimulated myometrical contractions in weak concentrations. In vivo there was a stimulating effect on both pregnant and non-pregnant cat myometrium with a dose of 2 mg/kg. Klingenberg et al. (1961) showed that protamine and acridine caused isolated strips of
guinea pig uterus to contract. These early observations suggested that the use of extra-amniotic injections of acridine dyes to induce abortion depended on a true oxytocic effect rather than mechanical distension and separation of chorion from decidua.

Manabe (1962) suggested that extra-ovular injections of Rivanol causes mechanical stimulation of the uterus. Extensive detachment of the membrane and the stimulation of the uterus caused by Rivanol in extra-ovular space can precipitate labour. The catheter left in situ also was thought to stimulate the uterine contractions. Mechanical stimulation can also cause reflex release of oxytocin.

Gustavi (1974) suggested that extra-ovular procedures (including injections of Rivanol) act by releasing lysosomal hydrolytic enzymes within decidual cells. The enzymes released are thought to cleave prostaglandin precursor from membrane phospholipids and thereby provide substrate for prostaglandin synthesis.

It seems probable that the observed damage to decidual lysosomes is followed by the synthesis and release of prostaglandins resulting in uterine contractions and finally in abortion.
FRONTIERS IN RESEARCH

The search for a safer solution for extra-amniotic injection for termination in the 2nd trimester has led to the discovery of many substances. Cohen in 1846 first described the extra-ovular injections of Rivanol for termination of pregnancy in second trimester. Kashiwara and Fujibayashi of Japan (1952) described the technique of injection of rivanol by catheter in the extra-ovular space.

Manabe from Japan (1969) used Rivanol along with oxytocin injections. Instillation abortion interval varied between 19 hours to 33 hours.

Lewis et al. (1971) described the oxytocic effect of the acridine dyes and their use in termination of mid-trimester pregnancy. All the patients aborted after a mean induction-delivery interval of 59 hours.

Carl-Axel-Ingemanson of Sweden (1973) compared the results of Rivanol with extra-amniotic injection of hypertonic saline. A higher percentage of successful abortions was obtained in the Rivanol-catheter group than with saline group.

Anjaneyulu (1977) used ethacredine lactate as extra amniotic injection and unitocin (spartine sulphate) 150 mg 1/m one hourly
for 3 doses were given to assist the expulsion. The average successful rate within 72 hours was 81.4%.

Ananthakrishnan et al. (1978) used ethacridine lactate with 10 units pitocin extra-amniotically. He found average induction abortion interval of 28 hours 10 minute with net success rate of 73.3%. Sepsis was seen in one patient who came for follow up after 10 days.

Karne et al. (1980) performed a comparative study of 392 mid-trimester abortions with intra-uterine injection of normal saline, 20% saline, prostaglandins and ethacridine lactate. He found success rate of 96% in 48 hours in prostaglandin group; 90% in intra-amniotic, 20% saline group, 87.5% in emcrecil with oxytocin infusion group and 80% in only emcrecil group.

A comparative study of middle trimester abortion by serial intramuscular injections of 15-methyl prostaglandin F₂α and by extra-amniotic infusion of 0.1% ethacridine lactate has been carried out by Mrs. R. Sofat (1984). Success rate in prostaglandin group was 100% and induction abortion interval was 14.23 hours.

Anirudh Malpani et al. (1986) did a comparative study of 2 prostaglandin analogues (Carboprost and sulprostone) with
ethacridine lactate for second trimester abortion. It was observed that the induction abortion interval was significantly shorter with carboprost. It was 20 hours 10 min. with sulprostone group and 14 hours 20 min. with carboprost group.

The Indian Council of Medical Research found a success rate of 78.1% in a series of over 1500 mid-trimester abortions with 1 mg of extra-amniotic 15(S)-15 Methyl PG F₂α.

Karim and Sharma (1988b) used single injections of 25 mg of PGF₂α extra-amniotically to terminate second trimester pregnancies. The extra-amniotic administrations of 15 Me-PGF₂α appears to be a more desirable route of administration than repeated intra-muscular injections which produce unacceptable level of gastro-intestinal side effects.

Kher R.A., Ingle M.K. et al. conducted a trial at NWM Hospital using ethacridine lactate and extra-amniotic single dose of 15(S)-15 Methyl PGF₂α to perform second trimester medical termination of pregnancy and the results were compared with those of ethacridine lactate used with oxytocin augmentation. It was found that the success rate and incidence of complete abortion was higher with ethacridine + carboprost combination.
J.N. Martin, M. Bygdeman, A. Leader and N. Wiqvist performed early second trimester abortions using extra-amniotic instillations of Rivanol solution and a single injection of PGF$_{2\alpha}$ and found a successful induction-abortion after 18 hours 20 min. It was found that this method combines the immediate uterotonic effect of prostaglandin with the delayed oxytocic response to Rivanol.

**Mid-trimester pregnancy termination by extra-ovular instillation of PG and PG analogues, Selected Studies**

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>No. of Patients</th>
<th>Type of PG</th>
<th>Dose</th>
<th>Trial Period</th>
<th>I.A. Interval</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiqvist et al.</td>
<td>50</td>
<td>PGF$_{2\alpha}$</td>
<td>250-750</td>
<td>30</td>
<td>24 hr 12 min</td>
<td>90</td>
</tr>
<tr>
<td>(1972)</td>
<td></td>
<td></td>
<td>µg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aingorani &amp; Ganesh</td>
<td>20</td>
<td>PGF$_{2\alpha}$</td>
<td>500 µg</td>
<td>30</td>
<td>19 hr</td>
<td>80</td>
</tr>
<tr>
<td>(1972)</td>
<td></td>
<td></td>
<td>µg</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WHO Multicentric</td>
<td>660</td>
<td>15MePGF$_{2\alpha}$</td>
<td>0.92 mg</td>
<td>36</td>
<td>-</td>
<td>83</td>
</tr>
<tr>
<td>trials (1976)</td>
<td></td>
<td></td>
<td>µg</td>
<td></td>
<td></td>
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<tr>
<td>ICMR Multicentric</td>
<td>1569</td>
<td>15MePGF$_{2\alpha}$</td>
<td>1 mg</td>
<td>36</td>
<td>14.8 hr</td>
<td>78</td>
</tr>
<tr>
<td>trials (1988)</td>
<td></td>
<td></td>
<td>µg</td>
<td></td>
<td></td>
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</table>

**ANALYSIS OF COMPLICATIONS**

The incidence and magnitude of the complications are detected by various factors, the foremost being the nature of the abortifacient agent. The other factors involved in modifying the results are the duration of pregnancy, parity and associated medical disorders.
1. HAEMORRHAGE

Haemorrhage is the commonest type of life threatening complication. Haemorrhage is not a problem in prostaglandin-induced abortions. PGF₂α was found superior to oxytocin in reducing excessive post-abortal bleeding in women at high risk of developing atonic postpartum haemorrhage (Nelson, 1980).

Ruoff et al. (Karuni, 1979) compared the amount of blood loss in both the groups and found that post-abortal blood loss was quite less in the PG group as compared to oxytocin. In a study of Rajan et al. (1980) by oxytocin augmentations there were seven fold increase in the incidence of haemorrhagic complications.

2. UTERINE ABNORMAL ACTIVITY

Prostaglandins induces uterine contractions at all stages of pregnancy. It causes an increase in oxytocin receptors on myometrium making it more sensitive to contractile action of oxytocin. Thus, the over stimulation of uterine myometrium can occur in any case or may fail to induce in some.

No case of uterine hypertonus was reported by Karim and Sharma (1971) and Craft and Yip (1978). Cervical injury was more
common with intra-amniotic than extra-amniotic procedures and was mainly seen in multipara women.

3. GASTRO-INTESTINAL EFFECTS

In isolated proportions longitudinal muscle of gut is contracted by PGF₂α while the circular muscle is relaxed. Hormone propulsion activity is enhanced in human and thus colic and diarrhoea are important side effects. PGs act directly on the intestinal mucosa and increase water content, electrolyte and mucus secretion. Episodes of vomiting and diarrhoea were frequent but not troublesome in majority of patients (Graft, 1972). Nausea, vomiting and diarrhoea were more frequently observed in multipara (Theiry and Amy, 1974).

Gastro-intestinal symptoms were the most common side effects with PG group as compared to oxytocin group (Hingorani et al., 1988).

4. COAGULOPATHY

Intravenous oxytocins were found to increase the risk of consumptive coagulopathy (Cohen and Ballard, 1974) as compared to prostaglandins. Oxytocin causes an increased release of thromboplastins into the maternal circulation and leads to coagulation abnormality.
In case of extra-ovular 0.1% Rivanol, and prostaglandins $\text{PGF}_{2\alpha}$; fibrinogen levels showed a slight increase after the instillations of the drug but euglobulin lysis time was normal throughout. The platelet count and prothrombin time showed no significant change; so by use of ethacridine + PGF$_{2\alpha}$ combination there is complete absence of haemorrhage complications.

5. CARDIOVASCULAR SYSTEM

Selective effect of prostaglandins on uterus without any side effect on cardiovascular system was reported by Karim (1971). Pulse, BP showed no changes during period of instillation (Craft Yip, 1972).

6. PROBLEMS IN SUBSEQUENT PREGNANCIES

Although it is not more than 20 years since the first abortion was carried out using prostaglandins, little information is available about the long term physical sequale of pregnancy termination in the second trimester of pregnancy. Mackenzie and Fry (1988) assessed the subsequent fertility of 140 women whose pregnancies were terminated with prostaglandins in second trimester.

Reduced fertility after prostaglandin induced abortion was shown to be very infrequent.
Since abortion, 104 women in this series have conceived (97% within 24 months of abortion and five of them after some delay). Only one woman had not succeeded in achieving a desired pregnancy.

7. BODY TEMPERATURE

There is no evidence that prostaglandin used for abortion act as pyretic agent (Nelson and Bryans, 1979).

8. OTHERS

Fraser and Brash (1974) reported two cases of bronchospasm after prostaglandin instillation. Prostaglandin in the usual dose used for induction of abortion do not cause convulsions (Fraser and Gray, 1974).