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PREGNANCY TERMINATION

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Pregnancy Termination In Midtrimester —Review of Major Methods—

SUMMARY

Termination of midtrimester pregnancy—abortion between 13 and 26 weeks' gestation*—no longer requires high risk surgical procedures. Today there are relatively safe and effective alternatives—minor surgical procedures and the administration of abortifacients, such as saline, prostaglandins, and urea.

To date there is no simple procedure for terminating midtrimester pregnancy. All available methods require the services of experienced physicians and medical staff. Research is under way, however, with prostaglandin analogues that may lead to development of a simpler procedure.

Most physicians define effectiveness in terms of the time interval between initiation of the procedures and fetal expulsion. Criteria vary, but procedures are generally considered to be failures if abortion does not occur within 48-72 hours. Some practitioners also consider the percentage of complete abortions (expulsion of all products of conception, including the placenta) when judging the effectiveness of a particular method.

Incidence

The proportion of total abortions that are performed during the midtrimester is declining in all countries for which data are available. Ideally, the earlier a termination occurs the better. Procedures performed during the first weeks of pregnancy are less complex and safer than those performed later. Also, they can often be completed on an outpatient basis. Midtrimester abortion morbidity rates are likely to be three to four times greater than those associated with first trimester pregnancy terminations (see Fig. 1). Similarly, the mortality rate is significantly higher during the midtrimester. In the United States during 1972-74, the mortality rate ranged from 0.4 per 100,000 legal abortions at 8 weeks or less to 18 per 100,000 for abortions at 16 weeks or more (see Fig. 2) (151).

*Gestational age is calculated by adding the number of completed weeks from the first day of the last normal menstrual period, rather than days or weeks from the time of presumed ovulation or conception (47).

This report on methods of midtrimester pregnancy termination was prepared by Susan L. Chaudry, William Burr Hunt II, and Judith Wortman, with the assistance of Brenda J. Vumbaco and Margot Zimmerman, on the basis of published reports and articles, unpublished papers, personal interviews, and correspondence.

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Frances G. Conn is Executive Editor. Comments and additional updated material are welcome.

Nevertheless, the need for midtrimester termination exists and, for many reasons, is likely to continue. Women may delay seeking abortion due to:

- lack of information on the availability of abortion;
- ignorance or psychological denial of pregnancy, especially by young women, until signs and symptoms become obvious;
- ambivalence regarding the desirability of abortion;
- late identification of medical disorders contraindicating pregnancy;
- discovery of fetal abnormalities (most often detected by amniocentesis performed after the 16th week of gestation).

Physician and hospital resistance to performing abortions and administrative delays in processing applications and securing approvals may further limit the possibility of obtaining early termination of pregnancy.

The actual worldwide incidence of midtrimester abortion is not known because gestational age is not uniformly defined and reported. Also, data collected in many countries do not include gestational age at the time of termina-

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tion. Nevertheless, available statistics indicate that the proportion of total abortions performed at 13 weeks' gestation or more is high in England and Wales (18.1 percent of all abortions in 1973); the USA (15.0 percent in 1974, 17.1 in 1973); and Sweden (13.3 percent in 1974, 19.7 in 1973) (148, 151). The percentage of midtrimester abortions was lower in Japan (3.2 percent of the total in 1974) and Denmark (2.7 percent in 1974), and also low in countries such as Czechoslovakia and Hungary which permit midtrimester abortion for medical reasons only (148).

Methods

Brenner classifies midtrimester abortion methods into four categories:

- surgical evacuation (for example, hysterotomy, hysterectomy, dilatation and curettage, vacuum aspiration);
- intrauterine injection of solutions (for example, hypertonic saline, prostaglandins, urea, glucose, Rivanol®*);
- intrauterine insertion of devices (for example, bougie, metreurynter);
- extrauterine (oral, intravenous, intramuscular, intravaginal) administration of drugs (for example, oxytocin, prostaglandins) (23).

A single method may be used, or several in combination. The administration of oxytoxic drugs (substances that stimulate myometrial contractions) and/or the insertion into the cervix of laminaria tents (sterile dried marine plant stems) may be used to augment the effects of the primary abortifacients. Some physicians administer oxytocin at the time of the main procedure, while others use it several hours later to help promote uterine contractility and reduce blood loss. Laminaria have been used prior to or at the same time as other methods. When inserted into the cervix, the stems attract body fluids, expand in the presence of moisture, and gradually dilate the cervix (see Fig. 3) (148).

Surgical Evacuation

Few countries permitted midtrimester abortion except for medical indications, until the liberalization of abortion laws in recent years. The few legal abortions performed were almost always major surgical procedures—hysterotomy (cesarean section before the fetus is viable) or hysterectomy (removal of the uterus). These procedures are associated with high morbidity and mortality rates and are not generally used for routine pregnancy termination.

Today such surgery is limited to cases requiring correction of gynecologic pathology, such as ovarian cysts, and occasionally when another method has failed. In 1974, hysterotomy was the method chosen for only 2.1 percent of midtrimester abortions reported in the USA, and hysterectomy for 1.3 percent (151). Although many hysterotomies are still performed in England and Wales, the number has declined sharply from 47.8 percent of all midtrimester abortions in 1968 to 8.9 percent in 1973 (148). In these countries hysterotomy is sometimes done when the woman wants to combine abortion with sterilization. Today, however, there are other alternatives for those who want to combine abortion and sterilization. Procedures such as laparoscopy, minilaparotomy, and the modified Pomeroy technique allow sterilization in conjunction with or soon after abortion, and do not require the large abdominal incision necessary for hysterotomy.

Many procedures used during the first trimester are also used for midtrimester abortions. Surgical evacuation—dilatation, evacuation, and curettage—and vacuum aspiration of the uterus are widely used for first and second trimester abortions in Eastern Europe, the USSR, and the People's Republic of China. In Britain, as the incidence of hysterotomy declines, evacuation procedures have also gained popularity (148). During 1974 in the USA, curettage was used to perform one-third of all midtrimester abortions (151).

Uterine evacuation and curettage procedures can be performed early in the second trimester, when intra-amniotic injection of solutions is difficult because of the small size of the uterus and its location in the pelvic cavity. However, they require considerable skill and experience. Most physicians do not use evacuation and curettage procedures for abortions beyond 15 weeks' gestation. In the USA (1974), curettage procedures were used in 63.8 percent of abortions of 13-15 weeks' gestation, but in only 11.0 percent of those of 16-20 weeks' gestation (151).

Instillation of Solutions

Instillation (slow injection) of solutions, such as saline, prostaglandins, and urea, into the amniotic sac or the extraovular space (see Fig. 4) is the most widely used of all

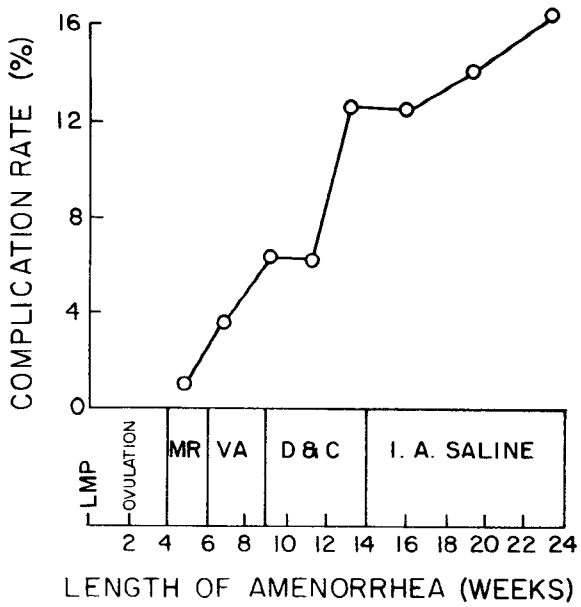

Fig. 1. Complication rates by length of amenorrhea, for selected abortion methods (MR = menstrual regulation, VA = vacuum aspiration, D&C = dilatation and curettage, I.A. SALINE = intraamniotic saline).

COURTESY: Dr. William E. Brenner, University of North Carolina School of Medicine, Chapel Hill, NC, USA.

*Rivanol® manufactured by Winthrop Laboratories, NY, NY.

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midtrimester abortion methods. Of the solutions, hypertonic saline is most commonly used. In 1974, hypertonic saline was used for 53.1 percent of all midtrimester abortions reported in the USA and for 70.3 percent of all abortions of 16 weeks' or more gestation (151). The extraovular administration of saline is used extensively in Scandinavia.

In addition to saline, a variety of substances and solutions have been used to induce midtrimester abortion by intrauterine instillation, including:

- glucose
- utus paste
- Rivanol
- prostaglandins
- urea.

Intraamniotic instillation of glucose was found to be associated with a high risk of infection and other complications, and with a prolonged instillation to abortion time (32, 34, 44, 57, 93). Utus paste (a semi-solid soap mixed with potassium iodide and astringents) instilled into the extraovular space was tried many years ago. It is seldom used today due to high rates of failure and infection (32, 34, 57, 144). Extraovular instillation of Rivanol (a yellow dye derivative of acridine) has been reported from several countries, but it appears to be less effective than other available abortifacients (23, 32, 65, 69). Only prostaglandins and urea appear to be safe and effective alternatives to hypertonic saline.

Intraamniotic instillation of the natural prostaglandin $F_2\alpha$ has gained popularity in recent years. In the USA (1974), where $PGF_2\alpha$ is the only prostaglandin approved for use by the US Food and Drug Administration (USFDA), 3.5 percent of midtrimester abortions were performed by intraamniotic instillation of $PGF_2\alpha$ (151). The instillation to abortion time is generally shorter and the incidence of serious complications appears to be lower than with saline. Side effects such as diarrhea and vomiting are common, however, and further experience with $PGF_2\alpha$ in a variety of clinical settings is necessary.

Other prostaglandins, such as natural PGE_2 and the $PGF_2\alpha$ and PGE_2 analogues, appear promising and are receiving worldwide attention. Alternate techniques of administration, including intramuscular injection and intravaginal suppositories, are being explored to develop less complicated, safer procedures which might be suitable for nonhospital use. (For additional information, see **Population Reports**, G-7, "Clinical Use of Prostaglandins For Pregnancy Termination," September 1976.)

Research with intraamniotic instillation of urea indicates that it may be an acceptable alternative to saline or prostaglandin administration with a lower incidence of side effects and major complications. Because it is less effective than saline or prostaglandin, however, it requires augmentation with oxytocin, laminaria, or other abortifacients such as $PGF_2\alpha$.

Insertion of Devices

Another method of midtrimester termination involves insertion of inert devices such as the metreurynter (a rubber bag) or bougie (a slender, cylindrical instrument) into the extraovular space. These devices are used primarily in Japan. They cause uterine irritation or inflammation which results in uterine contractions and fetal expulsion. There are three major disadvantages:

- Insertion to abortion time is often prolonged, thus increasing the risk of morbidity due to infection.
- Hospitalization and continuous medical care are required during the prolonged period of confinement.
- There is a high incidence of live births associated with these methods (23, 32, 101, 102).

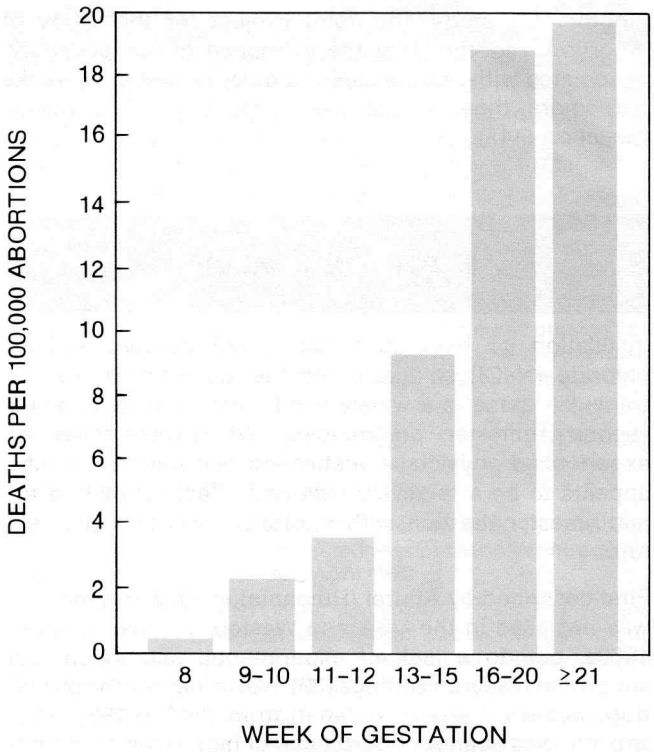

Fig. 2. Mortality related to legal abortion, by week of gestation, USA, 1972-1974.
SOURCE: US Center for Disease Control (151).

SURGICAL PROCEDURES

Today, the performance of major procedures such as hysterotomy or hysterectomy for second trimester pregnancy termination is decreasing worldwide (32, 146, 148). They are now used primarily to correct gynecologic disorders such as ovarian cysts or uterine fibroids, or as alternatives when other methods fail (112).

Although major surgery is no longer acceptable for routine termination of midtrimester pregnancy, minor procedures continue to be used, especially during the 13-15 week gestational period. For example, dilatation of the cervix and evacuation of the uterine contents either by curette (D&C) or vacuum aspiration are two commonly used minor surgical procedures. However, they become increasingly risky and more difficult to perform as pregnancy advances. These two procedures have a greater complication rate in the midtrimester than if performed during earlier stages of pregnancy.

Brenner and Edelman reported that there is a high risk of uterine injury, incomplete abortion, infection, and hemorrhage when evacuation procedures are performed during the midtrimester, especially after 16 weeks' gestation (26).

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Another US study, the Joint Project for the Study of Abortion, reported that the incidence of complications associated with uterine aspiration performed at 15 weeks was more than double the incidence at 7-8 weeks' gestation (147).

HYPERTONIC SALINE

Instillation of hypertonic saline (20 percent sodium chloride [NaCl] solution) into the amniotic sac or extraovular space is a widely used method of terminating second trimester pregnancies. When performed by experienced physicians, instillation of hypertonic saline appears to be a relatively safe and effective method for midtrimester abortion, with reports of live births extremely rare.

First described by Aburel (Rumania) in 1939, this method was not used in the USA and Western Europe until the 1960s, due to a lack of experimental and theoretical support in research settings (39). Nevertheless, the procedure was used widely in Japan from 1946 to 1952, after which it was abandoned because of high rates of complications and mortality. According to Wagatsuma, these high rates may have resulted from procedures performed by inexperienced practitioners in ill-equipped facilities on patients who were not screened for preexisting medical disorders (155).

Saline instillation was reexamined in the 1960s by Csapo and associates in the USA and established as an effective and relatively safe alternative to surgical termination procedures (79). In the USA, the saline method is most commonly performed by transabdominal instillation of the solution directly into the amniotic sac. Instillation may also be made transcervically into the amniotic sac or the extraovular space. Investigators have reported that transcervical intraamniotic and extraovular instillations are useful early in the midtrimester when transabdominal instillation into the amniotic sac is technically difficult, or when patients cannot tolerate a transabdominal procedure due, for example, to previous abdominal surgery.

The exact mechanism of action by which saline induces abortion is not fully understood. Its major effect appears to be an increase in the uterine production and release of prostaglandins which causes uterine contractions and expulsion of the fetus (60, 61, 122). Other physiologic changes described include:

- Suppression of placental progesterone synthesis, thus suspending the block to uterine activity (13, 70, 79).
- Acute salt poisoning of the products of conception (hypertonicity and dehydration of the fetal-placental unit) resulting in fetal death (53, 54).
- Release of oxytocin from the pituitary gland which stimulates the uterine musculature to contract (53).

There is a difference of opinion as to how long or whether or not a woman should be hospitalized following the instillation of hypertonic saline. In some clinics, women have been permitted to leave following instillation and advised to return to the health facility when uterine contractions begin (76, 147). Most physicians, however, believe that patients should be hospitalized in a fully-equipped, well-staffed facility following the procedure (162). Careful screening of patients for preexisting medical conditions, such as sickle cell anemia, cardiac, or renal disorders, is advisable before carrying out the procedure (23, 77, 84, 97, 162).

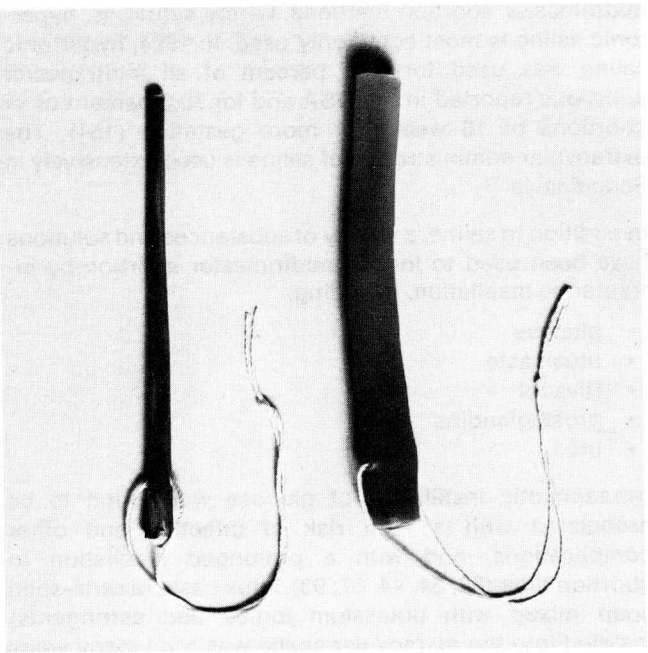

Fig. 3. Two laminaria tents (actual size) used to dilate the cervix. Tent on left is unused. Tent on right has been soaked in water to show expansion that would occur upon exposure to body fluids.

INTRAAMNIOTIC INSTILLATION. Transabdominal instillation of hypertonic saline into the amniotic sac is used to induce abortion throughout the second trimester, but is most commonly used for gestations of 16 weeks or more. Most physicians advise that other approaches or methods be used during the 13-16 week period, or that intraamniotic instillation via the transabdominal approach be postponed until after 16 weeks (32, 84).

Technique

Prior to the instillation, the patient voids, her abdomen is wiped or sprayed with an antiseptic solution and draped with sterile towels. Local anesthetic is used in the region of the instillation site. Then, a spinal needle (for example, 18 gauge) is introduced through the abdomen into the amniotic sac. To be sure that the needle is in the amniotic sac, a small amount of amniotic fluid is withdrawn before instillation of the saline solution (77).

Most physicians perform amniocentesis (aspiration of amniotic fluid) by withdrawing more than just the diagnostic sample to verify needle location. They believe that aspirating 35-250 ml of amniotic fluid prior to the introduction of saline may prevent a sudden increase in pressure that might rupture the fetal membranes (amniotic sac) (138). Another advantage of aspirating fluid is the production of a concentration of saline sufficient to cause fetal death and expulsion (79).

The amount of saline and the technique used for instillation vary according to the week of gestation and the amount of amniotic fluid withdrawn prior to saline

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instillation. Most physicians instill 150-250 ml of 20 percent saline. To reduce the chances of the needle's displacement during instillation, some practitioners instill saline through a catheter placed through a larger bore needle (for example, 14 gauge) (see Fig. 5) (23, 85, 97, 120). Others use the gravity drip technique of infusion (gravity flow without pressure from a syringe), developed by Kerenyi and associates, which requires an elevated solution bottle connected to a spinal needle by a plastic tube (77). The saline is then infused slowly, at no greater pressure than gravity to avoid excessive pressure. This infusion method also allows the operator to discontinue administration if there is any adverse reaction by the patient (77, 78, 162).

Saline may also be instilled intraamniotically by inserting a long needle (for example, spinal or transthoracic) through the cervical canal into the amniotic sac (86, 109, 111, 126). Ruttner of Hungary first reported the transcervical approach, which may be useful in the early weeks of the midtrimester (13-15 weeks) when the transabdominal approach is technically difficult (86, 126). Some physicians, however, have found transcervical instillation difficult to perform and associated with high complication rates (109).

Effectiveness

Reports of the time interval between hypertonic saline instillation and fetal expulsion vary considerably, but most fall within a 24-36 hour range. About 97 percent of patients can be expected to abort within 72 hours (23). The use of oxytocin and/or laminaria tents augments the effect of hypertonic saline and shortens instillation to abortion intervals (see Table 1).

Morbidity

Many physicians who routinely perform intraamniotic instillation of hypertonic saline find it a safe method of terminating midtrimester pregnancy, but several medical complications have been associated with it. These include:

- hemorrhage (blood loss greater than 500 ml);
- infection and/or fever;
- uterine injury (such as cervical lacerations);
- hypernatremia (increase in serum sodium above 160 milliequivalents per liter);
- coagulopathy (blood coagulation disorders).

Hemorrhage and infection are the most frequent complications following intraamniotic instillation of hypertonic saline. In a New York study of over 4,000 patients, Berger and Kerenyi reported an overall rate of 5.5 complications per 100 cases; 96 percent of all complications were due to hemorrhage and/or infection (16).

Hemorrhage requiring transfusion has been reported in 2-7 percent of patients (32). It is more likely to occur when oxytocin is used to augment saline or when the placenta is retained for several hours following expulsion of the fetus. Thus some physicians suggest that the risk of hemorrhage can be substantially reduced if the placenta is manually or surgically removed, if not expelled within one hour after delivery of the fetus (16).

Fever, presumed due to infection, has been reported in 2.2-16.6 percent of patients (32). The risk of infection increases when abortion time exceeds 48 hours (14, 16). Therefore, some physicians advocate the use of augmenting agents, such as oxytocin and laminaria, which may

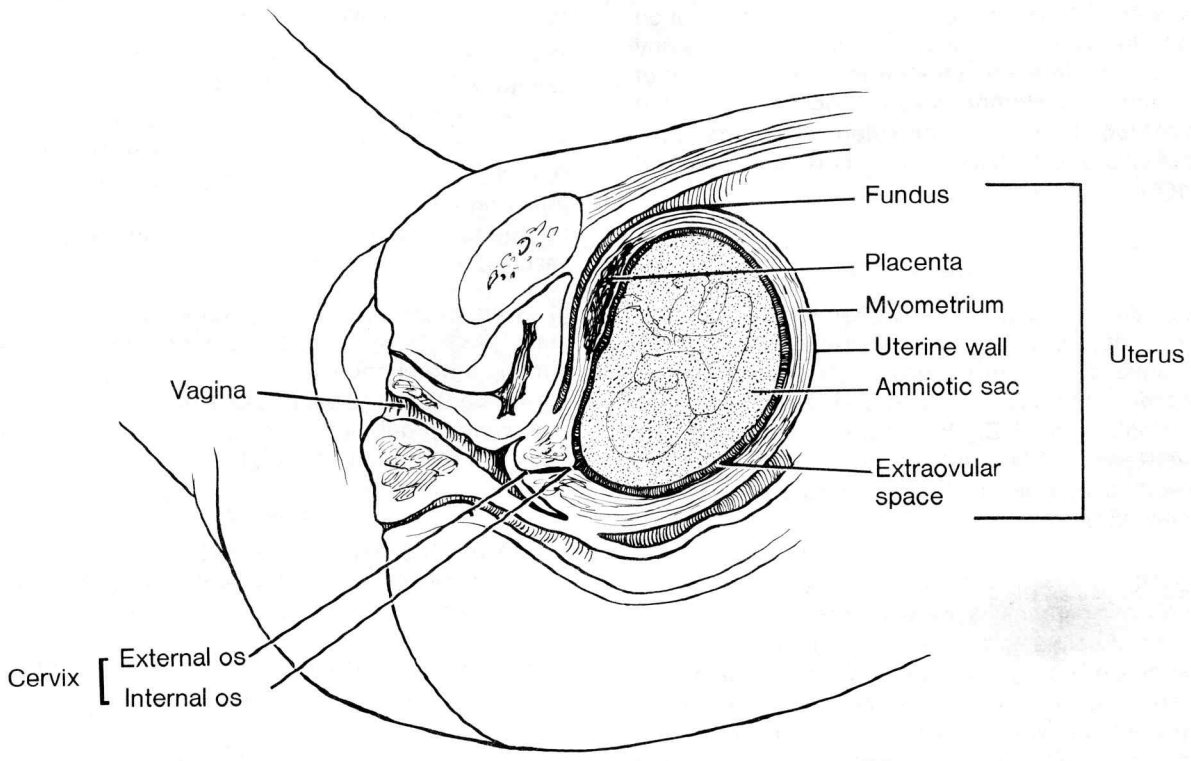

Fig. 4. Female reproductive organs during midtrimester pregnancy.

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shorten the instillation to abortion interval and reduce the risk of infection (16). The risk of bacterial infection can be reduced by a high standard of sterile technique (32). Treatment of infection consists of antibiotic therapy. If infection persists, a more precise diagnosis may be based on cultures taken from the patient. Persistent fever due to infection may require surgical evacuation of the uterine contents.

Injuries to the uterus, such as cervical lacerations, are rarely associated with intraamniotic instillation of saline, but may occur if the cervix does not dilate despite uterine contractions and oxytocin administration (68). Should uterine injuries occur, they may be repaired vaginally or via laparotomy, depending on location and extent of injury (23).

Signs and symptoms of mild hypernatremia—which appear in about 1 of 200 patients—include thirst, headache, and cardiorespiratory abnormalities such as hypotension, bradycardia, and apnea (23). Hypernatremia may result from the inadvertent intravascular injection of saline or from rapid absorption of sodium from the amniotic cavity, thus transferring salt from the uterus to the patient's vascular system. Severe hypernatremia, characterized by the development of central nervous system abnormalities such as seizures or coma, occurs rarely, but may be life-threatening when it does (16, 23, 32). Most physicians treat suspected hypernatremia by intravenous or oral administration of fluids, such as normal saline, water, or a 5 percent dextrose solution. Treatment should be followed by diagnostic measures and careful monitoring of vital signs and urinary output (23).

Although many patients experience changes in blood coagulation factors after intraamniotic instillation of saline, severe clotting disorders are rare (23, 32, 35). In a six-year review of almost 5,000 saline-induced abortions, Cohen and Ballard found only 10 cases of serious coagulopathy (35). Early oxytocin administration increased the risk of coagulopathy. If a clotting disorder occurs, treatment consists of blood transfusions and uterine examination to insure that all products of conception have been removed (23, 35, 106).

Mortality

The risk of death is highest for women with preexisting medical disorders, such as sickle cell disease, moderate to severe anemia, cardiac or cardiovascular disorders, and renal disorders (23, 77, 84, 97, 162). According to 1974 data reported to the US Center for Disease Control, nine deaths were associated with 59,368 saline-induced abortions, resulting in a mortality rate of 15.2 per 100,000 procedures (151).

EXTRAOVULAR ADMINISTRATION. Several investigators, mainly in Scandinavia, have studied the extraovular introduction of saline as an alternative method of midtrimester abortion. The main advantage of this method is that it can be used any time during the midtrimester, including the first few weeks when intraamniotic instillation is technically difficult. Nevertheless, extraovular saline appears to be less effective and is associated with complications similar to those found with intraamniotic saline.

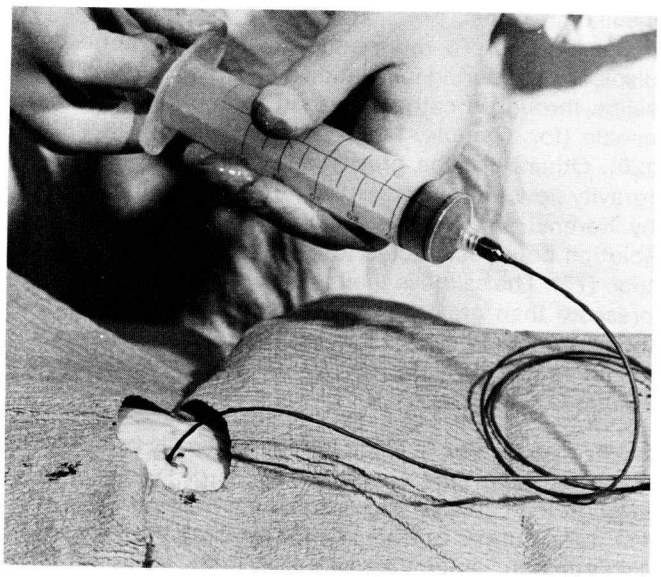

Fig. 5. Catheter threaded through intraamniotic needle, to withdraw amniotic fluid and instill hypertonic saline for midtrimester abortion.
COURTESY: Dr. Harold Schulman, Albert Einstein College of Medicine, Bronx, NY, USA (used with permission of Little, Brown and Company, Boston, MA).

Technique

With the extraovular method, hypertonic saline is instilled through a catheter inserted through the cervix into the extraovular space, 7-12 cm from the external cervical os. A soft, Foley catheter is suitable because inflation of its balloon with 5-10 cc of liquid usually seals the cervix to prevent leakage of the saline and holds the catheter in place (60, 62, 96). The catheter may be left in place 2-4 hours after instillation to prevent saline leakage back into the vagina which might reduce intended dosage and effectiveness (116). It is seldom left in place longer since the risk of intrauterine infection increases with prolonged use of a transcervical catheter (96).

Quantities of saline instilled depend on week of gestation, but are generally smaller than those used with intraamniotic instillation (48). Most investigators inject 7.5-11 ml of saline per week of gestation, up to a maximum of 200 ml (60, 116). The saline solution may be administered by slow injection (96, 116) or by drip infusion at 1-15 drops per minute to facilitate early recognition of inadvertent intravascular administration (62).

In order to reduce the instillation to abortion interval, many physicians administer oxytocin intravenously, beginning several hours after saline instillation (96) or after uterine contractions begin (62). Nummi (Finland) administers oxytocin only to women who have not delivered the fetus and placenta within 24 hours (116).

Effectiveness

Extraovular instillation of saline is generally less effective than intraamniotic instillation with reported mean instillation to abortion times ranging from 29 to 39 hours (60, 96, 116). Reported failure rates with extraovular instillation range from 6 to 8 percent (96, 116), compared to about 3 percent for intraamniotic administration (23).

Morbidity

Complications following extraovular instillation of hypertonic saline are similar to those for the intraamniotic

Table 1—Midtrimester Pregnancy Termination with Intraamniotic Saline, Selected Studies, 1973-1975

Author & Date	Ref. No.	Number of Patients	Weeks Gestation	Amniocentesis (ml)	Dosage (ml)	Augmenting Agents	Mean Instillation-Abortion Time (Hours)	Patients with Complications and Side Effects									
								Retained Products of Conception		Nausea, Vomiting, Diarrhea		Hemorrhage		Fever and/or Infection		Cervical Injuries		Coagulopathy	
								No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Berger & Kerenyi 1975	16	4,252	17-20	yes (amount not specified)	200 (20% saline)	oxytocin beginning several hours after instillation	NR	NR		NR		110	2.6	95	2.2	NR		NR	
Cohen & Ballard 1974	35	4,112	16-20	30-50	maximum 200 (20% saline)	oxytocin if contractions did not begin within 48 hours	37.9	NR		NR		110	2.2	NR		NR		5	0.1
		807	16-20	30-50	maximum 200 (20% saline)	oxytocin beginning 1-2 hours after instillation	22.1	NR		NR				NR		NR		5	0.6
Gaitonde et al. 1974	53	200	12-20	small amount, only to confirm needle placement	200 (20% saline)	none	NR	6	3	2	1	NR		1	0.5	NR		NR	
Hanson et al. 1974	63	26	13-20	100	200 (17.5% saline)	none	41.26	4	15	NR		NR		0	0	NR		NR	
		25				oxytocin beginning 12 hours after instillation	30.67	0	0					1	4				
		50				same, plus one laminaria tent at time of instillation (removed 12 hours later)	26.84	9	18					11	22				
		41				same as above	22.96	10	24.4					5	12.2				
Horowitz & Barr 1974	67	183	16-20	60-70	200 (20% saline)	oxytocin beginning at time of instillation plus two laminaria tents following instillation	17.7	28	15.3	NR		3	1.6	6	3.3	NR		NR	
Kerenyi et al. 1973	78	5,000	14-24	50-500	150-250 (20% saline)	oxytocin beginning 4-6 hours after instillation	22.5 (with high oxytocin doses); 25 (with lower doses)	129[a]	12.9	NR		23[a]	2.3	23[a]	2.3	3[a]	0.3	3[a]	0.3
Singh 1975	138	50	14-20	35-240	500 (3-5% saline)	oxytocin for some patients (number not specified)	34	10	20	NR		2	4	5	10	NR		NR	

[a]Reported only for last 1,000 patients in series.
NR = Not Reported

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route. Signs and symptoms reported by Llewellyn-Jones include vomiting (5 percent), fever (4 percent), infection (1 percent), hemorrhage (less than 1 percent), placental products not expelled within 8 hours following abortion (53 percent), and symptoms of intravascular injection (3 percent) (96). Some practitioners administer antibiotics during and/or following the procedure in an attempt to reduce infection (62, 111), and perform curettage to remove unexpelled fetal and placental tissue (62, 116).

PROSTAGLANDINS

Natural prostaglandins (PGs)—a group of biologically related fatty acids—and their analogues (synthetic derivatives) are effective in inducing abortion at any stage of gestation (see **Population Reports**, Series G, Numbers 1-7). Although transient gastrointestinal side effects (nausea, vomiting, and diarrhea) are often associated with the administration of prostaglandins, serious complications are rare. The instillation to abortion interval with prostaglandins is generally shorter than with other midtrimester abortifacients (saline, urea) but the proportion of live births is higher (22, 66).

Prostaglandins may be administered by a variety of routes. The most commonly reported are the intraamniotic and extraovular routes for intrauterine instillation. Other routes—intravenous, intramuscular, intravaginal, oral, or rectal—have been investigated to deliver the drug.

Exactly how prostaglandins induce abortion is not known, but investigators have described a variety of effects, including:

- alterations in cell membrane potentials;
- stimulation of the myometrium;
- changes in circulating progesterone levels.

The combination of effects leads to uterine contractions and fetal expulsion (22, 50, 140).

Compared to natural prostaglandins, prostaglandin analogues appear to have several advantages:

- The analogues are less rapidly metabolized than natural compounds.
- They are less likely to require augmentation or additional doses to achieve abortion, due to longer duration of action.
- They are more suitable for extrauterine administration, with a lower incidence of side effects (82, 123).

As with other midtrimester abortion procedures, patients with preexisting medical conditions, such as severe cardiac and renal disorders, should be carefully monitored. Severe complications, however, are rare, and many physicians believe that prostaglandins may be safer than saline for high risk patients.

INTRAAMNIOTIC INSTILLATION. Studies indicate that $PGF_2\alpha$ instilled transabdominally into the amniotic sac compares favorably with saline in inducing midtrimester abortion effectively and safely (22, 124). As with saline, however, intraamniotic instillation of prostaglandins has the disadvantage of requiring transabdominal puncture. Further evaluation of $PGF_2\alpha$ in a variety of medical environments is necessary before conclusions can be drawn about its merits relative to other midtrimester abortifacients (23).

Technique

The technique used to instill $PGF_2\alpha$ is similar to that used with the intraamniotic instillation of hypertonic saline. First, a small amount of amniotic fluid is withdrawn to be sure that the needle is properly located in the amniotic sac. The prostaglandin solution is then instilled transabdominally into the amniotic sac. An indwelling (intraamniotic) catheter is sometimes used to avoid multiple punctures if additional prostaglandin doses will be required (32).

Several single and multiple dose schedules of PGF_2 associated with clinically acceptable rates of side effects seem to be effective in inducing abortion. Many physicians use a single dose schedule of 40 mg followed by a second dose of 10-40 mg if, after 24 hours, abortion is not imminent (22). This is the only dose schedule approved by the USFDA (153). Other investigators use multiple dose schedules of 15-25 mg administered twice within a 24-hour period.

Effectiveness

The use of $PGF_2\alpha$ generally results in a shorter instillation to abortion interval than with saline and has higher success rates in the first 48 hours (1). Investigators report mean abortion times ranging from 18 to 32 hours (see Table 2). However, because $PGF_2\alpha$ is rapidly metabolized, a second dose is frequently used to hasten abortion in about 30 percent of patients (23, 43).

Intravenous oxytocin infusions have been used by some investigators to augment $PGF_2\alpha$ (124). Anderson, however, states that oxytocin does not increase the effectiveness of $PGF_2\alpha$ and may, in fact, increase the blood loss and incidence of cervical injury (lacerations and fistulas) and gastrointestinal side effects (9).

Insertion of laminaria tents 12-16 hours before intraamniotic administration of $PGF_2\alpha$ reportedly shortens the instillation to abortion time (124, 162) and may also reduce the risk of cervical injury (46, 96, 162). According to Bieniarz, insertion of laminaria prior to injection

- decreases the number of uterine contractions needed to expel the fetus by facilitating cervical dilatation;
- reduces the instillation to abortion time by one-half;
- hastens the expulsion of the placenta.

The combined effects of laminaria insertion thus permit the use of smaller doses of $PGF_2\alpha$ (162).

Morbidity

Gastrointestinal side effects are common with intraamniotic instillation of $PGF_2\alpha$. In most studies, at least 50 percent of the patients experience one or more gastrointestinal side effect (nausea, vomiting, diarrhea). However, these are transitory, rarely serious, and can be treated prophylactically and symptomatically with antiemetics and antidiarrheal drugs (22).

Chills, fever, and minor episodes of coughing and shortness of breath have occasionally been observed but severe respiratory and cardiovascular complications have been reported in less than one in 200 patients (162). Although rare, bronchospasm, bradycardia, and grand

Table 2—Midtrimester Pregnancy Termination with Intraamniotic Prostaglandin $F_2\alpha$, Selected Studies, 1973–1976

Author & Date	Ref. No.	Number of Patients	Weeks Gestation	Dosage	Augmenting Agent	Mean Instillation–Abortion Time (Hours)	Patients with Side Effects and Complications															
							Retained Products of Conception		Failures[a]		Nausea, Vomiting		Diarrhea		Hemorrhage		Fever and/or Infection		Cervical Injuries		Respiratory Problems	
							No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Brenner et al. 1973	27	22	10–23	25 mg, repeated 6, 24, & 30 hours after instillation	none	18.9	3	13.4	1	5	10	45	1	5	1	5	1	5	0	0	NR	
		24	10–23	50 mg, repeated 24 hours after instillation	none	23.8	15	62.5	1	4	15	62	6	25	3	13	5	21	2	8	NR	
		25	10–23	25 mg, repeated every 6 hours	none	21.5	10	40	1	4	14	56	0	0	1	4	10	40	0	0	NR	
Corlett & Ballard 1974	36	30	14–20	40 mg instilled over 5-minute period	oxytocin, if abortion did not occur within 48 hours	18.6 (multiparas) 32.2 (nulliparas)	14	46.6	2	6	12	40	6	20	1	3	3	10	NR		NR	
Duenhoelter & Gant 1975	45	122	14–20	40 mg instilled over 5-minute period; 20 mg instilled after 24 hours if membranes not ruptured or if contractions stopped	oxytocin, if abortion did not occur within 48 hours, or if membranes ruptured without uterine contractions	25.51 (multiparas) 29.31 (nulliparas)	2	1.6	16	13.1	35	29.5	NR		16	13.1	18	14.8	4	3.3	NR	
Duenhoelter et al. 1976	46	116	14–20	same as above	laminaria tents inserted shortly before or after instillation	21.1 (multiparas) 24.33 (nulliparas)	NR		5	4.3	NR		NR		18	15.5	14	12.1	2	1.7	NR	
Robins et al. 1976	124	20	14–20	40 mg instilled over 5-minute period; 20 mg instilled after 24 hours if membranes not ruptured	none	21.7	5	25	5	25	NR[b]		NR[b]		1	5	NR		NR		3	15
		34	14–20	same	laminaria tents inserted shortly before instillation	17.4	7	20.5	9	26.5	NR[b]		NR[b]				3	8.8	NR		1	3
		20	14–20	same	laminaria tents inserted shortly before instillation; oxytocin (69.5 mU/min.) beginning 2 hours after instillation	16.6	3	15	0	0	NR[b]		NR[b]		9	5.8	NR		NR		NR	
		100	14–20	same	same as above, but higher oxytocin dose (139 mU/min.)	16.2	26	26	1	1	NR[b]		NR[b]				NR		NR		2	2
Saldana et al. 1974	128	50	13–20	25.4 mg (average dose)	oxytocin beginning 90 minutes after instillation	17.4	16	32	NR		11	22	5	10	NR		NR		1	2	1	2

[a]Failure to abort within 48 hours after instillation.
[b]Observed, but reported as not clinically significant.
NR = Not Reported

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mal seizures may be caused by too rapid absorption of $PGF_2\alpha$ from the amniotic fluid, by a hypersensitivity to prostaglandins, or by inadvertent intravascular administration by the physician (22). In most healthy women, inadvertent intravascular injection causes only transient nausea and vomiting or temporary change in blood pressure, but no central nervous system damage (112). To detect possible intravascular administration or hypersensitivity to prostaglandins, a patient should be given a small test dose before receiving the full dose.

Complications such as hemorrhage, infection, and uterine rupture—possible with all methods of midtrimester abortion—are infrequent (22). Infection is more likely to occur with multiple dose schedules of intraamniotic prostaglandins, rather than with a single dose schedule (162). According to a World Health Organization (WHO) report, a 1.2 percent incidence of endometritis (infection of the endometrium) can be expected with prostaglandins (161).

Since rates of hemorrhage and infection are higher when the placenta is not expelled within 1-2 hours following delivery of the fetus, surgical or manual removal of the placenta should be considered (23). Compared to saline, intraamniotic instillation of $PGF_2\alpha$ has not been associated with serious complications, such as clotting disorders or hypernatremia, if inadvertent myometrial administration occurs (22).

Mortality

A recent US review of midtrimester abortions performed with intraamniotic $PGF_2\alpha$ reported a projected mortality rate of 10.5 per 100,000, less than the 15.2 deaths per 100,000 abortions performed with hypertonic saline. The total number of cases reported, however, is small (about 2,000), and the relative safety of prostaglandins for midtrimester abortion remains to be established (5).

The Methyl Analogue of $PGF_2\alpha$

The $PGF_2\alpha$ analogue — 15(S)15 $MePGF_2\alpha$ — instilled intraamniotically for midtrimester abortion has been reported only in relatively small, experimental studies. Using a single dose schedule of the methyl analogue, Dingfelder and associates reported high abortion rates, with clinically acceptable side effects (nausea, vomiting, diarrhea), and with instillation to abortion intervals comparable to intraamniotic $PGF_2\alpha$, saline, and urea with oxytocin (43). Bygdeman reported that the frequency of gastrointestinal side effects was lower than with its parent compound when administered intraamniotically, although for a multiple dose schedule, the use of the 15 methyl $PGF_2\alpha$ analogue showed no significant advantage over the natural compound (33).

Greer obtained a high percentage of complete abortions by combining natural $PGF_2\alpha$ with its longer-acting methyl analogue, and shortened instillation to abortion time by using both oxytocin and laminaria (58). Such combined procedures may be effective, but their application requires considerable monitoring.

EXTRAOVULAR ADMINISTRATION. Prostaglandins and their analogues are sometimes injected into the extraovular space for early second trimester (13-15 weeks) terminations when intraamniotic instillation is technically difficult. Compared to the intraamniotic route, smaller but more frequent doses are required and the average total dose is lower (132). Disadvantages of extraovular administration include:

- unpredictable rates of effectiveness;
- necessity of frequent drug administration;
- inconvenience to the patient due to the maintenance of an indwelling transcervical catheter;
- increased likelihood of infection (32).

Technique

After cleaning the cervix and vagina, a catheter is inserted transcervically into the lower uterine segment for the instillation of the prostaglandin solution. The ostium of the catheter is located immediately above the internal cervical os or in the fundus, between the fetal membranes and the uterine wall.

Some physicians administer a single dose of prostaglandins extraovularly; others use a multiple dose schedule or continuous infusion (22). Several dose schedules and amounts of $PGF_2\alpha$ and PGE_2 have been reported effective (132, 135). Single doses of 3-5 mg of $PGF_2\alpha$ have been reported effective, but are associated with clinically unacceptable rates of side effects unless attenuated by large amounts of analgesics. However, multiple doses of $PGF_2\alpha$ ranging from 250-500 μg every 2-4 hours have been reported effective with clinically acceptable rates of side effects (22, 161).

Effectiveness

Extraovular administration of prostaglandins, in terms of effectiveness, appears to offer no advantages over intraamniotic instillation of prostaglandins. Reported mean instillation to abortion intervals range from 12 to 24 hours (see Table 3). Continuous extraovular infusion of $PGF_2\alpha$ 12-18 hours following the insertion of laminaria reportedly is 90 percent effective in inducing abortion within 24 hours (66), but is inconvenient and may be associated with increased risks of endometrial infection (22).

Several studies have shown that the extraovular instillation of PGE_2 in a viscous aqueous solution or gel increases its efficacy and duration of action, resulting in shorter instillation to abortion intervals. Intrauterine pellets which slowly release PGE_2 are also being investigated (22, 50, 98, 99).

Morbidity

The incidence of side effects and complications is similar to that for intraamniotic prostaglandin administration. Gastrointestinal side effects are common but serious complications are rare. The incidence of postabortal uterine infection is low, but incomplete abortions requiring surgical or manual removal occur frequently, in up to one-third of the patients (22).

EXTRAUTERINE ADMINISTRATION. Recent research has focused on methods of delivering prostaglandins which avoid the inherent disadvantages of intrauterine injections (medical risks, patient inconvenience, need for medical supervision).

Oral administration of prostaglandins or their analogues would be especially convenient and would offer the

Table 3—Midtrimester Pregnancy Termination by Extraovular Instillation of Prostaglandins and PG Analogues, Selected Studies, 1974-1976

Author & Date	Ref. No.	Number of Patients	Weeks Gestation	PG or Analogue	Dosage	Augmenting Agent	Mean Instillation-Abortion Time (Hours)	Patients with Side Effects and Complications											
								Retained Products of Conception		Failures[a]		Nausea, Vomiting		Diarrhea		Hemorrhage		Fever and/or Infection		Cervical Injuries	
								No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Himmelmann et al. 1975	65	50	13-20	$PGF_2\alpha$	250 μg followed by 750 μg 2 hours later	oxytocin administered after 24 hours to one-third of patients	24[b]	NR		10	20	9	18	0	0	8	16	14	28	NR	
Hodgson & Van Gorp 1976	66	60	12-22	$PGF_2\alpha$	500 μg followed by 500 μg 5 minutes later; 2 mg 15 minutes later, and 2 mg 30 minutes later (5 mg total)	laminaria tents prior to instillation; oxytocin beginning 6-8 hours after instillation or if membranes ruptured	13.40 (multiparas) 10.41 (nulliparas)	NR		5	8.3	12	20	NR		4	6.6	3	5	1	1.6
MacKenzie et al. 1975	99	24	12-26	PGE_2	1.5 mg in viscous gel (9 ml solution)	oxytocin administered to patients who did not abort within 24 hours	11.3 (multiparas) 15.75 (nulliparas)	4	16.7	0	0	7	29.1	NR		3[c]	12.5	0	0	NR	
Shapiro 1975	135	20	13-15	$PGF_2\alpha$	3 mg every 1-3 hours	oxytocin administered to complete abortion when necessary	17.75	6	30	1	5	9	45	NR		1	5	1	5	NR	
Wiqvist et al. 1974	160	40	13-16	$PGF_2\alpha$	250-750 μg every 2-4 hours	none	20.9	NR		4[d]	10	1.5[e]		1.5[e]		2	5	4	10	NR	
		55	13-16	15-me-$PGF_2\alpha$	500-850 μg (single instillation)	none	13.6	NR		8.8[d]	16	1.5[e]		1.5[e]		2.7	5	1.9	3.6	NR	

[a]Failure to abort within 48 hours after instillation.
[b]Median time
[c]Blood loss greater than 250 ml.
[d]Failure to abort within 36 hours after instillation.
[e]Average number of episodes per patient.
NR = Not Reported

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potential for nonphysician- or self-administration. Investigators working with $PGF_2\alpha$ and PGE_2 and their analogues have not yet found a formulation suitable for oral administration that does not also result in high rates of gastrointestinal side effects. Research with other prostaglandin analogues is underway (23).

Intramuscular Injections

Intramuscular prostaglandin injections may be useful in clinical situations when intraamniotic injection is contraindicated due to ruptured membranes, for example, or is impractical due to vaginal bleeding (22). Both $PGF_2\alpha$ and PGE_2, however, are rapidly metabolized and repeated injections, at least every two hours, are necessary to induce abortion. The natural prostaglandins are also locally irritating. The amount of pain and erythema (redness, swelling) at the injection site makes intramuscular injection of $PGF_2\alpha$ and PGE_2 unacceptable for clinical use (22). The prostaglandin 15 methyl analogues, however, require fewer injections since they are more potent and active for a longer period of time than the natural compounds. Although the 15 methyl analogues are not locally irritating at the injection site (22), they still require several injections and are associated with gastrointestinal side effects comparable to those of the natural prostaglandins (6) (see Table 4).

Intravaginal Administration

Reports indicate that intravaginal administration of $PGF_2\alpha$ and PGE_2 and their analogues can be effective, relatively safe, simple to perform, and may be suitable for self-administration.

In 1975, Lauersen reported that PGE_2 suppositories effectively induced abortion during the midtrimester with rates of side effects comparable to other acceptable prostaglandin routes (89). Schulman inserted PGE_2 suppositories vaginally inside a contraceptive diaphragm and found that when used with intravenous oxytocin, effectiveness increased and side effects decreased (131). Bygdeman has used 15(S)15 methyl $PGF_2\alpha$ methyl ester and reported that it was a safe and effective second trimester abortifacient when administered as a vaginal suppository (33).

Lauersen reported a number of studies using a silicone rubber disk impregnated with various concentrations of 15 (S) 15 methyl $PGF_2\alpha$ methyl ester. Once inserted high into the vaginal vault (with or without prior cleaning of the vagina), the disk may be held in place over the cervix with either a diaphragm or tampon. The patient is kept in a supine position for at least 30 minutes to prevent immediate expulsion (4).

Unlike prostaglandin suppositories, the silicone device does not require repeated insertion and provides a steady release of the drug until abortion occurs. According to Lauersen the device is designed to release the prostaglandin gradually, peaking at two hours after insertion and continuing up to 48 hours or more. Abortion usually occurs within 24 hours. The only side effects—nausea and diarrhea—can be countered by pretreatment with antidiarrheal and antiemetic agents. The device can be removed quickly and easily if the patient feels too uncomfortable, if side effects are intolerable, or if complications occur (4, 6).

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UREA

Intraamniotic instillation of urea, first reported in 1970, is another experimental method of midtrimester abortion receiving wide attention as a possible alternative to hypertonic saline or prostaglandin instillation. Some investigators claim that, compared to saline, urea is safer and less likely to result in serious complications (37, 38, 80, 157). Also, compared to prostaglandins, urea is associated with a lower incidence of transient gastrointestinal side effects, is more readily obtainable, and is less expensive. There are no reports of live births, occasionally associated with saline and more frequently with prostaglandins, following urea instillation (37). However, urea is less potent than saline or prostaglandins and requires augmentation with intravenous oxytocin, laminaria, or intraamniotic prostaglandins (23, 29, 32, 37, 80).

The mode of action of intraamniotic urea is thought to be similar to that of saline. Urea exerts a toxic effect on the fetal-placental unit, causes a reduction in the circulating progesterone levels, and produces changes in the decidua (mucous lining of the uterus) that result in the release of prostaglandins. The combination of these effects causes stimulation of uterine contractions, fetal death, and expulsion (38, 56, 57, 80, 114, 133).

Technique

Amniocentesis is usually performed prior to urea instillation to determine that the needle has been correctly placed and to avoid rupture of membranes due to increased amniotic volume when the urea solution is added. Using a catheter or needle, such as a 16 gauge Tuohy needle, 100–250 ml of 30–60 percent urea solution (60–80 gm dissolved in 5 percent dextrose and water or normal saline) is then instilled (31, 55, 56, 57, 80, 94).

Investigators report the use of several agents for augmenting urea, including:

- continuous intravenous infusion of oxytocin, beginning shortly after urea instillation (31, 55, 117, 157);
- insertion of laminaria tents prior to the time of instillation (55):
- intraamniotic injection of prostaglandins at the time of urea instillation (29, 37, 38, 80).

Effectiveness

Investigators report that the mean instillation to abortion interval varies widely, from 10 to 43 hours depending on the initial concentration of urea, augmenting agent used, amount of amniotic fluid withdrawn, and amount of urea instilled (see Table 5). Urea used alone usually results in lengthy instillation to abortion intervals (57). Some investigators report that urea plus intravenous oxytocin results in shorter mean intervals, ranging from 16 to 43 hours, which have been further reduced by using laminaria tents. Urea and prostaglandins (PGE_2 and $PGF_2\alpha$) have yielded the most consistent instillation to abortion intervals, ranging from 10 to 16 hours (see Table 5).

The Johns Hopkins University Fertility Control Center recently reported a failure rate of only 1.4 percent, using 80 gm urea plus 10 mg $PGF_2\alpha$, compared to 3 percent for

Table 4—Midtrimester Pregnancy Termination by Extrauterine Administration of Prostaglandins and PG Analogues, Selected Studies, 1974-1975

Author & Date	Ref. No.	Number of Patients	Weeks Gestation	PG or Analogue	Route of Administration and Dosage	Other Agents Used	Mean Instillation-Abortion Time (Hours)	Patients with Side Effects and Complications													
								Retained Products of Conception		Failures[a]		Nausea, Vomiting		Diarrhea		Shivering		Hemorrhage		Fever[b]		Respiratory Problems	
								No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Ballard & Quilligan 1974	11	15	12-20	15-me-PGE_2	intramuscular injection of 10 μg every 2 hours (maximum: 8 injections)	antiemetic drugs administered before PG injection	7.8 (multiparas)	5	20	1	5	6	40	17	85	20	100	0	0	20	100	NR	
		5	12-20	15-me-PGE_2	same as above	none	11.2 (nulliparas)					4	80										
Brenner et al. 1975	24	21	7-20	15(S)-15-me-PGE_2-me-ester	intramuscular injection of 10 μg every 4 hours	antiemetic drugs administered for persistent vomiting	17.6	7	33	0	0	13	62	18	86	16	76	0	0	16	76	3	14
		21	7-20	15(S)-15-me-PGE_2-me-ester	intramuscular injection of 10 μg every 4 hours	antiemetic and antidiarrheal drugs administered before PG injection	19.5	5	24	2	10	9	43	4	19	11	52	0	0	9	43	2	1
Bygdeman et al. 1974	33	10	15.5 (mean)	15(S)-15-me-$PGF_2\alpha$	intravaginal insertion of 1-2 suppositories of 1 mg each every 6 hours	none	24.5	3[c]	42	3	30	3.2[d]		3.2[d]		NR		NR		NR		NR	
		10	15.5 (mean)	15(S)-15-me-$PGF_2\alpha$-me-ester	intravaginal insertion of 1-2 suppositories of 1 mg each every 6 hours	none	18.4	4[c]	44	1	10	5.5[d]		5.5[d]		NR		NR		12	52	NR	
		13	15.5 (mean)	15(S)-15-me-$PGF_2\alpha$-me-ester	intravaginal insertion of test dose of 0.5 mg followed by 1-2 suppositories of 1 mg each every 3 hours	antiemetic drugs administered every 3 hours (maximum: 4 doses)	16.4	NR	NR	0	0	3.1[d]		3.1[d]		NR		NR				NR	
		30	15.2 (mean)	15(S)-15-me-$PGF_2\alpha$	intramuscular injection of 200-500 μg every 3 hours	antiemetic and antidiarrheal drugs administered before injection and every 3 hours (maximum: 3 doses)	16.1	18	60	0	0	4.7[d]		0.7[d]		NR		NR		NR		NR	
Lauersen et al. 1975	89	71	8-27	PGE_2	intravaginal insertion of suppository of 10 mg repeated after 1 hour; 20 mg suppository every 2 hours until abortion	antiemetic and antidiarrheal drugs administered before and after insertion; oxytocin used to complete abortion for 5 patients who expelled suppositories	10.79 (multiparas) 13.18 (nulliparas)	13	18	1	1.4	36	50	13	18	5	7	0	0	71	100	NR	
Schulman et al. 1974	131	15	16.7 (mean)	PGE_2	intravaginal insertion of suppositories of 20 mg at repeated intervals (mean total dose: 57.3 mg)	antiemetic and antidiarrheal drugs administered before and after insertion	12.6	10	67	6[e]	40	11	73	4	26	NR		NR		5	33	NR	
		16	16.0 (mean)		intravaginal insertion of suppositories of 20 mg at repeated intervals (mean total dose: 70.0 mg)	suppositories administered in a contraceptive diaphragm; antiemetic and antidiarrheal drugs administered before and after insertion	12.8	1	6	0	0	4	25	2	12	NR		NR		1	6	NR	

[a]Failure to abort within 48 hours after first administration.
[b]Drug fever, not believed due to infection.
[c]Excluding failures
[d]Mean number of episodes per patient.
[e]Failure defined as minimal uterine contractions and presence of fetal heart beat 24 hours after first administration.
NR = Not Reported

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Table 5—Midtrimester Pregnancy Termination with Intraamniotic Urea, Selected Studies, 1974-1975

Author & Date	Ref. No.	Number of Patients	Weeks Gestation	Amniocentesis (ml)	Dosage	Augmenting Agents	Mean Instillation-Abortion Time (Hours)	Patients with Complications and Side Effects											
								Retained Products of Conception		Nausea, Vomiting		Headache		Diarrhea		Hemorrhage		Fever and/or Infection		Cervical Injuries	
								No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Anteby et al. 1974	10	38	17-26	70-600 depending on gestation	50-200 ml over amount of fluid withdrawn of 30% urea solution	oxytocin beginning 6-36 hours after instillation	26.1	NR		4	11	3	8	NR		0	0	4	11	NR	
Burkman et al. (to be published)	29	30	15-24	150-425 depending on gestation	134 ml of 59.7% urea solution	oxytocin (332 mU/min.) beginning 30 minutes after instillation	18.93	9[a]	30	18	60	↑		0	0	1	3.3	0	0	0	0
		30	17-24.5	same as above	same as above	10 $PGF_2\alpha$ intraamniotically immediately after urea instillation	15.75	11[a]	36.7	21	70	NR		0	0	4	13.3	0	0	0	0
		150	16-24	same as above	same as above	same as above[a]	16.45	70[a]	46.7	105	70	↓		2	1.3	10	6.6	3	2	6	4
Burnett et al. 1975	31	39	16-20	100-250	150 ml of 53% urea solution	oxytocin (166 mU/min.) within one hour after instillation	19.06	↑	↑	↑	↑	↑		↑		↑	↑	↑	↑	↑	
		32	16-20	100-250	150 ml of 53% urea solution	oxytocin (332 mU/min.) within one hour after instillation	17.39	29[a]	40.8	23	31	NR		NR		5	7	2	2.8	NR	
								↓	↓	↓	↓	↓		↓		↓	↓	↓	↓	↓	
Craft 1975	38	110	15-24	100	137 ml of 80g urea in 80 ml solution	2.5 mg PGE_2 intraamniotically immediately after urea instillation	10.67	25[c]	24	51	46	NR		1	1	2[d]	2	3	3	5	4.5
Golditch & Solberg 1975	55	42	16-20	small amount ("until free flow ceased")	150-265 ml of 30% urea solution	oxytocin (200 mU/min.) beginning two hours after instillation	29.4	8[e]	19	↑		↑		↑		↑		1	2	0	0
		33	16-20	small amount ("until free flow ceased")	150-265 ml of 30% urea solution	2-3 laminaria shortly before or immediately after instillation; oxytocin (200 mU/min.) beginning two hours later	21.3	6[e]	18	NR		NR		NR		NR		1	3	0	0
										↓		↓		↓		↓					
King et al. 1974	80	30	14-24	105-240	134 ml of 59.7% urea solution	oxytocin (332 mU/min.) beginning 30 minutes after instillation	16.56	9	25	18	60	↑		0	0	1	3.3	3	10	0	0
		30	14-24	85-350	134 ml of 59.7% urea solution	20 mg $PGF_2\alpha$ intraamniotically immediately after instillation	16.29	14	43	22	73	NR		1	3.3	2	6.6	1	3.3	1	3.3
												↓									
Weinberg et al. 1975	157	508	16-19	30-100	200 ml of 40% urea solution	oxytocin (400 mU/min.) beginning one hour after instillation	43.4 (for 440 patients who aborted within 7 days	149[g]	29.3	39	7.7	10	2	NR		7	1.4	36	7.1	NR	

[a]Two hours after fetal expulsion.
[b]Oxytocin administered to unaborted patients not in labor 24 hours after instillation.
[c]One hour after fetal expulsion.
[d]Hemorrhage requiring transfusion.
[e]Six hours after fetal expulsion.
[f]Oxytocin administered to unaborted patients not in labor 48 hours after instillation.
[g]Twelve hours after fetal expulsion.
NR = Not Reported

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urea plus intravenous oxytocin (29). Procedures were considered failures if fetal expulsion did not occur within 48 hours following the initial instillation, or if there were episodes of excessive bleeding or persistent fever requiring evacuation of the uterine contents. In the Johns Hopkins review of 2,045 midtrimester abortions, the 1.4 percent failure rate of the urea-$PGF_2\alpha$ combination was comparable to that for intraamniotic saline instillation (1.3 percent) but lower than for either intraamniotic $PGF_2\alpha$ (3.4 percent) or extraovular $PGF_2\alpha$ (13.1 percent) (29).

Morbidity

Intraamniotic urea is safer than other midtrimester abortifacients, according to some physicians. For example, urea has not been associated with the life-threatening complications such as hypernatremia that are sometimes encountered with hypertonic saline. Also, urea is generally associated with less severe gastrointestinal side effects than found with prostaglandins (10, 29, 80, 119, 157). Thus, some practitioners believe that urea may be especially suitable for medically high-risk patients (117).

The most common side effects reported with intraamniotic urea instillation are nausea and vomiting (especially when prostaglandins are used as augmenting agents), but diarrhea rarely occurs. As with other midtrimester abortion methods, however, there are potential risks of hemorrhage and infection. Hemorrhage associated with urea has not been so severe that transfusions have been required; infections, which occur infrequently, have been successfully treated with antibiotics (29, 37, 38, 80). Manual or surgical removal of placentas which have not been spontaneously expelled 1-2 hours after the fetus may reduce these risks (29, 80).

Cervical lacerations have been reported in about 4 percent of the patients. As with all methods, a complete vaginal examination should be performed following abortion to detect and treat lacerations (29, 37, 38).

Changes in clotting factors that sometimes occur with urea are not clinically significant and occur less frequently than with saline. Because urea is less toxic and is associated with a lower incidence of coagulopathy, it appears to be safer than saline if inadvertent intravascular administration should occur (29, 31, 80, 119, 157).

The *Population/Fertility Control Thesaurus*, published by the Population Information Program, is available to family planning personnel in developing countries upon request. It is a compilation in depth of terminology in the field of fertility control with emphasis on the various methods of family planning. Terms are arranged in four formats: alphabetical, descriptor, hierarchical, and categorical. It may be used for indexing documents for manual or automatic retrieval either specifically or broadly. In addition, it indicates the current areas of knowledge and research in this field.

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