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The Effect of a prostaglandin F_2alpha analogue, fenprostalene, and oxytocin on both in vivo and isolated uterine motility in the cow

William Herbert Byrd

To the Graduate Council:

I am submitting herewith a thesis written by William Herbert Byrd entitled "The Effect of a prostaglandin F_2alpha analogue, fenprostalene, and oxytocin on both in vivo and isolated uterine motility in the cow." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Animal Science.

Hugo Eiler, Major Professor

We have read this thesis and recommend its acceptance:

Fred Hopkins, John D. Smalling

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To the Graduate Council:

I am submitting herewith a thesis written by William Herbert Byrd, III entitled "The Effect of a Prostaglandin F_2 alpha Analogue, Fenprostalene, and Oxytocin on Both In Vivo and Isolated Uterine Motility in the Cow." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Animal Science.

Hugo Eiler

Hugo Eiler, Major Professor

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and recommend its acceptance:

Accepted for the Council:

The Graduate School

THE EFFECT OF A PROSTAGLANDIN F_2ALPHA ANALOGUE, FENPROSTALENE, AND OXYTOCIN ON BOTH IN VIVO AND ISOLATED UTERINE MOTILITY IN THE COW

A Thesis

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Degree

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William Herbert Byrd, III

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ABSTRACT

With the discovery of the uterokinetic properties of prostaglandin $F_2\alpha$ much interest in the possible application of this substance in the expulsion of retained fetal membranes has arisen. Although the bovine uterus has been found to become refractory to $PGF_2\alpha$, the development of a high-activity, long half-life $PGF_2\alpha$ analogue, fenprostalene, has renewed interest in the prostaglandin's usefulness in the expulsion of retained fetal membranes.

Uterine motility was measured on two consecutive days in eight early-postpartum and six open cycling cows; and in open isolated bovine uterine horns by the intrauterine balloon technique. Fenprostalene and/or oxytocin was administered and uterine contractility was measured by a physiograph.

Results indicate that the early-postpartum cow myometrium was not responsive to fenprostalene when administered intramuscularly or intravenously. However, the open cycling cow exhibited a slight (non-significant, $P>0.05$) increase in average area under the tracing (1414.7±135.3 vs. 1555.5±95.9 mm^2) and contraction amplitude (20.3±2.4 vs. 22.3±1.4 mm Hg) following intramuscular fenprostalene injection. Oxytocin injection by both routes caused a significantly ($P<0.05$) marked stimulation of uterine contractility in both postpartum and open cow groups. In the isolated horn experiments oxytocin and fenprostalene were statistically equal ($P>0.05$) in the response observed following addition to the bath. Although the uterus was refractory to repeated

dosages of the same drug, alternated treatments of fenprostalene and oxytocin on the same uterine horn increased ($P<0.05$) mean measures of motility for each treatment. This result is supportive of the proposed two receptor system. However, after halved dosages of each drug were instilled together into the bath solution, no additiveness or synergism was observed from the mixture affect on uterine contractility.

Results obtained in this study do not support the use of prostaglandins in cases where evacuation of uterine contents is desired.

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CHAPTER I

INTRODUCTION

A. STATEMENT OF THE PROBLEM

Retained fetal membranes (RFM) are a costly postpartum disorder in cattle resulting from a diverse range of predisposing factors. Much research has been conducted on the prevention of RFM; however, because of the wide variety of factors involved, no single preventive measure can be relied upon. Similarly, although several treatment programs are widely used, problems involved with each program inherently limit success. Most researchers agree that membranes should be expelled as soon as possible after calving, but it is now established that manual removal is contraindicated. Therefore, in an effort to hasten expulsion of RFM, treatments of oxytocin or ergot derivitives have been used in RFM treatment due to their stimulatory effect on smooth muscle contraction. With the discovery of the prostaglandins and their apparent role in various reproductive functions at or following parturition, the smooth muscle modifier prostaglandin $F_2\alpha$ ($PGF_2\alpha$) has been indicated as a possible means of inducing membrane expulsion. The relatively short half-life of $PGF_2\alpha$ along with a possible refractoriness of the postpartum uterus to repeated injections, has caused limited clinical success as a treatment for RFM. Assuming the mode of action of $PGF_2\alpha$ in RFM treatment is on the myometrium, the effectiveness of this treatment could be evaluated by measuring uterine motility following injection of this drug.

Recently a $PGF_2\alpha$ analogue, fenprostalene, has been developed which possesses a half-life following subcutaneous injection of 18-23 hours compared to two to three minutes following an intravenous injection of $PGF_2\alpha$ Also, fenprostalene is approximately 25 times more active than $PGF_2\alpha$ in causing luteolysis in cattle. While chemically related to $PGF_2\alpha$, fenprostalene is the methyl ester of a synthetic prostaglandin (Figure A-1). The objective of this investigation was to determine the effect of the long half-life, high-activity prostaglandin $F_2\alpha$ analogue, fenprostalene, on uterine motility in postpartum cows as an indication of it's possible effectiveness as a treatment for the evacuation of RFM as compared to oxytocin. To further evaluate the uterokinetic effect of fenprostalene in vivo, the same experiment was conducted on open cycling cows. Further, several isolated uterine motility studies using fenprostalene and oxytocin were conducted to determine uterine contractility characteristics in the absence of central nervous system influences or the hormone inactivating capabilities of organs such as the liver or kidney.

B. LITERATURE REVIEW

1. Retained Fetal Membranes

Although the placenta should be expelled within two to three hours in 80 to 90% of normal calvings (Maas, 1982), most authors agree that a retained placenta is defined as one which has not been expelled by 12 hours postpartum (Arthur 1979). Various aspects associated with this problem are categorized in the following discussion.

Incidence. The incidence of RFM seems to vary with geographic location, environmental conditions such as season, and the level of management within an individual herd. Arthur (1979) estimates the incidence for all calvings in this country to be approximately 11%, and for uncomplicated calvings 8%. In contrast, the incidence of RFM in New Zealand (cows on pasture year-round) was 1.96% of 36,218 calvings (Moller et al., 1967). The incidence in Russia is reported to be 10-25% (Rubstrov, 1960). With the induction of brucellosis eradication programs the incidence of RFM has been decreased considerably over the last few decades. Other factors associated with RFM incidence are discussed later in this text.

Economic losses associated with RFM. Reproductive costs in dairy cattle separate from insemination costs are 21% of total expenses over a 305 day lactation (Shanks et al., 1981). These reproductive costs are highest during the first 30 days of lactation and were mostly concerned with calving, placental retention and involution. Estimated losses in 1972 for the United States because of the above mentioned or related problems totaled 394 million dollars (Pelissier 1972). Therefore, a major concern of management is for cows to calve normally, as well as to "clean" and involute satisfactorily.

Specifically, losses due to RFM can be divided into direct and indirect losses. Direct losses include cost of treatment, death due to severe toxemia, and lost milk production due to illness and/or antibiotic therapy (Pelissier, 1972; Maas, 1982). The indirect losses are costs of illnesses caused by RFM, increased insemination costs due to decreased conception rate, and increased culling of cows for

reproductive problems rather than production (Maas, 1982). Pelissier (1972) adds to the indirect loss list replacement costs and fewer calves obtained per cow per lifetime due to longer calving intervals caused by RFM. The later finding is also reported by Erb et al. (1958).

Predisposing Factors to RFM. As previously mentioned several factors have been found to be associated with retained placenta. Kennedy (1947) postulates that RFM is normally a secondary condition. Even though this observation may be correct, Erb et al.(1958) note that 85% of cows with RFM showed no gross reproductive clinical disorders prior to retaining.

Several pathogenic infections are often associated with RFM. These include brucellosis, vibriosis, leptospirosis, infectious bovine rhinotracheitis (IBR), bovine virus diarrhea (BVD), parainfluenza, bluetongue, and epizootic agents (Squire et al., 1980; Maas, 1982). These infections are often spread from cow to cow or by the herd bull (Fincher, 1941).

Nutritionally related problems also effect the occurrance of retained placenta. Milk fever is associated with a doubled incidence of RFM (Pelissier, 1976). This relationship has also been reported by several authors (Dyrendahl et al.,1977; Pelissier, 1972; Squire, 1980; Muller and Owens, 1974). Other mineral related causes of RFM are selenium deficiency (Bierschwal, 1980; Julien et al., 1976; Trinder et al., 1973), iron deficiency (Fincher, 1941) and iodine deficiency (Roberts, 1956). Vitamins A (Rooney et al., 1953) and E (Trinder et al., 1973) are also important for normal placental expulsion. This relationship has also been noted for feedstuff-seasonal influences on Vitamin E and

carotene content, and thus their effect on the incidence of RFM (Muller and Owens, 1974). The importance of dry cow ration is evidenced in the fact that cows fed low protien rations (Johnson and Otterby,.1981) or cows becoming overconditioned (Fat Cow Syndrome) during the dry period are more inclined to retain (Squire et al., 1980; Morrow, 1981).

It seems that RFM also has a genetic based tendency (Erb et al., 1958; Fincher,1941; Shanks et al., 1979). RFM can somewhat be attributed to service sire (Erb et al., 1958), breed differences (Dyrendahl et al. 1977; Erb and Martin, 1978), and genetic transmission from the dam to her female offspring (Erb et al., 1958).

Management decisions which result in short dry periods (Whitmore, 1974), hormone induced parturition (Piper,1978; Garverick et al., 1974; Carrol, 1974), or breeding mares on foal heat (Fincher, 1941) can also result in increased incidence of RFM. Several authors report that managing for high milk and fat production is also associated with a higher incidence of RFM (Muller and Owens, 1974; Rubstov, 1960; Whitmore et al., 1974; Morrow, 1956).

Other factors which increase RFM can be related to gestation length or problems associated with calving. One report (Boyd and Sellers, 1948) found that gestations greater than 291 days increased the likelyhood of RFM while several authors found shorter than normal gestation lengths resulted in increased RFM as well (Dyrendahl et al., 1977; Erb et al., 1958; Segerson et al., 1981; Martin et al., 1982; Morrow et al., 1966; Boyd and Sellers, 1948). Stillbirths or abortions regardless of cause also increase RFM incidence (Boyd and Sellers, 1948; Moller et al., 1967; Fincher, 1941). Cows having difficult calvings (Pelissier,

1972; Erb et al., 1981), twin births (Erb et al., 1958; Sandals et al., 1979; Muller and Owens, 1974), male calves (Erb et al., 1958; Patterson et al., 1981), uterine inertia following calving (Herschler, 1984), or abnormal uterine distension such as with hydrops (Wetherill, 1965) are also more likely to suffer from RFM. Finally, an increased tendency to retain has been reported as cow age increases (Dyrendahl et al., 1977; Erb and Martin, 1978), or under seasonal periods of stress (Erb et al., 1958; DuBois and Williams, 1980; Muller and Owens, 1974). Diagnostic methods for determining possible RFM cause are reviewed in Maas (1982).

Symptoms of RFM. Although not always the case, retained fetal membranes are usually present as a partially visible mass of placenta hanging out of the vagina. Weatherill (1965) has classified four types of retained membranes according to tissue structure and ease of removal. These are 1) thin, stringy membranes with large turgid cotyledons; difficult to remove, 2) thick, granular-type membranes which usually can be removed intact, 3) semi-liquid, jelly-like masses with very little tissue attached to cotyledons, 4) and extremely tough-type membranes showing little decay which are also difficult to detach. A fetid discharge may also accompany RFM (Bierschwal, 1980). Other symptoms which may occur with RFM are increased pulse, respiration rates and body temperature; decreased appetite and milk secretion; diarrhea, general depression, and metritis with or without toxemia (Arthur, 1979).

Problems occurring subsequent to RFM. In the most severe cases of RFM, acute septic metritis, peritonitis, and/or septicemia may develop (Maas, 1982). These complications result in cow death for between 1 to 4% of afflicted cases. More common complications include metritis,

endometritis, pyometra, salpingitis, perimetritis, and oophoritis (Maas, 1982). Many authors (Pelissier, 1972; DuBois and Williams, 1980; Fincher, 1941), have reported the cause-effect relationship between RFM and metritis, and Erb et al. (1981a) found this relationship to have a direct correlation coefficient of 0.60. In addition, Erb et al. (1981b) also noted that a cow with RFM was 19 times more likely to contract metritis than one which did not have RFM. Researchers are almost evenly divided on the issue of RFM solely decreasing reproductive performance, however, they all agree that RFM accompanied by any of the above-mentioned complications will seriously impair subsequent fertility for a variable length of time. Measures of reproductive performance which are adversely affected include conception to first service (Pelissier, 1972; Pelissier, 1976; Moller et al., 1967; Erbet al., 1958), conception rate (Pelissier, 1972; Pelissier, 1976; Studer and Morrow, 1978), time for uterine regression (Marion et al., 1968; Shanks et al., 1979), calving interval (Muller and Owens, 1974; Erb et al., 1981a; Erb et al. 1981b), and the total number of days open (Muller and Owens, 1974; DuBois and Williams, 1980). Palmer (1932) and Maas (1982) both report a larger number of cows leaving herds due to reproductive inefficiency when cows had been affected with RFM. It should be noted that Lynn et al. (1966) reported less endometritis, and uterine epithelium and gland damage in suckled cows vs. the non-suckled group.

Hormonal profiles associated with RFM. Hormone concentrations in blood plasma and milk have been measured for cows calving with normal membrane expulsion and RFM. In a series of studies, plasma progesterone concentrations were higher (3.4 ± 0.3 vs. 2.3 ± 0.1 mg/ml),

estradiol-17β concentrations were lower (225 ± 22 vs. 288 ± 20 pg/ml) and plasma prolactin concentratoins were also lower (34 ± 3 vs. 42 ± 3 mg/ml) in cows with RFM as opposed to cows with normal expulsion (Chew et al., 1976; Chew et al., 1977). Furthermore, plasma concentrations of estradiol-17α increased by approximately one-third per day from days six to one prepartum in cows with RFM while the same profiles for cows not retaining decreased daily. However, only on day six prepartum were the plasma progesterone and estradiol-17β concentrations indicative of subsequent RFM (Chew et al., 1979). The only hormone difference detectable in milk secretions was for estradiol-17β which was lower than for cows which had RFM (Chew et al., 1976). Either a combination of low progesterone (<30 ng/ml) and low estradiol-17β (<100 pg/ml) or high progesterone (>7.9 mg/ml) concentrations were associated with a ten-fold increase in RFM as opposed to intermediate progesterone (4-8 ng/ml) and estradiol-17β concentrations greater than 99 pg/ml which were associated with normal release of fetal membranes (Chew et al., 1979). The authors state that this is perhaps suggestive that estradiol-17β sustains maturation of cotyledonary tissues. Also it is possible that mechanisms necessary for normal release must become functional by day six prepartum.

In a study where premature parturition was induced with dexamethasone, the same generalities mentioned above seemed to occur. Corticoid-induced parturitions resulting in RFM were characterized by initially high progesterone and low estrogen, followed by a delayed increase in progesterone and a greater rate of increase in the estrogens prepartum than that in blood plasma of cows either treated with

dexamethasone and not retaining or untreated controls (Chew et al., 1978). Another study in which early parturition was induced by ovariectomy, reported RFM for nearly all cows even if gestation continued to term unless supplemental progesterone was provided (McDonald et al., 1954). This supports the theory that RFM could be due to progesterone defficiencies prior to induced calving. However, Garverick et al. (1974) reported similar decreases in progesterone prior to corticoid-induced parturition as compared to cows calving normally.

Treatment of RFM. Various methods of RFM treatment have been developed over the years and these are reviewed by several authors (Palmer, 1932; Fincher, 1941; Kennedy, 1947; Weatherill, 1965; Arthur, 1979; Squire, 1980; Bierschwal, 1980). Although manual removal has been widely used as a means of treatment in the past, even early sources (Palmer, 1932) have questioned this practice. More recent studies indicate an increase in mortality rate (Bierschwal, 1980) and a decrease in conception rate at first service (38.5 vs. 50.0%; Banerjee, 1963) when membranes were manually removed as compared to no removal. Although these findings contraindicate manual removal, Ryazanskii (1978) has obtained acceptable results using electrical stimulation for membrane separation. Although there is some argument as to the efficacy of cutting exposed membranes off at the vulva, Bretzlaff (1982) reported that this practice is a more suitable alternative than manual removal.

An option available for placental expulsion is the inducement of uterine contractions with oxytocin, prostaglandin, or ergonovine (Arthur, 1979). However, Kennedy (1947) did not believe that uterine

motility affected membrane expulsion. These substances are discussed separately below.

Oxytocin is an octapeptid hormone produced in the posterior pituitary gland, which, since its discovery in pituitary extracts, has become widely known for its effect on smooth muscle contractility in male accessory glands, and the uterus and mammary gland of the female. Because of this effect on smooth muscle, oxytocin has been used to induce expulsion of retained placentae (Arthur, 1979 for review). However, several authors report a suitable effect only if oxytocin is administered prior to 24 hours postpartum (Arthur, 1979; Weatherill, 1965; Fincher, 1941). Oxytocin can be administered by several routes with the route affecting the uterine response. Federov (1973) reported a much larger response to epidural injections of oxytocin than with subcutaneous injections. Oxytocin injection could also aid in the prevention of uterine damage since Lynn et al.(1966) reported less endometritis and damage to the uterine epithelium and glands when cows were suckled compared to those not suckled postpartum. Oxytocin has also been utilized in conjunction with antibiotic preparations. Britt (1980) reports a satisfactory release of RFM following intra-uterine infusion of Oxytet-100 (Oxytetracycline, 100 mg/ml) when given prior to 24 hours postpartum. A similar finding is reported by Banerjee (1973); intrauterine infusion of oxytetracycline increased conception to first service from 50% for untreated controls to 70% for treated animals.

Prostaglandins (especially $PGF_2\alpha$) have widespread functions in the reproductive processes of livestock. Prostaglandin $F_2\alpha$ is well known as the factor causing luteal regression in cattle, sheep and horses

(McCracken et al., 1973) is involved in lutenizing hormone release, and has a role in vasocontriction and bronchioconstriction (see the following for review: Horton and Poysner, 1976; Goldberg and Ramwell, 1975; Lauderdale, 1974; Pharriss and Shaw, 1974; Eliasson, 1973; Hansel et al., 1976; Ramwell and Shaw, 1970). Although the action of $PGF_2\alpha$ on smooth muscle is believed to be the most important consideration for RFM therapy, several physiological factors indicate a possible role. These include the effectiveness of $PGF_2\alpha$ in inducing abortion (Sloan, 1976; Green et al., 1974) and parturition (Hendricks et al., 1977) , in treatment of bovine pyometra (Olson et al., 1984; Ott and Gustaffson, 1981; Braun,1980) and endometritis(Jackson, 1977), and a role in the onset of normal parturition (Edqvist et al., 1978; Fairclough et al., 1975; Putnam, 1983; Comline et al., 1974). $PGF_2\alpha$ release has also been noted with dexamethasone induced parturitions in cattle (Lindell et al., 1977). The existence of $PGF_2\alpha$ metabolism in maternal cotyledons of sheep (Keirse et al., 1976) and concentration changes in both maternal and fetal cotyledons at parturition in sheep (Liggins and Grieves, 1971), indicate a direct possible role of prostaglandin $F_2\alpha$ in placental release. In a study with cattle cotyledons, Leidl et al. (1980) related $PGF_2\alpha$ concentrations to dNA content. Findings indicate higher concentrations of $PGF_2\alpha$ in the fetal cotyledon as opposed to the maternal caruncle. Placentomes from cows with RFM were found to contain significantly lower $PGF_2\alpha$ concentrations than those from cows expelling the placenta normally. This observation was also found when parturition was induced or severe pathological conditions existed at calving. Cotyledons which were very difficult to separate showed lower PGF content than

those easily separated. Two clinical studies have been conducted where prostaglandin was injected postpartum in cows with RFM. Haidry and Fathala (1982) injected ten cows which had RFM with 25 mg $PGF_2\alpha$ (IM) following which the placenta was expelled after 2-4 days compared to 3-7 days in ten untreated controls. In another investigation, Herschler (1984) injected 1 mg fenprostalene (a $PGF_2\alpha$ analogue), subcutaneously, as soon as RFM was diagnosed. The fenprostalene treated group was compared to uterine flushings with disinfectants and/or antibiotics, antibacterial bolus insertion, manual removal of membranes, and no treatment. Results indicated fenprostalene reduced mean retention time (59.6 ± 3.6 vs. 97.9 ± 4.8 for controls), reduced infection rate (41 vs. 75%) and increased the percentage of placentas naturally expelled (94 vs. 72). However, Lindell et al. (1982) questioned the efficacy of exogenous prostaglandin because concentrations were found to increase to a high level prior to calving and remained so until from 7-38 days postpartum. It is interesting to note that oxytocin may mediate prostaglandin release from the uterus (Roberts and McCracken, 1976; Newcomb et al., 1977; Roberts et al., 1976; Chan, 1977; Armstrong and Hansel, 1959).

A third means of increasing uterine motility for expulsion of RFM is the injection of ergonovine, an ergot derivative (Arthur, 1979). Squire (1980) reported uterine contractility in response to ergonovine to be much greater than that induced by oxytocin.

Other methods used in the treatment of RFM involve estrogens which increase the sensitivity of the uterus to oxytocin and provide several anti-infective properties (Arthur, 1979 for review). Stilbesterol has

been reported to decrease the 60 day nonreturn rate in cattle (Moller et al., 1967), while other researchers found no effect of estrogen on reproductive performance (Dyrendahl et al., 1977). When RFM is accompanied with infection, antibiotics may be indicated. Sulfonamide or tetracycline infusion into the uterus has been widely reported as well as intramuscular injections of penicillin (Arthur, 1979). Antibiotics should be chosen with care in that drug treatment may cause prolonged retention or delayed involution and time to first estrus (Sequin et al., 1974). In cases of severe metritis, siphonage of fluid prior to intrauterine therapy may be advisable (Weatherhill, 1965). Other treatments recommened include lavage with hot water only (Bierschwal, 1980), or with Betadine solution or Zepharin solution; local infusion of the proteolytic enzymes acroflavin or proflavin (Weatherill, 1965; Kennedy,1947), and intravenous infusion of dextrose and calcium gluconate even in the absence of milk fever or ketosis (Fincher, 1941). Fincher (1941) also indicates that intrauterine infusions of bismuth-iodide solutions in oil may be benficial in treating RFM-related problems.

Prevention of RFM. Prevention of retained placenta involves expert management and dietary efficiency. Britt (1980) recommends a thorough vaccination program, providing clean dry calving areas, and reducing stress as much as possible. Nutritional requirements for dry cows are reviewed by Britt (1980) and Maas (1982). In areas of selenium deficiency the benefits of feeding selenium and/or injecting vitamin E on subsequent RFM cases is very clear (Trinder et al., 1969; Trinder et al., 1973; Julien et al., 1976). Some researchers have found decreased incidence of RFM when oxytocin was infused intravenously or injected

repeatedly in cows beginning immediately after parturition (Kuhnle, 1981; Curtis, 1973). Most researchers agree that a 30 day postpartum reproductive exam is helpful in preventing decreased reproductive performance in a herd regardless of membrane expulsion status.

2. Uterine Motility

In Vivo Postpartum Motility. Uterine motility in postpartum cows has been recorded by a number of researchers under a variety of conditions. In a very comprehensive study, Jordan (1952) measured motility in 43 normal calving cows and motility of cows calving with varying problems. Contractility in normal cows (measured with an air-filled intrauterine balloon) averaged 13.3 contractions per hour with an amplitude of 20.2 mm Hg and a duration of 1.14 min. when measured prior to 12 hours postpartum. A report by Venable and McDonald (1958) indicates a similar frequency but the amplitude was much larger (20-40 mm Hg with durations of 1-25 minutes). Benesh (1952) recorded the highest frequency of any investigator (16-20 contractions/hr). As time after calving increased, uterine motility rapidly decreased. Recordings taken at 24 hours postpartum revealed an average frequency of 9 contractions per hour, had an average amplitude of 16 mm Hg, but average duration of contraction was slightly longer (1.26 min). Within two to three days, postpartum average contraction frequency had decreased to four per hour and average amplitude was 9 mm Hg (Jordan, 1952). These findings are in agreement with Venable and McDonald (1958) who found a frequency of less than 1 contraction per hr. by 42 hours postpartum. Benesh (1952) and

Giama (1975) observed that contractions were almost entirely absent on the fourth postpartal day.

Although investigators reported very similar motility patterns from normal calvings, there is some disagreement about the motility associated with RFM. Jordan (1952) reported greatly reduced or almost entirely absent motility in three cows with RFM, a situation which remained so until approximately three days postpartum. When parturition was induced with dexamethasone (Martin et al., 1981), cows with RFM showed an increased amount of uterine work over cows calving naturally with no RFM. Two dexamethasone treated cows not retaining fetal membranes showed the same level of contractility as the RFM group, as did one untreated cow which retained. Piper et al. (1978) also found uterine motility to be increased by experimentally produced RFM. It is also noted that motility from cows with experimentally produced RFM does not significantly differ in frequency or magnitude of contraction from that of cows retaining from other cause. Venable and McDonald (1958) also found increased motiity in cows with RFM produced by corpus luteum ablation, calving between 253 and 275 days of gestation. Cows aborting show similarly increased motility regardless of RFM (Jordan, 1952; Venable and Mcdonald, 1958). As expected, cows calving with milk fever show less motility, if any at all, several hours postpartum, although contractility resumed gradually following intravenous calcium administration (Jordan 1952; Martin et al., 1981). Cows experiencing difficult calvings did not differ from normally calving cows in motility (Giama, 1974).

Other investigations into postpartum cow motility have been more concerned with reactions under certain drug influences. Several studies have reported the effect of oxytocin on myometrial functions. Jordan (1952) reports an increased force and frequency of contraction within 20 seconds when 30 IU of pituitary extract was injected, intravenously. The response was greatest when the injection was given soon after parturition; the effect remained constant for about one hour and almost no effect was observed within two hours post-injection. A similar response was observed by Chen et al. (1966) for mechanical and electrical methods of recording. This effect is also observed when calves are allowed to nurse during recording (Benesh, 1952; Venable and McDonald, 1958) although the response may be more highly variable. Eiler et al. (1984) reported an 875% increase in uterine motiity following a 200 IU injection of oxytocin, intramuscularly. This increase was reported to be significantly above baseline values until 100 minutes after treatment.

The response of the postpartum uterus to oxytocin also appears to be affected by the physiological state of the cow. In the study by Jordan(1952), the cows with RFM exhibited a lesser response to pituitary extract than did cows with normal expulsion. Likewise, in one cow with parturient paresis, the effect was slight until recovery from low blood calcium levels was nearly complete. Cows which had aborted were more responsive to oxytocin than were normally calving herdmates.

Oxytocin has a marked influence on postpartum cow uterine contractility regardless of the route of administration, although there are differences in reactivity among routes. Giama et al. (1976) reported a

greater response to intravenous injections (30 IU) administered to postpartum (5-6 days) cows when compared to epidural, intramuscular, or subcutaneous injectons of the same dosage. Intravenous injection increased frequency by approximately four times and was characterized by contractions of 48 Torr amplitude and five minute duration. Intramuscular injection resulted in biphasic contractions of 40 Torr with duration varying from one to five minutes. Injections given subcutaneously exhibited the same motility pattern as intramuscular but amplitude was reduced (28 Torr) with a duration of about two minutes. Epidural injections resulted in lower amplitude contractions but higher frequency when compared to intravenous injection. Fedorov (1973), however, reported a more marked response to epidural injection of oxytocin than subcutaneous injection when administered to cows from days two to four postpartum.

Little work has been found on the effects of other drugs on uterine motility in postpartum cows. Estrogen injection at parturition was reported by Giama (1977) to increase uterine motility on the first postpartal day when compared to non-treated cows. Although Jordan (1952) did not observe an increase in motility due to estrogen treatment alone, both authors (Jordan, 1952; Giama, 1977) agree that estrogen injections preceding oxytocin injection enhance the response by the octapeptide hormone. In contrast, even though progesterone injection caused no visible change in motility, Jordan (1952) reported a decreased response to intravenous pituitary extract injection when this treatment followed the steroid injection. Further, Jordan (1952) found no effect of intravenous injection of testosterone (200 mg) on uterine motility, nor

did testosterone modify the oxytoxic response. Ergometrine (3 mg, 6 mg, or 12 mg; IV) initiated only a slight response from postpartum bovine uterus, while acetylcholine (3 cc of a 0.1% solution; IV) initiated a strong but brief (1-2 min.) contraction (Jordan 1952). Epidural anesthesia (procaine, 6 cc of a 2.25% solution as procaine hydrochloride) did not alter uterine activity but served to decrease restlessness of the cow.

Although the uterotonic activity of $PGF_2\alpha$ is well established in pregnant women (Bygdeman et al., 1974) and in surgically aborted goats (Cooke et al., 1977), little work has been done in the postpartum bovine. Eiler et al. (1984) found no significant increase in measures of motility when $PGF_2\alpha$ was injected intramuscularly at 48 hours postpartum. A moderate response was elicited when prostaglandin (10 mg) was administered intravenously. $PGF_2\alpha$ seemed to reduce the response obtained from a subsequent injection of oxytocin as opposed to injection of oxytocin preceding prostaglandin injection.

It is important to mention that as a result of some of the previously reviewed studies, several researchers have reached the conclusion that placental retention is not a condition resulting from decreased uterine motility (Piper et al., 1978; Martin et al., 1981; Venable and Mcdonald, 1958).

In Vivo Open Cow Motility. Information concerning uterine contractility in open cows in vivo is extremely limited. Studies on motility during the different stages of the estrus cycle have indicated increased mechanical and electrical activity of the open cow uterus nearing estrus or during estrus (Chen et al., 1966; Ruckebusch and Bayard, 1975; Evans

and Miller, 1936). Chen et al. (1966) reported the occurrence of slow regular contractions of 4-5 minute duration during the luteal phase of the estrus cycle and contractons of great magnitude lasting 4-5 minutes and occurring at 5 to 6 minute intervals during early to late estrus as recorded by an open-ended, air-filled catheter inserted into the cervix. Uterine activity developed into synchronized phases during estrus as recorded by electromyography (Ruckebusch and Bayard, 1975). In contrast, Hays and VanDemark (1953) found no significant differences in motility measurements taken during the estrous cycle.

The effects of $PGF_2\alpha$, oxytocin, adrenalin, noradrenaline, and ergometrine have been investigated in open cows. Eiler et al. (1981) and Chen et al. (1966) have reported significant increases in uterine contractility following intravenous injection of oxytocin as measured by a fluid-filled intrauterine balloon and open-ended catheter (air conduction), respectively. Chen et al. (1966) reported a greater response to oxytocin when cows were in or near estrus. A similar response to oxytocin injection is obtained when recording motility by electrical activity (Chen et al., 1966; Ruckebusch and Bayard, 1975). Ruckebusch and Babapour (1976) and Eiler et al. (1981) have established that $PGF_2\alpha$ does increase myometrial activity of the open cow uterus. However, Eiler et al. (1981) noted that the open cow uterus does not respond to $PGF_2\alpha$ in a dose-response relationship, but becomes relatively refractory to large or repeated dosages of the prostaglandin. It was also noted that cows which had become refractory to $PGF_2\alpha$ administration were, however, responsive to oxytocin. Epinephrine and norepinephrine when injected intravenously caused a brief increase in uterine electrical activity,

followed by a marked inhibition of motility for two to four minutes (Ruckebush and Bayard, 1975). Intramuscular injections of ergometrine (0.005-0.015 mg) seem to increase uterine motility in open cows more dramatically than any other drug. A marked increase in uterine activity as evidenced by increased uterine tone and amplitude was observed within ten minutes after drug injection, lasting 2.5 to 3.5 hours (Voskoboinikov and Kurchevskii, 1973). The effect of various hormones, especially $PGF_2\alpha$, and changes during the estrus cycle on uterine motility in ewes and goats is well documented (Lehrer and Schindler, 1974; Rexroad and Barb, 1975; Jones and Knifton, 1975; Mitchell et al., 1976; Lye and Porter, 1978).

Bovine Uterine Motility in Vitro. Once again, little literature has been found in which bovine uterine motility has been measured in vitro. Likewise, no study found in this literature search utilized isolated uterine horns, therefore, investigations reported are those which involved uterine strips. This increases the difficulty of comparison because contractility patterns have been found to differ among transverse, circular, and longitudinal sections (King, 1927). The difficulty in preparing suitable strips of bovine uterus also supports investigation into better methods of in vitro recording of uterine motility (Patil et al., 1980).

Tissue strips of bovine uterus have been suitably maintained in Tyrode's Solution (Patil et al., 1980) and Kreb's-Ringer bicarbonate solution in vitro (Singh et al., 1979). In several studies the effect of $PGF_2\alpha$ on uterine strips has been evaluated. The threshold dose for $PGF_2\alpha$ is reported to be 10 ng per ml of culture solution for cattle

(Bobrik, 1973). In the study by Singh et al. (1979), when motility of uterine strips from open cows (follicular phase) was compared to that of uterus from cows in mid-gestation, open cow motility was significantly higher in amplitude and frequency. In contrast, uterine strips from pregnant cows exhibited 50% less frequency and 67% less amplitude. However, the uterine strips from pregnant cows reacted much more strongly to $PGF_2\alpha$ than did uterine strips from follicular-phase open cows, which reacted slowly and mildly. The response lasted from 8 to 10 minutes before returning to baseline values.

In another study, Patil et al. (1980) reported the effects of oxytocin and $PGF_2\alpha$ on uterine motility of strips under different phases of the estrus cycle. Concentrations of prostaglandin used were 5, 50, and 500 ng/ml and 0.25, 2.5 and 25 mU/ml of culture solution for oxytocin. Increasing dosages for oxytocin exhibited a linear dose-response relationship, whereas, the highest prostaglandin dose produced the least uterine response. Spontaneous activity of strips from follicular phase horns was somewhat higher than that of luteal phase strips or those associated with ovarian cysts. $PGF_2\alpha$ caused an immediate increase in frequency and uterine tonus from initial values (9 contractions/20 min, amplitude of 12 mm). The duration of increased tonus was 15 minutes for this group. Likewise, oxytocin caused a similar increase in uterine tonus and contraction frequency but the effect was of shorter duration than observed with prostaglandin. Strips from horns obtained from luteal phase cows exhibited spontaneous activity which was more irregular with a lower amplitude than during the follicular phase. The frequency of contraction was 6 per 10 minutes with an amplitude of 5 mm

prior to drug treatment. Both oxytocin and $PGF_2\alpha$ stimulated increased activity. $PGF_2\alpha$ caused an increased uterine tonus for 11, 18, and 17 minutes for the 5, 50, and 500 ng/ml solution doses, respectively. In the group of strips from animals with ovarian cysts, the spontaneous contractions observed were the most irregular, with strips from two cows showing no "real" contractions during the recording period. Average contraction frequency was 6 per 10 minutes, averaging 6 mm in amplitude. Prostaglandin treatment caused the least response in uterine contractility in this group, increasing tonus for only 8 minutes. Oxytocin administration had a stimulatory effect on all tissue strips.

CHAPTER II.

THE EFFECT OF FENPROSTALENE AND OXYTOCIN ON UTERINE MOTILITY IN EARLY POSTPARTUM AND OPEN CYCLING COWS

A. INTRODUCTION

Drugs which stimulate increased uterine contractility have found widespread use in the treatment of retained fetal membranes (RFM). In the past, oxytocin and an ergot derivitave, ergonovine, have been used for this purpose (Arthur, 1979, for review). With the discovery of the prostaglandins, especially prostaglandin $F_2\alpha$, and the uterokinetic effects of these drugs, some interest has been expressed as to the effectiveness of $PGF_2\alpha$ as a treatment of RFM.

Several physiological and clinical findings indicate a possible role for $PGF_2\alpha$ in RFM treatment. Hormonal profiles of cows with from RFM, because of corticoid induced parturition or other cause, show a significantly higher plasma level of progesterone compared with profiles of cows with normal postpartum release (Chew et al., 1977; Chew et al., 1978; Chew et al., 1979a; Chew et al., 1979b). The leuteolytic properties of $PGF_2\alpha$ could be of benefit if this were due to a persistant corpus luteum (Horton and Poysner, 1976). $PGF_2\alpha$ has been used as an abortifacient (Sloan, 1976; Green et al., 1974), and as a treatment of bovine pyometra (Olson et al., 1984; Ott and Gustaffson, 1981; Braun, 1980) and endometritis (Jackson, 1977). Not only does $PGF_2\alpha$ have a role in natural (Edquist et al., 1978; Fairclough et al., 1975; Putnam, 1983;

Comline et al., 1974) and corticoid-induced parturition (Lindell et al., 1977), but it seems that placental release is also possibly regulated by the prostaglandin. Kierse et al. (1976) reported evidence of $PGF_2\alpha$ metabolism in ovine cotyledons while Liggins and Grieves (1971) noted $PGF_2\alpha$ concentration changes in maternal and fetal cotyledons at parturition. Futher, Leidl et al. (1980) found decreased levels of $PGF_2\alpha$ in placentomes of cows which retained as compared to those where normal expulsion occurred. Clinically, cows with RFM which were injected with $PGF_2\alpha$ retained for 2-4 days as compared to untreated controls which retained 3-7 days (Haidry and Fathala, 1982). Herschler (1984) reported a reduced mean retention time and infection rate, and an increased number of naturally expelled placentas when cows were injected with fenprostalene, a $PGF_2\alpha$ analogue, as opposed to various other treatments and untreated controls. It must be noted, however, that $PGF_2\alpha$ levels following parturition are naturally high and remain so from 7 to 38 days postpartum.

It would seem that if a drug was effective in causing release and/or expulsion of RFM, this effect would largely be due to an increase in uterine motility. The effect of oxytocin (or pituitary extract) on uterine motility in postpartum cows is well documented (Jordan, 1952; Venable and McDonald, 1958; Chen et al., 1966; Benesh, 1952; Eiler et al., 1984; Giama, 1975, 1976, 1977; Federov, 1973). In contrast, little work has been done in postpartum cows on the effect of $PGF_2\alpha$. Eiler et al. (1984) found no significant response to an intramuscular injection of $PGF_2\alpha$ at 48 hours postpartum, although a moderate response was observed from an intravenous injection.

Ruckebusch and Babapour (1976) and Eiler et al. (1981) have established that $PGF_2\alpha$ does significantly increase uterine motility of the open cycling cow. Eiler et al. (1981) noted that the response did not follow a dose-related trend and that the uterus was relatively refractory to large or repeated injections of the drug. It was also noted that the PG-refractory uterus was, however, responsive to oxytocin. Chen et al. (1966) found an estrous stage-related response when open cows were injected with oxytocin.

The objective of this study was to evaluate the effect of a long half-life (18-24 hrs. from a subcutaneous injection), high activity (25 times the leutolytic activity of $PGF_2\alpha$) prostaglandin $F_2\alpha$ analogue, fenprostalene, on uterine motilty of postpartum and open, cycling cows as compared to the effect of oxytocin.

B. MATERIALS AND METHODS

Uterine motility was measured in eight early-postpartum cows (six mixed- breed beef and two grade holstein cows) by the intrauterine balloon technique. All cows were maintained on fescue pasture and hay prepartum with mineral supplementation but no additional protein. Uterine motility measurements were conducted in two consecutive days, beginning between twelve and twenty-four hours postpartum on day one and between thirty-six and fourty-eight hours postpartum on day two. Each cow was separated from her calf and restrained in a darkened chute to reduce activity. Drinking water was available to the cow during the entire recording period.

An epidural injection of Lidocaine with epinephrine (0.5 ml per 100 pounds body weight as Lidocaine hydrochloride - 2%; American Veterinary Products, Inc., Fort Collins, CO) was administered at the onset and mid-point of each recording period. The area around the vulva was cleansed with antiseptic solution. Balloons were prepared by tying a latex condom on a modified 32 fr. Foley catheter. Any retained fetal membranes, if present but not visible, were detected at this time. All intrauterine devices were flushed with Novalsan solution prior to trans vaginal placement deep in the uterine horn. As an attempt to prevent uterine contractions from expelling the balloon, the Foley cuff was inflated with 30 cc water and the cervix was retracted with and clamped closed around the catheter by two vulcellum forceps. The catheter was then attached to a length of tygon tubing, the intrauterine balloon was distended with water (about 80 cc) to give a slight positive pressure at the level of the uterus, and the tubing was connected to a pre-calibrated pressure transducer (Model P-1000B, 10 mm Hg to 100 mm Hg, Narco Bio-Systems Inc., Houston, Tx.). Treatments were administered over approximately a six hour period of time and are shown in figure 1. On each day a one hour baseline recording with no treatment was followed by the hormone injections. The injections on day one were fenprostalene (Bovilene™ Sterile Solution Diamond Laboratories Inc., Des Moines, Iowa, lot no. 100047), 1 mg intramuscularly, after which motility was recorded for two hours; fenprostalene, 1 mg intravenously and motility recorded for thirty minutes; and oxytocin (Vedco, Inc., Overland Park, KS., lot no. 6075), 40 units intravenously followed by a thirty minute to one hour recording time. Injections on day two were different than day one

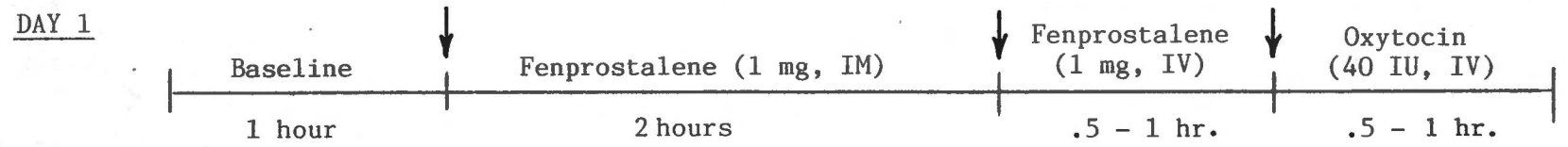


Figure 1. Schematic of treatment administration during in vivo measurement of uterine motility in early postpartum and open cycling cows. Arrows indicate injection times.

DAY 2

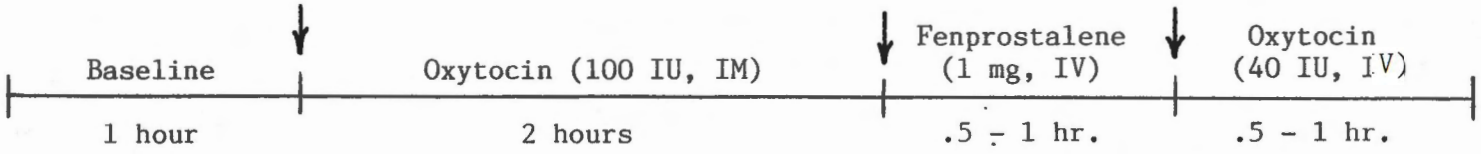


Figure 1 (continued)

in that oxytocin (100 units, intramuscularly) replaced fenprostalene (0.1 mg, IM) as the first treatment. During recording, any events other than or accompaning uterine contraction were noted on the tracing (i.e. urination, defication, nervousness, etc.). Each cow was returned to pasture and her calf following each day of experimentation.

A similar study was conducted to evaluate uterine motility in six lactating holstein cows. All cows were beyond peak production (average milk production of approximately 40 pounds/day) and were on a balanced ration of corn silage, sorghum-sudan grass as green chop, alfalfa hay, and concentrate. Cows were restrained, and experimental procedure conducted as previously mentioned for the postpartum cows except as follows. Because there was no parturition related cervical dilation, a 12 or 16 fr. foley catheter with the attached condom was passed through the cervix into the lumen of one uterine horn by the recto-vaginal technique. Balloon fluid volume was standardized as for the postpartum cows as well as by rectal palpation of the distended balloon and thus the horn itself. It was not necessary to mechanically retract the cervix or clamp it closed since the catheter cuff could be sufficiently inflated to retain the balloon in the uterus. Treatments were as discussed for the postpartum cows (Fig. 1). Following contractility measurement on day one the ovaries were palpated to estimate the stage of the estrous cycle of each cow.

The following measurements were derived from each physiograph recording for intervals of five minute duration. The area under the tracing was measured by a digitizer (Videoplan, Carl Zeiss, Inc., Thornwood, N. Y.) and is reported as mm^2 for each time interval. Frequency

of contraction is reported as counts per five minutes with average amplitude [mm of mercury (Hg)] and average duration (seconds) of contraction also given. Uterine tone was calculated by measuring the differential in slope between the beginning and end of each time period and that value was then added to the previous tonus level to obtain a continuous tonus change reported in mm of mercury.

Expermental design was a time-response relationship. Statistical analysis was by SAS (SAS Institute, Cary, N.C.). The following general model and minor modifications thereof was used in the analysis: Y_{ijklm} = μ + treatment $_i$(day $_j$) time$_k$ (treatment $_i$) + cow status$_l$ + treatment $_i$ (day $_j$)*cow status$_l$+ e_{ijklm} , where:

Y_{ijklm} = amplitude, duration, uterine tone, frequency, and area as affected by the i^{th} treatment within the j^{th} experimental day, the k^{th} sampling time within the i^{th} treatment, the l^{th} cow status and the m^{th} observation

μ = the estimate of the mean amplitude, duration, uterine tonus, frequency and area for the population;

treatment$_i$(day $_j$) = the effect of the i^{th} treatment within the j^{th} experimental day on amplitude, duration, frequency, uterine tone and area;

time$_k$(treatment $_i$) = the effect of the k^{th} sampling time within the i^{th} treatment on amplitude, duration, frequency, uterine tone, and area;

cow status$_l$ = the effect of the l^{th} cow status (open or early postpartum) on amplitude, duration, frequency, tone, and area;

and e_{ijklm} = random error.

Mean separation was with orthogonal contrasts or Student-Newman-Keul's test. Probability of significance is reported at the five percent level of significance unless otherwise indicated.

C. RESULTS

1. Postpartum Cow Motility

Of the eight postpartum cows in which uterine motility was measured, one cow was excluded from statistical analysis due to technical problems encountered during recording. One cow of the remaining seven suffered from retained fetal membranes for eleven days following parturition. Because only one cow retained, no statistical comparisons were possible for motility in cows with normal postpartum placental release and motility associated with retained fetal membranes. However, the cow which retained exhibited substantially higher spontaneous activity and seemed more reactive to exogenous hormone treatment than the cows expelling the placenta within twelve hours postpartum (Figures 2-5). On the first experimental day, mean baseline area for the cow with retained placenta was 1201.1±49.9 compared to 425.4±28.7 mm^2 for cows with normal explusion. This difference in area also was seen on day 2 (1203.3±85.9 vs 459.9±33.3 mm^2, RFM vs normal). When compared over time, RFM motility was generally higher for the experiment duration. An exception existed following intravenous injection of fenprostalene on day 1 where average amplitude and duration of contraction became similar, remaining so until oxytocin administration (Figure 3). Intramuscular injection of oxytocin caused an increase in area of approximately 1000 mm^2 for cows with normal placental release and the

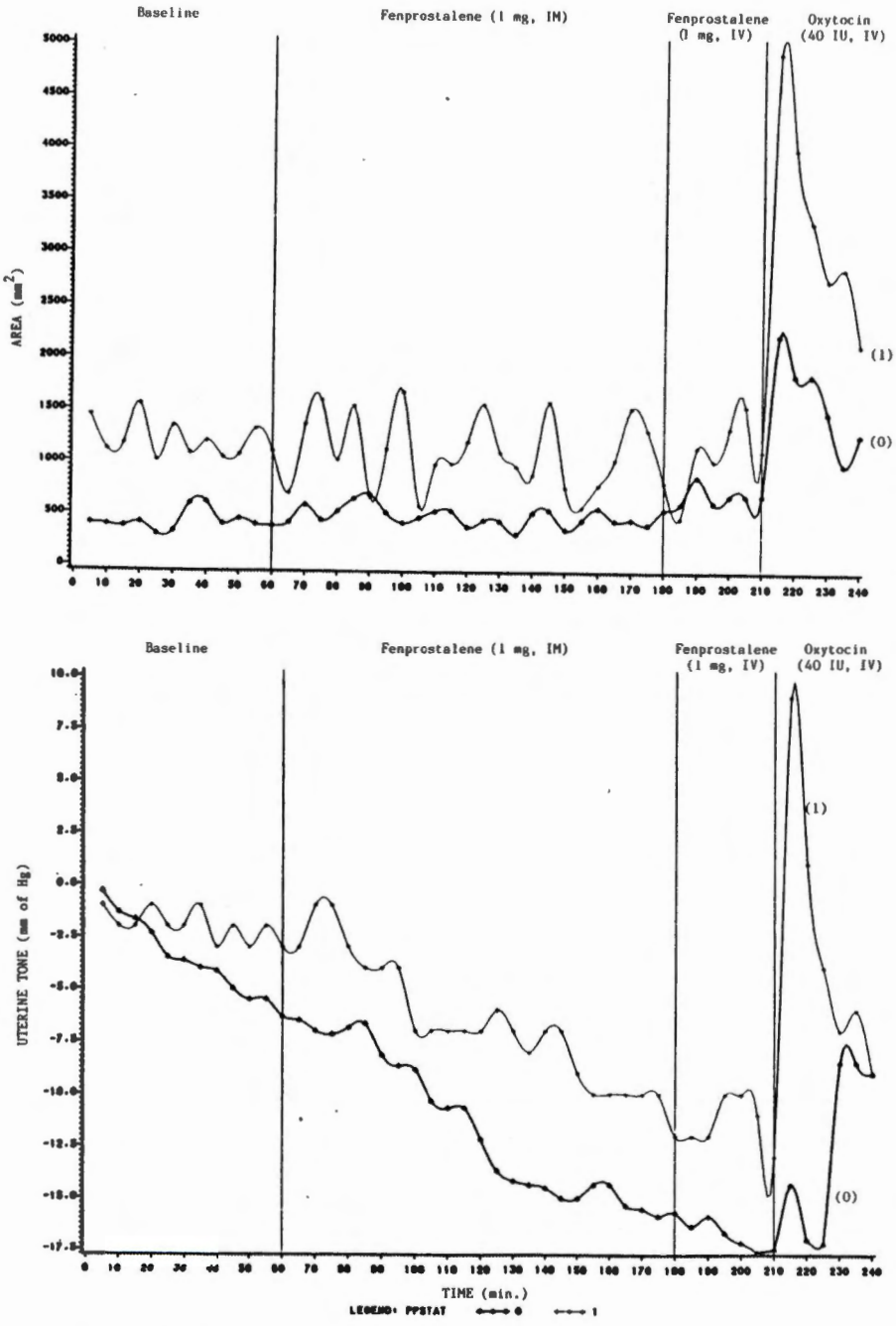


Figure 2. Effect of various hormonal treatments on uterine motility as indicated by area and uterine tone of one cow retaining fetal membranes and six cows with normal postpartum release, beginning between twelve and twenty-four hours postpartum. Vertical lines represent the time of drug treatment. PPSTAT 0 = normal expulsion group. PPSTAT 1 = RFM.

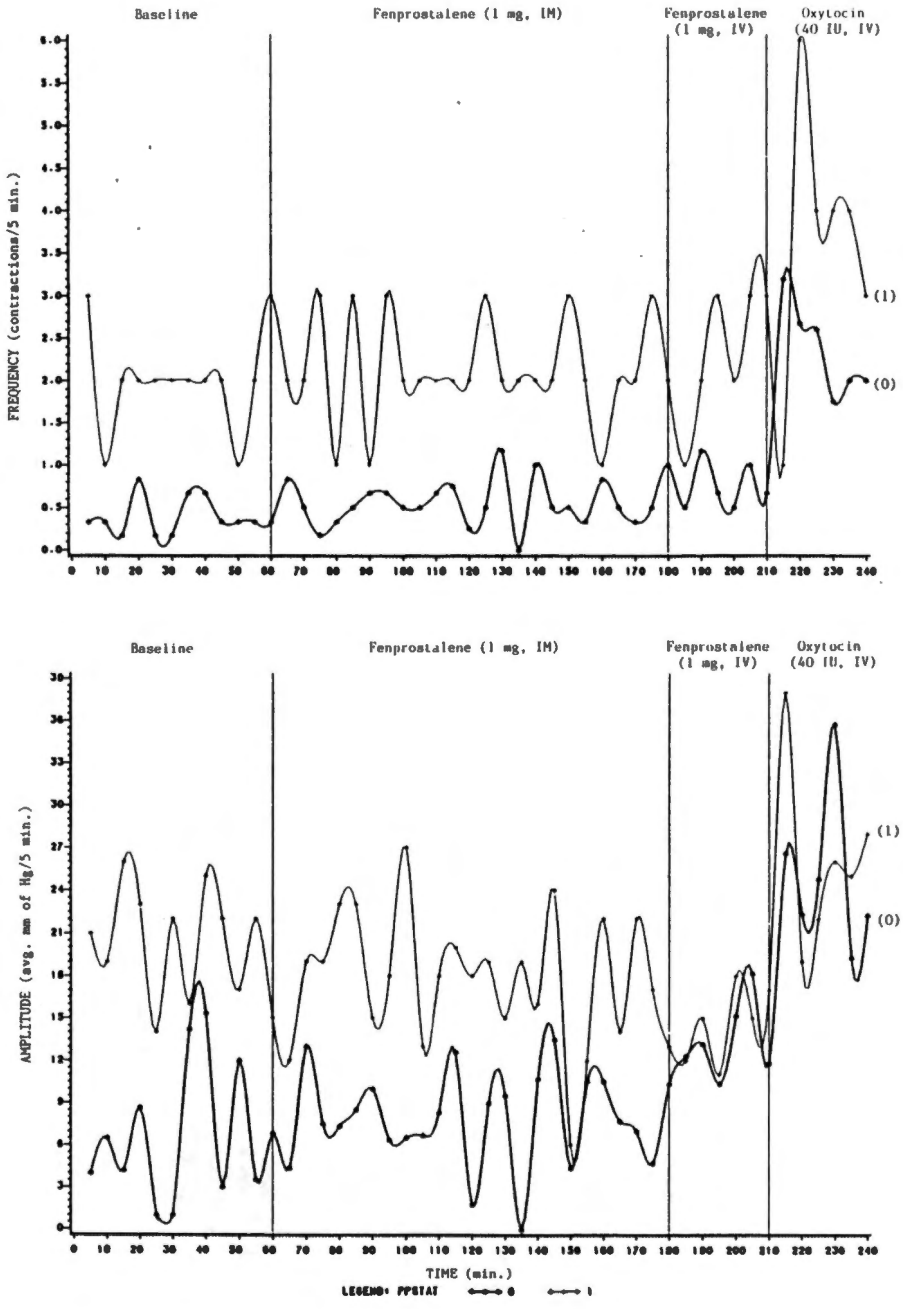


Figure 3. Effect of various hormonal treatments on uterine contraction variables of one cow retaining fetal membranes and six cows with normal postpartum release, beginning between twelve and twenty-four hours postpartum. Vertical lines indicate the time of drug injection. PPSTAT 0 = normal expulsion group. PPSTAT 1 = RFM.

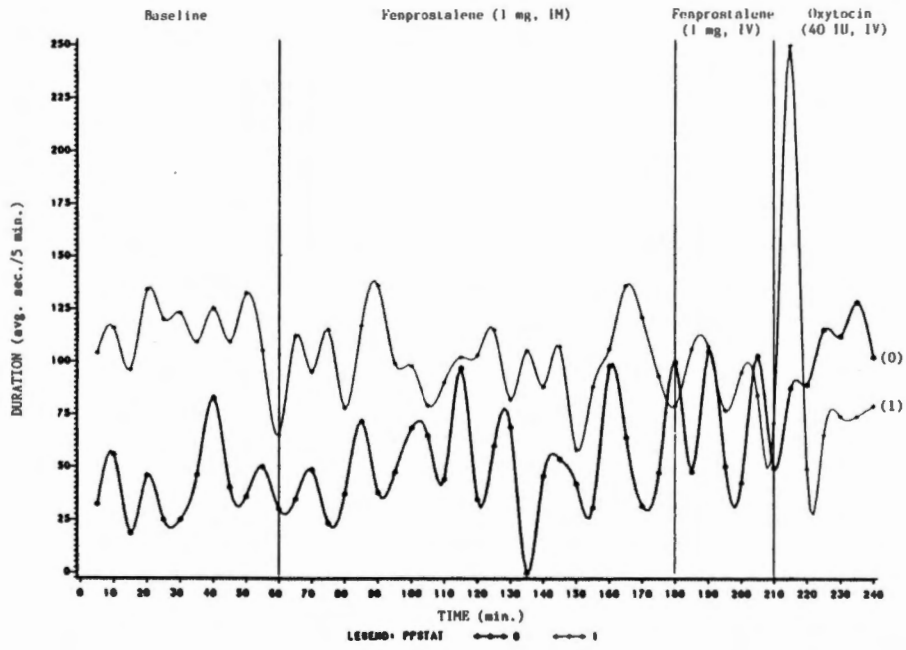


Figure 3 (continued)

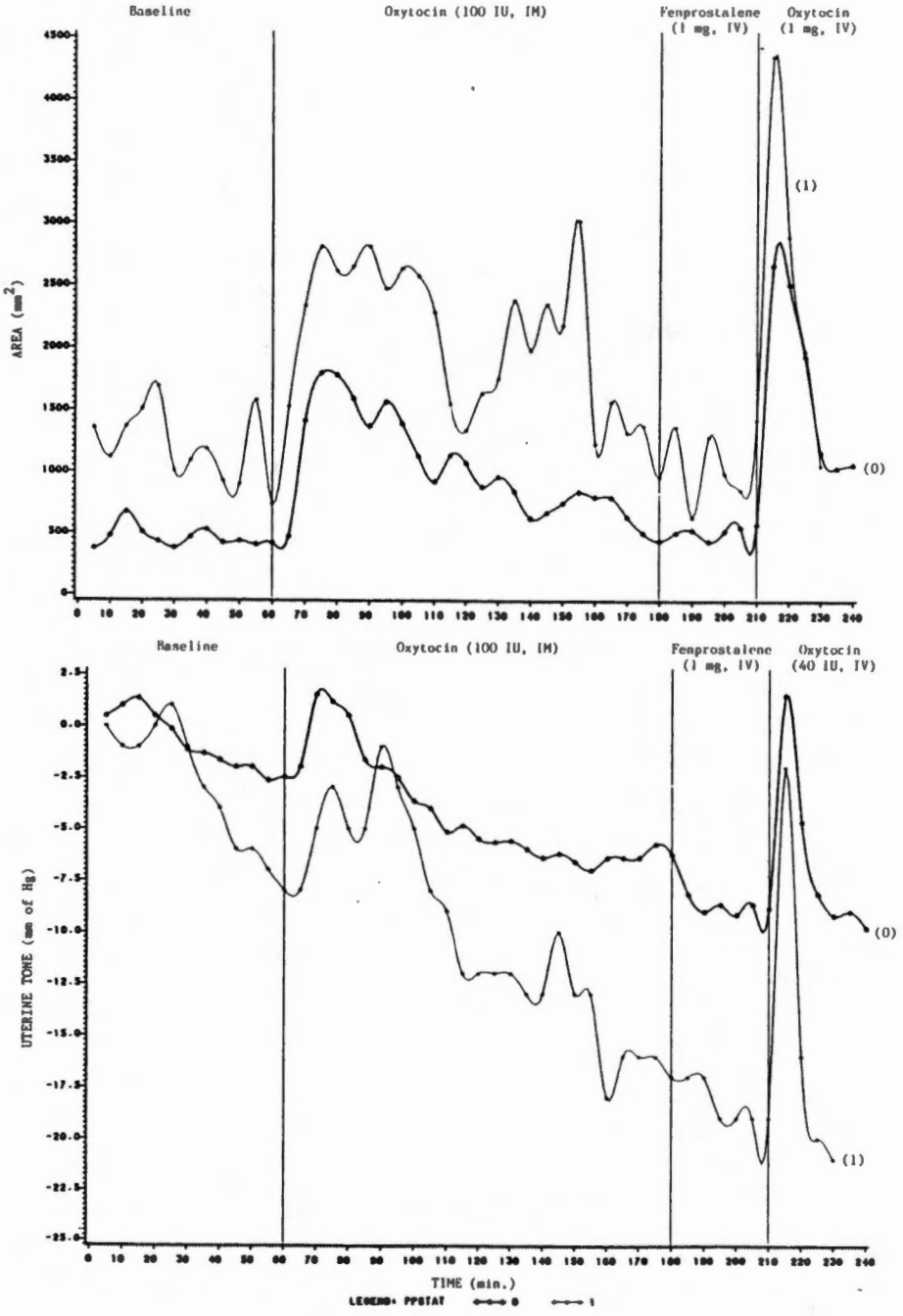


Figure 4. Effect of various hormonal treatments on uterine motility as indicated by area and uterine tone of one cow retaining fetal membranes and six cows with normal postpartum release, on the second postpartal day. Vertical lines represent the time of drug treatment. PPSTAT 0 = normal expulsion group. PPSTAT 1 = RFM.

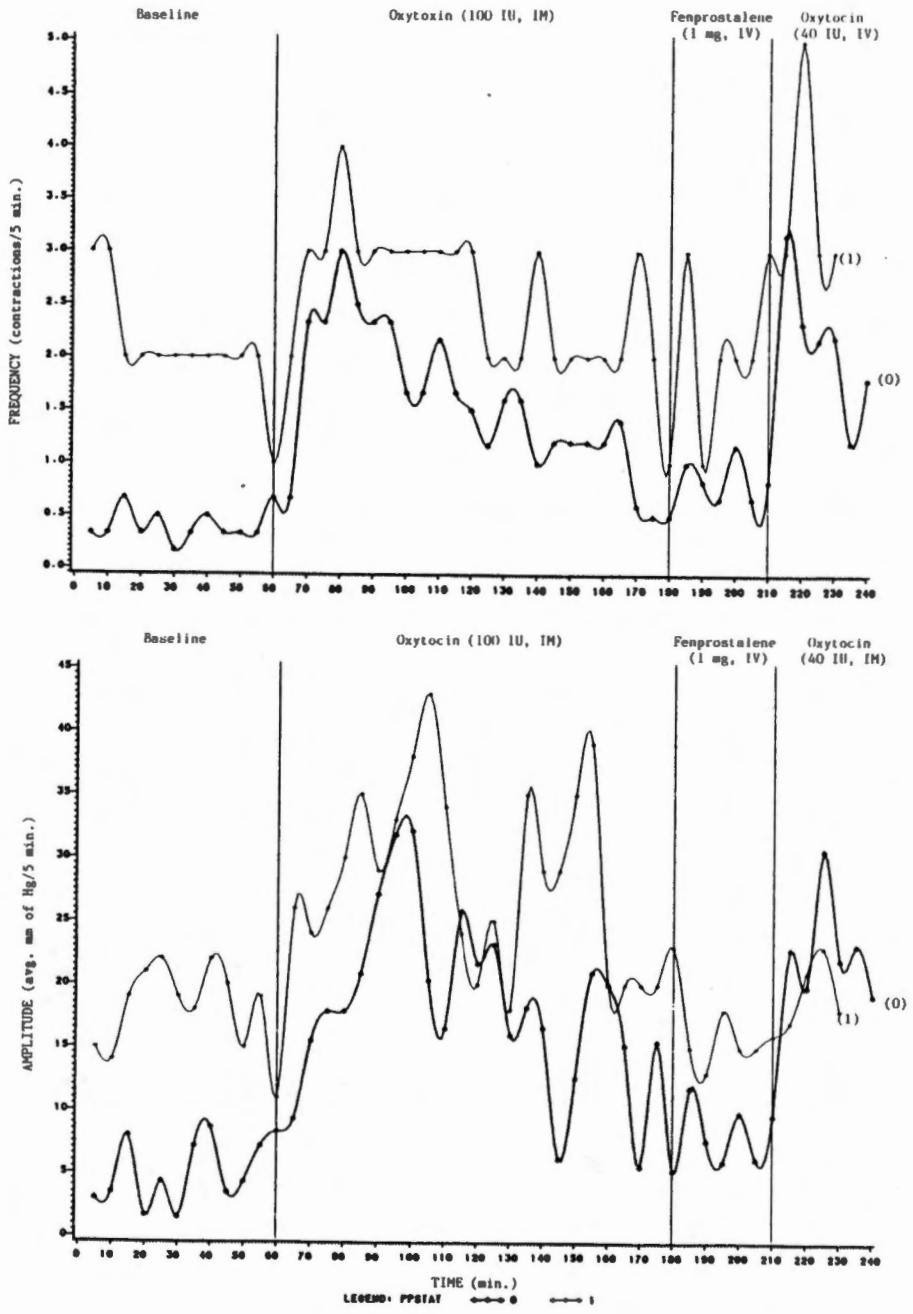


Figure 5. Effect of various hormonal treatments on uterine contraction variables of one cow retaining fetal membranes and six cows with normal postpartum release, on the second postpartal day. Vertical lines indicate the time of drug treatment. PPSTAT 0 = normal release group. PPSTAT 1 = RFM.

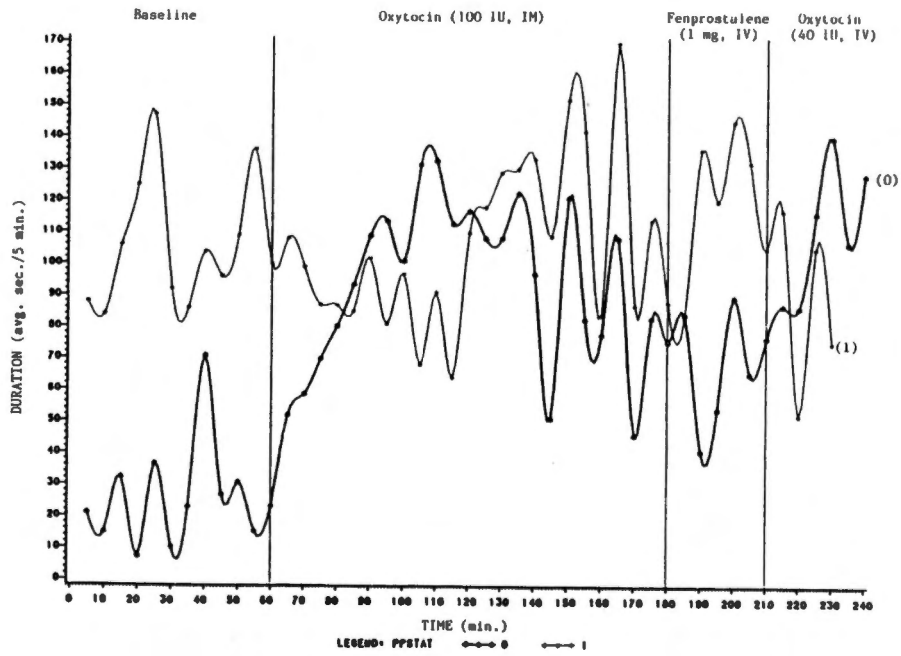


Figure 5 (continued)

cow with RFM. Once again, the RFM cow exhibited a higher level of contractility, although a more dramatic decline in uterine tone was evident (Figure 4). Also, as seen in figure 5, duration of contraction became similar for both groups at an earlier time than on the first day of experimentation.

As a group a general trend was observed toward increased mean values for the three contraction variables from one treatment to the next on day one. Fenprostalene (day 1) caused a slight (nonsignificant) increase in area, but failed to alter the trend of decreasing uterine tone (Figure 6). There was, however, a significant ($P<0.05$) increase in mean frequency, amplitude, and duration of contraction by fenprostalene (IV) over baseline measurements (Figure 7). Oxytocin (IV) caused a significant ($P<0.02$) increase in all motility variables measured (Figures 6 and 7). The postpartum cow uterus was also highly responsive to oxytocin at thirty-six to fourty-eight hours after calving. An intramuscular injection of oxytocin (100 units) caused a significant ($P<0.05$) increase in mean baseline area, frequency, amplitude, and duration of contraction (Figures 6 and 7). In contrast, a subsequent intravenous injection of fenprostalene caused no noticable changes. Values for area, frequency, and amplitude had returned to baseline levels at this time. Intravenous injection of oxytocin once again caused a marked increase in most measures of motility, similar to the response on day 1. Mean comparisons and differences are shown in table A-1 for treatments within each day and across days.

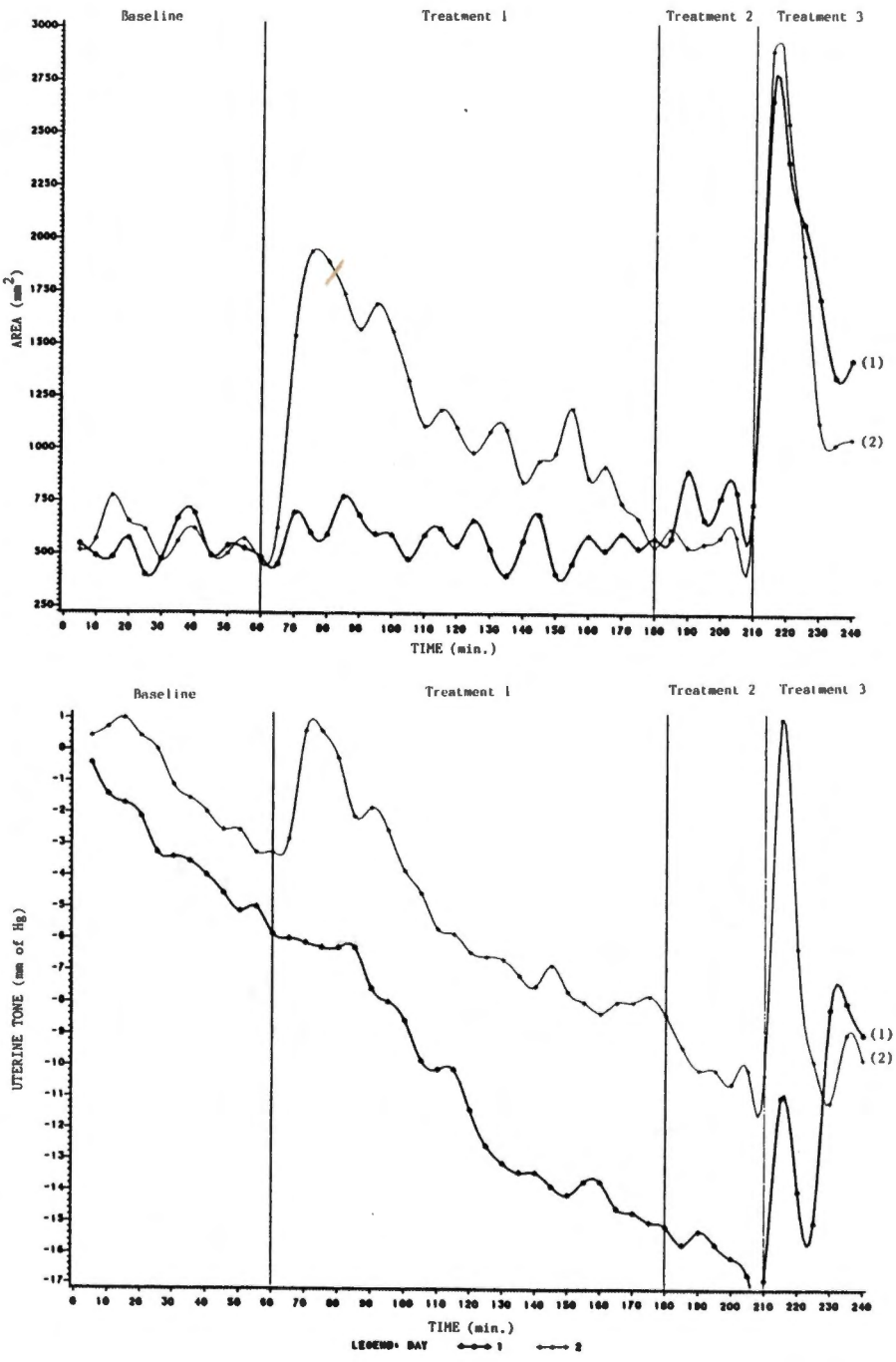


Figure 6. Comparison of uterine motility of postpartum cows for day one and day two of experimentation as measured by area and uterine tone. Vertical lines represent injection times. Treatment 1 on day one was fenprostalene (1 mg, IM). Treatment 1 on day two was oxytocin (100 IU, IM). Treatments 2 and 3 on both days were fenprostalene (1 mg, IV) and oxytocin (40 IU, IV), respectively.

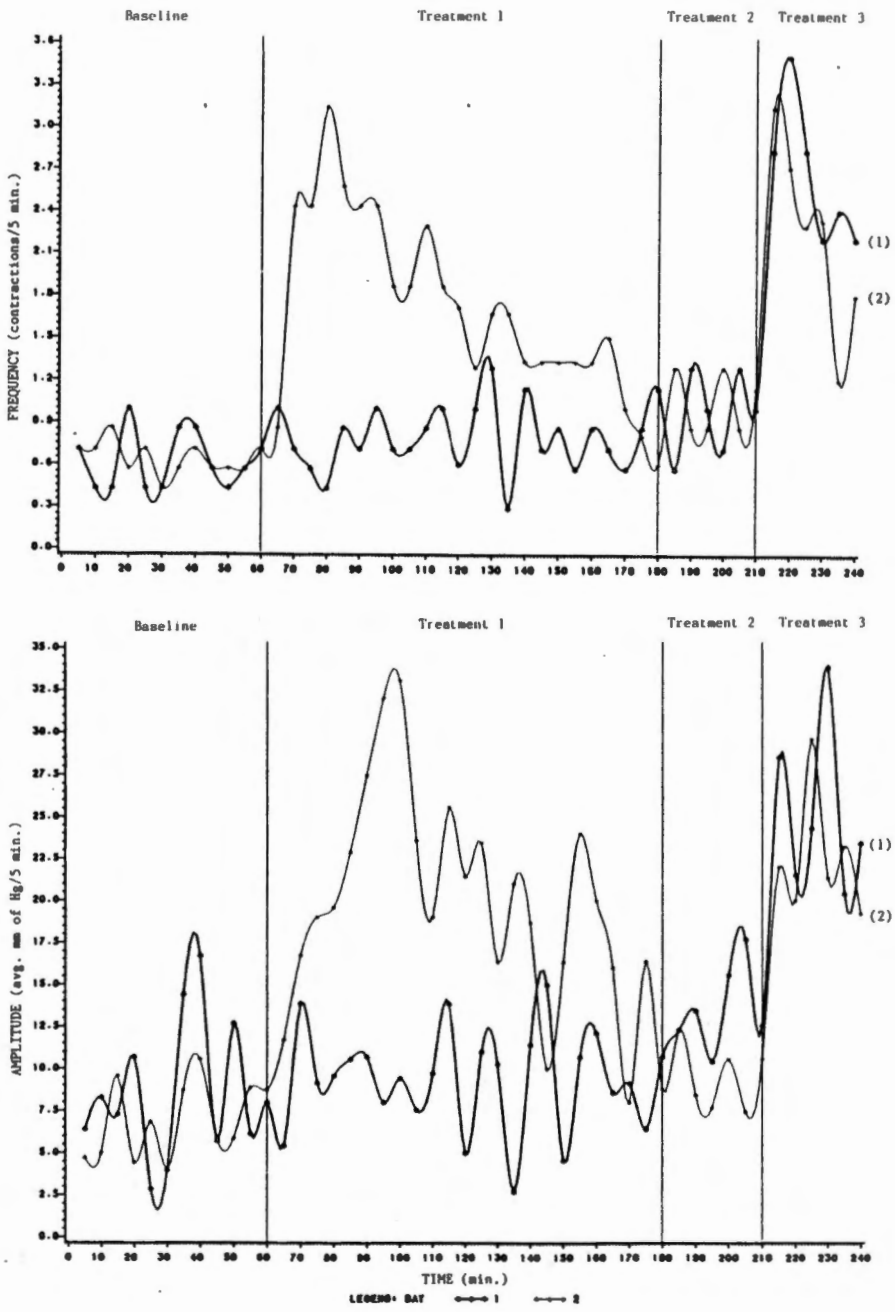


Figure 7. Comparison of uterine motility of postpartum cows for day one and day two of experimentation as measured by contraction variables. Vertical lines represent injection times. Treatment 1 on day one was fenprostalene (1 mg, IM). Treatment 1 on day two was oxytocin (100 IU, IV). Treatments 2 and 3 on both days were fenprostalene (1 mg, IV) and oxytocin (40 IU, IV), respectively.

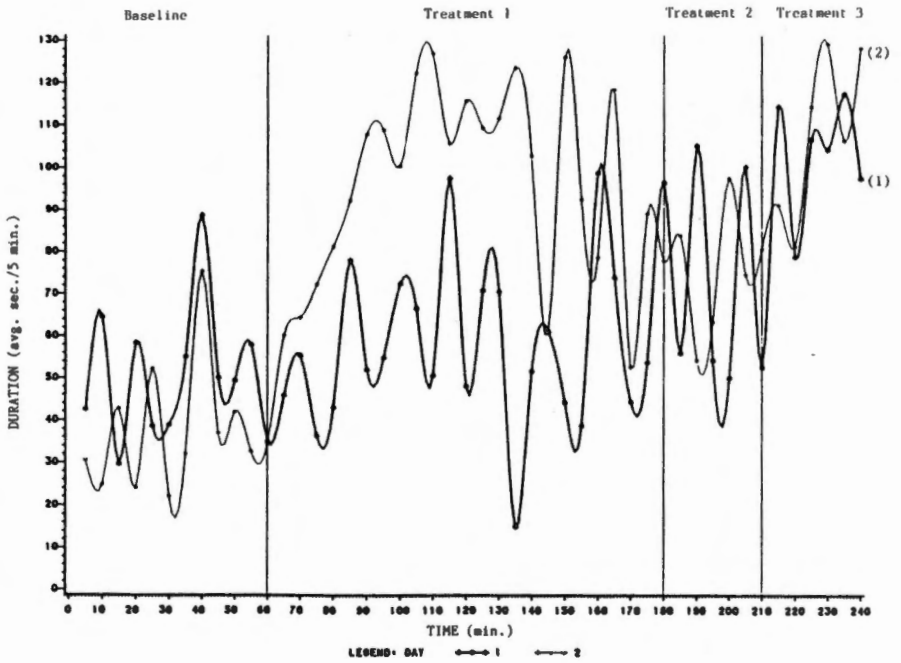


Figure 7 (continued)

2. Open Cow Motility

Within the group of open cycling cows, five cows were in diestrus and one cow was in proestrus, therefore, statistical comparisons were not possible between the two groups. Those cows in diestrus seemed to demonstrate higher baseline area and amplitude on day one (Figures 8 and 9). This effect is also evident in figures 9 and 10 which contrast the two estrus stages on the following day of treatment. Mean area following fenprostalene injection (0.1 mg, IM) was 853.5±54.4 for the cow in proestrus compared to 1716.1±112.2 mm^2 for the five cows in diestrus on day one. Cows in diestrus also exhibited a greater tonus increase following fenprostalene as compared to the cow in proestrus (Figure 8). The cow in proestrus and the cows in diestrus reacted similarly to all other hormone injections on both the first and second day. Day two comparisons are shown in figures 10 and 11.

With all open cows included in the statistical analysis, these results show no significant ($P>0.05$) increase in any contractility measure utilized in this study for fenprostalene-treated as compared to baseline on day one (Table A-2). Although fenprostalene (1 mg, IM) increased area slightly over baseline (1555.5±95.9 vs 1414.7±135.3 mm^2, respectively), a subsequent injection intravenously significantly decreased mean area (1364.3±103.7 mm^2) from baseline levels. Figure 12 indicates a possible short-lived response to fenprostalene for area and tone, but contraction variables (Figure 13) reveal no noticable effect. The presence of a higher initial area and amplitude as well as the dramatic reactivity of the uterus to oxytocin on day two is highly evident in these figures. Baseline area and amplitude were significantly

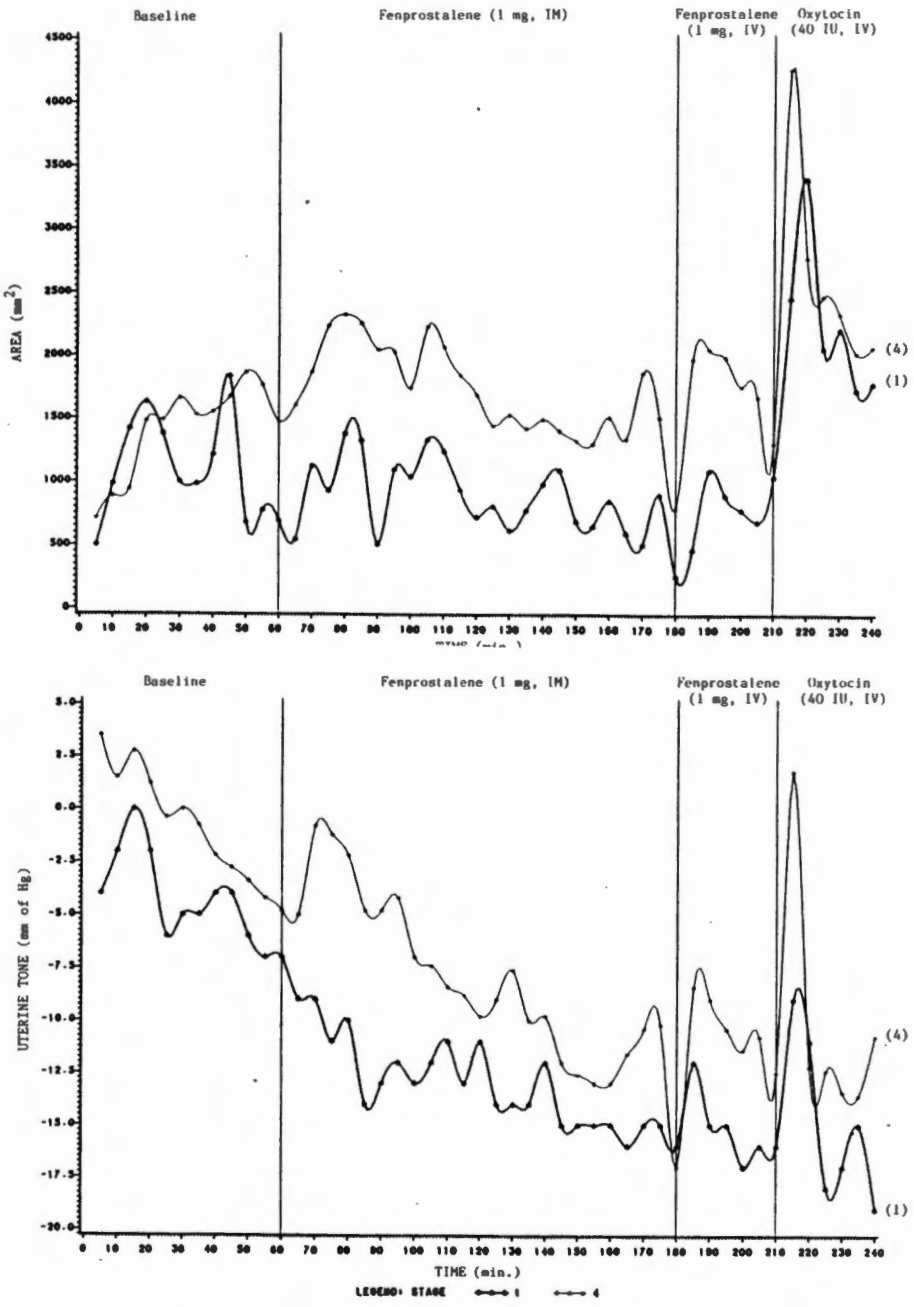


Figure 8. A comparison of uterine motility, in response to various hormonal treatments, of one cow in proestrus and the mean of five cows in diestrus as measured by area and tone on the first day of experimentation. Vertical lines represent drug injection times. STAGE 1 = Proestrus. STAGE 4 = Diestrus.

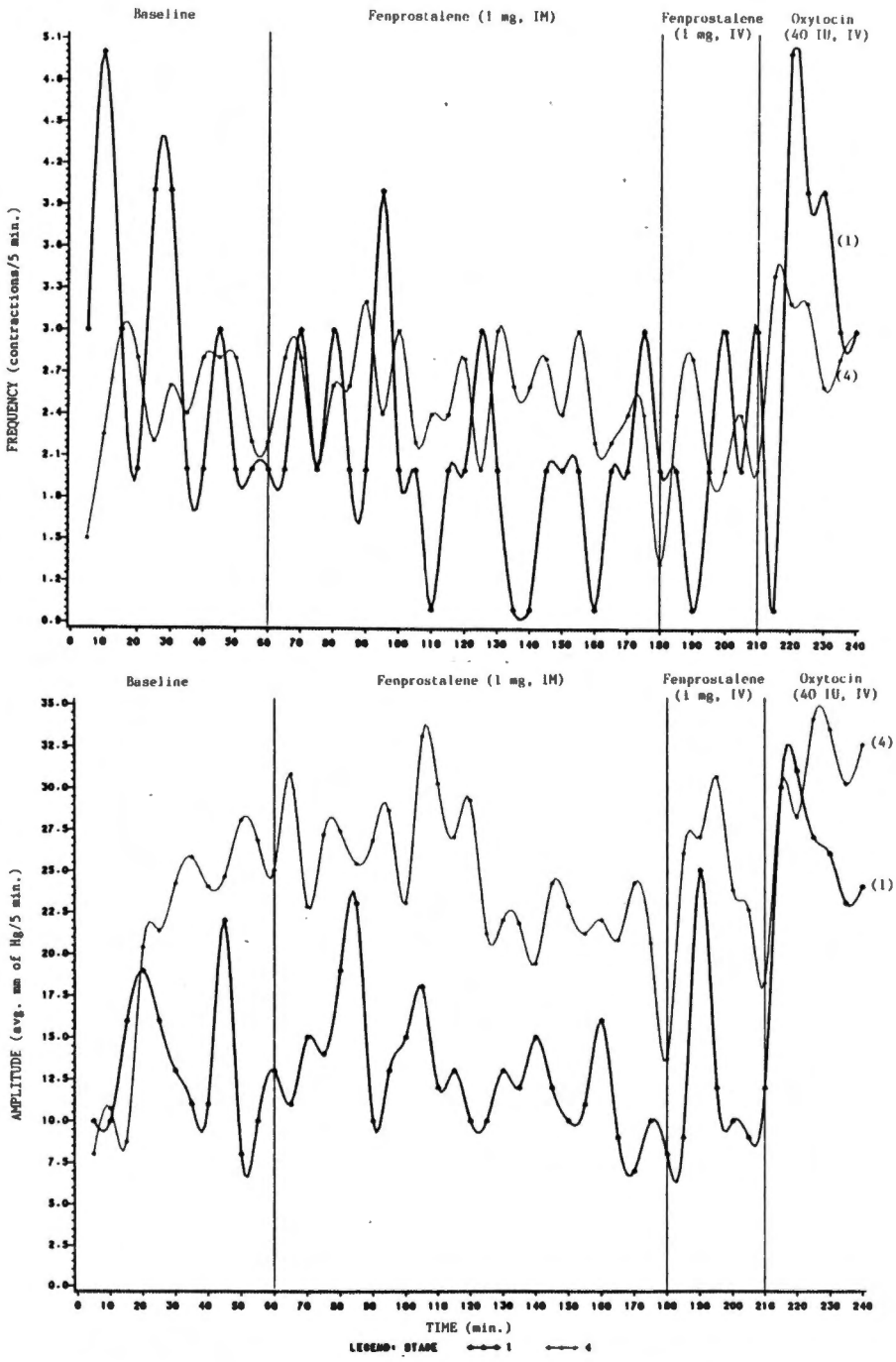


Figure 9. A comparison of uterine motility, in response to various hormonal treatments, of one cow in proestrus and the mean of five cows in diestrus as measured by contraction variables on the first day of experimentation. Vertical lines represent injection times. STAGE 1 = proestrus. STAGE 4 = diestrus.

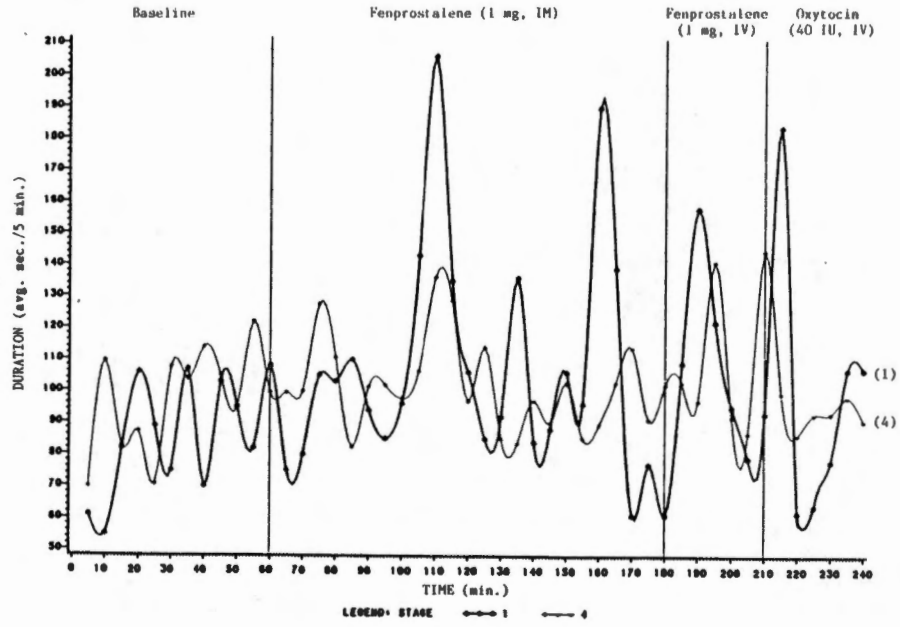


Figure 9 (continued)

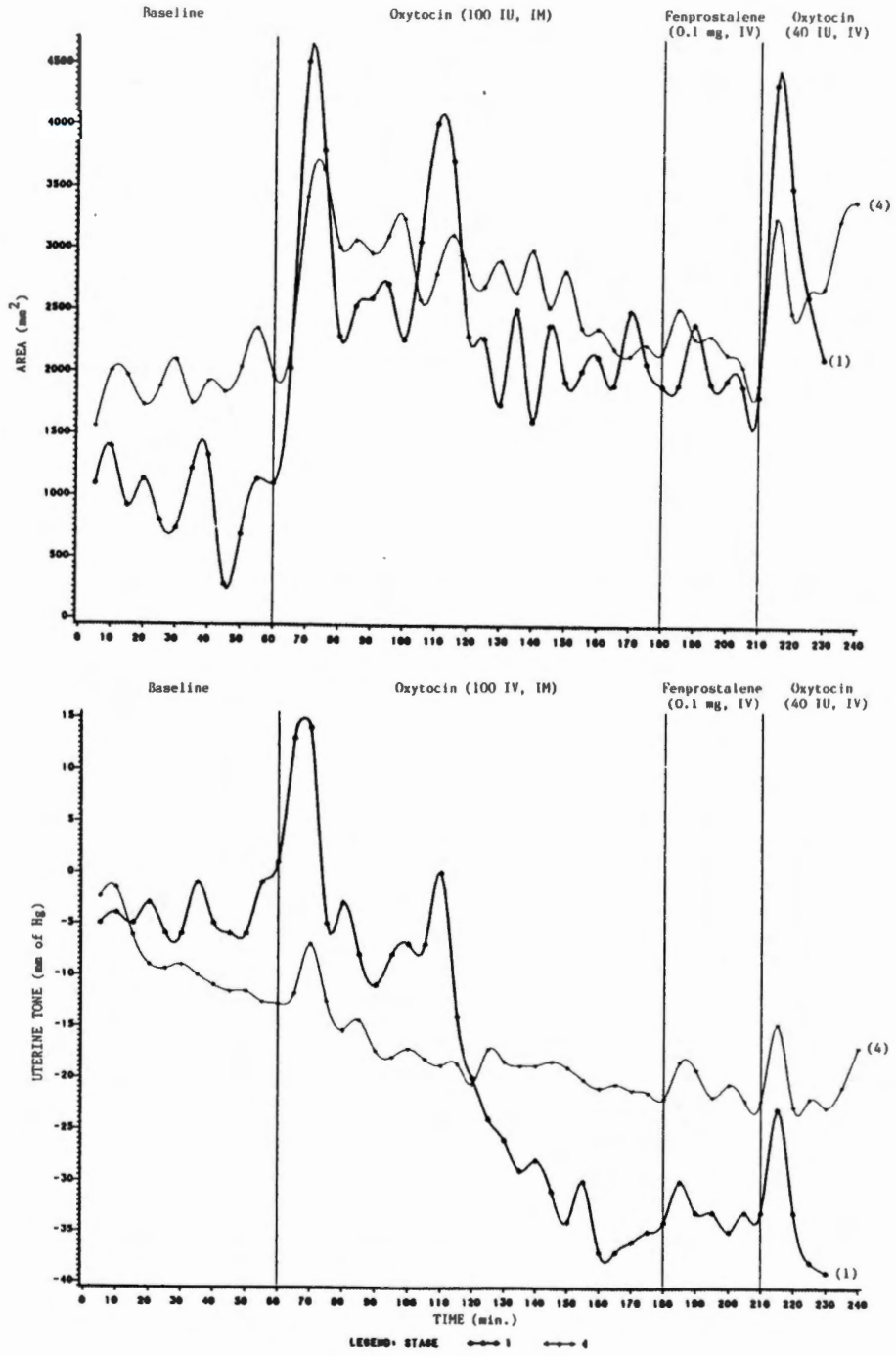


Figure 10. Comparison of uterine motility of one cow previously in proestrus vs the mean of five cows previously in diestrus as measured by area and uterine tone in response to various hormonal treatments on the second day of experimentation. Vertical lines represent injection times. STAGE 1 = proestrus. STAGE 4 = diestrus.

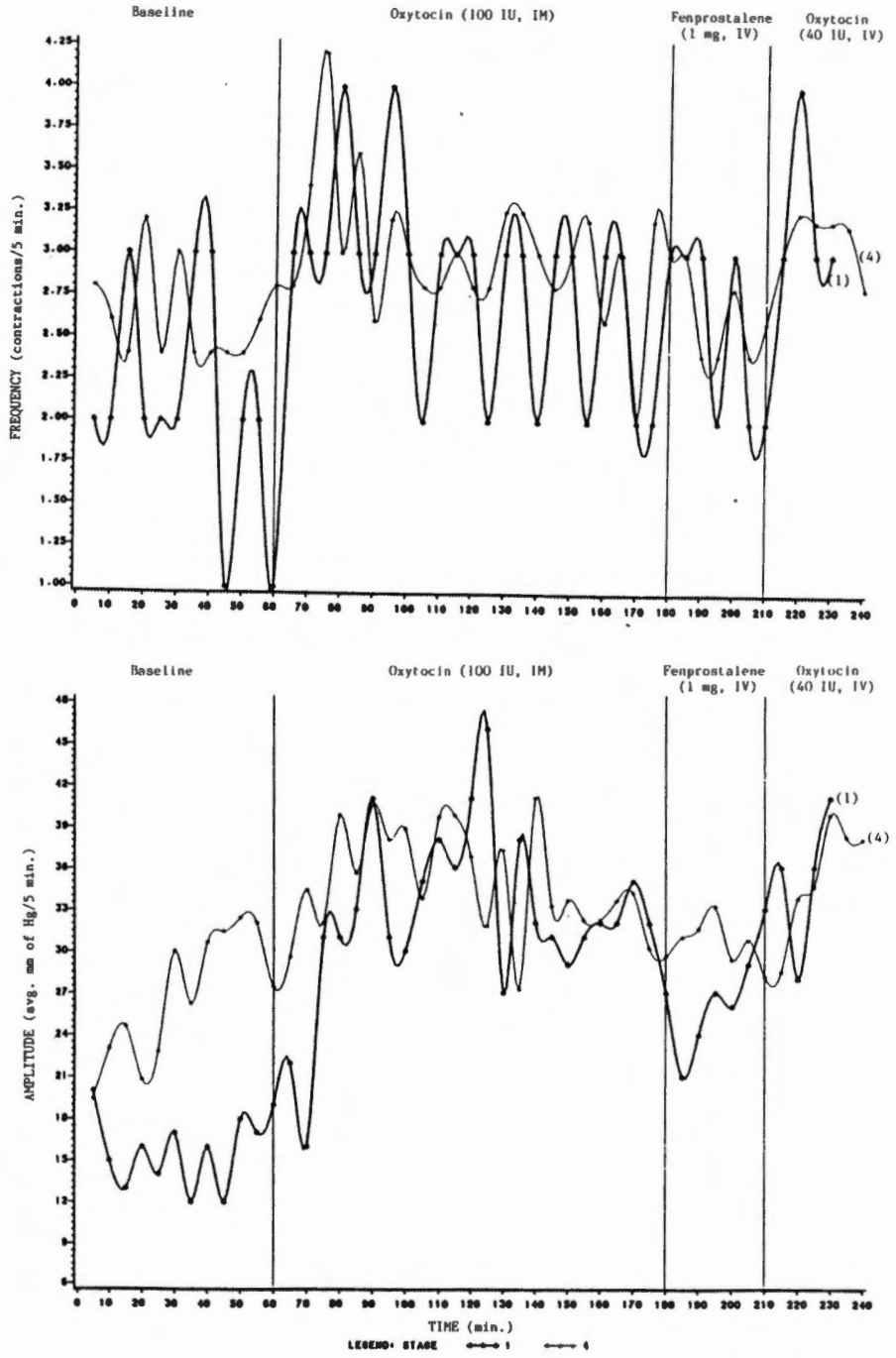


Figure 11. Comparison of uterine motility of one cow previously in proestrus vs the mean of five cows previously in diestrus as measured by contraction variables in response to various hormonal treatments on the second day of experimentation. Vertical lines represent injection times. STAGE 1 = proestrus. STAGE 4 = diestrus.

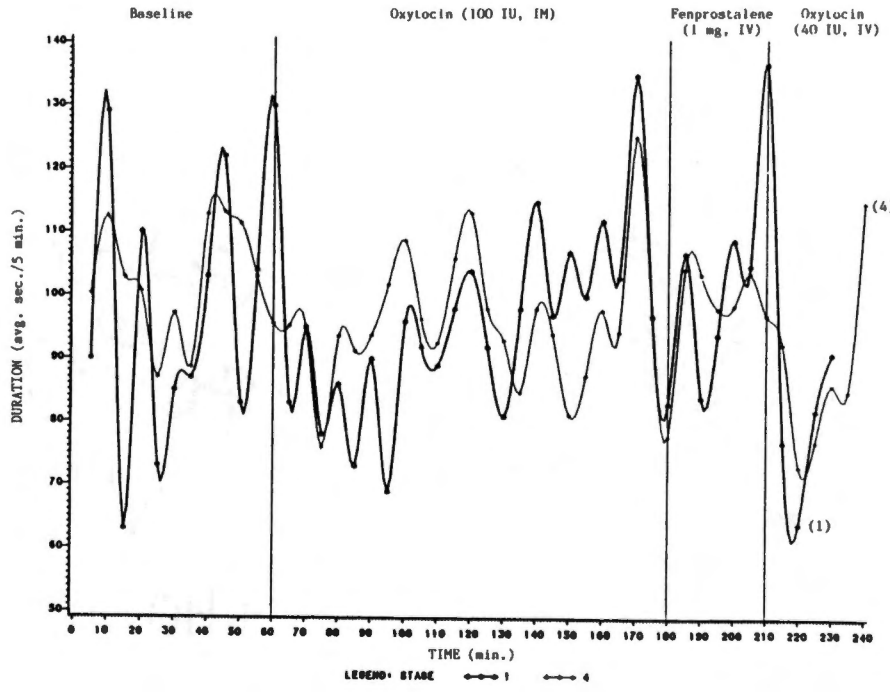


Figure 11 (continued)

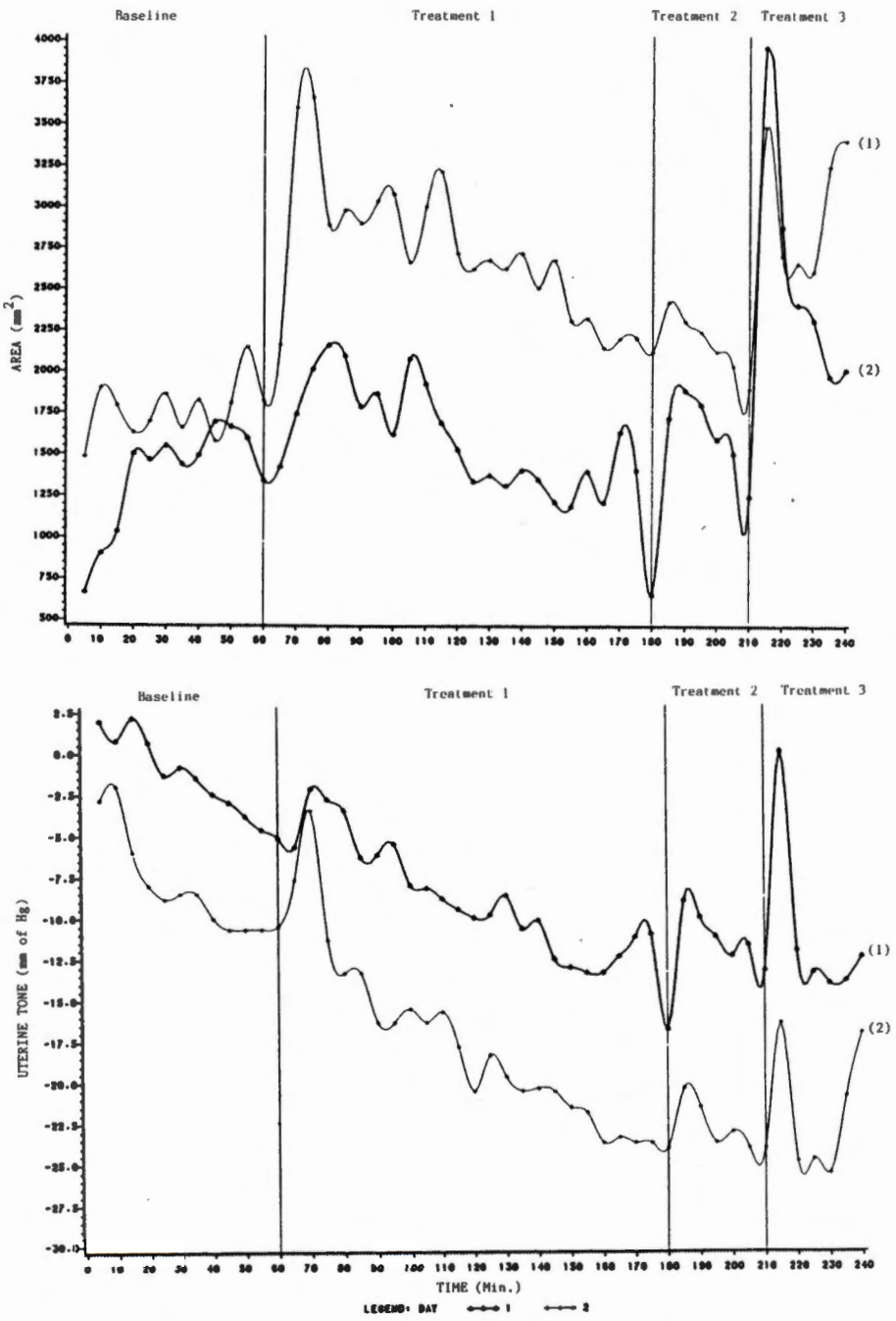


Figure 12. Open cow uterine motility on day one and day two of experimentation as measured by area and uterine tone following various hormonal treatments. Vertical lines represent injection times. Treatment 1 on day one was fenprostalene (1 mg, IM). Treatment 1 on day 2 was oxytocin (100 IU, IM). Treatments 2 and 3 on both days were fenprostalene (1 mg, IV) and oxytocin (40 IU, IV), respectively.

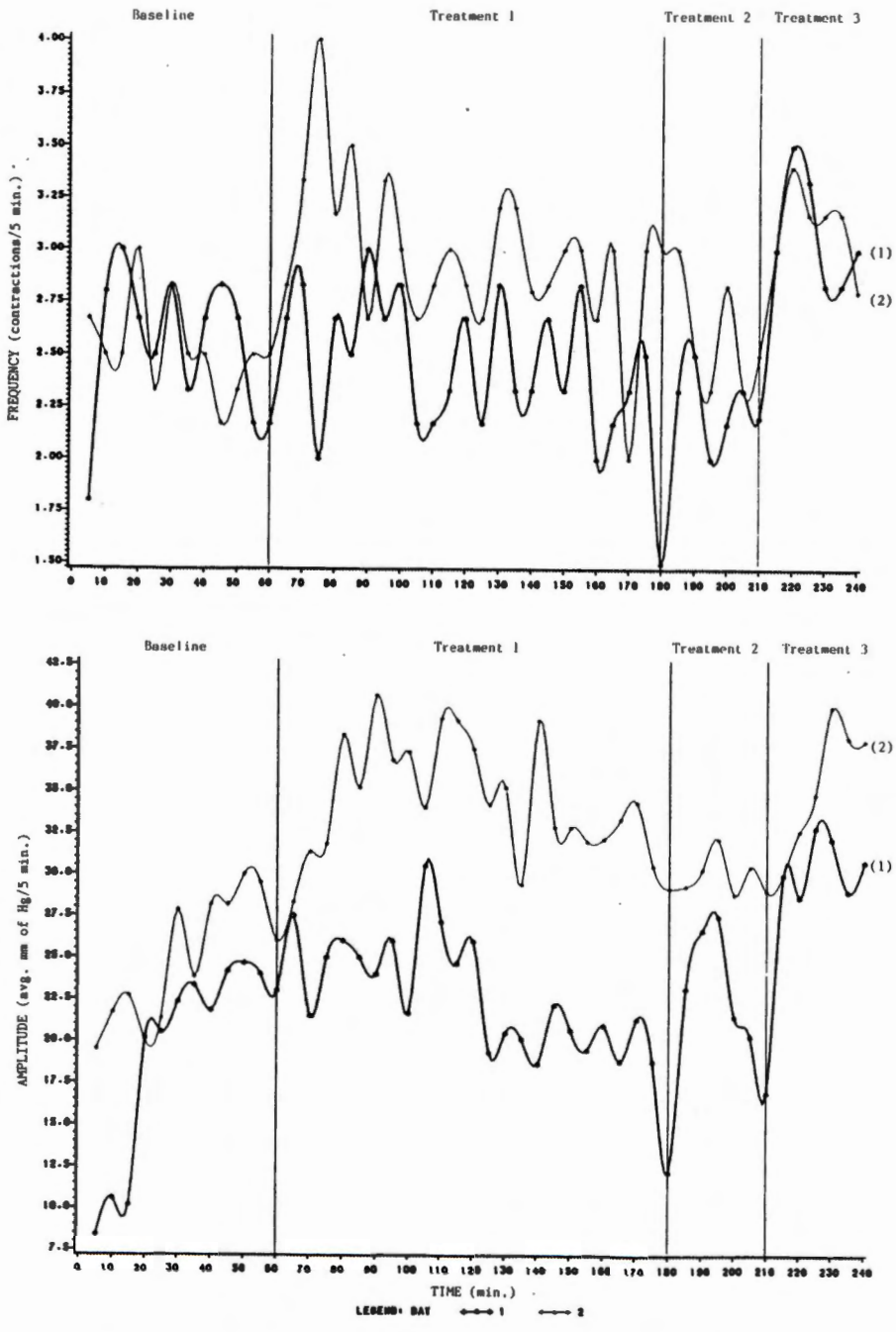


Figure 13. Open cow uterine motility on days one and two of experimentation as measured by contraction variables following various hormonal treatments. Vertical lines represent injection times. Treatment 1 on day one was fenprostalene (1 mg, IM). Treatment 1 on day two was oxytocin (100 IU, IM). Treatments 2 and 3 on both days were fenprostalene (1 mg, IV) and oxytocin (40 IU, IV), respectively.

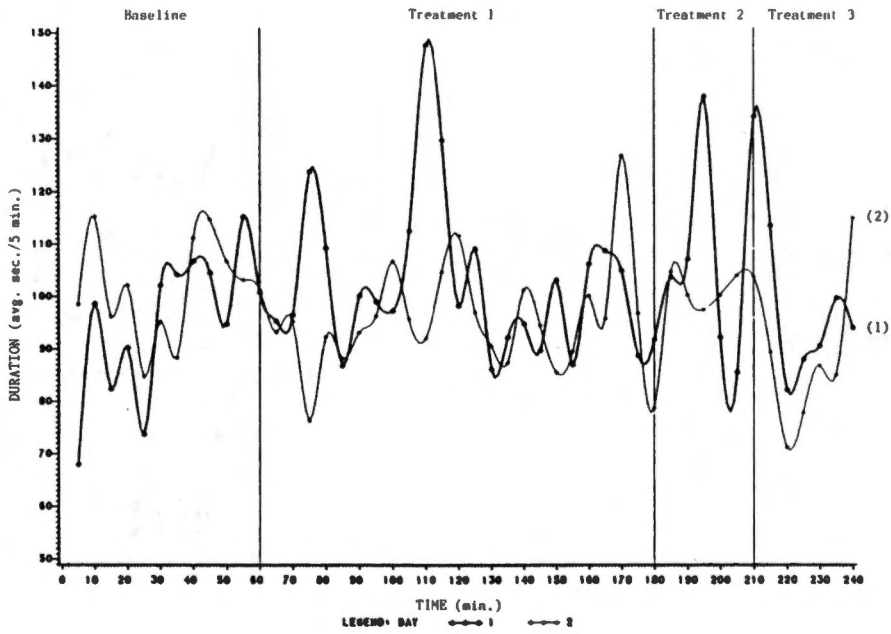


Figure 13 (continued)

($P<0.05$) higher on day 2 of experimentation as compared to day one. The initial oxytocin treatment increased area and frequency of contraction to levels significantly ($P<0.05$) above baseline, while the subsequent fenprostalene injection failed to increase any measure above baseline values. There was also no difference in contraction duration for either day. The intravenous injection of oxytocin on each day caused the greatest increase in area, uterine tone, frequency, and amplitude (see Table A-2).

3. Comparison of Postpartum vs Open Cow Motility

A comparison of early-postpartum cow and open cycling cow uterine motility for day one can be found in figures 14 and 15. Motility was obviously much higher for the cycling cow group when compared across corresponding treatments. Contractility was most similar when oxytocin was injected intravenously at the close of the experiment. Means in table A-3 indicated significant ($P<0.05$) differences in all corresponding treatment period means except uterine tone baseline, fenprostalene (IM) and oxytocin (IV); amplitude for fenprostalene (IV); and contraction duration for the intravenous oxytocin injection. The differences in motility were even more marked for motility measurements on day two (Figures 16 and 17; Table A-4). The only corresponding treatments which were not significantly different were oxytocin, intramuscularly, and oxytocin, intravenouly, for duration of contraction. It should be noted from these figures that each variable tends to possess a highly cyclical nature over time, therefore causing statistical prediction of regression line types to be difficult with any level of confidence. There were, however, highly significant correlations between the indepentent

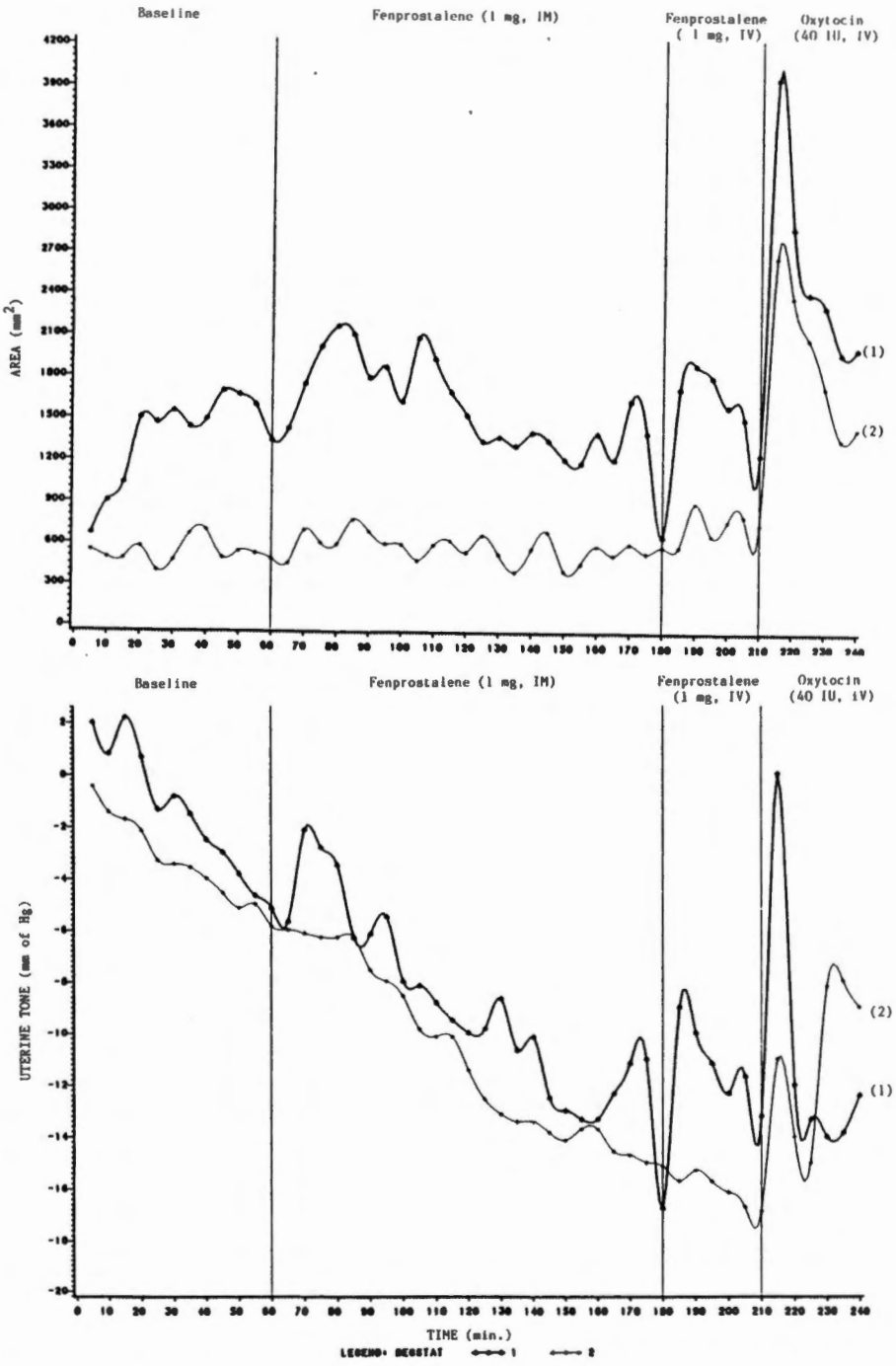


Figure 14. Postpartum cow vs open cycling cow uterine motility on the first experimental day as measured by area and uterine tone and affected by various hormonal treatments. Vertical lines indicate injection times. BEGSTAT 1 = open cow group (n = 6). BEGSTAT 2 = postpartum cow group (n = 7).

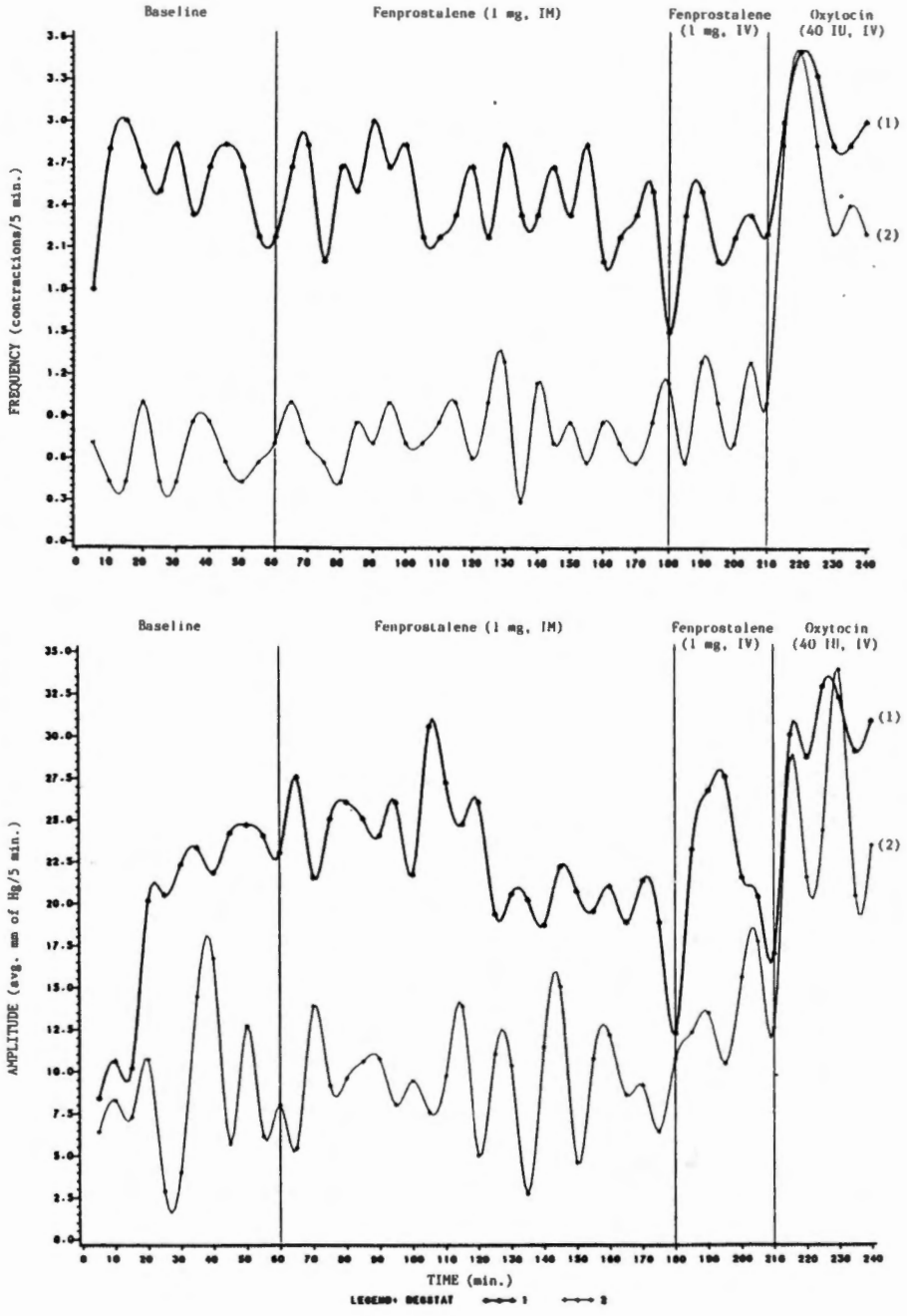


Figure 15. Postpartum cow vs open cycling cow uterine motility on the first experimental day as measured by contraction variables and affected by various hormonal treatments. Vertical lines indicate injection times. BEGSTAT 1 = open cow group (n = 6). BEGSTAT 2 = postpartum cow group (n = 7).

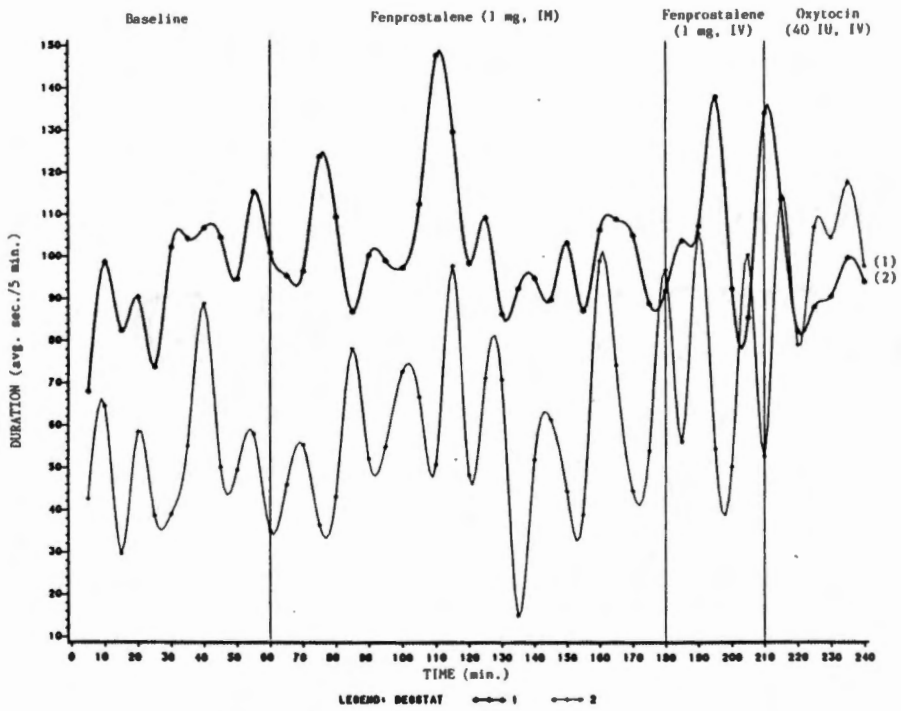


Figure 15 (continued)

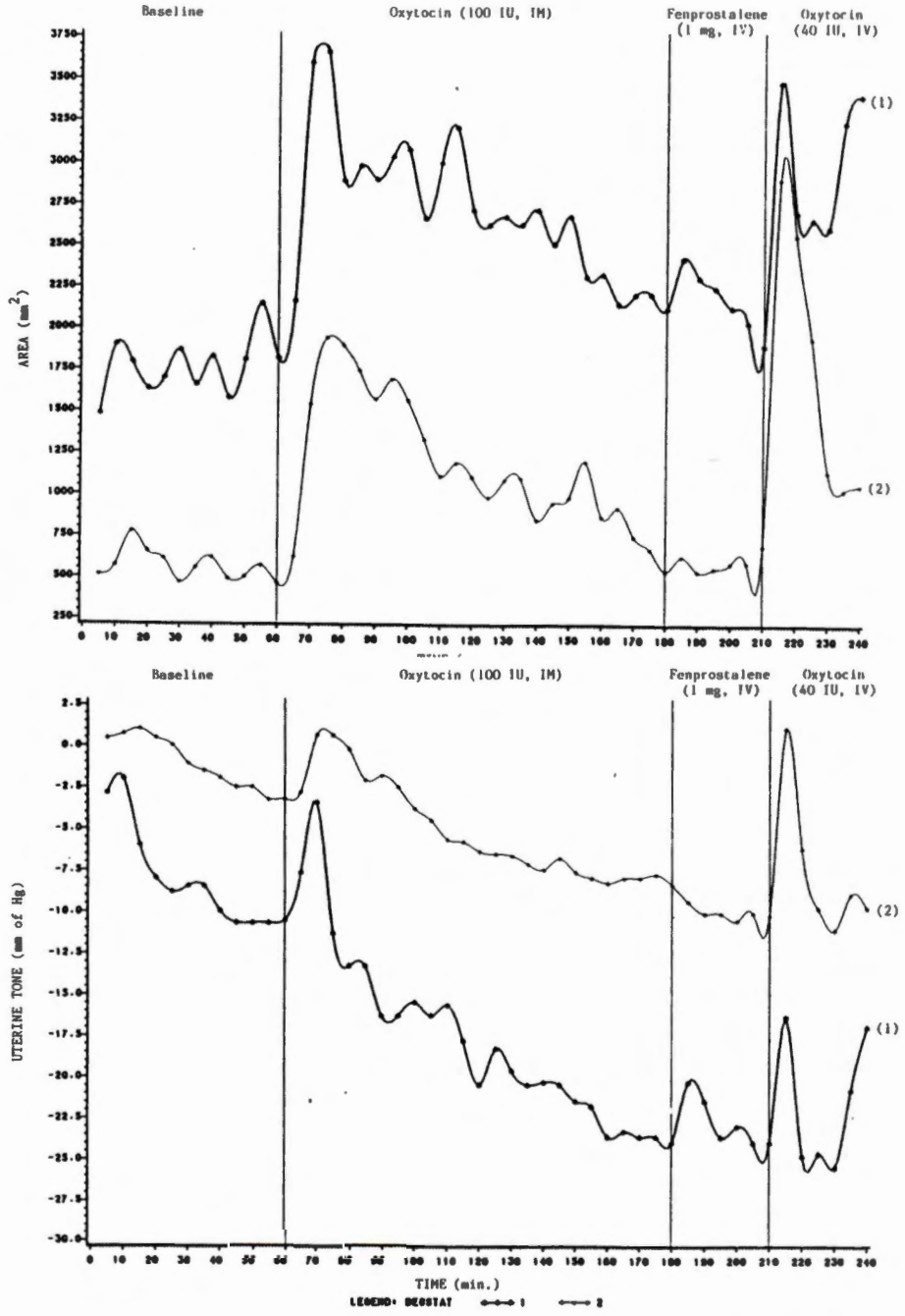


Figure 16. Postpartum cow vs open cycling cow uterine motility on the second experimental day as measured by area and uterine tone and affected by various hormonal treatments. Vertical lines indicate injection times. BEGSTAT 1 = open cow group (n = 6). BEGSTAT 2 = postpartum cow group (n = 7).

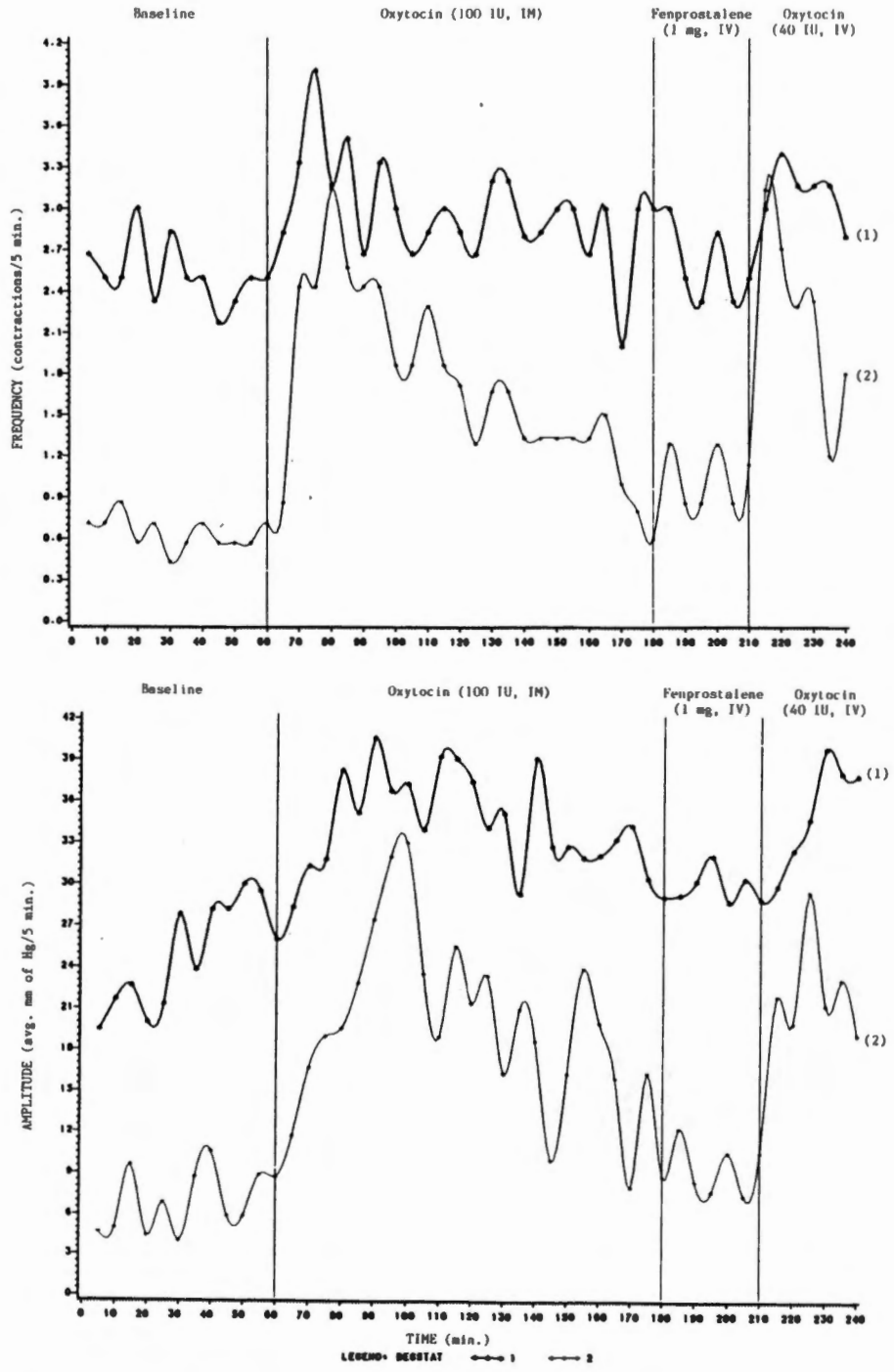


Figure 17. Postpartum cow vs open cycling cow uterine motility on the second experimental day as measured by contraction variables and affected by various hormonal treatments. Vertical lines indicate injection times. BEGSTAT 1 = open cow group (n = 6). BEGSTAT 2 = postpartum cow group (n = 7).

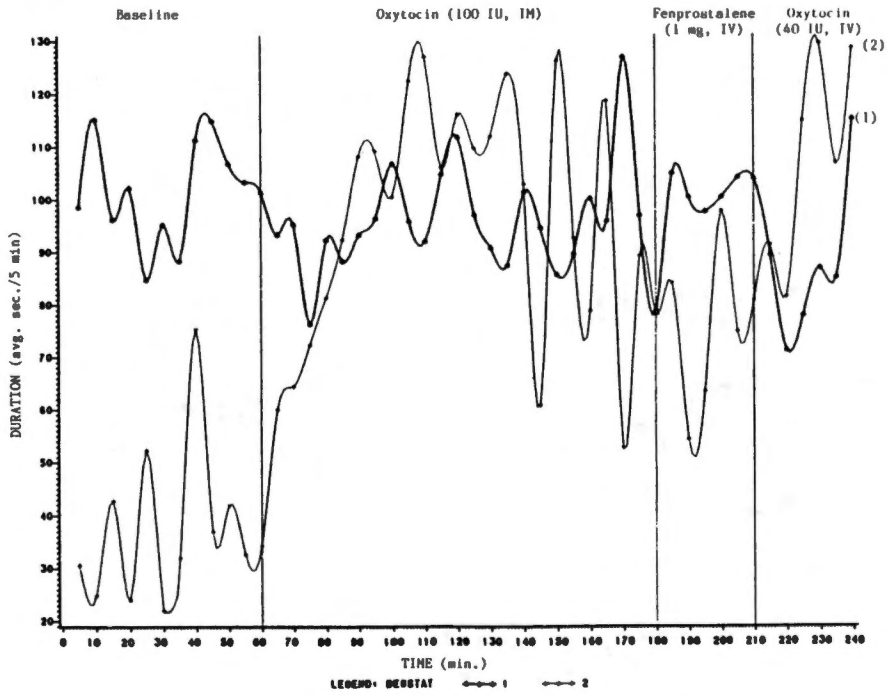


Figure 17 (continued)

variables indicating linearity among the measures of uterine motility reported in this study (Table 1). The highest correlation coefficient was between area and frequency (0.789, $P>0.0001$) while the lowest, although still significant ($P<0.0077$), was the correlation of area to uterine tone (-0.06911).

D. DISCUSSION

The results obtained in this experiment are consistent with those reported by other investigators. Values for quantitative measurements such as frequency and duration differed somewhat but this could be explained by the fact that early studies utilized an air conduction system to measure uterine pressure changes. The fact that air is compressable could be the reason for this variation. The increased motility of the cow suffering from RFM agrees with that reported by several investigators (Venable and McDonald, 1958; Martin et al., 1981; Piper et al., 1978).

Fenprostalene, when given IM to cows between 12 and 24 hours post-partum, elicited no significant response in uterine activity, while 24 hours later an IM injection of oxytocin produced a large increase in uterine motility. This response to oxytocin was observed at a time when drug reactivity and spontaneous contractility are reported to be on the decline (Arthur, 1979; Weatherill, 1965; Fincher, 1941). A slight (NS) response to fenprostalene (IV) was observed on the first day of experimentation but not on day two following oxytocin administration. Intravenous injection of oxytocin did, however, increase motility many times over pre-injection levels. Responses to fenprostalene

TABLE 1

CORRELATION COEFFICIENTS OF DEPENDENT VARIABLES USED IN THE EVALUATION OF UTEROKINETICS IN EARLY POSTPARTUM AND OPEN CYCLING COWS

Variable	Uterine Tone	Frequency	Amplitude	Duration
Area	-0.06911**	0.57706*	0.78869*	0.34903*
Uterine Tone		-0.12858*	-0.26008*	-0.17634*
Frequency			0.45903*	0.38469*
Amplitude				0.50664*

* $P < 0.0001$

** $P < 0.0077$

administration were similar to those reported for $PGF_2\alpha$ (Eiler et al., 1984) even though fenprostalene exhibits a 25 times greater activity in causing luteolysis. There is no information as to the difference in half-life since that for $PGF_2\alpha$ is reported for intravenous injections and fenprostalene for subcutaneous injection.

In the open cow study the relative findings were similar to those reported for postpartum cows. Oxytocin elicited a much greater myokinetic effect than did fenprostalene. Fenprostalene caused a moderate (NS) increase when injected IM but a lesser response was gained when a second injection (IV) was given. This relative refractoriness has been observed by Eiler et al. (1981) with $PGF_2\alpha$. An injection of oxytocin at the end of experimentation on day two resulted in a response equal to or greater than that observed earlier for the IM injection.

Chen et al. (1966), Ruckebusch and Bayard (1975), and Evans and Miller (1936) reported increased motility in cycling cows as they neared estrus. The one cow in this study which was in proestrus exhibited lesser motility than the average for cows in diestrus. The only reasonable explanation for this is individual variation. The cow in proestrus was less responsive to fenprostalene than the cows in the luteal phase of the cycle.

Open cow motility was much greater than that of the postpartum cows. The open cows were also much more responsive to fenprostalene. This finding, in light of the relative refractoriness of bovine uterus to repeated dosages, could be explained if prostaglandin levels are already high following parturition as reported by Lindell et al. (1982).

These results also support the presence of separate and specific $PGF_2\alpha$ and oxytocin receptors in the uterus as reported by Chan (1977).

There was a tendency for motility to be increased on day two of experimentation as opposed to day one in both open cows and postpartum cows. This instance in the postpartum cows may have been due to the rapid uterine involution which is occurring at this time (Gier and Marion, 1968). Because $PGF_2\alpha$ can be used to synchronize estrus in cattle (Rowson et al., 1972; Hafs et al., 1974; Adeyemo et al., 1979), the increase in the open cows may have been due to reduced plasma progesterone levels and increased estrogen influence. However, the possibitly of a carry-over effect from day one must be considered.

Even though undesirable side effects were not seen in this study following fenprostalene injection as had been observed with $PGF_2\alpha$, the therapeutic value of the prostaglandins for expelling retained fetal membranes is in question. The favorable clinical findings by Herschler (1984) and Haidry and Fathala (1982) after fenprostalene and $PGF_2\alpha$ injection, respectively, indicate that if $PGF_2\alpha$ is effective in causing the release of retained fetal membranes, it is by a means other than stimulatory action on the myometrium.

CHAPTER III.

THE EFFECT OF FENPROSTALENE AND OXYTOCIN ON UTERINE MOTILITY OF ISOLATED BOVINE UTERINE HORNS

A. INTRODUCTION

Studies on the motility of bovine uterus in vitro are much less numerus than for other species. However, the effect of $PGF_2\alpha$ on uterine strips has been established (Palil et al., 1980; Singh et al., 1979; Bobrik, 1973). Only in one study was a comparison of the stimulatory effect of oxytocin and $PGF_2\alpha$ on the bovine myometrium in vitro reported (Patil et al., 1980). Patil et al. (1980) reported a dose-dependent response of uterus in vitro to oxytocin while $PGF_2\alpha$- treated strips did not respond in a dose related manner. Differences have been established in drug reactivity when strips were obtained during different stages of the estrous cycle or when obtained from pregnant animals (Singh et al., 1979; Patil et al., 1980).

At least one investigator has reported problems in comparing in vitro studies of motility using uterine strips because contractility patterns differ among transverse, circular and longitudinal sections (King, 1927). As Patil et al. (1980) reports, there is also some difficulty in proper bovine uterine strip preparation because of the thickness of the tissue. The available literature yielded no information on investigations of uterine motility using isolated bovine uterus.

The purpose of this study was two-fold. The first objective was to develop a procedure to measure uterine motility of isolated bovine uterine horns rather than uterine strips. The second objective was to investigate various aspects of contractility measured spontaneously or following administration of a prostaglandin $F_2\alpha$ analogue, fenprostalene, or oxytocin in a system where no central nervous system influence or no liver or kidney inactivation of either smooth muscle stimulant would occur.

The objective of experiment one was to determine the duration of spontaneous uterine horn contractility over a period of six hours. The second experiment was to establish the dose of each hormone required to increase motility by approximately eighty percent. A third experiment was designed to compare alternate treatments of oxytocin and fenprostalene where an injection of oxytocin was followed by fenprostalene and vice versa. Experiment four was conducted to determine the existence or absence of uterine refractoriness to a repeated dosage of each smooth muscle stimulant. The final experiment was to study the effect of a mixture of both oxytocin and synthetic prostaglandin on subsequent uterine motility.

B. MATERIALS AND METHODS

After experimental technique was determined from several preliminary studies, the uterokinetic effect of fenprostalene (Bovilene™ Sterile Solution - Diamond Laboratories, Inc., Des Moines, IA; lot no. 10004) and synthetic oxytocin (Vedco, INC., Overland Park, KS; lot no. 6075) on isolated bovine uterus was investigated in a series of five

experiments. All uterii were obtained at Lay Packing Co. (Knoxville, Tn) and were available for removal within twenty minutes post-slaughter. Each uterus was separated from the vagina at mid-cervix, roughly trimmed of excess tissue, and immediately placed in room temperature Tyrode's Physiological Solution (Tyrode, M. V. 1910) adjusted to pH 7.4 (Table 2). The uterii were transported to the lab where, after further trimming, the horns were separated at the uterine body and the ovaries were removed. A balloon attached to a modified Foley catheter was placed in each horn (prepared as in Ch.II; 16 fr. Foley catheter) and secured by inflating the catheter cuff with distilled water. The posterior end of the horn was then tied to a rack (modified test tube rack; 29.2×12.4×9.3 cm) and a 20 gm weight was tied to the free end, with the weight hanging over the end of the rack (Figure 18). Distilled water was used to inflate the intrauterine balloon. The amount of fluid added to the balloon was determined by visual appraisal and horn palpation in order to standardize uterine distension. The uterus attached to the rack was then immersed in Tyrode's solution (39° C, pH 7.2-7.4) under constant stirring (Tecam TE-7 Tempette, Duxford Cambridge, Eng.). Solution pH was monitered by a pH meter hourly (Fisher Scientific Co. Accumet, Model 805-MP) and the bath was under constant aeration with 95% O_2, and 5% CO_2(0.5ℓ/min./bath) via an aeration stone (13×2×1.2 cm). When the pH rose above or fell below the range of 7.2 to 7.4 ,adjustments were made by bubbling pure CO_2 (10 ℓ/min.) to decrease pH or air (10 ℓ/min.) to increase solution pH. Motility was recorded with a physiograph (Model CPM, Narco B10 - Systems Inc., Houston, Tx.) attached to a pressure transducer (Model P-1000B, Narco B10-Systems Inc., Houston, Tx.). The

TABLE 2

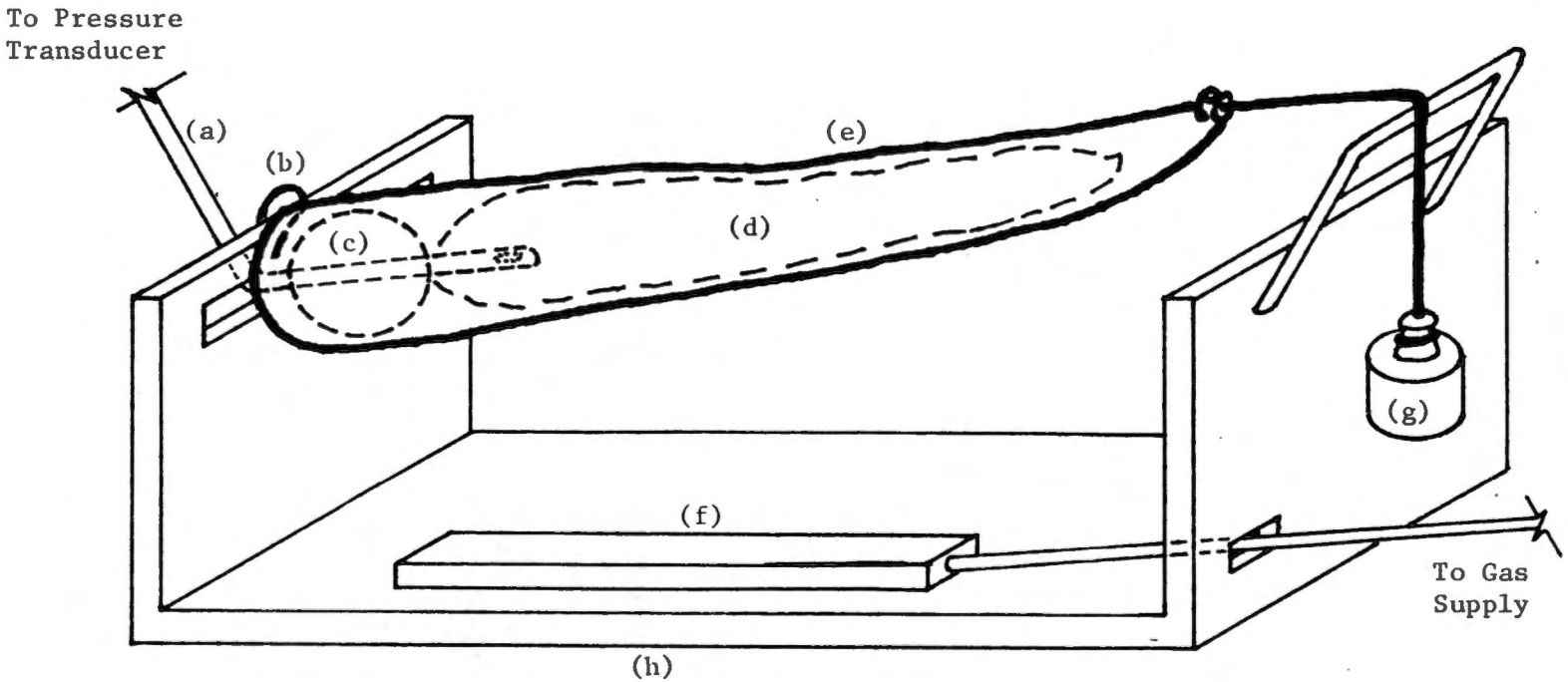
CHEMICAL COMPOSITION OF TYRODE'S PHYSIOLOGICAL SOLUTION

Chemical	Amount
$CaCl_2$	200 mg/l
$MgCl_2 \cdot 6H_2O$	100 mg/l
KCl	200 mg/l
$NaHCO_3$	1000 mg/l
NaCl	8000 mg/l
$NaH_2PO_4 \cdot H_2O$	50 mg/l
Glucose	1000 mg/l

* Contents dissolved in distilled deionized water.

pH adjusted to 7.2 with CO_2 aeration.

Reference: Tyrode, M.V. 1910. Arch. Int. Pharmacodyn. Ther. 20:205.



Legend:
a) Foley catheter
b) Ligature to rack
c) Catheter cuff
d) Balloon
e) Uterine horn
f) Aeration stone
g) 20 gm weight
h) Rack

Figure 18. Apparatus and experimental set-up for the measurement of isolated uterine motility.

presence of a corpus luteum and estimated follicle size was recorded for the corresponding uterus and horn. Uterine horns were weighed (wet) for each experiment and the volume of fluid in each balloon was recorded.

The treatment schedule used for each of the five isolated uterus experiments are presented diagramatically in figures 19 to 23. Drugs were instilled directly into the isolated uterine bath near to the stirring unit.

Experiment one consisted of six horns from three uterii which were allowed to contract spontaneously for six hours to enable an estimation of contraction rate and magnitude change over time (figure 19).

The second experiment involved the dose-response of either oxytocin or fenprostalene. Dosages for oxytocin were 1, 2, 3, or 10 IU per 17 liters of physiological solution or 0.059, 0.176, 0.235 and 0.588 IU /ℓ, respectively. Likewise, fenprostalene was instilled into the uterine bath in dosages of 0.1, 0.2, 0.3, and 0.5 mg per 17 liters of solution or 0.0059 mg, 0.0118 mg, 0.0176 mg, and 0.0294 mg/liter, respectively. Four horns from four different uterii were used as replicates to test each dosage level. Therefore, each uterus is represented by two dosages, one for each horn (i.e. one uterus was treated with the two lower dosages and one uterus the two higher dosages of either oxytocin or fenprostalene). For each dosage level baseline motility was recorded for thirty minutes followed by a recording period of one hour after the first dosage of either oxytocin or fenprostalene. The same drug level was then repeated and motility was measured for an additional hour. Experiment three was conducted to investigate the effect of fenprostalene on a subsequent dose of oxytocin and vice versa, (8 horns per

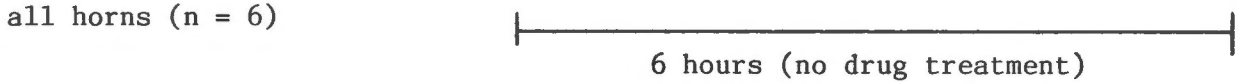


Figure 19. Diagram of experimental procedure for measurement of spontaneous contractility over time (Exp. 1).

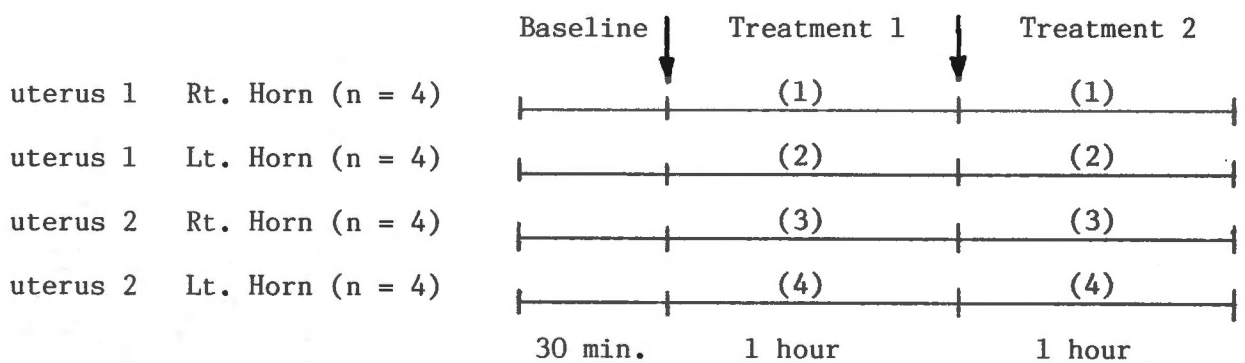


Figure 20. Diagram of the dose-response experiment for oxytocin and fenprostalene (Exp. 2). Arrows represent treatment times. Numbers in parentheses represent dosages of either oxytocin or fenprostalene.

Oxytocin:		Fenprostalene:	
(1)	1 IU	(1)	0.1 mg
(2)	2 IU	(2)	0.2 mg
(3)	3 IU	(3)	0.3 mg
(4)	10 IU	(4)	0.5 mg

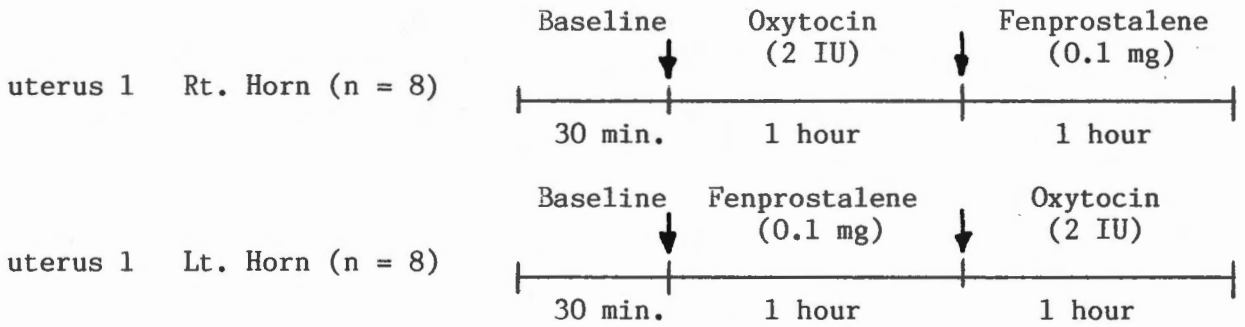


Figure 21. Schematic representation of alternate treatments of isolated uterine horns with oxytocin and fenprostalene (Exp.3). Arrows represent treatment times.

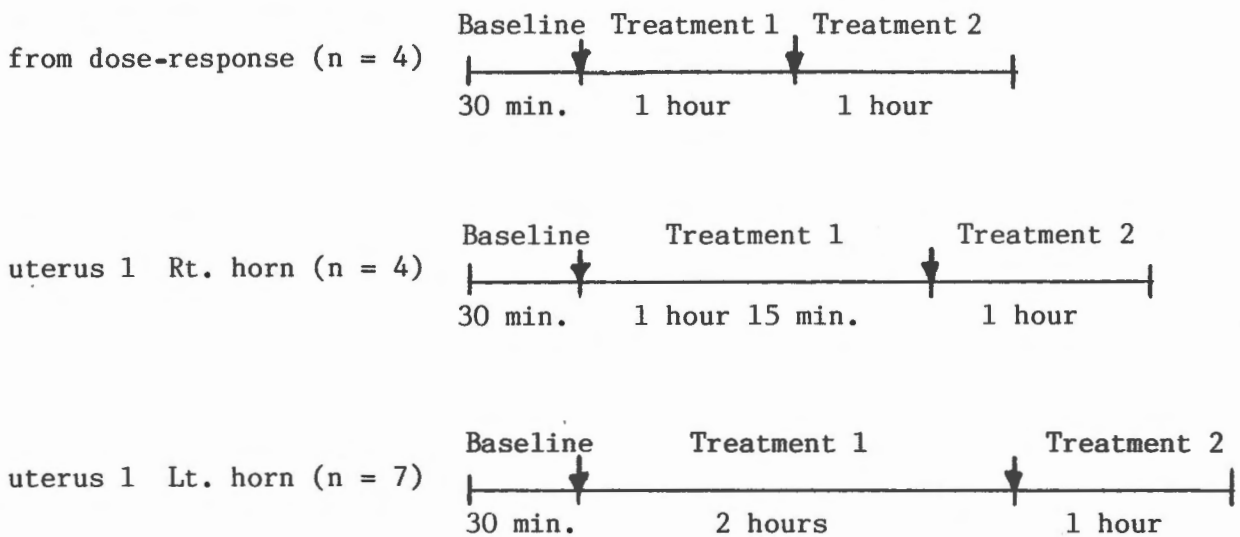


Figure 22. Diagramatical representation of the treatment schedule used in the investigation into refractoriness of bovine isolated horns to repeated treatment of oxytocin (2 IU) or fenprostalene (0.1 mg), allowing different resting periods between treatments (Exp. 4). Arrows represent treatment times.

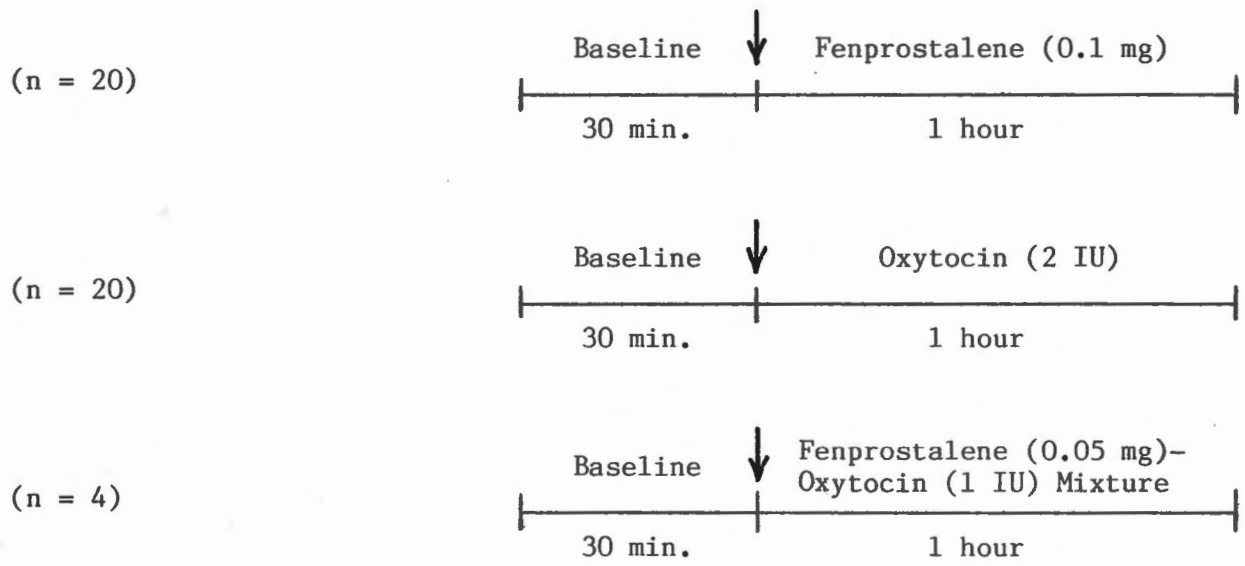


Figure 23. Schematic of experimental procedure in an experiment comparing a mixture of oxytocin and fenprostalene to the effect of either drug alone on the uterokinetic response of isolated uterine horns (Exp. 5). Arrows represent treatment times.

treatment). After a thirty minute recording of spontaneous contractility, oxytocin (2 IU) was instilled into one isolated uterine bath and fenprostalene (0.1 mg) to the other such that each uterus was exposed to each of the two treatments. A one hour recording period was followed by the reversal of drugs where the oxytocin-treated horn received fenprostalene (0.1 mg) and the fenprostalene-treated horn received oxytocin (2 IU). Motility was then recorded for an additional hour.

Refractoriness of uterus to subsequent dosages of the same hormone was investigated using four horns per time interval per treatment (Exp. 4). After baseline motility was recorded for thirty minutes, eight horns were treated with oxytocin (2 IU/17ℓ bath) and eight horns were treated with 0.1 mg fenprostalene. Each horn was treated with the same hormone. Treatments differed in that one horn was allowed seventy-five minutes before the treatment was repeated while the other was allowed 120 minutes of recording time prior to the second dosage. The corresponding drug and dosage from the dose-response experiment was also used as a comparison (four horns per drug), with a sixty minute interval between treatments.

Experiment five was designed to compare the effect on contractility of a mixture of oxytocin (1 IU) and fenprostalene (.05 mg) to either drug administered alone (oxytocin and fenprostalene, 2 IU and 0.1 mg, respectively). Once again spontaneous motility was recorded for thirty minutes (four horns, two uterii) followed by a one hour recording period after treatment with the mixture. Results were compared to experiments where either oxytocin or fenprostalene was used as the treatment on the first injection in previous isolated experiments.

Area (mm^2) under the tracing was measured by a digitizer (Videoplan, Carl Zeiss, Inc., Thornwood, N. Y.) in five minute time increments. Frequency was denoted as the number of contractions per five minutes. Uterine tonus change was measured and calculated as described in chapter two. Average amplitude and average duration of contraction was estimated by visual appraisal for each treatment period.

Experimental design was a time-response or dose-response relationship. Statistical evaluation was by SAS (SAS Institute, Inc., Cary, N. C.). Although some modifications were made for specific comparisons, the general model used in the isolated study was:

$$Y_{ijklmn} = \mu + \text{horn weight}_i + \text{balloon volume}_j + \text{treatment}_k \, \text{drug}_l (\text{treatment}_k) + \text{time}_m (\text{drug}_l) + e_{ijklmn},$$

where: Y_{ijklmn} = the area, frequency, and uterine tone as affected by the i^{th} horn weight, the j^{th} balloon volume, the k^{th} treatment, the l^{th} drug within the k^{th} treatment, the m^{th} time within the l^{th} drug and the n^{th} observation

μ= the estimate of the mean area, frequency of contraction, and uterine tone for the population;

horn weight_i = the effect of the i^{th} horn weight on area, frequency of contraction and uterine tone; balloon volume_j = the effect of the j^{th} balloon volume on area, frequency and tone;

treatment_k = the effect of the k^{th} treatment on area, frequency and tone;

$\text{drug}_l(\text{treatment}_k)$ = the effect of the l^{th} drug within the k^{th} treatment on area, frequency and tone

$time_m(drug_l)$ = the effect of the m^{th} time within the l^{th} drug on area, frequency and tone;

and e_{ijklmn} = the random error.

Mean separation was by orthogonal contrasts and Student-Newman-Keul's test. Probability of significance is reported at the five percent level of significance unless otherwise indicated.

C. RESULTS

1. Establishment of Technique

Preliminary experiments to determine the efficacy of using isolated uterine horns rather than the uterine strip preparation for motility studies in vitro showed that entire uterine horns are suitable for such measurements under proper conditions. Physiological solution compostion and solution pH were found to influence contractility. Ringers solution, USP with 5% Glucose and Lactated Ringers solution (Abbott Labs, North Chicago, IL., adjusted to pH 7.2) inhibited spontaneous uterine contraction. However, horns maintained in Tyrode's Physiological solution (pH adjusted to 7.2) demonstrated spontaneous motility patterns similar to those seen for open cycling cows in vivo. As a general rule, when solution pH fell below 7.0 or increased to above 7.8 uterine motility decreased until no deflection could be observed in the recording. It was, however, possible to regulate solution pH by gas aeration. The effect of air, oxygen, 5% CO^2 in oxygen, and pure CO^2 on solution pH are shown in figure 24. In several preliminary experiments where the horns were transported from the slaughter house to the laboratory in 4^0 C Tyrodes solution, spontaneous contractility was decreased during the

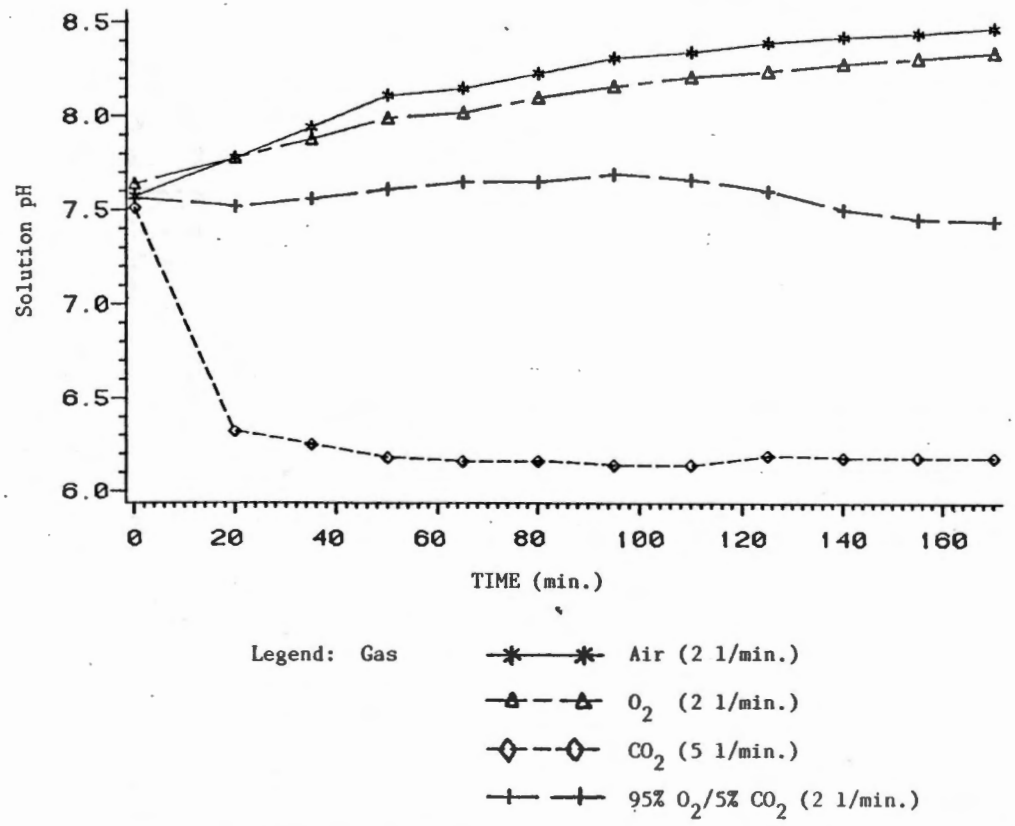


Figure 24. Tyrode's Physiological Solution pH change in response to aeration with different gases. Approximated flow rates are shown in parentheses following the gas.

experiment. Due to this effect, horns were transported thereafter in room temperature Tyrode's solution. Under these conditions motility was almost immediately evident and stable when placed in the bath (39° C). This practice caused no apparent tissue damage in that survival time was remarkably long. Horns from two uterii were allowed to contract until no visible contractions were recorded. Two horns were active and responsive to oxytocin and prostaglandin at ten and thirteen hours after removal from the respective cow.

It was anticipated that oxytocin and fenprostalene might increase glucose uptake by the tissue and therefore glucose clearance from the Tyrode's solution could be used as an indication of uterine metabolism. However, several preliminary studies in which solution samples were evaluated for glucose concentration over time showed no differences. Because of this, the glucose analysis was discontinued and is not reported further in this study.

Finally, because classical studies on intestinal absorption in vitro are performed on everted sections to increase absorption, everted uterus was compared to normal uterus. The everted horns exhibited no contractility nor was there any tonus change over time in the absence or presence of oxytocin. The contralateral uneverted mate, however, showed normal activity throughout the recording period.

2. Type of Motility

As a general rule horns from the same uterus exhibited the same type of contraction throughout the entire experiment regardless of hormone addition. However, over the five experiments four basic types of contraction were observed (figure 25). Motility consisted of

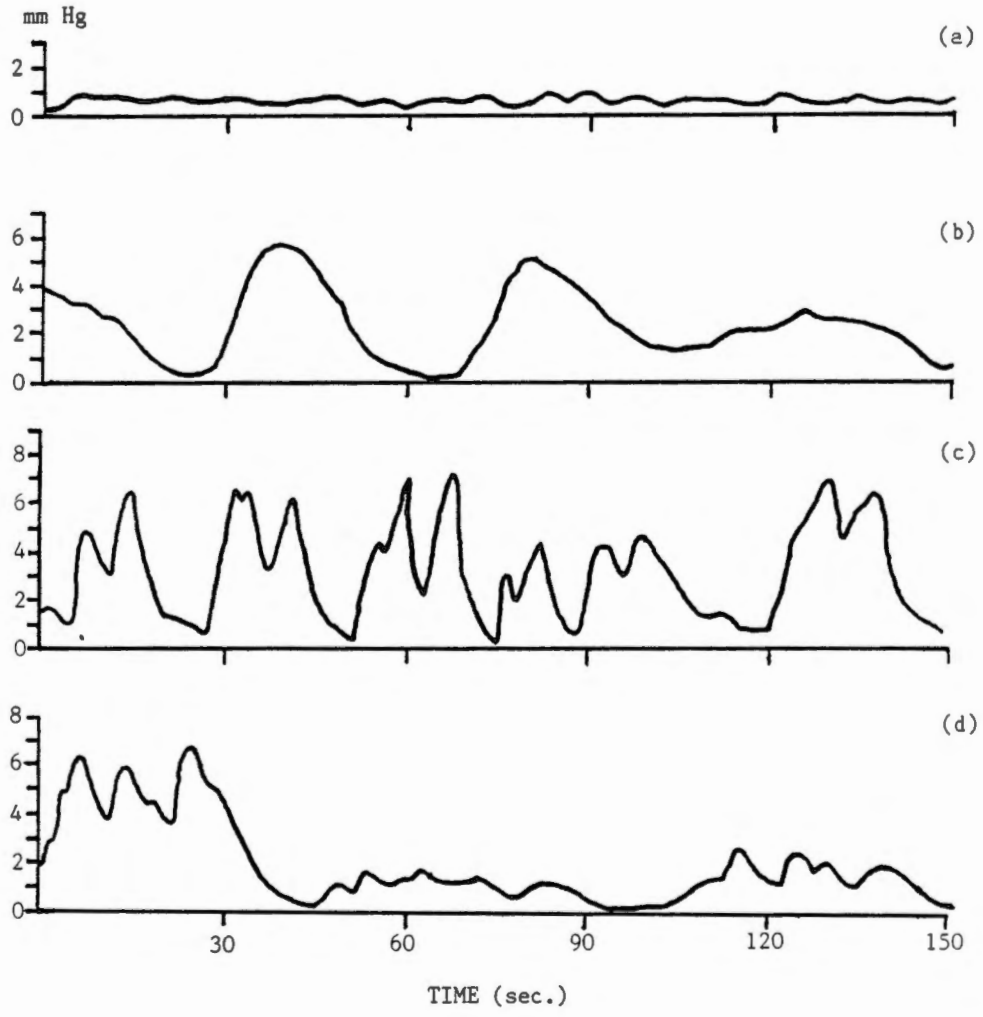


Figure 25. Types of contraction observed in isolated uterine horn physiograph recordings. [(a) "asynchronous," (b) monophasic, (c) biphasic, (d) triphasic].

monophasic, biphasic, triphasic, and seemingly asynchronous contractions. In the few cases where "asynchronous" motility patterns were prevalent, frequency counts were not possible and were omitted from the regression of the various treatments on frequency.

3. Relationship of Dependent Variables

Area under the tracing was inherently affected by amplitude, duration, and frequency of contraction as well as uterine tonus changes over time. In pooled isolated uterus experiments the relationship between area, frequency, and tone was highly significant ($P<0.0001$). The correlation coefficients of frequency to area, tone to area, and frequency to tone were 0.46, 0.54, and 0.10, respectively.

4. Effect of Ovarian Structures on Uterine Contractility

The effect of ovarian structure (corpus luteum, follicle, NSS) on spontaneous uterine motility and motility in response to either oxytocin or fenprostalene was evaluated from combined isolated study data. The means presented in table 3 indicate no significant ($P<0.05$) effect of structure on mean baseline area or uterine tone. Horns accompanied with a follicle or a corpus luteum (CL) exhibited a higher ($P<0.05$) spontaneous frequency of contraction than did those with no significant structures (NSS) or both a follicle and a CL on the same ovary. When fenprostalene (0.1 mg) was administered, area was greatest ($P<0.05$) for follicle-affected horns than those with any other structure. Horns with NSS reacted more strongly than those with both a follicle and a CL on the same ovary. The area response fenprostalene-treated horns with CL's was approximately five times less than horns associated with ovarian follicles. Contrary to this finding, however, oxytocin-treated horns

exhibited no significant difference in area between horns with an ovarian follicle or those with a CL. Differences were significant ($P<0.05$) between these structures and NSS or both structures on the same ovary. NSS yielded the lowest ($P<0.05$) area response when horns were treated with oxytocin. There was no difference in frequency of contraction following oxytocin (2 IU) treatment for the structure groups. In general, uterine tonicity followed the same pattern as did area when observed within treatment groups. Mean comparisons by treatment and structure are shown in Table 3.

5. Effect of Horn Weight on Uterine Contractility

Horn weight was negatively correlated ($P<0.0001$) with area, frequency of contraction, and tonus change. Respective coefficients were -0.31, -0.22, and -0.27 when derived from pooled isolated horn data. Although pooled data indicated a high positive correlation between horn weight and balloon volume (0.52, $P<0.0001$) a significant correlation of balloon volume to area, frequency, or tone was not found.

6. EXP. 1. Spontaneous Contractility Over Time

Area under the curve, frequency, and tone showed a cyclical cubic response over a six hour period of time (figure 26). Area gradually increased until approximately four and one half hours after which there was a gradual decline. Frequency of contraction (figure 26) increased rapidly until two hours after the experiment's beginning and remained at a level of approximately three contractions per five minutes to the end of the experiment. Uterine tone exhibited a brief increase followed by a rapid decline from 1.5 to -3.4 mm of Hg at three hours after the initial five minute period (figure 26). From three hours to four hours

TABLE 3

MEAN COMPARISONS OF THE EFFECT OF OVARIAN STRUCTURE ON ISOLATED UTERINE HORN MOTILITY WHEN TREATED WITH NO EXOGENOUS HORMONE (BASELINE), FENPROSTALENE (0.1MG) OR OXYTOCIN (2 IU)

		Measure of Uterine Motility*		
Treatment	Ovarian Structure	Area (mm^2)	Frequency (counts/5 min.)	Tone (mm Hg)
Baseline	No Significant Structures	528.2 ± 63.1^{a}	1.33 ± 0.16^{abd}	-0.43 ± 0.44^{a}
	Follicle	546.6 ± 33.4^{a}	2.31 ± 0.14^{bd}	-0.87 ± 0.12^{a}
	Corpus Luteum	488.8 ± 122.0^{a}	2.00 ± 0.48^{b}	-0.10 ± 0.38^{a}
	Follicle and Corpus Luteum	344.3 ± 47.0^{a}	0.88 ± 0.16^{a}	-1.64 ± 0.15^{a}
Fenprostalene	No Significant Structures	2163.4 ± 176.1^{b}	3.90 ± 0.13^{ce}	-1.50 ± 0.54^{a}
	Follicle	3157.7 ± 152.9^{c}	4.15 ± 0.09^{c}	1.63 ± 0.31^{b}
	Corpus Luteum	529.5 ± 60.6^{a}	2.73 ± 0.15^{d}	-3.60 ± 0.15^{c}
	Follicle and Corpus Luteum	1327.0 ± 139.9^{d}	3.31 ± 0.14^{e}	-1.24 ± 0.38^{a}
Oxytocin	No Significant Structures	1208.8 ± 71.9^{d}	3.70 ± 0.10^{ce}	-1.82 ± 0.42^{d}
	Follicle	2832.7 ± 199.4^{c}	3.90 ± 0.10^{ce}	1.88 ± 0.39^{b}
	Corpus Luteum	3516.3 ± 219.2^{c}	3.83 ± 0.17^{ce}	3.32 ± 0.59^{b}
	Follicle and Corpus Luteum	2147.2 ± 174.4^{b}	3.50 ± 0.18^{ce}	-4.90 ± 0.29^{c}

* Mean ± SEM.

$^{a-e}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).

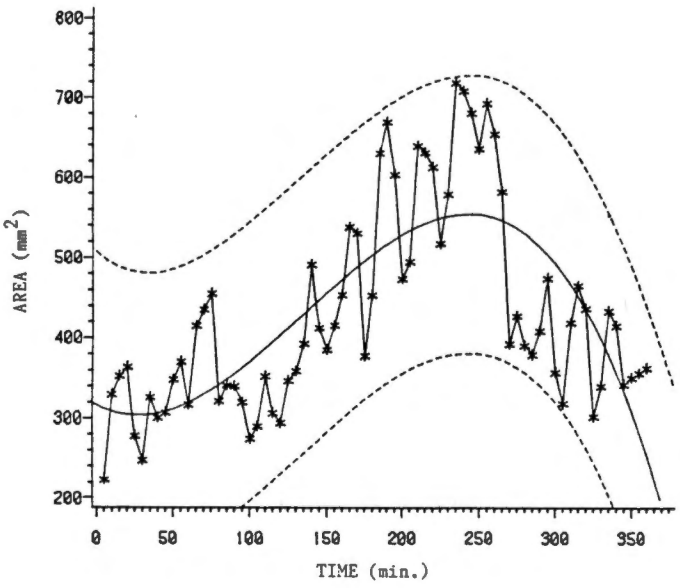


Figure 26. Behavior of spontaneous uterine motility of isolated horns over a six-hour period of time (Exp. 1). The figure shows mean motility of six uterine horns with the cubic regression line plotted through the data points. Broken lines are 95% confidence limits about an individual. The regression lines are $Y_1 = 315 - 0.93X + 0.50X^2 - 0.006X^3$, $Y_2 = 0.00 + 0.05X - 0.006X^2 + 4.7X^3$, and $Y_3 = 2.15 - 0.06X^2 - 5.11X^3$ where Y_1 = Area, Y_2 = Frequency, Y_3 = Uterine tone and X = Time.

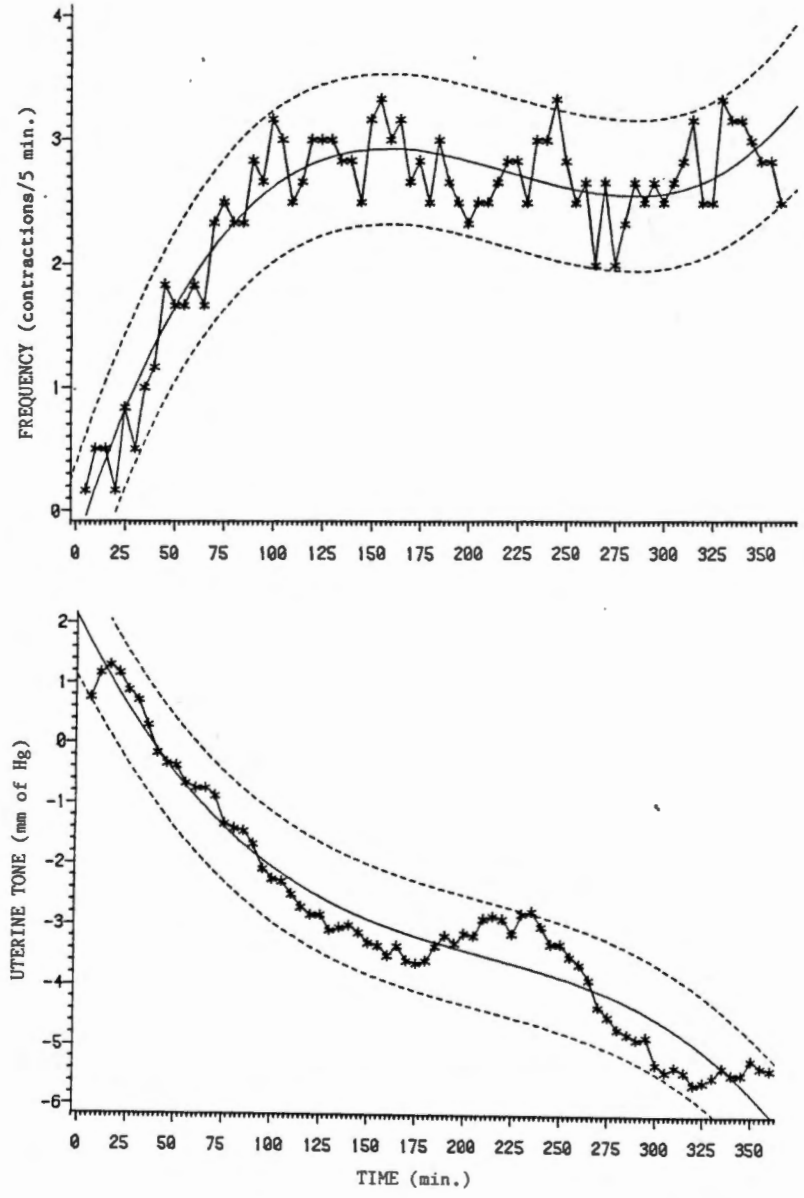


Figure 26 (continued)

there was an increase of approximately 1.5 mm of Hg and another decline to 5.5 mm of Hg below the starting level. Amplitude of contraction ranged from 0.25 mm Hg to 3.0 mm Hg, increasing from an approximate average of 0.35 mm Hg during the first hour to 1 mm Hg by the fourth hour and throughout the rest of the experiment. Duration of contraction ranged from 30 seconds to 2.5 min. Estimated average duration was 45 seconds/contraction during the first hour, peaked at 1 minute/contraction during the second and third hour, then returned to 45 seconds/contraction for the duration. Correlations between the dependent variables were highly significant ($P<0.0001$). The correlation coefficients for area to frequency, area to tone, and frequency to tone were 0.38, -0.22, and -0.52, respectively. The correlation coefficient for horn weight to balloon volume was 0.94 ($P<0.0001$).

7. EXP. 2. Dose-response (Fenprostalene and Oxytocin)

Uterine contractility in response to four dosages of fenprostalene (figure 27) and to four dosages of oxytocin (figure 28) shows no dose related effect for either drug. The dosage for fenprostalene and oxytocin which best approximated 80% of maximum area increase (0.1 mg and 2 IU, respectively) was selected for use in further experiments. Although the first injection of each drug caused a marked increase in area, frequency of contraction and uterine tone, a second treatment at the same dosage failed to significantly alter the general trend of contractility. Frequency tended to behave in a highly cyclical manner.

Fenprostalene dose-response. Comparisons of dosages in the fenprostalene dose-response experiment (Table A- 5) show no difference in baseline means for area and uterine tone, however, mean baseline

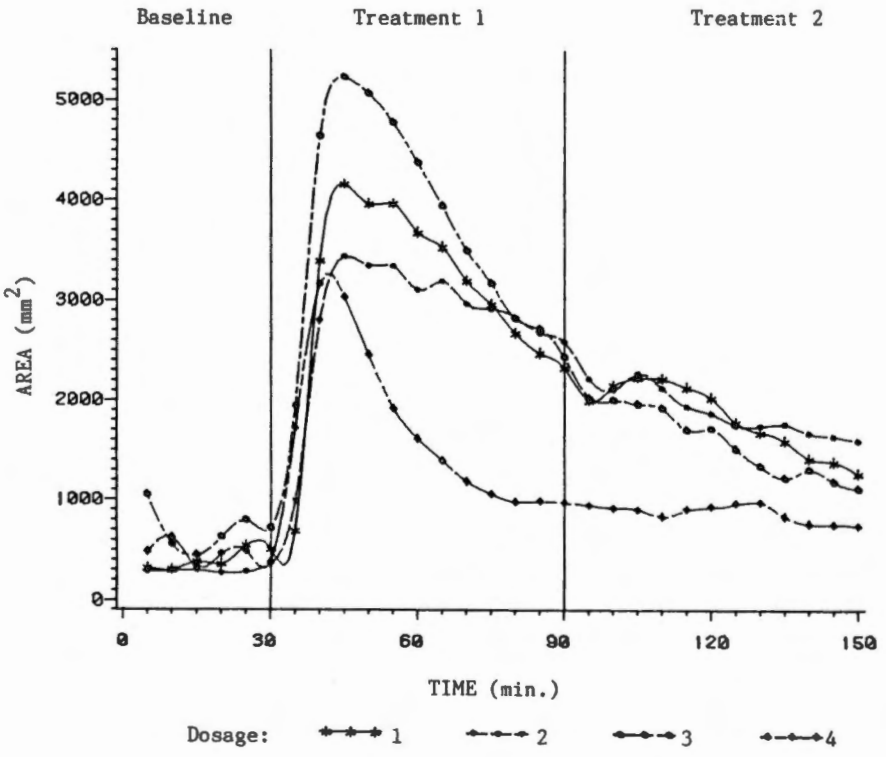
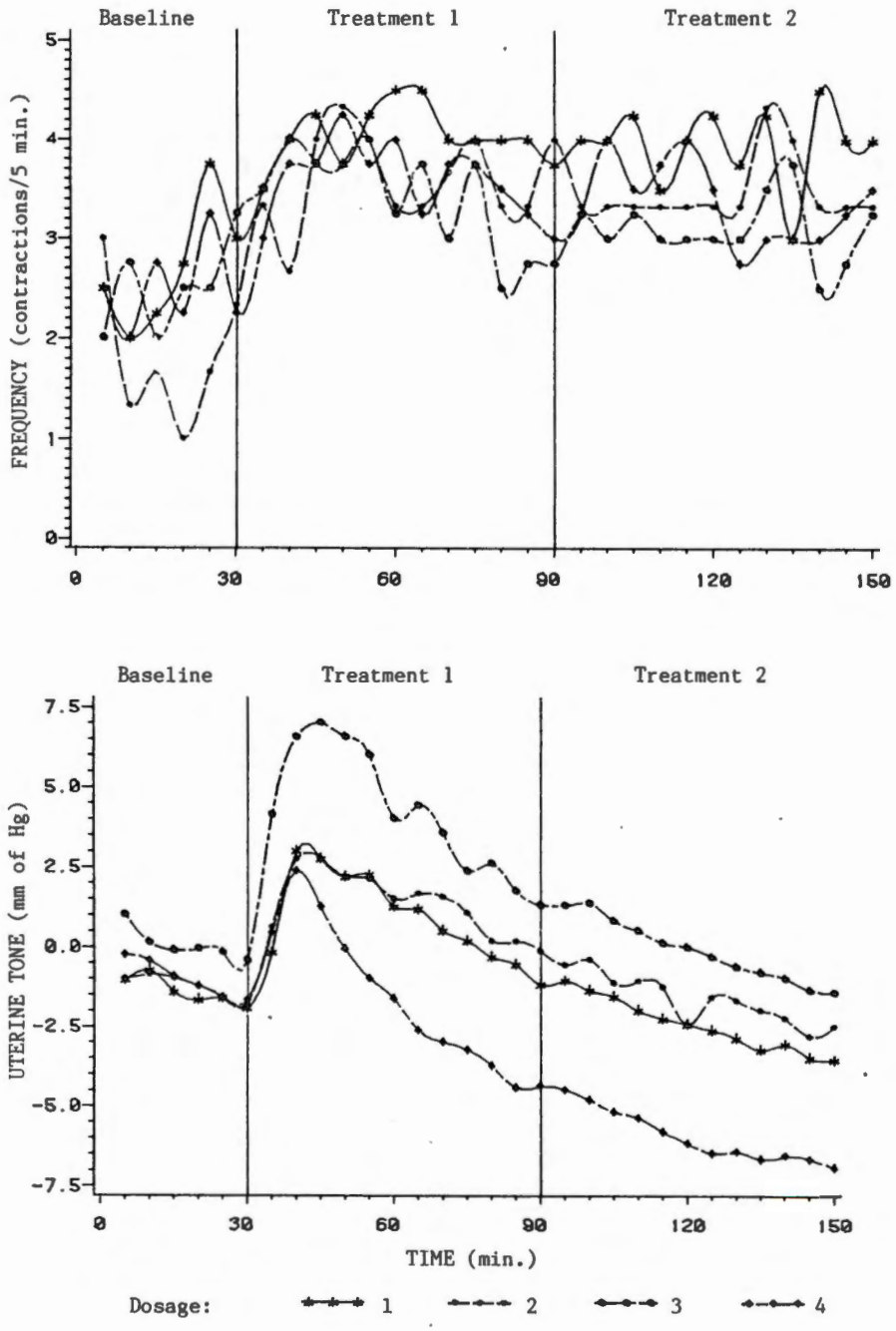


Figure 27. Uterine motility of isolated uterine horns treated with one of four dosages of fenprostalene (Exp. 2). Vertical lines indicate the times of drug treatment. Dosages were: 1) 0.1 mg, 2) 0.2 mg, 3) 0.3 mg, and 4) 0.5 mg. The same dosage was repeated at treatment 2.



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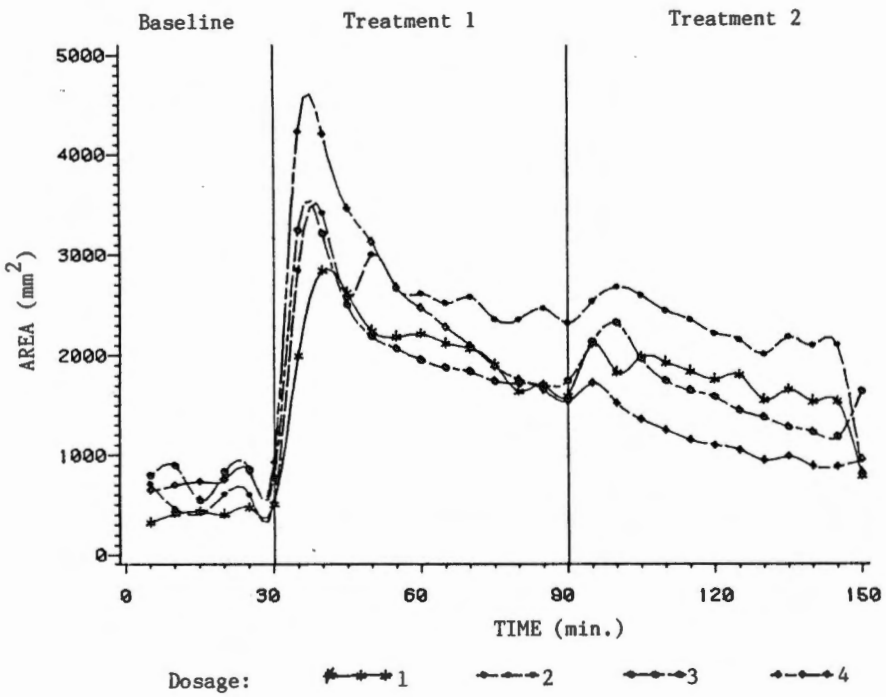

Figure 28. Uterine motility of isolated uterine horns treated with one of four dosages of oxytocin (Exp. 2). Vertical lines indicate the times of drug treatment. Dosages were: 1) 1 IU, 2) 2 IU, 3) 3 IU, and 4) 10 IU. The same dosage was repeated at treatment 2.

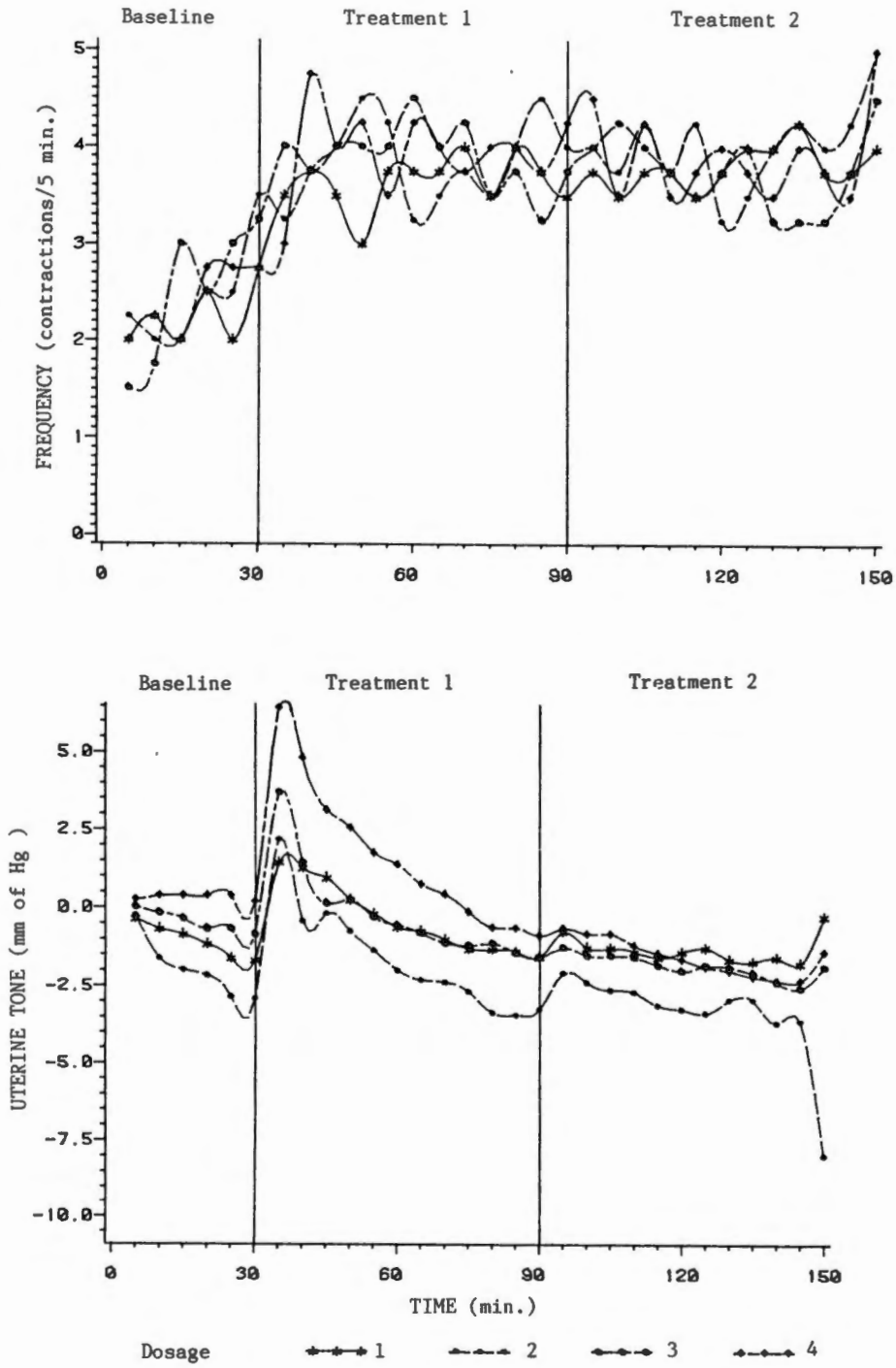

Figure 28 (continued)

frequency was higher ($P<0.05$) in the horns which later received 0.1 mg than the horns which received 0.2 mg or 0.3 mg (2.72±0.34, 1.90±0.48, and 2.10±0.24 contractions/5 min, respectively). All initial treatments significantly ($P<0.05$) increased mean area and frequency above baseline means. The 0.3 mg dosage caused the greatest ($P<0.05$) increase in mean area and tone, followed by the 0.1 and 0.2 mg dosages which were significantly higher ($P<0.05$) than the largest dosage, 0.5 mg. Uterine tonus changes over time followed the same general pattern as that of area. Seemingly, a second treatment of fenprostalene produced little change in area, frequency of contraction, or uterine tonus level (figure 27). Comparisons of means for dosages and treatments within dosage groups are shown in Table A-5. Estimated average amplitude increased from less than one mm Hg for baseline to approximately four mm Hg and eight mm Hg when treated with 0.1 mg and 0.2 mg fenprostalene, respectively. For the horns treated with 0.3 and 0.5 mg fenprostalene, baseline values for amplitude were approximately 2.5 and 1.5 mm Hg, respectively, increasing to 6.0 and 4.0 mm Hg following hormone treatment. A slight increase in amplitude was noted for a repeated treatment of the two lowest dosages (0.1 and 0.2 mg), while horns treated a second time with 0.3 or 0.5 mg tended to decline in amplitude. Measurable contraction amplitude ranged from 0.20 mm Hg to a maximum of 15.5 mm Hg. No consistent trend was noted for contraction duration (range 45-210 seconds).

Oxytocin dose-response. Mean area, frequency of contraction, and uterine tonus change over time and in response to oxytocin dosage are shown in figure 28. The first treatment of horns with 10 IU caused the greatest initial increase in area, followed by a rapid decline. This

decline resulted in a mean area for the 1 hour recording period which was not significantly ($P>0.05$) different from the other dosage levels. Means for each treatment within dosages are compared in Table A-6. Treatment of horns with 2 IU oxytocin resulted in a significantly ($P<0.05$) higher area increase than 1 IU or 3 IU (2652.5±124.9 vs 2100.9±108.3 and 2058.5±264.3 mm^2, respectively). Once again, a second treatment of horns with the same dosage resulted in little or no significant change in the trends elicited after the first injection. Area and frequency of contraction were, however, still signficantly ($P<0.05$) higher than baseline levels following the second hormone treatment. For uterine tone, generally, baseline tonus levels were intermediate to uterine tone following the initial treatment and the repeated treatment of oxytocin. Estimated average amplitude was approximately 1 mm Hg for baseline and was increased by approximately four times by oxytocin injection. Detectable amplitude ranges from 0.20 mm Hg to 16.5 mm Hg. Duration of contraction ranged from thirty seconds to 180 seconds with no noticeable trends occurring following hormone treatment.

8. Exp.3. Alternate Treatments of Oxytocin and Fenprostalene

Figure 29 shows the behavior of uterine horns when subjected to alternate treatments of oxytocin and fenprostalene. Baseline values were similar for measures of area, frequency, and uterine tone for the two treatment groups. When oxytocin (2 IU) was the initial treatment, area peaked at a level over 6 times that of baseline compared to approximately a five-fold increase when fenprostalene was the initial treatment. Mean area was increased by oxytocin from a baseline level of 378.1±278.1 mm^2 to 2072.8±198.4 mm^2. Unlike results seen in the

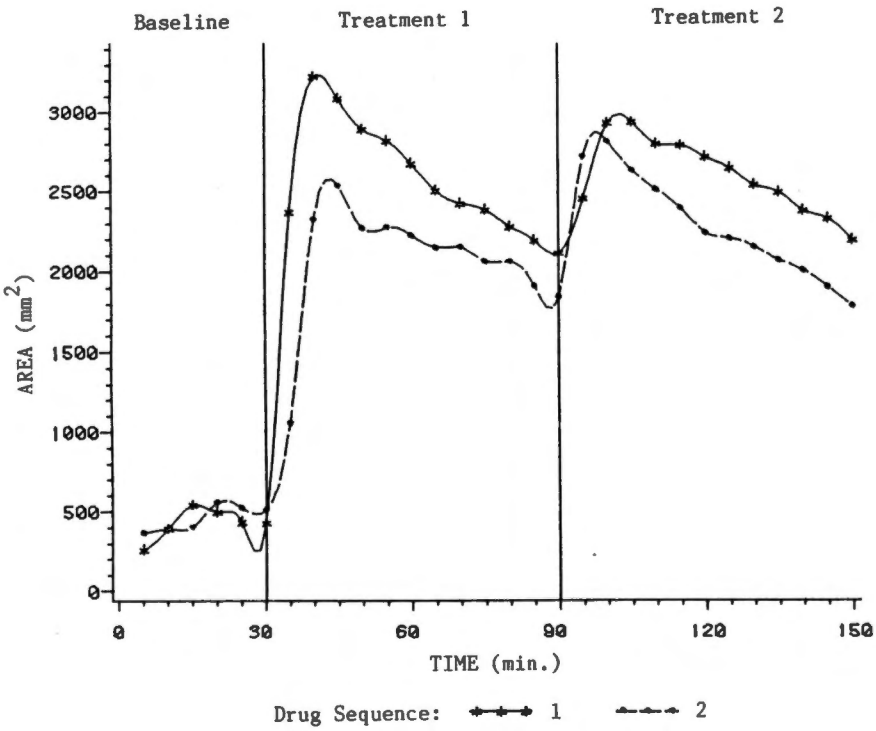

Figure 29. The effect of alternate treatments of oxytocin and fenprostalene on isolated uterine motility (Exp. 3). Vertical lines indicate the times of drug treatment. Drug sequence 1 was oxytocin (2 IU) then fenprostalene (0.1 mg). Drug sequence 2 was the reverse order.

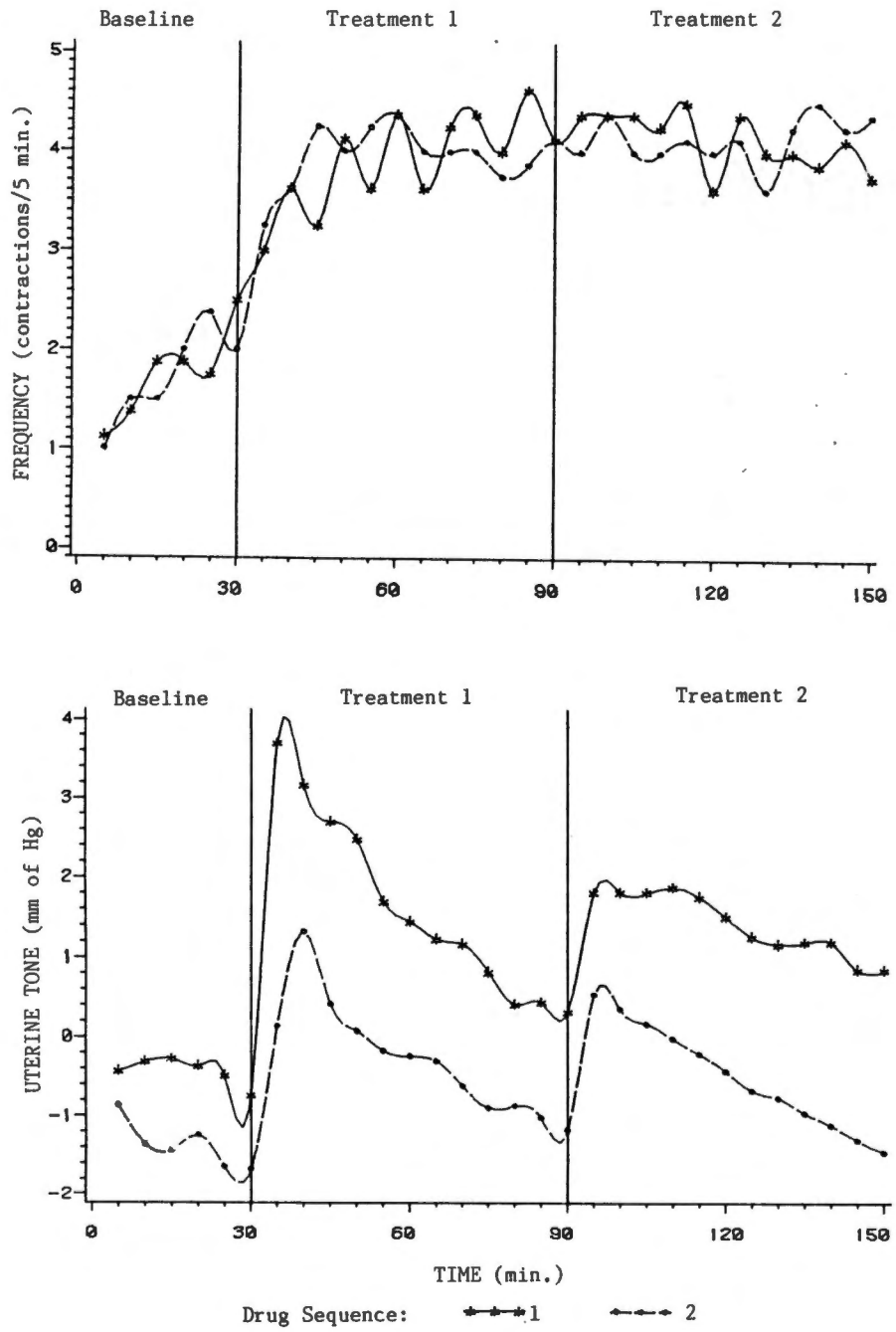

Figure 29 (continued)

dose-response experiments, when fenprostalene followed an initial oxytocin treatment or when oxytocin followed an initial fenprostalene treatment, a substantial secondary increase in area and uterine tone was observed (figure 29). These differences for treatment period means were significantly ($P<0.05$) higher than baseline means for area and frequency. Although still higher than baseline, the mean uterine tonus level for the second injection was no longer significantly different as seen in Table A-7. Estimated average amplitude was 1.0 mm Hg, 3.0 mm Hg, and 4.0 mm Hg for baseline, treatment one and treatment two respectively. Measurable amplitude ranged from 0.20 mm Hg to 8.5 mm Hg over the entire experiment. Contraction duration ranged from thirty seconds to 150 seconds. The correlation coefficients for area to frequency, area to tone, and frequency to tone were 0.51, 0.80, and 0.34 ($P<0.0001$), respectively.

9. Repeated Treatment of the Same Drug on Uterine Motility

Fenprostalene. Figure 30 shows the effect of the second treatment of fenprostalene (0.1 mg) on uterine motility in isolated uterine horns. The initial treatment of fenprostalene significantly ($P<0.05$) increased area and frequency above baseline values. This difference was maintained by a second treatment but little secondary increase was observed. When 60 minutes were allowed between treatments a slight (NS) peak in area (approximately 300 mm^2) was elicited but area had returned to pre-injection levels within 25 minutes. The horns which received a 75 minute time interval between treatments exhibited an even smaller response in area while the gradual area decline seen in horns receiving a time interval of 150 minutes between treatments was unaltered by the

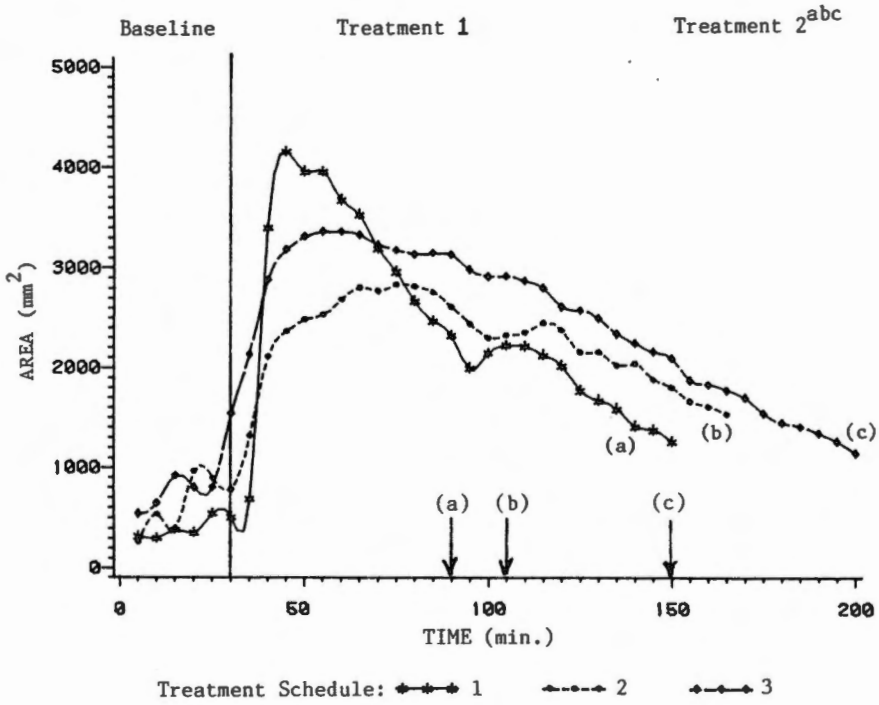

Figure 30. The effect of a second treatment of fenprostalene (0.1 mg) and different time intervals between treatments on isolated uterine horn motility (Exp. 4). The vertical line indicates the initial treatment. Arrows indicate the time of the second treatment for the line with the corresponding letter. Treatment schedules 1, 2, and 3 allowed a 60, 75, and 120 min. time interval between treatments, respectively.

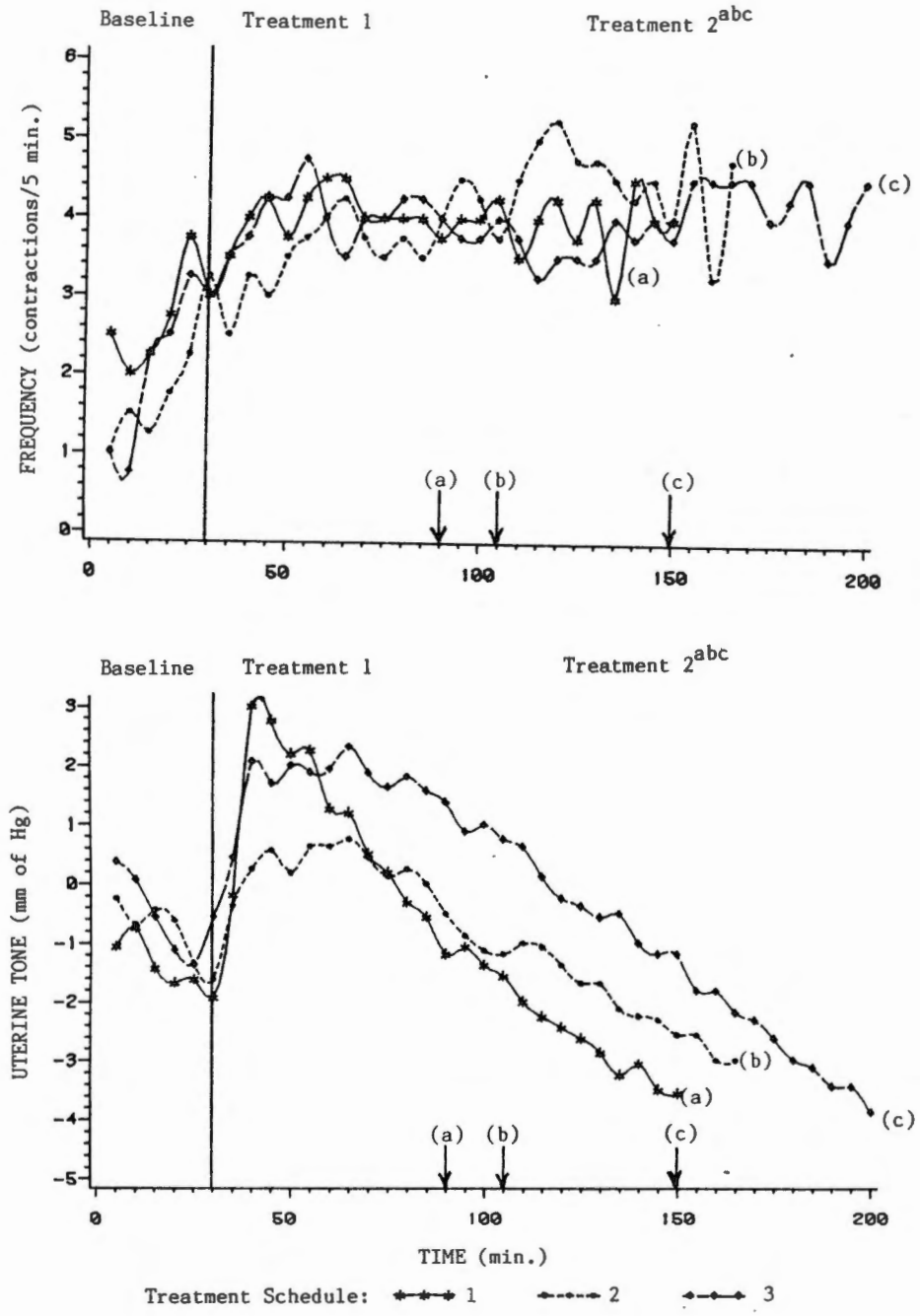

Figure 30 (continued)

latter treatment. A comparison of initial and secondary drug treatments (Table A-8) shows that the first treatment of fenprostalene yielded a significantly ($P<0.05$) larger area response than the second when 60 or 120 minute time intervals were allowed between treatments. Mean area for the first and second treatments of the intermediate time interval group were statistially equal, however, the second treatment initiated a significantly ($P<0.05$) greater frequency of contraction than the first. The behavior of uterine tone over time was very much like that of area for the corresponding time interval. Neither treatment or time interval had a noticable effect on amplitude or contraction. Amplitude ranged from 0.25 to 6.0 mm Hg while contraction duration ranged from 25 to 170 minutes. The correlation coefficients for area to tone, area to frequency and frequency to tone were 0.71, 0.43, and 0.16, respectively.

Oxytocin. The effect of a previous injection of oxytocin (2 IU) on a subsequent treatment of oxytocin (2 IU) with various time intervals between treatments is shown in figure 31. All initial treatments caused a significant ($P<0.05$) increase in area over baseline values. When a second treatment of oxytocin was administerd at 60, 75, or 120 minutes after the initial treatment a different response was obtained for each group. The horns treated at a one hour interval exhibited a slight short-termed (25 min) peak of motility but the mean response did not vary significantly ($P>0.05$) from the general downward trend following the initial treatment response. When 75 minutes were allowed between treatments, the second treatment caused a larger (but non-significant) increase than the initial treatment. In contrast, when there was 120 min. between treatments, a rapid decline in area was observed fifteen

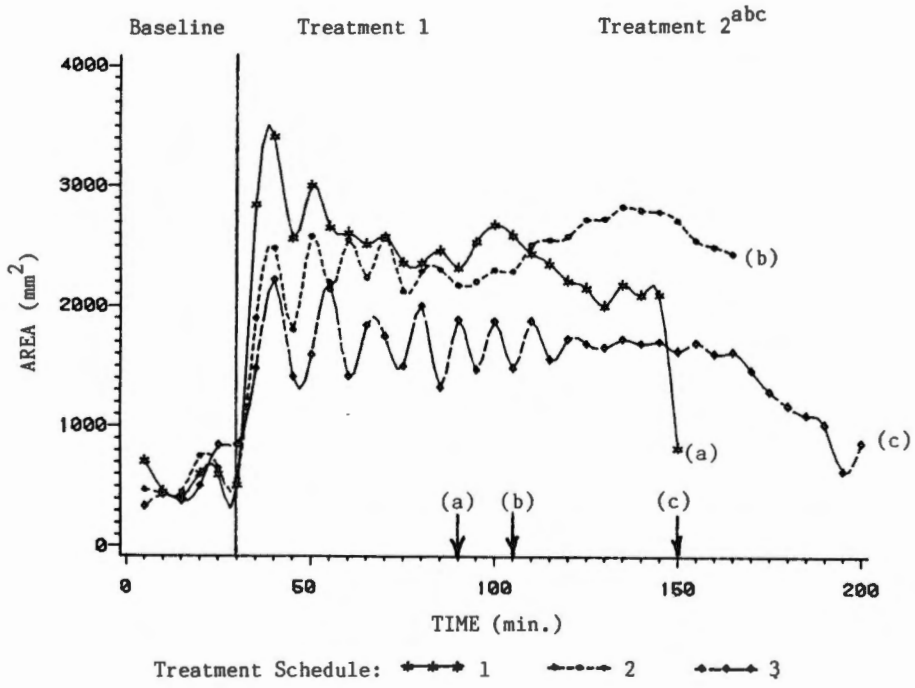

Figure 31. The effect of a second treatment of oxytocin (2 IU) and different time intervals between treatments on isolated uterine horn motility (Exp. 4). The vertical line indicates the initial treatment. Arrows indicate the time of the second treatment for the line with the corresponding letter. Treatment schedules 1, 2, and 3 allowed a 60, 75, and 120 min. time interval between treatments, respectively.

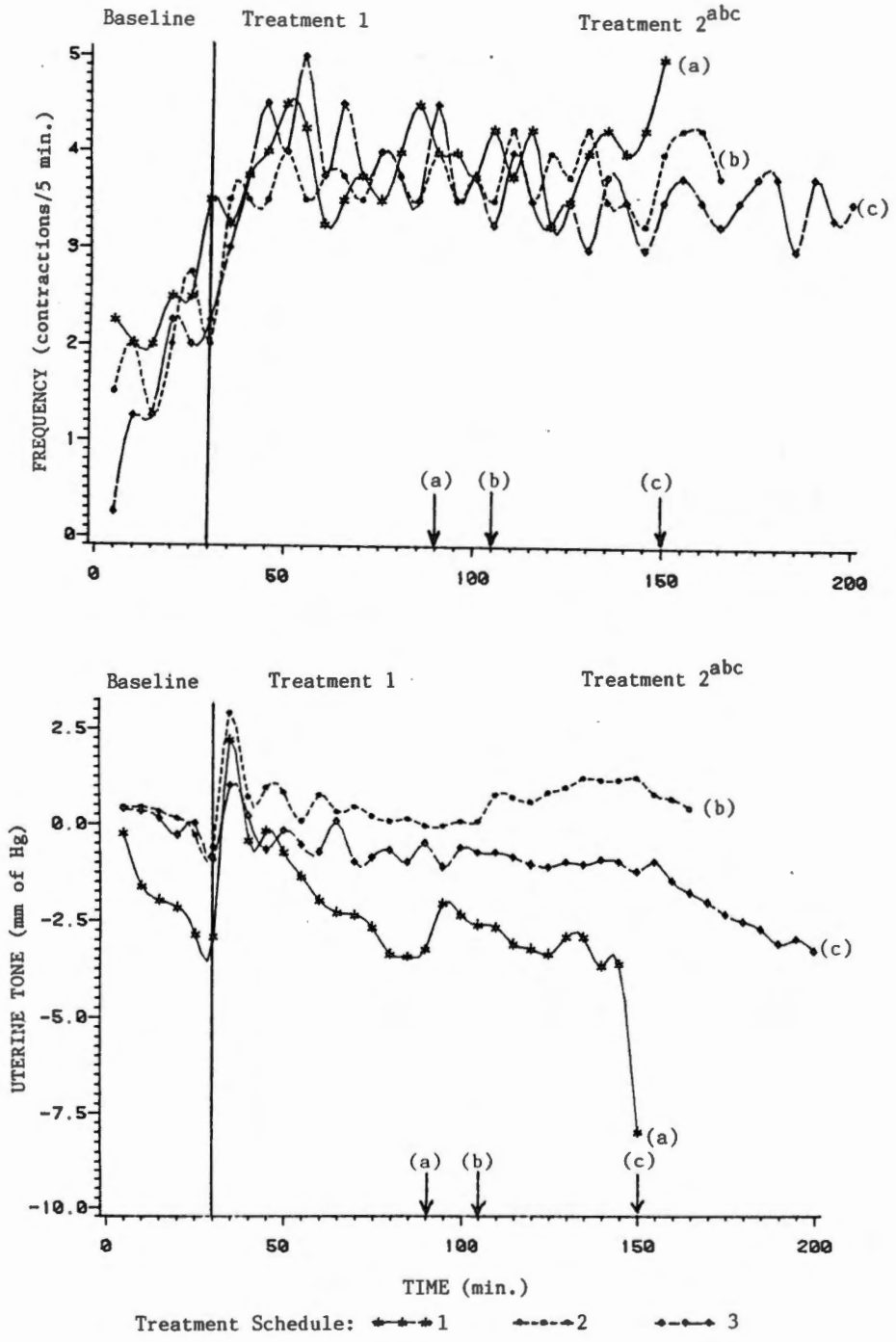

Figure 31 (continued)

minutes following the second drug injection. This resulted in a significantly ($P<0.05$) lower mean area value than that following the first treatment. The area for the two shorter time interval treatments was significantly higher than that of the longest time interval (Table A-9). Frequency values for each time interval were similar as was tone for the first injection. However, mean uterine tone was significantly ($P<0.05$) higher for the intermediate time interval when compared to the short (60 min) or long (120 min) intervals. The rate of tonus change over time closely resembled the trend of area change over time. Estimated amplitude and duration of contraction ranged from 0.25 to 6.5 mm Hg and 30 to 180 seconds, respectively. Neither mean amplitude nor mean duration appeared to be altered by hormone treatment. Correlation coefficients of area to frequency, area to tone, and frequency to tone were 0.46, 0.58, amd 0.17, respectively.

Comparison of fenprostalene and oxytocin by time intervals. When horns treated with oxytocin or fenprostalene and allowed a 60 minute time interval were compared (Figure 32), no significant ($P>0.05$) difference was observed in mean area, frequency, or uterine tone for any treatment administered. However, significant ($P<0.05$) differences were detected in the behavior of fenprostalene and oxytocin-treated horns allowed a time interval of 75 minutes between treatments (Figure 33). Oxytocin as the second injection caused a much larger response in area and uterine tone than did the second injection of fenprostalene, although the reverse was true for frequency. With the longest time interval, fenprostalene caused a significantly ($P<0.05$) higher frequency of contraction as compared to the second injection of oxytocin (Figure

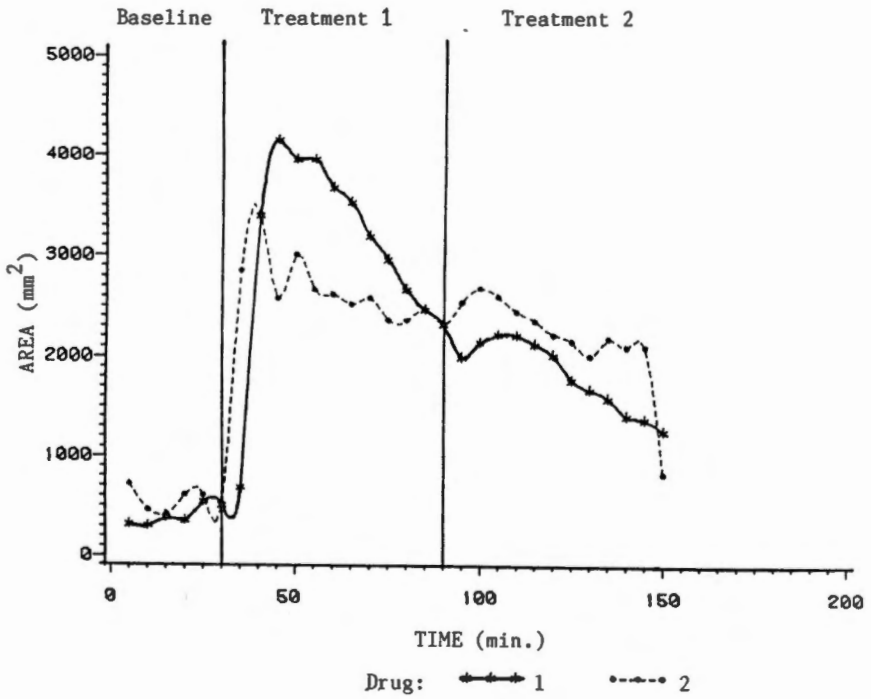

Figure 32. A comparison of the effect of a second treatment of oxytocin to fenprostalene on isolated uterine motility when a 60-minute time interval was allowed between drug treatments. Vertical lines represent treatment times. Drug 1 = fenprostalene (0.1 mg). Drug 2 = oxytocin (2 IU).

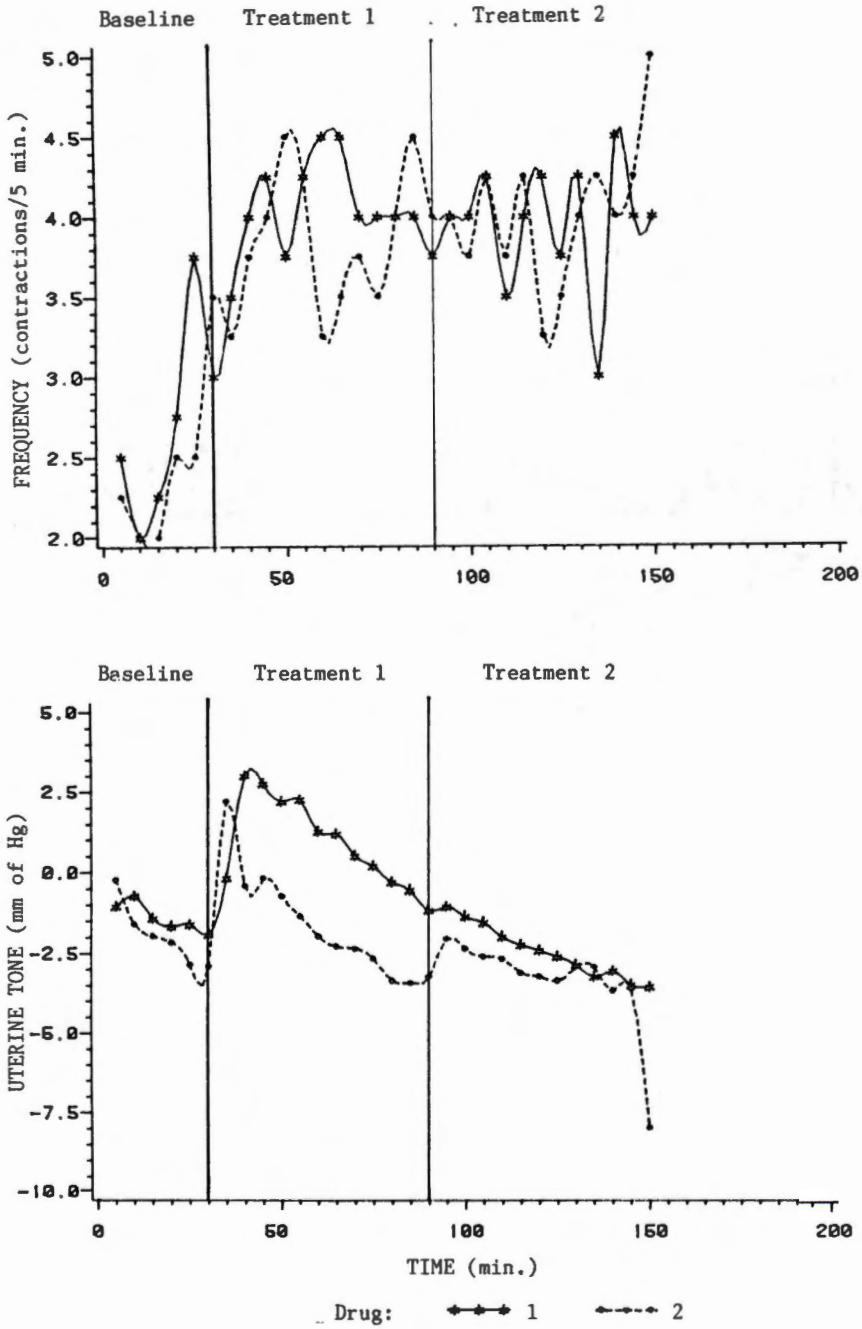

Figure 32 (continued)

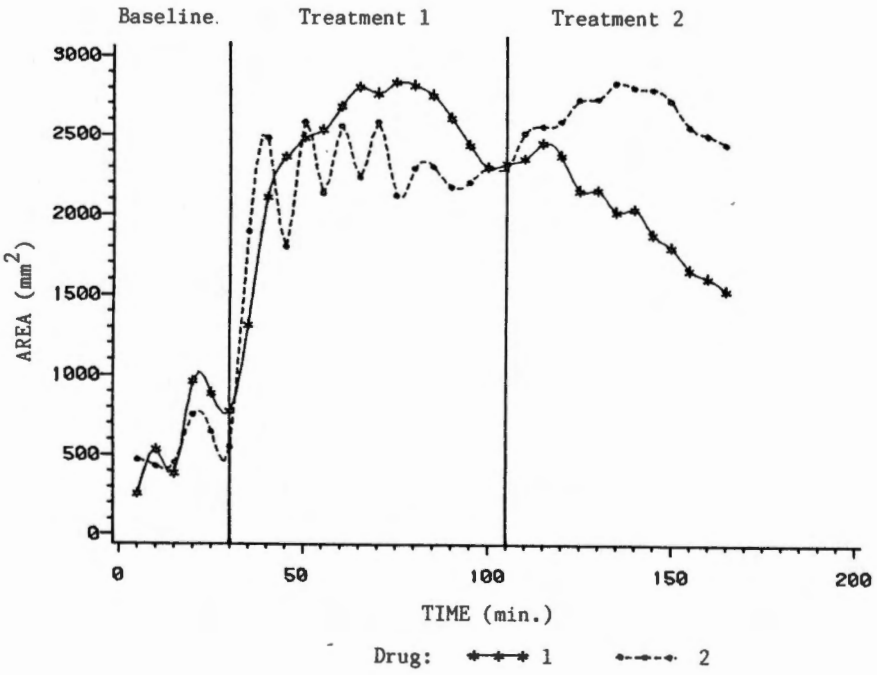

Figure 33. A comparison of the effect of a second treatment of oxytocin to fenprostalene on isolated uterine motility when a 75-minute time interval was allowed between drug treatments. Vertical lines represent treatment times. Drug 1 = fenprostalene (0.1 mg). Drug 2 = oxytocin (2 IU).

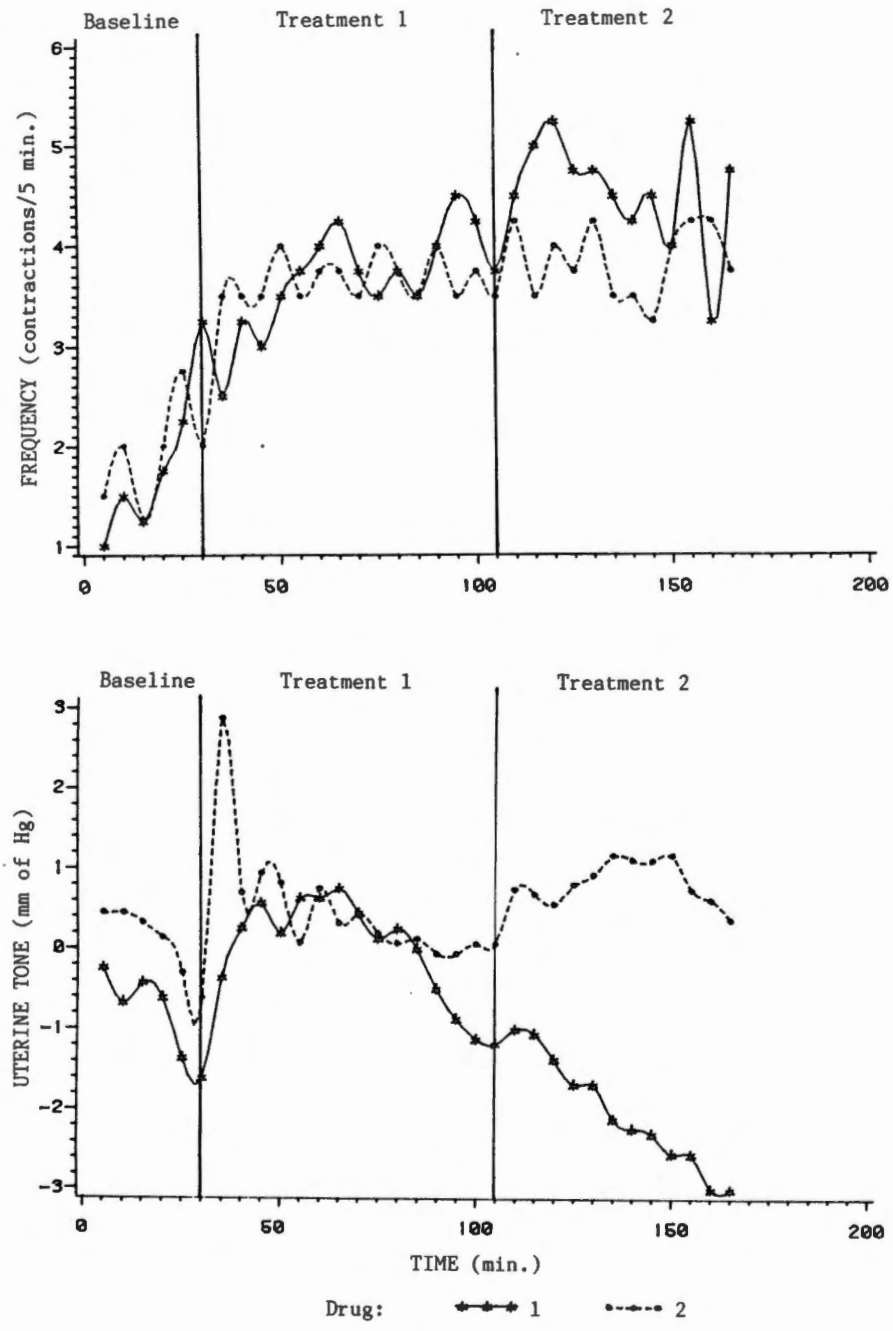

Figure 33 (continued)

34). Fenprostalene elicited a much larger ($P<0.05$) response of area and uterine tone at the first injection, however, oxytocin and fenprostalene horns were very similar in behavior for these variables following the second treatment (Figure 34).

10. EXP.5. Fenprostalene, Oxytocin, and a Mixture on Motility

The effect of fenprostalene (0.1 mg),. oxytocin (2 IU), and a mixture of half fenprostalene (0.05 mg) and half oxytocin (1 IU) on uterine motility was evaluated (Figure 35). A much greater ($P<0.05$) response to oxytocin alone or fenprostalene alone was noted as compared to the mixture of the two when area and uterine tone were the variables measured. A slight response was observed in uterine tone and area following the addition of the mixture to the tissue, but this response was not significantly ($P<0.05$) different from baseline. However, the effect of either drug alone, as well as the mixture of the two, on mean frequency was significantly ($P<0.05$) above mean baseline frequency (Table A-10). Contraction amplitude following the mixture administration was only slightly affected (1.5 vs 2.5 mm Hg, baseline vs treated, respectively). Increased frequency associated with drug treatment decreased estimated average duration of contraction from 60 to 45 seconds. The only significant independent variable correlation in this experiment was between area and frequency (0.61, $P<0.0001$).

D. DISCUSSION

Results from this study indicate that isolated uterine horns are very much suitable for in vitro measurement of motility. It is believed that utilization of the entire horn rather than strips more nearly

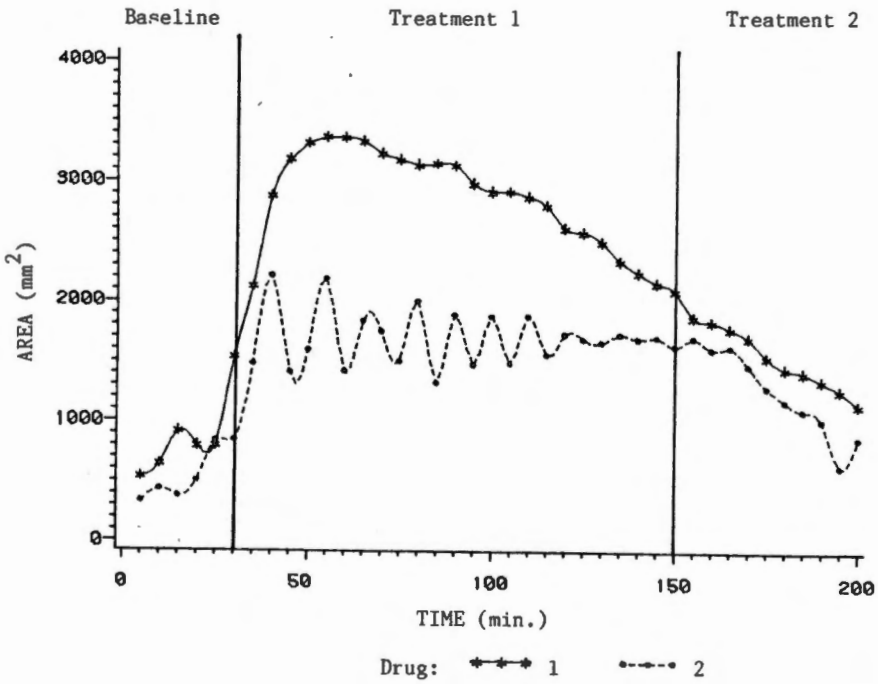

Figure 34. A comparison of the effect of a second treatment of oxytocin to fenprostalene on isolated uterine motility when a 120-minute time interval was allowed between drug treatments. Vertical lines represent treatment times. Drug 1 = fenprostalene (0.1 mg). Drug 2 = oxytocin (2 IU).

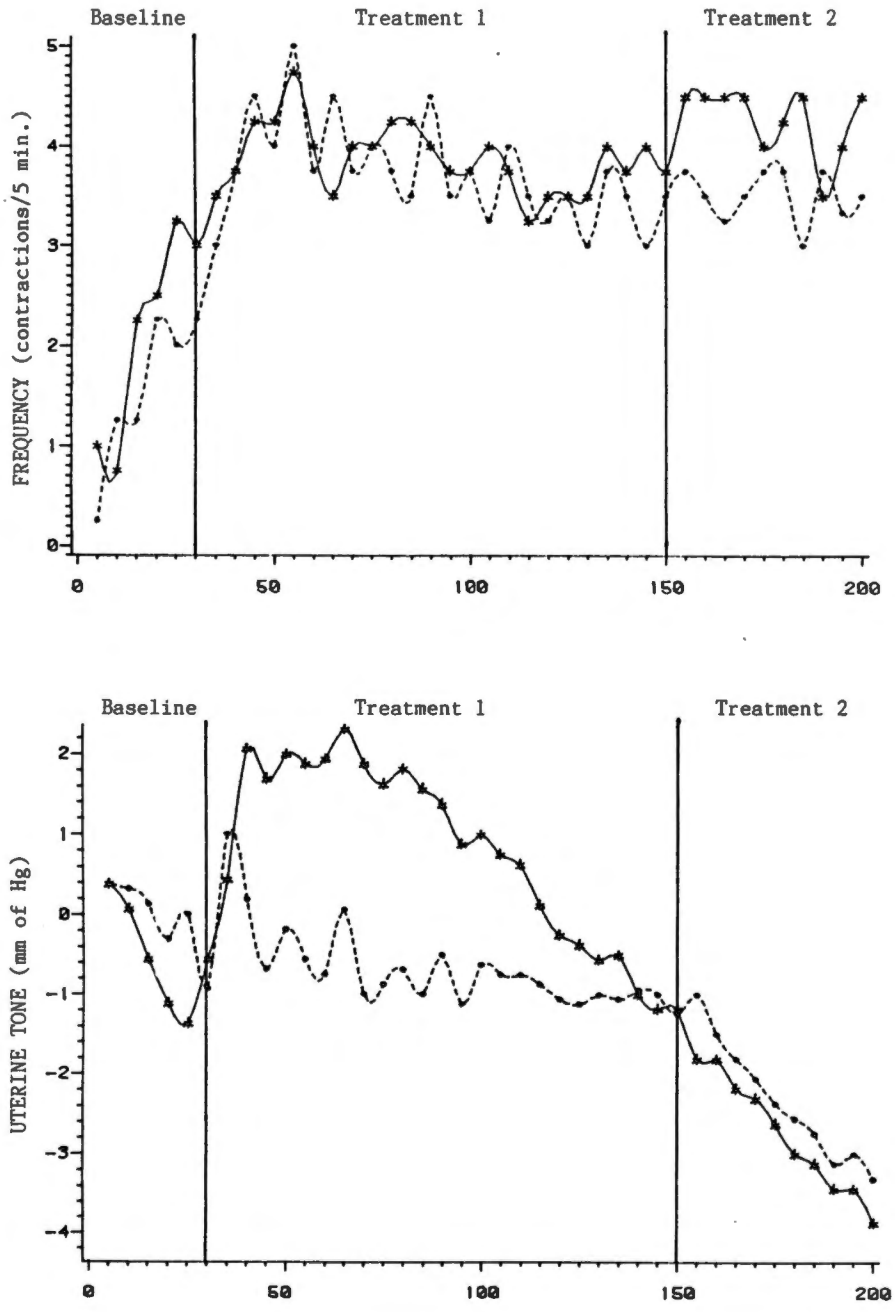

Figure 34 (continued)

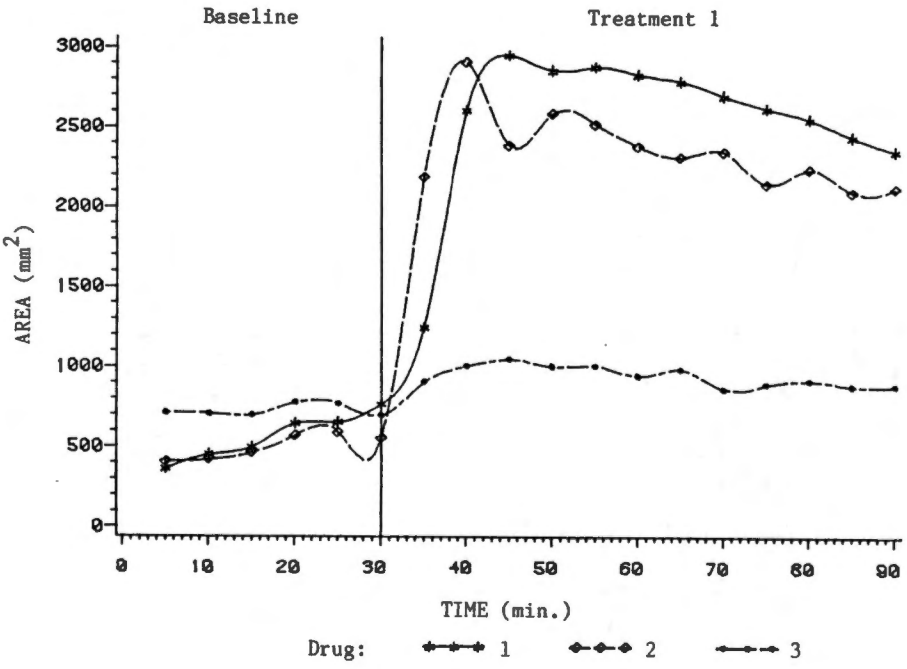

Figure 35. The effect of a single treatment of fenprostalene, oxytocin, or a mixture of the two on isolated uterine motility (Exp. 5). The vertical line indicates time of treatment. Drugs were 1) fenprostalene (0.1 mg), 2) oxytocin (2 IU), and 3) a mixture containing 0.05 mg fenprostalene and 1 IU oxytocin.

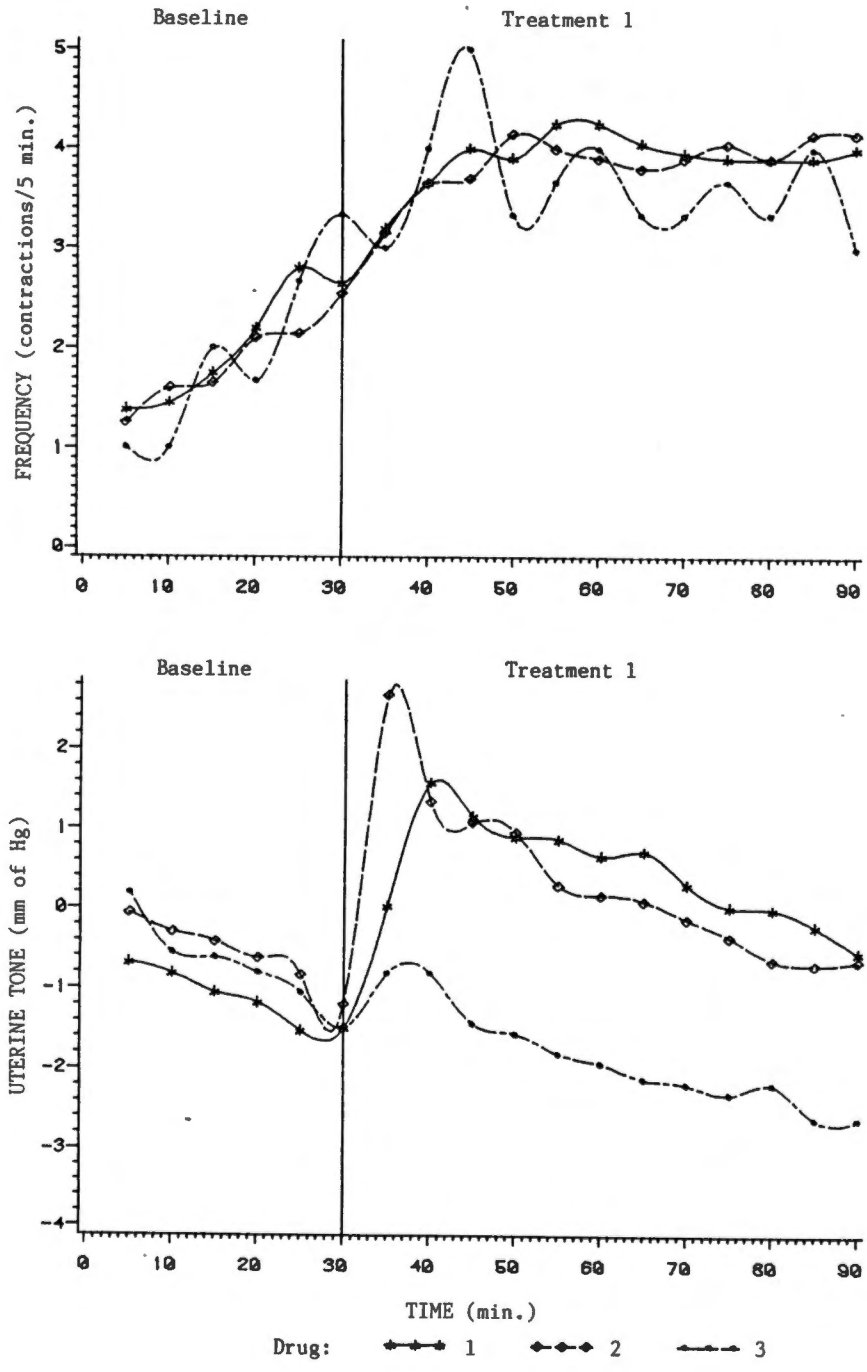

Figure 35 (continued)

mimics the situation of the live animal because both circular and longitudinal strips are involved in any recorded contractions. The isolated horn, however, does require a strictly regulated environment to achieve favorable results. In preliminary experiments, no motility was observed in uterine horns maintained in Lactated Ringers or Ringers solution with glucose. It would then seem that the electrolyte balance is critical, assuming energy requirements were met. Tyrode's solution provided magnesium and phosphate whereas the other physiological solutions did not. Although not as critical, solution pH was also important in maintaining suitable contractility. In most cases, solution pH tended to increase over time because of the large percentage of oxygen being bubbled through the tissue bath. This oxygen displaced a hydrogen from the bicarbonate ion therefore decreasing the hydrogen ion concentration of the solution and making water. Motility decreased with pH change due to decreased or increased electron potentials across the cellular membrane, preventing normal ion flux. It was also discovered that when uterine horns were transported in 4° C Tyrode's solution, spontaneous motility was reduced and delayed for a minimum of thirty minutes. A certain degree of cold shock was apparently responsible for this behavior. The survival time of horns transported in room temperature Tyrode's in that contractility remained at near initail levels for two horns allowed to contract for approximately twelve hours. This amazing durability of bovine isolated horns is supportive of this technique over uterine strips.

It was somewhat disappointing that glucose uptake could not be measured in the isolated uterus set-up. Although fluid volume was

periodically adjusted for evaporation, glucose concentrations did not show any trend over the recording period. This could indicate that glucose is not utilized by the tissue or more likely, that the glucose assay was not sensitive enough to detect minute changes. The glucose concentration was 100 mg/100 ml in 17 liters of solution per bath. Therefore, a large amount of glucose utilization would be required to significantly alter the bath concentration.

As noted, everted uterine horns exhibited no uterine activity either spontaneously or in response to oxytocin or fenprostalene. It is unlikely that this was caused by the manipulation procedure. Decreased rumen motility is used in the diagnosis of displacement or torsion in cattle. It is also known that intestinal peristalisis ceased when there is a constriction or prolapse. In such a case, cessation of motility could be a protective mechanism to prevent further damage. This finding warrants further investigation.

The effect of ovarian structure on uterine strip motility has been established (Patil et al., 1980). The same general trends were observed in this study with follicular phase exhibiting greater motility than horns from a luteal phase environment. Follicular phase horns were more responsive to fenprostalene than were other phases, however, luteal phase horns were most responsive to oxytocin. In this study follicles were not discerned from follicular cysts so if a larger number of cystic influenced horns were treated with oxytocin and motility was reduced as reported by Patil et al. (1980), this could explain the difference. Patil et al.(1980) did report the incidence of "no real contractions" in

two cows with follicular cysts and the same asynchrony of contraction was observed in this study.

It was discovered that as horn weight increased, measures of uterine motility tended to decrease in magnitude. This would lead one to believe that proper nutrient availability to the innermost cells was not maintained. Future experimentation might be advised to selectively include uterii from young non-parous females to maximize the surface area to tissue ratio and thus nutrient availability. The balloon fluid volume also exhibited the same relationship in isolated cases. However, horn weight and balloon were highly correlated and therefore were confounded to some extent in the statistical model. One would not expect balloon volume to effect any variable except the initial tonus level. Balloon volume and horn weight should in most cases be used to judge the efficiency of volume standardization.

In the measurement of spontaneous motility over time a cubic response was observed. No logical explanation for this exists. Uterine tone showed a steady decline over time while frequency increased to a maximal level after approximately two hours of recording. Area under the recording increased until about four hours after recording started and then steadily declined. It appears that frequency was the principal varialbe affecting area until uterine tonus decline reached a certain level.

Neither fenprostalene or oxytocin demonstrated dose-response behavior in this experiment. This has been reported for $PGF_2\alpha$ both in vivo and in vitro (Eiler et al., 1981; Patil et al., 1980). Preventative mechanisms against overstimulation may be involved. Only slight

reactivity was observed for a second injection of either drug indicating refractoriness to multiple treatments.

However, when oxytocin and fenprostalene treatments were alternated response to the second injection was comparable to that of the first. This is almost conclusive evidence of a two receptor mechanism. When ocytocin treatment followed fenprostalene an even greater response was observed. This could be a result of the difference in half-life between the two drugs (i.e. fenprostalene may be still present in the bath solution and could add to motility to a minor extent).

When the same drug treatment was repeated in experiment four little response was gained from a second treatment when one or two hours were allowed between treatments. When 75 minutes were allowed between treatments the average response was greater than for the second treatment for 60 or 120 minutes. Speculation on the cause should consider the drug half-life and possible protective mechanisms inherent to the tissue.

As noted in experiment five, there seems to be no synergism or additiveness between oxytocin and fenprostalene when administered as a mixture. Dosages for each used in the mixture were above the threshold dosage, therefore one would expect a larger response than seen here. This result would seem to conflict with the oxytocin-prostaglandin relationships reported in the literature (Roberts and McCracken, 1976; Newcomb et al., 1977; Roberts et al., 1976; Armstrong and Hansel, 1959). Further investigation is warranted to more fully understand the response obtained in this experiment.

CHAPTER IV

GENERAL DISCUSSION

In this study, results demonstrated that fenprostalene, although active, did not elicit a significant ($P > 0.05$) response in the bovine uterus in vivo. The response was greatest in open cycling cows as compared to postpartum cows. Therefore, in light of the large response following oxytocin injection, fenprostalene alone is not suitable for therapeutical treatments where an increase in uterine contractility is desired.

In contrast, fenprostalene is very much comparable to oxytocin in the isolated system. Also, the isolated uterine horn shows contractility patterns very much like the live open cow. Similarities include type of contraction, a shorter latency of response to oxytocin than prostaglandin, and refractoriness to repeated injections of the same drug. In addition, in all three situations of motility (postpartum, open cycling, and isolated) the correlations between the variables followed the same type of trend. As a general rule, an increase in frequency caused a decrease in uterine tone over time. This would indicate that as more work was done relaxation between contractions increased. This could indicate a mechanism inherent to the tissue for maximizing output during periods of intense work such as during parturition.

The isolated uterine horn set-up seems to be an excellent model for open cow motility measurements, especially when recordings will be taken over an extended time period.

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APPENDIX

TABLE A-1

COMPARISON OF MEAN MEASURES OF UTERINE CONTRACTILITY IN RESPONSE TO VARIOUS DRUG TREATMENTS ADMINISTERED TO EARLY POSTPARTUM COWS (n = 7) ON TWO CONSECUTIVE DAYS

			Measure of Uterine Motility*				
Day	Treatment	Dose/Route	Area (mm^2)	Tone (mm of Hg)	Frequency (counts/5 min.)	Amplitude (mm of Hg)	Duration (seconds)
1	Baseline	-----	534.9 ± 39.0^{a}	-3.35 ± 0.66^{ab}	0.62 ± 0.009^{a}	8.79 ± 1.29^{a}	51.6 ± 6.67^{a}
	Fenprostalene	0.1 mg, IM	570.7 ± 28.6^{a}	-10.92 ± 1.29^{c}	0.79 ± 0.06^{ab}	9.29 ± 0.84^{a}	58.3 ± 4.42^{at}
	Fenprostalene	0.1 mg, IV	734.5 ± 49.0^{a}	-23.69 ± 2.70^{d}	0.99 ± 0.09^{ab}	15.85 ± 2.05^{b}	71.1 ± 7.06^{b}
	Oxytocin	40 IU, IV	1654.1 ± 155.9^{b}	-11.70 ± 2.16^{c}	2.32 ± 0.20^{c}	24.40 ± 1.89^{c}	101.7 ± 6.94^{c}
2	Baseline	------	566.1 ± 42.1^{a}	-1.16 ± 0.47^{a}	0.64 ± 0.09^{a}	6.93 ± 0.95^{a}	37.5 ± 5.47^{a}
	Oxytocin	100 IU, IM	1174.1 ± 52.3^{c}	-5.63 ± 0.41^{ab}	1.70 ± 0.08^{b}	19.78 ± 0.91^{d}	98.1 ± 3.68^{c}
	Fenprostalene	0.1 mg, IV	597.4 ± 37.1^{a}	-7.50 ± 1.07^{bc}	1.04 ± 0.12^{c}	8.85 ± 0.88^{a}	72.8 ± 6.94^{b}
	Oxytocin	40 IU, IV	1694.5 ± 213.2^{b}	-7.02 ± 1.53^{bc}	2.12 ± 0.18^{c}	20.98 ± 1.66^{cd}	104.2 ± 5.40^{c}

* Mean ± SEM.

$^{a-d}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-2

COMPARISON OF MEAN MEASURES OF UTERINE CONTRACTILITY IN RESPONSE TO VARIOUS DRUG TREATMENTS ADMINISTERED TO OPEN CYCLING HOLSTEIN COWS (n = 6) ON TWO CONSECUTIVE DAYS

			Measure of Uterine Motility*				
Day	Treatment	Dose/Route	Area (mm^2)	Tone (mm Hg)	Frequency (counts/5 min.)	Amplitude (mm Hg)	Duration (seconds)
1	Baseline	------	1414.7 ± 135.3^{a}	-1.33 ± 0.60^{a}	2.56 ± 0.12^{a}	20.29 ± 2.42^{a}	95.7 ± 3.98^{a}
	Fenprostalene	0.1 mg, IM	1555.5 ± 95.9^{a}	-8.99 ± 0.50^{b}	2.44 ± 0.07^{a}	22.32 ± 1.44^{a}	102.5 ± 2.50^{a}
	Fenprostalene	0.1 mg, IV	1364.3 ± 103.7^{a}	-13.51 ± 0.94^{c}	2.32 ± 0.12^{a}	18.91 ± 2.02^{a}	101.2 ± 5.96^{a}
	Oxytocin	40 IU, IV	2482.4 ± 208.1^{b}	-11.51 ± 1.26^{c}	2.93 ± 0.15^{b}	30.81 ± 2.36^{bc}	96.5 ± 3.94^{a}
2	Baseline	------	1780.3 ± 112.6^{bc}	-7.93 ± 0.52^{b}	2.53 ± 0.09^{a}	24.85 ± 1.55^{bc}	102.1 ± 3.42^{a}
	Oxytocin	100 IU, IM	2675.3 ± 81.6^{bd}	-18.25 ± 0.74^{d}	2.98 ± 0.07^{b}	33.95 ± 1.20^{b}	95.3 ± 2.16^{a}
	Fenprostalene	0.1 mg, IV	2054.7 ± 99.3^{c}	-23.84 ± 1.05^{e}	2.59 ± 0.10^{a}	29.16 ± 1.62^{bc}	102.9 ± 3.86^{a}
	Oxytocin	40 IU, IV	3008.3 ± 269.4^{d}	-21.68 ± 2.01^{e}	3.09 ± 0.15^{b}	36.18 ± 2.66^{b}	88.4 ± 5.30^{a}

* Mean ± SEM.

[a-e] Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-3

COMPARISONS OF MEAN MEASURES OF UTERINE CONTRACTILITY IN RESPONSE TO VARIOUS DRUG TREATMENTS ADMINISTERED TO EARLY POSTPARTUM AND OPEN CYCLING COWS ON THE FIRST EXPERIMENTAL DAY*

			Measure of Uterine Motility**				
Cow Status	Treatment	Dose/Route	Area (mm^2)	Tone (mm Hg)	Frequency (counts/5 min.)	Amplitude (avg. mm Hg)	Duration (seconds)
Postpartum	Baseline	------	534.9 ± 39.0^{a}	- 3.35 ± 0.66^{a}	0.62 ± 0.09^{a}	8.79 ± 1.29^{a}	51.7 ± 6.67^{a}
	Fenprostalene	0.1 mg/IM	570.7 ± 28.6^{a}	-10.93 ± 1.29^{b}	0.79 ± 0.06^{ab}	9.29 ± 0.84^{a}	58.3 ± 4.41^{a}
	Fenprostalene	0.1 mg/IV	734.5 ± 49.0^{a}	-23.69 ± 2.70^{c}	0.99 ± 0.09^{b}	15.85 ± 2.05^{b}	77.1 ± 7.06^{b}
	Oxytocin	40 IU/IV	1654.1 ± 155.9^{b}	-11.70 ± 2.16^{b}	2.33 ± 0.20^{c}	24.40 ± 1.89^{c}	101.7 ± 6.94^{c}
Open	Baseline	------	1414.7 ± 135.3^{b}	- 1.33 ± 0.60^{a}	2.56 ± 0.12^{c}	20.29 ± 2.42^{bc}	95.7 ± 3.98^{c}
	Fenprostalene	0.1 mg/IM	1555.5 ± 95.9^{b}	- 8.99 ± 0.50^{b}	2.44 ± 0.07^{c}	22.32 ± 1.44^{bc}	102.5 ± 2.50^{c}
	Fenprostalene	0.1 mg/IV	1364.3 ± 103.7^{b}	-13.51 ± 0.94^{b}	2.32 ± 0.12^{c}	18.91 ± 2.02^{d}	101.2 ± 5.96^{c}
	Oxytocin	40 IU/IV	2482.4 ± 208.1^{c}	-11.51 ± 1.26^{b}	2.93 ± 0.15^{d}	30.81 ± 2.36^{d}	96.5 ± 3.94^{c}

* Twelve to twenty-four hours postpartum for postpartum cows (n = 7). Day was at random for open cycling cows (n = 6).

** Mean ± SEM.

$^{a-d}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-4

COMPARISONS OF MEAN MEASURES OF UTERINE CONTRACTILITY IN RESPONSE TO VARIOUS DRUG TREATMENTS ADMINISTERED TO EARLY POSTPARTUM AND OPEN CYCLING COWS ON THE SECOND EXPERIMENTAL DAY*

			Measure of Uterine Motility**				
Cow Status	Treatment	Dose/Route	Area (mm^2)	Tone (mm Hg)	Frequency (counts/5 min.)	Amplitude (avg. mm Hg)	Duration (seconds)
Postpartum	Baseline	------	566.1 ± 42.1^{a}	-1.15 ± 0.47^{a}	0.64 ± 0.09^{a}	6.93 ± 0.95^{a}	37.5 ± 5.47^{a}
	Oxytocin	100 IU, IM	1174.1 ± 52.3^{b}	-5.63 ± 0.41^{b}	1.70 ± 0.08^{b}	19.78 ± 0.91^{b}	98.1 ± 3.68^{c}
	Fenprostalene	0.1 mg, IV	597.4 ± 37.1^{a}	-7.50 ± 1.07^{c}	1.04 ± 0.12^{c}	8.85 ± 0.88^{a}	72.8 ± 6.94^{b}
	Oxytocin	40 IU, IV	1694.5 ± 213.2^{c}	-7.02 ± 1.53^{c}	2.12 ± 0.18^{d}	20.98 ± 1.66^{bc}	104.2 ± 5.40^{b}
Open	Baseline	------	1780.3 ± 112.6^{cd}	-7.93 ± 0.52^{d}	$2.53 \pm 0/09^{e}$	24.85 ± 1.55^{c}	102.1 ± 3.42^{b}
	Oxytocin	100 IV, IM	2675.3 ± 81.6^{e}	-18.25 ± 0.74^{a}	2.98 ± 0.07^{f}	33.95 ± 1.20^{d}	95.3 ± 2.16^{b}
	Fenprostalene	0.1 mg, IV	2054.7 ± 99.3^{d}	-23.84 ± 1.05^{a}	2.54 ± 0.10^{e}	29.16 ± 1.62^{d}	102.9 ± 3.86^{b}
	Oxytocin	40 IU, IV	3008.3 ± 269.4^{f}	-21.68 ± 2.01^{a}	3.09 ± 0.15^{f}	36.18 ± 2.66^{d}	88.4 ± 5.30^{b}

* Thirty-six to forty-eight hours postpartum for postpartum cows (n = 7). Twenty-four hours after starting time on day one for open cycling cows (n = 6).

** Mean ± SEM.

$^{a-f}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-5

MEAN UTERINE CONTRACTILITY OF ISOLATED HORNS IN RESPONSE TO TREATMENT WITH FOUR DOSAGE LEVELS OF FENPROSTALENE (EXP. 2)

		Uterokinetic Indicator		
Treatment	Dosage	Area (mm^2)**	Frequency (counts/5 min.)**	Tone (mm Hg)**
Baseline	none	433.9 ± 52.7^{d}	3.72 ± 0.84^{a}	-1.26 ± 0.30^{abc}
1	0.1 mg	2926.6 ± 366.9^{b}	4.02 ± 0.12^{b}	0.76 ± 0.45^{d}
2	0.1 mg	1624.9 ± 166.4^{c}	3.92 ± 0.09^{b}	-2.81 ± 0.41^{e}
Baseline	none	282.9 ± 45.4^{a}	1.90 ± 0.42^{c}	-1.19 ± 0.41^{abc}
1	0.2 mg	2659.1 ± 408.3^{b}	3.53 ± 0.11^{bd}	1.16 ± 0.42^{d}
2	0.2 mg	1830.1 ± 186.7^{c}	3.51 ± 0.10^{bd}	-2.26 ± 0.54^{ce}
Baseline	none	615.9 ± 107.6^{a}	2.10 ± 0.24^{c}	0.02 ± 0.29^{ad}
1	0.3 mg	3665.8 ± 276.1^{e}	3.42 ± 0.17^{bd}	3.86 ± 0.43^{f}
2	0.3 mg	1372.8 ± 107.4^{cd}	2.94 ± 0.13^{ad}	-0.48 ± 0.22^{ab}
Baseline	none	475.0 ± 39.8^{a}	2.46 ± 0.26^{ac}	-0.88 ± 0.27^{abc}
1	0.5 mg	1685.7 ± 150.2^{cd}	3.36 ± 0.10^{bd}	-1.75 ± 0.50^{bce}
2	0.5 mg	808.4 ± 49.3^{a}	3.35 ± 0.11^{bd}	-6.32 ± 0.39^{g}

* Four uterine horns per dosage.

** Mean ± SEM.

$^{a-g}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-6

MEAN UTERINE CONTRACTILITY OF ISOLATED HORNS IN RESPONSE TO TREATMENT WITH FOUR DOSAGE LEVELS OF OXYTOCIN (EXP. 2)

		Uterokinetic Indicator		
Treatment	Dosage*	Area (mm^2)**	Frequency (counts/5 min.)**	Tone (mm Hg)**
Baseline	None	393.1 ± 41.4^{a}	2.10 ± 0.15^{a}	-0.92 ± 0.35^{ab}
1	1 IU	2100.9 ± 108.3^{bd}	3.63 ± 0.10^{b}	-0.66 ± 0.67^{ab}
2	1 IU	1678.9 ± 125.2^{b}	3.81 ± 0.10^{b}	-1.35 ± 0.66^{ac}
Baseline	None	530.0 ± 60.2^{a}	2.41 ± 0.23^{a}	-1.61 ± 0.79^{ac}
1	2 IU	2652.5 ± 124.9^{c}	3.80 ± 0.11^{b}	-1.57 ± 0.92^{ac}
2	2 IU	2177.3 ± 182.6^{bcd}	3.98 ± 0.13^{b}	-3.68 ± 1.07^{c}
Baseline	None	710.9 ± 113.8^{a}	2.28 ± 0.27^{a}	-0.32 ± 0.22^{ab}
1	3 IU	2058.5 ± 264.3^{bd}	3.84 ± 0.14^{b}	-0.38 ± 0.42^{ab}
2	3 IU	1658.3 ± 160.2^{b}	3.77 ± 0.15^{b}	-1.76 ± 0.37^{ac}
Baseline	None	684.8 ± 120.9^{a}	2.31 ± 0.39^{a}	0.25 ± 0.26^{ab}
1	10 IU	2495.5 ± 252.7^{cd}	3.94 ± 0.17^{b}	1.36 ± 0.40^{b}
2	10 IU	1158.6 ± 89.9^{e}	3.92 ± 0.18^{b}	-1.53 ± 0.22^{ac}

* Four uterine horns per dosage.

** Mean ± SEM.

$^{a-e}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-7

COMPARISONS OF MEAN UTERINE CONTRACTILITY OF ISOLATED HORNS IN RESPONSE TO ALTERNATE TREATMENTS OF OXYTOCIN AND FENPROSTALENE (EXP. 3)

		Uterokinetic Indicator		
Treatment	Dosage	Area (mm^2)**	Frequency (counts/5 min)**	Tone (mm Hg)**
Baseline	None	378.1 ± 37.0[a]	1.55 ± 0.19[a]	0.52 ± 0.23[a]
Oxytocin	2 IU	2579.5 ± 287.0[b]	3.92 ± 0.14[b]	1.62 ± 0.52[b]
Fenprostalene	0.1 mg	2545.8 ± 173.8[b]	4.11 ± 0.11[b]	1.34 ± 0.42[b]
Baseline	None	439.2 ± 50.4[a]	1.41 ± 0.19[a]	-1.28 ± 0.14[a]
Fenprostalene	0.1 mg	2072.8 ± 198.4[b]	3.96 ± 0.13[b]	-0.29 ± 0.33[a]
Oxytocin	2 IU	2223.7 ± 168.8[b]	4.18 ± 0.11[b]	-0.62 ± 0.31[a]

* Eight horns per group.

** Mean ± SEM.

[a-b] Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-8

MEAN UTERINE CONTRACTILITY OF ISOLATED HORNS WHEN SUBJECTED TO CONSECUTIVE TREATMENTS OF FENPROSTALENE (0.1 mg) WITH DIFFERENT TIME INTERVALS BETWEEN TREATMENTS

		Uterokinetic Indicator		
Treatment	Time (min.)	Area (mm^2)*	Frequency (counts/5 min.)*	Tone (mm Hg)*
Baseline	30	433.9 ± 52.7^{a}	2.72 ± 0.34^{a}	-1.26 ± 0.30^{acd}
1	60	2926.6 ± 366.9^{b}	4.02 ± 0.12^{cd}	0.76 ± 0.45^{b}
2	60	1624.9 ± 166.4^{c}	3.92 ± 0.09^{cd}	-2.81 ± 0.41^{d}
Baseline	30	665.6 ± 111.3^{a}	1.91 ± 0.40^{b}	-0.89 ± 0.41^{abc}
1	75	2477.9 ± 259.3^{bd}	3.68 ± 0.16^{d}	-0.02 ± 0.83^{bc}
2	60	2005.4 ± 183.7^{cd}	4.56 ± 0.20^{c}	-2.05 ± 1.06^{d}
Baseline	30	896.8 ± 148.6^{a}	2.23 ± 0.37^{ab}	-0.61 ± 0.23^{abc}
1	120	2837.8 ± 126.6^{b}	3.91 ± 0.11^{cd}	0.81 ± 0.40^{b}
2	60	1447.0 ± 82.8^{c}	4.25 ± 0.12^{cd}	-2.96 ± 0.82^{d}

* Four horns per group.

** Mean ± SEM.

$^{a-d}$ Means in the same column with different superscripts are significantly different ($P \leq 0.05$).

TABLE A-9

MEAN UTERINE CONTRACTILITY OF ISOLATED HORNS WHEN SUBJECTED TO CONSECUTIVE TREATMENTS OF OXYTOCIN (2 IU) WITH DIFFERENT TIME INTERVALS BETWEEN TREATMENTS

		Uterokinetic Indicator		
Treatment	Time (min.)	Area (mm^2)**	Frequency (counts/5 min.)**	Tone (mm Hg)**
Baseline	30	530.0 ± 60.2^{a}	2.41 ± 0.23^{a}	-1.61 ± 0.79^{ab}
1	60	2652.5 ± 124.9^{b}	3.80 ± 0.11^{b}	-1.57 ± 0.92^{ab}
2	60	2177.3 ± 182.6^{b}	3.98 ± 0.13^{b}	-3.68 ± 1.07^{c}
Baseline	30	546.3 ± 98.8^{a}	1.92 ± 0.36^{c}	0.06 ± 0.53^{ad}
1	75	2264.6 ± 203.7^{b}	3.67 ± 0.13^{b}	0.48 ± 0.44^{ad}
2	60	2651.2 ± 256.1^{b}	3.85 ± 0.13^{b}	0.84 ± 0.57^{d}
Baseline	30	551.4 ± 86.9^{a}	1.54 ± 0.32^{c}	-0.07 ± 0.29^{ad}
1	120	1694.2 ± 109.4^{c}	3.73 ± 0.10^{b}	-0.69 ± 0.39^{abd}
2	60	1195.3 ± 108.3^{d}	3.49 ± 0.12^{b}	-2.54 ± 0.49^{bc}

* Four horns per group.

** Mean ± SEM.

[a-d] Means in the same column with different superscripts are significantly different ($P < 0.05$).

TABLE A-10

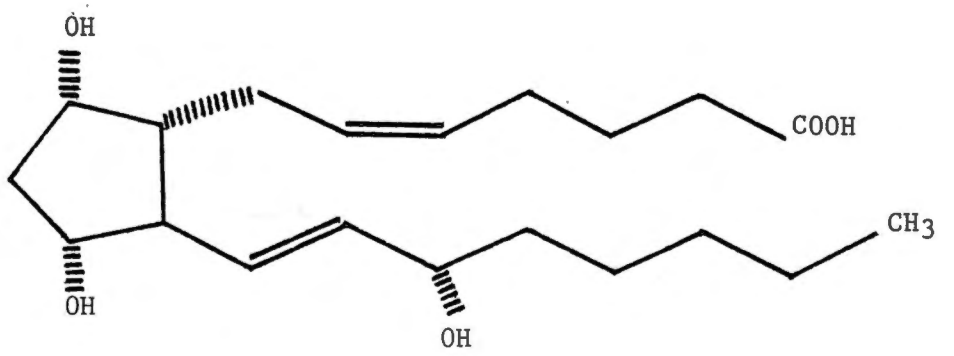
MEAN UTERINE CONTRACTILITY OF ISOLATED HORNS IN RESPONSE TO TREATMENT WITH FENPROSTALENE (0.1 mg), OXYTOCIN (2 IU) OR A MIXTURE OF EACH DRUG (0.5 mg FENPROSTALENE, 1 IU OXYTOCIN) (EXP. 5)

	Uterokinetic Indicator		
Treatment*	Area (mm^2)**	Frequency (counts/5 min.)**	Tone (mm Hg)**
Baseline	550.4 ± 42.1^{a}	2.32 ± 0.15^{a}	-0.95 ± 0.12^{ab}
Fenprostalene	2570.2 ± 133.9^{b}	3.91 ± 0.08^{b}	0.46 ± 0.25^{a}
Baseline	468.7 ± 31.1^{a}	1.99 ± 0.13^{ac}	-0.61 ± 0.22^{ab}
Oxytocin	2356.2 ± 131.7^{b}	3.88 ± 0.07^{b}	0.35 ± 0.33^{a}
Baseline	681.3 ± 111.6^{a}	1.62 ± 0.29^{c}	-0.45 ± 0.19^{ab}
Mixture	943.5 ± 96.7^{a}	3.64 ± 0.20^{b}	-1.87 ± 0.25^{b}

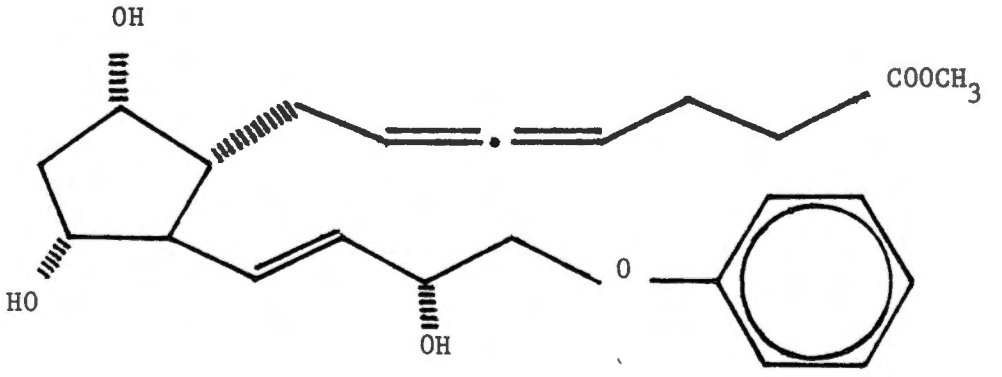
* Horns per group: Fenprostalene n = 20; Oxytocin n = 20; Mixture n = 4.

** Mean ± SEM.

$^{a-c}$ Means in the same column with different superscripts are significantly different ($P < 0.05$).



$PGF_2\ \alpha$



Fenprostalene

Figure A-1. Comparison of the chemical structures of $PGF_2\alpha$ and fenprostalene.

VITA

William Herbert Byrd, III was born in Nashville, Tennessee on September 29, 1959. He attended elementary schools in Maryville, Tennessee and was graduated from Everett High School in June 1977. The following September he entered Harding College in Searcy, Arkansas. Following a two year stay he then entered The University of Tennessee, Knoxville and in December 1981 he received the Bachelor of Science degree in Animal Science. In the winter of 1982 he accepted a teaching assistantship at The University of Tennessee, Knoxville and was awarded the Master of Science degree in December 1984.

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