A PROSPECTIVE RANDOMIZED CONTROL TRIAL COMPARING VAGINAL MISOPROSTOL AGAINST GEMEPROST AS CERVICAL PRIMING AGENT IN PRE-SURGICAL EVACUATION OF MISSED ABORTION.

BY

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Lastly and most importantly, I would like to thanks my parent, my wife and my childrens for their continuous support, prayers and love.

Dr. Mansor bin Md. Noor. November, 2000.

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ABSTRAK:

OBJEKTIF: Untuk membandingkan keberkesanan, kesan sampingan dan kos efektif diantara vaginal misoprostol dengan gemeprost dalam mengubah dan membuka pangkal rahim sebelum pembedahan cuci untuk keguguran 'missed'.

BENTUK: Penyelidikan prospektif secara random (rawak)

TEMPAT: Wad Sakit Puan, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan dari 1 hb. Disember 1999 sehingga 30 hb. Jun 2000.

METODOLOGI: Wanita yang dan memenuhi syarat-syarat 'inclusion' dan 'exclusion' yang mengalami keguguran ' missed ' telah dipilih secara rawak sama ada menerima 400-microgram misoprostol atau 1-microgram gemeprost melalui vagina sekurang-kurangnya 2 jam sebelum pembedahan cuci dijalankan. Dengan mengunakan Hegar dilator, pembukaan pangkal rahim akan dicatitkan. Lain-lain catitan dan pemerhatian yang dijalankan ialah mudah/susah cucian dijalankan, pendarahan ketika cucian dan kejadian kesan sampingan.

KEPUTUSAN: Kami dapati tiada perbezaan yang nyata didalam pembukaan pangkal rahim diantara misoprostol dengan gemeprost ($p = 0.912$). Purata saiz Hegar bagi misoprostol ialah 10.05 (SD = 4.45) dan 10.20 (SD = 4.11)

bagi gemeprost. Kejadian kesan sampingan bagi kedua-dua ubat adalah sama iaitu sakit di bahagian abdomen (45% untuk misoprostol dan 35% untuk gemeprost) dan pendarahan vagina (50% dan 55%), lain-lain kesan sampingan adalah kecil,rendah bilangannya dan serupa..

KESIMPULAN: Misoprostol yang digunakan adalah sebaik gemeprost dalam menyediakan pangkal rahim sebelum pembedahan-cuci bagi keguguran ' missed '. Kesan sampingan bagi kedua-dua ubat adalah kecil, rendah dan serupa. Misoprostol (RM. 02.00) adalah lebih menjimatkan berbanding dengan gemeprost (RM. 98.00) dalam menyediakan pangkal rahim sebelum pembedahan-cuci dalam kes keguguran 'missed' pada trimester pertama dan awal trimester kedua pengandungan.

ABSTRACT:

OBJECTIVE: To compare the effectiveness, side effect and cost effectiveness of vaginal misoprostol against the standard drug, gemeprost, as cervical priming agent in pre-surgical evacuation in first and early second trimester missed abortion.

DESIGN: A prospective randomised controlled study.

SETTING: Gynaecology ward, Hospital University Sains Malaysia, Kubang Kerian, Kelantan, from the 1st. of December 1999 till 30th. of June 2000.

METHODS: Women who fulfilled the inclusion and exclusion criteria were randomly allocated to either receive 400-microgram misoprostol or 1-milligram gemeprost vaginally for at least 2 hours before surgical evacuation of missed abortion. The degree of the cervical dilatation was measured using Hegar's dilator. The easiness of the evacuation procedure, intra-operative blood loss and associated side effect were also assessed. The inclusion criteria's include confirmed missed abortion by ultrasound, period of gestation up to early second trimesters, cervical length more than 1 cm,

cervical Os less than 0.5 cm and patient consented to be included in the study.

While the exclusion criteria were uterine size of 14 weeks or more on abdominal palpation, patient known to have had history of allergic reaction to any prostaglandin products, severe medical disease, abnormal coagulation profile and patient refusal to be included in this study.

RESULTS: Both misoprostrol and gemeprost used has satisfactory cervical ripening effect, although there was **no significant difference** in the dilatation ability between them ($p = 0.912$). The mean Hegar's dilator for misoprostol and gemeprost were 10.05 (SD 4.43) and 10.20 (SD = 4.11) respectively. The commonest side effects were per-vaginal bleeding (50% for misoprostol and 55% for gemeprost) and abdominal pain (45% vs.30%), occurred with almost similar frequency in the misoprostol and gemeprost group, while the other side effects (headache, nausea and febrile episode) of both drugs were minimal and negligible. There was no side effect of vomiting, shivering or diarrhoea in any of our patients.

CONCLUSION: Vaginally applied misoprostol was as effective as gemeprost in cervical priming prior to surgical evacuation of missed abortion. The mean Hegar's dilator were10.05 for misoprostol and 10.20 for gemeprost. The occurrences of side effect in both drugs were minor,

small in numbers and were similar in nature. Misoprostol (RM 02.00) was more cost effective than gemeprost (RM 98.00) in cervical priming prior to surgical evacuation of missed abortion in first and early second trimesters..

KELANTAN:

To discover the soul of Malaysia, one should visit the state of Kelantan, bordered by Thailand on the north, isolated from the west by a chain of rugged mountains and separated from the south by the oil rich state of Terengganu.

The east coast state of Kelantan's exquisite silver artisan, cloth and mat weavers, and batik weavers are renowned throughout the countries. And where else but in Kelantan that you can see farmers competing in top-spinning and kite- flying, as well as watch fisherman with their beautifully painted boats pushing or landing at the same stretch of beach that has been unchanged since centuries.

Peaceful, timeless fishing villages dotted the coastline, coconut palm bending out to the blue sea are common scenery that will tranquillise you as you passed the quiet coastal road in the coastal area of Kelantan.

History: Kelantan has a long story of independent existence going back to the dawn of history. Cave dwellers once roamed its interior, this important traces of New Stone Age people has

been found at various places in the state, which later emerged as an important kingdom in the days of the Malaccan sultanate and was ruled by the legendary beauty, Puteri Sa'adong, in the 17th. Century. In the more modern times, Kelantan was under the shadow of its powerful northern neighbour, Thailand, and Thai or Siamese influence did not come to the end until a treaty, signed in1909 between the Thais and the British that placed Kelantan under British protection. However, Thai influences can still be seen in the Kelantan architectures, dialect, food and arts form of today.

Kelantan is a place to explore. Do not hesitate to travel off the beaten track to a small fishing village. A friendly gesture will be the return of a smile, or perhaps to an invitation to tour the village where the soothing rhythms of a Malay life have endured for centuries.

Its people: The population of Kelantan is just over a million people in the last population census done in 1990, with an annual growth rate of 2.5%. The majority of its population is predominantly Malay, which constitutes 93%, while the Chinese, Indian and the Siamese make for the other 7% of the total population. The Malay traditionally lives in the outskirts

of the town areas, kampong and the coastal villages, while the Chinese and Indian are mostly concentrated in the town areas.

Economy: Kelantan gross economic product has grown steadily. The GDP grew from RM. 1,463 million in 1985 to RM. 2,485 million in 1993.This growth has been attributed to a strong commitment by both the public and private sector. The per capita income in 1995 is RM. 2,081. The economic growth rate for 1994-95 is 6.4%.

Agriculture and fishing industries form the backbone of the Kelantan economy. It accounts about 35% of the state GDP in the past years.

Tourism: With its rich cultural and traditional heritage, Kelantan is one of the most interesting and unique destinations for a vacation. The long stretches of clean sparkling white virgin beaches, with the blue seas in the background are great for swimming and picnic.

Kelantan's traditional pastime games of top-spinning, kite-flying, drum beating and traditional singing (dikir barat) are well and alive in spite of the modernization of its people. The

handicraft are superb for example the hand printed ***batik*** cloth, ***songket*** and exquisite silverware are renown and popular with the tourist, whether local or foreign. The crafts persons of Kelantan are truly gifted and skilled which is a tribute to Kelantan's rich cultural heritage and liven to its **' soul of Malaysia'** reputation.

The Medical Faculty of University Science of Malaysia:

The school of Medical Sciences, University of Science of Malaysia (HUSM), cawangan Kelantan was set-up in 1984, after it was transferred from its main campus in Pulau Pinang. It is surrounded in a lush green environment about 6 kilometres from Kota Bahru.

Currently the school offers undergraduate and various post-graduate including limited Doctorate research in medical sciences. The post- graduate (M.Med.) was started in 1988 with the initial course offered to Internal Medicine. Then in 1991 Master programme was introduce for O & G, general surgery and orthopaedic.

Beside teaching and research, the University also provides excellent medical and surgical services to Kelantan and neighbouring state Terengganu, especially for special sub-specialty such as neurosurgery, plastic surgery and orthopaedic oncology.

The hospital has a total of 570 beds for the whole discipline and was corporatised in 1998. This has improved the quality and efficiency of the service.

In the future, University of Sciences Malaysia is determine to become the centre of excellence not only in Malaysia but in the world by having more research and development of exceptional standard.

OBSTETRIC AND GYNAECOLOGY DEPARTMENT, UNIVERSITY SCIENCES OF MALAYSIA.

Currently our department has a total of 11 consultant/lecturers, 6 registrars (final year students) 29 medical officers. Fourteen of the medical officers are currently in the university, while 15 are in the other state general hospitals as ' Pendidikan Jarak Jauh' or long distance learning medical officer.

Associate Professor Dr. Mohd Shukri Othman who has been instrumental in developing and training the Master of O & G students, heads the department.

The labour room is situated on the new block since 1997. It is currently in renovation to make it more husband friendly i.e. so that the husband of women who are in labour can stay by their wife until delivery, as recommended by the Ministry of Health, Malaysia. The operation theatre is situated in the labour room itself to expedite operative delivery.

Daily Department Activities.

Day	Morning	Afternoon
Saturday	Booking Antenatal Clinic	Booking Antenatal Clinic
Sunday	CME for all M.Med students and antenatal Clinic.	Gynaecology Clinic
Monday	Menopause Clinic and Combined Clinic	Oncology and Molar Clinic
Tuesday	Antenatal Clinic	Gynaecology Clinic
Wednesday	Fertility Augmentation Clinic	Family Planning and Post Natal Clinic
Thursday	CME and Pre-Operative discussion	Department Presentation

Our department is currently embarking on several sub-specialties, although, it is still in its infancy state such as feto-maternal, fertility augmentation unit, menopause together with our medical colleague and gynae-oncology.

The future looks bright in view of the young and dynamic lecturers/consultants in O & G, and with the economic recovery is gaining pace, more can be done to improve our services to the people.

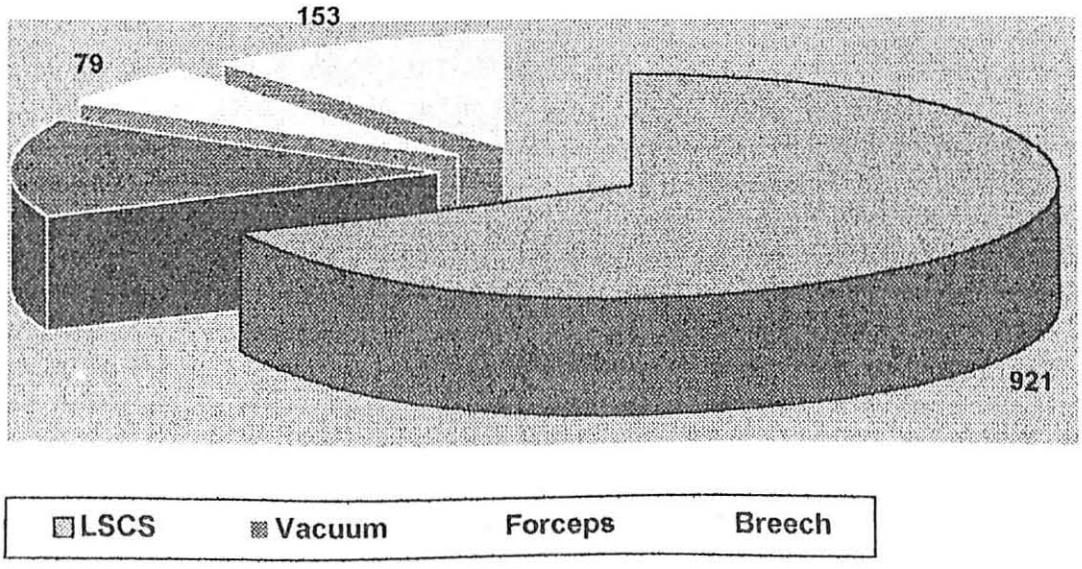
A GLANCE THROUGH HUSM LABOUR ROOM STATISTICS :

Year 1999:

	Numbers
Live birth	7687
Still birth	91
Total	7778

	Numbers
Spontaneous vaginal deliveries	6431
LSCS	921
Breech	153
Vacuum	194
Forceps	79
Total	7778

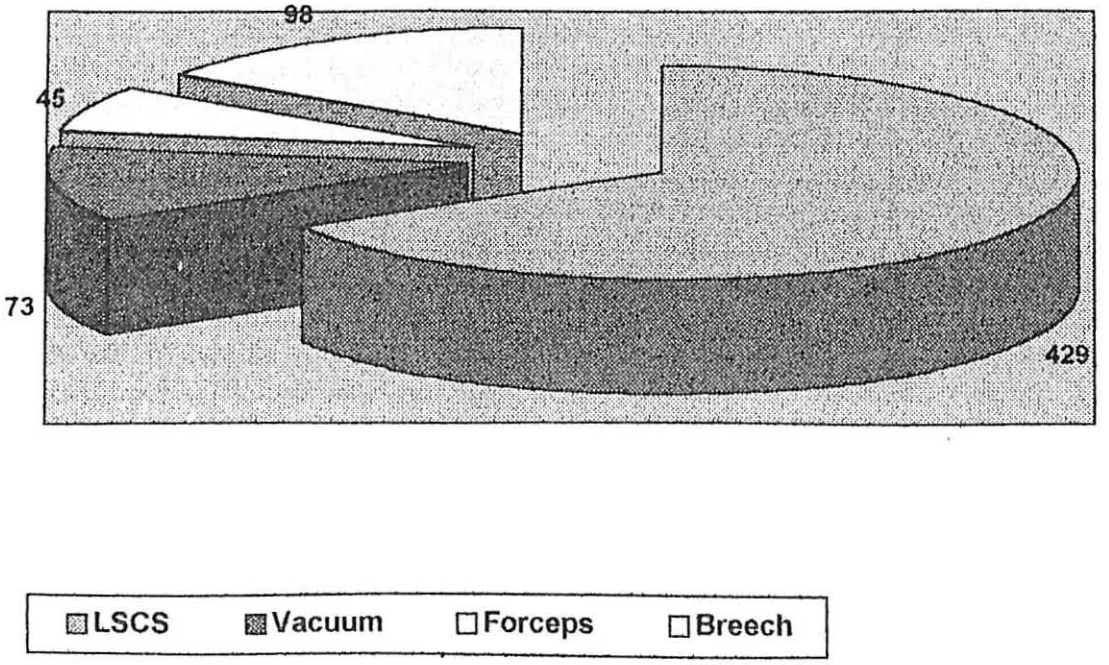
Deliveries other than SVD.



Statistic from January 2000 till June 2000:

	Numbers. (Percentage)
Live birth	3893 (99%)
Still birth	41 (1%)
Total	3934

Type of deliveries other than SVD:



Numbers of LSCS and Instrumental Deliveries from Jannuary untill June 2000.

	Numbers
LSCS	429
Vacuum	73
Forceps	45
Breech	98
Total	645

THE ANATOMY AND PHYSIOLOGY OF THE UTERUS AND CERVIX IN NON-PREGNANT AND PREGNANT HUMAN.

1. Anatomy:

The uterus is truly a remarkable organ; in its non-pregnant state it is a small 7.5 cm x 5 cm x 2.5 cm in length and weighing approximately 50 to 60 gram. In pregnancy, it gradually transforms itself under multiple influences to accommodate one or multiple foetuses of 2.5 to 3.5 kilogram in just approximately 278 days, weighing close to one kilogram, and again after parturition it will transform back to it original form in less than 2 months.

The uterus basically consists of two basic parts, the corpus or body and its endometrium, and the uterine cervix, which is approximately 2.5 cm long, lying inferior to the corpus.

Primarily a muscular organ, the uterus is located in the pelvic cavity of a non-pregnant woman and in pregnant women during the first trimester of pregnancy. In later stages of pregnancy it becomes an abdominal organ.

The non-pregnant uterus is situated between the bladder on its anterior surface and the rectum on its posterior surface. On naked eyes it appears as an up side down flatten pear shaped organ. The uterus of a nulliparous measured 7.5 cm long, 5 cm wide, and 2.5 cm from front to back and a wall thickness of 1 to 2 cm thick. Its lumen has a triangular shape and smooth and is connected to the peritoneal cavity via the both uterine tubes above and to the external milieu by the vagina below. The part between and above the tube is known as the fundus. In multiparous women, the uterus measures 9 to 10 cm long and weights approximately 80 gram.

2. Development and Histology.

The corpus or the body of the uterus and cervix develop from paramesonephric ducts on each side that extended caudally to reach the dorsal wall at the urogenital sinus at about nine weeks gestation. As the paramesonephric ducts progress caudally their lower portions come together in the middle and fused, from the fused part the uterus and the cervix develop, and from the still separated upper part of the both paramesonephric ducts the fallopian tubes developed. The muscular walls of the uterus and the cervix form from the proliferation of mesoderm around the lower part of the paramesonephric duct.

The myometrium or the smooth muscle layer of the uterus makes up the bulk of the uterine wall. It has three groups of muscle, an outer circular, the middle oblique and the inner circular muscle.

Endometrium which lines the uterine triangular cavity is a constantly changing tissue due to the effect on it by the ovarian hormones oestrogen and progesterone, most of it is shed at menstruation leaving a layers of 0.5 mm. residual endometrium, which is, called zona basalis. In the first half of the cycle under the influence of oestrogen, the endometrium thickens to 2-3 mm. This is called the proliferative phase, in which later, under the influence of

progesterone hormones it further thicken to average 5-6 mm. in the secretory phase. In this two phases, three layers of endometrium become distinguishable – the zona basalis, which is adjacent to the myometrium, zona spongiosa, the middle portion and zona compacta that is thin and superficial.

During menstruation, ischemia of the middle layer is followed by necrosis and subepithelial haematoma, followed by haemorrhage and shedding of the detached portion of the endometrium, secretion of leukocyte and oedematous fluid. The blood loss varies between 50 ml. to 150 ml.

If pregnancy occurs, menstruation does not take place, instead the endometriums under influence of corpus luteum hormones proliferates and thicken to 10 to 12 mm. This layer is call decidua in pregnancy.

3. The Cervix:

The caudal inferior portion of the uterus protrudes into the vagina and is approximately 2.5-cm. long, 0.5-1 cm. wide and cylindrical in shape, it is called the cervix. The internal Os and its caudal end bound this cylindrical shaped portion of uterus at its cephalic end by the external Os. The internal Os is located at the peritoneal reflection of the bladder. The part of the cervix that protrudes into the vagina is called portovaginalis. The external Os is connected to the internal Os by a slender passage called the endocervical canal.

Histologically the mucosa of cervix consists of tall columnar epithelium and contains many large with highly branched glands. This columnar epithelium ends abruptly at the level of external Os, giving away to the stratified squamous epithelium that covers the portiovaginalis and enters the vagina itself. In multiparous women, the tall columnar epitheliums usually extrude past the external Os into the lower portion of the cervix.

The cervix contains only 10 to 15 percent of smooth muscle compare to the predominantly muscular of the uterine corpus. This muscle layer tends to run circularly around the cervix except at the outer layer, which is longitudinal.

The stroma of the cervix consists predominantly of extracellular connective tissue matrix, which consists of type 1 and type 11 collagen and a small amount of type 1V collagen in the basement membrane (Kao K. Y. T. 1977 and Kleissi H. P. et al, 1978)

Water, glycosamine glycans and proteoglycans are important constituents of the uterine cervix matrix, as well as dermatan sulfate, hyaluronic acid and heparin sulfate (Golichowski A. M. et al. 1980 and Woessner J. F. Junior et al. 1986). Fibronectin, a different kind of protein from the fetal fibronectin is also present in the cervical stroma.

Elastin, the functional protein of the elastic fibre is also found in physiologic amount (Leppert P. C. et al. 1983). The elastin fibres are 2-4 micrometers wide and run between the bundles of collagen fibres. The elastin located in a band that is 20 to 30 micrometers thick and run parallel to a plane from the external Os to the internal Os, under the epithelium and basal membrane. Compare to other tissues the elastin are thinner, and importantly, the ratio of elastin to collagen is highest at the area of the internal Os than the external Os. Thus this mean that the elastin fibres are greater in quantity compare to collagen at the internal Os (Leppert P. C. et al. 1983).

The smooth muscle which consists merely 10 to 15 % of the cervix tissue, its amount is greatest just below the internal Os and its quantity decreases toward the external Os.

In non-pregnant woman, the cervical canal is collapsed, fusiform and firm, with the consistency of nasal cartilage, but in pregnancy, its consistency becomes like the lips of the oral cavity (Huzar G. 1984). During this period the uterine cervix undergoes profound morphologic changes. These changes occur early in pregnancy and well before labour and passage of the fetus begin.

4. Physiology and Biochemical of Cervix

The uterine cervix is a remarkable organ, on one hand the cervix, which is 2.5 cm. long, must remain firm and close throughout the pregnancy to ensure that the fetus is retained until fully developed and therefore able to survive outside the uterus. On the other hand this firm, unyielding portion of the uterus, consisting of primarily extracellular matrix, must dilates sufficiently to allow the fetus to be expelled from the uterus spontaneously at term.

The cervical tissue changes are the result of a complex biochemical process involving many pathways and a rearrangement and realignment of the collagen and elastin fibre (Yu S.Y.et al. 1994). These changes are noted as early as one month after conception, these early changes of cervix comprises of increased water retention and increased vascularity, along with hypertrophy and hyperplasia of the cervical gland, it is these changes that are responsible for the earliest anatomic sign of pregnancy in women.

The water that interacts with proteins matrix, is essential for the function of elastin, although elastin concentration does not appear to change in pregnancy, however, mRNA for tropoelastin (the precursor of elastin) is increased in pregnancy and again after birth (Leppert P.C. et al. 1992).

Type 1 and type 111 collagens undergo marked changes as early as eight to fourteen weeks' gestation, where the space between collagen bundles becomes dilated. The rate of collagen synthesis is increased but of lower rate than the increased of water, the end result is decreased in collagen concentration in cervical matrix. Production and degradation of collagen occur continuously in pregnancy. More importantly is the role of collagen rearrangement in contribution to cervical ripening in which newly formed collagen are poorly cross-linked.

Collagenase (now called matrix metalloprotein-1) helps to maintain a balance between newly synthesized collagen and degraded collagen, while hyaluronic acid weakly interacts with collagen and fibronectin. This will help loosen the collagenous network of cervix (Rath W. et al. 1990).

5. Role of Hormones

Several types of hormones have long been known to influence the matrix and biochemical changes that occur in a pregnant cervix. Both oestrogen and progesterone regulate biochemical modulation of the uterine cervix at pre-translational levels of several proteins.

Oestrogen increases collagen concentration in the skin. Unopposed oestrogen in rats increases the uterine concentration of elastin cross-link and the collagen cross-link. It can also initiate the process of programmed cell death called apoptosis in the cervix. The cervical ripening process and apoptosis are associated with down regulation of oestrogen receptor.

Progesterone softens the cervix by decreasing in collagen and glyco-aminoglycan concentration mediated by apparent decreased in progesterone through the progesterone receptor. Dehydroepianandrosterone sulfate concentration is increased in plasma of women with clinically ripened cervix. A direct effect of dehydroandrosterone sulfate in the production of collagenase and prostromelysin by fibroblast from the pregnant rat uterine cervix was also observed (Leppert et al. 1994)

Relaxin is an ovarian hormone released during pregnancy, it softens the cervix of rodent and decreases the delivery time in rats. In human, there are two types of relaxin genes H1 and H2. H1 is expressed by human ovaries while both H1 and H2 are produced by both decidua and trophoblast cells. Preliminary evidence shows that relaxin features in the apoptosis of the cell, but the exact effect in softening of the cervix is still unknown.

Prostaglandin is known to regulate the uterine extracellular matrix in several ways. Prostaglandin 2-alfa increases the constituent of glycoaminoglycan and the total glycoaminoglycan activity. Prostaglandin E induced cervical ripening is associated with time-limited enzymatic collagen degradation, increases synthesis of non-collagen protein and a substantial increase in the hyaluronic acid concentration.

Increased in hyaluronic acid may induce the production of interleukine-1 of the cytokines, this dilates the cervical small blood vessels and produce chemotactic response on leukocytes. This **theory of the role of inflammatory cellular in the rearrangement of the extracelullar matrix** was proposed more than ten years ago but till today its details has still elude us.

ABORTION.

1. Definition and Epidemiology:

The term abortion is usually used to describe spontaneous demise of first and early second trimester pregnancy of known or unknown aetiology. World Health Organisation has defined abortion as "...the expulsion or extraction of a fetus or embryo weighing 500 gram or less (approximately equivalent to twenty to twenty-two weeks of gestation) or an otherwise product of gestation of any weight and specifically designated (e.g. hydatidiform mole) irrespective of gestational age and whether or not there is evidence of life...". This definition is not in tandem with the United Kingdom, which define abortion as expulsion of a fetus without sign of viability before twenty-four weeks of gestation. Some argue that the definition is in need of review due to the recent improvement in neonatal intensive care, which increased the survivability, and to the level of neonatal intensive care unit of the corresponding countries. This is in view that the survivability of a pre- term infant in developed countries probably will be significantly increased.

Pregnancy begins with the implantation of the conceptus onto endometrium, and the subsequently invasion of trophoblast into the endometrium.

Biochemical evidence of a pregnancy is based on the appearance of the beta-chain of human chorionic gonadotropin in the maternal serum or urine. The pregnancy test is 'positive' when the gonadotropin is synthesied by the syncytiotrophoblast. The test does not prove viability of the pregnancy because the hormone produces by the syncytiotrophoblast may occur even without a fetus or in neoplastic trophoblast disease.

Between 10% to 20% of recognised pregnancy ended up in abortion, mostly some time after fetal death has occurred. It is also estimated that another 10% to 20% biochemical and clinically unrecognised pregnancy ended in the same way with the women only noted it as a delayed and heavy menstruation.

The actual number of loss described varies according to definition or registration of confirmed abortion. Different countries have different definition of viability, thus making it difficult to compare data between countries.

There are also problems regarding definition of gestational age at the time of expulsion of aborted fetuses. In general, this is considered to be the age at the time of expulsion, and not at the time of fetal death. This may be misleading because fetal death usually occur long before fetal demise is noted clinically,

biochemically or by ultrasound. The fullest ascertainment, and therefore the best estimation of incidence for fetal loss, is in self selected groups intending to conceive who are repeatedly screened for sign of pregnancy until pregnancy is established, and are followed until pregnancy termination. Even under ideal circumstances, such a prospective longitudinal study will still miss the earliest pre-implantation losses, where it is only can be attained from in-vitro studies.

Apart from missing unrecognised losses, studies, which depend on the recall of the mother, will be influence by two events, by the stages of gestation at which it occurred and by the background of the mother. Those with a medical background appear to recall more such events than those without such training.

Data from in-vitro fertilization studies support the estimation of 40% to 50% incidence of abortion of clinically and biochemically known pregnancy including unrecognised ones, in which approximately 30% of the losses occur between implantation and fetal stage of pregnancy.

Wilcox et al (1988) estimated that of 100 post-implantation losses, 70 were based only on biochemical diagnosis, and 30 are clinically recognised, and of

those 30, 24 were lost at the pre-fetal stage and 6 reached the fetal stage (some seven weeks gestation). Klein et al (1989) estimated that overall 50% of conception are lost and that once the pregnancy was clinically recognised, about 12% were subsequently lost.

2. Aetiology of Pregnancy Losses:

Factors contributing to early losses are considerable but genetic factors are found to the commonest cause, perhaps up to 50% of the total losses. In simpler words the pregnancy losses can be divided into maternal, environmental and fetal causes.

a. Role of the Conceptus in Pregnancy Failure.

Hertig et al in 1959 reported the result of a 17 years histological study of human fertilised ovum. From their finding it were noted that morphologic abnormalities of the pre-implantation blastocyst and the implanted embryos were frequently seen; half of the blastocyst and a quarter of the implanted embryos were abnormal by light microscope.

They then suggested that the conceptus itself rather than the environment or local cause were responsible for the main cause of abortion.

Evidences now have confirmed that Hertig study of more than fifty years ago was correct, this via the chromosomal studies of the germ cells, using oocyte available through in-vitro fertilisation techniques. These techniques enable it to be estimated at the earliest cleavage stage of fertilised ovum.

Overall, about half of the aborted conceptus were abnormal. Trisomies were the most frequent type of karyotypic abnormalities, with triplody and monosomy X being the next two groups in abnormal occurrence. The kinds of abnormalities detected indicate failure in meiosis, fertilisation and early zygote division. Non-disjunction of the gamete in meiosis may explain the numerical errors of the chromosomes: triploidy and monosomy X. Fertilisation of two sperms may yield triploidy. Tetraploidy and mosaicism may occur because of abnormalities of the early divisions of the fertilise ovum.

Factors associated with chromosomal abnormalities have been identified consistently with, parental age, and gestational age of fertilise conceptuses. Maternal age has long been associated with trisomy 21. Mikado et al (1970) speculated that the ageing ovum was the most important defect leading to abortion. Boue et al (1975) found that parental age correlated closely with for trisomies but not with triplodies, tetraploidies, monosomy X or translocation. These findings may explain the increased incidence of abortions in older women.

The gestational age of the conceptus also correlates with the frequency of abnormal chromosomes. The earlier the spontaneous abortion occurs, the more likely the occurrence of an abnormal karyotype. Two studies have found a peak incidence of chromosomal abnormalities at about 11 weeks gestational age, with the proportion of abnormalities dropping sharply to nearly 0% after 20 weeks of gestation.

The other main abnormalities that are found in aborted conceptuses are abnormal villi and trophoblast development. Histology of the villi have a good correlation with abnormal chromosomes, this is best seen in trophoblastic molar pregnancy. Hydatidiform villous changes are diagnose when villi are swollen and filled with fluid that leads to formation of cistern. Hustin et al (1990) reviewed 184 cases of

spontaneous abortion noted that the trophoblastic shell was hypocellular and discontinuous. There was abnormal contact between the maternal decidua and the cytotrophoblastic X-cells. Khong et al (1987) found the abnormal X-cells migration and a lack of maternal vessel changes in the placental bed of women with recurrent abortion.

b. Maternal and Environmental Cause of Pregnancy Failure.

i. Vascular abnormality in which there is failure or inadequate transformation of maternal spiral arteries in pregnancy may predispose to abortion and hypertensive disease in pregnancy, if it progresses further. In the utero-plancental arteries, its vessels are dilated and lost its availability to invade the maternal spiral arteries.

ii. Organised smooth muscle layers and elastic membrane. Hustin (1990) study earlier demonstrated that the maternal vessels did not show normal physiologic transformation. There was no correlation of the lack of this transformation with chromosomal abnormalities.

iii. In normal pregnancy, the fetal antigen doesn't provoke an untoward response from the maternal immune system. Autoimmune disease such as systemic lupus erythematosus, scleroderma and other connective tissue diseases are associated with abortion. The association between autoantibody and abortion remains unclear because there is no direct correlation between antibody titres and pregnancy loss.

iv. Structural abnormalities of the uterus, both congenital and acquired are found in many women with a history of repeated spontaneous abortion. Uterine abnormalities together with cervical incompetence are seen in 18% of women with recurrent abortion.

v. Endocrine diseases in the mother are associated with increased incidence of pregnancy failure, as can be seen in pregnant women with uncontrolled diabetes mellitus. Anomalies of the fetus are seen 6 to 9% in the aborted tissue, but the rate are similar in normally control diabetic

women. Thyroid and luteal phase deficiencies are also implicated in cases of early pregnancy losses.

vi. Infection, environmental toxic and smoking contribute significantly to miscarriage. Quinn et al (1983) detected U. Urealyticum and Mycoplasma in couple with abortion, and treatment improve pregnancy outcome in those which was infected.

MANAGEMENT OPTION OF MISSED ABORTION.

Missed abortion and anembryonic pregnancy are diagnosed during ultrasonography by the presence of a normal or abnormal gestational sac without fetal pole or by the presence of fetal pole without fetal heart activity. Current technology allows the diagnosis only at 5 to 6 weeks pregnancy at its earliest. Its overall incidence at ultrasonography is 11-15%. (Cashner et al. 1987)

In 1996, 89% of abortion (induced) in England and Wales were performed at less than 13 weeks gestation, while 40% are less than 9 weeks gestation. Out of this, only 1.1% was done because of fetal abnormalities.

Hertig et al (1992) stated in the New England Medical Journal that 'treatment becomes a matter of emptying the uterus as quickly and as safely as possible, justification of this statement is on the ground that the retained product of conception within the uterus may lead to serious infection and haemorrhage. Thus the surgical approached has become the mainstay in the way we managed cases of missed, anembryonic and retained product of conception Alternatively 'Medical' approached has slowly but firmly regained a foothold.

1. Medical Evacuation of Missed Abortion.

The principle of a medical method in evacuating product of conception is not new. Herbal remedies were given for many years before the nineteenth century to encourage the uterus to expel its content. Even today in the third world and even in Malaysia, traditional healers have various crude and scientifically unproven methods in uterine evacuation using herbal plant.

Medical management of abortion basically involves the use of drug either given orally, parenterally or trans-vaginally in inducing the uterus to expel its content completely. The main classes of drugs used are prostaglandin, prostaglandin analogue or anti-progesterone, either alone or in combination.

Mifepristone (RU 486) an orally active progesterone antagonist, which is a derivative of norethisterone, binds with high affinity to progesterone receptors thus blocking the action of endogenous progesterone. This action will cause the pregnancy to fail. An early study has demonstrated that doses of 200 to 600 milligram of mifepristone might induce complete abortion in 60-85% of women depending on gestation age. Further studies found a higher rate of complete abortion, over 95% of complete abortion if

prostaglandin analogue was given 48 hours after mifepristone, in gestation of up to 63 days.

Modern medical methods of uterine evacuation actually developed from the successful work in the field of therapeutic abortion. This method offers several benefits including: improve choice for women who miscarry; avoidance of the risks associated with surgery and anaesthesia; reduction of emergency evacuation, unsupervised operation by trainees and the potential for significant economic savings, in term of beds, staff and operating theatre time.

The main drawbacks of this method are that the drug regime needs further evaluation and refine in order to increase its efficacy and reduce its side effect.

The other thing is that patient who can be offered with this method are those who are educated and have transport or means of getting to hospital fast, thus eliminating most of the patient we have in third world countries or Malaysia.

2. Surgical Evacuation.

The history of abortion has been documented since thousand of years ago. Dilatation and curettage had been use in the Egyptian Middle Kingdom since 4000 years ago. In modern medicine, vacuum aspiration which had been reintroduce by Wu and Wu in China (1958), has been recognised as the method of choice throughout the world.

The surgical method of evacuation involves the insertion of a hollow cannula through the cervix and application of negative pressure suction at the other end, either mechanically or manually, will then removes the product of conception. The other surgical method that can be used is by inserting a sponge forceps and clamping onto the product of conception directly. Both of these procedures may be followed by sharp curettage to remove the remaining products of conception inside the uterine cavity.

In patient whose cervical Os is closed, dilatation of the cervical canal is necessary. This step involve pre-dilatation or ripening of the cervix either with prostaglandin analogue, intra-cervical tent or by mechanical means. This procedure is one of the critical steps in surgical abortion, where most of the complications occur.