EFFECT OF AN INTRA-UTERINE DEVICE ON UTERINE MOTILITY IN THE RHESUS MONKEY

J. H. MARSTON,* W. A. KELLY† AND P. ECKSTEIN

Department of Anatomy, Medical School, Birmingham 15

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Summary. Attempts to compare the pattern of myometrial activity in restrained, fully conscious, control and IUD rhesus monkeys by using a chronically implanted, strain-gauge transducer attached to the external surface of the uterus, were not successful.

‘Egg transfers’ were made to the uterus on Days 15 and 18 of the menstrual cycle using fertilized rabbit eggs and radio-active silver-110m-coated, resin spheres as natural and artificial substitutes for monkey eggs. There was no marked difference in the rate of egg recovery from control and IUD monkeys at 48 hr after transfer.

It was concluded that premature expulsion of the eggs from the uterus was not the principal contraceptive effect of an IUD in the rhesus monkey.

INTRODUCTION

A previous report (Kelly & Marston, 1967) implied that the principal contraceptive effect of an IUD in the rhesus monkey was most probably exerted within the uterus by causing premature expulsion and/or premature destruction of the fertilized egg. The presence of an IUD may therefore disturb the normal pattern of uterine motility in the rhesus monkey.

The possibility that an IUD might alter uterine motility in women has been tested by Bengtsson & Moawad (1966, 1967) and Johnson, Ek & Brewer (1966) who used the open-ended, intra-uterine catheter technique devised by Hendricks (1964). By contrast, Behrman & Burchfield (1968) used an IUD with a built-in pressure-sensitive transducer to obtain a direct record of the mechanical activity of the uterus on the IUD.

Apart from the authors' previous report (Marston & Kelly, 1968), there have been no attempts to study the effect of an IUD on uterine motility of rhesus monkeys. The application of the open-ended catheter technique to this species has been investigated in preliminary studies by Martin & Eckstein (1966) and Harry & Pickles (1968).

This paper is the fourth in a series of communications dealing with the effects of an IUD on the processes of conception in the rhesus monkey. It
reports on attempts to compare the uterine activity of fully conscious control and IUD monkeys by (a) a direct technique, involving the use of chronically implanted strain-gauge transducers attached to the external surface of the uterus, and (b) an indirect technique, based on the transfer of natural and artificial substitutes for monkey eggs to the uterus to test the rate at which they were expelled from the uterus.

**MATERIALS AND METHODS**

Full details of the management and preparation of the rhesus monkeys used in the series of experiments have been given by Eckstein, Kelly & Marston (1969).

*Direct comparison*  
*Transducer unit.* This was designed and fully described by Bass & Callantine (1964), who used it to study uterine motility in the unanaesthetized dog and subsequently in the unanaesthetized rabbit (Callantine, O'Brien, Windsor & Brown, 1967). The external dimensions of the encapsulated transducer unit were about 17 x 6 x 4 mm and it could lie transversely across the ventral face of the rhesus monkey uterus.

*Surgical implantation.* In the first series of experiments (five monkeys), the transducer unit was attached to the ventral, serosal surface of the uterus (Pl. 1, Fig. 1) by two nylon sutures placed in the superficial myometrium. The lead from the unit was sutured to one round ligament and passed through the mesosalpinx on that side so that it could be led behind the uterus to the dorsal surface of the cervix. It was then grasped by forceps and pulled through a blunt stab wound in the dorsal fornix of the vagina. After the lead had been delivered to the exterior, the laparotomy wound was repaired.

This technique was modified in the second series of experiments (ten monkeys). The transducer unit was covered with omentum after it had been attached to the uterus and the omentum was secured to the serosal surface of the uterus by four nylon sutures placed one at each corner of the transducer unit. This prevented adhesions forming between the colon and the, supposedly inert, surface of the unit.

The transducer lead was attached externally to a miniature plug (Subminiature plug SM 2: Ether (Connectors) Ltd, Biggleswade, U.K.) placed as close as possible to the opening of the vagina. The inside of the plug was filled with dental cement to insulate and encapsulate the contacts and it was then easily placed within the vagina where it lay close beside the cervix. The plugs were retained within the vaginæ of all the experimental monkeys (Pl. 1, Fig. 2) and caused no apparent discomfort to the animals, nor any reaction within the vagina. The monkeys were rested for approximately 10 days following insertion of the transducer.

*Recording uterine motility.* Recordings were made over periods of 1 to 3 hr while the fully conscious, unmedicated monkey was seated in a restraint chair. The monkeys had previously been habituated to this restraint.

Before the monkey was placed in the restraint chair, the transducer plug was removed from the vagina and connected to a twin channel recording system
Fig. 1. Transducer unit (Bass & Callantine, 1964) implanted on ventral surface of uterus. \( \times 2 \) approx.

Fig. 2. X-ray to show transducer unit, vaginal plug and IUD in uterus. \( \times 1.5 \) approx.

(Facing p. 322)
('Oscillo-riter', Texas Instruments Inc.). This procedure appeared to cause little discomfort to the monkey. A separate external transducer was attached to the chest during each observation to monitor both respiratory activity and gross bodily movements.

**Indirect comparison**

In the first experiment, resin spheres coated with the radio-active silver isotope, silver-110m, afterwards referred to as R/A eggs, were transferred to the uterus as artificial substitutes for rhesus monkey eggs. They were similar in size (about 150 µ) and density to natural monkey eggs and resembled the radio-active, artificial eggs used by Harper, Bennett, Bournsell & Rowson (1960). Three R/A eggs were transferred at laparotomy on Day 15 of the menstrual cycle, to the uteri of four control and four IUD monkeys.

The eggs were drawn into a fine nylon cannula attached to a micrometer syringe and containing physiological saline. The tip of the cannula was passed into the uterine lumen through a No. 19 gauge serum needle which pierced the fundus. The needle was withdrawn and the eggs were expelled into the uterine lumen in 10 µl of fluid as the cannula was itself being gently withdrawn. The position of the R/A eggs within the uterine lumen was monitored with a miniature Geiger-counter probe (Type B 1 N, 20th Century Electronics Ltd).

In the second series of experiments, fertilized rabbit eggs were transferred, as natural substitutes for monkey eggs, to the uteri of eight control and ten IUD monkeys on Day 15 of the menstrual cycle, and to two IUD monkeys on Day 18.

The rabbit eggs were usually at the 8- to 16- cell stage and were transferred in groups of four to eight immediately after being flushed from the rabbit’s Fallopian tube. In two monkeys, groups of ten and fourteen eggs were transferred, while in another seven animals pro-nuclear and two-cell eggs were used. These variables did not affect the results of the transfer. A single R/A egg was included with the rabbit eggs in each case so that it could act as a marker to facilitate transfer.

The rabbit and R/A eggs were recovered at autopsy by removing the entire genital tract and dividing it so that the uterus, cervix and vagina could be separately flushed with Ringer’s solution. The uterus and cervix were then monitored with a Geiger-counter. With a single exception, eggs were only recovered from the uterus, though the mucus and cellular debris in the cervical flushing, and the mass of seminal coagulum in the vaginal flushing could have hidden any rabbit eggs that were present.

**RESULTS**

**Direct comparison**

Transducer units were implanted in seven control and eight IUD monkeys and recordings were made over two or three consecutive menstrual cycles during which the monkeys showed normal menstrual periodicity. When the transducers were removed at the end of the experimental observations, six animals (on Days 15 to 22) showed active corpora lutea and eight (on Days 7 to 10) had ovaries with pre-ovulatory or developing follicles. One control monkey
Text-fig. 1. Part of record to show spontaneous activity of uterus and effect of oxytocin administration: IUD monkey on Day 3 of menstrual cycle.

Text-fig. 2. Part of record from IUD monkey on Day 23 of menstrual cycle.
conceived while she was fitted with a transducer and a vaginal plug. These observations show that the transducer units did not markedly disturb the reproductive physiology of the monkeys.

It was occasionally possible to obtain convincing records of uterine motility (Text-figs. 1 and 2), but the records were frequently and severely distorted by reflections from respiratory and gross bodily movements (Text-fig. 3). In practice, none of the records was suitable for useful quantitative and qualitative comparison of uterine motility.

![Text-fig. 3. Part of record to show effect of respiratory (a and c) and gross bodily movements (b).](image)

There was no doubt that the transducer system was sensitive to variations in uterine motility, but it was also sensitive to changes in abdominal pressure. The experimental monkeys could be trained to sit quietly in the restraint chair, but this did, by necessity, hold them in an unnatural position and the restraint exerted abnormal pressure on the lower abdomen. There was a tendency for the recording system to be thrown completely out of balance when the monkey moved, and it was difficult to compensate for this. Observation showed that the monkeys were restless and disturbed as they sat in the restraint chair, and could be alarmed by the slightest change in the experimental environment. This behaviour was markedly in contrast with the placidity usually shown by the monkeys when they were left undisturbed in their own cage.

**Indirect comparison**

Histological examination showed that three of the monkeys killed in the egg transfer experiment had inactive ovaries, two showed ovaries with large atretic follicles and twenty-three had active corpora lutea. The morphological ages of the corpora lutea ranged from 3 to 8 days, with nineteen ovaries showing a luteal age of 5 to 8 days (cf. Corner, 1945; Kelly, Marston & Eckstein, 1969).
In most animals, egg transfers were made close to the time at which eggs would naturally have entered the uterus.

The results of rabbit and R/A egg transfer experiments are summarized in Tables 1 and 2. These show that there was no difference in the recovery of the transferred eggs between the groups of control and IUD monkeys examined 48 hr after transfer. The majority of the rabbit and R/A eggs could be recovered from the uterus at this time, and there was no evidence to suggest that premature expulsion of the transferred eggs from the IUD monkeys had occurred.

**Table 1**

RADIO-ACTIVE EGGS RECOVERED FROM THE UTERUS AT AUTOPSY FOLLOWING TRANSFER ON DAY 15

<table>
<thead>
<tr>
<th>Autopsy (hr after transfer)</th>
<th>Group</th>
<th>Total monkeys yielding transferred eggs/examined</th>
<th>Total radio-active eggs recovered/ transferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>Control</td>
<td>3/4*</td>
<td>7/12</td>
</tr>
<tr>
<td></td>
<td>IUD</td>
<td>4/4</td>
<td>10/12</td>
</tr>
</tbody>
</table>

* One monkey had not ovulated; the ovary had a large atretic follicle.

**Table 2**

RADIO-ACTIVE AND RABBIT EGGS RECOVERED FROM THE UTERUS AT AUTOPSY

<table>
<thead>
<tr>
<th>Autopsy (hr after transfer)</th>
<th>Group</th>
<th>Total monkeys yielding transferred eggs/examined</th>
<th>Total radio-active eggs recovered/ transferred</th>
<th>Total rabbit eggs recovered/ transferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Following transfer on Day 15</td>
<td>48</td>
<td>Control</td>
<td>2/2†</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IUD</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>Control</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IUD</td>
<td>1/4</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>Control</td>
<td>1/2†</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IUD</td>
<td>0/2†</td>
<td>0/2</td>
</tr>
<tr>
<td>Following transfer on Day 18</td>
<td>48</td>
<td>IUD</td>
<td>2/2*</td>
<td>2/2</td>
</tr>
</tbody>
</table>

* One monkey had inactive ovaries.
† Both monkeys had inactive ovaries.
‡ One monkey ovulated between laparotomy and autopsy.

The transferred eggs had virtually disappeared from the uteri of IUD monkeys examined at 72 hr and from both groups at 96 hr. None of the R/A eggs showed signs of deterioration when they were recovered. All the rabbit eggs had an intact zona pellucida at recovery, and the natural 'albumen' layer, which had coated most of the eggs at the time of transfer, was also intact and apparently unchanged. This evidence suggested that it was unlikely that the eggs could have been completely destroyed within the uterus. One control
monkey examined after 72 hr yielded two rabbit eggs and an R/A egg in the cervical flushing. It seemed that, in this case, the eggs were actually in the process of expelled from the uterus.

At 72 hr after transfer (Table 2), only one egg could be recovered from the IUD monkeys, yet all the R/A eggs and 36% of the rabbit eggs were found in the control animals. The result might suggest that the transferred eggs had a somewhat shorter uterine life in the presence of an IUD, but it is not possible to draw any conclusions on the uterine survival of eggs taken from groups of animals that had to be examined at intervals 24 hr apart.

DISCUSSION

Present knowledge of the possible modes of action of an intra-uterine device in women has been largely derived from the results of animal experimentation, and particularly from studies on the rhesus monkey. The authors have previously shown that the contraceptive action of an IUD in the naturally cyclic rhesus monkey is exerted within the uterus, and that the processes of ovulation, fertilization and tubal transport are not obviously disturbed (Kelly & Marston, 1967; Eckstein et al., 1969; Kelly et al., 1969; Marston, Kelly & Eckstein, 1969). Moreover, it can be inferred from the results of comparable clinical studies (WHO, 1968; Noyes, Clewe, Bonney, Burrus, DeFeo & Morgenstern, 1966) that the contraceptive action of an IUD in women is also exerted within the uterus.

There are, however, important differences between the two species in the anatomy of the uterus, the process of implantation and other aspects of reproductive physiology (Eckstein & Zuckerman, 1956; Ramsey & Harris, 1966). The contraceptive action of an IUD within the uterus of the rhesus monkey is therefore not necessarily identical with that occurring in women.

If it had been possible to obtain consistent records of the pattern of uterine motility in rhesus monkeys, these could have been compared with the results obtained in women by Bengtsson & Moawad (1967) and Behrman & Burchfield (1968). It would not have been possible to use repeatedly anaesthetized or deeply sedated animals during such a long series of observations without seriously disturbing them and upsetting their pattern of reproductive activity. The transducer system was very sensitive but it was activated by deformation of the copper beryllium clip on which the strain-gauge was mounted. As the transducer unit was itself mounted on the serosal surface of the uterus, this deformation could not only be produced by uterine activity but also by peristalsis, excursions of the abdominal viscera, respiratory efforts and gross bodily movements.

To overcome these disadvantages, it would be necessary to use a device which is activated only by changes in uterine activity. If a minute encapsulated strain-gauge, surgically implanted in the myometrium could be linked with an implanted radio-telemetry system, it should be possible to obtain useful and consistent records of myometrial activity from completely unrestrained and undisturbed rhesus monkeys.

There appeared to be no advantage in attempting to apply the open-ended
catheter technique of Hendricks (1964) to the study of uterine motility in rhesus monkeys. In our experience (Eckstein et al., 1969), satisfactory canalization of the endo-cervical canal cannot be achieved without gross traumatization of the cervix, unless this is carried out within 3 weeks of parturition. If the open-ended catheter has to be placed in position for each observation (Martin & Eckstein, 1966), the monkey must be anaesthetized and there is likely to be marked stimulation of the cervix. Recordings of uterine motility obtained after such manipulation may be not be typical of the normal pattern of uterine motility. Harry & Pickles (1968) permanently implanted an open-ended catheter so as to by-pass the endo-cervical canal. By definition, their catheter must be regarded as an IUD and their observations may not have been normal because they were made on deeply sedated monkeys.

By contrast, there is wide agreement that the open-ended catheter technique is very suitable for use in women and it can provide consistent results (Hendricks, 1964, 1966; Moawad & Bengtsson, 1967). These workers showed that there were cyclical variations in the pattern of human myometrial motility. Johnson et al. (1966) studied the uterine motility of post partum women at the time of IUD insertion and again 2 weeks later. They found no differences between their two groups of observations. The value of these results is uncertain because no mention was made of the time at which the observations were made within the menstrual cycle, nor whether the patients were cyclic. Bengtsson & Moawad (1967) found that a group of IUD patients showed no differences in myometrial activity until the 4th or 5th post-ovulatory day (about Day 19), when there was a precocious appearance of the 'pre-labour like' activity normally characteristic of the immediate pre-menstrual period. The onset of this activity was thought to be close to the time implantation might be expected to occur. They suggested that this abnormal pattern of myometrial activity might be one of the factors associated with the contraceptive action of an IUD. By contrast, Behrman & Burchfield (1968) could find no abnormal pattern of activity in patients fitted with an IUD containing a built-in transducer. There was some increase in myometrial activity immediately after insertion of this device, but it rapidly subsided and was absent 3 days after insertion. A period of quiescence followed ovulation until the day before menstruation and the authors concluded that myometrial activity plays a minimal role in the mechanism of IUD action. The difference between their results and those of Bengtsson & Moawad (1967) may have been due to differences in the sensitivity of the two techniques. The transducer-IUDs probably responded to local changes in muscle activity rather than to changes in luminal pressure produced by the activity of the entire myometrium. If groups of patients were first studied by using the open-ended catheter technique before being fitted with a transducer-IUD and then regularly examined with both techniques, this problem might be resolved.

Our indirect comparison of uterine motility in the rhesus monkey tested the ability of control and IUD uteri to expel eggs after they had been artificially placed in the uterine lumen. The results show that up to 48 hr after transfer, there was little difference in the rate at which eggs were expelled. There may have been more rapid expulsion of eggs from the IUD uterus at later stages. This can only be established by killing additional groups of monkeys at
IUDs and uterine motility

intervals of 6 to 8 hr between 48 and 72 hr after transfer, which does not seem justifiable at the present time.

The egg transfer experiments could not test whether the presence of an IUD induced subtle changes in myometrial activity. It seems reasonable to expect that implantation could be inhibited by slight alterations of myometrial activity, and degeneration of the fertilized egg might also be induced by similar changes occurring during the pre-implantation period.

It is concluded that premature expulsion of the egg from the uterus is not the principal contraceptive action of an IUD in the rhesus monkey. By inference, the evidence must favour the alternative explanation that, in the presence of an IUD, fertilized rhesus monkey eggs undergo premature degeneration within the uterine lumen.

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REFERENCES


