RABBIT UTERINE CONTRACTILE ACTIVITY IN THE PRESENCE OF AN INTRAUTERINE DEVICE

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ABSTRACT

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By

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Rabbit uterine contractile activity patterns in the presence of an intrauterine device (IUD) were monitored with extraluminal contractile force transducers (ECFTs). ECFTs were oriented either longitudinally or transversely and thereby monitored either longitudinal or circular uterine muscle contractile activity.

These patterns were recorded daily during estrus, following coitus, and through the first sixteen days post-coitus.

Circular muscle contractile activity (but not that of longitudinal) initially increased following coitus. Subsequent increases in contractile force and frequency were recorded from both myometrial layers but for a longer period from longitudinal muscle than from circular muscle.

Smaller decreases in uterine motility were recorded from the IUD containing horn during the initial sixteen days of pregnancy.

Mean contractile force was greater for the longitudinal than for the circular muscle layer. The converse was recorded for frequency.

The IUD introduced local fetal degeneration. ECFTs influenced neither nidation nor normal fetal development.

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Intrauterine devices (IUDs) offer a promising contraceptive method to control the increasing human population. Although the contraceptive efficiency of the IUD in women has been completely established, the exact mode of action is unknown. Comparative studies on experimental animals have been the most common approach utilized to study IUD effects and modes of action.

In general, experimental observations made on women, subhuman primates, and other animals suggest that the IUD exerts its action upon the uterus. The following review will show that the effect and modes of action of the IUD though similar are to some extent species specific.

Contraceptive Effects of the Intrauterine Device

Women

Marston (36) stated that, in women, it appears that the IUD does not disturb the menstrual cycle, ovulation, sperm transport, fertilization and transport of the egg through the Fallopian tube. Implantation occurs only rarely in the presence of an IUD (21,27) and the usual contraceptive action may occur while the egg is free in the uterine lumen. The IUD may evoke the destruction of the egg through alteration in the uterine environment, direct interference with the implantation process, or premature expulsion from the uterus in response to alteration in uterine motility (36).

Rhesus Monkey

In the castrate Rhesus monkey the presence of an IUD for 14 weeks does not grossly modify endometrial response to exogenous ovarian steriods (53). The endometrial histochemistry has not been shown to be altered in the presence of an IUD, although the IUD does appear to increase oxygen uptake in adjacent endometrial tissue (31). The fertilized eggs enter the uterus normally and then undergo rapid degeneration and/or premature explusion (37). The general pattern of IUD action in monkeys, therefore, agrees closely with that which has been observed in women.

Ruminants

A total of 236 breedings without the establishment of pregnancy has been reported in cows fitted with IUDs (24). During that study the recovery of one fertilized egg and only two uterine fetal resorptions were reported. Ginther *et al*. (20) state that cow corpora lutea degenerate adjacent to the IUD containing uterine horn. Hawk *et al*. (24) suggest that IUD size was a factor influencing the observed estrous cycle length variability and corpus luteum development patterns.

In sheep an IUD interfered with the normal periodicity of the estrous cycle (23). The IUD was contraceptive and appeared to inhibit sperm transport and fertilization. Ewe eggs were transported normally in the Fallopian tubes (52). IUD influence was suggested to cause unilateral degeneration of the corpora lutea in the ewe (52).

Thus, in the cow and sheep the IUD induces estrous cycle variability and local corpora lutea degeneration. IUD spermicidal activity has been reported for the sheep but not for the bovine.

Rodents

In most experiments using the rat, mouse, or rabbit the IUD was a length of suture thread lying longitudinally within the uterine lumen. Plastic and metal IUDs were utilized in the rabbit in some experiments. Use of thread, plastic, or metal IUDs produced similar results in the various experiments.

Mouse and Rat

The IUD acts as a contraceptive in the mouse and rat (16, 22, 30, 35). The action is reversible in the rat if the IUD is removed up to the third or fourth day of pregnancy (35). In the mouse the IUD exerts a bilateral effect when it is inserted unilaterally (16). This could be due to the small continuity which exists between the two uterine horns at the beginning of the cervical canal (16). In the rat the IUD effects are unilateral (22, 30, 35) and the two cervices are separate (45).

The processes of ovulation, sperm transportation, fertilization, early cleavage, and tubal transport are normal in both the rat and mouse (36). Contraceptive action of the IUD occurs within the uterine lumen in both species. Egg degeneration, premature expulsion, and failure of deciduoma formation prevent implantation in both the rat and the mouse (16, 35, 36).

Rabbit

The rabbit's uterine horns are completely separated and have separate cervices (45). IUDs placed unilaterally exert unilateral effects (36).

In the rabbit the IUD does not affect ovulation, sperm transportation, fertilization, and early cleavage (1, 2, 12, 32, 35). Premature expulsion of eggs from the uterus has not been reported (2, 36).

Rabbit blastocysts can survive and develop normally within the uterine lumen for at least three days (35). The principal action of the IUD appears to be blastocyst degeneration occurring from 144 to 168 hours after ovulation (1, 2, 35). Blastocyst destruction is not complete and implantation has been reported in the immediate presence of the IUD (1, 2, 32, 35). Further fetal destruction occurs after implantation (35). In the rabbit, the extent of blastocyst destruction appears to be dependent upon the length of the uterine lumen occupied by the IUD (36).

The Intrauterine Device and Uterine Motility

Uterine motility has been recorded in various species in the presence of an intrauterine device. A review of the recording methods will show that although they have provided basic uterine motility patterns in the presence of an IUD, they have been unsatisfactory for studying discrete, unidirectional contractile activity patterns associated with estrus, coitus, spermatozoa and ova transportation, blastocyst implantation, and pregnancy. These studies require a method that will permit the chronic extraluminal recording of uterine contractile activity in the intact, unanesthetized animal.

Review of Methods

Sheep uterine motility has been reported to increase in the presence of a spiral IUD (8). This increased uterine motility was recorded *in vivo* using the intraluminal open-end catheter technique as well as *in vitro*. *In vitro* motility increases were localized and confined to the area adjacent to the IUD. The greatest recorded effect *in vivo* was the increased amplitude of uterine contractions.

Marcus et al. (33) recorded increased rat uterine contractile activity in vitro from the IUD containing horn.

Human uterine volume in the presence of the IUD was studied by Rozin et al. (46) using cinematography. An oil media was placed within the uterine lumen and pictures were taken of the uterus. Records were obtained prior to and at various intervals from one day to one year following insertion of the device. Uterine lumen capacity was analyzed using a qualitative contractile grading system. Results suggested that in the presence of an IUD uterine tone decreased as time progressed. In 1967 Mazer et al. (38) using barium hysterography reported localized uterine spasms in patients fitted with intrauterine devices. These spasms were reported to be the most severe in the patients complaining of post-insertion complications.

Johnson et al. (29) attempted to quantify human uterine motility by chronic measurement of intrauterine pressure using an open-tipped catheter. A Lippes loop (IUD) had been inserted 6-8 weeks postpartum and two weeks prior to the first recording period. For the 10-30 minute recording period an open end polyvinyl catheter was filled with saline and fitted into the uterine lumen through the cervix. The catheter passed from the vagina and was connected to a strain gauge pressure transducer and an amplifier-recording system. No significant changes in amplitude or frequency of contractions were recorded.

Using open-tipped catheters Bengtsson and Mroueh (4) recorded a precocious development of prelabor-like activity coincident with the period of ovum transportation and implantation in the presence of an IUD.

More recently Behrman and Burchfield (5, 6) placed strain gages on a Lippes loop and indirectly measured human myometrial contractile activity. The authors recorded an initial increase in uterine contractile activity following loop insertion. Uterine adaptation occurred in approximately three days. The recorded uterine contractile activity showed daily cyclic variation.

Simmons _et al_. (48) measured bovine uterine motility with a radio telemetry system. Battery powered FM transmitters float in the peritoneal cavity and were attached to electrodes recording uterine muscular potential changes. The audio signal was then converted to an electrical potential and recorded with a DC amplifier and a recorder. Fromm (19) has monitored rabbit uterine contractile activity with a modified radio telemetry-transducer system. Effects of Pitocin upon uterine motility in that study compared favorably with those recorded by previous methods. To date these methods have not been used for IUD-uterine motility study.

Limitations of Existing Methods

In vitro recording methods have demonstrated some response characteristics of uterine smooth muscle in the presence of an IUD, but cannot satisfactorily monitor chronic uterine motility patterns.

Chronic *in vivo* studies utilizing photographic techniques, while qualitatively describing uterine responses to IUD presence, do not quantitatively describe the recorded uterine events.

Quantitative methods utilizing the open-tipped catheter to record human uterine motility has produced conflicting results. This method, while measuring net intrauterine pressure is limited due to: (a) possible recording artifacts created by intra-abdominal pressure changes and (b) inability to monitor discrete unidirectional contractile activity of the two uterine muscle layers, because an increase in intraluminal pressure might be due to either longitudinal and/or circular muscle contraction.

The incorporation of strain gages into the IUD enabled Behrman and Burchfield (5) to measure the contractile activity indirectly by monitoring the distortion of the Lippes loop beneath the strain gage. Although discrete local IUD loop movement was recorded, this method is limited because of: (a) the inability to monitor discrete uterine muscle contractile activity of either the longitudinal or circular muscle, and (b) possible uterine effects introduced by the presence of the strain gage, Lippes loop, or lead wires within the vagina, cervix, or uterine lumen.

Radio telemetry transmitted electrical activity but electrical activity can neither quantify nor monitor discrete longitudinal and circular uterine muscle layer contractile activity. The radio telemetry-transducer system (19) may offer significant progress in future uterine motility investigations.

The Extraluminal Contractile Force Transducer

The extraluminal contractile force transducer (ECFT) has been shown to reliably monitor *in vivo* duodenal contractile activity in chronic studies on the unanesthetized dog (28). The transducer consisted of a strain gage bonded to the convex surface of an arched metal clip. Lead wires were attached to the gage and the unit was encapsulated with Silastic silicone rubber. Contractile force developed by the muscle beneath the transducer resulted in a linear deformation along the longitudinal axis of the metal clip and a change in the electrical resistance of the strain gage. Two transducers sutured to the duodenal serosa and dependent upon the axis of orientation, monitored separately and simultaneously the contractile activity of longitudinal and circular muscle. Reinke *et al*. (42) increased the sensitivity of the transducer by bonding a second strain gage to the concave surface of the metal clip, changed the configuration from an "I" to a "T", and investigated dog gastrointestinal contractile activity patterns.

Bass and Callantine (3) simultaneously monitored electrical and mechanical activity with combination electrode-force transducer units sutured on the serosal surface of the uterus in the unanesthetized dog. The ECFT has been used to record uterine contractile activity in the intact, unanesthetized guinea pig (17). Callantine _et al_. (10) used the ECFT for _in vivo_ drug studies on the rabbit uterus. Dominic and Reinke (14, 15) have recently monitored separately and simultaneously contractile activity for longitudinal and circular uterine muscle and defined patterns of rabbit uterine contractile activity during estrus and pseudopregnancy using the ECFT. Rabbit myometrium consists of an inner circular and outer longitudinal layer (51), muscle layers similar in morphology to that successfully monitored from dog intestinal smooth muscle using ECFTs (28, 42).

Statement of Problem

The purpose of this study is to monitor rabbit uterine contractile activity in the presence of an intrauterine device using the extraluminal contractile force transducer. Uterine contractile activity will be monitored during estrus, following coitus, and during pregnancy.

METHODS

Transducer Fabrication

Transducer fabrication is essentially the same as that described by Reinke et al. (42). The strain gages employed in this study were described previously by Dominic (15). A single etched-foil 350 ohm strain gage (No. SK-09-031-DE-350)[1] was bonded to both the convex and concave surface of a cleaned, heat-treated beryllium-copper shim stock[2] (0.15 mm. thick, 3.5 mm. wide, 6.0 mm. long). The strain gages were bonded with a filled epoxy cement (GA-5)[3] and cured under pressure (approx. 1 psi) at 220° F for four hours. The lead wires (Teflon insulated, 36 gauge, 7 stranded, 3 conductor)[4] were soldered with a special strain gage solder.[4] The transducer was water-proofed with a nitrile rubber solution (Gagekote No. 2).[4] The lead wires were drawn through a 40 cm. length of medical grade Silastic silicone rubber tubing (0.062 in.

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[1]Micro-Measurements, Inc., Romulus, Michigan.

[2]Berylco 25, Beryllium Corp., Reading, Pennsylvania.

[3]The Budd Company, Philadelphia, Pennsylvania.

[4]William T. Bean, Detroit, Michigan.

I.D., 0.095 in. O.D.).[5] The transducers and initial soldered portions of the lead wires were encapsulated with Dacron mesh reinforced raw Silastic (0.020 in. thickness)[6] and vulcanized under pressure (approx. 2 psi) at 220° F for 24 hours.

The lead wires were soldered to an electrical connector plus (Cannon MD1-9SL1)[7] which was imbedded in a mold fabricated from an epoxy adhesive.[8] The bottom of the plug along with the Silastic tubing ends, were covered with a medical grade Silastic silicone adhesive (Type A),[5] a sheet of raw unreinforced Silastic, and a sheet of Teflon mesh.[9] The entire unit was cured for 24 hours at 220° F.

Transducer Circuit

The transducer, which contained the two active strain gages in a Wheatstone bridge circuit, was connected (via Cannon plug, MD1-95L1)[7] to a switching panel containing the two 350 ohm fixed resistors and a fixed dummy gage (350 ohms), which enabled the operator to use a half bridge or a quarter bridge circuit (Fig. 1). This Wheatstone

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[5]V. Mueller Co., Chicago, Illinois.

[6]Compliments of Dow Corning Corp., Hemlock, Michigan.

[7]ITT Cannon Electric Inc., Los Angeles, California.

[8]The Door Company, Houston, Texas.

[9]C. R. Bard. Inc., Murray Hill, New Jersey.

Figure 1: Balanced Wheatstone bridge circuit. The solid line at switch denotes the half bridge circuit utilizing R_1 (concave strain gage), R_2 (convex strain gage, R_3 and R_4 (fixed resistor arms). Quarter bridge circuits (available with switching) use either R_1 or R_2 with R_c (dummy gage) and R_3 and R_4. DC activation voltage 5v.

bridge circuit was connected to a chopper preamplifier of an curvilinear ink writing oscillograph (Dynograph Type R).[10] The DC activation voltage was five volts.

Transducer Calibration

The transducer was calibrated by the method described by Dominic (14). Weights were added to each free end of the Mersilene[11] and oscillograph pen deflections obtained between a 4-44 gram range. Each transducer was calibrated for the half bridge circuit and both quarter bridge circuits at recording sensitivities of: 0.05 mv./cm., 0.1 mv./cm., and 0.2 mv./cm. The mean calibration curves for all transducers shown in Figure 2 indicate that the transducer output is linear for the load range used.

Experimental Design

New Zealand White female rabbits (4 kg. - 5 kg.) were anesthetized with sodium pentobarbital[12] (15 mg./kg., i.v.) and methoxyflurane[12] (administered via a nose cone). Initial amount of methoxyflurane delivered to the nose cone was 1.0 ml. with additional 0.5 ml. increments added as needed (approximately every 20 minutes) during the two hour operation. Under aseptic conditions a 0.75 in. diameter circular incision was made in the mid-scapular

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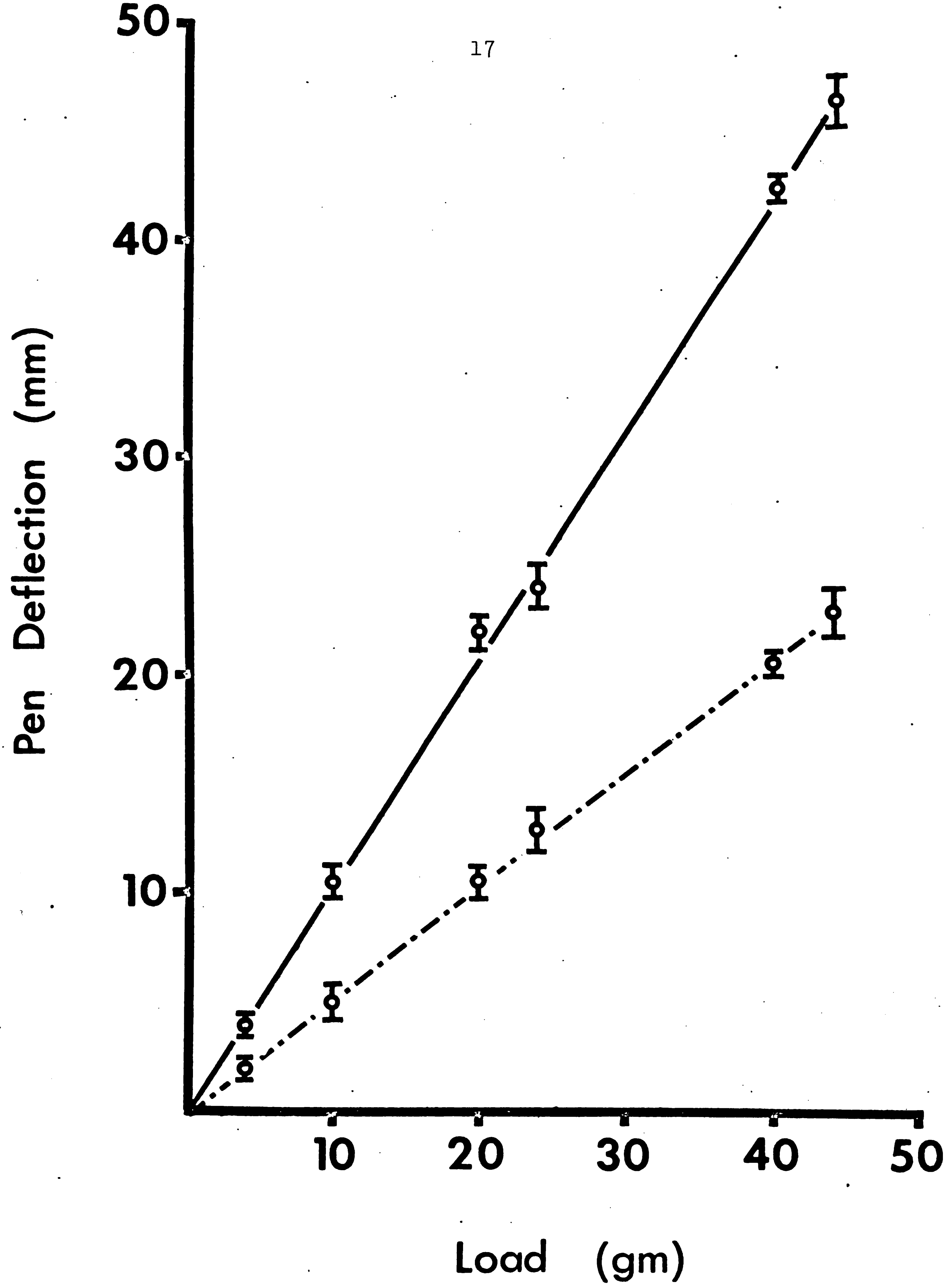
[10] Spinco Div., Beckman Instruments, Lincolnwood, Illinois.

[11] Ethicon, Inc., Somerville, New Jersey.

[12] Pitman-Moore, Indianapolis, Indiana.

Figure 2: Calibration lines at the recording sensitivity of 0.05 mv./cm. for the half bridge (solid line) and quarter bridge (broken line) circuits. Points on lines represent mean deflection values ± standard error. N = 14 for half bridge circuit, N = 28 for quarter bridge circuit. Total gram weight ranged from 4-44 grams.



50
40
30
20
10
Pen Deflection (mm)
10
20
30
40
50
Load (gm)

region and a 1 in. incision was made in the left flank. A 0.75 in. diameter stainless steel trocar was passed subcutaneously from the scapular to the flank incision. The transducers were brought through the trocar and it was withdrawn leaving the tubing subcutaneous. The electrical connector plug[7] was positioned in the scapular region by securely closing the scapular incision (2-0 gut)[11] around the plug. A 3 in. abdominal mid-line incision was made and the transducers were brought through the abdominal wall into the abdominal cavity at the point of the flank incision. A transducer was sutured with 3-0 Mersilene (Ethicon R552) to the antimesometrial serosal surface of each uterine horn (equidistant, 25-30 mm., from the utero-tubal junction). Both transducers were oriented in either the transverse or longitudinal myometrial axis. Following transducer attachment two 10-15 mm. Mersilene threads (IUD) were anchored with serosal knots to each end, longitudinally at the same level in one uterine lumen proximal to, distal to, or immediately beneath the ECFT. The midline and flank incisions were closed and Type SR penicillin[13] (100,000 units) was administered intramuscularly.

During the daily one to two hour recording period (between 6-11 a.m.) the connector plug from the Dynograph was brought through the top of the rabbit's permanent

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[13]Parke, Davis & Co., Detroit, Michigan.

cage (Type AC-3)[14] and connected to the scapular plug in the animal. For recording purposes the rabbit was provided freedom of movement, but confined by a board which spanned the width of the cage. On the fifth day following transducer implantation the doe was recorded for one hour, removed from the cage and mated, then returned to her cage for an additional one-two hour recording period. The doe was subsequently recorded daily for one-two hours until autopsy on the sixteenth day postcoitus.

Definition of Parameters

Daily records were analyzed utilizing the following parameters: (a) frequency, defined as the number of bursts of contractile activity/minute, (b) contractile force, calculated as the average maximum contraction/burst divided by the shim stock concave surface area, permitting force comparisons (units = grams/mm.^{2}); (c) motility index, calculated as the average frequency/recording period/rabbit multiplied by average contractile force/recording period/rabbit.

Statistical Analysis

Analysis of the mean uterine contractile activity for uterine layers employed the preliminary analysis of variance F-test and the appropriate t-test (50). Uterine

[14] Acme Metal Products, Inc., Div. Scientific Products, Allen Park, Michigan.

motility differences between the control horn and IUD horn with individual animals were computed with the Fisher paired t-test (50).

Time Intervals Analyzed

Contractile activity parameters were statistically analyzed on a time interval basis. Intervals utilized in this study were: (a) estrus (E) which included daily records from the third day precoitus to day of coitus, (b) first postcoital interval (P1) including records from day of coitus to the fifth day postcoitus, and (c) second post coital interval (P2) using records from the sixth to the sixteenth day postcoitus.

RESULTS

Contractile activity patterns of the rabbit uterine longitudinal and circular muscle layers were recorded during estrus and the parameters of contractile force, frequency, and motility index were determined. Post-coital contractile activity changes and the subsequent changes associated with progressing pregnancy were also recorded.

Contractile Activity During Estrus

During estrus the uterus exhibited rhythmic coordinated contractile activity with a comparatively high contractile force and low frequency. Other than the short period following coitus, the motility index was the greatest during estrus.

Longitudinal Muscle

Contractions occurred either as a single contraction or as a multiple contraction burst (one or more contractions superimposed on increased tone). Frequency as determined by the number of bursts varied from 0.25 to 1.0 bursts per minute. Daily average maximal amplitude of contraction recorded from longitudinal muscle ranged from

15-24 gm. Figures 3 and 4 show typical estrous contractile activity for both the control and IUD horns.

Circular Muscle

Contractions of the circular muscle layer usually occurred as a single contraction burst. The frequency of contractions varied from 0.5 to 1.5 bursts per minute. The average daily maximum amplitude ranged from 10 to 20 grams. Figures 5 and 6 show typical estrous contractile activity patterns for circular uterine muscle for both the control and IUD containing horns.

Contractile Activity Following Coitus

Increased contractile activity was recorded from both uterine muscle layers in both the control and IUD horns following coitus. These increased contractile activity data are summarized in Table 1.

Longitudinal Muscle

Decreased amplitude (less than 10 grams) and frequency (less than 0.25 bursts per minute) were recorded for a short period (less than 3 minutes) following coitus. This uterine quiescence was followed by a 20-45 minute period of increased amplitude to 20-30 grams and frequencies to 0.75-2.0 bursts per minute. A gradual return to precoital contractile activity occurred within one hour. Figure 3 shows typical contractile activity pattern changes following coitus.

Figure 3: Tracing of contractile activity of rabbit uterine longitudinal muscle just prior to and following coitus (arrow) monitored from control horn (C) and IUD containing horn (I). Time elapsed for transfer and mating (at the arrow) was eight minutes. In this and subsequent figures, force calibration bars are at the right. Calibration bar height variability is due to transducer individuality.

Figure 4: Tracing of contractile activity of longitudinal uterine muscle monitored from the control horn (C) and IUD containing horn (I) during estrus (E), 4, and 16 days post-coitus. Calibration bars for estrous tracings apply to postcoital contractile activity.

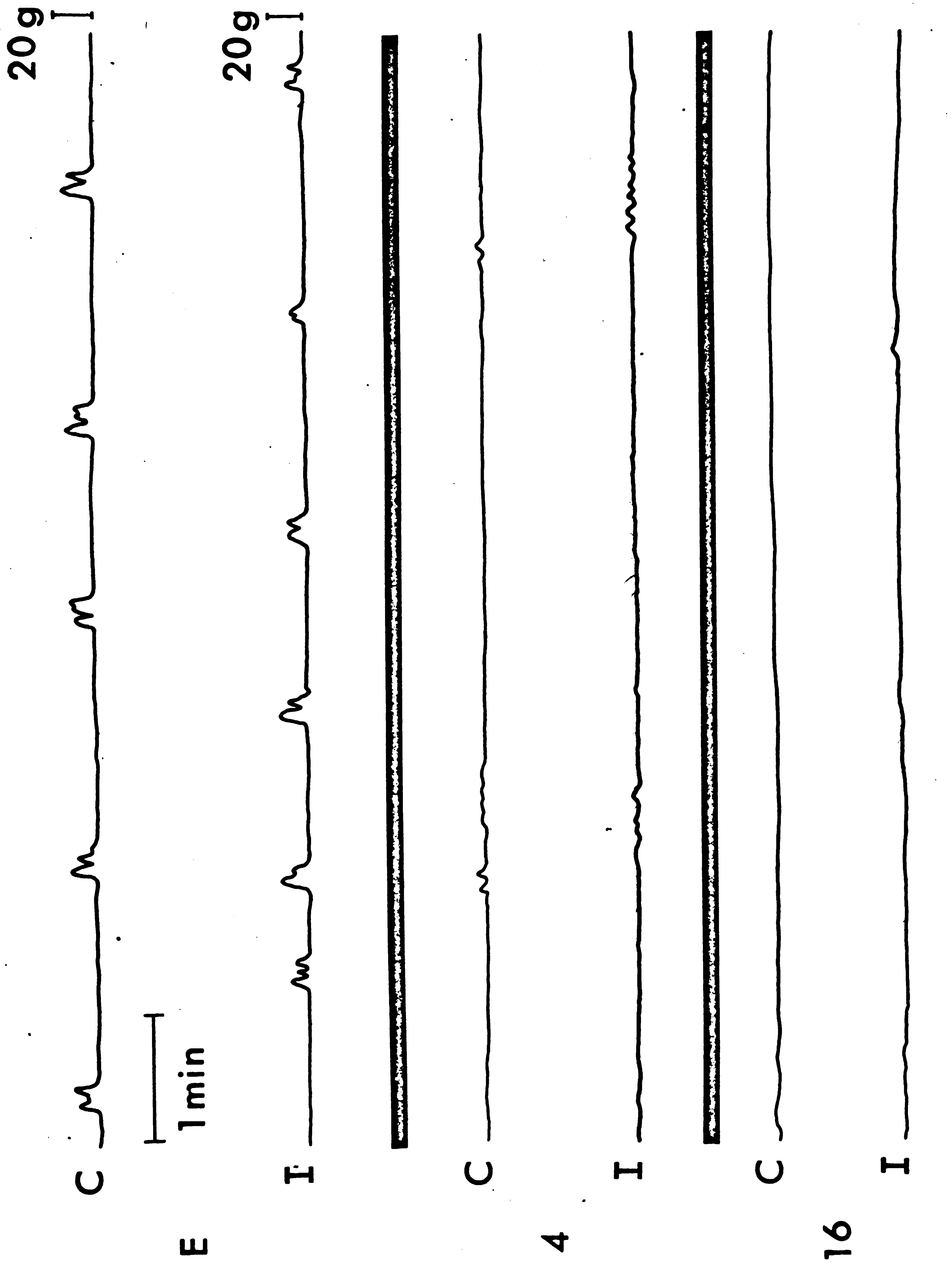
20g
20g
1min
C
I
C
I
C
I
E
4
16

Figure 5: Tracing of contractile activity of circular uterine muscle just prior to and following coitus (arrow) monitored from control horn (C) and IUD containing horn (I). Time elapsed for transfer and mating (at arrow) was 10 minutes.

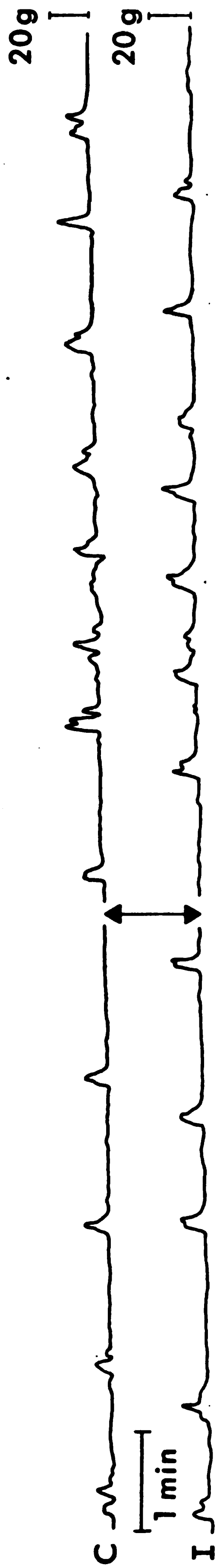
20g
20g
1 min
C
I

Figure 6: Tracing of contractile activity of transverse uterine muscle monitored from the control horn (C) and IUD containing horn (I) during estrus (E), 4, and 16 days postcoitus. Calibration bars for estrous tracings apply to postcoital contractile activity.

TABLE 1.--Average force and frequency just prior to and following coitus*

Parameter	Longitudinal Muscle n=3			Circular Muscle n=3		
	Estrus	Post-coitus	p**	Estrus	Post-coitus	p
Contractile Force (gm/mm^2)	.67 (.73)	1.07 (1.07)	<0.01 (<0.01)	.49 (.51)	.90 (.87)	<0.01 (<0.01)
Frequency (bursts/min)	.31 (.46)	.53 (.80)	<0.01 (<0.01	.63 (.71)	.67 (.78)	<0.05 (<0.02)

*Ten minute intervals before and after mating (do not include time elapsed for transfer and mating).

**Calculated with Fisher paired-t analysis of differences.

IUD horn values are in parentheses, control values are without parentheses.

Circular Muscle

Increased amplitudes to 15-25 grams and frequencies to 1-2 bursts per minute were recorded from the circular muscle layer following coitus. Circular muscle contractile activity returned to precoital patterns within 20 minutes. The quiescence recorded from longitudinal muscle was not recorded from the circular muscle layer following coitus. The increased contractile activity following coitus is shown in Figure 5.

Contractile Activity for Initial Sixteen Days Postcoitus

Decreasing amplitudes and frequencies were recorded from both uterine muscle layers as the luteal phase progressed. The motility index was calculated at the lowest values from the 10th to the 16th day postcoitus.

Longitudinal Muscle

Amplitude and frequency decreased as pregnancy progressed (Figure 4). Frequency decreased less rapidly than force. By the sixteenth day postcoitus the uterus was relatively inactive.

Circular Muscle

Figure 6 shows decreased contractile activity as pregnancy progressed. Contractile force and frequency both decreased, but at different rates as pregnancy progressed. The minimal values for all parameters were recorded from the 10th to the 16th day postcoitus.

Contractile Activity of the Uterine Muscle Layers

Comparisons of contractile activity of the uterine muscle layers are shown in Table 2. Control horn longitudinal muscle had a greater mean contractile force than circular muscle, and mean frequency for circular muscle was greater than the frequency recorded for longitudinal muscle for all time intervals (E, P1, and P2). Although the contractile force and frequency were statistically

TABLE 2.--Group comparisons of longitudinal vs. circular myometrial contractile activity (control horn and IUD horn) before and after fertile coitus.

Average Parameters	Control Horn					IUD Horn				
	N	Longitudinal Muscle+	N	Circular Muscle++	P**	N	Longitudinal Muscle	N	Circular Muscle	P
3rd day pre-coitus to coitus										
Frequency[a]	11	.58	15	.84	<0.05	11	.52	15	.79	<0.05
Force[b]	11	.71	15	.44	<0.05	11	.68	16	.48	ns
Index[c]	11	.41	15	.38	ns	11	.36	15	.39	ns
Coitus to 5th day postcoitus (P1)										
Frequency	17	.46	21	.82	<0.001	17	.52	21	.86	<0.01
Force	16	.54	21	.32	<0.05	16	.50	21	.41	ns
Index	16	.32	21	.29	<0.05	14	.36	21	.41	ns
6th to 16th day postcoitus (P2)										
Frequency	16	.18	28	.45	<0.05	16	.23	28	.56	<0.001
Force	16	.10	28	.08	<0.05	16	.11	28	.10	ns
Index	16	.02	28	.04	<0.01	16	.02	28	.06	<0.05

+Data from 3 rabbits ++Data from 4 Rabbits
*N = Rabbit Days (45-60 min. recording period/rabbit/day).
**Computed on basis of preliminary analysis of variance and appropriate t-test
[a]Frequency is defined as the number of bursts of contractile activity/minute
[b]Force is calculated as the average maximum/burst divided by the transducer concave surface (21 mm^2). Units = $grams/mm^2$.
[c]Index is defined as average frequency/recording period/rabbit x average force recording period/rabbit (units = bursts/min x gms/mm^2).

different, the motility indexes which sampled overall estrous motility were not statistically different. Mean contractile force in IUD horns was not statistically different for the two uterine muscle layers. As in the control data, mean frequency for the circular muscle was greater than that recorded for longitudinal muscle. Control horn layers showed the longitudinal motility index to be greater than the circular motility index during interval P1, while the converse was true during P2. The motility indexes of the IUD horn layers indicated circular muscle motility was greater than longitudinal muscle motility during interval P2, but no difference during interval P1.

IUD and ECFT Effects Upon Fetal Mortality

Effects of the IUD upon implantation and conceptus mortality are presented in Table 3. In all animals the effects appeared to be local with degenerating fetuses always found immediately beneath and adjacent to the IUD. Viable fetuses were found implanted above and below the IUD site (determined by visual observation) during autopsy on the sixteenth day postcoitus.

Normally developing viable fetuses were found proximal to, distal to, and immediately beneath the ECFTs, except where the ECFT was over the IUD.

TABLE 3.--IUD effects upon implantation and conceptus mortality sixteen days postcoitus.

Control Horn					IUD Horn				
CL*	Implanted		Viable		CL	Implanted		Viable	
	No.	%	No.	%		No.	%	No.	%
24	23	94	19	71	32	28	88	19	56

*corpora lutea

Data from 6 rabbits.

Contractile Activity of the Uterine Horns

Contractile activity differences for the control horn and the IUD horn are compared in Table 4. Mean frequency of the longitudinal muscle in the IUD horn was greater than that recorded for the control horn during both pregnancy intervals (P1 and P2) and the differences were significant ($p < 0.001$). Contractile force differences between uterine horns were not significant for longitudinal muscle during any time interval.

Circular layer mean contractile force differences (IUD horn > control horn) were significant for both horns (P1, $p < 0.001$: P2, $p < 0.02$) during both pregnancy intervals. Mean frequency of the IUD horn was greater than mean frequency of the control horn during P2.

TABLE 4.--Comparisons of myometrial contractile activity (IUD horn vs. control horn) before and after fertile coitus.

Average Parameters	Longitudinal Muscle				Circular Muscle			
	N	IUD	Control	p**	N	IUD	Control	p
3rd day precoitus to coitus								
Frequency*	8	.53	.57	ns	15	.79	.84	ns
Force*	8	.82	.87	ns	15	.50	.44	ns
Index*	8	.44	.48	ns	15	.39	.35	ns
Coitus to 5th day postcoitus (P1)								
Frequency	17	.52	.46	<0.001	21	.86	.83	ns
Force	16	.50	.54	ns	21	.41	.32	<0.001
Index	16	.32	.32	ns	21	.41	.29	<0.001
6th to 16th day postcoitus (P2)								
Frequency	16	.25	.18	<0.001	28	.56	.45	<0.05
Force	16	.11	.10	ns	28	.10	.08	<0.02
Index	16	.03	.02	<0.001	28	.06	.04	<0.05

*Refer to Legend Table 2 (p. 33).

**Computed on basis of daily paired comparison (Fisher paired-t).

Differences (IUD horn > control horn) in the longitudinal motility index (Table 4) were significant ($p<0.001$) only during interval P2.

DISCUSSION

Estrous Contractile Activity Patterns

Rabbit uterine contractile activity during estrus has been reported by other investigators (3, 14, 15, 45, 46). Dominic (14, 15) reported variations in the high contractile forces and rhythmic coordinated contractile activity patterns during estrus, which have been confirmed by the present study.

Contractile Activity Patterns Following Coitus

The uterine events following coitus in the rabbit have been described. Reynolds (43) has reported a decrease in uterine motility within 5-8 hours and ovulation 10-12 hours postcoitus. Sperm were found in the Fallopian tube as early as two hours postcoitus (56) and within four hours were found in similar quantities in both the uterine lumen and Fallopian tubes (39). Fertilized ova enter the progesterone influenced uteri 72-96 hours following coitus (7).

Oxytocin has been shown to be released from the posterior hypophysis upon mechanical stimulation of the vagina, cervix, or uterus in intact and in spinal sectioned rabbits (18, 45). Oxytocin administration has been reported to facilitate sperm transport via increased uterine contractile activity (39), presumably due to its hypopolarization of the myometrial cell membrane (11). High estrogen levels in the estrous rabbit increase the cell membrane permeability to extracellular sodium ions. Coincident oxytocic hypopolarization and estrogen influenced membrane permeability would further increase the likelihood of spontaneous coordinated uterine contractile activity. Initiating nervous reflexes by dilation of the uterus, cervix, or vagina increases the frequency of uterine contractions, a reflex which can be blocked by intrauterine administration of 2% lidocaine (47).

The influence of the sympathetic nervous system may be important in the mediation of the recorded postcoital longitudinal muscle quiescence. Although norepinephrine is the catecholamine present in the largest amounts in estrogen dominated rabbit uteri (40, 49), epinephrine has been shown to depress estrogen dominated uterine motility in the human (55), rat (13), and bovine (25). The period of uterine longitudinal muscle quiescence could be elicited by adrenal epinephrine release during coital excitation, causing activation of beta adrenergic receptors (13). Thus the recorded increase in rabbit uterine contractile activity following coitus may be due to oxytocin facilitation coupled with diminishing adrenergic inhibition.

Coitus causes increased bovine uterine motility within seconds (54). The present results show that increased uterine contractile activity occurs in the rabbit following coitus. If sperm transport is occurring within the first hour following coitus, then sperm transport could be the primary function of this increased myometrial contractile activity.

Contractile Activity During Pregnancy

The present contractile activity data for pregnant rabbits confirm previously reported results found for pseudopregnant rabbits (14, 15): (a) contractile force decreased and there was an initial increase in frequency, (b) both contractile force and frequency decreased as the luteal phase progressed, and (c) longitudinal muscle contractile forces were greater than circular muscle contractile forces.

Though both are decreasing during pregnancy, circular muscle frequency exceeds that of longitudinal. The converse has been reported in pseudopregnancy (15).

Apparent pacemaker activity has been found to predominate in the ovarian end of the longitudinal myometrial layer with contractions propagated distally (14, 15). Markee (34) indicates ova are distributed evenly up to five days after human chorionic gonadotropin induced ovulation in rabbits. Present results (control horn, Table 2) suggest that uterine longitudinal muscle contractile force and transverse myometrial frequency may be factors in rabbit ova distribution during the initial five days following coitus. Reported variations in uterine contractile activity during the initial five days following coitus may be a factor in the advent of pseudopregnancy (14, 15). This pseudopregnancy could be caused by lack of sperm transport, tubual retention of ova, failure of deciduoma formation, increased tubual transport, and/or egg explusion.

Motility Index

The problem of the recorded phenomenon of increased frequencies associated with decreased contractile forces during estrus (15) prompted the calculation of a motility index. The motility index was a calculated value which sampled overall contractile activity patterns. While both contractile force and frequency were significantly different ($p < 0.05$) for the control horn uterine muscle layers during estrus (Table 2), the motility index was not statistically different. The motility index used in this study indicates contractile activity trends in a manner similar to those quantified by linear displacement analysis (6, 10).

Fertility Effects of the Intrauterine Device

The present study confirms previous results in rabbits indicating that normally developing fetuses can be found both proximal to and distal to the IUD site (1, 2, 9, 41). The IUD effect on rabbit fertility is therefore not due to changes in sperm migration. The IUD in the rabbit has been previously shown not to prevent implantation (1, 2, 35, 41), in fact, ova have been found implanted at the IUD site (1, 2, 35). IUD removal on the 5th or 6th day following coitus will allow normal rabbit fetal development (1, 2, 35). IUD provoked fetal degradation will approach 100% by the fourteenth day postcoitus (35). The increased fetal mortality reported by Marston and Chang can be attributed to the length of the uterine lumen covered by the IUD in that study, while the present data (Table 3) are comparable to those of Adams and Eckstein (1) who used shorter IUDs.

Intrauterine Device Effects on Uterine Motility

Adams and Eckstein (2) inferred no changes in uterine motility in the presence of an IUD based on the lack of premature expulsion of ova or to prolonged gestation period in rabbits. The present data indicate that the analysis of any single day's records does not show contractile activity differences between the control and IUD containing horns. Paired observations of grouped data for the intervals, P1 and P2, show statistical changes in contractile activity (Table 4). These differences indicate that contractile activity changes occur with time (i.e. five to six days).

Rabbit fetal degradation has been prevented by IUD removal before the 5th day following coitus (1, 34). It appears that if contractile activity has any direct effects on fetal mortality it will be recorded after the 5th day postcoitus. The results (Table 4) show differences in the frequency (IUD horn > control horn) of longitudinal muscle during P2. During the same interval postcoital effects on the IUD horn transverse myometrial activity show both increased contractile force and frequency, IUD induced differences which are coincident with fetal degradation.

Reynolds (44) has shown that rabbit corpora lutea function until the middle of the fourth week of pregnancy and maintain initial uterine quiescence. Hypophysectomy will cause the degeneration of the corpora lutea with the return of estrous uterine motility rhythms within six days. Behrman and Burchfield (6) have suggested that the presence of an IUD leads to early corpora lutea degeneration in the ovary adjacent to the IUD horn in the rabbit as has been shown for the ewe (52), but involution of the corpora lutea is not associated with increased fetal mortality in the rabbit (9, 26). The present results confirm the idea that the local IUD effects upon fetal mortality are not due to corpora lutea degeneration. An

IUD induced increase in lysosome activity in the rodent uterus (41) indicates a possible inflammatory response. After the sixth day postcoitus the increased IUD horn contractile activity may be due to increased local irritability initiated by an inflammatory response.

SUMMARY

I. The extraluminal strain gage transducer has been confirmed to be a satisfactory method for studying *in vivo* contractile activity of both the longitudinal and circular uterine muscle layers of the rabbit.

II. The presence of the extraluminal strain gage transducer on the serosal surface of the rabbit uterus does not interfere with normal nidation.

III. The contractile activity patterns found in various rabbit ovarian stages were recorded and analyzed.

1. During estrus, the uterus exhibited high contractile force and rhythmic contractile activity patterns. Variations in contractile force and frequency were common during estrus. Variations of the contractile force were inversely related to the variations of frequency.
2. Increased amplitudes and frequency of contractions were recorded from both uterine muscle layers following coitus. Contractile activity differences found for the longitudinal and circular muscle layers

following coitus were: (a) a period of uterine quiescence recorded only from the longitudinal muscle and (b) increased myometrial contractile activity recorded for a longer period in the longitudinal muscle before returning to precoital contractile activity patterns.

3. The immediate post-ovulatory contractile activity patterns of pregnancy (one day postcoitus) resembled that of estrus, but thereafter the activity declined rapidly and the uterus remained essentially quiescent until autopsy on the sixteenth day postcoitus.

IV. Contractile activity pattern during estrus, following coitus, and during pregnancy exhibited differences between the uterine muscle layers.

1. Mean contractile forces were greater for longitudinal muscle.
2. Mean frequency of contractions were greater for circular muscle.
3. Longitudinal muscle usually exhibited patterns of multiple contraction bursts while single contraction bursts were more characteristic of circular muscle.

V. IUD effects upon uterine contractile activity parameters were found to be statistically different only when analyzed over an interval of five or more days during pregnancy. These IUD induced uterine motility effects were:

1. Mean frequency of the longitudinal muscle was greater for the IUD horn.
2. Both mean frequency (P2) and mean contractile force (P1, P2) were greater for the circular muscle in the IUD horn.

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