Prof.MARC BYGDEMAN

Professor Emeritus of Obstetrics and Gynecology at Karolinska Hospital in Stockholm, Sweden. He served as Department Chairman, Medical Director, as well as Director of the Karolinska Hospital. Professor Bygdeman was awarded a Gold Medal by the King of Sweden for outstanding performance in clinical work, research, and education, particularly in collaboration with the World Health Organization. (Editorial Note)

Introduction

WHEN THE WHO SYSTEM OF COLLABORATING CENTRES FOR RESEARCH IN HUMAN REPRODUCTION WAS INITIATED IN 1972 BOTH DEPARTMENT OF OBSTETRICS AND GYNECOLOGY IN SZEGED AND STOCKHOLM WERE PART OF THE NETWORK. DURING THE FOLLOWING YEARS BOTH CENTRES HAD A CLOSE AND VERY SUCCESSFUL COLLABORATION IN THE DEVELOPMENT OF ABORTION METHODS. DURING THESE YEARS PROFESSOR, DR, JANOS HERCZEG BECAME A DEAR COLLEAGUE AND FRIEND TO US AT THE KAROLINSKA HOSPITAL IN STOCKHOLM. WHEN INVITED TO CONTRIBUTE TO AN EBOOK ON THE OCCASION OF HIS 70TH BIRTHDAY I FELT IT SUITABLE TO WRITE AN HISTORICAL REVIEW OF THE DEVELOPMENT OF ABORTION METHODS. THE ARTICLE WILL INCLUDE BOTH SURGICAL AND MEDICAL METHODS BUT WITH AN EMPHASIS ON MEDICAL ONES SINCE SUCH METHODS HAVE BEEN THE FOCUS OF OUR COLLABORATION.

Termination of pregnancy.
A historical review

First trimester abortion

During the first half of the twentieth century Dilatation and Curettage (D&C) was the dominating procedure for termination of first trimester pregnancy. In the middle of 1950 Vaccumaspiration was introduced as an alternative first in eastern Europe. To-day both electric (EVA) and manual (MVA) vacuum aspiration are available and replaced D&C because of the significantly higher complication rate with the latter procedure. In USA 1970 the distribution of procedures performed by sharp curettage and vacuum aspiration was similar; 54% were by suction and 46% by sharp curettage. Over the next few years the percentage of suction curettage procedures gradually increased and by 1976 accounted for 96% of all curettage procedures used at 12 weeks´gestation or earlier.

Vacuumaspiration procedure.
During the first weeks after the last menstruation (LMP) the suction canula may be inserted without prior dilatation through the canal. However as the duration of pregnancy advances, an incremental dilatation of the cervical canal to a diameter in mm that approximates the gestational age in weeks is needed. The uterine content is then aspirated with a corresponding size cannula. Detection of a "gritty" sensation as the cannula moves across the endometrial surface suggest completion of the abortion. A large number of studies have documented the effectiveness of vacuum aspiration in completely evacuation the content of the uterus; most reports an effectiveness rate exceeding 98%.

Complications
The major complications of vacuum aspiration during first trimester pregnancy include excess bleeding, pelvic infection, cervical injury and uterine perforation.

Table 1. Major complications associated with vacuum aspiration during first trimester. (Ref. 1)

Excess bleeding (%)	0.05-4.9
Pelvic infection (%)	0.1-2.2
Cervical injury (%)	0.01-1.6
Uterine perforation (%)	0.01-1.6

Both local anestesia in the form of paracervical block (PCB) and general anaesthesia are used for vacuum aspiration with a low frequency of complications. However, general anaesthesia has been associated with an increased frequency of complications such as bleeding, cervical injury and uterine perforation.

There are strong evidence that the risk of complications increases with increasing gestational age with the exception for continuing pregnancy and incomplete abortion. A 30% increased risk for complications during pregnancy week 9-12 compared with before 9 weeks gestation has been reported. The risk for incomplete abortion is 3 times higher for a surgical abortion performed before the 7^{th} week compared with 7-12 weeks (14).

An examination of the fresh aspirate is an effective method to secure that the abortion is complete. An alternative method is an ultrasound examination of the uterus postoperatively.

Table 2. Major complication rate following vacuum aspiration in relation to gestational age. (Ref. 1).

Gestational age(weeks)	Major complication rate Per 100 vacuum aspirations
≤ 6	0.6
7-8	0.3
9-10	0.3
11-12	0.5

Some studies but not all indicate that operation complications is related to the experience of the operater. In Ljubliana operaters performing between 100 and 300 abortions over a 2-year study interval had lower complication rates than those who performed fewer than 100 or more than 300 procedures.

The presence of C. Trachomatis, N. gonorrhea and bacterial vaginosis at the time of the abortion is associated with an increased postoperative infection rate. Prophylactic treatment with antibiotics reduced the postoperative infection rate by 50%. A comparable outcome could be obtained by a screening program. However, this alternative was more expensive but will on the other hand reduce the risk for development of resistant bacteria.

To perform vacuum aspiration except for very early pregnancy it is necessary to dilate the cervical canal. Earlier different forms of dilaters such as laminaria tents introduced into the cervical canal several hours prior to surgery were used. In a large multicentre study it was shown that vaginal pretreatment with a prostaglandin $F_{2\alpha}$ which softens the cervix and dilates the cervical canal significantly reduced the complication rate.

More recent studies indicate that vaginal administration of 400µg of the prostaglandin analogue misoprostol 3 hours prior to surgery is the optimal regimen with regard to cost, side effects and cost.

Medical methods.

Prostaglandin

Prostaglandins are naturally occurring fatty acids that are produced by many tissues in the human body. Primary prostaglandins such as PGE_2 and $PGF_{2\alpha}$ stimulate uterine contractility at any stage of pregnancy. An increased production of these prostaglandins is believed to be the final step in the complicated series of events resulting in an increased uterine activity during spontaneous abortion and labour at term.

Synthetic analogues of the natural prostaglandins have been developed which are more resistant to metabolism and hence have a prolonged duration of action. The prostaglandins mainly used for medical abortion are gemeprost and misoprostol which are PGE_1 analogues. Gemeprost is available in vaginal suppositories containing 1 mg of the drug and misoprostol in tablet form containing 0.2 mg of the drug. Misoprostol is more convenient since it is stable at room temperature is on the market in a large number of countries and is also considerably cheaper. Although misoprostol is meant for oral use, vaginal administration is often more effective in stimulating uterine contractility. Both pharmacokinetic results and the effect on uterine contractility indicate that vaginal administration could have advantages both with regard to abortifacient efficacy and treatment intervals. The interval from start of treatment to a noticeable effect is significantly shorter following oral administration bur more importantly the duration of stimulation is significantly longer following vaginal treatment.

Prostaglandin analogues can be used alone for termination of early pregnancy. Repeated vaginal administration of gemeprost (1 mg every 3 hours up to five times) has been shown equally effective as vacuum aspiration. However pain due to uterine contractility, gastrointestinal side effects and longer duration of bleeding are more common. Misoprostol, 0.8 mg administered vaginally up to three times with a 24 hour interval resulted in a cumulative abortion rate was 65, 83 and 90% after one, two and three doses of misoprostol, respectively.

Mifepriston in combination with prostaglandin.

Mifepriston is a derivative of norethisterone which binds to the progesterone receptor with an affinity five times as great as that of progesterone and prevents endogenous progesterone from exerting its effect.

Treatment with mifepristone will convert the quiet pregnant uterus into an organ of spontaneous activity with regular uterine contractions. The increased contractility of the uterus can be demonstrated after 24 hours and is fully developed 36 to 48 hours. Treatment with mifepristone will also increase the sensitivity to prostaglandin which is demonstrable after the same time interval.

Following the first report of Herrmann et al.. a number of studies were performed to evaluate the possibility of using mifepristone alone for termination of early pregnancy. However, the outcome of these studies was disappointing. Although different doses and different dose intervals were evaluated, the complete abortion rate was generally less than 70%.

Of great importance for the development of an effective, safe and acceptable medical method for termination of early pregnancy was our finding that a combination of mifepristone and a prostaglandin analogue was a possible solution. The increased sensitivity of the myometrium to prostaglandin following pretreatment with mifepristone meant that the prostaglandin dose could be reduced approximately five times.

Initially the dose of mifepriston was 600 mg. However, studies have shown that the pharmacokinetics of mifepristone are non-linear and after a single doses higher than 100 mg, the serum concentration will increase only slightly or not at all. The prostaglandin used are mainly vaginal gemeprost 1 mg or misoprostol orally 0.4-0.6 mg or vaginally 0.8 mg. The initial most used treatment was mifepristone 600 mg and 36 to 48 hours later vaginal gemeprost 1.0 mg. Gemeprost has during the years more and more been replaced by misoprostol and the dose of mifepriston been reduced from 600 to 200 mg. If the gestational age is limited to 49 days after the last menstrual period oral treatment with misoprostol is an alternative. If the treatment period is extended to 63 days after LMP the preferred dose is 0.8 mg vaginally.

In a report on 2000 consecutive women treated up to 63 days after LMP with mifepristone 200 mg followed 36-48 hours later by vaginal misoprostol 0.8 mg, the frequency of complete abortion was 97.5%. Surgical intervention was required in 49 women (2.5%); for incomplete abortion 1.4%, for missed abortion 0.4% and for continuing pregnancy 0.6%.

Table 3. Outcome of medical abortion up to 63 days of pregnancy.

Treatment	No. of pts	Pregn. (d)	Complete abort. (%)	Blood transf(%)	Emerg curettage (%)	Ref..
Mifepristone 600mg+ Gemeprost 1mg	588	<63	94	1.0	1.0	2
Mifepristone 200mg+ Misopr. 0.8mg vaginal	2000	<63	97.5	0.15	0.35	3
Mifepristone 200mg Misopr. 0.4mg oral	294	<56	95.6	0.34	<2	4

Comparison between surgical and medical abortion.

There are a number of factors that need to be taken into account when comparing different methods for termination of early pregnancy. These include efficacy, complication rates, adverse effects and the presence of contra-indications and also convenience and acceptability for the women and the cost of the procedure..

The frequency of complete abortion following vacuum aspiration in first trimester generally ranges from 96 to 99% which is comparable to or slightly higher than the efficacy reported for the medical method in large multicentre studies, between 94 and 95.5%. Both in the few randomised studies performed and in comparative studies the conclusion is the same, the surgical procedure is either more effective or equally effective as the medical procedure.

There is a general consensus that the duration of bleeding is longer and the amount of blood loss higher after medical abortion than vacuum aspiration. In a randomised study, the mean duration

of bleeding was 12,7 to 13.1 days after medical abortion compared with 10.2 days for vacuum aspiration. However, the experience from multicentre studies is that the frequency of serious haemorrhage and the need for blood transfusion is similar to those reported for vacuum aspiration.

The frequency of infection is difficult to compare since the definition is not very precise and varies considerably. In a randomised study the frequency of presumed infection requiring antibacterials during the first weeks was the same following medical and surgical abortion. However, at the follow-up visit within 8 weeks the infection rate was higher following the surgical procedure.

Adverse effects, specially vomiting and diarrhoea are more common after medical than surgical abortion and occur mainly during the first hours after prostaglandin administration. Vaginal administration of misoprostol seems to be associated with a lower rate of vomiting and diarrhoea than oral treatment of the same dose (0.8 mg); it is probably also lower than after gemeprost as indicated by randomised studies.

It is difficult to compare pain . Obviously most patients undergoing vacuum aspiration will need some form of analgesia at operation, while thereafter the need is much less. For medical abortion the pain is related to the uterine activity mainly following prostaglandin treatment until expulsion of the conceptus and approximately some 60% of the patients would need either parental or oral analgesia.

If the woman could choose, which method to be used a majority seems to prefer the medical one.

Vacuumaspiration is the method mostly used during the last weeks of the first trimester. Pilot studies have, however, showed that medical abortion could be an effective alternative but in that case repeated doses of misoprostol after pretreatment with mifepristone.

Second trimester abortion.

In the first half of the 20th century only surgical abortion methods such as hysterotomi and dilatation and curettage (D&C) were available. The situation changed in the middle of the century when medical methods started to be introduced. Among these were hypertonic saline, urea and ethacridine lactate (Rivanol) followed

1971 by primary prostaglandins. These compounds, administered into the uterus, stimulate uterine contractility, resulting in expulsion of the fetus and placenta. The development of prostaglandin analogues. such as gemeprost and misoprostol, which could be administered by non-invasive routes was an important step forward in the development of effective and safe medical methods also during the second trimester. A further improvement was the introduction of mifepristone in combination with a prostaglandin analogue. To-day mifepristone followed by repeated vaginal administration of misoprostol is the preferred method for medical method for termination of second trimester pregnancy according to WHO Also the surgical procedures have changed. Hysterotomy and D&C has been replaced by Dilatation and Evacuation (D&E).

Surgical procedures.

The traditionally used surgical procedure for terminating 2nd trimester pregnancy was hysterotomy, a surgical procedure akin to caesarean section. Since a number of studies, mainly in the USA in the 1970s and 1980s, showed that of all abortion methods available at that time, hysterotomy was associated with the highest mortality rate, it is no longer recommended and should no longer be used.

The WHO-recommended surgical procedure today is D&E. Normally this operation is performed with local anaesthesia and sedation. It involves preoperative dilatation of the cervical canal by e.g. laminaria tent or misoprostol, evacuation of the amniotic fluid with vacuumaspiration and extraction of the fetus and placenta using forceps.

Medically induced abortion

Invasive routes of administration.

When non-surgical methods started to be introduced in the late 1960s the drugs were administrated either intra- or extra-amniotically. Intra-amniotic administration was mainly used from gestational week 15 and onwards when the amniotic cavity is easier to puncture. Several compounds were evaluated historically such as urea, hypertonic saline, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and 15.methyl $PGF_{2\alpha}$ (carboprost). After local anaesthesia a spindle needle was inserted through the abdominal wall into the amniotic sac. To be

sure that the needle was in the right place, a free flow of amniotic fluid was established before instillation of the drug.

With saline 200 ml of a 20% solution was used. The instillation-to-abortion time was long. About 80% of patients expelled the fetus within 48 hours and almost all patients within 72 hours. Complications included hypernatremia, blood coagulation disorders, haemorrhage, infection and cervical damage.

With $PGF_{2\alpha}$ both single- and multiple-dose schedules were found effective in inducing abortion. Doses ranged from 25 mg repeated after 6, 24 and 30 hours if necessary or 40 mg followed by 10-40 mg after 24 hours or a single dose of 50 mg. A major advantage of $PGF_{2\alpha}$ was a shorter induction-to-abortion interval than with saline. The reason for the more rapid abortion is that the compound has a direct stimulatory effect on the myometrium while the effect of saline is probably secondary to an increased release of endogenous prostaglandin. Gastrointestinal side effects such as vomiting and diarrhoea were common. Other complications reported include haemorrhage, infection, bronchospasm, hypotension, bradycardia and cervical damage.

Primary prostaglandins are rapidly metabolised. In order to be more practical for clinical use, a number of analogues have been developed. The first was carboprost. Following intra-amniotic administration of carboprost the half-life of the compound was 31-37 hours which is approximately twice that of $PGF_{2\alpha.}$. With carboprost a single dose of 2.5 mg was used. In a large multicentre, multinational study it was shown that carboprost was more effective to induce abortion within 48 hours than a single dose of $PGF_{2\alpha}$ 40 or 50 mg, but the mean induction-to-abortion interval was 18-20 hours for all three treatments.

Which method saline or prostaglandin is safer has been a matter of discussion. From a theoretical point of view prostaglandin would be expected to be safer, since cardiovascular effects appear to be fewer, clotting factors do not change significantly, tissue damage following inappropriate administration appears to be less and the compounds are rapidly metabolised if accidentally injected into the bloodstream. In studies from USA the mortality following $PGF_{2\alpha}$ was found to be lower than for saline ands (2.8 and 4.3 per 100.000 abortions respectively).

Extra-amniotic administration means administration of drugs between the fetal membranes and the uterine wall. A major advantage of the method is that it could be used also during early 2nd trimester when intra-amniotic administration is not suitable.
Compounds mainly used included PGE_2 , $PGF_{2\alpha}$ and Rivanol. PGE_2 and $PGF_{2\alpha}$ was given by repeated instillations with an initial test of 50µg PGE_2 or 250µg $PGF_{2\alpha}$ followed by 200µg and 750µg respectively every 2nd hour for up to 36 hours. A schedule like this would be expected to have a success rate of 80-90% within 24 hours and over 90% within 36 hours. Side effects included occasional episodes of vomiting and diarrhoea. Because of the low doses of prostaglandins used serious side effects were not expected.

Rivanol is a yellow dye with antiseptic properties and a weak oxytocic effect in experimental animals. At least in part the abortifaccient effect is related to an increased endogenous prostaglandin production. With this treatment a 0.1% solution of Rivanol was instilled, 10 ml per week of pregnancy up to a maximum of 150ml through a catheter inserted 4-5 cm past the internal os , tied off and left in place until abortion occurred. The mean induction-to-abortion interval was about 24 hours and 90% of the women aborted within 72 hours. A common side effect was temperature elevation while vomiting and diarrhoea were uncommon. More serious side effects were very uncommon. A major advantage with Rivanol is that a single administration is sufficient. On the other hand addition of an oxytocin infusion is necessary to get the same induction-to-abortion interval as for prostaglandins.

Non-invasive routes

During the years there was always a wish to develop abortion methods based on non-invasive routes of administration in order to avoid serious complications due to inadvertent administration and because the simplicity of the treatment would allow e.g. trained midwives or nurses to be responsible for the management of the patient.

Intramuscular administration

The compounds which have been used for this route of administration is sulprostone (a PGE_2 analogue) and carboprost.
The most successful therapies has been a laminaria tent administered 12 hours before intramuscular administration of either carboprost (0.25mg every second hour) and sulprostone (0.5 mg

every fourth hour). Both treatment were equally effective in terminating 2nd trimester. 98,3% had aborted within 24 hours of prostaglandin therapy. The mean interval between the first injection and abortion was the same in the two treatment groups, approximately 10 hours. However, gastro-intestinal side effects were significantly more common following carboprost.

Today sulprostone for intramuscular administration has been withdrawn from the market since myocardial infarctions attributed to coronary spasm induced by sulprostone has occurred. Due the relatively high frequency of gastro-intestinal side effects carboprost is of limited value when given by intramuscular injections but can be useful as a supplement when other methods have failed to complete the abortion process.

Vaginal administration

Both the PGE_1 analogues misoprostol and gemeprost are administered by the vaginal route. Misoprostol is also given orally but the efficacy by this route is less.

The recommended dose of gemeprost is 1 mg administered every 3 hour up to five times in the first 24 hours and to be repeated if necessary. Addition of a oxytocin infusion was recommended 36 hours from the onset of the trial. With such a regimen 80% aborted within 24 hours and 95% within 48 hours. The median induction-abortion interval was 16.9 hours. Twenty-six per cent of the women had diarrhoea and 23% vomiting following administration of gemeprost. The incidence off pelvic sepsis (0.1%), cervical tears (0.1%) bleeding more than 500 ml (1.6%) and blood transfusion (0.6%) was low. It has been well established that gemeprost is more efficacious than intra- or extra-amniotic administration of primary prostaglandins.

Vaginal administration of misoprostol is significantly more effective than oral misoprostol. Vaginal administration of misoprostol seems at least equally effective as gemeprost. In a prospective randomised study 1 mg gemeprost every 3hour for a maximum of 5 doses was compared with 400µg misoprostol also given every 3 hour for a maximum of 5 doses. The percentage of women who achieved abortion within 24 hours was significantly higher for misoprostol and the mean induction-to-abortion interval shorter. If the treatment was repeated all women aborted.

There were no significant differences in side effects except for diarrhoea which was more common following gemeprost and fever which was more common following misoprostol.

Medical abortion. Selected studies

Treatment	Abortion rate (%) 24 hours	48hours	Induction-abortion interval hours	Curretage rate (%)	Ref
600mg Mifepriston	94		6.8		
Placebo	80		15.8		5
1mg gemeprost 5 times to both groups					
200mg Mifepriston 1mg gemeprost every 6 hours 4times	96.4	98.8	7.8	11.5	6
200mg Mifepriston 0.8mg misoprostol Vaginally followed by 0.4mg orally every 3hours Four times	97.1	99.2	6.25	8.1	7

Pretreatment with mifepriston prior to vaginal administration of either vaginal misoprostol or gemeprost will increase the abortion rate within 24 hours to over 95% and reduce the median induction-to-abortion time from around 16 hours to around 6 hours.

Women often prefer oral in comparison to vaginal administration and therefore, to improve acceptability. A regimen using a combination of an initial high dose administered vaginally followed by repeated oral doses of misoprostol was developed, which involved pretreatment with mifepriston followed by 600µg of vaginal misoprostol as the first dose followed by 400µg of oral misoprostol for every 3hour. The abortion rate (97%) and the induction-to-abortion interval (6.5 hours) were the same as using similar doses of repeated vaginal misoprostol.

Gemeprost was considered the standard PG analogue in medical abortion until misoprostol emerged and was made available. Although shown to be highly effective gemeprost has today been replaced by misoprostol since gemeprost is only available as vaginal pessaries, more costly, need to be refrigerated and not available in many countries

Comparison of surgical and medical methods for termination oof 2nd trimester pregnancy.

There are no agreement which method to be preferred D&E or non-invasive administration of prostaglandin analogues especially if combined with with mifepristone. Sufficient large randomised studies comparing the tw procedures are lacking. Both methods are highly effective and safe. The abortion process following a medical method in the second trimester is very similar to delivery, and therefore both midwives and doctors are familiar with the process and its complications. D&E at least after the 15th week needs a skilled doctor and a centralized abortion service to obtain the workload to keep the experience of the doctor. Local conditions might be the most important factor in the choice of method.

Summary

The development of abortion methods during the last 50 years have been impressive. Of great importance has been the work performed under the guidance of the WHO Prostaglandin Task Force and the task Force on Postovularory Methods for Fertility Regulation. We have today effective and safe medical methods as an alternative to surgical procedures and useful for both first and second trimester abortion. The medical methods can be managed by skill midwives or nurses of great importance for the availability of abortion services in many countries.

References

1. Cates W, Schultz KF, GrimesDA, Tayler CW. Short term complications of uterine evacuation techniques for abortion at 12 weeks gestation or earlier. In Pregnancy Termination (Eds G. Zatuchni, J. Sciarra, J. Speidel) Harper &Row Publisher, Harperstown 1979. 127-135.
2. UK Multicentre trial. The efficacy and tolerance of mifepristone and prostaglandin in first trimester termination of pregnancy. Br J Obstet Gynaecol 1990; 97:480-6.
3. Ashok PW, Penny GC, Flett GMM et al. An effective regimen for early medical abortion: a report of 2000 consecutive cases. Hum Reprod 1998; 13:2962-5
4. McKinley C, JooThong K, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. Hum Reprod 1993; 8:1502-5
5. Rodger MW, Baird DT. Pretreatment with mifepristone (RU 486) reduces interval between prostaglandin administration and expulsion in second trimester abortion Br J Obstet Gynaecol 1990; 97:41-5
6. Tang OS, Thong KJ, Baird DT,Second trimester medical abortion with mifepristone and gemeprost; a review of 956 cases. Contraception 2001; 64:29-32.
7. Ashok PW, Templeton A, Wagaaarachchi PT. Midtrimester medical termination of pregnancy; a review of 1002 consecutive cases. Contraception 2004; 69:51-58.

<u>Further references could be found:</u>

Bygdeman M, Gemzell K. Options for early therapeutic abortion. Drugs 2002; 62:2459-70

Lalitkumar S, Bygdeman M, Gemzell-Danielsson K. Mid-trimester abortion: a review. Hum Reprod Update 2007; 13:37-52.

Bygdeman M, Gemzell-Danielsson K. Reproductive Health Matters. 2008; 16(31 Supplement) 196-2004.