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PN-AAJ-242

RESEARCH ON SIMPLIFIED TECHNIQUES OF FERTILITY MANAGEMENT

SIX MONTHS REPORT

OCTOBER, 1980

PROJECT I

COMPARISON OF OPTIC VISOR VS SURGICAL MICROSCOPE FOR RECONSTRUCTION OF THE FALLOPIAN TUBE

The objective is to determine which method will prove the most effective and less expensive for tubal sterilization reversal

Principal Investigator: Dr. John A. Rock

The Johns Hopkins Medical Institutions

Department of Gynecology and Obstetrics
Division of Reproductive Endocrinology
John A. Rock, M.D., Director
Telephone (301) 955-3355
Nights and weekends (301) 955-4331

Please address replies to:
Halsted 124
The Johns Hopkins Hospital
Baltimore, Maryland 21205

September 24, 1980

MEMO TO: Theodore M. King, M.D., Ph.D.

FROM: John A. Rock, M.D. John Rock

SUBJECT: Comparison of Optic Visor and Surgical Microscope - Site Visit

Dr. King, I am enclosing a copy of our list of randomization which has been supplied by Dr. Allyn Kimball in the Department of Biostatistics. We have completed the first 18 pairs which have been matched for the types of anastomoses. Ten pairs remain to be completed. I anticipate we shall have no problem in completing this project by the termination date. I have discussed with Dr. Kimball some of the pregnancy outcomes, but as you can see, data is still accumulating and any conclusion from this study at this time would be premature and may very well change over the next year and a half during the follow-up phase.

If I can be of further service, please do not hesitate to contact me.

With best wishes.

JAR:pag

file: microsurgery
3719

THE JOHNS HOPKINS UNIVERSITY

SCHOOL OF HYGIENE AND PUBLIC HEALTH

DEPARTMENT OF BIOSTATISTICS

615 North Wolfe Street • Baltimore, Maryland 21205

August 4, 1978

A. John Rock, M.D.
Womans Clinic 225
Johns Hopkins Hospital

Dear John:

In the following list of randomized treatment assignments, the patient number refers to the order in which patients became eligible for the study. Also O stands for old technique, N for new technique.

	Patient Number	Treatment		Patient Number	Treatment
1	1	O	7	13	O
	2	N		14	N
2	3	N	8	15	N
	4	O		16	O
3	5	O	9	17	O
	6	N		18	N
4	7	O	10	19	O
	8	N		20	N
5	9	N	11	21	O
	10	O		22	N
6	11	N	12	23	N
	12	O		24	O

The dotted lines separate the patients by pair. In each pair, both techniques are present, and we will use these pairs, together with results for tubular patency, to examine the data sequentially.

Please call me if there are any questions.

Sincerely,

Allyn

Allyn Kimball
Professor

AK/cad

THE JOHNS HOPKINS UNIVERSITY

SCHOOL OF HYGIENE AND PUBLIC HEALTH

DEPARTMENT OF BIOSTATISTICS

615 North Wolfe Street • Baltimore, Maryland 21205

March 31, 1980

John A. Rock, M.D.
Harvey GYN 08
Johns Hopkins

Dear John:

Here are randomized treatment assignments for 16 additional pairs of patients (0 = old, N = new).

	Patient Number	Treatment		Patient Number	Treatment
13	25	0	21	41	N
	26	N		42	0
14	27	0	22	43	0
	28	N		44	N
15	29	N	23	45	0
	30	0		46	N
16	31	0	24	47	N
	32	N		48	0
17	33	0	25	49	N
	34	N		50	0
18	35	0	26	51	0
	36	N		52	N
19	37	N	27	53	N
	38	0		54	0
20	39	N	28	55	0
	40	0		56	N

Sincerely,

Allyn W. Kimball
Professor

AWK:pah

ORDERED PAIRS	INITIALS	AGE	STERILIZATION PROCEDURE	ANASTOMOSIS (SEGMENTS)	MAGNIFICATION	PREGNANCY INTERVAL	PREGNANCY OUTCOME
PAIR #1							
Old	C.C.	22	Pomeroy	Ampullary-Isthmic	Hood and Loop	4 mo.	Premature delivery, los at 6 mo. - Baby died.
New	E.M.	28	Falope Ring	Ampullary-Isthmic	OMPI	6 mo.	Term Delivery
PAIR #2							
New	C.K.		Pomeroy	Ampullary-Isthmic	Hood-Loop	3 mo.	Spontaneous abortion at 6 weeks.
Old	M.A.	27	Single Burn Electrocautery (Monopolar)	Ampullaty-Isthmic	OMPI	2 mo.	Term Delivery
PAIR #3							
Old	J.W.	30	Modified Irving	Ampullary-Isthmic	Hood-Loop	5 mo.	Term Delivery
New	A.N.		Double Burn Electrocautery	Ampullary-Isthmic	OMPI	9 mo.	Term Delivery
PAIR #4							
Old	J.T.	29	Pomery	Ampullary-Ampullary	Hood-Loop		
New	F.W.		Falope Ring	Ampullary-Ampullary	OMPI	5 mo.	Term Delivery
PAIR #5							
New	B.G.	29	Pomeroy	Ampullary-Ampullary	OMPI (HSG: Patency; 2nd look laparoscopy: patency)		
Old	M.U.	26	Pomeroy	Ampullary-Ampullary	Hood-Loop	10 mo.	Spontaneous abortion at 8

MATCHED PAIRS	INITIALS	AGE	STERILIZATION PROCEDURE	ANASTOMOSIS (SEGMENTS)	MAGNIFICATION	PREGNANCY INTERVAL	PREGNANCY OUTCOME
PAIR #6							
New	M.U.		Single Burn Electrocautery	Ampullary-Isthmic	OMPI	5 mo.	Spontaneous abortion at 8
Old	J.S.		Single Burn	Ampullary-Isthmic	Hood and Loop	6 wks. 7 mos.	Right ectopic pregnancy. IUP Spontaneo abortion at 6
PAIR #7							
New	A.E.	24	Falope Ring	Ampullary-Isthmic	OMPI	3 mo.	Pregnancy in Progress
Old	M.S.	29	Electrocautery	Ampullary-Isthmic	Hood	2 mo.	Pregnancy in Progress
PAIR #8							
New	A.A.	32	Electrocautery	Ampullary-Isthmic	OMPI		
Old	S.S.	27	Electrocautery	Ampullary-Isthmic	Hood (2nd look laparoscopy: bilateral patency)		
PAIR #9							
Old	L.J.	32	Electrocautery	Ampullary-Isthmic	Hood		
New	D.P.	25	Pomeroy	Ampullary-Isthmic	OMPI (HSG: unilateral patency)		Irregular men since procedu Evaluation in progress.
PAIR #10							
Old	M.H.	35	Pomeroy	Ampullary-Isthmic	Hood	6 mo.	Pregnancy in Progress.
New	L.J.	27	Electrocautery	Ampullary-Isthmic	OMPI		

[illegible]	INITIALS	AGE	PROCEDURE	(SEGMENTS)	MAGNIFICATION	INTERVAL	OUTCOME
AIR #11							
Old	J.S.	29	Cautery	Ampullary-Isthmic	Hood	8 mo.	Pregnancy in Progress.
New	D.R.	32	Cautery	Bilateral Ampullary-Isthmic	OMPI		
AIR #12							
New	P.T. (W)	31	Pomeroy	Ampullary-Ampullary	OMPI		2nd look laparoscopy: tubal patency
Old	J.M.	35	Pomeroy	Ampullary-Ampullary	Hood	6 mo.	In progress
AIR #13							
Old	A.A.	26	Cautery	Ampullary-Isthmic	Hood		
New	P.C.	25	Pomeroy	Ampullary-Isthmic	OMPI	2 mo.	Pregnancy in Progress
AIR #14							
Old	J.H.	31	Cautery	Ampullary-Isthmic	Hood		
New	D.M.	28	Pomeroy	Ampullary-Isthmic	OMPI		
AIR #15							
New	D.M.	24	Pomeroy	Ampullary-Ampullary	OMPI		
Old	S.A.	32	Pomeroy	Ampullary-Ampullary	Hood		
AIR #16							
Old	M.S.	35	Pomeroy	Ampullary-Ampullary	Hood		
New	P.B.	27	Cautery	Ampullary-Ampullary	OMPI	3 mo.	Pregnancy in Progress

ERED PAIRS	INITIALS	AGE	STERILIZATION PROCEDURE	ANASTOMOSIS (SEGMENTS)	MAGNIFICATION	PREGNANCY INTERVAL	PREGNANCY OUTCOME
AIR #17							
Old	J.E.	31	Cautery	Ampullary-Isthmic	Hood		
New	D.M.	30	Cautery	Ampullary-Isthmic	OMPI		
AIR #18							
Old	A.W.	27	Falope Ring	Ampullary-Isthmic	Hood		
New	M.M.	17	Pomeroy	Ampullary-Isthmic	OMPI		

PROJECT II

HISTOPATHOLOGICAL DESCRIPTION OF FALLOPIAN TUBES FOLLOWING VARIOUS METHODS OF TUBAL OCCLUSION IN WHICH THERE HAVE BEEN BOTH SUBSEQUENT SUCCESS AND FAILURE

The objective of this study is to develop a hypothesis for the improvement of safety and efficacy of tubal ligation.

Principal Investigator: Dr. Timothy H. Parmley

A.I.D. Interim Progress Report

Since the beginning of the project, we have established a registry which now includes nine tubes, from five patients, which were removed incidentally as a part of surgery for major pelvic disease. Each of these tubes had previously been subjected to a tubal ligation. In addition, there are twenty tubes, from thirteen patients who had experienced a pregnancy failure after a previous ligation, and there are seventy tubes, from thirty-five patients, obtained at the time of elective reanastomosis. All but ten of the last group of patients are described in a publication which has been accepted by Fertility and Sterility and is currently in press. A copy of this publication is attached.

Briefly, the publication describes the fact that histopathologic examination of these tubes reveals that in cases in which the method of tubal ligation left a short proximal segment, i.e., less than 4cm., there was approximately a 75% incidence of endometriosis and a 40% incidence of fistula of which about half were tuboperitoneal fistulae. As there is no endometriosis elsewhere in these cases, and as the endometriosis when it is only rudimentary is always present in the interior of the tube, it would appear that actively growing endometriosis develops in short proximal segments after tubal ligations and with continued growth results in tuboperitoneal fistulae in approximately 40% of those cases with short proximal segments. By and large, this means patients subjected to laparoscopic tubal ligation methods. This same process occurs, but much less frequently after ligations that leave long proximal segments, i.e., the Pomeroy.

The numbers in this paper seem adequate to demonstrate that a process related to endometriosis develops in the proximal segment of tubes post tubal ligation and that this process may result in fistulae. However, the numbers

are not adequate to suitably refine the relative contribution of the type of prior tubal ligation, the length of proximal segment resulting from the ligation, or the time after the ligation. Additional factors such as patient age are also not properly evaluated by these numbers. Consequently, it seems appropriate to continue the collection of data until larger numbers have been amassed. Ten additional cases not fully analyzed as yet, would appear to be consistent with our previous material. We have definite knowledge of the number of cases available to be studied within the next few months and feel confident that there will be no problem in collecting the total number required for fulfillment of the contract.

ENDOMETRIOSIS AND THE DEVELOPMENT OF TUBO-PERITONEAL FISTULAE AFTER TUBAL LIGATION*

John A. Rock, M.D.+

Tim H. Parmley, M.D.

Theodore M. King, M.D., Ph.D.

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Brian Hsu, M.D.

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and

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ABSTRACT

The present study details gross and histologic findings of 79 previously ligated fallopian tubes from three groups of patients. Of 20 oviducts removed after documented sterilization failure (Group I), 6 revealed a process compatible with endometriosis. Four of 9 previously ligated fallopian tubes, removed at the Johns Hopkins Hospital (Group II), were successfully injected with India ink. In two patients histologic examination demonstrated the India ink in epithelial-lined spaces that lay beyond the muscle of the tube wall extending from the tubal lumen to the serosal surface.

Fifty oviducts were studied in 25 patients requesting reversal of their sterilization (Group III). A higher percentage of fistulae were demonstrated in patients with less than 4 cm length of remaining proximal tubal segment. Furthermore, a majority of these fistulae were demonstrated in patients where 3 years had lapsed since the original sterilization procedure. Patients sterilized by laparoscopic cautery methods were observed to have a higher percentage of fistula formation and histological documentation of endometriosis at the sterilization site as compared to other sterilization methods. Our observations suggest that ovid tal ligation within 4 cm of the uterine cornua may predispose to the development of endometriosis and subsequent fistulization i the tip of the ligated oviduct.

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INTRODUCTION

Extrauterine and intrauterine pregnancy occurring after surgical ligation of the fallopian tubes continues to be a clinical problem.[1-5] While luteal phase pregnancies seem preventable with the proper patient selection, and operator error can be minimized with proper training, some failures seem currently unpreventable. These occur months or years after the sterilization procedure, and many are extrauterine.[5] When examined, the fallopian tubes from these sterilization failures appeared to have been properly ligated. In the past, such late failures have been attributed to "recanalization". In the sense that this implies reestablishment of a lumen between the proximal and distal portions of properly ligated fallopian tubes, we have not seen such a case. On the other hand, tubo-peritoneal fistulae have been observed.[1-4] We have investigated the nature of these fistulae.

MATERIALS AND METHODS

Seventy-nine previously ligated fallopian tubes were studied. Twenty of these oviducts, from 13 patients (Group I), were referred from other institutions for evaluation of the cause of sterilization failure. This material was often fragmentary and could not be appropriately oriented for microscopic study. Frequently only one tube was received. Consequently, microscopic sections were taken at random.

Nine tubes (Group II) were surgically removed at the Johns Hopkins Hospital as an associated part of pelvic surgery performed for other reasons. These tubes were of sufficient length to allow the injection of India ink using a 2½ cc syringe and a 25 gauge needle. The syringe was filled and the needle was placed in the proximal lumen and the ink was injected until the tube dilated or the ink passed through the fistula. This was done carefully

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and the pressure was not monitored. Microscopic sections were prepared to demonstrate the India ink in the fallopian tube and/or fistulous tract.

Fifty oviducts (Group III) were studied both in vivo and in vitro. These studies occurred as a part of the routine evaluation and treatment of 25 patients admitted for tubal anastomosis. Preoperatively, all patients receive a hysterosalpingogram. Hysterosalpingograms were performed using a Rubin's cannula to which a 10 cc syringe, containing 5 cc of salpinx® was attached. Two cc's of contrast media were then injected into the uterus and an initial x-ray obtained. Then an additional 3 cc of dye was injected into the uterus and a second x-ray obtained. No patient had received a hysterosalpingogram prior to their previous sterilization. At the time of surgery, cervical obstruction was accomplished with a Shirodkar clamp and a transfundal needle was placed and used to fill the endometrial cavity and proximal fallopian tube with indigo carmine dye. Any tubal fistula was thus demonstrated. When the tip of the proximal segment of ligated tube was removed in order to perform the anastomosis, this area of the oviduct was sectioned in order to investigate the nature of a fistula detected by hysterosalpingography and/or transfundal indigo carmine injection. The presence or absence of any other pelvic disease, and the length of the proximal segment of tube, was also determined at the time of surgery. The length of the fallopian tube was measured such that the interstitial tube was not included in the measurement. The clinical record was reviewed to ascertain the interval of time since the tubal ligation, and the type of sterilization procedure performed.

RESULTS

Of the 20 fallopian tubes referred from other institutions after documented failure (Group I), 6 had evidence of a process that resembled salpingitis isthmica nodosa except that some of the epithelial inclusions clearly were associated with a stroma that qualified them for the diagnosis

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of endometriosis (Fig. 1). That is, stroma and glands histologically identical to that seen in the uterine endometrium were observed. In several cases, this process appeared to extend from the lumen to the serosal surface of the ligated tube. Unfortunately, careful documentation of a fistulous tract was not possible as the surgical material was fragmentary and could not be oriented for microscopic study. Furthermore, the oviducts were not of sufficient length to allow injection of dye to demonstrate the fistulous tract.

To investigate the nature of the fistulous tract associated with endometriosis, 9 previously ligated fallopian tubes, removed at the Johns Hopkins Hospital (Group II), were injected with India ink. It was possible to successfully inject 4 oviducts and to demonstrate 2 fistulae with this technique. When sectioned, the oviduct with fistula revealed India ink in the tubal lumen and in epithelial-lined spaces that lay in and beyond the muscle of the tube wall, extending from the tubal lumen to the serosal surface (Fig. 2). Many of these were apparently foci of endometriosis, in which gland lumina were the fistulous tract. The criteria for the diagnosis of endometriosis consists of glands and stroma identical to that normally found in the endometrial cavity.

With these observations in mind, 25 patients undergoing tubal anastomosis (Group III) were carefully evaluated preoperatively by hysterosalpingography. Eight cases and 11 tubes showed x-ray evidence of a fistula at the tip of the proximal segment of tube. At the time of operative injection of indigo carmine dye, all of the radiologically demonstrated fistulae were confirmed. Furthermore, 3 unsuspected fistulae in 3 additional patients were documented (Fig. 3). In all, 14 fistulae were documented with these techniques. It was also observed that 5 of the fistulae extended into the broad ligament

but did not reach the peritoneal surface.

Careful inspection of the pelvis at the time of operation revealed no evidence of peritoneal or ovarian endometriosis; however, in 15 patients apparent endometriosis was observed clinically at the tip of the proximal segment of a fallopian tube. In one of these neither a fistula nor the endometriosis was identified microscopically. Frequently, little blebs were seen beneath the peritoneum (Fig. 4). Similar foci were not seen on the distal segment of the fallopian tube. Microscopically, all but 1 of 14 tubes with a fistula appeared to have endometriosis at its tip extending through the wall of the tube. One of these fistulous tubes was not studied microscopically. In 10 cases, endometriosis without a fistula was seen microscopically. This process was not extensive and was not seen to extend through the wall of the tube. At operation, endometriosis was not observed in the distal segment of the ligated tube.

Type of prior ligation was correlated with the frequency of fistulae (Table 1). A high percentage of fistulae and endometriosis was observed in fallopian tubes ligated using the laparoscopic cautery methods. Although no fistulae were observed in tubes ligated with a silastic ring, 4 of these oviducts revealed endometriosis.

The percentage of fistulae and endometriosis was also correlated with the length of remaining proximal tubal segment. Thirteen fistulae were observed in 29 proximal oviducts of less than 4 cm. Furthermore, endometriosis was documented in 20 of 27 tubes of less than 4 cm in length. The percentage of fistulae and endometriosis in oviducts 4 or more centimeters in length was 5% and 20%, respectively (Table 2).

The time interval since prior ligation was correlated with the number of fistulae and endometriosis in each tube studied. The results suggest

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that by 3 years after the sterilization procedure a high percentage of fistulae have been formed (Table 3).

DISCUSSION

This report presents results and histological findings of oviducts from 3 groups of patients. The original group of oviducts referred from other institutions after failure, revealed a process compatible with endometriosis. It was possible to demonstrate a fistulous tract with the injection of India ink in 2 of 9 patients in the second group of ligated oviducts from patients undergoing pelvic surgery. To further ingestigate the nature of these findings, 25 patients requesting reversal of sterilization were carefully studied preoperatively by hysterosalpingography and at the time of anastomosis. After successful ligation of the oviduct within 4 cm of the uterine cornua, endometriosis developed in the tip of the proximal segment of ligated tube in a high percentage of patients. Prior to the development of the fistula, the tube appears to be dilated. Progressive extension of the endometriosis, perhaps aided by intra-tubal pressure, appeared to result in penetration of the muscular wall of the tube with subsequent fistulization either into the broad ligament or into the peritoneal cavity.

The authors speculate that regurgitated menstrual fluid may be responsible for the development of endometriosis and the dilatation of the tube. As the length of the proximal segment and the type of procedure is correlated with the number of fistulae and endometriosis, within the oviducts studied, it is not possible to know which of these two factors is more important in contributing to the subsequent development of fistula. Nevertheless, our observations suggest that the Pomeroy procedure, performed

greater than 4 cm from the cornua, results in fewer fistulae; furthermore, ligation proximal to the ampullary-isthmic junction may result in a proximal segment which is subject to fistula development.

As this process appears to develop within 1 to 4 years of tubal ligation, it is of interest to consider what role it may play in the so-called post-tubal ligation syndrome. It is certainly conceivable that pain and irregular bleeding might be concomitant symptoms. In future attempts to define a post-tubal ligation syndrome, the time course of developing endometriosis in the proximal ligated segment should be taken into account. Further, the time course supports the clinical experience of Cunanan, et al. with respect to pregnancy failure.[5]

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TABLE 1

STERILIZATION REVERSAL (GROUP III):

PERCENTAGE OF FISTULA AND ENDOMETRIOSIS VS. TYPE OF LIGATION

Type of Ligation	# of Fistulae/ # of tubes studied	# tubes with endometriosis/ # tubes studied
Coulory	12/23* (46%)	15/24* (6 %)
Pomeroy	2/18 (11%)	5/18 (28%)
Silastic Ring	0/6 (0%)	4/6 (66%)

*One case not submitted to pathology.

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TABLE 2

STERILIZATION REVERSAL (GROUP III):

PERCENTAGE OF FISTULA AND ENDOMETRIOSIS VS. LENGTH

OF REMAINING PROXIMAL TUBAL SEGMENT

Length of Remaining Proximal Tubal Segment	# of Fistulae/ # Tubes Studied	# Tubes with Endometriosis/ # Tubes Studied
Less than 4 cm.	13/29 (45%)	20/27* (74%)
4 or more cm.	1/21 (5%)	4/21 (20%)

*One case not submitted to pathology.

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TABLE 3

STERILIZATION REFERSAL (GROUP III):

NUMBER OF FISTULA AND ENDOMETRIOSIS VS. TIME SINCE ORIGINAL LIGATION

Time Since Original Ligation (Yrs.)	# of Fistulae/ # of Tubes Studied	# Tubes with Endometriosis/ # Tubes Studied
<1	0/4	0/4
1	0/0	0/0
2	1/2	1/2
3	6/14	10/14
4	3/8	7/8
5	1/6	1/6
6	2/8	3/8
7	1/4*	0/2*
8	0/4	2/4

*One case not submitted to pathology.

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FIGURE LEGENDS

Fig. 1) This focus of endometriosis is situated in the muscularis of the tube wall at the tip of the proximal segment. Similar foci were arranged from the lumen to the serosal surface. Not all had well-developed stroma however, and those more closely simulated salpingitis isthmica nodosa.

Fig. 2) After the proximal segment of fallopian tube was removed from the uterus, it was injected with India ink. In this case, a fistula was demonstrated and the section shows the ink in the endometriosis that lay between the lumen of the tube and the serosa.

Fig. 3) A fistula is demonstrated by the dark spot of indigo carmine seen at the cornua. The scarred top of the broad ligament extends to the right with the distal segment of tube just out of the picture. The ovary is posterior. The dye was injected through a needle in the top of the fundus just out of the picture on the left.

Fig. 4) Superficial blebs, associated with endometriosis, are seen at the tip of the proximal segment of tube. The scarred portion of tube and the distal segment are seen beneath this site.

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5. Cunanan RG, Courey NG, Lippes J: Complications of laparoscopy tubal sterilization. Obstet Gynecol 55:501, 1980.

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PROJECT III

THE EXPERIMENTAL PROTOCOL FOR DILATATION AND EVACUATION VS. INTRA-AMNIOTIC UREA PROSTAGLANDIN F_2a

The objective of this study is to identify and evaluate safer and more practical abortifacients.

Principal Investigator: Dr. Theodore M. King

PROJECT III

The initiation of this project was delayed in being started because of unavailability of surgical equipment to process these patients in an appropriate manner.

This work is now starting since this equipment has now been delivered.

Since the site visit on October 14, the principal investigator has visited the University of Indiana where on an outpatient basis, dilatation and evacuations are completed on pregnancies up to 22 weeks in duration. The operation is performed on women who have had laminaria inserted for 24 hours. The procedure is completed under cervical block anesthesia with no systemic analgesics. The principal surgeon at the University of Indiana is Dr. Robert Munsick and he has completed more than 220 cases in excess of 16 weeks duration and has not sustained a "major life-threatening complication".

This study has now started.

PROJECT IV

THE ANIMAL TESTING OF CHEMICAL ABORTIFACIENTS

The objective of this study is to identify and evaluate safer and more practical abortifacients.

Principal Investigator: Dr. Norman H. Dubin

PROJECT IV

Two projects currently in progress are described below. One study using LRH analogs is being tested in monkeys, and another using "suicide substrate" is being tested in rats. Our study involving epsilon amino caproic acid is in press in Biology of Reproduction and is included in this report. A rough draft concerning our experience with silver nitrate in monkeys is also included.

LRH-Analogues

We have received three LRH agonists from AID; viz. 1) HOE 766 2) D-Trp^6-Pro^9-Net 3) [imB_z 1-D-His^6-Pro^9-Net]-LRF

Following conversations with Dr. Shelton (AID); Vern Stevens (Ohio State) and Robert Casper (presently at Halifax, Nova Scotia), it was decided to initially test D-trp^6-Pro^9-Net in pregnant monkeys for anti-fertility activity. According to Dr. Casper we should try as large a dose over as long a period of time as possible. He also suggested subcutaneous injection in saline. Because of the limited amount of drug at our disposal (10 mg) we decided to inject 1 mg x 3 days at approximately 1 month of gestation. This would allow 2 initial monkeys to be examined with the drug.

Protocol

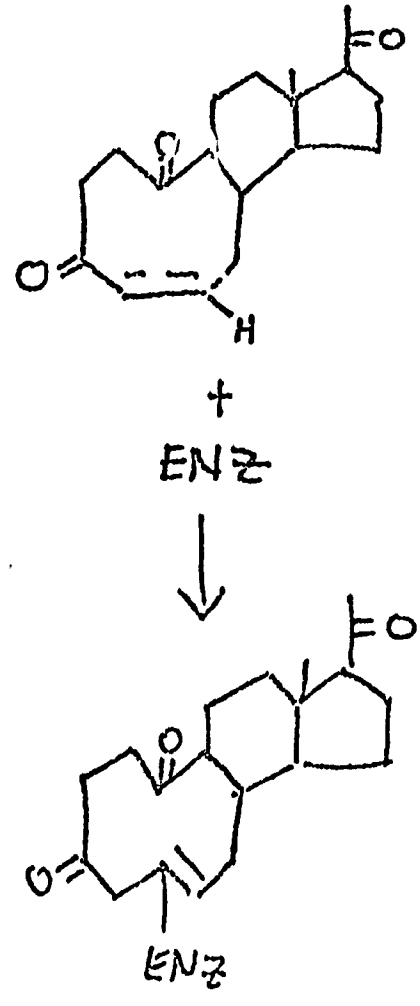
Monkeys will be followed for menstrual cycles and mated for restricted timed periods after vaginal bleeding. Pregnancy test will be performed 18-21 days after the middle of the mating period. If pregnant, as indicated by palpation and/or HCG hemagluttination inhibition test, the animal will be placed on protocol. Within 2 1/2 to 4 1/2 weeks of the estimated onset of pregnancy, monkeys will receive an injection of either LRH analogue or saline. Prior to administration of test drug, blood will be drawn for analysis of progesterone, estradiol and chronic gonadotropin. Blood will also be analyzed at 1, 2, 4, 7 and 28 days after injection. At 28 days animal will be rechecked for progress of pregnancy.

Current Status

Currently 15 monkeys are being followed for cycling activity. Several monkeys have been mated and 1 has become pregnant. This animal has been injected with D-Trp^6-Pro^9-Net and is currently being followed.

Suicide Substrate

Synthesis of a small amount of an allenic alcohol of the pregnane series has been completed by Dr. Cecil Robinson, Department of Pharmacology. This compound has been found to be a potent inhibitor of the 3-β-ol steroid dehydrogenase reaction as tested in an in vitro microsomal system. The compound is a "suicide substrate" in that when acted upon by the enzyme, it irreversibly binds to it (Figure 1), thus inactivating that enzyme. This compound will now be tested in pregnant rats for its antifertility effects as well as its effect on both progesterone and conticosterone induction.



In Press
Biology of Reproduction
Dec. 1980.

EFFECT OF EPSILON AMINO CAPROIC ACID, A FIBRINOLYTIC INHIBITOR, ON IMPLANTATION AND FETAL VIABILITY IN THE RAT

Norman H. Dubin

Doris B. Cummings

David A. Blake

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Running Page Heading: EACA and Early Pregnancy

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ABSTRACT

In vitro evidence suggests that fibrinolytic activity is involved in the implantation process. *In vivo* experiments were performed in rats to determine if fetal development can be prevented by epsilon amino caproic acid (EACA), a fibrinolytic inhibitor. Timed pregnant rats were laparotomized on various days of pregnancy and EACA or control injections were made directly into a uterine horn. Animals were autopsied on pregnancy Day 15 when implantation and fetal viability rates were determined. Intraluminal EACA did not effect implantation rate but fetal viability was adversely affected when 3 mg was injected on Day 6. This effect was dose-related and was partially reversed by simultaneous injection of plasmin. No effect was observed on Day 3, 7, 8. Day 4 and 5 could not be tested because sham injections alone caused a high resorption rate. Subcutaneous injections, as high as 60 mg daily from Day 3 to 10 did not affect fetal viability. The experiments support the hypothesis that fibrinolytic activity around the time of implantation is important for maintenance of pregnancy.

INTRODUCTION

The implantation process involves a complex series of interactions between the blastocyst and uterus (see Weitlauf, 1979 for review). Trophoblastic function in this process may depend upon several distinct biochemical events from the time of attachment to the uterine epithelium until a relationship with the maternal circulation is established. Recent *in vitro* evidence indicates that the mouse trophoblast contains plasminogen activator activity and its invasiveness may depend upon fibrinolytic activity (Sherman et al., 1976). This is consistent with the findings that other migratory cells also produce plasminogen activator (Ossowski et al., 1973; Unkeless et al., 1974). The present experiments utilizing epsilon amino caproic acid (EACA), a fibrinolytic inhibitor (Figure 1), provide *in vivo* evidence that plasminogen activator activity may be important in early stages of pregnancy in the rat.

MATERIALS AND METHODS

Rats were purchased timed pregnant from Charles River Breeding Laboratories (CD®), Wilmington, MA. The day sperm were observed in the vagina was defined as pregnancy Day 1. On various days of pregnancy, groups of rats were lightly anesthetized with ether and laparotomized under aseptic conditions. The uterine horn to be injected was grasped lightly with forceps near the cervical end and a sterile 25 gauge needle attached to a 1 ml tuberculin syringe was inserted through the uterine wall into the lumen. Various doses of drugs were injected into the lumen. Light pressure was placed on the forceps during the injection and for 10 seconds after removal of the needle to prevent backflow. The abdominal wall was sutured and the skin closed with wound clips. The

rats were returned to their cages until autopsy on Day 15. At autopsy, corpora lutea, implantation sites and viable fetuses (based on size and gross appearance) were counted. Appearances of normal and resorbed sites are photographically illustrated in another publication (Dubin et al., 1979). Percent implantation was determined by dividing the number of implantations by the number of corpora lutea; percent viability was determined by dividing the number of viable fetuses by the number of implantation sites.

Study 1. Effect of Day of Injection

Rats were injected once between Day 3 and 8 of gestation. Groups of rats received either EACA or the saline vehicle. Other groups were sham treated, that is, the needle was inserted into the uterine lumen but nothing was injected. The EACA dose used in this study was determined by the maximal solubility (30 mg/0.1 ml) and the volume that would yield an acceptable viability rate when the vehicle alone was injected (see Discussion). EACA was prepared fresh on the day before injection in 0.9% sterile sodium chloride.

Study 2. Effect of EACA Concentration

All rats received EACA in one uterine horn on Day 6 of pregnancy. Groups received either 0.3, 0.6, or 3.0 mg EACA in a 0.01 ml volume. The contralateral horn received 0.01 ml saline.

Study 3. Effect of Plasmin

Lyophilized plasmin was reconstituted in sterile 0.9% sodium chloride immediately before injection. Plasmin doses are expressed in caseinolytic units (CU; Sgouris et al., 1960). On pregnancy Day 6, rats received intraluminal injections of either 3 mg EACA, 3 mg EACA plus 0.5 CU

plasmin (KABI, Sweden), 0.5 CU plasmin alone, or saline in a 0.01 ml volume. In this experiment, both horns of the uterus were injected with the same substance.

Study 4. Effect of Systemic EACA

Groups of rats received subcutaneous injections of either 0, 15, 30 or 60 mg of EACA daily from Day 3 to 10. The concentration of the injection fluid was always 30 mg/0.1 ml.

Statistical Analysis

In study 1, comparisons were made by students' t test. In all other studies, analysis of variance were performed with F ratios used to test for significant differences between treatments.

RESULTS

Study 1. Effect of Day of Injection

In untreated rats the implantation rate was 82.2 ± 6.7% while the viability rate of those implantations was 93.8 ± 4.9% (Table 1). Sham intrauterine injections on any one day between pregnancy Day 3 and 8 did not affect the implantation rate, however, viability was affected when a sham injection was performed on Day 4 (46.1 ± 10.7%) or Day 5 (8.9 ± 6. .). Injection with normal sterile saline (0.1 ml) reduced percent implantation when injection was made on Day 4. Saline injections affected viability on Days 4 and 5 although this effect could be accounted for by merely inserting the needle since the percent viability these groups were not significantly different from the sham injections on comparable days of pregnancy. Injection of 0.01 ml saline on Day 6 decreased percent viability below the level of the sham control (47.3 ± 11.5 versus 82.7 ± 5.5%). Injection of 3 mg EACA in the same volume of saline further

reduced the percent viability to 13.3 ± 6.0%. EACA did not affect viability on any other day tested nor did it affect implantation on any day tested. EACA was not tested on Day 4 or 5 because of the low viability rates encountered with sham injection.

Study 2. Effect of EACA Concentration

When intrauterine injections were made on Day 6, the percent viability was dependent upon the dose of EACA administered (Figure 2). In this study, all injections were made in 0.01 ml saline.

Study 3. Effect of Plasmin

In another study, intrauterine injections of 3 mg again resulted in reduced viability (13.9 ± 4.3% versus 54.1 ± 5.4% for saline control; $P < .001$, Figure 3). Injection of EACA along with plasmin resulted in 35.5 ± 6.5% viability which was significantly higher than EACA treatment alone, yet less than the saline treated rats ($P < .05$). Plasmin alone reduced fetal viability to 39.7 ± 12.4%.

Study 4. Effect of Systemic EACA

No differences in either implantation or fetal viability were observed following systemic injection of up to 60 mg EACA/day from Day 3 to 10.

DISCUSSION

Implantation involves complex interactions between trophoblast and uterine tissue (Weitlauf, 1979). The trophoblastic function itself may involve numerous events which depend on different biochemical mechanisms. For example, blastocyst surface glycoproteins may be important for attachment to the uterine wall (Enders and Schlafke, 1974; Hicks and Guzman-Gonzalez, 1979). Estrogen production which has been noted in

rabbit blastocysts, may increase capillary permeability at the implantation site (Dickmann, 1975; Dickmann et al., 1979). Progesterone synthesis has been demonstrated in rat trophoblast (Salomon and Sherman, 1975) and this may cause local immunologic suppression and prevent rejection of the heterologus embryo (Siiteri, 1976).

Invasion through the intracellular matrix represents yet another trophoblastic process and it appears to be, in part, dependent upon fibrinolytic activity. Migratory cells, such as malignant cells (Ossowski et al., 1973) and macrophages (Unkeless et al., 1974), produce plasminogen activator. Plasminogen activators convert plasminogen to plasmin, a fibrinolytic enzyme (Figure 1). Plasmin, or closely related enzymes may be important in degradation of the intracellular matrix, thus fascilitating cell movement. Fibrinolytic activity has been reported in cultured mouse trophoblast (Sherman et al., 1976) and first appears on Day 6 and peaks on Day 9 corresponding to the time of trophoblast invasion in the mouse. The action of plasmin on connective tissue may be mediated, in part, by stimulation of collagenase production (Werb and Aggeler, 1978).

We have tested <u>in vivo</u> the effect of EACA, a fibrinolytic inhibitor on both implantation and fetal viability in pregnant rats. One approach was to inject the drug directly into the uterine lumen around the time of implantation. Some technical difficulties were encountered because of non-specific effects. We previously showed that intraluminal injections of 0.1 ml of normal sterile saline will result in a significant reduction in implantation rate when administered on Day 4 (Dubin et al., 1979). Furthermore, fetal viability was affected when saline was injected on Days 4, 5, 6 or 7. On Day 6, almost all implantation sites were resorbed

from horns receiving 0.1 ml saline. This effect was volume dependent. Since Day 6 is of particular interest because trophoblast invasion is occurring about this time (Enders and Schlafke, 1967), the highest concentration of EACA in the smallest volume (3 mg/.01 ml) was injected at this time.

Intrauterine EACA administration did not affect implantation rates when injected on Day 6, but it did increase the number of resorptions, possibly by preventing normal trophoblastic function. This effect was dose-dependent and could be partially reversed by simultaneously injecting plasmin along with the EACA. While the viability rates did not attain the level of the saline treated controls, they were close to the rates in the group receiving plasmin alone. The reason for reduction in viability due to plasmin alone is not known. The effect of EACA appears to be limited to a discrete time period. On Day 7, high doses (30 mg) had no effect on fetal viability. Also, no effect was observed when EACA was injected on Day 3, which is probably due to the fact that the ova has not yet reached the uterus. Day 4 and 5 could not be tested due to non-specific effects on viability merely due to insertion of the needle at these times. The present experiments do support the hypothesis that plasminogen activator activity is involved in the implantation process and provide *in vivo* evidence for its physiologic importance. Other proteases have been demonstrated to block implantation in mice (Dabich and Andary, 1974).

Although systemic (oral) antifibrinolytic agents including EACA are effective in women in reducing menstrual blood loss (Callender et al., 1970; Kullander, 1970), in our study systemic (subcutaneous) administration of EACA had no effect on fetal viability. This might be because of inaccessability of the drug to the blastocyst residing within the uterus.

It has been noted that IUD insertion increases plasminogen activator activity in the endometrium (Kasonde and Bonnar, 1976). EACA reduced IUD induced menorrhagia (Kasonde and Bonnar, 1975). There is no documentation that IUD's containing EACA are more effective in reducing fertility, however, in light of the present experiments and other evidence discussed, it is hypothesized that such devices provide additional protection because of EACA's effect on suppressing trophoblast invasiveness.

ACKNOWLEDGMENTS

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Table 1

EFFECT OF INTRAUTERINE EACA ON IMPLANTATION AND FETAL VIABILITY ON VARIOUS DAYS OF PREGNANCY

Treatment Day	Treatment	Number	Percent Implantation	Percent Viability
-	Untreated	6	82.2 ± 6.7	93.8 ± 4.9
3	Sham	5	92.0 ± 8.0	89-4 ± 6.8
	Saline	12	85.1 ± 4.4	88.0 ± 3.8
	EACA (30 mg)	9	89.1 ± 7.3	86.1 ± 11.3
4	Sham	10	80.9 ± 9.8	46.1 ± 10.7*
	Saline	10	62.6 ± 5.7x	25.0 ± 10.4*
	EACA	not determined		
5	Sham	9	85.8 ± 6.1	8.9 ± 6.1*
	Saline	6	65.9 ± 7.6	24.17 ± 12.9*
	EACA	not determined		
6	Sham	20	78.0 ± 4.9	82.7 ± 5.5
	Saline	7	65.2 ± 9.2	47.3 ± 11.5*†
	EACA (3 mg)	6	70.4 ± 10.9	13.3 ± 6.0**
7	Sham	17	78.8 ± 4.6	86.7 ± 6.7
	Saline	8	74.9 ± 8.6	75.9 ± 11.4
	EACA (3 mg)	8	70.9 ± 9.0	82.4 ± 5.9
8	Sham	8	68.2 ± 9.2	70.4 ± 15.4
	Saline	11	77.6 ± 8.6	77.8 ± 9.1
	EACA (30 mg)	9	81.9 ± 8.7	91.0 ± 5.6

x = $P < .05$ vs. untreated control

* = $P < .01$ vs. untreated control

† = $P < .01$ vs. sham control for the same day

** = $P < .05$ vs. saline control for the same day

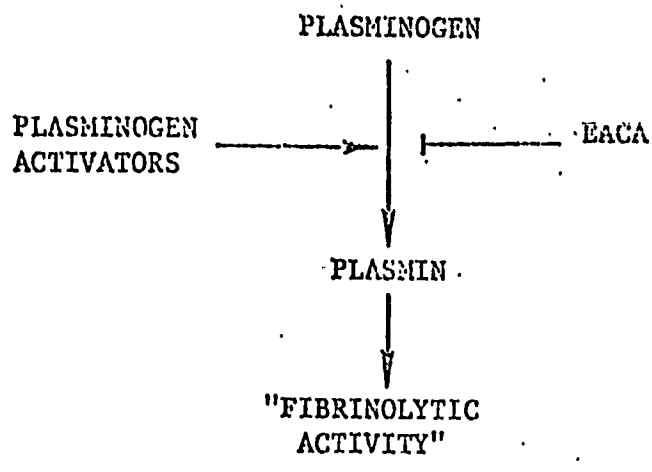


Figure 1. The Fibrinolytic System

Figure 2. Effect of various doses of EACA on fetal viability. All doses were injected directly into the uterine lumen on pregnancy Day 6. Volume of injection fluid was 0.01 ml in each horn, regardless of dose. Control horns (0 mg dose) were contralateral to a horn receiving EACA. Bracketed number designates number of treated uterine horns. Vertical line is standard error of the mean.

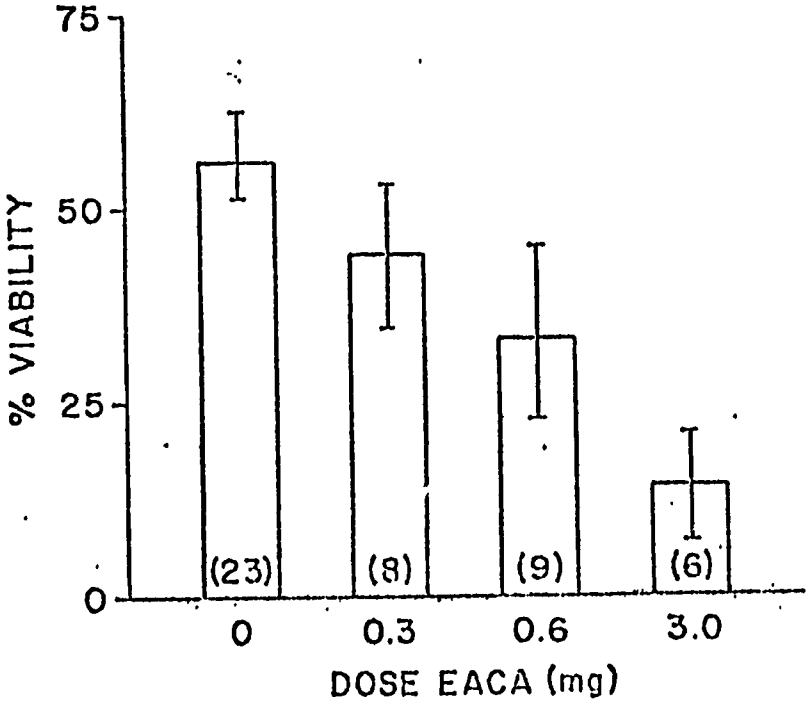
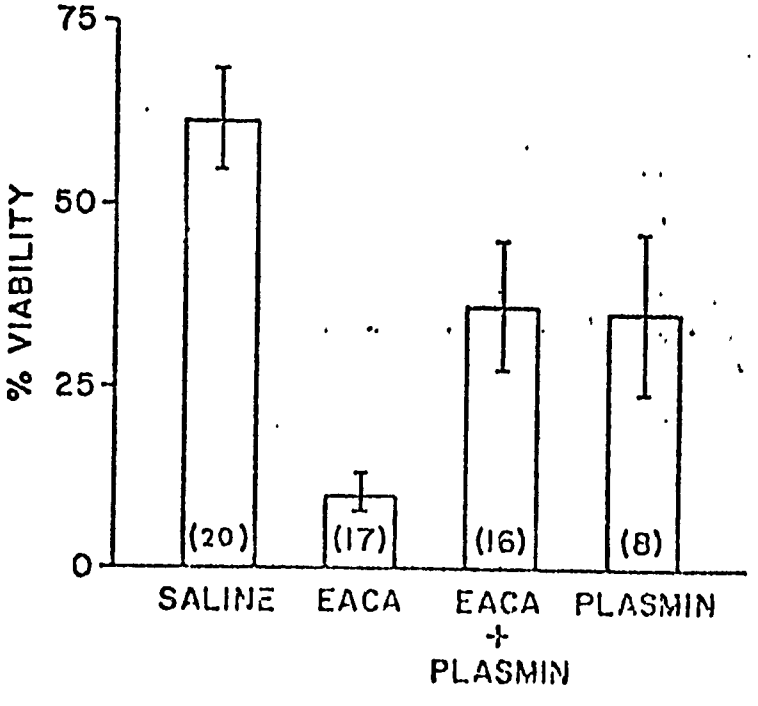


Figure 3. Effect of EACA (3 mg/horn) and plasmin (0.5 CU/horn) on fetal viability. All injections were made directly into the uterine lumen on pregnancy Day 6. Volume was 0.01 ml in each horn regardless of treatment. Bracketed numbers represent number of rats treated. In this experiment, both horns of each rat received the same treatment. Vertical line is standard error of the mean.



EFFECT OF SILVER NITRATE ON PREGNANCY TERMINATION IN CYNOMOLGUS MONKEYS

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INTRODUCTION

Chemical methods of menstrual induction are an alternative to early surgical procedures of abortion. A major advantage might be less need for skilled professionals. We have previously reported that several protein denaturants had antifertility activity in rats (Conner et al., 1976). At that time, it was decided to test several more active compounds for efficacy in monkeys. Results with ehtanol have previously been reported (Dubin et al., 1978, 1980). This paper reports our results with another of our selected compounds, silver nitrate.

MATERIALS AND METHODS

Cynomolgus monkeys (Macaca fascicularis) were obtained from Primate Imports (Port Washington, NY). They were fed Monkey Chow (Charles River Breeding Labs, Inc., Wilmington, MA), supplimented with fresh fruit. All monkeys were individually caged except during timed mating periods. Animals were checked daily (including weekends) for vaginal bleeding with cotton swabs. They were cohabitated for 8 days beginning 12 days after the onset of vaginal bleeding. Between 18 and 23 days after the midpoint of the cohabitation period, the mated female was subjected to rectal and abdominal bimanual palpation by an experienced caretaker of primates. At the same time, urine was collected from the bladder by urethral catherization and tested for monkey chorionic gonadotropin (mCG) by a hemagglutination inhibition test (Ortho Diagnostics Inc., Raritan, NJ).

If monkeys were documented pregnant by palpation or mCG testing, they were placed on the study protocol. Day of pregnancy was counted from the midpoint of the cohabitation period. Thus, cohabitation day 5 was counted as pregnancy day 1. At approximately 1 month (range 27-43 days) of pregnancy, the animal was immobilized with an intramuscular injection of

4.4 mg per killogram of body weight of Ketamine hydrochloride (Ketaset). A 12 cm long, 18 gauge, sterile blunt-end stainless steel needle was inserted through the cervix into the uterine cavity until resistance was encountered. A 1 ml solution of either 1% silver nitrate or 0.9% saline was injected. The treatment was randomized and the investigator performing the injection and the animal technician was unaware of which solution was being administered.

The monkeys were observed daily for vaginal bleeding. Blood samples were taken from a peripheral vein prior to treatment, on day 1, 2 and 3 following treatment and at month after treatment for blood chemistry and hematologic evaluations. Blood samples were analyzed by the Division of Clinical Laboratories of the Johns Hopkins Hospital. Also, 1 month after treatment, monkeys were repalpated to determine the pregression of pregnancy.

RESULTS AND DISCUSSION

All monkeys receiving intrauterine injections of 1 ml 1% silver nitrate between 27 and 43 days of pregnancy showed vaginal bleeding beginning one or two days after treatment (Figure 1). The bleeding lasted for an average of 5.3 days (range 4-7 days). These monkeys were found to have non-enlarged or subnormally enlarged uteri at the time of repalpation indicating that abortion had ensued. Continued observation of these monkeys confirmed that they were no longer pregnant. All monkeys recycled after silver nitrate treatment. Two subsequently became pregnant and had normal healthy infants.

Monkeys receiving 0.9% saline had variable outcomes (Figure 2). Two animals (#2 and 3) showed some spotting after injection but pregnancy progressed. These animals delivered normal healthy fetuses at 165 and 181 days. Number 6 had an uneventful pregnancy and a healthy infant was born at 148 days. Number 4 had uneventful pregnancy until delivered by C-section at 103 days of a living fetus as part of another study. Monkey #2 demonstr-

vaginal bleeding on days 6 and 7 following injection and aborted. Monkey #5 passed fetal tissue 29 days after injection.

Hematology and blood chemistry determinations revealed no significant difference between silver nitrate and saline treated monkeys (Tables 1 and 2).

Two monkeys, not in the randomized study, were injected with 1 ml silver nitrate as described in the previous study. Duration of pregnancy at injection was estimated at 37 and 38 days. Animals were hysterectomized and salpingo-oopherectomized at 7 days following injection.

On gross inspection, hemorrhage was observed between the gestational sac and decidua resulting in separation of these tissues (~~Figure 3~~). While there were hemorrhagic sites within the placenta, there was no associated necrosis of the adjacent villi. However, portions of the placenta were separated from the underlying decidua basalis and in these areas there was evidence of tissue autolysis (Figure 3).

The study indicates that 1% silver nitrate in an effective agent for terminating early pregnancy in monkeys.

Figure 1: Effect of intrauterine administration of 1 ml 0.9% saline on pregnancy in cynomolgus monkeys. The following legends apply to this figure and figure 2. Solid bars represent normal progress of pregnancy. Arrow indicates time of treatment. Stippled bar represents vaginal bleeding. A = abortion; B = birth of normal healthy infant; T = pregnancy artifically terminated but fetus viable.

Figure 2: Effect of intrauterine administration of 1 ml 1% silver nitrate on pregnancy in cynomolgus monkeys.

Fig 1

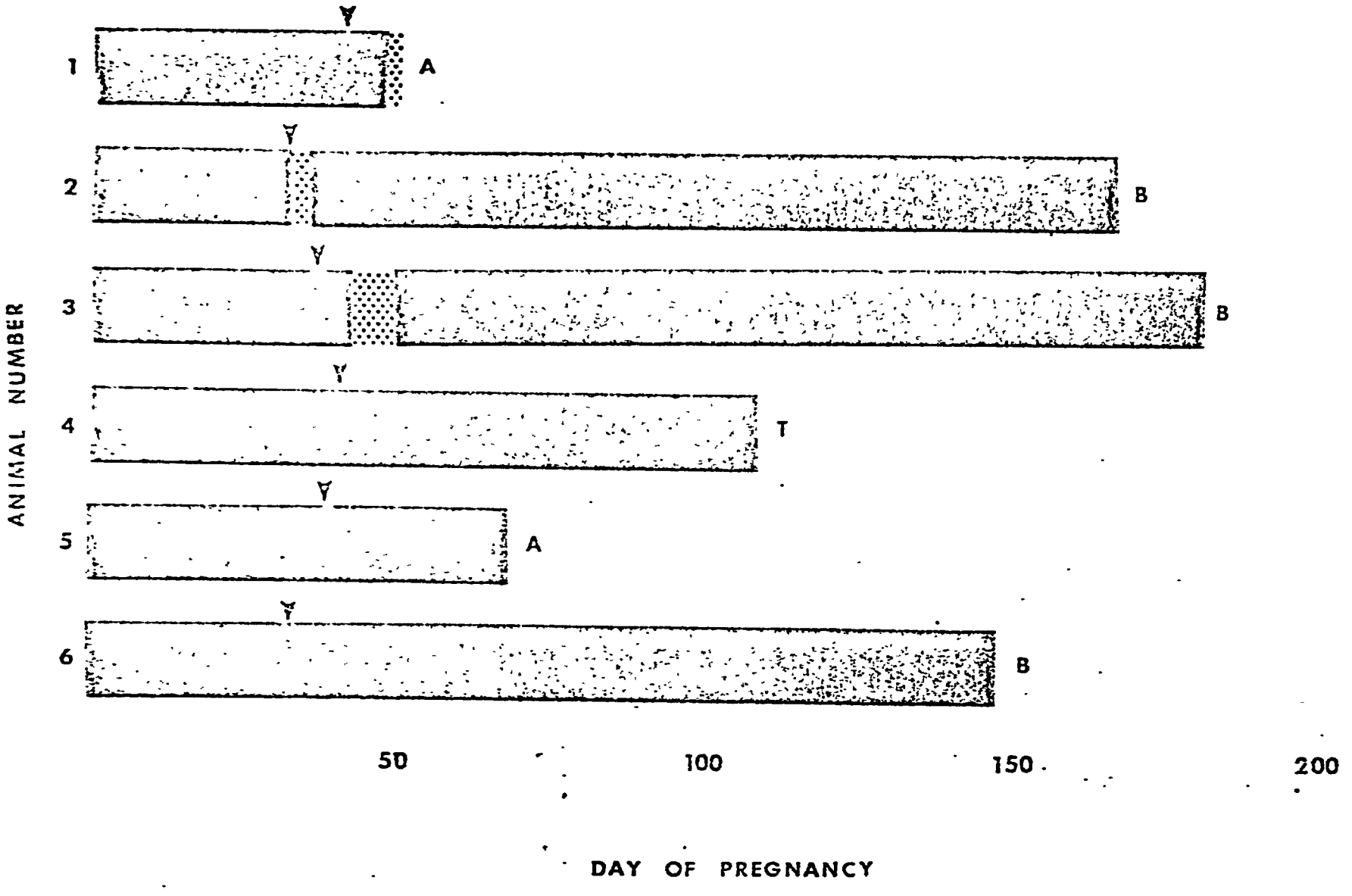


Fig 2

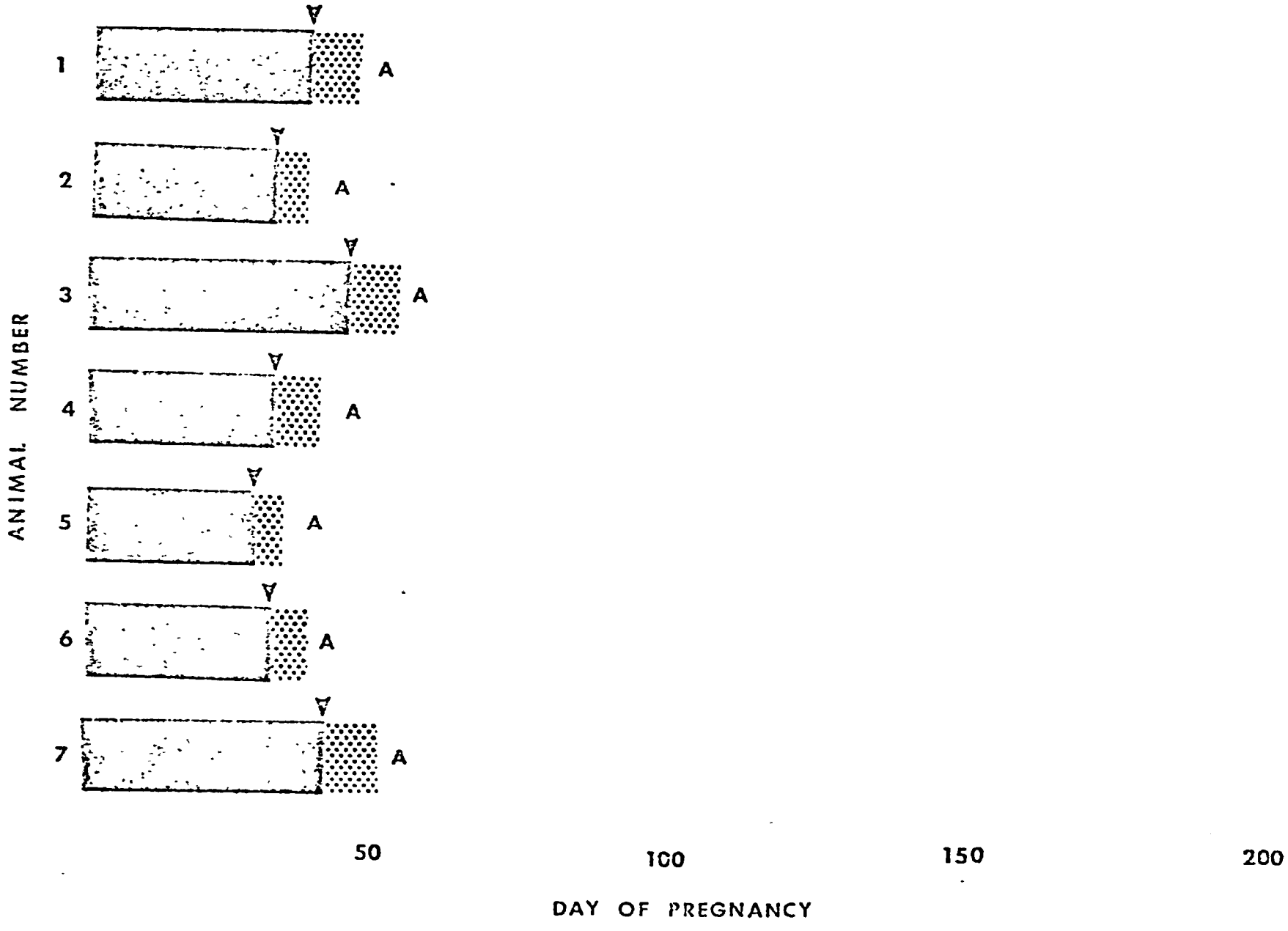


Table 1

Hematology Following Administration of 1 ml 1% Silver Nitrate or 0.9% Saline

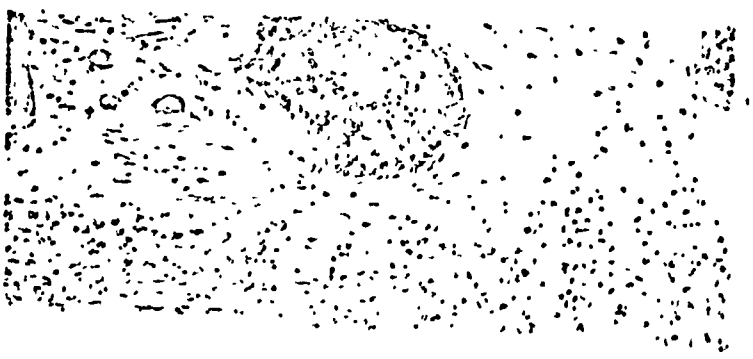
			Time after Drug Administration			
	Mating	Drug Admin	24 hr	48 hr	72 hr	1 month
White blood cells Count X 10^3						
Silver Nitrate	9.3±0.6	8.0±1.1	9.2±0.7	8.0±0.9	8.8±0.7	9.0±.5
Saline	8.7±1.0	8.4±1.3	8.1±1.6	8.6±1.0	8.8±1.0	
Red Blood Cells Count X 10^6						
Silver Nitrate	5.8±0.1	5.2±0.3	5.5±0.1	5.6±0.1	5.4±0.2	5.9±.3
Saline	5.8±0.3	5.7±0.4	5.9±0.2	5.4±0.5	5.4±0.6	
Hematocrit (%)						
Silver Nitrate	34.9±0.7	33.6±0.8	34.5±1.0	33.0±1.0	34.2±0.7	33.9±.6
Saline	33.4±1.6	35.1±1.8	34.7±1.2	32.8±1.6	33.1±2.5	

Table 2

Blood Chemistry Analysis following Administration of 1 ml 1% Silver Nitrate or 0.9% Saline

	Mating	Drug Admin.	Time After Drug Administration			
			24 hr	48 hr	72 hr	1 month
Sodium (mEq/L)						
Silver Nitrate	145.3±1.1	146.0±0.7	145.0±1.6	145.2±0.9	144.6±0.8	146.0±0.9
Saline	148.0±0.6	145.0±1.8	149.0±1.3	145.3±0.6	146.0±1.3	
Potassium (mEq/L)						
Silver Nitrate	3.77±.16	4.02±.20	3.93±.08	3.94±.18	4.02±.17	4.03±.22
Saline	3.63±.33	4.28±.17	3.90±.24	3.68±.20	4.05±.13	
Chloride (mEq/L)						
Silver Nitrate	106.5±1.5	107.0±1.8	108.2±1.1	108.4±1.0	106.6±1.0	108.3±.8
Saline	105.7±0.7	111.0±1.9	107.3±0.9	108.0±2.7	110.0±1.3	
Glucose (mg/dl)						
Silver Nitrate	71.2±5.2	62.2±7.3	59.3±6.3	66.8±3.2	67.4±2.6	71.5±2.8
Saline	66.0±7.5	55.0±10.5	52.5±8.9	62.5±7.6	59.0±9.4	
Urea Nitrogen (mg/dl)						
Silver Nitrate	19.5±0.9	19.0±1.1	20.8±1.4	19.2±1.1	19.8±1.4	18.5±1.5
Saline	20.3±4.7	20.5±1.6	21.3±2.3	19.0±4.1	23.0±2.5	
CO_2 (mEq/L)						
Silver Nitrate	22.8±0.9	23.6±1.2	23.8±0.4	24.0±1.6	23.0±1.5	23.5±1.0
Saline	21.3±2.6	20.3±0.9	24.5±1.9	22.7±1.1	25.0±2.4	

(normal)



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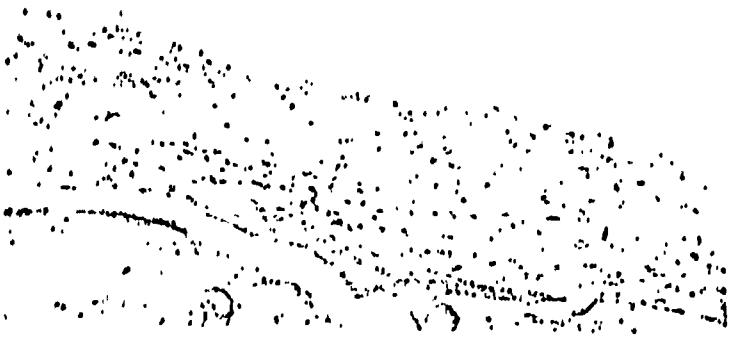

Fig 3

PROJECT IV

Trichosanthine, the mid-trimester abortifacient isolated from a Chinese tubor, is being actively sought for study in this contract.

I have received an invitation from the Research Institute in Shanghai that isolated and purified this protein for use in the People's Republic of China. The correspondence relating to this invitation has been forwarded to Dr. James D. Shelton for his information and approval for the planned trip.

A major difficulty with this chemical is that the active molocule is a protein which limits its usefulness clinically. However, the Chinese have been able to significantly reduce the potential for sensitization by the administration of the drug intra-amniotically. Of particular interest, the drugs activity seems to be directed specifically toward the villi of the placenta.

It is hoped that arrangements can be completed to obtain a continuing supply of this agent for study and animal testing in our laboratories.

PROJECT V

THE CLINICAL TESTING OF CHEMICAL ABORTIFACIENTS

The objective of this study is to evaluate agents which have been determined by animal studies to be efficacious and free of undesirable characterization.

Principal Investigator: Dr. M. F. Atienza

PROJECT V

A. Azastene

Azastene was obtained and initiation of the protocol was attempted. All patients identified at 8 weeks of duration who possessed the admitting characteristics required for the study, rejected participation.

The major problem in gaining volunteers for this study was that treatment was required for 7 to 8 days, while the patients were aware that their unwanted pregnancy could be terminated by suction curettage.

In further communication with the pharmaceutical company, Sterling-Winthrop, the company determined that they would withdraw any attempts to proceed with azastene-type agents at this point in time. It should be noted, however, that another drug is being developed by this pharmaceutical company that may require a shorter interval of active treatment.

B. Ethanol

A protocol will be submitted to the Johns Hopkins Medical Institutions Human Sub-Committee to initiate clinical trials.

C. Analgesia for Abortion and Other Surgical Procedures Completed Under Local Anesthesia

We will proceed to develop a regimen for the use of a combination of agents administered in very low doses which might in combination be unassociated with respiratory or cardiac depression. Because of recent life-threatening accidents with the use of demerol and valium, this approach seems to have merit.

PROJECT VI

The objective of this study is to assess methods of cervical dilatation for safety and efficacy.

Principal Investigator: Dr. Theodore M. King

PROJECT VI

We will be initiating in this portion of the proposal the use of the International Fertility Research Program's Osmotic Cervical Dilator. This will be submitted to the Johns Hopkins Human Subject's Committee for their approval prior to the initiation of investigative work.

WORK PLAN IN THE COMING SIX MONTHS

In the coming six months, the following activities will be addressed:

1) Ethanol and silver nitrate will be submitted to the Johns Hopkins Human Subject's Committee for approval for use in the termination of early pregnancies.
2) Arrangements will be completed with the Research Institute in Shanghai, for a supply of trichosanthine for initial animal studies in our laboratories.
3) The osmotic dilator of IFRP will be submitted to the Johns Hopkins Human Studies Committee for completion of clinical trials in this country.
4) A number of agents will be utilized in combination for the establishment of adequate analgesia for the completion of outpatient ambulatory surgical procedures in fertility management.
5) An IND submission will be completed on quinacrine based on the animal work that is now completed. In addition, the work that has been initiated on the suture device will continue. Finally, prostaglandin analogs will be identified and reviewed with Dr. Shelton for their possible use in studies in our laboratories.

SIMPLIFIED TECHNIQUES OF FERTILITY CONTROL

ANTICIPATED EXPENDITURE REPORT

10/1/80 - 3/31/81

Salaries	$ 69,222	
Fringe Benefits	12,806	
Equipment (Materials & Supplies)	10,160	
Travel	3,400	
Consultant	1,582	
Other Direct Costs	19,500	
Indirect Costs	59,502	
Total		$176,172

SIMPLIFIED TECHNIQUES OF FERTILITY CONTROL

AID/DSPE-C-0054

9/28/79-9/27/80

	Year I Budget Award	Expenditures 9/28/79-3/31/80	Expenditures 4/1/80-9/27/80	Unexpended Balance
Salaries	$123,604	$ 57,331	$ 67,135	$ (862)
Fringe Benefits	21,632	10,033	12,067	(468)
Equipment (materials and supplies)	30,724	17,425	5,786	7,513
Travel	300	71	149	80
Consultants	0	0	0	0
Other Direct Costs	47,236	10,787	18,436	18,013
Indirect Costs	105,504	30,498	64,748	10,258
Total	$329,000	$126,145	$168,321	$ 35,534

MANUSCRIPTS IN PRESS:

1) Midtrimester Amnio-Infusion

2) Endometriosis and the Development of Tubo-Peritoneal Fistulae After Tubal Ligation

3) The Effect of Epsilon Amino Caporic Acid - A Fibrinolytic Inhibitor on Implantation and Fetal Viability in Pregnant Rats

4) Cephalothin Prophylaxis for Midtrimester Abortion

5) The Effect of Silver Nitrate on Pregnancy Termination in Cynomolgus Monkeys

6) Hyperosmolar Urea for Elective Midtrimester Abortion - A Five Year Experience

MANUSCRIPTS BEING FINALIZED:

1) Non-Clostridial Myonecrosis with Induced Mid-Trimester Abortion

2) Pharmacokinetics of Lidocaine Administered by Paracervical Infiltration for Aspiration Abortion

MIDTRIMESTER AMNIO-INFUSION

INTRODUCTION

For elective abortion, midtrimester amnio-infusion is utilized in the United States approximately 10 percent of the time. With the liberalization of abortion laws, it certainly became clear that the technology and knowledge regarding midtrimester abortion has required rapid updating. Certainly, the experiences with concentrated saline solution by the Japanese following World War II prompted investigators to look at other methodologies. As a benefit of this added research, much of our knowledge regarding the mechanism for labor has been gained through research in this particular area. This presentation will discuss the training of individuals in the technique of midtrimester amnio-infusion and the recognition and management of complications. It should be recognized from the outset that the completion of amniocentesis and infusion of pharmacologic agents is easily achieved by obstetricians and gynecologists. However, acceptable morbidity and mortality rates asosciated with midtrimester abortion procedures can only be achieved by meticulous attention to the details of the described procedures by adherence to the proposed guidelines, and by recognition of early signs of complications which must be treated with appropriate therapy. I hope it is appreciated that physicians who elect to undertake these procedures should gain a large experience quickly and the occasional operation is not encouraged.

PRE-OPERATIVE PREPARATIONS

The pre-operative patient evaluation and equipment have been described in my other presentation. It is important that a bimanual pelvic examination be completed just prior to the procedure in order to ascertain uterine size as well as condition of the cervix. Furthermore, it is exceedingly important that the presence of a fetal heart tone be documented prior to any attempted midtrimester amnio-infusion. There have been a number of instances of injections of ovarian cysts because of failure to carry out this particular step. Therefore, the availability and utilization of an electronic Doppler device facilitates diagnosis of duration of pregnancy, location of amniotic fluid and presence of pelvic pathology. Also, prior to the actual injection, the risks and plans for the procedure should be explained in detail to the patient. About 3 to 4 hours prior to injection, 3 or more medium sized laminaria tents are placed intracervically using an aseptic technique The use of the tents both shortens the injection-abortion interval as well as markedly reduces the likelihood of serious cervical laceration.

TECHNIQUE

Regardless of the agent selected, the basic technqiue for midtrimester amnio-injection remains the same. The technique is designed to enter the amniotic cavity and instill various pharmacologic agents and to avoid inadvertent intravascular injection. For most surgeons, the site for amniocentesis for a uterus 16 to 20 weeks in size ideally is approximately one-third of the way to the umbilicus from the symphysis pubis. At this site, the amniocentesis needle usually is being placed into the upper protion of the lower uterine segment. The reasons for selecting this size are severalfold. In general, the thickness of the myometrium is less at this particular point than it is at the fundal portion of the uterus. Furthermore, the placenta tends to implant in the fundus either posteriorly or anteriorly and in many instances are

can avoid the anterior portion of the placenta if amnio-infusion is carried out at this lower site. Thus, bloody taps or missed taps can be markedly reduced. It should be noted that attempting to perform amniocentesis in uteri less than 16 weeks in size is associated with a high incidence of missed taps. Therefore, in general, midtrimester induced abortion by amnio-infusion should be utilized only for gestations of 16 to 20 weeks. Occasionally, the use of a bimanual technique is helpful with the smaller size uteri. In this technique, one hand is placed in the vagina to elevate and move the uterus anteriorly towards the abdominal wall and the other hand is used to palpate the lower uterine segment to select a site. With direct guidance by bimanual technique, the needle is then placed into the amniotic cavity.

Once a site has been selected, the abdomen should be meticulously prepped with an antiseptic solution. It has been demonstrated in a number of studies that failure to adhere to strict aseptic technique is associated with a high incidence of post-abortal infection. After prepping, the abdomen is draped with towels. We have found that the standard 3½ inch Tuohy needle (number 16 guage) is satisfactory for most forms of amnio-infusion. Occasionally, we utilize a six inch 17 guage spinal needle for patients who are particularly obese or who have an anterior placenta. Prior to the injection, approximately 5 to 10 cc of of 1% lidocaine is injected in the skin, subcutaneous tissue, rectus fascia, as well as peritoneum at the selected site. The patient should be flat in bed without the head being elevated to ensure relaxation of abdominal musculature. A tiny incision should be made in the skin prior to introduction of the Tuohy needle in order to allow easier passage. When introducing the needle, several distinct layers can be felt.

Initial introduction goes smoothly until the rectus sheath is encountered and at this point, one feels resistance. Further, resistance is usually encountered upon entry into the myometrium and than a small give or reduced resistance is felt when the needle traverses the amniotic membranes. With experience, one therefore detects three areas of resistance prior to introduction of the needle into the amniotic cavity. In general, the amniocentesis is carried out vertically in the midline. Once the needle has been introduced the stylet is removed and free flow of fluid is noted. At this point, the extension I.V. tubing with a three-way stop-cock is attached. During removal of the amniotic fluid and during injection of agents, it is extremely important that excessive motion of the needle be avoided. With excess motion, particularly after 200 cc of fluid has been removed, the cavity may be lost and unless another amniocentesis is successfully carried out, the procedure has to be terminated and re-scheduled a day later to allow re-accumulation of fluid. Therefore, gentle pressure on the fundus or the uterus may improve flow or, occasionally, gravity drainage can be utilized by placing the tubing in a sterile container below the level of the needle site and allowing the fluid to drain out.

HYPEROSMOLAR UREA INJECTION

With hyperosmolar urea injection, we remove up to 200 cc of amniotic fluid. Following this, we instill approximately 135 cc or 80 grams of urea via gravity. This concentration of 53% has been found to be most satisfactory. Upon completion of the infusion, 5 mg of Prostaglandin $F_{2}a$ is instilled and the needle is removed.

OTHER POINTS REGARDING THIS METHOD OF ABORTION

If a bloody tap occurs, one should not inject any of the pharmacologic agents unless clearing of the fluid occurs and one is totally confident that the amniotic cavity has been entered. Attempting to inject hypertonic or hyperosmolar agents in the presence of a grossly bloody tap can lead to a serious systemic reaction which in the past has been associated with maternal death. Should the amniotic cavity be lost during the process of injection, no further attempts at introducing pharmacologic agents should be carried out until replacement of the needle into the amniotic cavity has occurred. When a cavity is lost in this fashion, and if only a small amount of the pharmacologic agents has been introduced, one can re-tape the cavity the next day in order to allow re-accumulation of the amniotic fluid.

MANAGEMENT AFTER INJECTION

The use of high dose intravenous oxytocin in conjunction with urea alone significantly reduces the injection-abortion intervals to 24 hours or less. However, for reasons listed below, the primary use of oxytocin for augmentation of urea has been replaced by intra-amniotic Prostaglandin $F_{2}a$, except for instances of asthma or known Prostaglandin allergy. Our standard oxytocin dosage consists of adding 200 units of oxytocin to a 500 cc bottle of 5% Dextrose in half normal saline and infusing the medication at a rate of 50 cc per hour. This results in the introduction of oxytocin at a rate of 332 mu/min. The use of such high concentrations of oxytocin requires an electronic pumping device in order to avoid over-dosage. The risks from over-dosage include water intoxication secondary to the anti-diuretic effects of the oxytocin

as well as, in rare instances, uterine rupture particularly with multiparous patients. In addition to the use of mechanical pumps, one must also carefully monitor fluid and electrolyte balance and keep an accurate intake and output. In general, we do not allow the oral or intravenous intake of fluids to exceed the urinary output by more than 1500 cc over a 24 hour period. Also, we monitor serum sodiums at 12 hour intervals, and if they fall below 132 meq/liter, the oxytocin infusion is discontinued for at least a four hour period in order to allow diuresis to occur.

The use of intra-amniotic induced prostaglandin in conjunction with hyperosmolar urea appears to offer significant advantages from our viewpoint. First the requirement for mechanical pumps is either avoided or certainly significantly reduced leading to less cost. Secondly, less concern is imposed for fluid and electrolyte balance because prostaglandin does not have an anti-diuretic effect like oxytocin. However, in patients who are at risk for problems secondary to sudden changes in their fluid compartments, (for example, cardiac patients) one must also approach the use of these agents cautiously.

If during the injection-abortion process rupture of membranes occurs and after four hours abortion is not imminent and a good labor pattern has not been established, these patients are started on the high dose oxytocin regimen. Similarly at 24 hours post-injection, those patients whose abortions are not imminent or who are not in active labor are also started on the high dose oxytocin regimen. Rarely are re-injections ever performed. However, prior to starting such agents each patient must be carefully evaluated.

RETAINED PLACENTA

Our technique of managing retained placenta has evolved over the several year period that the Fertility Control Unit has been in operation. Our basic premise has been that retention of the placenta for more than two hours following abortion of the fetus is associated with increased risk for hemorrhage as well as infection. Therefore, we view that removal of unaborted placentae after two hours of observation is beneficial. With experience, the technique of operative removal is quite simple.

The patient is placed on a portable operating table in the dorsal lithotomy position. Immediately prior to the placenta removal, usually 10 mg of diazepam and 50 mg of meperidene are given intravenously by slow push. Mixing of the diazepam with some of the patient's blood will reduce some of the burning sensation experienced by most patients. The patient's vagina is then gently prepped with antiseptic solution. A bi-valve speculum is inserted and the anterior lip of the cervix is grasped with a sponge-stick. Following abortion of the fetus, the cervix is usually dilated to three or four centimeters and usually one observes placenta parts at the os. After grasping the anterior lip of the cervix, the tissues lying near the os are then grasped with another sponge forcep and gentle traction is carried out. The sponge-stick can be introduced into the lower uterine segment for further grasping of tissue and further removal of the placenta. For most patients, these maneuvers readily empty the uterus. However, occasionally the placenta will be firmly adherent and one may have to introduce the forceps multiple times in order to grasp tissue and loosen the placenta. The use of a large diameter serrated banjo curette is helpful in removing

adherent placentae as well as ensuring completeness following the initial sponge-stick removal. Upon completion, the cervix is carefully inspected for lacerations. Oxytocin is continued during the procedure and for approximately one or two hours afterwards. Methyergonovine maleate can also be utilized if necessary.

FAILED PRIMARY PROCEDURES

Depending upon the method of initiation, between 1.0 and 12.5% of midtrimester elective abortion cases result in failure of the primary method. Many such patients will achieve completion of abortion through repeat intra-amniotic injection or administration of oxytocic agents, though not without risk of sepsis, fluid electrolyte abnormality or uterine rupture. However, there still remains a number of patients where such measures fail and who require surgical management.

The vaginal evacuation method has been used in the Fertility Control Clinic since January 1973 without significant problems. Vaginal evacuation of the uterus for midtrimester abortion failures is carried out in the following manner. After Doppler examination to document absence of fetal heart tones, intravenous injection of 10 mg diazepam and 50 mg meperidene is carried out. Patients are then prepped vaginally with a povidone-iodine solution while in the dorsal lithotomy position. After draping and bimanual examination to determine uterine size and configuration, 10 to 15 cc of 1% lidocaine is injected paracervically in a circumferential manner. A ring forceps is utilized to grasp the anterior lip of the cervix and the endocervical canal is gently sounded to determine direction. Cervical dilatation is rarely necessary in that most cervices will readily admit a #41 Kay-Pratt dilator. Ring forceps are utilized to remove, by gentle traction, any pregnancy products

encountered in the lower uterine segment. Suction curettage using 12, 14, or 16 mm tips removes further pregnancy products as well as brings additional tissue into the lower uterine segment for grasping with the ring forceps. The suction curette and the ring forceps are never introduced further than what is estimated to be the confines of the lower uterine segment. After careful inspection of tissue to identify all major fetal parts and placental tissue, curettage of the endometrial cavity with a large diameter, serrated "banjo" curette is carried out to remove any remaining products of conception. During the procedure, patients receive oxytocin intravenously usually at a rate of 332 mu/min and usually also receive 0.2 mg of methylergonovine maleate by parenteral injection. Although the vaginal evacuation may take as long as 30 minutes to complete, most patients tolerate the operation without undue discomfort. Oxytocin is continued for about two hours post-operatively and some patients receive oral methylergonovine maleate for 24 to 36 hours. The majority of patients are discharged within 12 hours after completion of the abortion.

Some investigators view vaginal evacuation of large sized uteri as being hazardous. But in our experience the procedure has been accomplished without undue problems. Patients undergoing vaginal evacuation for failure of the primary method commonly have ruptured membranes, cervices that are partially effaced and dilated and lower uterine segments that are distended by displaced products of conception. Furthermore, the pregnancies are not viable and in the majority of instances the fetal parts are usually macerated. Furthermore, the majority of patients undergoing vaginal evacuation have been on high dose oxytocics for at

least two hours or longer prior to the procedure. Therefore, at the time of evacuation, the uteri become and remain well contracted. By not utilizing general anesthesia, for the most part, the occasional atony attributable to anesthetic agents is avoided. Furthermore, with the use of our particular technique of limiting instrumentation to the lower segment, the risk of uterine perforation is minimized. However, one should recognize that skill at removing retained placentae in the fashion previously described will enable an operator to gain experience prior to undertaking the vaginal evacuation of large sized uteri as just described.

INTRA-ABORTAL FEVER

Occasionally during the injection-abortion process, patients may develop fever. All such patients must be carefully examined. After ruling out urinary tract or upper respiratory tract infection, one usually assumes that genital tract infection is occurring. Exceptions to this may include the use of vaginal prostaglandins. If abortion is felt to be imminent or within a few hours, the patient can be observed initially. However, if it appears that abortion is not imminent, we culture the patient's endocervix as well as blood and urine and proceed with a vaginal evacuation as previously described. Prior to any such manipulations and after one has diagnosed probable genital tract infection, we utilize high-dose parenteral antibiotics such as ampicillin 1 gram I.V. every four hours or penicillin 5 million units I.V. every six hours in conjunction with kanamycin 1 gram stat, 500 mg I.M. every 12 hours. Some patients promptly defervesce immediately following the abortion process and we have found that observation over a 12 to 24 hour period

may be all that is necessary. Such patients are then sent home on oral antibiotics. Those patients who remain ill in general will respond in 24 to 48 hours to the antibiotics just listed. Those who do not respond occasionally have been found to have anaerobic infections and require additional antibiotics such as clindamycin.

INTRA-ABORTAL BLEEDING

Intra-abortal bleeding is not uncommon and if less than approximately 100 cc it is usually not felt to be significant. Occasionally, however, particularly when utilizing hyperosmolar solutions, coagulopathies may occur (see section on complications).

Occasionally, the reason for intra-abortal bleeding may be abruptio placenta or placenta previa. Such problems are usually detected at the time of the abortion process and the patient can be either observed or the abortion completed using the method described under the vaginal evacuation for failures.

MIDTRIMESTER ABORTION COMPLICATIONS

Midtrimester abortion complications include infection and post-abortal bleeding as major categories.

I. Infection

It is difficult to estimate the rate of infection following elective midtrimester abortions. The major problem in arriving at rates are the different methodologies as well as different definitions for infection. For example, in many papers reviewed,

objective criteria such as fever greater than 100.5 degrees F on two or more occasions has been utilized as indication of infection. However, in many instances, therapy is started before such criteria are realized. We recently completed a study of post-abortal endometritis and utilized the following definition. Post-abortal endometritis was defined as any condition requiring the use of antibiotics during the first four weeks after abortion. Patients with other diagnoses, such as urinary tract infection, were not included. Furthermore, patients receiving prophylactic antibiotics, such as patients with rheumatic valvular disorders, also were not included for the purposes of this recent study. Utilizing this particular definition, a rate of about 8% was realized for endometritis after midtrimester abortion.

The clinical manifestations of post-abortal endometritis consist of fever, uterine tenderness, occasional adnexal tenderness, purulent vaginal discharge, and often retained products of conception. Depending upon the severity of the infection, one can have varying combinations of the above signs and symptoms. For example, some patients may have uterine tenderness with some irregular vaginal bleeding as their only indication of early or latent infection. These symptoms may then progress to fever of 102 to 103 degrees F, increasing lower abdominal discomfort, increasing uterine tenderness, as well as adnexal tenderness. With such more severe manifestations, patients often have a foul, purulent vaginal discharge. Also, the cervix will be slightly dilated, and the uterus will appear larger than usual on exam. In general, post-abortal endometritis manifests itself within the first seven to 14

days after the abortion procedure.

The laboratory is not overly helpful in establishing the diagnosis. The CBC often indicates a white blood cell count ranging between 12,000 to 16,000 but occasionally exceeding 20,000. However, frequently the count will be in the normal range without a shift to the left. Cultures of the endometrial cavity show varying results. We recently evaluated the use of endometrial cultures obtained in the following fashion. The cervix is swabbed to remove any excess mucous and secretion, and a Q-tip is inserted into the endometrial cavity and then placed on Stewart's transport media. The culture is handled in the laboratory in a routine manner. No specific bedside attempts were made to increase the yield for organisms such as anaerobes. Utilizing this technique to obtain cultures, the most prevalent isolates either as single or multiple organisms included group B beta-streptococci, Neisseria gonorrhea, Bacteroides species and Staph aureus. However, there were large admixtures of multiple organisms; many of which probably were constituents of the normal vaginal flora.

Treatment should be tailored to the clinical situation. In patients with mild infection who do not appear toxic, and by examination do not appear to have retained tissue, (for example do not have an unusually enlarged and boggy uterus with cervical dilation and evidence of tissue in the os), outpatient therapy can be begun. We have had a great deal of success in patients not allergic to penicillin by treating them with ampicillin, 500 mg orally every six

hours for approximately ten days. The patients are seen one week after instituting therapy or sooner should symptomatology worsen. For patients who are more ill, hospitalization with the following studies is necessary. One obtains upon admission, BUN, glucose, blood cultures, endometrial culture (in the manner just described), and urine culture, (if the urinalysis shows pyuria). The antibiotics of choice include aqueous penicillin G, 5 million units I.V. every six hours and kanamycin, 1 gm stat I.M. followed by 500 mg I.M. every twelve hours. In general, the antibiotics are continued in this fashion for approximately five days to allow a full course of kanamycin. Occasionally, the amount of time has been shortened in those patients who rapidly defervesce and respond to this regimen and in whom the eventual culture results indicate no need for continuing kanamycin. A major component of the therapy for endometritis requiring hospitalization is a concomitant performance of a curettage. Curettage is carried out using the sponge-stick curettage technique. This curettage is usually carried out within six hours after admission following the initial dose of antibiotics. Using these basic regimens, less than 10% of patients with severe endometritis have required hospitalization beyond five days when our experience over three years was recently evaluated. Also only two patients have required hysterectomy due to severe pelvic infection. It should be noted that both of these patients developed fever during the abortion procedure, prior to passage of the products of conception, and both had cultures revealing Claustridia welchii.

Two further points regarding the bacteriology of post-abortal infection are worth mentioning.

In those patients who later are found to harbor group B beta streptococci, the clinical course often is quite striking. These patients may present with fevers as high as 103°F with significant pelvic tenderness, yet within twelve to 24 hours after institution of antibiotics, the temperature rapidly returns to normal and symptoms markedly improve. Another problem is the performance of abortions in patients with untreated endocervical gonorrhea. A recent case-controlled study done in our institution revealed that those patients who do not have their endocervical gonorrhea treated prior to the abortion procedure have a three-fold increased risk for post-abortal endometritis. Therefore in a patient population where cervical gonorrhea is quite prevalent, pre-treatment of this disorder will reduce the overall incidence of post-abortal endometritis. However, it should also be noted that such treatment will not necessarily prevent the development of endometritis in that we have had a few patients treated in such fashion who have also developed endometritis later.

Other antibiotics which have been utilized successfully for therapy include clindamycin for those patients who do not respond over 48 to 72 hours with the penicillin and kanamycin, and in general whose cultures reveal the presence of anaerobic organisms. Keflin has also been utilized for some patients allergic to penicillin with success. For outpatient therapy, success has also been realized using tetracycline for patients allergic to penicillin drugs.

II. Hemorrhage

Occurrence of hemorrhage during or after the abortion procedure has several etiologies including retained products, atony or placental site bleeding, laceration, and coagulopathy. It is important for the operator performing midtrimester abortion procedures to be able to evaluate and recognize these various causes of hemorrhage.

Retained products is probably the most common cause for hemorrhage at or after the abortion procedure. The basic means for dealing with this problem is the performance of the so-called sponge-stick curettage. In our experience, the following patients appear to more frequently experience hemorrhage and retained products: patients undergoing prostaglandin abortion, patients not on oxytocics at the time of abortion, and patients with retained placenta for more than four to eight hours. The ability to promptly carry out the sponge-stick curettage markedly reduces the incidence of significant bleeding. Therefore a 24 hours on-call system is needed when performing midtrimester elective abortions.

Placental site bleeding or atony is not unusual following mid-trimester abortion. The basic treatment consists of utilizing oxytocics such as intravenous oxytocin or methergine along with uterine massage. It is extremely important that other causes of hemorrhage such as retained products, laceration or coagulopathy be ruled out prior to attributing hemorrhage to this etiology. We have also had one or two instances of severe hemorrhage following the abortion process which could only be controlled with prolonged uterine massage over a five to ten minute period of time. We have

suspected that this problem may be due to bleeding from a placental site vessel or perhaps prolonged uterine atony. However, by utilizing prolonged massage, we have avoided the possible requirement for hypogastric artery ligation.

The occurrence of laceration particularly cervical laceration is a well known complication of midtrimester abortion procedures. The classical laceration described in the literature has been the so-called posterior transverse cervical laceration. This laceration, usually four to five centimeters in length, occurs transversely between the uterosacral ligaments approximately at a level of the internal os. However, reviews of midtrimester abortion cases in which routine speculum examination as well as bimanual examination is carried out after the abortion process indicate that vertical lacerations similar to those found following term vaginal delivery are probably more common. Exact rates for the occurrence of such lacerations are difficult to ascertain. A number of studies have postulated that the occurrence of such lacerations is related to nulliparity, shortening of the injection abortion interval as well as the use of oxytocic agents. There has been some success in reducing the incidence of such lacerations with the use of laminaria tents, however, such lacerations have occurred despite the use of such means. The basic treatment requires recognition first. Therefore, it is mandatory that all patients who have completed their midtrimester abortion procedure whether bleeding or not undergo both a vaginal speculum examination as well as a bimanual examination to detect such lacerations. Once detected, we have had success in repairing these lacerations without general anesthesia by giving

diazepam and meperidine intravenously in conjunction with the performance of paracervical and occasionally pudendal block with 1% lidocaine. We have carried out immediate repair of such lacerations by debriding non-viable tissue and then approximating the edges in layers using interrupted catgut suture. Occasionally, the small vertical lacerations are repaired utilizing continuous sutures. We have not utilized prophylactic antibiotics routinely for such patients. Despite such care, breakdown is not an uncommon problem. The management of patients following failure of the initial repair is unclear. Furthermore, attempts at re-repair often lead to further failure. The major questions concerning such lacerations is their behavior during future pregnancies. For example, it is conceivable that a certain percentage of patients with such lacerations may require the use of cerclage operations in order to maintain pregnancies to viability. Furthermore, due to endocervical mucosa damage following repair, some degree of secondary infertility may also be a problem with such patients. Therefore, long-term longititudinal follow-up of such patients will be required before such potential problems become apparent.

The final etiology for post-abortal bleeding is coagulopathy. In relationship to second trimester hypertonic saline amnio-infusion, the literature is replete with descriptions of this problem. However, it should be noted that theuse of almost any intra-amniotic agent causing midtrimester abortion has the potential of associated coagulopathy. A large number of studies indicate that decreases in clotting factors, such as fibrinogen platelets, factors 8, 9 and 12 all occurs normally during the abortion process following injection

of various pharmacologic agents. Furthermore, the appearance of fibrin split products is another common phenomenon. These changes are most apparent following the intra-amniotic injection of hypertonic saline and, in fact, are seen in all patients. The changes are maximal approximately 12 to 24 hours after initial injection but by approximately 24 hours begin returning towards normal. Similar changes have been demonstrated in patients undergoing hyperosmolar urea abortion (to a less significant degree), and recent literature indicates that such changes may also occur in patients undergoing intra-amniotic injection of prostaglandin F_2a or E_2. It should be noted, however, that in the vast majority of instances these coagulation changes are not of clinical significance. However, in 1 in 100 to 1 to 2500 saline abortions, clinical coagulopathy may occur.

The eitology for such coagulopathy is unclear. One mechanism proposed has been the release of tissue thromboplastin at the placental site due to damage by the hypertonic agents. Why hypertonic saline would predispose more so than urea is unclear. Another theory postulated is that hypernatremia may lead to such coagulopathy. For example, some animal studies reveal that hypernatremia can produce coagulopathy in animal models. Therefore, this phenomenon may contribute to the occurrence of clinical coagulopathy in some instances. Finally, it should be noted that even when hyperosmolar urea is used clinical coagulopathy may occur. In our experience, at least one well documented case has occurred over a three year period involving approximately 1000 abortion procedures utilizing hyperosmolar urea. Finally, the use of oxytocic agents particularly oxytocin may

predispose to the occurrence of clinical coagulopathy. Ballard and co-workers studied the occurrence of clinical coagulopathy in a large group of patients undergoing hypertonic saline amnio-infusion with or without immediate augmentation with intravenous oxytocin. They found that patients who had the immediate augmentation of their abortion procedure with oxytocin had significantly higher rates of clinical coagulopathy. The exact mechanism for such occurrences are unknown but could again be related to increased release of tissue thromboplastin.

Manifestations of coagulopathy basically consist of the appearance of unclotted blood in a patient with vaginal bleeding. The majority of clincial coagulopathies are recognized at the time of the abortion process or soon thereafter, though occasional cases have been described occurring prior to passage of the fetus. In conjunction with the appearance of unclotted blood, these patients may also demonstrate evidence of petechiae and easy bruisability as well as bleeding at venipuncture sites. As with the other causes of hemorrhage, one must quickly rule out retained products, laceration, or atony before assigning the diagnosis of coagulopathy to a patient.

The laboratory diagnosis is made by demonstrating diminution of fibrinogen and platelets, prolongation of clotting time, protime and partial thromboplastin time, as well as the demonstration of fibrin split products in high titers. From a clinical standpoint the performance of a simple Lee-White clotting test at the bedside enables one to rapidly establish the diagnosis. This is a very gross test and, if abnormal, indicates significant reduction in clotting factors and a clinical situation of true import. Other findings such

as a decrease in fibrinogen or platelets can be misleading particularly in attempting to establish an early diagnosis. For example, these factors ordinarily will fall to some extent during the normal abortion process without clinical coagulopathy. Furthermore, patients in the midtrimester of pregnancy will have somewhat physiologically elevated fibrinogen and platelet counts. Therefore a value determined initially could well be within the normal range, yet a significant coagulopathy may be occurring. However, these tests should be used to confirm the presence of coagulopathy as well as demonstrate return towards normal following treatment using such measurements.

A wide variety of modalities for treatment have been utilized for this problem including heparinization, expectant management, and in a few instances the use of epsilon amnio caproic acid. Our basic regimen has been as follows: the diagnosis of coagulopathy is rapidly established at the bedside by performing a simple Lee-White clotting test. If prolonged beyond ten or 12 minutes, a presumptive diagnosis of coagulopathy is made. Occasionally with mild or moderate prolongation, one will also note very poor clot formation. In patients with severe coagulopathy, the blood will not clot over prolonged periods of time. Once one has presumptively established the diagnosis, the patient is rapidly examined to rule out the occurrence of concomitant problems such as laceration. Also, a sponge-stick curettage is carried out so that retained products will not further complicate the course. Finally, oxytocin is utilized to keep the uterus well contracted, utilizing the constricting properties of the interlacing myometrial fibriles on the straight

arteries lining the endometrium or decidua. Blood is sent to the laboratory to confirm the coagulopathy as well as to the Blooc Bank to cross-match for fresh whole blood. One must use fresh whole blood for transfusion in order to replace the depleted clotting factors. In general, banked blood will have very low concentrations of such factors. To date, we have expectantly followed such patients with no other treatment such as heparinization and have avoided transfusion in most instances. Within eight to 12 hours, one notes return towards normal clotting function with the appearance of clotted blood in the vaginal pool. At this point, the clinical significance of the coagulopathy now has rapidly diminished. However, it should be noted that clotting studies may remain abnormal for several days until the clotting factors are regenerated. In unaborted patients who develop coagulopathy, most investigators favor prompt emptying of the uterus.

In conclusion, I hope it is recognized that the injection procedure is easily accomplished, and that the major requirement for clinical skill and competency is met in the recognition and management of the associated complications.

Attached to this document is a listing of relevent references necessary for the approach to midtrimester abortions.

ENDOMETRIOSIS AND THE DEVELOPMENT OF TUBO-PERITONEAL FISTULAE AFTER TUBAL LIGATION*

John A. Rock, M.D.+

Tim H. Parmley, M.D.

Theodore M. King, M.D., Ph.D.

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ABSTRACT

The present study details gross and histologic findings of 79 previously ligated fallopian tubes from three groups of patients. Of 20 oviducts removed after documented sterilization failure (Group I), 6 revealed a process compatible with endometriosis. Four of 9 previously ligated fallopian tubes, removed at the Johns Hopkins Hospital (Group II), were successfully injected with India ink. In two patients histologic examination demonstrated the India ink in epithelial-lined spaces that lay beyond the muscle of the tube wall extending from the tubal lumen to the serosal surface.

Fifty oviducts were studied in 25 patients requesting reversal of their sterilization (Group III). A higher percentage of fistulae were demonstrated in patients with less than 4 cm length of remaining proximal tubal segment. Furthermore, a majority of these fistulae were demonstrated in patients where 3 years had lapsed since the original sterilization procedure. Patients sterilized by laparoscopic cautery methods were observed to have a higher percentage of fistula formation and histological documentation of endometriosis at the sterilization site as compared to other sterilization methods. Our observations suggest that oviductal ligation within 4 cm of the uterine cornua may predispose to the development of endometriosis and subsequent fistulization in the lip of the ligated oviduct.

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INTRODUCTION

Extrauterine and intrauterine pregnancy occurring after surgical ligation of the fallopian tubes continues to be a clinical problem.[1-5] While tubal phase pregnancies seem preventable with the proper patient selection, and operator error can be minimized with proper training, some failures seem currently unpreventable. These occur months or years after the sterilization procedure, and many are extrauterine.[5] When examined, the fallopian tubes from these sterilization failures appeared to have been properly ligated. In the past, such late failures have been attributed to "recanalization". In the sense that this implies reestablishment of a lumen between the proximal and distal portions of properly ligated fallopian tubes, we have not seen such a case. On the other hand, tubo-peritoneal fistulae have been observed.[1-4] We have investigated the nature of these fistulae.

MATERIALS AND METHODS

Seventy-nine previously ligated fallopian tubes were studied. Twenty of these oviducts, from 13 patients (Group I), were referred from other institutions for evaluation of the cause of sterilization failure. This material was often fragmentary and could not be appropriately oriented for microscopic study. Frequently only one tube was received. Consequently, microscopic sections were taken at random.

Nine tubes (Group II) were surgically removed at the Johns Hopkins Hospital as an associated part of pelvic surgery performed for other reasons. These tubes were of sufficient length to allow the injection of India ink using a 2½ cc syringe and a 25 gauge needle. The syringe was filled and the needle was placed in the proximal lumen and the ink was injected until the tube dilated or the ink passed through the fistula. This was done carefully

Attached

and the pressure was not monitored. Microscopic sections were prepared to demonstrate the India ink in the fallopian tube and/or fistulous tract.

Fifty oviducts (Group III) were studied both in vivo and in vitro. These studies occurred as a part of the routine evaluation and treatment of 25 patients admitted for tubal anastomosis. Preoperatively, all patients receive a hysterosalpingogram. Hysterosalpingograms were performed using a Rubin's cannula to which a 10 cc syringe, containing 5 cc of salpinx® was attached. Two cc's of contrast media were then injected into the uterus and an initial x-ray obtained. Then an additional 3 cc of dye was injected into the uterus and a second x-ray obtained. No patient had received a hysterosalpingogram prior to their previous sterilization. At the time of surgery, cervical obstruction was accomplished with a Shirodkar clamp and a transfundal needle was placed and used to fill the endometrial cavity and proximal fallopian tube with indigo carmine dye. Any tubal fistula was thus demonstrated. When the tip of the proximal segment of ligated tube was removed in order to perform the anastomosis, this area of the oviduct was sectioned in order to investigate the nature of a fistula detected by hysterosalpingography and/or transfundal indigo carmine injection. The presence or absence of any other pelvic disease, and the length of the proximal segment of tube, was also determined at the time of surgery. The length of the fallopian tube was measured such that the interstitial tube was not included in the measurement. The clinical record was reviewed to ascertain the interval of time since the tubal ligation, and the type of sterilization procedure performed.

RESULTS

Of the 20 fallopian tubes returned from other institutions after documented failure (Group I), 6 had evidence of a process that resembled salpingitis isthmica nodosa except that some of the epithelial inclusions clearly were associated with a stroma that qualified them for the diagnosis

of endometriosis (Fig. 1). That is, stroma and glands histologically identical to that seen in the uterine endometrium were observed. In several cases, this process appeared to extend from the lumen to the serosal surfaces of the ligated tube. Unfortunately, careful documentation of a fistulous tract was not possible as the surgical material was fragmentary and could not be oriented for microscopic study. Furthermore, the oviducts were not of sufficient length to allow injection dye to demonstrate the fistulous tract.

To investigate the nature of the fistulous tract associated with endometriosis, 9 previously ligated fallopian tubes, removed at the Johns Hopkins Hospital (Group II), were injected with India ink. It was possible to successfully inject 4 oviducts and to demonstrate 2 fistulae with this technique. When sectioned, the oviduct with fistula revealed India ink in the tubal lumen and in epithelial-lined spaces that lay in and beyond the muscle of the tube wall, extending from the tubal lumen to the serosal surface (Fig. 2). Many of these were apparently foci of endometriosis, in which gland lumina were the fistulous tract. The criteria for the diagnosis of endometriosis consists of glands and stroma identical to that normally found in the endometrial cavity.

With these observations in mind, 25 patients undergoing tubal anastomosis (Group III) were carefully evaluated preoperatively by hysterosalpingography. Eight cases and 11 tubes showed x-ray evidence of a fistula at the tip of the proximal segment of tube. At the time of operative injection of indigo carmine dye, all of the radiologically demonstrated fistulae were confirmed. Furthermore, 3 unexpected fistulae in 3 additional patients were documented (Fig. 3). In all, 14 fistulae were documented with these techniques. It was also observed that 5 of the fistulae extended into the broad ligament

but did not reach the peritoneal surface.

Careful inspection of the pelvis at the time of operation revealed no evidence of peritoneal or ovarian endometriosis; however, in 15 patients apparent endometriosis was observed clinically at the tip of the proximal segment of a fallopian tube. In one of these neither a fistula nor the endometriosis was identified microscopically. Frequently, little blebs were seen beneath the peritoneum (Fig. 4). Similar foci were not seen on the distal segment of the fallopian tube. Microscopically, all but 1 of 14 tubes with a fistula appeared to have endometriosis at its tip extending through the wall of the tube. One of these fistulous tubes was not studied microscopically. In 10 cases, endometriosis without a fistula was seen microscopically. This process was not extensive and was not seen to extend through the wall of the tube. At operation, endometriosis was not observed in the distal segment of the ligated tube.

Type of prior ligation was correlated with the frequency of fistulae (Table 1). A high percentage of fistulae and endometriosis was observed in fallopian tubes ligated using the laparoscopic cautery methods. Although no fistulae were observed in tubes ligated with a silastic ring, 4 of these oviducts revealed endometriosis.

The percentage of fistulae and endometriosis was also correlated with the length of remaining proximal tubal segment. Thirteen fistulae were observed in 29 proximal oviducts of less than 4 cm. Furthermore, endometriosis was documented in 20 of 27 tubes of less than 4 cm in length. The percentage of fistulae and endometriosis in oviducts 4 or more centimeters in length was 5% and 20%, respectively (Table 2).

The time interval since prior ligation was correlated with the number of fistulae and endometriosis in each tube studied. The results suggest

that by 3 years after the sterilization procedure a high percentage of fistulae have been formed (Table 3).

DISCUSSION

This report presents results and histological findings of oviducts from 3 groups of patients. The original group of oviducts referred from other institutions after failure, revealed a process compatible with endometriosis. It was possible to demonstrate a fistulous tract with the injection of India ink in 2 of 9 patients in the second group of ligated oviducts from patients undergoing pelvic surgery. To further investigate the nature of these findings, 25 patients requesting reversal of sterilization were carefully studied preoperatively by hysterosalpingography and at the time of anastomosis. After successful ligation of the oviduct within 4 cm of the uterine cornua, endometriosis developed in the tip of the proximal segment of ligated tube in a high percentage of patients. Prior to the development of the fistula, the tube appears to be dilated. Progressive extension of the endometriosis, perhaps aided by intra-pressure, appeared to result in penetration of the muscular wall of the tube with subsequent fistulization either into the broad ligament or into the peritoneal cavity.

The authors speculate that regurgitated menstrual fluid may be responsible for the development of endometriosis and the dilatation of the tube. As the length of the proximal segment and the type of procedure is correlated with the number of fistulae and endometriosis, within the oviducts studied, it is not possible to know which of these two factors is more important in contributing to the subsequent development of fistula. Nevertheless, our observations suggest that the Pomeroy procedure, performed

greater than 4 cm from the cornua, results in fewer fistulae; furthermore, ligation proximal to the ampullary-isthmic junction may result in a proximal segment which is subject to fistula development.

As this process appears to develop within 1 to 4 years of tubal ligation, it is of interest to consider what role it may play in the so-called post-tubal ligation syndrome. It is certainly conceivable that pain and irregular bleeding might be concomitant symptoms. In future attempts to define a post-tubal ligation syndrome, the time course of developing endometriosis in the proximal ligated segment should be taken into account. Further, the time course supports the clinical experience of Cunanan, et al. with respect to pregnancy failure.[5]

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TABLE 1

STERILIZATION REVERSAL (GROUP III):

PERCENTAGE OF FISTULA AND ENDOMETRIOSIS VS. TYPE OF LIGATION

Type of Ligation	# of Fistulae/ # of tubes studied	# tubes with endometriosis/ # tubes studied
Cautery	12/23* (46%)	15/24* (63%)
Pomeroy	2/18 (11%)	5/18 (28%)
Silastic Ring	0/6 (0%)	4/6 (66%)

*One case not submitted to pathology.

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TABLE 2

STERILIZATION REVERSAL (GROUP III):

PERCENTAGE OF FISTULA AND ENDOMETRIOSIS VS. LENGTH

OF REMAINING PROXIMAL TUBAL SEGMENT

Length of Remaining Proximal Tubal Segment	# of Fistulae/ # Tubes Studied	# Tubes with Endometriosis/ # Tubes Studied
Less than 4 cm.	13/29 (45%)	20/27* (74%)
4 or more cm.	1/21 (5%)	4/21 (20%)

*One case not submitted to pathology.

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TABLE 3

STERILIZATION REFERSAL (GROUP III):

NUMBER OF FISTULA AND ENDOMETRIOSIS VS. TIME SINCE ORIGINAL LIGATION

Time Since Original Ligation (Yrs.)	# of Fistulae/ # of Tubes Studied	# Tubes with Endometriosis/ # Tubes Studied
<1	0/4	0/4
1	0/0	0/0
2	1/2	1/2
3	6/14	10/14
4	3/8	7/8
5	1/6	1/6
6	2/8	3/8
7	1/4*	0/2*
8	0/4	2/4

*One case not submitted to pathology.

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FIGURE LEGENDS

Fig. 1) This focus of endometriosis is situated in the muscularis of the tube wall at the tip of the proximal segment. Similar foci were arranged from the lumen to the serosal surface. Not all had well-developed stroma however, and these more closely simulated salpingitis isthmica nodosa.

Fig. 2) After the proximal segment of fallopian tube was removed from the uterus, it was injected with India ink. In this case, a fistula was demonstrated and the section shows the ink in the endometriosis that lay between the lumen of the tube and the serosa.

Fig. 3) A fistula is demonstrated by the dark spot of indigo carmine seen at the corrua. The scarred top of the broad ligament extends to the right with the distal segment of tube just out of the picture. The ovary is posterior. The dye was injected through a needle in the top of the fundus just out of the picture on the left.

Fig. 4) Superficial blebs, associated with endometriosis, are seen at the tip of the proximal segment of tube. The scarred portion of tube and the distal segment are seen beneath this site.

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EFFECT OF EPSILON AMINO CAPROIC ACID, A FIBRINOLYTIC INHIBITOR, ON IMPLANTATION AND FETAL VIABILITY IN THE RAT

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ABSTRACT

In vitro evidence suggests that fibrinolytic activity is involved in the implantation process. *In vivo* experiments were performed in rats to determine if fetal development can be prevented by epsilon amino caproic acid (EACA), a fibrinolytic inhibitor. Timed pregnant rats were laparotomized on various days of pregnancy and EACA or control injections were made directly into a uterine horn. Animals were autopsied on pregnancy Day 15 when implantation and fetal viability rates were determined. Intraluminal EACA did not effect implantation rate but fetal viability was adversely affected when 3 mg was injected on Day 6. This effect was dose-related and was partially reversed by simultaneous injection of plasmin. No effect was observed on Day 3, 7, 8. Day 4 and 5 could not be tested because sham injections alone caused a high resorption rate. Subcutaneous injections, as high as 60 mg daily from Day 3 to 10 did not affect fetal viability. The experiments support the hypothesis that fibrinolytic activity around the time of implantation is important for maintenance of pregnancy.

INTRODUCTION

The implantation process involves a complex series of interactions between the blastocyst and uterus (see Weitlauf, 1979 for review). Trophoblastic function in this process may depend upon several distinct biochemical events from the time of attachment to the uterine epithelium until a relationship with the maternal circulation is established. Recent *in vitro* evidence indicates that the mouse trophoblast contains plasminogen activator activity and its invasiveness may depend upon fibrinolytic activity (Sherman et al., 1976). This is consistent with the findings that other migratory cells also produce plasminogen activator (Ossowski et al., 1973; Unkeless et al., 1974). The present experiments utilizing epsilon amino caproic acid (EACA), a fibrinolytic inhibitor (Figure 1), provide *in vivo* evidence that plasminogen activator activity may be important in early stages of pregnancy in the rat.

MATERIALS AND METHODS

Rats were purchased timed pregnant from Charles River Breeding Laboratories (CD®), Wilmington, MA. The day sperm were observed in the vagina was defined as pregnancy Day 1. On various days of pregnancy, groups of rats were lightly anesthetized with ether and laparotomized under aseptic conditions. The uterine horn to be injected was grasped lightly with forceps near the cervical end and a sterile 25 gauge needle attached to a 1 ml tuberculin syringe was inserted through the uterine wall into the lumen. Various doses of drugs were injected into the lumen. Light pressure was placed on the forceps during the injection and for 10 seconds after removal of the needle to prevent backflow. The abdominal wall was sutured and the skin closed with wound clips. The

rats were returned to their cages until autopsy on Day 15. At autopsy, corpora lutea, implantation sites and viable fetuses (based on size and gross appearance) were counted. Appearances of normal and resorbed sites are photographically illustrated in another publication (Dubin et al., 1979). Percent implantation was determined by dividing the number of implantations by the number of corpora lutea; percent viability was determined by dividing the number of viable fetuses by the number of implantation sites.

Study 1. Effect of Day of Injection

Rats were injected once between Day 3 and 8 of gestation. Groups of rats received either EACA or the saline vehicle. Other groups were sham treated, that is, the needle was inserted into the uterine lumen but nothing was injected. The EACA dose used in this study was determined by the maximal solubility (30 mg/0.1 ml) and the volume that would yield an acceptable viability rate when the vehicle alone was injected (see Discussion). EACA was prepared fresh on the day before injection in 0.9% sterile sodium chloride.

Study 2. Effect of EACA Concentration

All rats received EACA in one uterine horn on Day 6 of pregnancy. Groups received either 0.3, 0.6, or 3.0 mg EACA in a 0.01 ml volume. The contralateral horn received 0.01 ml saline.

Study 3. Effect of Plasmin

Lyophilized plasmin was reconstituted in sterile 0.9% sodium chloride immediately before injection. Plasmin doses are expressed in caseinolytic units (CU; Sgouris et al., 1960). On pregnancy Day 6, rats received intraluminal injections of either 3 mg EACA, 3 mg EACA plus 0.5 CU

plasmin (KABI, Sweden), 0.5 CU plasmin alone, or saline in a 0.01 ml volume. In this experiment, both horns of the uterus were injected with the same substance.

Study 4. Effect of Systemic EACA

Groups of rats received subcataneous injections of either 0, 15, 30 or 60 mg of EACA daily from Day 3 to 10. The concentration of the injection fluid was always 30 mg/0.1 ml.

Statistical Analysis

In study 1, comparisons were made by students' t test. In all other studies, analysis of variance were performed with F ratios used to test for significant differences between treatments.

RESULTS

Study 1. Effect of Day of Injection

In untreated rats the implantation rate was 82.2 ± 6.7% while the viability rate of those implantations was 93.8 ± 4.9% (Table 1). Sham intrauterine injections on any one day between pregnancy Day 3 and 8 did not affect the implantation rate, however, viability was affected when a sham injection was performed on Day 4 (46.1 ± 10.7%) or Day 5 (8.9 ± 6. .). Injection with normal sterile saline (0.1 ml) reduced percent implantation when injection was made on Day 4. Saline injections affected viability on Days 4 and 5 although this effect could be accounted for by merely inserting the needle since the percent viability these groups were not significantly different from the sham injections on comparable days of pregnancy. Injection of 0.01 ml saline on Day 6 decreased percent viability below the level of the sham control (47.3 ± 11.5 versus 82.7 ± 5.5%). Injection of 3 mg EACA in the same volume of saline further

reduced the percent viability to 13.3 ± 6.0%. EACA did not affect viability on any other day tested nor did it affect implantation on any day tested. EACA was not tested on Day 4 or 5 because of the low viability rates encountered with sham injection.

Study 2. Effect of EACA Concentration

When intrauterine injections were made on Day 6, the percent viability was dependent upon the dose of EACA administered (Figure 2). In this study, all injections were made in 0.01 ml saline.

Study 3. Effect of Plasmin

In another study, intrauterine injections of 3 mg again resulted in reduced viability (13.9 ± 4.3% versus 54.1 ± 5.4% for saline control; $P < .001$, Figure 3). Injection of EACA along with plasmin resulted in 35.5 ± 6.5% viability which was significantly higher than EACA treatment alone, yet less than the saline treated rats ($P < .05$). Plasmin alone reduced fetal viability to 39.7 ± 12.4%.

Study 4. Effect of Systemic EACA

No differences in either implantation or fetal viability were observed following systemic injection of up to 60 mg EACA/day from Day 3 to 10.

DISCUSSION

Implantation involves complex interactions between trophoblast and uterine tissue (Weitlauf, 1979). The trophoblastic function itself may involve numerous events which depend on different biochemical mechanisms. For example, blastocyst surface glycoproteins may be important for attachment to the uterine wall (Enders and Schlafke, 1974; Hicks and Guzman-Gonzalez, 1979). Estrogen production which has been noted in

rabbit blastocysts, may increase capillary permeability at the implantation site (Dickmann, 1975; Dickmann et al., 1979). Progesterone synthesis has been demonstrated in rat trophoblast (Salomon and Sherman, 1975) and this may cause local immunologic suppression and prevent rejection of the heterologus embryo (Siiteri, 1976).

Invasion through the intracellular matrix represents yet another trophoblastic process and it appears to be, in part, dependent upon fibrinolytic activity. Migratory cells, such as malignant cells (Ossowski et al., 1973) and macrophages (Unkeless et al., 1974), produce plasminogen activator. Plasminogen activators convert plasminogen to plasmin, a fibrinolytic enzyme (Figure 1). Plasmin, or closely related enzymes may be important in degradation of the intracellular matrix, thus fascilitating cell movement. Fibrinolytic activity has been reported in cultured mouse trophoblast (Sherman et al., 1976) and first appears on Day 6 and peaks on Day 9 corresponding to the time of trophoblast invasion in the mouse. The action of plasmin on connective tissue may be mediated, in part, by stimulation of collagenase production (Werb and Aggeler, 1973).

We have tested <u>in vivo</u> the effect of EACA, a fibrinolytic inhibitor on both implantation and fetal viability in pregnant rats. One approach was to inject the drug directly into the uterine lumen around the time of implantation. Some technical difficulties were encountered because of non-specific effects. We previously showed that intraluminal injections of 0.1 ml of normal sterile saline will result in a significant reduction in implantation rate when administered on Day 4 (Dubin et al., 1979). Furthermore, fetal viability was affected when saline was injected on Days 4, 5, 6 or 7. On Day 6, almost all implantation sites were resorbed

from horns receiving 0.1 ml saline. This effect was volume dependent. Since Day 6 is of particular interest because trophoblast invasion is occurring about this time (Enders and Schlafke, 1967), the highest concentration of EACA in the smallest volume (3 mg/.01 ml) was injected at this time.

Intrauterine EACA administration did not affect implantation rates when injected on Day 6, but it did increase the number of resorptions, possibly by preventing normal trophoblastic function. This effect was dose-dependent and could be partially reversed by simultaneously injecting plasmin along with the EACA. While the viability rates did not attain the level of the saline treated controls, they were close to the rates in the group receiving plasmin alone. The reason for reduction in viability due to plasmin alone is not known. The effect of EACA appears to be limited to a discrete time period. On Day 7, high doses (30 mg) had no effect on fetal viability. Also, no effect was observed when EACA was injected on Day 3, which is probably due to the fact that the ova has not yet reached the uterus. Day 4 and 5 could not be tested due to non-specific effects on viability merely due to insertion of the needle at these times. The present experiments do support the hypothesis that plasminogen activator activity is involved in the implantation process and provide *in vivo* evidence for its physiologic importance. Other proteases have been demonstrated to block implantation in mice (Dabich and Andary, 1977).

Although systemic (oral) antifibrinolytic agents including EACA are effective in women in reducing menstrual blood loss (Callender et al., 1970; Kullander, 1970), in our study systemic (subcutaneous) administration of EACA had no effect on fetal viability. This might be because of inaccessability of the drug to the blastocyst residing within the uterus.

It has been noted that IUD insertion increases plasminogen activator activity in the endometrium (Kasonde and Bonnar, 1976). EACA reduced IUD induced menorrhagia (Kasonde and Bonnar, 1975). There is no documentation that IUD's containing EACA are more effective in reducing fertility, however, in light of the present experiments and other evidence discussed, it is hypothesized that such devices provide additional protection because of EACA's effect on suppressing trophoblast invasiveness.

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Table I

EFFECT OF INTRAUTERINE EACA ON IMPLANTATION AND FETAL VIABILITY ON VARIOUS DAYS OF PREGNANCY

Treatment Day	Treatment	Number	Percent Implantation	Percent Viability
–	Untreated	6	82.2 ± 6.7	93.8 ± 4.9
3	Sham	5	92.0 ± 8.0	89-4 ± 6.8
	Saline	12	85.1 ± 4.4	88.0 ± 3.8
	EACA (30 mg)	9	89.1 ± 7.3	86.1 ± 11.3
4	Sham	10	80.9 ± 9.8	46.1 ± 10.7*
	Saline	10	62.6 ± 5.7x	25.0 ± 10.4*
	EACA	not determined		
5	Sham	9	85.8 ± 6.1	8.9 ± 6.1*
	Saline	6	65.9 ± 7.6	24.17 ± 12.9*
	EACA	not determined		
6	Sham	20	78.0 ± 4.9	82.7 ± 5.5
	Saline	7	65.2 ± 9.2	47.3 ± 11.5*†
	EACA (3 mg)	6	70.4 ± 10.9	13.3 ± 6.0**
7	Sham	17	78.8 ± 4.6	86.7 ± 6.7
	Saline	8	74.9 ± 8.6	75.9 ± 11.4
	EACA (3 mg)	8	70.9 ± 9.0	82.4 ± 5.9
8	Sham	8	68.2 ± 9.2	70.4 ± 15.4
	Saline	11	77.6 ± 8.6	77.8 ± 9.1
	EACA (30 mg)	9	81.9 ± 8.7	91.0 ± 5.6

x = $P < .05$ vs. untreated control

* = $P < .01$ vs. untreated control

† = $P < .01$ vs. sham control for the same day

** = $P < .05$ vs. saline control for the same day

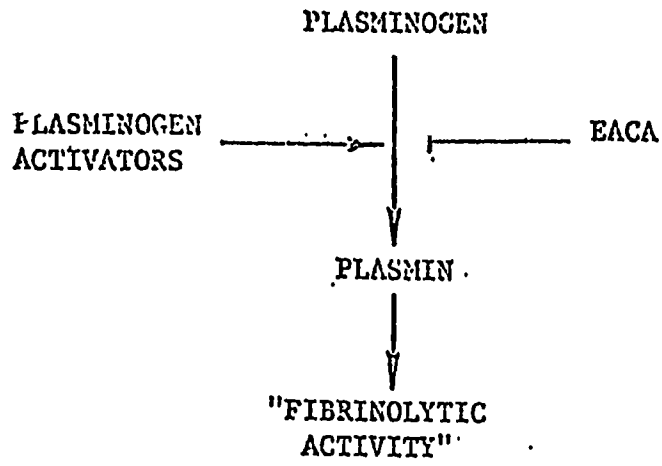


Figure 1. The Fibrinolytic System

Figure 2. Effect of various doses of EACA on fetal viability. All doses were injected directly into the uterine lumen on pregnancy Day 6. Volume of injection fluid was 0.01 ml in each horn, regardless of dose. Control horns (0 mg dose) were contralateral to a horn receiving EACA. Bracketed number designates number of treated uterine horns. Vertical line is standard error of the mean.

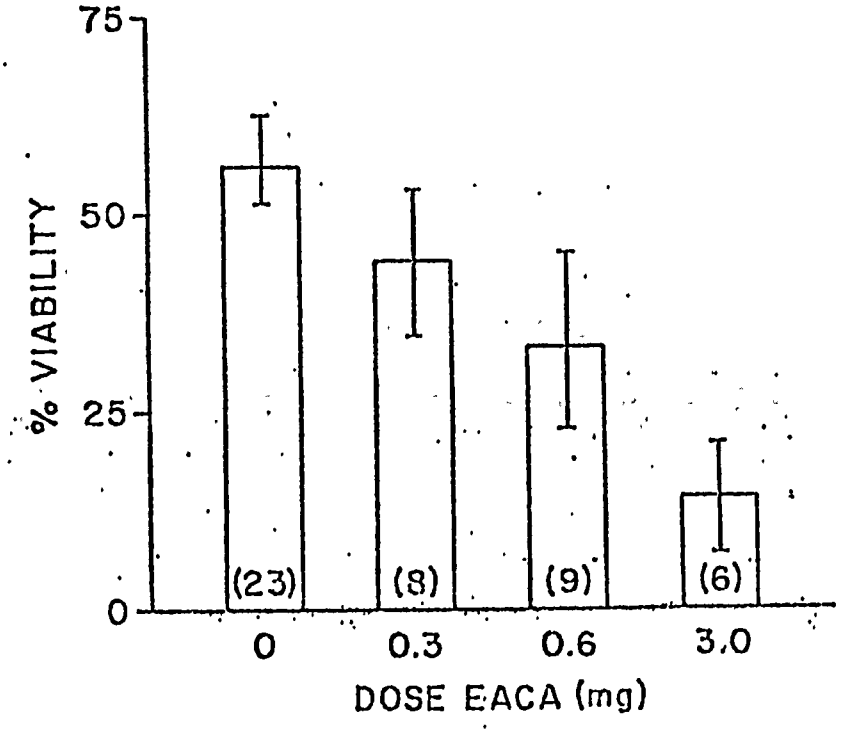
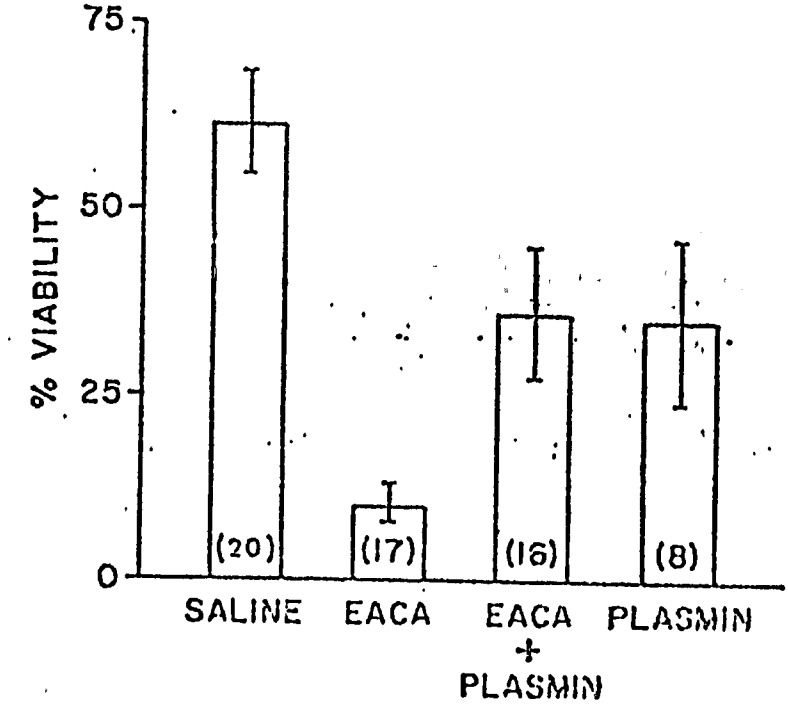


Figure 3. Effect of EACA (3 mg/horn) and plasmin (0.5 CU/horn) on fetal viability. All injections were made directly into the uterine lumen on pregnancy Day 6. Volume was 0.01 ml in each horn regardless of treatment. Bracketed numbers represent number of rats treated. In this experiment, both horns of each rat received the same treatment. Vertical line is standard error of the mean.



Cephalothin Prophylaxis for Midtrimester Abortion

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The prophylactic administration of antibiotics to prevent febrile morbidity has been shown to be effective in patients undergoing vaginal hysterectomy.[1-4] Ledger, and associates have suggested criteria for the employment of these agents for this operation.[1] These include administering the drug prior to the initiation of the procedure and employing an antibiotic that is active against the majority of organisms to be encountered.

Recently, there have been reports regarding the employment of prophylactic antibiotics in patients undergoing Cesarean section.[5-7] Although attempts have been made to identify risk factors for this operation, no uniform criteria have been established to define prophylactic antibiotic guidelines. In general, however, the employment of prophylactic antibiotics for patients undergoing Cesarean section has been shown to be effective in lowering febrile morbidity.[5-7]

Hence, it appears that for at least two procedures involving the genital tract, prophylactic antibiotics may have a role in decreasing the febrile morbidity.

The antibiotics most commonly employed as prophylaxis for patients undergoing vaginal hysterectomy and Cesarean section have been the cephalosporins. Cephalosporin antibiotics are broad spectrum agents that are effective against both gram positive and gram negative flora. These agents are readily available, relatively inexpensive, and have been associated with a low degree of toxicity. The cephalosporins are not considered either first line antibiotics for gynecologic infections or drugs that should be held in reserve for the more resistant organisms. Hence, they fullfill some of the suggested criteria in choosing a prophylactic antibiotic.[1]

Prophylactic antibiotics have also been administered to patients undergoing first trimester abortion procedures.[8,9] Determining their efficacy in this situation has been difficult since this is a procedure that is associated with a very small risk for infection. It has been demonstrated at our institution that the risk of febrile morbidity in women undergoing first trimester abortion procedures approximates 1%. This is much lower than individuals undergoing second trimester abortion procedures where the risk of febrile morbidity increases to approximately 8%.[10] Additionally, Burkman and associates have defined the flora that are causative of infectious processes in postabortal patients with febrile morbidity. The organisms most frequently isolated constitute part of the normal flora of the genital tract.[11]

Since prophylactic antibiotics have been useful in decreasing febrile morbidity in patients undergoing vaginal hysterectomy and Cesarean section, it was decided to determine if these agents would affect the febrile morbidity associated with midtrimester abortion. The purpose of this investigation is to determine if prophylactic sodium cephalothin as compared to placebo offers any advantage with regard to reducing febrile morbidity associated with endometritis in patients undergoing midtrimester injection-abortion procedures. There have been no prior prospective, randomized studies of the subject to our knowledge.

MATERIALS AND METHODS

The study population consisted of patients at the Fertility Control Center of the Johns Hopkins Hospital undergoing midtrimester abortion procedures. All patients were between 15 and 22 weeks pregnant. Pregnancies were terminated by the intraamnionic injection of hypertonic solution (urea 80 gm in 132 cc solution) supplemented by the intraamnionic injection of

prostaglandin $F_2\alpha$ and/or the intravenous administration of oxytocin.

The nature of the study was explained to each of the patients and informed written consent was obtained. The patients were then randomly assigned into one of two groups; those receiving Keflin 2 grams by intravenous minibottle, followed by 1 gram every 6 hours for up to 8 additional doses; those receiving a placebo administered in minibottles over the same time schedule. The assignment of patients into either the control or study group was double-blinded with the pharmacy keeping the code and preparing all solutions. The code was not broken until 200 patients had been studied. Patients excluded from the study included; those less than 18 years of age without parental consent, patients in whom antibiotics were indicated for prophylaxis and/or other attendant conditions, and individuals with a history of allergy to cephalosporins and/or penicillin drugs.

Once a patient had entered into the study an intravenous line was established with fluids administered at a rate of 50 cc per hour. Approximately one hour prior to the initiation of the abortion procedure, a 100 cc minibottle containing either drug or placebo was infused intravenously over a period of 30 minutes. The patient subsequently was administered 100 cc minibottles containing either sodium cephalothin or placebo as previously outlined.

The study and placebo groups were compared for age, ethnic origin, socioeconomic status, marital status, parity, height, weight, method of contraception prior to abortion, duration of gestation, and admission hematocrit. Other parameters evaluated included: the injection-abortion interval, the duration of membrane rupture prior to abortion, time interval from passage of the fetus to passage of the placenta, total abortion time, and estimated blood loss. All patients were evaluated in a standardized manner and followed during their hospitalization for the presence of a febrile response.

Patients were considered to be prophylaxis failures if they developed endometritis in the postabortion period. Endometritis was defined as any condition associated with a tender uterus that required antibiotic therapy and/or a lengthened hospital stay. Complete data were available on 198 patients; 101 of whom received placebo and 97 of whom received sodium cephalothin. The discrepency in the group sizes was the result of an error in obtaining equal groups in the generation of the random numbers. One patient in the placebo group was excluded from the study after being found to have a recent positive gonorrhea culture at pre-abortion outpatient evaluation, and a second patient in the cephalothin group did not undergo the injection-abortion procedure.

The data were tabulated and analyzed for the presence of differences employing Chi-squared analysis, and Student's 't' test for unpaired variates.

RESULTS

The characteristics for the two groups of patients are displayed in table 1. There were no statistically significant differences between the placebo and cephalothin groups in all parameters evaluated except for estimated blood loss and prophylaxis failures.

The estimated blood loss of patients receiving placebo was greater than those receiving sodium cephalothin ($0.025 < p < 0.05$). It should be noted that 10 patients in the placebo group had blood losses in excess of 500 cc, where only five patients in the sodium cephalothin group had blood losses this great. Three of the 10 placebo patients had losses in excess of 1000 cc. There were no patients in the treatment group that lost this amount of blood. None of the patients in this study required a blood transfusion.

There were 11 patients that developed endometritis, and required therapy. Two of these received sodium cephalothin and 9 received placebo. This difference is statistically significant ($\chi^2 = 4.35$; $0.025 < p < 0.05$).

The demographic characteristics of age, parity, race, and socio-economic status were evaluated and found not to be different between the infected and uninfected patients. The abortion parameters for these patients are displayed in table 2. The injection-abortion interval for the infected patients was 28.6 hours. This is significantly greater than the average value for the placebo group of 15.7 hours ($p < 0.0001$). This difference did not appear to be a function of parity. The cumulative abortion rates at 12, 24, and 36 hours were evaluated. Chi-squared analysis of the differences in the cumulative abortion rate between the endometritis and placebo groups revealed $0.05 < p < 0.1$; $0.005 < p < 0.01$; and $p < 0.005$ for the rates at 12, 24, and 36 hours respectively.

Seven of the 11 patients with endometritis had injection-abortion intervals of greater than 24 hours. Only 33 of the remaining 187 patients had an injection-abortion interval in excess of 24 hours. This difference is statistically significant ($\chi^2 = 13.9$, $p < 0.0001$).

The mean interval between injection and the rupture of membranes tended to be longer in the patients developing endometritis compared to the cephalothin and placebo groups. These differences were not found to be significant when subjected to Chi-squared analysis.

The length of time the membranes were ruptured prior to abortion were almost twice as long in the patients with endometritis (11.9 $\pm$ 13.4 hours) compared to the placebo group (5.9 $\pm$ 7.7 hours). Although this time period tended to be longer in the endometritis group, it was not significant at the $\alpha = 0.05$ level. Although a trend toward higher failure rates is apparent, the differences in the complete, incomplete, and abortion failure rates between the placebo group and the endometritis group were not significantly different. It should be noted, however, that 9 of the 11 patients in the

endometritis group are also in the placebo group.

The average estimated blood loss for patients with endometritis was 316 cc. However, one patient had a blood loss of 1850 cc which was greater than the total of all of the other patients combined (1612 cc). Hence, if one regards this patient's blood loss as being non-representative of group, it lowers the magnitude of this parameter to an average value of 161 cc.

Two of the patients with endometritis, one receiving cephalothin and one receiving placebo, had complaints consistent with cystitis prior to the procedure. Urinalysis and urine cultures in these patients did not support an infectious diagnosis. Two of the infected patients required hospital admission and parenteral antibiotics.

The organisms isolated from the genital tracts of the endometritis patients were considered to be part of the normal flora of the female reproductive tract and no predominant group was represented.

DISCUSSION

Prophylactic antibiotics have been demonstrated to be helpful for the prevention of febrile morbidity in patients undergoing vaginal hysterectomy. Their impact on the development of serious pelvic infections is less clear. However, recent evidence indicates that delayed infections are not problems. The role of these agents in altering the postoperative course of patients undergoing Cesarean section is less clear.

Prophylactic antibiotics have been employed in patients undergoing first trimester abortion.[8,9] The validity of such a practice, however, must be questioned since this is a procedure that uniformly is associated with such a low risk of infectious morbidity. It seems difficult to justify subjecting 100 patients to antibiotics to prevent one from developing a fever. This is even more irrational when one considers that the majority of the patients that develop postabortal febrile morbidity can be treated as outpatients with

basically uncomplicated courses.

The risk of febrile morbidity is increased in patients undergoing midtrimester abortion procedures. Our placebo group had 9 infections in 101 patients which is similar to our previous results.[11] There were only 2 infections in the 97 patients receiving Keflin. The differences in these two groups was highly significant.

Even though we were able to reduce febrile morbidity in patients undergoing midtrimester abortions with prophylactic antibiotics; does this justify their employment in all patients undergoing this procedure? Two of our patients were hospitalized and required extensive therapy. The cost of their hospitalization would easily cover the expense encountered in purchasing the antibiotics for the remaining 196 patients.

There were 92 of 101 patients that received placebo and had no febrile morbidity. This might imply that although prophylactic antibiotics appear useful for patients undergoing midtrimester abortion there are probably subgroups at increased risk that should be identified for therapy. The randomization scheme we employed resulted in the placebo and active drug group being quite similar in most parameters. This would imply that the difference in febrile morbidity between the two groups (placebo and cephalothin) is real. The question then becomes, what is the difference between the patients that became infected and those that did not? Comparing the 11 infected patients to the entire group (table 2) does not disclose many readily apparent differences. The interval of time from intraamnionic injection to abortion of the fetus exceeded 24 hours in 7 of the 11 patients with febrile morbidity. This only occurred in 33 of the remaining 187 patients that did not become febrile. Eighteen of these 33 patients (55%) received placebo. Hence, it would appear that in injection-abortion interval greater than 24 hours may be a risk factor for developing febrile

morbidity in patients undergoing midtrimester abortion. This was further supported by the differences in the cumulative abortion rate at various time intervals in the endometritis cases. The differences between cumulative abortion rates reached significance after 24 hours.

We could not document that the time of membrane rupture was significantly different in the infected cases. The data do demonstrate that the length of time an abortion takes and the length of time the membranes are ruptured prior to abortion, in those cases unaborted in 24 hours, is associated with an increased risk of endometritis.

We administered prophylactic antibiotics every six hours up to one dose beyond the pregnancy termination or 48 hours, whichever came first. Recent data suggest that fewer doses of prophylactic antibiotics may be equally efficacious.[12] In vaginal hysterectomy, the operative process is conducted during a well-defined time period. This is not the case with midtrimester abortions. The optimum time to initiate therapy cannot be determined from this study. However, this investigation was not designed for that purpose. It might be appropriate to administer prophylactic antibiotics only to patients who have not aborted after 24 hours. In our population, 3 of 11 (27%) of the infected patients would not have received therapy. However, it should be noted that the febrile morbidity occurred late in 2 of the 3 patients. Although they had an injection-abortion interval of less than 24 hours, the total procedure time exceeded 24 hours. If it is determined that the prolonged injection-abortion interval is a guideline that may be employed for determining at risk patients for febrile morbidity; how long should the course of antibiotics be? Existing data indicate that one dose is adequate for defined time procedures. A prophylactic antibiotic schedule for midtrimester injection-abortions will have to be determined by

appropriately designed studies.

In this first randomized, prospectiye study of the use of prophylactic antibiotics in patients undergoing midtrimester abortion, it has been demonstrated that these agents decrease the frequency of febrile morbidity.

DDC AVAILABLE DOCUMENT

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Table I

Patient Characteristics

Parameter	Placebo	Cephalothin
Number of Group	101	97
Age (years)	21.2 ± 5.3	20.8 ± 5.0
Number of White Patients	47 (46.5%)	43 (44%)
Number of Single Patient	88 (87.1%)	87 (89.7%)
Socioeconomic Status		
Medical Assistance	39	34
Private Insurance	22	13
Cash	40	48
Unknown	0	2
Height (inches)	64.6 ± 3.1	63.9 ± 2.8
Weight (pounds)	137.8 ± 29.1	140.5 ± 26.4
Admission Hematocrit (%)	34.6 ± 2.9	34.3 ± 2.4
Number of Patients with Previous Abortions	26 (25.7%)	29 (29.9%)
Number of Nulliparous Patients	48 (47.5%)	49 (50.5%)
Contraception Type Prior to Abortion		
Intrauterine device	2 (2%)	2 (2%)
Oral Contraceptive	25 (24.8%)	14 (14.4%)
Barrier (foam, condom, diaphragm)	9 (8.9%)	17 (17.5%)
None	65 (64.4%)	64 (66%)
Gestational Age (weeks)	19.2 ± 3.7	19.2 ± 5.5
Injection to ROM Interval (hours)	10.6 ± 8.5	9.3 ± 8.3
Length of Time Membranes Ruptured Prior to Abortion (hours)	5.9 ± 7.7	6.6 ± 7.8
Injection to Abortion of Fetus (hours)	15.7 ± 11.1	14.9 ± 9.4
Fetus to Placenta (hours)	1.2 ± 1.3	1.0 ± 1.1
Total Abortion Time (hours)	16.8 ± 10.7	15.9 ± 9.4
Estimated Blood Loss (cc)	254.8 ± 16.9	182.7 ± 13.4
Patients with Estimated Blood Loss ≥ 500 cc	10	6
Prophylaxis Failures	9	2

Table 2

Clinical Characteristics of Patients in the Midtrimester Abortion Prophylactic Antibiotic Study

Characteristics	Cephalothin Group N=97	Placebo Group N=101	Endometritis Cases N=11
Mean injection-abortion interval (hours)	14.9 ± 9.4	15.7 ± 11.1	28.6 ± 14.2
Para 0	15.4 ± 8.9	16.8 ± 11.0	28.5 ± 13.6
Para 1 or greater	14.4 ± 9.9	14.8 ± 11.2	21.8 ± 20.5
Cumulative abortion rate (%)			
At 12 hours	49	49	23
At 24 hours	82	76	36
At 36 hours	95	94	64
Membrane rupture			
Mean injection to ROM* (hours)	9.3 ± 8.3	10.6 ± 8.5	16.6 ± 13.8
Mean ROM to abortion interval (hours)	6.6 ± 7.8	5.9 ± 7.7	11.9 ± 13.4
Abortion type (%)			
Complete	68	64	36.4
Incomplete	32	33	54.5
Failure	0	3	9.1
Blood Loss			
Mean estimated loss (ml)	183	255	316
Loss exceeding 500 ml (%)	5.2	9.9	9.1

* ROM - Rupture of Membranes

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EFFECT OF SILVER NITRATE ON PREGNANCY TERMINATION IN CYNOMOLGUS MONKEYS

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INTRODUCTION

Chemical methods of menstrual induction are an alternative to early surgical procedures of abortion. A major advantage might be less need for skilled professionals. We have previously reported that several protein denaturants had antifertility activity in rats (Conner et al., 1976). At that time, it was decided to test several more active compounds for efficacy in monkeys. Results with ehtanol have previously been reported (Dubin et al., 1978, 1980). This paper reports our results with another of our selected compounds, silver nitrate.

MATERIALS AND METHODS

Cynomolgus monkeys (Macaca fascicularis) were obtained from Primate Imports (Port Washington, NY). They were fed Monkey Chow (Charles River Breeding Labs, Inc., Wilmington, MA), supplimented with fresh fruit. All monkeys were individually caged except during timed mating periods. Animals were checked daily (including weekends) for vaginal bleeding with cotton swabs. They were cohabitated for 8 days beginning 12 days after the onset of vaginal bleeding. Between 18 and 23 days after the midpoint of the cohabitation period, the mated female was subjected to rectal and abdominal bimanual palpation by an experienced caretaker of primates. At the same time, urine was collected from the bladder by urethral catherization and tested for monkey chorionic gonadotropin (mCG) by a hemagglutination inhibition test (Ortho Diagnostics Inc., Raritan, NJ).

If monkeys were documented pregnant by palpation or mCG testing, they were placed on the study protocol. Day of pregnancy was counted from the midpoint of the cohabitation period. Thus, cohabitation day 5 was counted as pregnancy day 1. At approximately 1 month (range 27-43 days) of pregnancy, the animal was immobilized with an intramuscular injection of

4.4 mg per killogram of body weight of Ketamine hydrochloride (Ketaset). A 12 cm long, 18 gauge, sterile blunt-end stainless steel needle was inserted through the cervix into the uterine cavity until resistance was encountered. A 1 ml solution of either 1% silver nitrate or 0.9% saline was injected. The treatment was randomized and the investigator performing the injection and the animal technician was unaware of which solution was being administered.

The monkeys were observed daily for vaginal bleeding. Blood samples were taken from a peripheral vein prior to treatment, on day 1, 2 and 3 following treatment and at month after treatment for blood chemistry and hematologic evaluations. Blood samples were analyzed by the Division of Clinical Laboratories of the Johns Hopkins Hospital. Also, 1 month after treatment, monkeys were repalpated to determine the pregression of pregnancy.

RESULTS AND DISCUSSION

All monkeys receiving intrauterine injections of 1 ml 1% silver nitrate between 27 and 43 days of pregnancy showed vaginal bleeding beginning one or two days after treatment (Figure 1). The bleeding lasted for an average of 5.3 days (range 4-7 days). These monkeys were found to have non-enlarged or subnormally enlarged uteri at the time of repalpation indicating that abortion had ensued. Continued observation of these monkeys confirmed that they were no longer pregnant. All monkeys recycled after silver nitrate treatment. Two subsequently became pregnant and had normal healthy infants.

Monkeys receiving 0.9% saline had variable outcomes (Figure 2). Two animals (#2 and 3) showed some spotting after injection but pregnancy progressed. These animals delivered normal healthy fetuses at 165 and 181 days. Number 6 had an uneventful pregnancy and a healthy infant was born at 148 days. Number 4 had uneventful pregnancy until delivered by C-section at 108 days of a living fetus as part of another study. Monkey #2 demonstrated

vaginal bleeding on days 6 and 7 following injection and aborted. Monkey #5 passed fetal tissue 29 days after injection.

Hematology and blood chemistry determinations revealed no significant difference between silver nitrate and saline treated monkeys (Tables 1 and 2).

Two monkeys, not in the randomized study, were injected with 1 ml silver nitrate as described in the previous study. Duration of pregnancy at injection was estimated at 37 and 38 days. Animals were hysterectomized and salpingo-oopherectomized at 7 days following injection.

On gross inspection, hemorrhage was observed between the gestational sac and decidua resulting in separation of these tissues (~~Figure 3~~). While there were hemorrhagic sites within the placenta, there was no associated necrosis of the adjacent villi. However, portions of the placenta were separated from the underlying decidua basalis and in these areas there was evidence of tissue autolysis (Figure 3).

The study indicates that 1% silver nitrate in an effective agent for terminating early pregnancy in monkeys.

Figure 1: Effect of intrauterine administration of 1 ml 0.9% saline on pregnancy in cynomolgus monkeys. The following legends apply to this figure and figure 2. Solid bars represent normal progress of pregnancy. Arrow indicates time of treatment. Stippled bar represents vaginal bleeding. A = abortion; B = birth of normal healthy infant; T = pregnancy artifically terminated but fetus viable.

Figure 2: Effect of intrauterine administration of 1 ml 1% silver nitrate on pregnancy in cynomolgus monkeys.

Fig 1

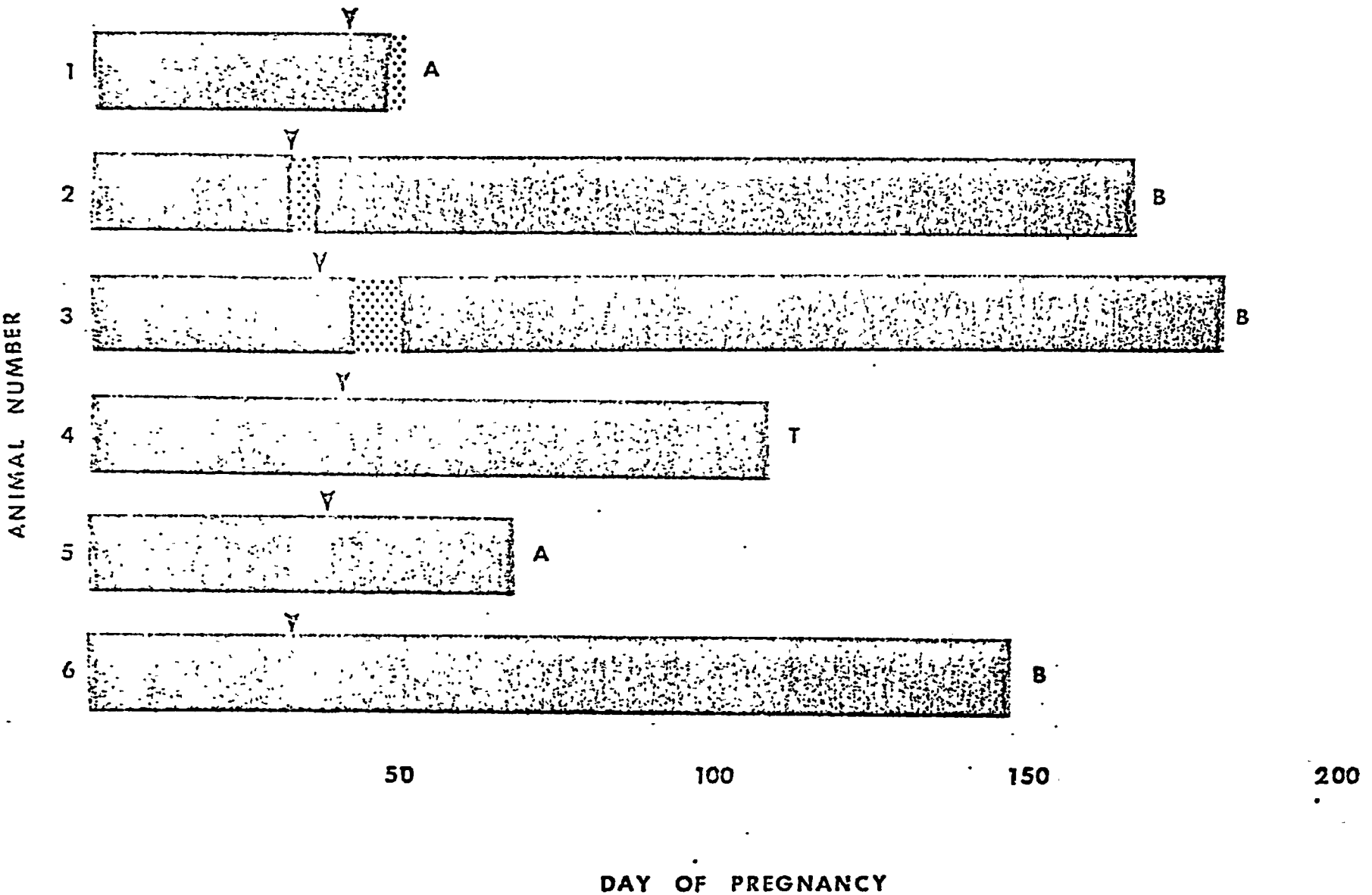
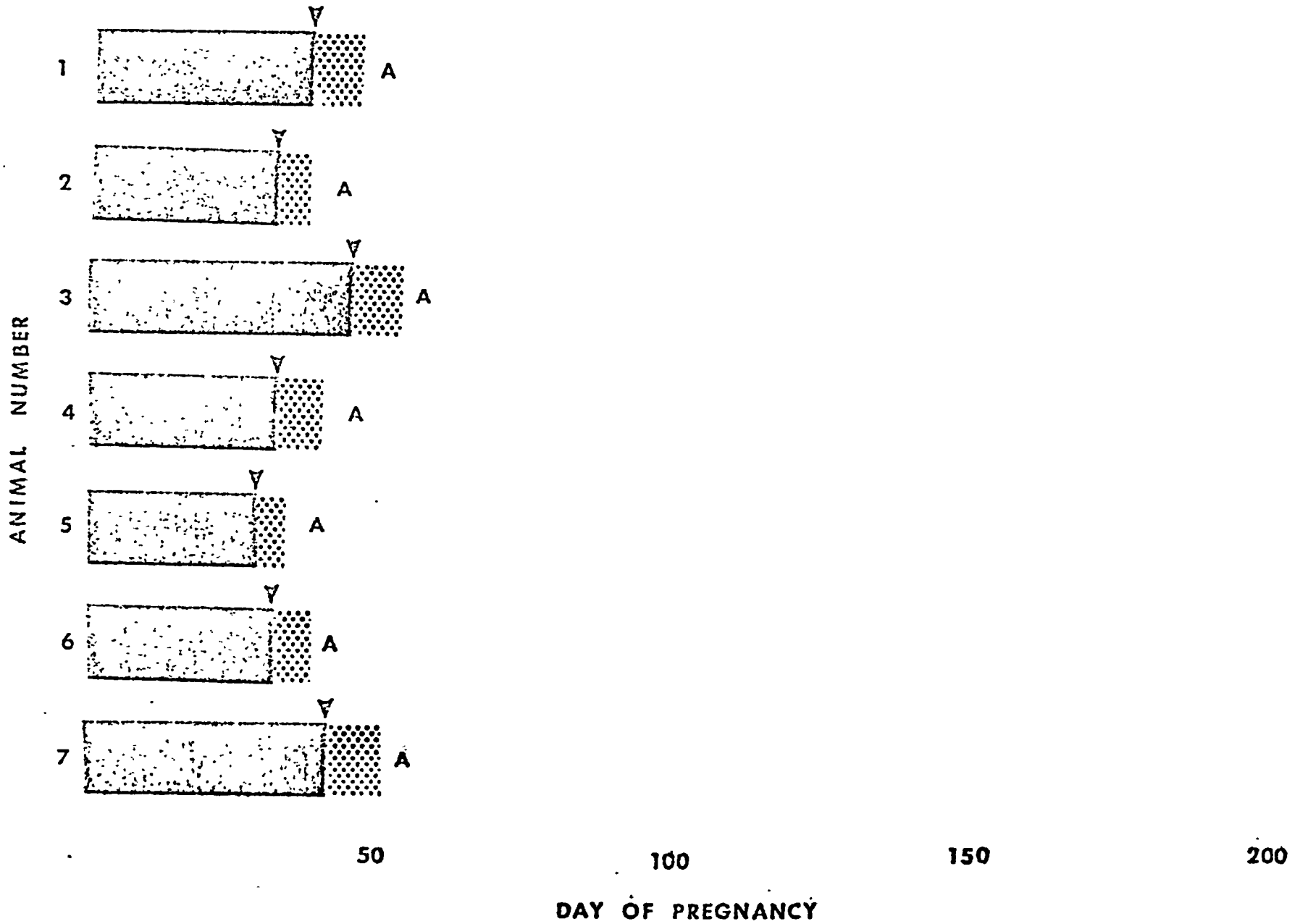


Fig 2


ANIMAL NUMBER
1
2
3
4
5
6
7
A
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A
A
A
A
50
100
150
200
DAY OF PREGNANCY

Table 1

Hematology Following Administration of 1 ml 1% Silver Nitrate or 0.9% Saline

	Mating	Drug Admin	Time after Drug Administration			
			24 hr	48 hr	72 hr	1 month
White blood cells Count X 10^3						
Silver Nitrate	9.3±0.6	8.0±1.1	9.2±0.7	8.0±0.9	8.8±0.7	9.0±.5
Saline	8.7±1.0	8.4±1.3	8.1±1.6	8.6±1.0	8.8±1.0	
Red Blood Cells Count X 10^6						
Silver Nitrate	5.8±0.1	5.2±0.3	5.5±0.1	5.6±0.1	5.4±0.2	5.9±.3
Saline	5.8±0.3	5.7±0.4	5.9±0.2	5.4±0.5	5.4±0.6	
Hematocrit (%)						
Silver Nitrate	34.9±0.7	33.6±0.8	34.5±1.0	33.0±1.0	34.2±0.7	33.9±.6
Saline	33.4±1.6	35.1±1.8	34.7±1.2	32.8±1.6	33.1±2.5	

Table 2

Blood Chemistry Analysis following Administration of 1 ml 1% Silver Nitrate or 0.9% Saline

	Mating	Drug Admin.	Time After Drug Administration			
			24 hr	48 hr	72 hr	1 month
Sodium (mEq/L)						
Silver Nitrate	145.3±1.1	146.0±0.7	145.0±1.6	145.2±0.9	144.6±0.8	146.0±0.9
Saline	148.0±0.6	145.0±1.8	149.0±1.3	145.3±0.6	146.0±1.3	
Potassium (mEq/L)						
Silver Nitrate	3.77±.16	4.02±.20	3.93±.08	3.94±.18	4.02±.17	4.03±.22
Saline	3.63±.33	4.28±.17	3.90±.24	3.68±.20	4.05±.13	
Chloride (mEq/L)						
Silver Nitrate	106.5±1.5	107.0±1.8	108.2±1.1	108.4±1.0	106.6±1.0	108.3±.8
Saline	105.7±0.7	111.0±1.9	107.3±0.9	108.0±2.7	110.0±1.3	
Glucose (mg/dl)						
Silver Nitrate	71.2±5.2	62.2±7.3	59.3±6.3	66.8±3.2	67.4±2.6	71.5±2.8
Saline	66.0±7.5	55.0±10.5	52.5±8.9	62.5±7.6	59.0±9.4	
Urea Nitrogen (mg/dl)						
Silver Nitrate	19.5±0.9	19.0±1.1	20.8±1.4	19.2±1.1	19.8±1.4	18.5±1.5
Saline	20.3±4.7	20.5±1.6	21.3±2.3	19.0±4.1	23.0±2.5	
CO_2 (mEq/L)						
Silver Nitrate	22.8±0.9	23.6±1.2	23.8±0.4	24.0±1.6	23.0±1.5	23.5±1.0
Saline	21.3±2.6	20.3±0.9	24.5±1.9	22.7±1.1	25.0±2.4	

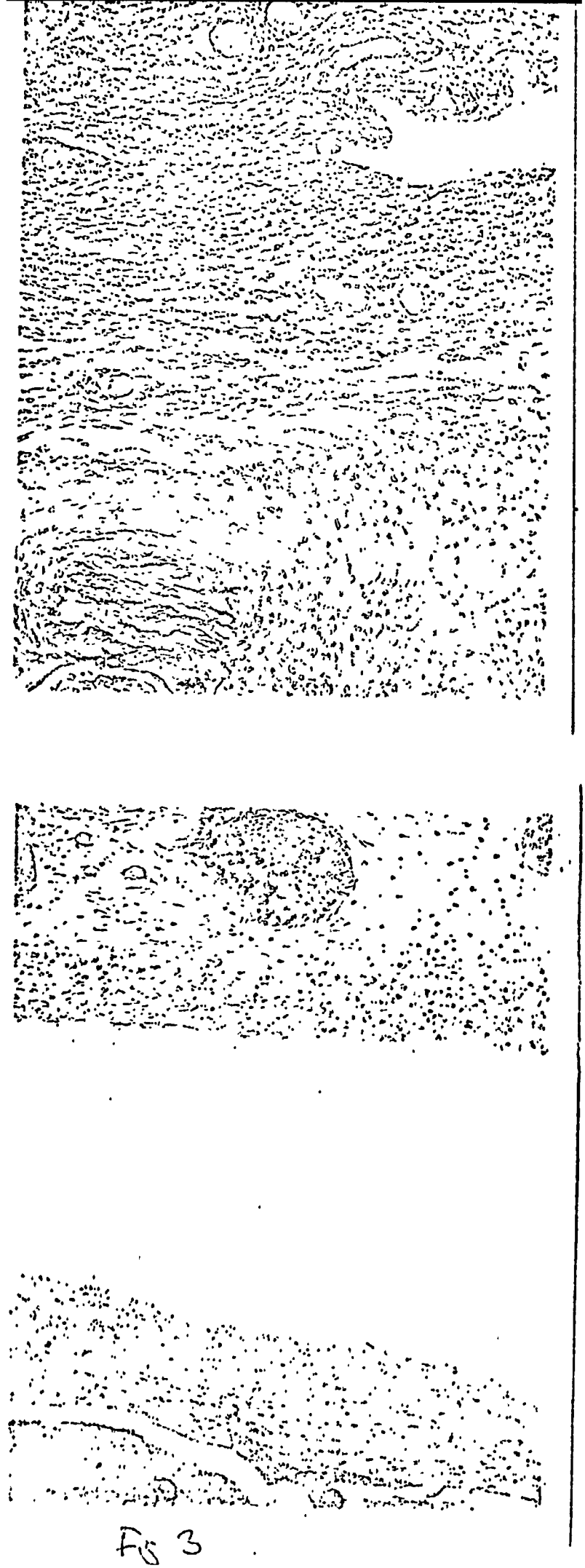

Fig 3

HYPEROSMOLAR UREA FOR ELECTIVE MIDTRIMESTER ABORTION

A FIVE YEAR EXPERIENCE

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Abstract

The use of hyperosmolar urea as a midtrimester abortifacient is safe and efficacious. Using either intravenous oxytocin or low doses of intra-amniotic PGF_2a for augmentation, injection-abortion intervals of less than 24 hours can be consistently achieved. Failed procedures are rare although incomplete abortion occurs in 30 to 40% of cases. Complications with the drug include occasional hemorrhage, infection, and nausea and vomiting. Cervical injury can occur but the frequency and severity appears to be less with lower doses of PGF_2a and with the pre-instillation use of laminaria tents. The major advantages of hyperosmolar urea include predictable 24 hour or less injection-abortion intervals, ease of mastering the technique, infrequent life threatening complications, and rarity of live fetal abortion.

Introduction

The ideal method of managing patients requesting midtrimester abortion is still a matter of considerable controversy. At this time, the most widely used approaches include the intra-amniotic administration of hypertonic sodium chloride, hyperosmolar urea, and prostaglandin F_2a (PGF_2a) and dilatation and evacuation. All methods have advantages and disadvantages and to date no one method has emerged as the best overall approach. This chapter will review the experience at the Fertility Control Center of the Johns Hopkins Hospital with the administration of hyperosmolar urea for the induction of elective midtrimester abortion.

Method of Administration

Prior to instituting the instillation procedure, all patients undergo a careful history and physical examination, a thorough discussion of the procedure including risks, and all patients sign a detailed informed consent. Routine laboratory testing includes a hematocrit, urinalysis, Pap smear, gonorrhea culture, Rh determination, syphilis serology and pregnancy test. At the Fertility Control Center, patients are candidates for the procedure if the duration of gestation is between 16 and 22 weeks from the first day of the last menstrual period.

Sonography is utilized for evaluation of borderline patients and those patients who have abnormalities such as dates significantly unequal to exam, or uterine myomas. In our experience so far, we have not encountered an absolute contraindication to the procedure.

Prior to the instillation, hyperosmolar urea is prepared by mixing 40 mililiters (ml) of 5% dextrose and water with 40 grams of lyophilized urea salt. Two bottles or 80 grams are utilized for each patient. For the total 80 gram dose, this will constitute a final volume of about 135 ml or a 59.7% concentration.

Each patient undergoes an immediate pre-operative abdominal and pelvic examination and confirmation of the presence of fetal heart tones with a Dopler device. All patients currently undergo insertion of laminaria tents for a minimum of six hours prior to the procedure. Between one and five 5 millimeter tents are inserted under antiseptic conditions and the patients are kept at bedrest. Following insertion of the tents, no further routine vaginal examinations are performed until the time of abortion or until 24 hours have elapsed since the instillation of urea. All tents still in place in unaborted patients are

removed at the 24 hour examination.

To carry out the instillation, patients empty their bladder, the abdomen is prepped with antiseptic, and draping is carried out with sterile towels. The usual site for amniocentesis is in the midline 2 to 3 centimeters above the pubic hairline. About 5 to 10 ml of 1% lidocaine is injected around the amniocentesis site. Amniocentesis is carried out using a 3.5 inch number 16 Tuohy epidural needle. After obtainment of free flow of clear fluid, at least 100 ml and usually 200 ml of amniotic fluid is removed using a disposable extension tubing with a three-way stopcock. If the fluid cannot be readily removed using a syringe, the fluid is removed by syphoning with the exertion of gentle pressure on the uterine fundus. If a tap is bloody and does not immediately clear, the Tuohy needle is either re-positioned or a second amniocentesis is performed. Urea instillation is not carried out until free flow of amniotic fluid is obtained. The usual causes for failed amniocentesis or bloody taps are large anterior placentae, gestational ages less than 16 weeks, and occasionally abnormal pregnancies with oligohydramnios. It should be noted that pre-operative medications such as tranquilizers or analgesics are

not utilized.

Following removal of the amniotic fluid, the prepared urea is slowly infused via gravity. Currently, all patients are augmented with 5 milligrams (mg) of PGF_2a given intra-amniotically following the urea infusion. An initial 2.5 mg dose is slowly given, and if no untoward reactions occur, an additional 2.5 mg is infused after 5 minutes. PGF_2a is not utilized for patients with a history of asthma or known sensitivity to PGF_2a. For such patients, intravenous oxytocin at 332 mu/min is started immediately following urea infusion. This dose is achieved by mixing 200 units of oxytocin with 500 ml of 5% dextrose and 0.2% sodium chloride and administering it at a rate of 50 milliliters per hour with an electronic pump.

Routine post-injection care includes frequent monitoring of vital signs, careful monitoring of intake and output, and observation for membrane rupture, hemorrhage, labor and abortion. Oxytocin given intravenously in the dose just described is indicated in the absence of labor, approximately 4 hours after rupture of membranes; 24 hours after injection if labor has not occurred; and after fetal abortion to control bleeding or to assist in placental expulsion.

When oxytocin is given at this dose, serum electrolytes are monitored at least every 12 hours. The oxytocin infusion is stopped for 2 to 4 hours if there is clinical evidence of water intoxication, a serum sodium is less than 132 milliequivalents per liter, intake exceeds output by more than 1500 milliliters, urinary output of the patient is poor, or if there has been a suspected intravascular injection of urea. Recently, with the routine use of pre-infusion laminaria tents, most patients unaborted by 24 hours no longer receive intravenous oxytocin but rather are given a vaginal suppository of 10 milligrams of prostaglandin E_2 (PGE_2) every 3 to 4 hours if they are not in active labor. Patients who have risk factors for coronary vascular disease are not given PGE_2 and instead receive intravenous oxytocin. If fetal abortion has not occurred within 48 hours and is not felt to be imminent, vaginal evacuation of the uterus with intravenous analgesia of 50 mg meperidene and 10 mg of diazepam is carried out. Also, prior to 48 hours, if hemorrhage or evidence of chorioamnionitis occur, vaginal evacuation is also utilized.

Following fetal abortion, if the placenta is not passed within about 2 hours, curettage with ring

forceps is carried out using the same form of intravenous analgesia. After observation for at least 4 hours after completion of abortion, patients are given detailed instructions regarding potential complications, are provided with contraception or contraceptive advice, and are given follow-up appointments for about 4 weeks later. In our 5 year experience with this technique in the Fertility Control Center, follow-up information has been obtained on about 80% of our abortion population.

Summary of Results

A number of clinical studies have been completed in the Fertility Control Center in the evaluation of the efficacy and safety of hyperosmolar urea as an abortifacient. Studies both in our center[1] and elsewhere[2,3] have shown that one needs to supplement the actions of urea with other agents such as intravenous oxytocin or intra-amniotic PGF_2a in order to obtain injection-abortion intervals of less than 24 hours. Although initial experience with the use of intravenous oxytocin for augmentation at a rate of 332 mu per minute yielded satisfactory injection-abortion intervals,[4] the antidiuretic actions of oxytocin and the potential risk of water intoxication led to the

evaluation of other approaches. Accordingly, studies evaluating the intra-amniotic use of PGF_2a in doses of 20 mg,[5] 10 mg,[6] and 5 mg[1,7] were completed in a sequential fashion in an effort to determine a minimally effective dose. Finally, in an effort to reduce the potential for cervical injury, the use of intracervical laminaria tents is now being evaluated.

The clinical characteristics of the patients for the various groups studied are outlined in Table I. When the studies with PGF_2a for augmentation were initiated, the fetal foot length measurements of Streeter were used to estimate gestational age.[8] Therefore, the earlier gestational age for patients augmented with oxytocin as opposed to PGF_2a may reflect a change in the means of estimation. Among all patients, over 20% had a significant pre-existing medical condition. For example, pre-existing conditions most frequently encountered included asthma, gonorrhea, obesity, anemia, heart disease, urinary tract infection, and hypertension. In addition, about 60% of the patients were teenagers with over one-third being age 17 or less.

The injection-abortion intervals are summarized in Table II. All injection-abortion intervals are consistently less than 24 hours with lengthier times usually

being reported for nulliparious patients as opposed to parous patients. In addition, the percentage of patients receiving PGF_2a augmentation unaborted after 24 hours ranged from 10 to 20%. In our experience to date, there have been no instances of live fetal abortion.

Table III outlines the clinical outcome. As shown, incomplete abortion still remains as an important problem although failed abortion has become quite uncommon. In addition, as has been reported previously,[7] the need for utilization of oxytocin has been reduced.

The more frequent complications of the procedure are presented in Table IV. In addition to the listed complications, there have been 2 instances of coagulopathy, 3 cases of intravascular urea spill, and 1 case of subacute bacterial endocarditis. In addition, 1 patient required hysterectomy due to Clostridia perfringens sepsis.

Discussion and Review

Each of the currently available methods of inducing midtrimester abortion have disadvantages so that an ideal approach has not yet evolved. Intravascular spill of hypertonic sodium chloride has been associated with hemolysis, seizures, comma, cardiac arrest, and death.[9] Furthermore, clinical coagulopathy may be experienced

by up to 1% of patients particularly if oxytocin augmentation is begun immediately following hypertonic sodium chloride injection.[10,11]

PGF_2a has increased failure rates and a need for frequent re-injection. In addition, the drug is expensive and, when utilized for gestations greater than 18 weeks, live fetal abortion can occur occasionally.[12] Finally, all intra-amniotic methods require hospital back-up and support staff knowledgeable in the management of incomplete and failed abortion, hemorrhage, infection and cervical laceration.

Dilatation and evacuation for second trimester pregnancies has received a great deal of support recently.[13,14] This approach, in most hands, requires multiple patient visits or even hospitalization for pre-evacuation cervical treatment with multiple laminaria tents. In addition, one needs a more advanced degree of operator skill to carry out these procedures as compared to suction curettage in the first trimester. Although the short duration of the evacuation procedure has obvious psychological advantages for the patient as compared to instillation techniques, there can be a considerable degree of psychological adjustment required for the operator.[16]

Finally, the safety and efficacy of this technique for gestations beyond 18 weeks has not yet been evaluated in series involving large numbers of patients.

Unfortunately, the utilization of intra-amniotic instillation of urea for midtrimester abortion has not provided a solution for all the disadvantages and problems listed with other methods. The remaining discussion will briefly review the mechanism of action, hematological changes, biochemical changes, and complications associated with this agent and will contrast the findings with those known for other midtrimester techniques.

One possible mechanism of urea action is that decidual or placental damage leads to synthesis and release of prostaglandins. It has been demonstrated pathologically that hyperosmolar urea will produce varying types of "coagulation necrosis" and other damage to the placenta.[17] This damage presumable is secondary to the hyperosmolarity of the urea and could lead to resultant prostaglandin release. Supportive of this theory is a study by Niebyl and co-workers[18] where patients undergoing urea abortion who were pre-treated with aspirin, a prostaglandin inhibitor, had longer injection-abortion intervals

than placebo pre-treated patients. However, in another study completed in our center,[19] when isolated rat uterine strips were pre-incubated in baths containing indomethacin, another prostaglandin inhibitor, prostaglandin release was reduced but contractile force was not changed. Thus, at least in the rat, prostaglandin did not appear to be an obligatory factor in hyperosmolar urea-induced contractions. Finally, when levels of prostaglandin E and F and their metabolites were measured serially in the blood and amniotic fluid of patients undergoing a urea induced abortion it also appeared that uterine contractions could occur independent of the rise in prostaglandin production.[20]

In addition to producing uterine contractions, it also appears that hyperosmolar urea is fetal toxic. Studies in rhesus monkeys have shown that urea is rapidly taken up by the fetus from the surrounding amniotic fluid and that the fetus plays a role in distributing the drug to the placenta.[21] Furthermore, it has been shown that fetal heat tones are lost by approximately two hours in human studies[1] such that it has been postulated that passage of hyperosmolar solute into the fetus results in a loss of cardiac

function when a certain critical fetal osmolarity is exceeded.

The hematologic and coagulation factor changes following urea instillation have also been evaluated.[4,5] Hematocrit levels do not vary significantly over the first 24 hours, but leukocyte counts do show a gradual rise for the first 16 hours. However, this latter change is seen when midtrimester abortion is induced by other agents as well. Measurements of fibrinogen and platelets show some variation over 24 hours but without a consistent pattern. In 18 to 36% of patients, a significant increase in fibrinogen-fibrin degradation products has been shown in the 24 hours following injection. However, the frequency of such change and degree of change are less in comparison to the changes seen following instillation with hypertonic saline.[9] Despite the changes in coagulation factors seen with urea, it should be noted that clinical evidence of a disseminated intravascular coagulopathy is quite rare. For example, in the Fertility Control Center in our experience with over 2,500 cases, there have been only two instances of clinical coagulopathy.[10] In contrast, almost 1% of patients undergoing hypertonic sodium chloride instillation with immediate oxytocin augmentation

experienced a clinically significant coagulation disorder.

A number of biochemical changes can be noted following urea instillation in the midtrimester. Characteristically, serum urea nitrogen levels rise to a peak of 25 to 30 mg percent at 4 hours after instillation with a gradual return towards normal levels by 24 hours.[5] This change is more pronounced when oxytocin is utilized for augmentation due to its antidiuretic properties. In addition, there are some variations in levels of serum electrolytes, but all the variations occur within the normal range expected for patients. Following instillation, serum bilirubin, serum glutamic oxalcetic transaminase, lactic dehydrogenase, and alkaline phosphatase all show some elevation over the first 24 hours, but this is probably due to destruction of the fetal-placental unit. Finally, uric acid, calcium, phosphate, cholesterol, total protein and albumin levels do not vary significantly when measured serially over the first 24 hours after urea instillation.

A number of investigators at centers other than our own have demonstrated the efficacy of hyperosmolar urea as a midtrimester abortifacient.[22-25] In reviewing these studies and our own results, it is clear that the injection-abortion interval is influenced by a

number of factors. First, nulliparous patients usually experience longer intervals than do multiparous patients Secondly, augmentation soon after injection with either intravenous oxytocin or intra-amniotic prostaglandin is necessary in order to achieve injection-abortion intervals consistently less than 24 hours. The final intra-amniotic concentration of urea appears to be important in that shorter intervals are reported when the final infused urea concentration approaches 60% and when the amount of amniotic fluid removed at amniocentesis is 100 ml or greater. Finally, the utilization of pre-injection laminaria tents appears to also shorten the injection-abortion interval.

In reviewing the various problems and complications that can occur with this agent, one can make a number of points. Incomplete abortion remains as a problem in that about 30 to 40% of patients will require curettage if one uses our definition for incomplete abortion. Failure of the primary procedure still is an occasional problem, but can be readily managed with vaginal evacuation.[26] Such evacuations are easily carried out since labor has already effaced and dilated the cervix to some extent and the products of conception are in the lower uterine segment. Furthermore, the fetal products

are macerated and can be readily removed with sponge forceps. However, operators should have considerable experience with curettage for incomplete midtrimester abortion before attempting such procedures.

Hemorrhage to the extent that transfusion is required is quite uncommon in our experience. The most frequent causes include retained placental tissue and uterine atony. The former can be managed by curettage while the latter may require continuous bimanual uterine massage for several minutes. Coagulopathy as discussed previously is extremely rare.

Endometritis is somewhat uncommon though with our recent series of urea plus PGF_2a (5 mg.), between 1 and 2% of patients still require hospitalization for therapy. The most frequently encountered organisms include E. coli, Staphylococcus aureus, Group B beta streptococci, and Bacteroides.[27] However, it should be noted that flora found in the endometrium post-abortally is quite similar to the flora of the vagina and cervix pre-abortion.[28] Standard treatment for in-patients has included broad spectrum parenteral antibiotics such as ampicillin or penicillin plus an aminoglycoside. Early curettage is also an important part of the therapy. These rates for infection are quite similar to those reported in

other series of midtrimester terminations.[23,24]

Cervical injury is still an important problem with all midtrimester abortion procedures. Injuries range from small vertical lacerations to complete detachments of the posterior or anterior cervix.[29] With the use of laminaria tents the frequency of such injuries is decreased and the extent of injury is less.[24,25] For example, the 3 lacerations in association with laminaria shown in the results were all small and required only 2 or 3 interrupted sutures to close. When large lacerations are encountered, our treatment has consisted of immediate debridement followed by closure in layers. Despite care in the repair, breakdown is not uncommon and to date there is no information available regarding future reproductive outcome of such patients. It should be emphasized that these injuries do not usually lead to extensive bleeding such that unless careful speculum and digital examinations are part of one's post-abortal routine, these lacerations can be easily missed.

Gastrointestinal side effects, particularly nausea-vomiting, are not uncommon. However, diarrhea is rare due to the low doses of intra-amniotic PGF_2a utilized for augmentation. In general the gastrointestinal side

effects do not present a difficult problem for management although intravenous hydration is occasionally needed.

Intravascular spill of hyperosmolar urea is uncommon if one checks carefully to be sure that free flow of clear amniotic fluid is obtained at amniocentesis.[30] With such spills one sees symptoms that include nauesa, headache, sensations of warmth, and intense uterine cramping. In addition, abnormal blood pigments may occasionally be noted in the urine. Therapy includes careful monitoring of intake and output, monitoring of renal function, avoidance of oxytocics, and intravenous hydration. Urea probably poses less concern with such spills than does hypertonic sodium chloride because of its action as an osmotic diuretic and because of its ability to readily cross cell membranes.

In summary, the advantages of urea include: predictable injection-abortion intervals; ease of mastering the technique; limited hematologic, coagulation, and biochemical changes; and a relatively low frequency of life-threatening complications. In addition, live fetal abortion is extremely rare and the cost of the drug is reasonable. To date, controlled

clinical trials testing hyperosmolar urea versus other modalities such as hypertonic sodium chloride and dilatation and evacuation have not been carried out. Therefore, it is impossible to state whether or not the utilization of this approach is the safest and most efficacious means of accomplishing midtrimester abortion particularly for later gestations.

TABLE I

CLINICAL CHARACTERISTICS OF UREA PATIENTS*

	No.	Mean Age	Para 0	Para 1 or Greater	Mean Duration of Gestation (Weeks)
Urea + oxytocin (332 mu/min)	650	20.7 (11-48)	355	295	17.0 (13-22)
Urea + PGF_2a (20 mg.)	30	20.4 (13-40)	17	13	19.3 (13-22)
Urea + PGF_2a (10 mg.)	1083	20.3 (12-42)	624	459	19.9 (13-24)
Urea + PGF_2a (5 mg.) (No laminaria tents)	349	20.0 (13-40)	216	133	19.6 (14-24)
Urea + PGF_2a (5 mg.) (One laminaria tent)	197	19.5 (13-38)	160	37	19.9 (16-22)

* Ranges in parentheses

TABLE II

INJECTION-ABORTION INTERVALS OF UREA PATIENTS

	No.	Injection-Abortion Interval (Hours)* Mean	Range
Parity: 0			
Urea + Oxytocin	341	21.5	3-61
Urea + PGF_2a (20 mg.)	16	18.2	4-36
Urea + PGF_2a (10 mg.)	632	15.9	2-60
Urea + PGF_2a (5 mg.) (No laminaria)	213	17.0	6-45
Urea + PGF_2a (5 mg.) (One laminaria)	160	12.0	4-46
Parity: 1 or greater			
Urea + Oxytocin	289	16.6	4-54
Urea + PGF_2a (20 mg.)	12	13.7	3-30
Urea + PGF_2a (10 mg.)	434	13.9	1-47
Urea + PGF_2a (5 mg.) (No laminaria)	133	16.3	3-46
Urea + PGF_2a (5 mg.) (One laminaria)	37	13.9	4-44
Total Groups			
Urea + Oxytocin	630	19.2	3-61
Urea + PGF_2a (20 mg.)	28	16.3	3-36
Urea + PGF_2a (10 mg.)	1066	15.1	1-60
Urea + PGF_2a (5 mg.) (No laminaria)	346	16.7	3-46
Urea + PGF_2a (5 mg.) (One laminaria)	197	12.3	4-46

* From intra-amniotic injection of medication to abortion of fetus

TABLE III

CLINICAL OUTCOME OF UREA PATIENTS

		Complete Abortion		Incomplete Abortion		Failure	
	No.	No.	%	No.	%	No.	%
Urea + Oxytocin	650	385	59.2	245	37.7	20	3.1
Urea + PGF_2a (20 mg.)	30	16	53.3	12	40.0	2	6.7
Urea + PGF_2a (10 mg.)	1083	566	52.2	500	46.2	17	1.6
Urea + PGF_2a (5 mg.) (No laminaria)	349	222	63.6	124	35.5	3	0.9
Urea + PGF_2a (5 mg.) (One laminaria)	197	140	71.1	55	27.9	2	1.0

TABLE IV

COMPLICATIONS OF UREA PATIENTS

	Urea + Oxytocin (650 Cases)		Urea + PGF_2a (20 mg.) (30 Cases)		Urea + PGF_2a (10 mg.) (1083 Cases)		Urea + PGF_2a (5 mg.) (No Laminaria) (349 Cases)		Urea + PGF_2a (5 mg.) (One Laminaria) (197 Cases)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Hemorrhage (500 cc. or need for curettage)*	35	5.4	3	10.0	102	9.4	31	8.9	7	3.6
Endometritis										
Hospitalization	29	4.5	1	3.3	54	5.0	6	1.7	2	1.0
Outpatient	30	4.6	1	3.3	66	6.1	11	3.2	2	1.0
Cervical Laceration										
Transverse	6**	0.9	1	3.3	4	0.4	3	0.9	1	1.0
Vertical	0	—	0	—	31	2.9	5	1.4	2	0.5
Gastrointestinal ***										
Nausea-vomiting	347	53.4	22	73.3	788	72.8	213	61.0	—	—
Diarrhea	5	0.8	1	3.3	51	4.7	9	2.6	—	—

* Five patients required blood transfusion

** Post-abortal examinations not routine for this entire group

*** Gastrointestinal sequelae not analyzed for Urea + PGF_2a (5 mg.), one laminaria group

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Midtrimester abortion induced by hyperosmolar urea and prostaglandin $F_{2\alpha}$ in patients with previous cesarean section: Clinical course and potential for uterine rupture

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Reviewed was the clinical course of 76 patients with a history of previous cesarean section from among 1,626 patients undergoing midtrimester abortion induced with intra-amniotic hyperosmolar urea and prostaglandin $F_{2\alpha}$. The cesarean section group had long injection-abortion intervals, more frequently received additional oxytocin for augmentation, and more frequently experienced incomplete abortion. Also, one patient experienced a uterine rupture. A review of the literature dealing with uterine rupture subsequent to induced midtrimester abortion revealed that the typical patient was older and multiparous, had an injection-abortion interval of more than 24 hours, and had received intravenous oxytocin continuously for more than 12 hours. Although there has been no previous report of a uterine rupture with midtrimester abortion in patients who have undergone a prior cesarean section, because of the present findings, such patients require careful monitoring and the judicious use of oxytocic agents. (AM. J. OBSTET. GYNECOL. 138:55, 1980)

THE UTILIZATION of cesarean section for the management of obstetric problems has shown a gradual increase in the United States over the past several years. The factors responsible for such increased use were reviewed recently.[1] Therefore, in many institutions, the frequency of cesarean section per number of live births approaches or even exceeds 20%.

During the same period of time, although the percentage of patients in the United States who requested midtrimester termination of pregnancy gradually declined to approximately 9% in 1977,[2] the absolute number of patients presenting in the midtrimester did not appreciably change during the past several years. Therefore, there will be a number of patients requesting midtrimester termination who have undergone a prior cesarean section. This article describes the experience at the Fertility Control Center of The Johns Hopkins Hospital with the management of such patients, and also presents a case report of uterine rupture after midtrimester amnioinfusion in a patient who had previously undergone a cesarean section.

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Material and methods

Midtrimester terminations of pregnancy in the Fertility Control Center have been carried out on patients presenting between 16 and 22 weeks from the first day of the last menstrual period. Most of the patients in the Center have been managed by the intra-amniotic injection of hyperosmolar urea, augmented with either intra-amniotic prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or intravenous oxytocin, or both. For the purpose of this review, only cases were included in which intra-amniotic $PGF_{2\alpha}$ was used initially for augmentation in doses of 10 and 5 milligrams, since such cases represented over 70% of the midtrimester amnioinfusions completed between October, 1972, and June, 1979.

Detailed methodology with regard to the use of hyperosmolar urea for midtrimester abortion has been the subject of previous reports.[1-5] After removal of approximately 200 milliliters of fluid at amniocentesis,

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Table I. Injection-abortion intervals*

	No.	Injection-abortion interval (hr) Mean	Range
Urea + $PGF_{2\alpha}$ (10 mg), no laminaria tent			
No prior cesarean section			
Para 0	624	15.9	2-60
Para 1 or more	425	13.8	1-47
Previous cesarean section	34	17.2	3-40
Urea + $PGF_{2\alpha}$ (5 mg), no laminaria tent			
No prior cesarean section			
Para 0	213	17.0	6-45
Para 1 or more	107	14.7	3-46
Previous cesarean section	26	23.4	8-40
Urea + $PGF_{2\alpha}$ (5 mg), one laminaria tent			
No prior cesarean section			
Para 0	160	12.7	4-46
Para 1 or more	21	14.4	4-45
Previous cesarean section	16	15.1	2-38

*From intra-amniotic injection of medication to abortion of the fetus.

Table II. Injection-abortion intervals* greater than 24 hours

	No.	Patients with injection-abortion intervals greater than 24 hr No.	%
Urea + $PGF_{2\alpha}$ (10 mg), no laminaria tent			
No prior cesarean section	1,049	135	12.9
Previous cesarean section	34	12	35.3
Urea + $PGF_{2\alpha}$ (5 mg), no laminaria tent			
No prior cesarean section	320	48	15.0
Previous cesarean section	26	14	53.8
Urea + $PGF_{2\alpha}$ (5 mg), one laminaria tent			
No prior cesarean section	181	13	7.2
Previous cesarean section	16	6	37.5

*From intra-amniotic injection of medication to abortion of the fetus.

135 ml of a 59.7% solution of urea is slowly infused via gravity. Immediately after the infusion of urea, $PGF_{2\alpha}$ in a dose of either 10 or 5 mg is injected intra-amniotically. The lower dose of $PGF_{2\alpha}$ is used because research efforts have defined it as the minimally effective dose which still maintains an injection-abortion interval consistently less than 24 hours. In addition, recent efforts to reduce the frequency of cervical injury have led to the intracervical placement of one or more laminaria tents for 1 to 6 hours prior to infusion of urea. Only patients in whom one laminaria tent was placed are included in this review, since there were insufficient numbers of patients with more than one laminaria tent to be useful for analyses. Intravenous oxytocin at a rate of 332 mU per minute is also employed for three indications: failure to abort within 24 hours after infusion of urea when there is no evidence of labor; absence of labor 4 hours after rupture of membranes; and management of incomplete abortion.

In the Fertility Control Center, failed abortion is defined as the requirement for vaginal evacuation of the products of conception at 48 hours, or sooner in instances of suspected chorioamnionitis or significant hemorrhage. Incomplete abortion is defined as failure to pass all or part of the placenta within 2 hours after abortion of the fetus. Such patients are managed by ring forceps curettage with intravenous analgesia of meperidine and diazepam.

For the purpose of this review, patients with a history of prior cesarean section who underwent amnioinfusion of urea, augmented with either 10 or 5 mg of $PGF_{2\alpha}$, were compared with the general group of patients at the Fertility Control Center in whom this methodology was employed. Factors examined included clinical characteristics of the patients, outcome, injection-abortion intervals, requirements for oxytocin, and complications. When appropriate, the means and standard errors of the means were calculated, and these data were analyzed by an F test and Student's t test in order to determine statistical significance.

Results

There were 1,083 patients who underwent infusion of hyperosmolar urea and $PGF_{2\alpha}$ (10 mg) without the use of laminaria tents, 346 patients who received urea and $PGF_{2\alpha}$ (5 mg) without the use of laminaria tents, and 197 patients who received urea and $PGF_{2\alpha}$ (5 mg) plus the intracervical insertion of one laminaria tent before the injection. The frequencies of prior cesarean section among patients in the three groups were, respectively, 3.1%, 7.5%, and 8.1%.

A review of the clinical characteristics of the various study groups showed some differences. The average age of patients presenting to the Fertility Control Center for the urea method of abortion was 20.5 years, whereas patients with a previous history of cesarean section were about 2 years older. All patients with a history of prior cesarean section had been delivered of a fetus beyond 24 weeks' gestation. In contrast, between 42 and 46% of all Fertility Control Center patients in the groups studied were para 0 at presentation for abortion. The mean duration of gestation at the time of injection ranged between 19 and 20 weeks from the first day of the last menstrual period, and an aver-

Table III. Outcome

		Complete abortion		Incomplete abortion		Failure	
	No.	No.	%	No.	%	No.	%
Urea × $PGF_{2\alpha}$ (10 mg), no laminaria tent							
No prior cesarean section	1,049	551	52.5	482	46.0	16	1.5
Previous cesarean section	34	15	44.1	18	47.0	1	2.9
Urea + $PGF_{2\alpha}$ (5 mg), no laminaria tent							
No prior cesarean section	320	208	65.0	110	34.4	2	0.6
Previous cesarean section	26	11	42.4	14	53.8	1	3.8
Urea + $PGF_{2\alpha}$ (5 mg), one laminaria tent							
No prior cesarean section	181	130	71.8	49	27.1	2	1.1
Previous cesarean section	16	10	62.5	6	37.5	0	—

age of between 195 and 210 ml of amniotic fluid was removed at the time of amniocentesis. No important differences were discernible between the various groups studied and prior cesarean section patients versus other patients for these two characteristics.

Table I lists the injection-abortion intervals for the various groups in the review. As shown, the injection-abortion intervals of patients with a history of a previous cesarean section were consistently longer than those of any of the other groups of patients. The difference between patients who were para 1 or more and those with prior cesarean section in the group given urea plus $PGF_{2\alpha}$ (5 mg) with no laminaria tent was statistically significant ($p < 0.05$), but similar comparisons in the other groups were not significant. In addition, the preinjection use of a laminaria tent appeared to have only a modest effect in reducing the mean injection-abortion interval of patients who had previously had a cesarean section.

Table II compares the injection-abortion intervals exceeding 24 hours among the various study groups. As demonstrated in the table, patients with a history of prior cesarean section had a high proportion of injection-abortion intervals that exceeded 24 hours. Therefore, such patients also had a greater requirement for additional augmentation with oxytocin according to the protocol followed in the Fertility Control Center. An examination of the groups given urea plus $PGF_{2\alpha}$ (10 mg) and urea plus $PGF_{2\alpha}$ (5 mg) with no laminaria tent showed that the percentages of patients without a previous cesarean section not receiving oxytocin during their hospital admission were 32.1 and 29.3, respectively. In contrast, only 20.6% and 11.9% of the patients with a history of previous cesarean section in each of those same groups did not receive oxytocin during the course of their hospital admission.

Table III details the clinical outcome in the various study groups. Although few differences were noted in the groups of patients given urea plus $PGF_{2\alpha}$ (10 mg), the rate of incomplete abortion for patients with previous cesarean section was consistently higher in the groups of patients given urea plus $PGF_{2\alpha}$ (5 mg) regardless of whether a laminaria tent was employed.

In a comparison of the complications encountered by patients with previous cesarean section versus other patients in the study groups, no significant differences were discernible among the groups in rates of hemorrhage, infection, cervical laceration, and gastrointestinal problems. These complications have been presented and discussed in detail previously.[3-5] However, one patient with a history of a previous cesarean section in the group given urea plus $PGF_{2\alpha}$ (5 mg) without a laminaria tent experienced a uterine rupture. Her clinical course is summarized below.

Case report

This 32-year-old patient, para 5, presented for termination of pregnancy at 18 weeks from the first day of her last menstrual period. Her obstetric history was significant in that, after four spontaneous vaginal deliveries, her last delivery (12 years ago) had been effected by cesarean section because of premature rupture of the membranes. Preoperative physical examination and laboratory studies gave findings that were within normal limits, except for an enlargement of the uterus to 18 weeks in size.

Clinical course. An intra-amniotic injection of 135 ml of 59.7% urea and 5 mg of $PGF_{2\alpha}$ was completed without incident on the day of hospital admission. After 21 hours of regular uterine contractions, the cervix was partially effaced and dilated 2 cm. Infusion of oxytocin at 332 milliunits per minute was started, but the cervix remained unchanged at 31 hours after intra-amniotic injection. At 37 hours, the patient complained of generalized myalgia associated with increasing pain in the left lower quadrant of the abdomen. The vital signs revealed a temperature of 100.2° F, blood pressure of 118/80 mm Hg, and a pulse rate of

132 beats per minute. Examination of the abdomen demonstrated diffuse tenderness and guarding in both the right and left lower quadrants, with exquisite pain elicited by palpation of the left flank. Pelvic examination disclosed a brownish discharge emerging from the cervix, which was high in the vagina and displaced to the right. Bimanual examination confirmed the existence of tenderness and guarding in both lower abdominal quadrants, and deviation of the uterine fundus toward the right lower abdomen; an ill-defined mass filled the left lower quadrant. The clinical impression was that of uterine rupture with intra-abdominal expulsion of the products of gestation, and an associated hematoma of the left pelvic wall.

Exploratory laparotomy revealed that the left broad ligament was displaced by a large hematoma of approximately 1,500 ml. A uterine laceration about 5 cm in length was located at the left lateral aspect of the previous transverse uterine cesarean section scar, and the laceration extended into the left broad ligament. The placenta and fetus were protruding from the laceration into the left posterior pelvis. A supracervical hysterectomy was completed, along with excision of the left fallopian tube and ovary and drainage of the hematoma. About 2,000 ml of blood was lost during the operation, and hemostasis was achieved with difficulty, so that the patient required seven units of whole blood and two units of fresh frozen plasma.

The postoperative course of the patient was complicated by the need for two additional units of blood, persistent ileus that required treatment with a long intestinal tube, and fever. However, she was discharged from the hospital on the seventeenth postoperative day in good condition.

Comment

There are some interesting facets to this review of patients with a history of previous cesarean section who presented to the Fertility Control Center for subsequent midtrimester termination of pregnancy via intra-amniotic instillation of hyperosmolar urea. The frequency of previous cesarean section as a pre-existing medical condition appears to parallel the increasing use of cesarean section in obstetric practice. Therefore, one might predict that, unless the requirement for second-trimester abortion procedures declines, those who provide abortions will see an increasing number of patients who present with this condition. The review also indicated that patients with a history of previous cesarean section had long injection-abortion intervals, more frequently received additional oxytocin for augmentation of labor, and more frequently experienced incomplete abortion. In addition, the pre-injection use of a laminaria tent did not markedly improve matters, although injection-abortion intervals were shortened somewhat. Therefore, such patients may be at increased risk for uterine rupture unless the use of oxytocic drugs is judiciously monitored. Similarly, because of this potential risk of uterine rupture, the attempt to shorten the injection-abortion interval to less than 24 hours consistently with the use of oxytocic drugs in high doses may be inappropriate for the management of such patients. Unfortunately, because of the numbers involved, we cannot determine whether the described case of uterine rupture in a patient with a previous cesarean section represents an unusually high incidence of this complication.

Six cases of uterine rupture associated with induced midtrimester abortions have been reported previously, but none of the patients had undergone any previous uterine operation.[6-9] The abortifacients employed included intra-amniotic hypertonic saline, $PGF_{2\alpha}$, and, in one instance, 40% urea. In two of the reported cases, death occurred as a result of a delay in diagnosis before the required definitive operation was carried out. All reported cases were unaborted for 24 or more hours after intra-amniotic injection; and in all, large quantities of oxytocin were given continuously for more than 12 hours. Three of the six patients were over 30 years of age, and all were multiparous, para 2 or greater.

The patient reported on here had many of the characteristics of patients who experience uterine rupture associated with induced midtrimester abortion. These characteristics included age, multiparity, prolonged injection-abortion interval, and continuous use of intravenous oxytocin for more than 12 hours. In addition, this patient had a history of prior delivery of an infant by cesarean section (12 years earlier).

In regard to the location of the uterine laceration, in the previous case reports, five of the six uterine ruptures involved the lower uterine segment. These lacerations were usually vertical, not uncommonly in the lateral aspect of the uterus, and were associated with the development of hematomas of the broad ligaments, with expulsion of the products of gestation either into the peritoneal cavity or into the retroperitoneal space. In patients with a history of prior uterine operations, one would anticipate rupture of the uterine scar, as was observed in the current case.

The symptomatology of patients with uterine rupture in this situation includes increased or constant pelvic and abdominal pain and tenderness in the flanks, particularly with an associated ascending retroperitoneal dissection of an enlarging pelvic hematoma. The commonly observed clinical signs include guarding, rebound tenderness, suggestion of more than one pelvic mass, and tachycardia. Delay in recognizing the significance of these findings can result in a catas-

trophic outcome. The prompt recognition of the signs and symptoms of uterine rupture in the currently reported case allowed definitive surgical therapy prior to shock.

At this point, the proper approach to termination of a midtrimester pregnancy in patients who have had previous cesarean sections or prior uterine operations has not been adequately defined. However, our opinion is that such patients constitute a high-risk group which requires careful monitoring and the judicious use of oxytocic drugs. In addition, the pre-injection use of laminaria tents may offer some, although not complete, protection against the possibility of uterine rupture.

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Non-Clostridial Myonecrosis with

Induced Mid-Trimester Abortion

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A case of non-clostridial gas myonecrosis following mid-trimester abortion is reported. Infection of the uterus associated with gas production is rare and associated with a high rate of mortality[1]. Infection with non-clostridial organisms may simulate clostridial myonecrosis;[2] however, treatment of this entity may not necessitate hysterectomy.

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Gas myonecrosis of the uterus although uncommon, is potentially lethal. An incidence of 0.02% of clostridial infection is reported in patients with septic abortion[3]. Post abortion gas myonecrosis with Clostridium perfringens, accounting for 85% of cultured stains,[3] is associated with a mortality of 25-50%[1]. Non-clostridial bacteria, particularly the coliforms, may invade the myometrium and produce a picture similar to that of clostridial gas gangrene[2]. This report concerns a case of non-clostridial gas myonecrosis following mid-trimester induced abortion.

REPORT OF A CASE

L.S. (JHH 1902707)

A 19 year old nulliparous woman was admitted to The Johns Hopkins Hospital Fertility Control Center at an estimated 18 weeks gestation for elective mid-trimester abortion. Amnioinfusion of hyperosmolar urea was completed. Severe uterine contractions, fever of 38^{3o} C and tachycardia followed the administration of 2.5 mg of PGF_2a and the procedure was terminated. Fever, diffuse abdominal pain, and severe uterine tenderness persisted for 24 hours. Blood, endocervical, + urine cultures were obtained. On hospital day 2, therapy with penicillin G 20 million units a day IV and kanamycin 2 grams a day was instituted. Dilatation and evacuation was performed with endometrial cultures obtained. Gram stain of the endometrium showed gram negative rods and gram positive cocci. Due to a post operative hematocrit of 25.0 the patient received two units of packed red blood cells. Coagulation studies were normal and

there was no evidence of hemolysis or jaundice. On hospital day 3, fever to 40°C developed and clindamycin 2.4g a day IV was added. Abdominal roentgenogram showed a honeycomb air pattern in the uterus consistent with gas bubbles in the myometrium (Figure 1). Abdominal ultrasonogram showed a circumferential gas pattern in the lower uterine segment compatible with gas in the myometrium (Figure 2). On hospital day 4, fever and abdominal pain abated. Repeat abdominal films showed no increase in uterine gas. Sonogram showed slight decrease in myometrial gas on serial examinations. Blood, urine, and cervical cutlures were negative. The endometrial culture grew gas forming E.Coli and group D streptococci. The patient received a total o. ten days of IV antibiotics, remaining afebrile for the last seven days of hospitalization. She was discharged on hospital day 13.

Hysterogram done four months after discharge showed a normal appearing uterus and lower uterine segment (Figure 3).

COMMENT

Gas in the uterus may be from an accidental or infectious source. The invasion of gas producing organisms into the uterine endometrium and myometrium is favored by the presence of necrotic tissue,[4] retained products of conception,[5] or prolonged injection-abortion intervals in mid-trimester induced abortion. Clostridium perfringens is present in cervical and vaginal cultures in 5% of normal women,[6] with E.Coli accounting of 21% and aerobic streptococci for 31%[7] of bacteria isolated in patients with female genital tract infections. The entry of these organisms into the uterine cavity during or following abortion may result in a localized chorioamnionitis,[8] low grade endometritis, or pyometra and invasion of the myometrium with necrosis[5].

The clinical presentation of non-clostridial uterine gas myonecrosis is similar to that of clostridial gas infection. Fever, abdominal pain, uterine tenderness, and crepitation are predominant features[3]. Clostridial infections are characterized by extensive necrosis with rapid progression to septicemia, whereas the pace of the non-clostridial myometrial infection is slower with a limited amount of necrosis.

Non-clostridial gas myonecrosis was first described as occuring in the lower limb of a diabetic,[9] from which a colon bacillus was isolated. Since the introduction of antibiotics, infection with colidorm organisms particularly E.Coli, anaerobic and aerobic streptococci, and Klebsiella aerogenes has increased[10]. Invasion of subcutaneous tissue occurs with these organisms, occasionally with muscle involvement with production of necrosis, crepitation, and gas bubbles.

The first demonstration of intramyometrial gas was in 1939[11]. In clostridial myonecrosis soft tissue gas is seen as intramuscular multilinear streaks[3] whereas in non-clostridial infections, as in the presented case, the gas is seen as intramuscular bubbles.

Intravenous penicillin is the antimicrobial agent of choice in clostridial infections, with the addition of other broad spectrum agents in coliform infections. Curettage should be the initia surgical therapy[12] especially if the infection is localized to the uterus[2]. Hysterectomy with bilateral salpingoophorectomy appears to be the treatment of choice once the diagnosis of macroscopic necrosis, i.e., gangrene,[2] septotoxemia, intramyometrial gas, or myonecrosis is evident[12]. In our patient therapy was curative with IV antibiotics and dilatation and curettage, in the presence of intramyometrial gas and uterine myonecrosis.

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PHARMACOKINETICS OF LIDOCAINE ADMINISTERED BY PARACERVICAL INFILTRATION FOR ASPIRATION ABORTION

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INTRODUCTION:

Termination of pregnancy in the first trimester by suction currettage is associated with low rates of morbidity and mortality. The anesthetic technique utilized for such procedures is known to influence the rates for specific complications although the overall major complication rates are similar when either general or local anesthesia is employed[1]. General anesthesia is associated with a higher incidence of hemorrhage, cervical injury and uterine perforation whereas local anesthesia is associated with higher rates of post- bortal fever and convulsions.

Convulsive morbidity appears to be associated exclusively with local anesthesia[1]. In at least 2 fatal cases of this particular complication, blood levels of the anesthetic agent (lidocaine) were clearly in the toxic range (>5μg/ml)[2].

The pharmacokinetics of intravenously administered lidocaine have been studied in several clinical situations. However, there is little data regarding the disposition of this drug when it is administered in a paracervical block. McKenzie and Shaffer[3] reported blood levels of lidocaine in 12 patients undergoing suction currettage under paracervical block. Six patients received 20 ml of 1% lidocaine by the usual technique and 6 were treated by jet injection with 2 ml of 2% lidocaine. Their findings are summarized in Table I.

This study was performed in order to elucidate the following points:

1) to evaluate the time course of lidocaine plasma levels following paracervical infiltration for suction abortion
2) to determine if any individual lidocaine concentration reached potentially toxic levels

3) to determine if the lidocaine concentration-time curve was similar between groups of patients who did or did not receive intracervical laminaria

MATERIALS AND METHODS:

Fifty healthy volunteers with pregnancies up to 14 weeks menstrual age participated in the study. Laminaria tents were inserted in 25 of the 50 patients 2 to 4 hours prior to the suction procedure. Blood samples were not analyzed from one case in the laminaria group due to several missing samples. Informed consent was obtained from all participants prior to the procedure. All patients received 50 mg meperidine hydrochloride and 10 mg diazepam intravenously. Paracervical block was carried out utilizing 9 ml of 1% lidocaine hydrochloride (90 mg) injected circumferentially into the cervix. Blood samples were obtained prior to the administration of lidocaine and 1, 3, 6, 10, 15, 20, 30, 45, and 60 minutes after the paracervical block was completed. Some demographic characteristics of the study population are summarized in Table II.

Two milliliters of heparinized plasma combined with the internal standard (methylethylglycinexylidide) were made alkaline with NaOH and extracted with methylene chloride. The aqueous fraction was discarded and the organic phase brought to complete dryness under an air steam. The residue was reconstituted in methylene chloride and injected into a Shimadzu G3-B gas chromatograph equipped with FID. The chromatographic column was 2.1 m (i.d. - 2mm) and packed with 3% SP2250 (Supelco) 100/120 mesh.

A duplicate four point standard curve was constructed from the ratio of the internal standard to lidocaine. The ratio of the unknown lidocaine sample to the internal standard was compared to the standard curve. Results were expressed as lidocaine hydrochloride in ug/ml.

RESULTS:

At the dosages employed, no lidocaine levels near the toxic range (>5 g/ml) were found. The single highest measurement was observed in a 19 year old patient in the laminaria group at six minutes after administration of the paracervical block. This patient's serum lidocaine was 4.41 μg/ml. No acute adverse reactions due to the anesthetic were noted in the entire study group.

Table III shows the mean lidocaine concentrations observed in the study group. Figure 1 presents the curves for lidocaine concentration vs time in the 2 groups. The laminaria group shows higher plasma levels at all times as compared to the group without laminaria. Furthermore, peak lidocaine levels were reached earlier in the laminaria group. Although there may not be a statistically significant difference between the individual time points, the two curves taken as a whole are significantly different ($p < .0001$).

DISCUSSION:

As expected, our results show a rise and gradual fall in plasma lidocaine levels as would occur in an infiltration type of local anesthesia. An unexpected finding was the significantly different concentration time course in the laminaria group. These patients not only had higher mean plasma levels, but also reached peak levels at an earlier point (6 min) as compared to the "no laminaria" group (10 min).

The reason for this difference may involve several factors. Pretreatment with laminaria may alter the microvasculature of the cervix in such fashion as to facilitate absorption into the vascular space. Alternatively, the laminaria may cause a decrease in extracellular fluid in the cervix which produces a local increase in concentration of the injected drug due to reduced dilution by ECF. This

increased concentration would result in more rapid diffusion into the vascular compartment.

Other factors unrelated to laminaria use may be involved. It may be that the two groups are not really comparable. Indeed, the laminaria group is significantly younger than the no-laminaria group. Similarly, the laminaria patients are of lower parity. Due to the small number of patients, it is not possible to evaluate these factors separately by statistical methods.

The concomitant adminstration of other drugs may influence blood levels of lidocaine. Propranolol is known to increase the elimination half-life and decrease the clearance of lidocaine, resulting in higher blood lidocaine levels[4]. In the present study, all patients received the same amounts of diazepam and meperidine, so that the observed differences cannot be attributed to the use of other drugs.

No episode of convulsive morbidity occurred in this group of patients, as would be expected in light of our results. In addition, all patients received diazepam prior to the paracervical block. This drug is known to elevate the threshold for lidocaine-induced convulsions.[5]

The observations made by McKenzie and Shaffer are in general agreement with our observations. The blood levels in the patients who received 200 mg of lidocaine are somewhat higher than in our "no laminaria" patients. However, these investigators did not begin their sampling until 10 minutes after the paracervical block. One can only speculate on the earlier blood levels, but considering the short half-life of lidocaine in blood (6-8 minutes), these earlier levels were probably much higher than the ones we observed.

From these observations, we conclude that paracervical block utilizing 90 mg of lidocaine is associated with safe blood levels of lidocaine. In order to increase the safety margin, however, we now

employ 10 ml of 0.5% lidocaine. This provides satisfactory anesthesia and should result in even lower blood levels than those reported in this study.

TABLE I

MEAN VENOUS BLOOD LEVELS OF LIDOCAINE*

	TIME (MINS)					
	10	20	30	40	50	60
JET INJECTOR 40 mg Lidocaine	0.53	0.47	0.44	0.27	0.24	0.22
SYRINGE 200 mg Lidocaine	1.61	1.54	1.28	1.10	0.99	0.90

*Re[illegible] expressed in μg/ml

[illegible]m McKenzie and Shaffer, AJOG 130:317, 1978.

TABLE II

STUDY POPULATION

	LAMINARIA	NO LAMINARIA
AVERAGE AGE	19.3	26.6
% PAROUS	12.5%	84%
AVERAGE WEIGHT (LBS)	133.7	136.2

TABLE 3

MEAN PLASMA LIDOCAINE LEVELS (μg/ml)

TIME	LAMINARIA		NO LAMINARIA	
	MEAN	S.D.*	MEAN	S.D.*
1 min	0.6713	0.7293	0.0260	0.0919
3 min	1.3846	0.8233	0.6344	0.3833
6 min	1.7108	0.9620	1.1444	0.5715
10 min	1.7188	0.6448	1.3180	0.4276
15 min	1.5138	0.5913	1.1448	0.3572
20 min	1.2696	0.3993	1.0856	0.3367
30 min	0.9925	0.4192	0.9176	0.2894
45 min	0.8229	0.4126	0.7240	0.2333
60 min	0.7413	0.3767	0.5972	0.2465

*Standard Deviation

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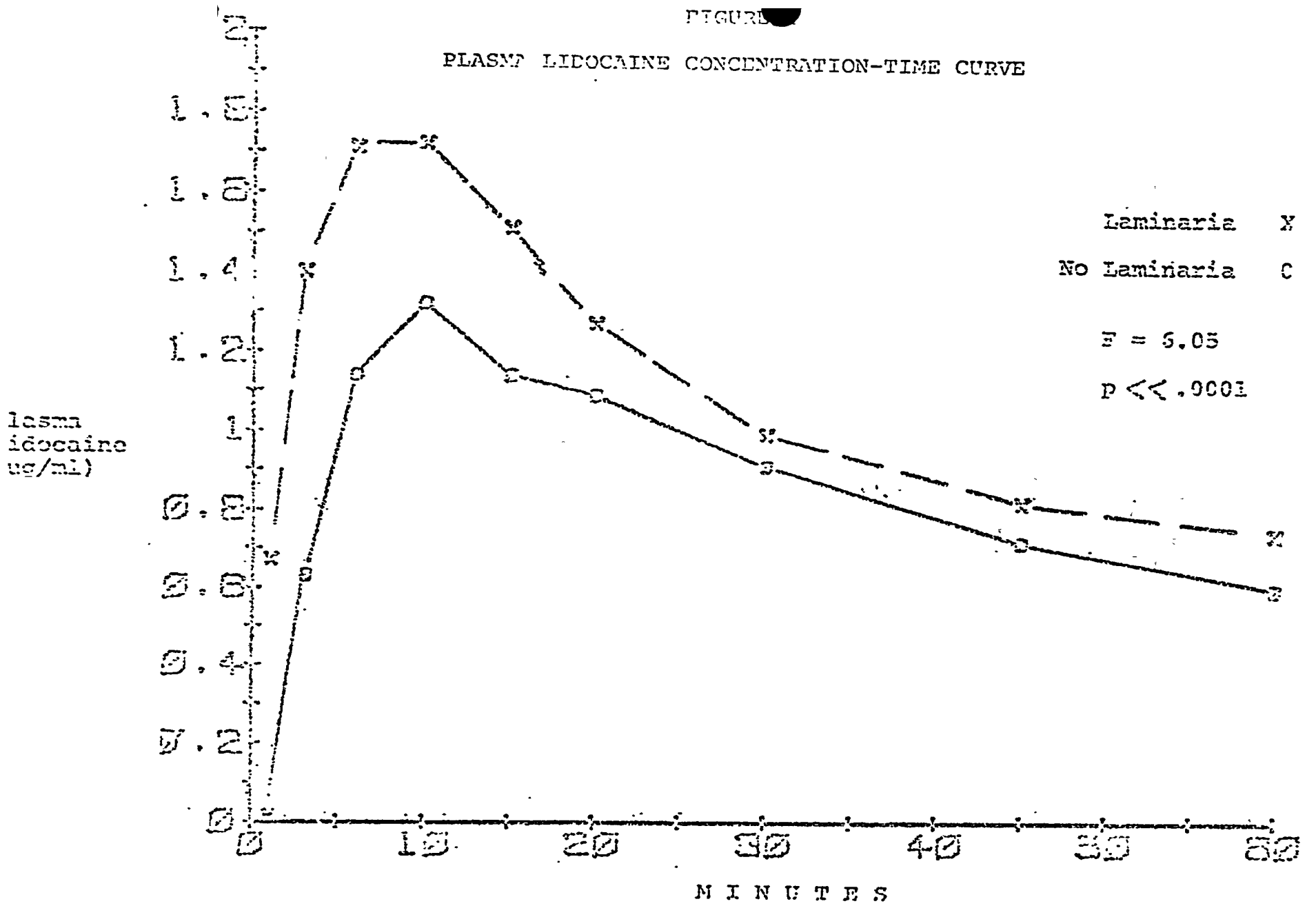
FIGURE

PLASMA LIDOCAINE CONCENTRATION-TIME CURVE



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