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THE PROSPECTS OF PGs IN POSTCONCEPTIONAL THERAPY

by

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To Esther, the student who may
further examine these prospects.

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Abbreviations: IUP=intrauterine pressure; OR=oxytocin response; P=progesterone; E_2=estradiol-17β; IAT=instillation-abortion time.

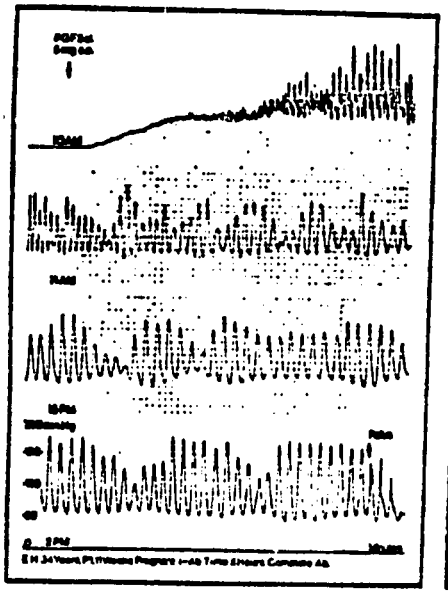
GENERAL CONSIDERATIONS

Prostaglandins (PGs) are normal constituents of a variety of mammalian tissues (1-9). Their involvement in regulatory functions is so basic and broad (1-9) that it would be pretentious to consider the whole spectrum of their therapeutic prospects in one article. A survey of the role of PGs in Reproduction alone seriously challenges the competence of any reviewer. Considerations in this article are limited, therefore, to the prospects of PG in postconceptional therapy.

However, this broad involvement of endogenous PGs in regulatory functions must be recognized because of its therapeutic implications. Unless highly organ (indeed cell) specific PGs are discovered, the recipient of PG therapy shall be burdened by a wide spectrum of unacceptable side effects! This crude reality restricts advances in PG therapy to the:

(1) development of effective topical treatments;
(2) mobilization of endogenous PGs in target organs; and
(3) discovery of highly organ specific PGs.

Clinical research alone cannot, only broadly overlapping basic and clinical studies can accomplish these goals.



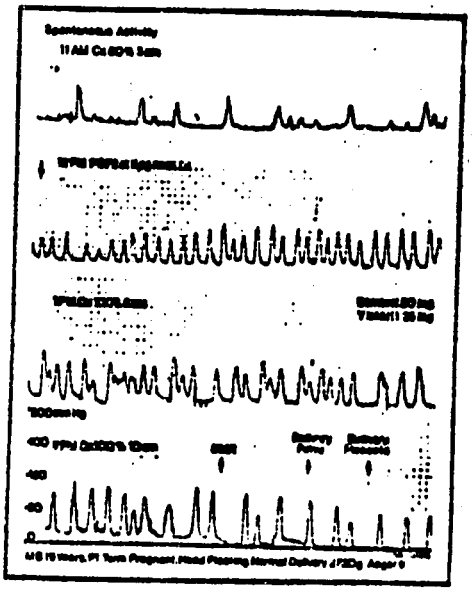


Figure 1. PG-induced abortion. In this first trimester pregnant patient a single extraovular dose of 5mg PG F2α induced high level contracture, gradual evolution of cyclic IUP and complete abortion in 5 hours.

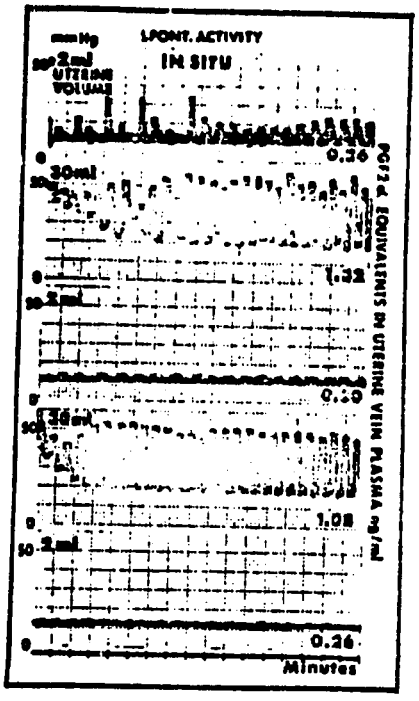
Figure 2. PG-induced labor. In this normal term pregnant patient, the intravenous infusion of 5μg/min PG F2α elevated the cyclic IUP to the labor range and induced parturition in 2.7 hours.

The choice of topic for this article is not arbitrary. Figures 1 and 2 illustrate that PGs are documented abortifacients and labor inducers (9-20). Both endogenous and exogenous PGs are implicated in fertility control and perinatology (1-20), the two broadest fields in Reproduction, yet to be fully explored. Uncontrolled population growth must be curtailed and the physical and mental potential of the wanted child must be protected by all available means from pre- and perinatal hazards. Only advanced therapeutic measures can prevent arguments about their urgent necessity.

Postconceptional therapy seems preferable to preconceptional measures, because it could spare millions of women from chronic exposures to powerful synthetic steroids. The aim of postconceptional therapy is the acute withdrawal of an endogenous regulator, vitally important in pregnancy maintenance. Its endpoint is complete spontaneous abortion. Figure 1 documents that PG can accomplish this goal. In this patient, the circulating plasma progesterone (P) decreased during the instillation-abortion time (IAT) from 23.7 to 12.8ng/ml and the estradiol-17β (E_2) from 0.5 to 0.2ng/ml. Apparently, two vitally important regulatory factors had been acutely withdrawn during the IAT. This indicated relationship between PG-induced uterine contracture, steroid withdrawals, evolution of cyclic IUP and abortion is a major theme of this article and will be further discussed. Postconceptional therapy is also preferable because in a given menstrual cycle, only about one-third of the unprotected fertile women conceive and about one-half of these desire motherhood. Thus, only a fraction of unprotected women are candidates of abortifacient therapy, which must be fully predictable, efficacious and acceptable, if it is to reduce the massive exposure of patients to contraceptives.

The role of PGs in postconceptional therapy have been discussed competently in several pioneering reports and reviews (1-20). This article merely presents the reasons of a uterine physiologist for believing that PGs are here to stay. This opinion is prompted by the recognition that the decisive step in abortion and parturition is the activation of the myometrium (a problem of uterine physiology(21)) and that PGs promote this activation process (22, 23).

Recent clinical achievements with PGs are impressive (20). However, further developments demand a better understanding of the mechanism, through which PGs regulate uterine function and clinical data which complement this knowledge. Only basic studies can bring out the challenging therapeutic potential of endogenous PGs and the proper choice in treatment form for the routine clinical use of the exogenous compounds (23).



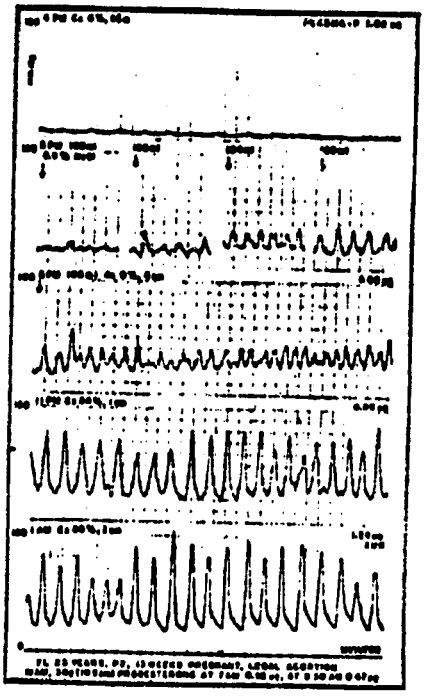


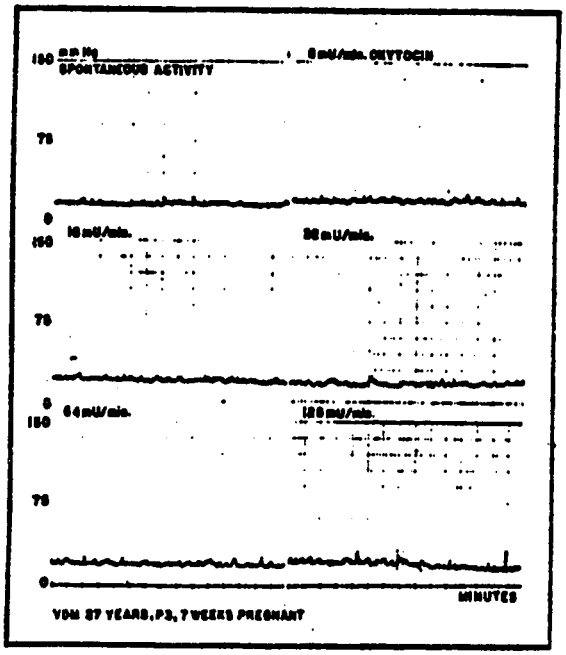
Figure 3. Stretch-induced PG synthesis and uterine activity. The rabbit uterus is stretched and released from stretch postpartum, during periods of 15 minutes each. Note the increased concentration of PG (equivalent) in the uterine vein blood and the increased cyclic IUP, each time the uterus is stretched.

Figure 4. Stretch-induced abortion. The uterus of this 13 weeks pregnant patient (with low plasma progesterone levels) was stretched, by the intraamniotic instillation of physiological saline. With the progress of time, cyclic IUP evolved and the patient aborted.

To put it bluntly, I believe in the prospects of PGs in post-conceptional therapy, because (Figure 3) the "intrinsic myometrial stimulant" appears to be PG (21-24). I also believe that these prospects will become self-evident, when the regulatory role of the intrinsic PGs is clarified. Such a strategy, aiming at both fundamental and clinical advances is broad; but so is the challenge. It would be unwise to narrow it, for current clinical experiences with PGs (20) emphasize the urgency of basic considerations. However, the interest expressed here in endogenous PGs merely underlines the therapeutic importance of the exogenous compounds. For, it appears that through stretch (Figure 1), exogenous PGs can mobilize (Figure 3) this powerful endogenous regulator (21-24). It seems advisable, therefore, to examine the characteristics of the PG-controlled myometrial cell, before engaging in clinical considerations.

THE BASIC FUNCTIONAL CHARACTER OF THE PREGNANT HUMAN UTERUS

It is not feasible to ask what are the prospects of PGs in postconceptional therapy, unless one asked already: how does the uterus, affected by PGs, work? This basic question is yet to be answered.



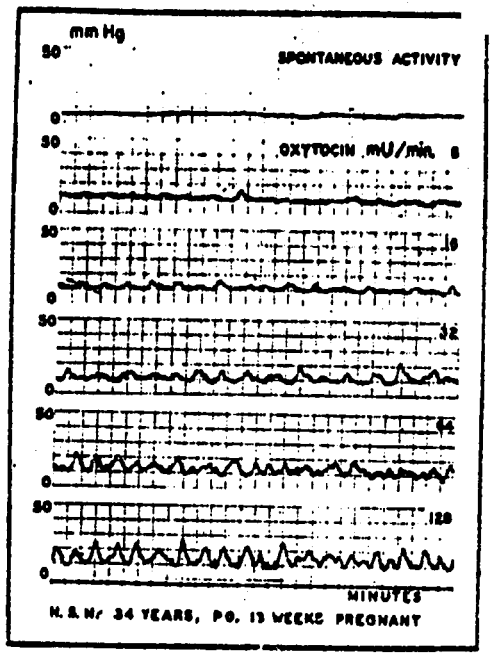


Figure 5. The oxytocin response of the first trimester pregnant human uterus. The normal 7 weeks pregnant uterus only shows restricted oscillations in IUP. The intravenous infusion of 8-128mU/min oxytocin does not increase IUP significantly, although this uterus has over 150mm Hg IUP potential and at term 8mU/min oxytocin triggers parturient activity.

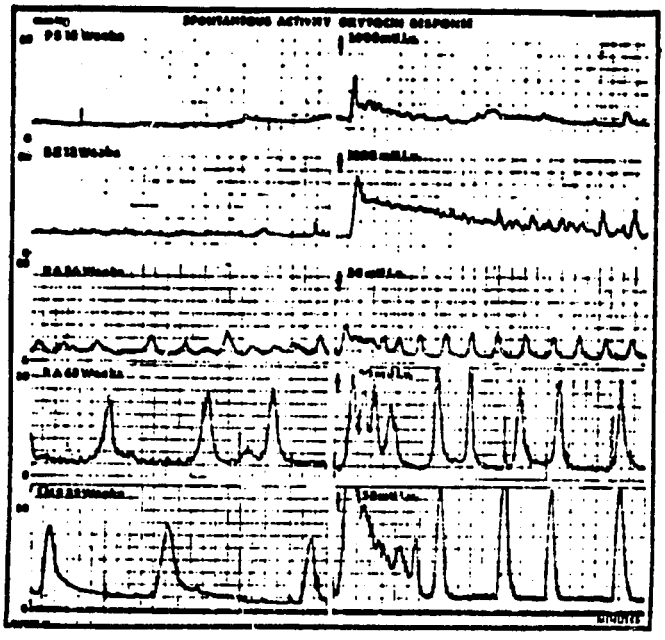
Figure 6. The oxytocin response of the second trimester pregnant human uterus. The normal 13 weeks pregnant uterus does respond to the intravenous infusion of 8-128mU/min oxytocin. However, the response is greatly limited and is far from the over 150mm Hg IUP potential of this organ.

The multibillion cell community of the normal pregnant human myometrium is "dormant" until the approach of term (see initial tracings of Figures 5 and 6). This is its functional character, in spite of being equipped with all the regulatory factors necessary for the release of its maximum working potential (21). This dormant state manifests in restricted intrauterine pressure (IUP) oscillations and in relative refractoriness to stimulants (measured by the oxytocin response (OR)). Figures 5, 6 and 7 illustrate the distinct effect of gestational age on the OR. Before the "luteo-placental shift" in progesteronegenesis (25, 26), there is no appreciable OR, in spite of excessive stimulation (Figure 5) while after this shift, there is a response, although a greatly limited one (Figure 6). A definition of this regulatory state of "dormancy" and the quantitation of the endocrine changes underlying the evolution of IUP and OR near term are mandatory. These achievements can provide the key to predictable postconceptional therapy, because this therapy has only two primary purposes: to promote or to terminate this state of dormancy. The acceptance of the phrase "changing uterine sensitivity to stimulants" merely avoids the basic issue: the regulatory mechanism of the pregnant uterus.

(A) Uterine Models

In explaining the functional character of the pregnant human uterus, two basically different models can be considered (21). One describes an inert muscle chamber, which is activated in proportion to the level of stimulation. This model explains the restricted cyclic IUP of the normal pregnant uterus by the lack of effective stimulants. It predicts a stepwise increase in cyclic IUP, when the level of stimulation is increased.

The normal pregnant human uterus repeatedly failed in substantiating these predictions and thus this model (21). Stepwise increasing oxytocin stimulation (no matter how excessive) did not increase in graded steps the cyclic IUP of the first (Figure 5) and second (Figure 6) trimester uteri, in spite of their over 150mm Hg IUP potential. That this potential is a reality can be documented by the removal of the corpus luteum, which sustains the dormant state of the human uterus until the 7th week of pregnancy (25, 26), or by interfering with placental endocrine function at later stages of gestation (21). This point will be further discussed in detail.



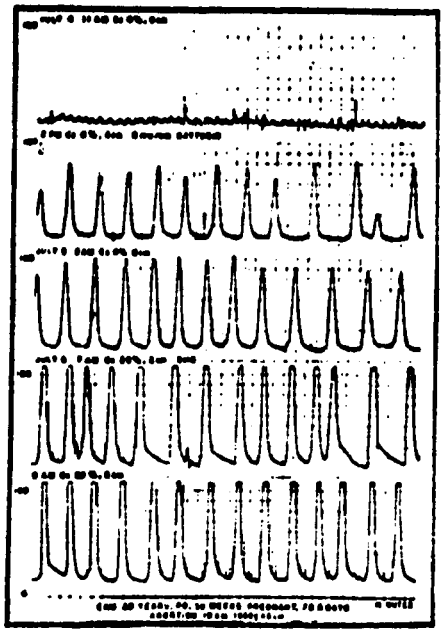


Figure 7. The changing oxytocin response during pregnancy. At 10 and 13 weeks of gestation (first and second tracings), the cyclic IUP is limited to low level oscillations (left). Such a massive dose of oxytocin as 1000mU i.v., only provokes a transient contracture with small cyclic activity (right). At 36 weeks (third tracing), cyclic IUP is partly evolved and the "test dose" of 50mU oxytocin i.v. triggers a moderate response. However, this effect does not approximate the response of the same patient 4 weeks later (fourth tracing). The "oxytocin test" is distinct in the "readily inducible" term patients (fifth line).

Figure 8. The oxytocin response after fetal death in utero. After fetal death in utero (when the progesterone levels decrease) the oxytocin response becomes distinct, as a rule.

As late in pregnancy as the 36th week, the "test dose" of oxytocin (50mU, single i.v. dose) only induced a moderate response (Figure 7, third tracing), while 4 weeks later it triggered maximum IUP (Figure 7, fourth tracing) in the same patient. At earlier stage of gestation, this test dose was ineffective and even the massive dose of 1000mU, i.v., only provoked a transient contracture, without significant cyclic IUP (Figure 7, first and second tracings). However, when the P levels decreased after fetal death in utero (21) oxytocin stimulation became effective (Figure 8).

In spite of the obvious shortcomings of this model, the early work with PGs began with protracted,stepwise increasing (intravenous or extraovular) infusions. Several investigators considered the clinical outcome of these studies unsatisfactory and recommended therapeutic modifications (27). Apparently, the pregnant human uterus is not an inert organ. It can be forced to contract under massive PG stimulation, if the infusion is sustained during unreasonable hours. However, the mounting apprehension of the patients and the repeated failures in inducing abortion are warnings that protracted PG infusions are objectionable conceptionally. Some uteri eventually "gave in" and displayed high level cyclic IUP, but the regulatory conditions of those uteri which did should not be considered normal, after prolonged exposure of the patients to massive PG stimulation (20-23).

This conclusion has important therapeutic implications and, therefore, should be further supported. This could be best accomplished by considering evidence which not only rules out an untenable uterine model, but promotes the alternative one. The model, to be adopted throughout these pages (21) describes the pregnant human uterus as an intrinsically active, but endogenously suppressed organ. It explains its restricted IUP, not by a lack of effective stimulants, but by the regulatory dominance of a suppressor. It predicts that high level cyclic IUP can be readily provoked during the entire duration of pregnancy, by the mere withdrawal of suppression, since the intrinsic stimulant is present in the uterus and need not be supplied. However, if it is supplied, so much the better, for then a lesser degree of withdrawal is demanded for elevating the IUP to the desired level. It is my contention to propose that the intrinsic uterine stimulant is PG and the suppressor is P.

(B) The Intrinsic Myometrial Stimulant

Under controlled in vitro conditions, the parturient uterus develops maximum isometric tension in repeated cycles for several hours, when stimulated electrically with optimum stimuli (Figure 9). Evidently the working potential of the uterus is sustained in vitro. Near maximum tension also develops spontaneously, in spite of the complete absence in vitro of the regulatory influences of the maternal and fetal endocrine systems (Figure 9). This "intrinsic activity" is a characteristic feature of smooth muscles in general, partly explained (21) by their limited "safety potential," e.g. the small membrane potential excess over the "critical" threshold value (Figure 10) Cross striated muscle (for example, the frog sartorius) has a considerably greater safety potential. It only develops spontaneous activity, when this excess potential, over the critical value, is greatly reduced, by rendering the muscle Ca deficient (21).

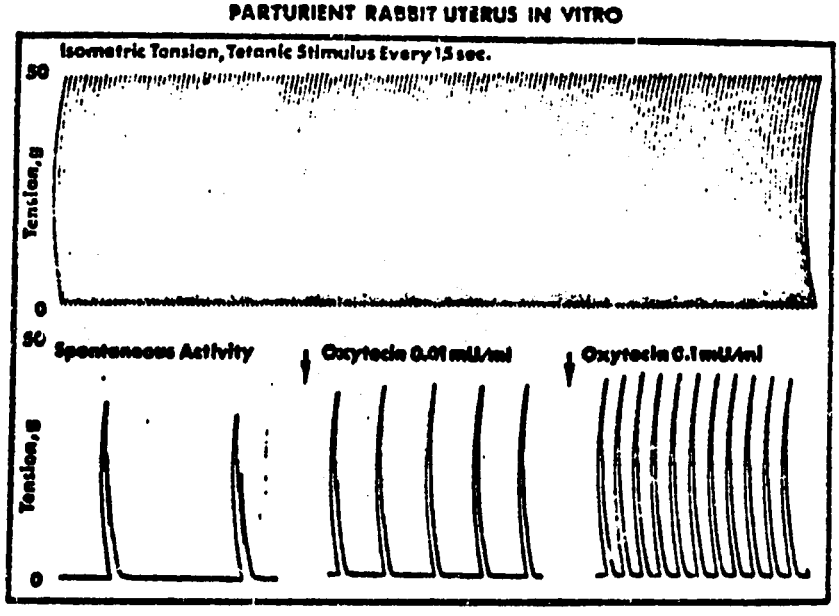


Figure 9. The isometric tension, spontaneous activity and oxytocin response of the excised uterus, in vitro. Parturient rabbit uterus, suspended isometrically in oxygenated mammalian Krebs' solution. Optimum electric stimulus triggers 50g tension in this 0.6g uterine strip in a steady state. Spontaneous activity is 35g, increased by 10 and 100μU oxytocin/ml to 40-44g. The repetition frequency is also increased by oxytocin.

All agents (for example, oxytocin, Figure 9; KCl, Figure 10), capable of reducing the membrane potential of the myometrial cell toward the critical value, promote spontaneous activity. This effect of depolarization is readily explained by the endogenous mechanism of activation (21).

Conductive tissues, including muscle, are activated when their membrane potential is reduced to the critical "threshold" level (28). Depolarization of the excitable membrane to this critical value generates an action potential in the myometrial cell (Figure 11), which sweeps over the membranes with high conduction velocity, depolarizing them along its path (21). This process is followed by a release of Ca (29), which in turn activates the contractile (actomysin-ATP) system of the myofilaments. The end result is isometric tension, or isotonic work. The uterus is activated in this manner, its extreme Ca sensitivity had been an early clue for Ca-dependent activation (21).

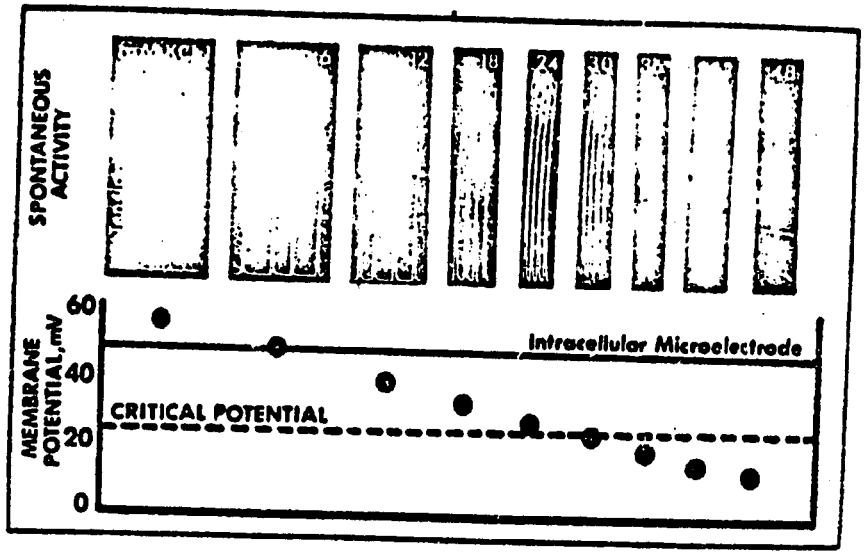


Figure 10. The effect of KCl on the membrane potential and spontaneous activity. Parturient rabbit uterus, in vitro. Reducing the concentration of KCl in the Krebs' solution increases the membrane potential and abolishes spontaneous activity. Increasing the KCl reduces the membrane potential toward the critical value and increases spontaneous activity. At the critical potential spontaneous activity is maximal and further depolarization provokes contracture.

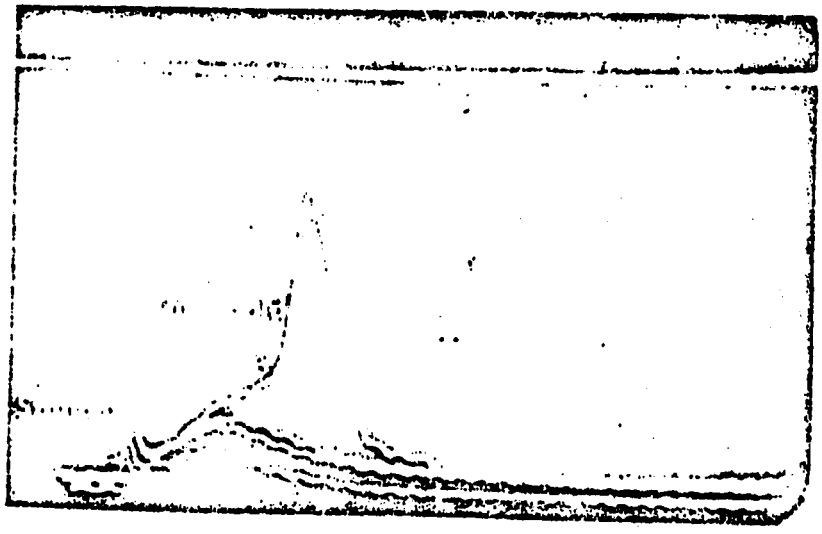


Figure 11. The generation of the action potential. Term pregnant mouse myometrium, intracellular recording. Increasing electric stimulation increases the extent of depolarization. An action potential is only generated, however, when depolarization reaches a critical "threshold" value.

In a final sense, therefore, Ca is the intrinsic myometrial stimulant, because it is Ca which activates the contractile system. However, since Ca release demands the triggering effect of the action potential, the intrinsic myometrial stimulant at the level of the excitable membrane is a regulatory agent which promotes the generation (and probably the propagation) of the action potentials. Attempts in identifying the intrinsic myometrial stimulant have failed. However, the dependence of intrinsic activity on stretch had been repeatedly demonstrated, both in vitro and in situ (21) under a great variety of experimental conditions.

Disregarding the regulatory effect of this stretch dependent intrinsic stimulant was a serious oversight in the endocrine approach to the "initiation of labor." For, changes in the plasma levels of maternal and fetal hormones, no matter how definitive, can not possibly explain this ancient puzzle, if the trigger for membrane and myoplasmic activation originates from the myometrial cells themselves. Maternal and fetal regulatory factors are important, because they control the myometrial response to stimuli. However, the decisive step in the initiation of abortion and labor is the evolution of uterine activity; a process which is (to a larger degree) under the direct control of the stretch dependent intrinsic stimulatory system (21-24). PG synthesis in the uterus is stretch dependent (Figure 3) and the concentration of PG controls the activity of the reactive myometrium (Figure 14).

The current arguments about whether the mother or the fetus contributes more to the initiation of labor are obsolete. For, the uterus is not only capable of delivering its contents at any time during pregnancy but it can expel dead fetuses, stretch balloons, IUDs, (or whatever is in its cavity) even in vitro. This fact alone, that under a great variety of regulatory conditions high level cyclic IUP can develop, with the only common background that the uterine cavity is filled with an object, is a reminder that the uterus is equipped with an intrinsic mechanism of self activation. Of course, normal parturition demands a highly precise regulatory interplay (between the various controlling factors), for precise timing is of the utmost importance in the protection of perinatal life.

The premise that the intrinsic myometrial stimulant might be PG rests on two independent findings. An elegant study (24) brought out the significant evidence that the stretched horn of the excised guinea pig uterus releases more PG F2α into the perfusion medium than the unstretched (control) horn. This observation was complemented by the additional finding (Figure 14) that PG F2α lowers threshold at pg/ml concentrations, in uteri freed from the P block (22,23). What remained to be determined was, whether or not PG synthesis is stretch dependent in vivo and whether a quantitative correlation exists between stretch-induced PG synthesis and myometrial response.

Therefore, the uterus of the post partum rabbit has been equipped with a "stretch balloon" in situ and subjected cyclically to stretch (30ml volume) and release (3ml volume), for periods of 15 minutes each (Figure 3). The cyclic IUP increased and decreased markedly (22, 23) following stretch and release from stretch. Plasma, collected from the uterine vein, at the end of each period of 15 minutes, showed marked cyclic increase and decrease in PG (F2α equivalents), measured by a sensitive bioassay method (22, 23). Since the PG values were similar at the end of subsequent periods of release and also at the end of subsequent periods of stretch, it became apparent that not only the release of PG, but also its synthesis in the uterus is stretch dependent.

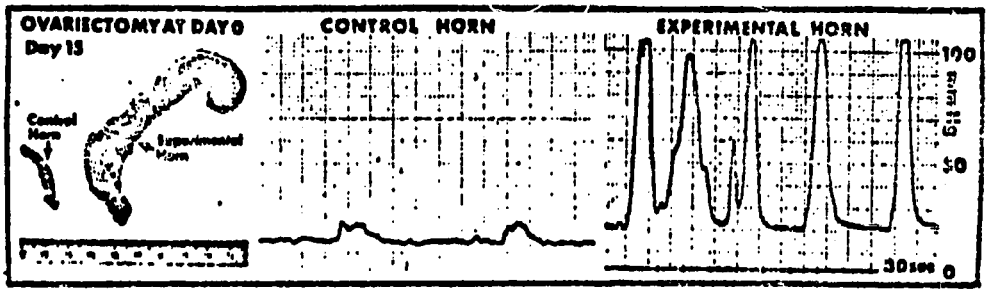


Figure 12. The effect of stretch on the working potential and activity of the uterus. The experimental uterine horn of ovariectomized rabbits had been stretched (by 10ml imposed volume) for 15 days in vivo, while the control horn remained unstretched. The control horn had castrate atrophy and restricted IUP, while the experimental horn showed marked hypertrophy and maximum IUP. Thus in the same endocrine environment the two horns of the same uterus had different working potentials and activity, depending on whether or not they were stretched.

These observations of stretch-induced PG synthesis in the uterus (22-24) are of considerable academic and therapeutic interests, in that they clarify a number of unexplained findings (Figures 12 and 13). If the uterus is capable at all times of synthesizing PG and if the rate of synthesis (and thus the myometrial PG concentration) is stretch dependent, then the growing uterine contents can sustain the triggering mechanism of the myometrium in functional readiness during the entire duration of pregnancy (21-23). The working potential is there (due to the effects of estrogen and stretch-induced myometrial hypertrophy, Figure 12) and would be released intrinsically (Figure 13) without endogenous or exogenous support with oxytocics, if P would not "freeze" threshold at a high level.

Of course, additional stimuli could facilitate the effect of the intrinsic stimulant and such a facilitation during labor is indicated by a variety of observations (21). The increasing P concentrations during pregnancy (21), paralleling the increase in uterine volume (V) (the increasing degree of stretch), most probabl serve the regulatory purpose of preventing PG from lowering threshold effectively and thus activating the uterus precociously (21). The intrinsic myometrial stimulant in abortifacient therapy might be important, because being present throughout pregnancy its effect could be mobilized by a mere withdrawal of the P-block. This prediction of our model had been verified recently in luteectomized patients (25, 26).

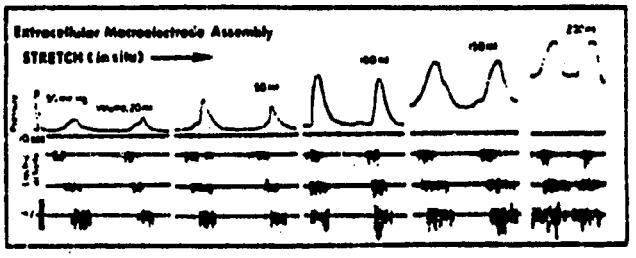


Figure 13. The effect of stretch on the electric activity and IUP of the uterus. One uterine horn of the parturient rabbit had been stretched in graded steps (by a stretch balloon) in vivo. Electric activity had been recorded (at 3 distant points by implanted electrodes) together with the IUP. Note that up to an optimum value (100ml volume in this instance), increasing stretch promoted electric and mechanic activity. Excessive stretch provoked contracture.

(C) The PG Effect on Threshold

In investigative work, the two major problems of postconceptional therapy, the promotions of the activation and inactivation respectively of the myometrium, might be reduced to a two directional control over threshold. The prospects of PG therapy are more dependent on the understanding of this two directional control of threshold, than on further accumulation of purely clinical data. For, predictable therapy demands basic understanding. It is already established (Figure 14) that PG lowers threshold, and in so doing promotes uterine activity (23), unless P "freezes" threshold, to such a degree that about 1000 times more PG is needed for a limited effect (23).

There is a reliable technique for measuring the effects of various regulatory factors on the threshold of uterine excitability (22, 23). Longitudinal strips are excised from the pregnant rabbit uterus and suspended isometrically in mammalian Krebs' solution (Figure 14). These strips develop maximum tension (∿50g/0.5g tissue) in a steady state for several hours (Figure 9), if stimulated (for 4 seconds) in an electric field of optimum strength (∿2V/cm). When the field strength is decreased in graded steps, tension decreases. Threshold is defined by the minimum field strength, which triggers measurable tension (Figure 14). Stimulating the uterus repeatedly with threshold stimuli, provokes suboptimal tension, which reaches steady state in a few minutes.

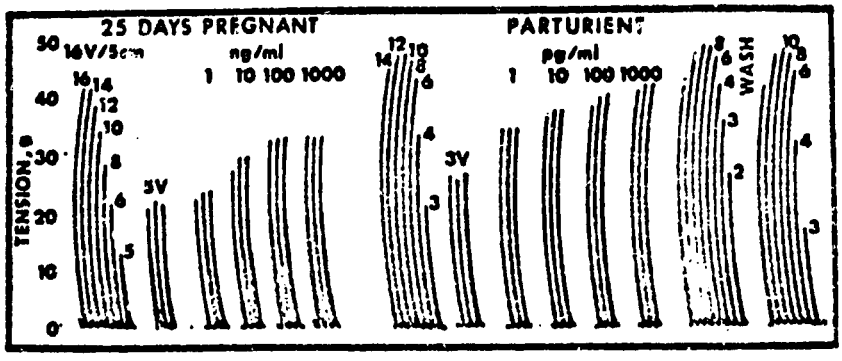


Figure 14. The effect of PG on threshold. Uterine strips, removed from 25 days pregnant and parturient rabbits, are stimulated electrically in vitro. As the field strength is reduced in steps, tensions decreases. The pregnant uterus displays threshold response at 5V, while the parturient uterus at 3V/5cm stimuli. PG F2α lowers threshold and increases the tension triggered by threshold stimuli in both muscles. However, 1000 times higher PG F2α concentrations are needed for a lesser effect, when the uterus is pregnant than when it is parturient. The threshold lowering effect of PG is further documented by the additional finding that in the presence of 100pg/ml PG F2α, 2V/5cm field strength, which had been ineffective before PG treatment ("subthreshold" stimulus), is effective in triggering tension. Removing PG F2α restores the status quo.

If the uterus is removed during parturition, when the P levels measure 1.6±0.4ng/ml (30), PG F2α concentrations as low as pg/ml decrease threshold and increase tension to maximum, in spite of low level (threshold) stimuli (Figure 14). In contrast, if the uterus originates from a 25 days pregnant rabbit, when the P levels are 9.1±1.2ng/ml (30), about 1000 times higher PG F2α concentrations are needed for an appreciable effect on threshold (Figure 14). Apparently, progesterone controls the threshold of the uterus and under P dominance PG F2α can only alter threshold at unphysiological concentrations. However, even at excessive PG levels, maximum effect is not achieved as long as the P-block is complete (23).

Whether or not the PG $F2_{\alpha}$ concentrations in the human myometrium are sufficiently high to lower threshold, but can not effectively do so because the P-control is dominant, is yet to be determined. Probably, they are, since the mere removal of the corpus luteum (at or before the 7th week of gestation) provokes the evolution of IUP and abortion (25, 26). The effective doses used in therapeutic abortions must produce excessive concentrations, since the contracture response signals overstimulation. Nevertheless, maximum cyclic IUP does not evolve promptly, probably because the P-block disallows a physiological uterine response.

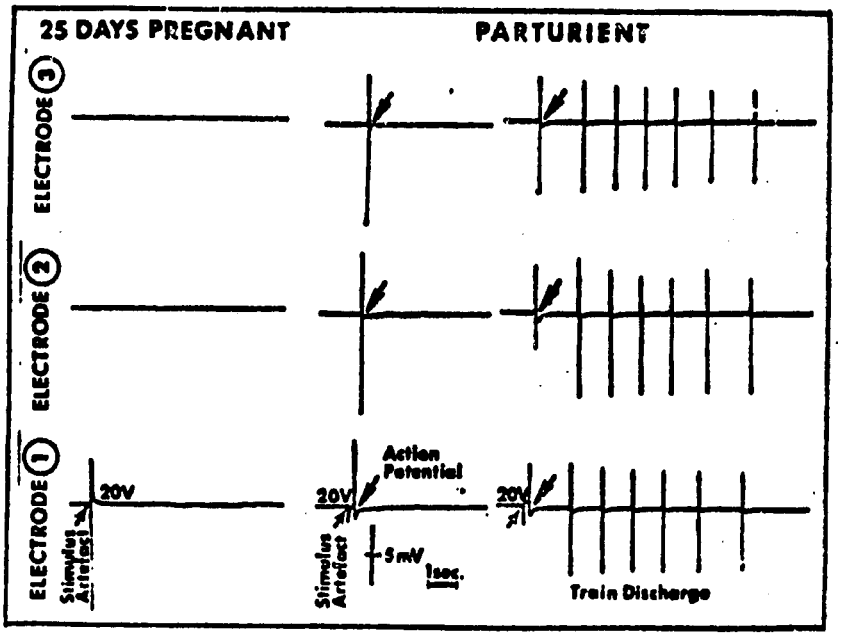


Figure 15. The P-block. Uterine strips excised from 25 days pregnant and parturient rabbits are stimulated electrically at one end. The action potentials generated are recorded (with suction electrodes) at 3 distant uterine positions. Only a stimulus artifact, but no action potential, is recorded from the pregnant uterus, not even near the stimulating electrode. In contrast, propagating action potentials are recorded over the entire strip of the parturient uterus. Frequently, train discharges, rather than single potentials, are triggered by a single d.c. pulse.

Advanced cyclic IUP demands synchronic activity between distant uterine regions and until continued P-withdrawal lowers threshold and permits the propagation of the electric train discharges, synchronic activity can not develop (21). Propagating action potentials are recorded during parturition (Figure 15), or after ovariectomy induced abortion, when the P levels decrease to 2ng/ml value. Normal pregnancy (Figure 15) or P substitution therapy prevents propagating electric activity(21).

The recording of action potentials at distant regions in electrically stimulated uterine strips firmly established the reality of the two distinct regulatory conditions: the P-block and the recovery from it (Figure 15). Further studies are in progress to clarify the interdependence of the PG effects on threshold and propagation. However, since the P sustains a high threshold during normal pregnancy, the activation of the uterus can not be achieved predictably until term and clinical trials can not be designed or interpreted properly, unless the controlling effects on threshold of P and PG are considered.

It is of unique therapeutic importance that within a few hours PGs are capable of upsetting the P-block and activating the uterus (Figure 1). However, by disregarding the fact that this regulatory takeover is time dependent, does not make PGs therapeutically more precious, only less useful. For, efficacious, acceptable and predictable postconceptional therapy demands full knowledge of how PGs gain control over threshold when P, an equally powerful regulatory factor, is dominant.

(D) The Effect of Luteectomy on the Pregnant Human Uterus

Even at a stage of maximum suppression the working potential of the pregnant human uterus is readily released without endogenous stimulation. This is accomplished by luteectomy, the removal of an "indispensable" regulatory factor, progesterone (Figure 16). Two studies had been completed so far. In the first (25), the effects of luteectomy had been compared in 12 patients; 7 less than 7 weeks, 5 more than 7 weeks pregnant (Nagele). In the second, 24 patients averaging 7 weeks of pregnancy were studied (26). Only tubal ligation was performed in 6 controls, 11 patients were luteectomized and 7 received P substitution therapy after luteectomy. When the corpus luteum was removed by luteectomy at or before the 7th week of pregnancy (Nagele) the P levels fell precipitously (Figure 16), the IUP and OR evolved and the patients aborted (25, 26).

However, if luteectomy was delayed beyond the 7th week of gestation, when the "luteal-placental shift" in progesteronegenesis was so far advanced, that only a transient P-withdrawal occurred, the IUP and OR failed to evolve and pregnancy continued undisturbed (Figure 17).

Tubal ligation alone (without luteectomy in the Control patients) provoked no significant changes in P levels, IUP, OR and normal pregnancy (Figure 18). Since luteectomy only removed a vitally important regulatory factor in pregnancy maintenance, the spontaneous evolution of IUP and OR must have been provoked by the intrinsic myometrial stimulant. This endogenous regulator had been present, but became effective only after threshold was lowered, by P-withdrawal. This

conclusion: that luteectomy lowers threshold by P-withdrawal, rather than by the removal of some other luteal hormone, had been substantiated by the additional demonstration (Figure 19) that when the luteectomy-induced P-withdrawal was prevented by P substitution therapy, the IUP and OR did not evolve and pregnancy continued undisturbed (26). These findings (25, 26) verified the model: the intrinsically active, endogenously suppressed pregnant uterus.

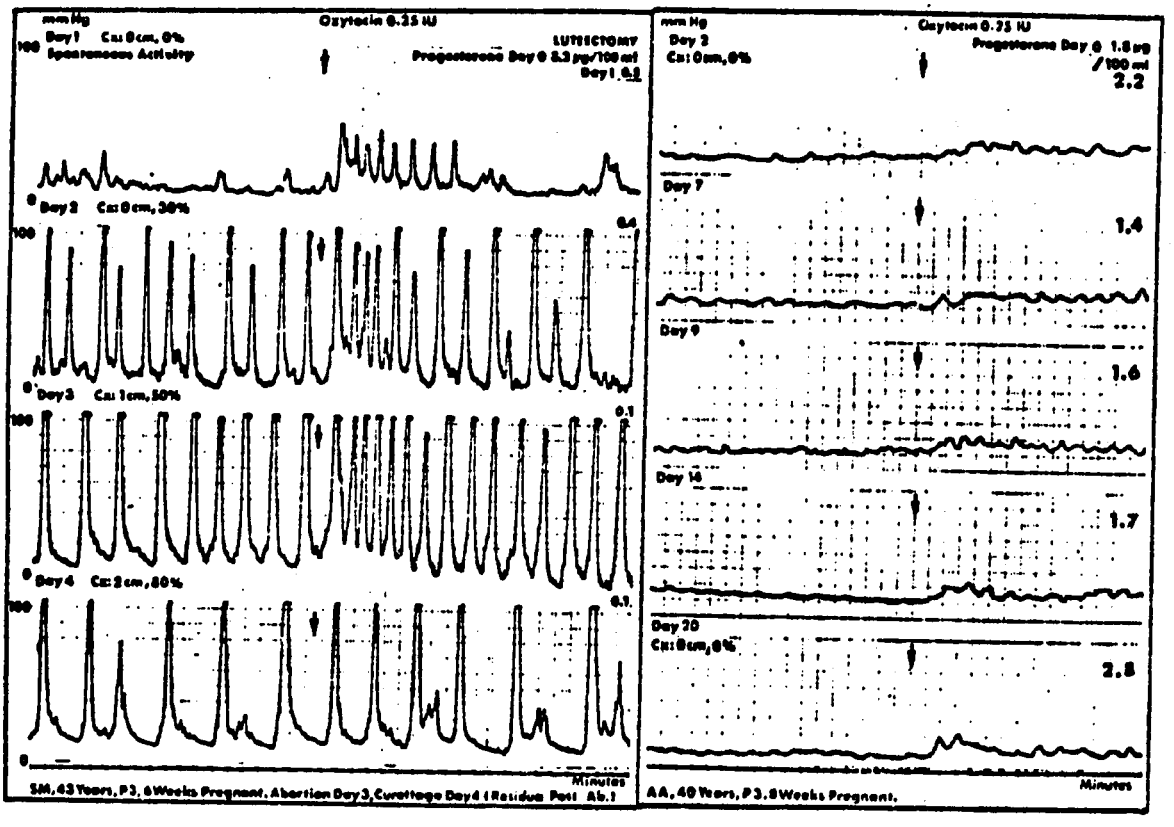
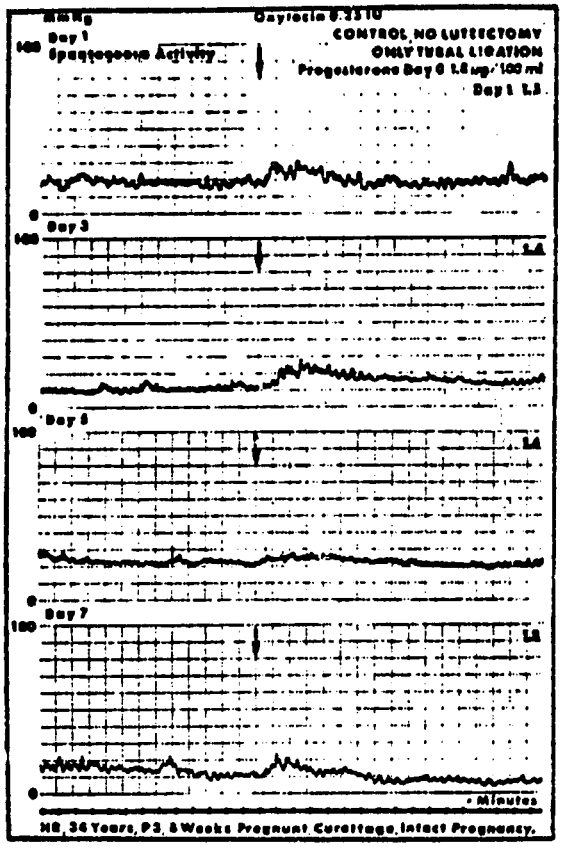


Figure 16. The effect of luteectomy on the early pregnant human uterus. Luteectomy in this normal 6 weeks pregnant patient reduced the P level from 32ng/ml to 5ng/ml in 24 hours and provoked the evolution of IUP and OR. During the subsequent 48 hours P decreased to 4ng/ml, the cervix began to dilate and the patient aborted. Note that no exogenous stimulation had been employed, only the corpus luteum was removed. The P levels in Figures 16, 17, 18 and 19 are shown on the upper right corner of the sequential tracings.

Figure 17. The effect of luteectomy on the pregnant human uterus. Luteectomy in this normal 8 weeks pregnant patient only reduced the P levels slightly and transiently and failed in provoking the evolution of IUP, OR, cervical dilatation and abortion during 20 days of observation. Apparently, the "luteo-placental shift" in progesterone-genesis had been far advanced.



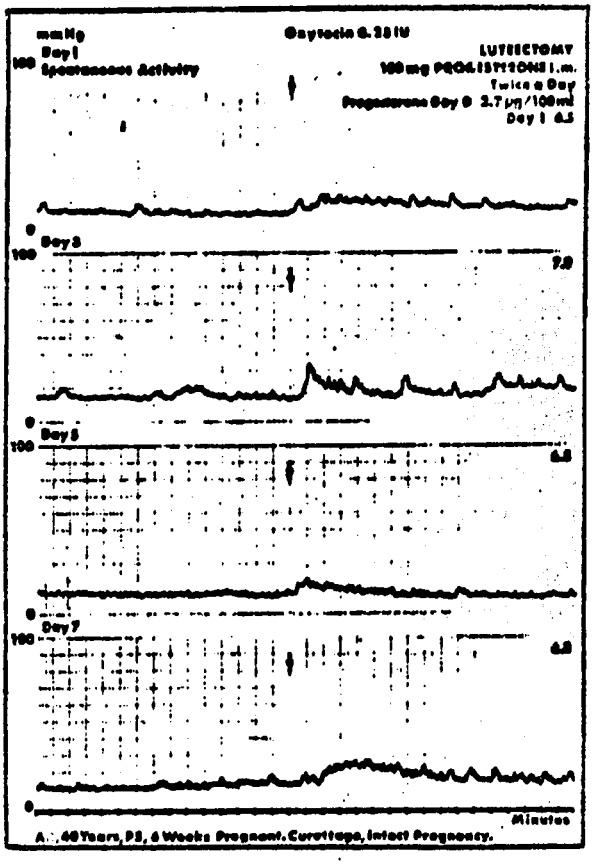


Figure 18. The effect of tubal ligation on the early pregnant human uterus. Tubal ligation alone (without luteectomy) provoked no significant changes in P, IUP, OR, cervical conditions and normal pregnancy.

Figure 19. The effect of luteectomy and progesterone substitution therapy on the early pregnant human uterus. Progesterone substitution therapy (100mg, i.m, twice a day) prevented in this luteectomized 6 weeks pregnant patient the precipitous fall in P level; in fact increased P. It also prevented the evolution of IUP, OR, cervical dilatation and abortion.

The IUP evolved fully, culminating in abortion in those patients whose initial fall in P levels was followed by a continued decline. Only partial evolution and incipient abortion occurred in those 4 patients whose P-withdrawal did not continue after an initial fall. No evolution of IUP, OR and abortion occurred in the 6 Controls and in the 7 P-treated luteectomized women whose P levels did not decrease (Figure 20). Evidently, the evolution of uterine activity failed in all patients (25, 26) whose P-withdrawal was moderate, or transient, or who had no P-withdrawal. Experiments in progress indicate that estradiol-17β (unlike progesterone) substitution therapy does not prevent the luteectomy-induced evolution of IUP, OR, and abortion. However, since luteectomy does induce E_2 withdrawal (Figure 20), the significance of this regulatory change demands full scale investigation.

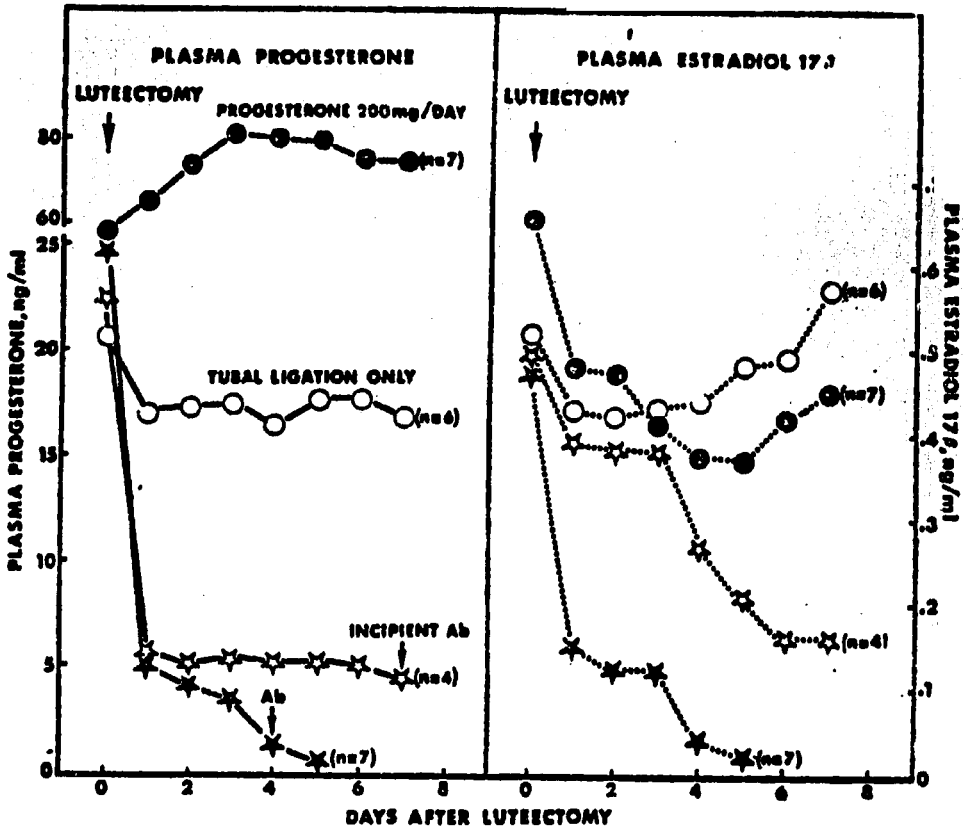


Figure 20. The effects of tubal ligation, luteectomy and progesterone treatment on the P and E_2 levels of early pregnant patients. Tubal ligation in the 6 Controls provoked no significant changes in steroid levels. Luteectomy induced precipitous and continued fall in P and E_2 in 7 patients and an initial but not continued decrease in P and slow decline in E_2 in 4 patients. In the 7 progesterone treated luteectomized patients, P was elevated and E_2 only decreased transiently.

These observations in 30 luteectomized and 6 Control patients (25,26) verified the premise that during normal pregnancy, the human, like the rabbit, uterus is controlled by P to a significant degree. Earlier studies revealed (21) that this hormone sustains a high threshold (Figure 14); prohibits propagation of the electric train discharges from one uterine region to another (Figure 15); and only permits local (asynchronic) activity. It is, therefore, a "blocking agent" prohibiting the evolution of advanced cyclic IUP and OR. Effective P-withdrawal weakens the block and permits the evolution of high level IUP. Lesser degree of P-withdrawal is needed for the evolution of IUP if uterine activity is promoted by exogenous stimulation (23). This finding substantiates the position (21) that P is only one of the many factors controlling the evolution of IUP and that the level of cyclic IUP is a reflection of the overall regulatory imbalance.

These theoretic considerations, basic studies and clinical trials together revealed, that a regulatory imbalance has to precede the display of advanced cyclic IUP, under both intrinsic and exogenous stimulatory conditions. The clinical relevance of this conclusion had been examined during PG-induced abortions.

PROSTAGLANDIN INDUCED ABORTIONS

The first three series of clinical trials were conducted primarily to reexamine earlier work in PG induced abortions and to satisfy FDA regulations. In all instances, protracted PG infusions were used and no attempt was made to harmonize these clinical trials with the basic work, described above. These trials were clinically disappointing, but they nevertheless deserve description here because of their academic messages.

(1) The Abortifacient Effect of Intravenous PG Infusion

Figure 21 illustrates that as late in normal pregnancy as the 16th week(where the P level was 35ng/ml) the intravenous infusion of 1500μg/hour PG F2α did not provoke promptly the over 150mm Hg working potential of this uterus. Only an unphysiological contracture response developed (second tracing), a definite sign of uterine overstimulation. High level cyclic IUP was only recorded with the progress of time.

All the 10 study patients, exposed to stepwise increasing massive PG F2α infusion (up to 12,000μg/hour) responded similarly, except that they displayed lesser activity. Systemic side effects (nausea, vomiting and diarrhea) were marked and repeated, causing considerable apprehension in patients and Staff. This experience served as a reminder that PG F2α is a general smooth muscle stimulant, with limited uterine specificity. In spite of continued treatment for 12 hours, repeated (on the following day) in case of "first day failure" and of the administration of a total average dose as high as 118±19mg. only 3 patients aborted completely, 3 had placental residues of various degrees and 4 failed to abort. The ideal abortion score (AbS) of 100 had not been approximated, by the low value of only 64, obtained in this study (Table 1). Similar results were obtained by others (20, 27).

However, the academic benefits of these trials were considerable. They revealed that the pregnant human uterus is not an inert organ. Its activity is more dependent on the time of effective stimulation, than on the level of exogenous PG infused. It would be a serious mistake to ignore this finding, when future studies are designed. High level cyclic IUP only evolved with the progress of time when P level decreased from 35ng/ml to 17ng/ml (Figure 21). In several patients the IUP did not reach the magnitude usually recorded during abortion.

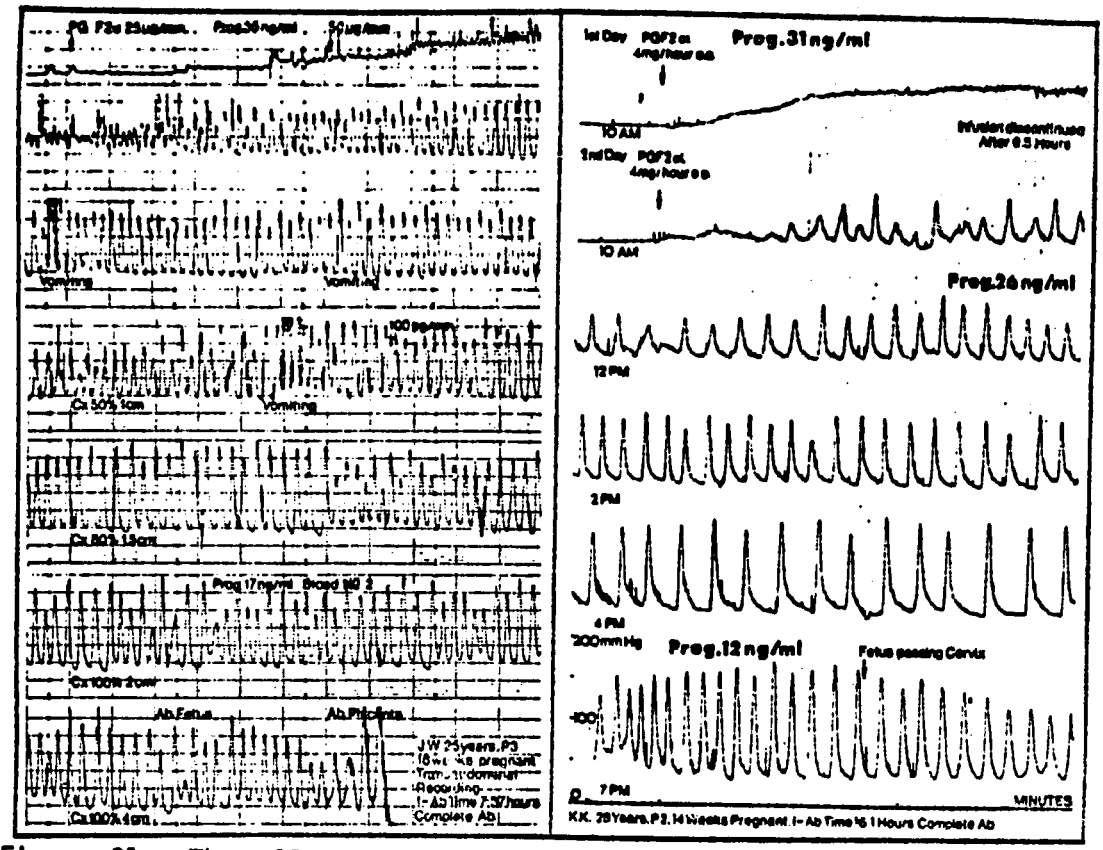


Figure 21. The effect of intravenous PG F2α infusion on a 16 weeks pregnant human uterus. Massive i.v. PG F2α infusion (25-50μg/min) induced initially a sustained contracture. High level cyclic IUP only evolved with the progress of time. Maximum IUP and cervical progress was evident when the P level decreased from 35ng/ml to 17ng/ml. When during abortion the placenta closed the cervical canal, ~150mm Hg IUP was recorded. Note the repeated vomiting.

Figure 22. The effect of extraovular PG F2α infusion on a 14 weeks pregnant human uterus. Massive extraovular PG F2αinfusion (66.6ug/min) only induced initially a sustained contracture. High level cyclic IUP did not evolve during 6.5 hours of continued infusion and there was no evidence of clinical progress. The study was discontinued. The following day the patient was reinfused and at that time, cyclic IUP evolved rapidly and maximum IUP was recorded, when the P levels decreased from 31ng/ml to 12ng/ml. Note the 130mm Hg IUP during the abortion of the fetus.

It is to be remembered that clinical progress is promoted by uterine wall tension (WT), rather than IUP. Due to the small radius (R) of the midtrimester pregnant uterus, its WT only becomes comparable (31) to that of the parturient term uterus (3.2×10^5dynes/cm), when its IUP is over 150mm Hg (Pascal's Theorem: WT=PR/2).

Table 1. Summary of Abortions Induced by PG F2α Infusions.

SUMMARY OF ABORTIONS INDUCED BY PGF2α INFUSIONS

PGF2α Treatment	No. of Patients	Parity No.	Gest. Age	Total PGF2α, mg	IAT hours	Clinical Outcome	Abortion Score
			Intravenous and Extraovular Infusions				
I.V. Infusion up to 12,000μg/hour	10	2.5 ±1.7	15.5 ±1.2	116.0 ±19.2	17.3 ±1.8	6 Abortions 4 Failures	64
E.O. Infusion 500μg/hour	10	1.1 ±0.5	11.3 ±0.4	5.0 ±0.0	12.9 ±1.3	3 Abortions 7 Failures	44
E.O. Infusion up to 4,000μg/hour	12	1.7 ±0.5	10.8 ±0.4	29.1 ±3.9	12.0 ±1.9	9 Abortions 3 Failures	62

The additional finding that the evolution of IUP is time dependent, posed the question of what changes occurred in myometrial regulation during the long periods of PG infusion? This preliminary study revealed that during IAT, the E_2 and P levels only decreased in those patients who aborted (31). These experiences called attention to the necessity of reducing systemic side effects and of clarifying the nature of the PG-induced, time dependent, regulatory changes.

(2) The Abortifacient Effect of Extraovular PG Infusion

In 10 obstetrically normal 11.3±0.4 weeks pregnant patients the earlier finding of others (20, 27) was reexamined, that intrauterine PG treatment is more effective than intravenous, and that it reduces side effects. An infusion rate of only 500μg/hour (during 10 hours) and a total dose of 5.0±0.0mg, did eliminate the side effects. However, only 3 patients aborted (in 12.9±1.3 hours), the remaining 7 only progressed to 1-2cm cervical dilatation. The AbS was only 44 (Table 1). Evidently, what had been gained in patient's comfort was lost in clinical success. This unsatisfactory clinical outcome is academically informative, however. Here, as before, the initial uterine response of all patients to PG F2α was a sustained contracture and high level cyclic IUP only developed with the progress of time.

(3) The Abortifacient Effect of Massive Extraovular PG Infusion

Increasing the infusion rate, in 12 obstetrically normal 10.8±0.4 weeks pregnant patients to 2,000-4,000μg/hour and using a total average dose of 29.1±3.9mg did increase the AbS to 68 (Table 1). However, it also brought back the side effects. Evidently, the small gain in clinical outcome was lost in patient's comfort.

However, the academic message of this study was again considerable. As before, the immediate response of the uterus to PG F2α infusion was an unphysiological contracture (Figure 22) and high level cyclic IUP only developed with the progress of time. As early as 3 hours after the start of infusion, the P levels decreased significantly, but only in those 9 patients who subsequently aborted. In contrast, those women who failed to abort showed no steroid withdrawals (32).

The conclusion is inescapable, therefore, that the normal pregnant human uterus is not an inert, but a suppressed organ. When challenged by PG F2α, none of the 32 pregnant uteri displayed promptly their maximum working potential. Only contractures were provoked initially and advanced cyclic IUP evolved with the progress of time, when the steroid withdrawals partly released these uteri from suppression. Only those patients aborted whose P-withdrawal was distinct.

This indicated correlation between P, IUP, OR and clinical progress was brought out by considering averages. When individual cases do not reflect it, the assay and recording techniques should be first scrutinized. They are not infallible! If the numerical values stand valid, it should be remembered that:(a) while 60mm Hg IUP induces labor at term, during the first and second trimesters, this IUP is only a fraction of the maximum value; (b) small changes in P could be biologically significant if PG stimulation is massive; (c) the degree of uterine activity is a reflection of the extent of the PG-provoked overall regulatory imbalance, rather than the change in P levels alone; and (d) current measurements only include the quantitation of some, but not all the regulatory factors. Thus individual deviations from the rule must be cautiously interpreted.

THE MECHANISM OF THE BIPHASIC ACTION OF PG F2α, A WORKING HYPOTHESIS

Apparently, the PG F2α effect on the pregnant human uterus is biphasic. The recognition of this biphasic action prompted a working hypothesis about the mechanism of PG action. This working hypothesis was based on the following considerations.

PG F2α, delivered to the uterus by any route, promptly provokes a high level contracture. At this time of maximal PG stimulation, the cyclic IUP is only a fraction of its maximum value (31, 32). The mechanism of this contracture (the first phase of the biphasic uterine response) is not explained by the clinical trials. Judging from the level of contracture, a significant uterine region is involved in sustained shortening. Contracture might be provoked by a direct myometrial effect of PG F2α on low threshold uterine regions, or by an indirect action of ischemia, caused by vasoconstriction. Whatever is the initial target of PG, the sustained shortening it provokes in the active uterine region must stretch the inactive regions, since the amniotic sac is incompressible. Therefore, during the entire duration of PG-provoked contracture, a sizable uterine region is stretched and becomes further stretched each time when an IUP cycle develops. Stretch (Figure 2) is a powerful uterine stimulant (21). The point of importance is, that exogenous PG F2α can not generate instantly high level cyclic IUP, needed for clinical progress in abortion. However, by provoking a contracture, PG does generate internal shortening and stretch in the myometrial wall. This initial response in turn promotes cyclic IUP by a complex mechanism, to be discussed.

Jointly, vasoconstriction contracture and cyclic IUP reduce uterine blood flow. The degree of this effect is apparently sufficient for compromising the endocrine function of the "feto-placental unit," for the E2 and P levels decrease (31, 32). The withdrawals of these steroids mark the delayed (second) phase of the biphasic PG effect. Having been relieved from suppression, the uterus is allowed to undergo the "evolution" process. This process demands a decrease in threshold and manifests in a gradual increase in cyclic IUP and OR (21-23). Once in progress, PG converted the dormant pregnant human uterus into a spontaneously active, pharmacologically reactive organ, only seen normally near term.

The rate of evolution of IUP and OR is controlled by many regulatory factors. It is affected by the degree of initial stretch, the extent of P-withdrawal and the level of exogenous stimulation. Of course, other factors (for example, changes in E2, oxytocin, a direct effect of PGs on steroidogenesis, etc.) might also be involved in the promotion of this PG-induced regulatory imbalance and should be considered, when experimentally documented.

However, the salient point of this working hypothesis is that it brings out the therapeutic significance of the "initial PG impact." It predicts that the greater is this impact, the more effective is the abortifacient therapy. In retrospect, it offers also a plausible explanation for the prolonged IAT and the frequent failures, observed when PG was administered by protracted infusions (Table 1). For, during the 32 clinical studies described (31,32), the patients had not been exposed to massive initial PG impacts, but only to protracted infusions. This working hypothesis also predicts that once the uterus had been "converted", by the initial PG impact, protracted treatment with PGs may not be needed, since the sequence of events provoked by the initial impact are "autocatalytic" and can run to completion without exogenous support. If the impact had been only partial, any oxytocic agent could promote its completion, by increasing the cyclic IUP of the moderately imbalanced uterus. Since the "PG impact" is a new therapeutic concept (22,23), it should be scrutinized extensively before adopting it clinically. The basic and clinical studies, which tested its therapeutic merits are described in the following pages.

PG INDUCED VASOCONSTRICTION

There is an accurate in situ method, which directly measures the degree of vasoconstriction in the small arteries of the rat omentum uteri (33). This method revealed that the local application of PG F2α (in doses which were abortifacient in both the rat and rabbit) not only provoked marked vasoconstriction, but often complete stasis (Figure 23).

After only 1 minute exposure of the tissue to PG F2α,continuous perfusion did not terminate vasoconstriction completely during observation periods of 30 minutes. Apparently, PG F2α is strongly bound by the smooth muscles of the small arteries, sustaining ischemia. It is probable, therefore, that the PG-provoked uterine contracture is (at least partly) an ischemic response.

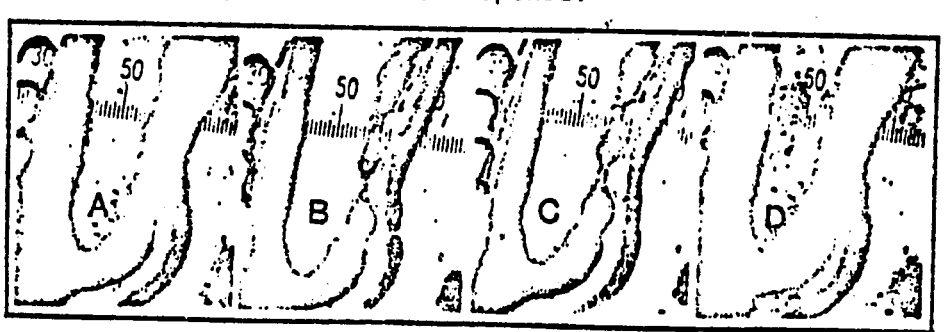


Figure 23. PG induced vasoconstriction. A single dose of 100μg PG F2α is applied topically on the omentum uteri and vasoconstriction observed (A). After 1 minute exposure to PG, the organ is perfused and photographed at 10 (B), 15 (C) and 20 (D) minutes. Note that in spite of perfusion the vasoconstriction is sustained.

THE PG "IMPACT"

When studying the endocrine function of the "feto-placental unit"(34), investigators could not foresee that the abortifacient action of PGs will be found critically dependent on their impact on this intrauterine hormone factory, vitally important in pregnancy maintenance. Nor was it obvious at the time when basic studies were conducted on the human corpus luteum and the "luteo-placental shift" in progesteronegenesis (25, 26), the luteotrophic action of feto-placental E_2 (30), the stretch dependent intrinsic uterine stimulant (22, 24) and the threshold control by P and PG (23), that these experiments would all promote the understanding of the mechansim of the abortifacient action of PGs.

Yet it now appears that what distinguishes PGs, as postconceptional agents, is not only their oxytocic potency (as has been generally assumed), but their ability to "convert" the P-blocked uterus into a spontaneously active and pharmacological reactive organ (22, 23). The findings that PGs can accomplish this conversion by compromising the endocrine function of the feto-placental unit (inducing its luteotrophic support) and in addition mobilize endogenous PG by provoking stretch (22, 24) is of considerable therapeutic interest. The problem remains, however, that the presently available PGs are not highly uterine specific. Therefore, in effective doses they provoke undesirable systemic side effects. This reality demands the development of treatment forms which permit significant reductions in the total PG dose administered.

When given by extraovular infusion, a total average dose of 29.1±3.9mg PG $F2\alpha$ only yielded an AbS of 68 (Table 1) and the side effects were frequent and recurring. Basic studies brought out the possibility (30) that this dose may be reduced considerably without loss of efficacy, if it is used in the form of a massive intrauterine injection, provoking a "PG impact." This therapeutic principle was expected to be effective, in both first and second trimester patients if the dilution effect, in case of intraamniotic administration, could be compensated for by an increase in dose. The therapeutic merits of the "initial PG impact" principle was examined firts in pregnant rabbits (30), in preparation for clinical trials.

Some investigators may wonder about the possible clinical benefits of conducting experiments in animal models at a time, when the studies in human patients are in progress for several years. This reviewer believes that only model experiments can clarify basic issues and that clinical trials should be restricted to the verification of the broad validity and the therapeutic usefulness of a biological principle. The following pages seem to substantiate this belief.

THE PG IMPACT IN PREGNANT RABBITS

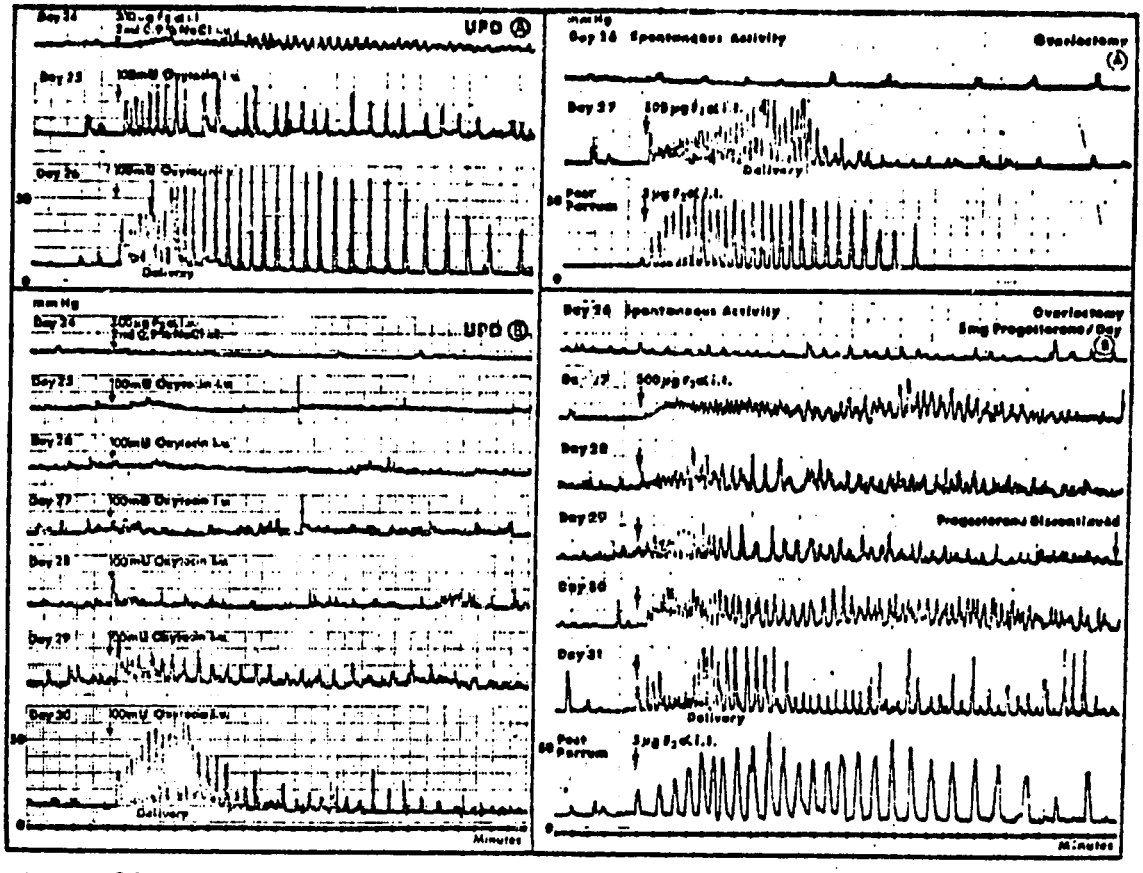


Figure 24. The effect of PG on the pregnant rabbit uterus. Unilaterally pregnant rabbits (at day 24) were given a single injection of 500ug PG F2α intraluminally (i.l., extraovular) (A) and intravenously(B). Intravenous treatment was ineffective (B) (even if repeated on subsequent days) and the normal OR (to 100mU, i.v.) did not appear until term, when it induced delivery. In contrast, the extraovular injection of the same 500ug PG F2α dose provoked contracture with only limited cyclic activity. The next day the P levels were reduced, the OR was distinct and the following day it was so far advanced that it provoked abortion.

Figure 25. The modifying effects of ovariectomy and progesterone substitution therapy on the PG response of the uterus. One day after ovariectomy, when the P levels fell below 2ng/ml, the extraovular injection of 500ug PG F2α provoked high level cyclic IUP and delivery (A). When this P-withdrawal was prevented by substitution therapy (5mg/day, i.m.), only contractures with restricted cyclic IUP were provoked by the same PG treatment. Only after P treatment was discontinued (day 29) did PG provoke advanced cyclic IUP and delivery (B). Postpartum as little as 5ug PG F2α (rather than 500ug) provoked maximum responses (A and B, last tracings).

At the 25th day of normal pregnancy, when the P levels are 9.1±1.2ng/ml in rabbits, massive extraovular PG F2α treatment (500μg, which was ineffective intravenously, Figure 24B) only provoked a sustained uterine contracture with restricted cyclic IUP (Figure 24A) In contrast, at term, when the P levels decreased to 2.1±0.7ng/ml (in unilaterally pregnant animals), this treatment provoked advanced cyclic IUP and delivery (30). However, once the pregnant uterus and its contents had been exposed to this sustained contracture, the P levels fell (in 48 hours, Figure 26) to the critical 2ng/ml value. After this regulatory change had been provoked, the cyclic IUP began to evolve, and could be increased markedly by exogenous (oxytocin or PG) stimulation, to provoke abortion (Figure 24A).

When the P levels were reduced by ovariectomy, to this critical 2ng/ml value (Figure 26), the first PG F2α treatment readily provoked advanced cyclic IUP (rather than contracture) and abortion (Figure 25A). If P-withdrawal had been prevented (in ovariectomized rabbits, Figure 26) by P substitution therapy (Figure 25B), PG F2α could not provoke high level cyclic IUP, but only contracture with restricted cyclic activity (30).

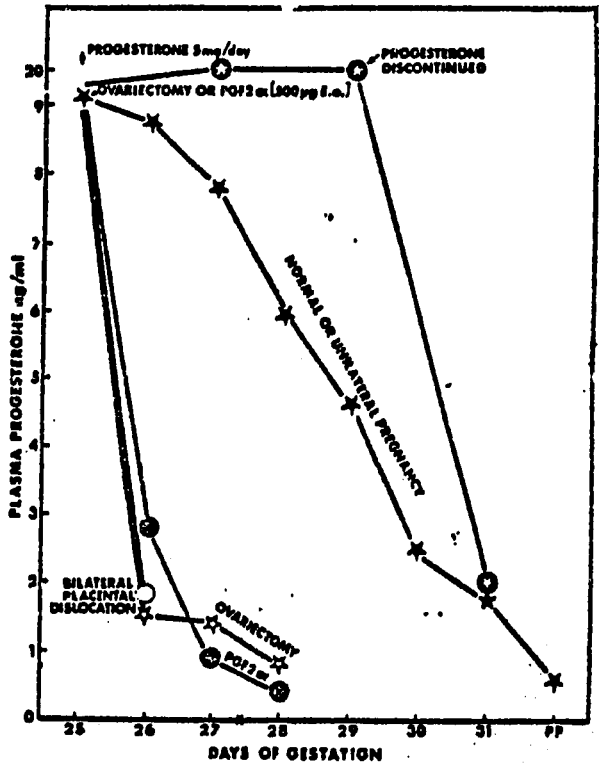


Figure 26. The changing P levels after surgical interference and hormone treatment in pregnant rabbits. In normal, unilaterally pregnant rabbits, the critical 2ng/ml P level is reached at term. Ovariectomy or placental dislocation reduces the P levels to this critical value in 24 hours. Effective PG F2α treatment (500μg, extraovular) provokes a similar effect in 48 hours. Progesterone substitution therapy (5mg/day) prevents the ovariectomy induced P-withdrawal, but when treatment is discontinued, the P levels fall precipitously.

When the P levels fell below 1ng/ml (post partum or post abortion, Figure 26), as little as 5μg (rather than 500μg) PG F2α provoked maximum cyclic IUP response (30). This finding (Figures 25A and B, last tracings) strengthened the evidence (21) that uterine "sensitivity" to stimulants is controlled by the effect of P on threshold.

The E_2 levels did not change appreciable (30) after the various surgical treatments (excepting bilateral placental dislocation). Furthermore, in contrast to P, E_2 substitution therapy in ovariectomized rabbits did not affect the uterine response to PG F2α (or to oxytocin) and did not change the course of abortion appreciably.

These studies (30) reemphasized the biphasic nature of the PG effect on the pregnant uterus. The immediate contracture response was followed with delay by P-withdrawal. This finding suggested that the luteotrophic function of the feto-placental unit had been suppressed, since in pregnant rabbits P originates from the corpora lutea. Once this delayed response developed, threshold decreased and low level PG or oxytocin stimulation induced advanced IUP. The prevention of P-withdrawal by substitution therapy, prevented these changes in uterine activity and reactivity.

It appeared, therefore, that the initial PG impact (the sustained uterine contracture and the associated change)created precociously a regulatory imbalance, resembling that which normally occurs during late pregnancy. In so doing, it converted the refractory uterus to a reactive organ. A direct luteotrophic action of PG has also been considered, but the experimental data were more consistent with the interpretation that the primary effect was directed toward the uterus and its contents.

CURRENT CLINICAL STUDIES OF PG INDUCED ABORTIONS

(1) The Extraovular PG Impact

A group of 10 obstetrically normal 9.3±0.4 weeks pregnant patients were studied (Table 2). They received during 10 minutes an extra-ovular injection of 10mg PG F2α. Supportive therapy (with additional PG or oxytocin treatment) was not provided, so as to bring out the uncontaminated effect of the initial PG impact (35).

The contracture response developed already during the 10 minute injection period and reached maximum in 15 minutes (Figure 27). All patients developed systemic side effects during treatment, indicating a rapid absorption of PG F2α, from the extraovular space. However, while the uterine contracture was sustained, the side effects disappeared (shortly after treatment was completed)and did not reoccur later. With the progress of time, cyclic IUP evolved, and when it did, clinical progress began. In 11.1±1.8 hours six patients aborted completely and four incompletely. The AbS was 80 (Table 2).

Table 2. Summary of Abortions Induced by Massive PG F2α Injections.

SUMMARY OF ABORTIONS INDUCED BY MASSIVE PGF2α INJECTIONS

PGF2α Treatment	No. of Patients	Parity No.	Gest. Age	Total PGF2α, mg	IAT hours	Clinical Outcome	Abortion Score
Massive Single Injection With Or Without Additional Treatment							
E.O. Injection 10mg Initial	10	1.6 ±0.5	9.3 ±0.4	10.0 ±0.0	11.1 ±1.8	10 Abortions 0 Failures	80
I.A. Instillation 10mg Initial+Support	12	1.6 ±0.7	16.0 ±0.4	34.4 ±4.3	14.8 ±1.2	12 Abortions 0 Failures	90
E.O. Injection 8mg Initial+Support	10	1.8 ±0.5	12.2 ±0.6	12.3 ±1.1	10.9 ±2.0	10 Abortions 0 Failures	92

This AbS is clinically unsatisfactory. However, the study revealed that a single extraovular injection of 10mg PG F2α is clinically more efficacious (AbS 80) than the continous extraovular infusion of 29mg (AbS 68), verifying the anticipated therapeutic and efficacious merits of the PG impact. Having provoked a marked and sustained uterine contracture, PG F2α did induce abortion several hours later; e.g. at a time when this rapidly metabolized (exogenous) compound could hardly have affected uterine function directly. It was of interest, therefore, to explore further the therapeutic value of this PG impact.

(2) The Intraamniotic PG Impact

A group of 12 obstetrically normal, 16.0±0.4 weeks pregnant patients were injected intraamniotically with 10mg PG F2α (Table 2). This treatment did provoke contracture in all cases (Figure 28). However, the rise in pressure was slower and its maximum value less than after the extraovular injection of 10mg PG F2α. Cyclic IUP evolved gradually and had to be promoted (at three hour intervals), by additional doses of 5mg PG F2α. In 14.8±1.2 hours, nine patients aborted completely and three incompletely. The AbS was 90 (Table 2). The systemic side effects were acceptable. Therefore, this form of PG F2α therapy might be recommended for routine use, if extensive field trials confirm the pilot studies (36). It is also apparent (37) that larger than 10mg initial doses can and need to be administered intraamniotically (20-30mg) specifically in advanced cases of midtrimester pregnancies. When they are, no further treatment might be necessary, for oxytocin can promote the full evolution of cyclic IUP, once the uterus is "converted" by the PG impact into a reactive organ.

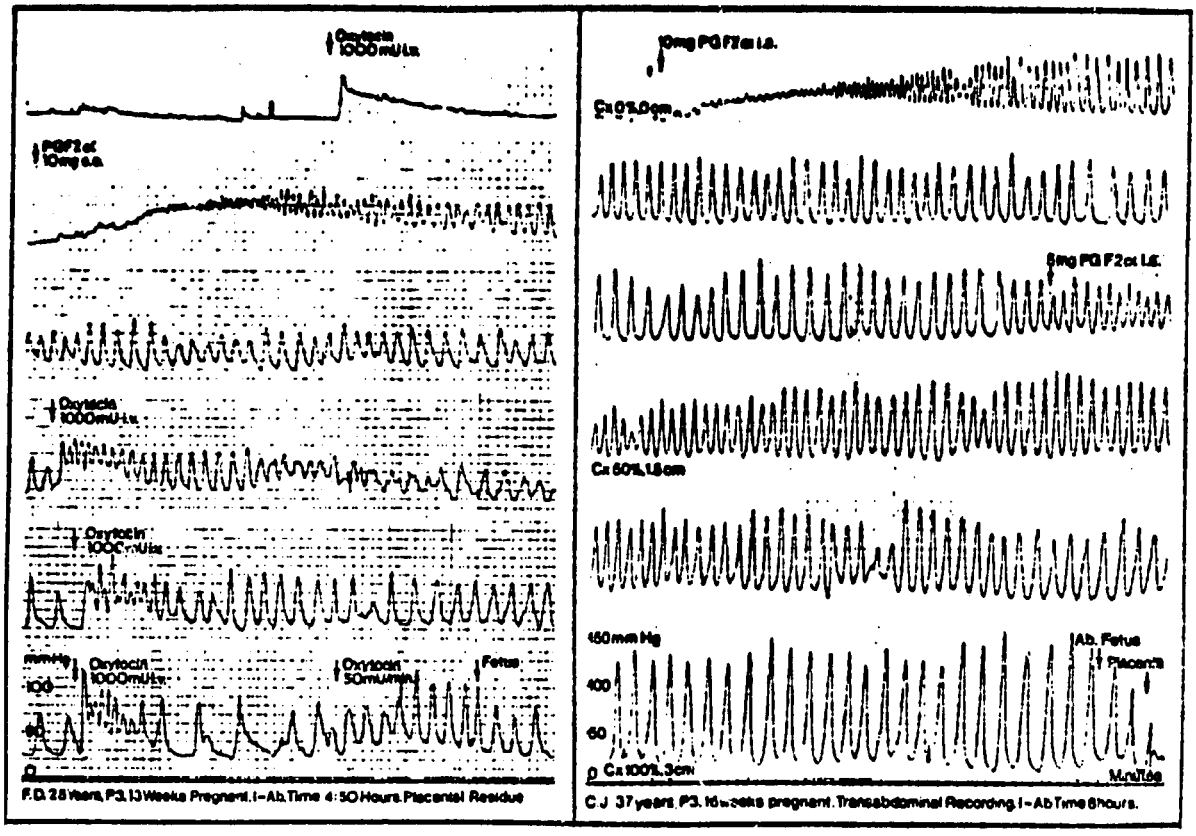


Figure 27. The extraovular PG impact. A single i.v. injection of 1000mU oxytocin only provokes a transient contracture response in this normal 13 weeks pregnant patient (tracing 1). In contrast, the extraovular injection of 10mg PG F2α provokes a sustained contracture, with gradually increasing cyclic IUP (tracing 2). At 2.3 and 4 hours after PG treatment, 1000mU oxytocin, which only provoked initially a transient contracture, now triggers advanced cyclic activity in this increasingly reactive uterus. Note that abortion was induced successfully in less than 5 hours by a single (10mg) dose of PG.

Figure 28. The intraamniotic PG impact. The intraamniotic instillation of 10mg PG F2α provokes a sustained contracture with gradually increasing cyclic IUP. At 3 hours after treatment when IUP decreases, an additional 5mg PG F2α reinforces activity. When IUP oversteps 100mm Hg, clinical progress accelerates and abortion is completed in 6 hours.

(3) The Extraovular PG Impact, With Supportive Therapy

In this study, the validity of the premise had been examined that once the PG impact did provoke a regulatory imbalance, the evolution of IUP and abortion could be promoted by oxytocic agents. A group of 10 obstetrically normal, 12.2±0.6 weeks pregnant patients were studied (Table 2). In order to reduce the short-lived but distinct systemic side effects (including uterine pain, observed in the 2 previous studies)

30 minutes before PG F2α injection the patients were treated with Compazine 10mg (prochlorperazine) to prevent nausea and Vistaril 50mg (hydroxyzine hydrochloride) and Demerol 50mg (meperidine hydrochloride) to reduce pain. If,in spite of sedation, side effects developed, the PG injection was interrupted, to be resumed when the side effects subsided. However, only hot flashes and mild episodes of nausea and vomiting were occasionally observed (38).

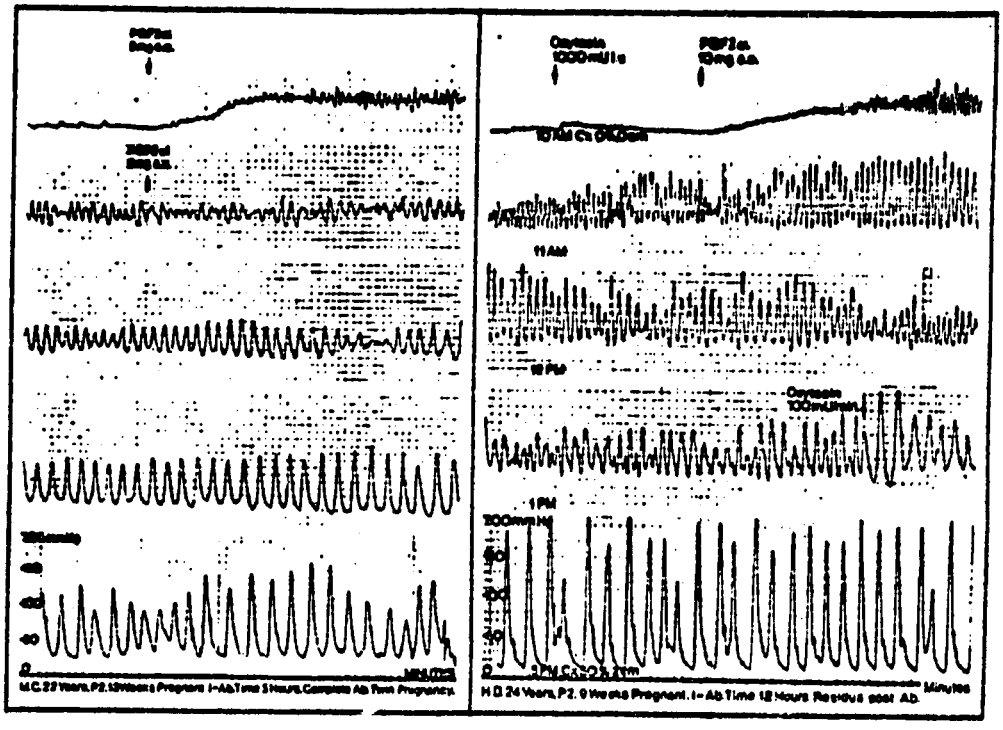


Figure 29. The extraovular PG impact without supportive oxytocin therapy. A total of 10mg PG F2α was injected extraovularly to this 13 weeks pregnant patient in two divided 5mg doses one hour apart. The contracture response developed promptly and the second dose had no recognizable effect. However, with the progress of time, cyclic IUP evolved and when it overstepped 100mm Hg, twin pregnancy terminated in complete abortion.

Figure 30. The extraovular PG impact, supported by delayed oxytocin therapy. In this 9 weeks pregnant patient 1000mU oxytocin provoked a hardly measurable response. A single dose of 10mg PG F2α provoked sustained contracture and gradually evolving cyclic IUP. When IUP tended to decline the i.v. infusion of 100mU/min oxytocin increased it markedly. At 4 hours after the start of oxytocin infusion, the IUP approximated 200mm Hg, clinical progress accelerated and the patient aborted.

Initially 8.1±0.8mg PG F2α had been injected extraovularly, to be increased later to a total dose of 12.2±1.1mg. Uterine contracture developed rapidly and reached 83.2±11.3mm Hg in 21.3±4.2 minutes, when the cyclic IUP only measured 14.6±7.5mm Hg (Figures 29 and 30).

With the progress of time, the IUP evolved, and when activity was supported by 50-100mU/min oxytocin infusion (in 4 patients), the IUP rose to 129.8±12.2mm Hg, in spite of bulging or leaky membranes. The patients aborted in 10.9±2.0 hours, seven completely, two retained placental residues and one incompletely. This clinical assessment has been verified (post curettage) by histological evidence. The AbS was 92 (Table 2), the highest value obtained in six consecutive studies. If this clinical outcome is duplicated in extensive field trials, this form of PG F2α therapy might be favorably considered for routine clinical use (38).

THE PROSPECTS OF PGs AS ABORTIFACIENTS

The therapeutic principle of "initial PG impact" apparently offers an abortifacient method, which is simple, effective and acceptable. Its prospects in therapy are, therefore, considerable. The AbS achieved by it is already high and might be improved further with experience. The reduction of side effects (during and shortly after treatment) demands prophylactic sedation, which, however, is routine procedure in labor management, in several Institutions.

If the mechanism of the abortifacient action of PGs is correctly interpreted here, it is unlikely that other treatment forms can surpass this therapeutic measure. A PG of high uterine specificity (which permits systemic administration without side effects) could, of course, challenge the merits of topical administration. Such a compound can revolutionize abortifacient therapy, being suitable for per os, or per vaginam, self administration. However, such a PG of high uterine specificity is not within reach at present. The characteristic feature of PGs is that they are general smooth muscle stimulants and mammalian smooth muscles are highly similar, structurally and functionally.

It seems feasible, therefore, to anticipate that intrauterine PG treatment will remain the preferential choice of therapy, at least for the time being. This treatment form does not exclude, of course, self administration. However, the resolution of this problem would demand investigative ingenuity and continued studies. Pilot experiments, exploring this possibility, are already in progress.

Current clinical studies are also extended to the examination of the effect of the PG impact within 2 weeks after the missed menstrual period. In these instances the outstanding problem to be resolved is a meaningful end point. In the human (and probably in other species as well, at comparable doses), PGs are not directly luteolytic (39), although they are luteolytic indirectly (30), through their effect on the feto-placental unit. The luteotrophic function of the placenta is indispensable during early pregnancy in all mammals and in luteal dependent species even at later stages of gestation (30).

Near the missed menstrual period, the human feto-placental unit only consists of a few cells. Its luteotrophic function and vulnerability to PGs are undetermined. It is difficult, therefore, to assess the degree of success in abortifacient therapy, because discharged tissue may remain unrecognized and curettage brings out chorionic elements even if pregnancy had been terminated. Provided bleeding does not demand curettage, the only reliable end point seems to be the negative pregnancy test, followed by a normal menstrual period, about one month after treatment. Twenty complete studies in progress indicate that the impact of 5mg PG F2α is an effective abortifacient near the missed menstrual period. No supportive therapy is required (except occasional curettage, in case of persistent bleeding, or positive pregnancy test), the PG impact alone is sufficient.

Considerable further therapeutic improvements might result from experiences in the proper timing of the effective PG impact, and from the examination of various PG formulations, some of which might be suitable for intrauterine self administration.

There is still another challenging therapeutic prospect, the mobilization of endogenous PGs. This approach is attractive because it offers more uterine specificity than any chemical manipulation can ever achieve. Apparently, stretch does promote uterine PG synthesis (Figure 3) and increased PG levels in turn facilitate uterine activity (Figures 3 and 14). However, the realization of this novel therapeutic principle demands the development of appropriate methodology, specifically the discovery of effective measures for decreasing threshold, by reducing simultaneously P and increasing PG.

Can stretch alone generate high enough uterine PG concentration to unbalance an effective P-block? The answer to this question is not available, but is accessible. Stretch might be used supportively to reduce the dose of PG demanded for an effective impact and to sustain the stimulation of the uterus. Basic research revealed already that stretch (induced by an increase in uterine volume) promotes the evolution of IUP and OR during non-pregnancy as well as throughout pregnancy (21). Indeed, sustained stretch occasionally induced abortion in obstetrically normal patients (Figure 4) and more frequently in cases of marked P deficiency, e.g. fetal death in utero and missed abortion (21). The basic work had been done, but the effect of stretch should be further explored and implemented therapeutically.

Whether PGs are effective postconceptional agents prior to implantation is doubtful. The available evidence indicates that they are not directly luteolytic in patients (39). This being the case they might not cause sufficient disturbance in the contractile activity of the oviduct and the uterus, to upset the early reproductive events terminating in implantation. There are certainly more promising leads, demanding urgent exploration.

A COMPARISON BETWEEN PG AND CURRENT ABORTIFACIENT THERAPIES

Can one expect PGs to compete favorably, with current abortifacient methods? An opinion on this point, of course, is speculative. Hundreds of thousands of clinical trials stand in support of current abortifacient therapies, whereas the studies with PGs are as yet limited.

By 1960, Aburells' hypertonic saline method had been completely abandoned and second trimester pregnancies were terminated by hysterotomy (40). At about this time, the purely academic question emerged: what are the consequences of the suppression of placental endocrine function? The simplest procedure which promised an answer to this question was the dehydration of the placenta and fetal membranes by hypertonic solutions, injected into the amniotic fluid. Experiments in animals revealed that abortion can be induced by the intraamniotic injection of any hypertonic solution, without regard of the ionic character of the agent used (40). Indeed, even hypertonic $MgCl_2$, a strong myometrial blocking agent, provoked abortion, of course, long after the ionic effects disappeared but the consequences of induced hypertonicity remained. However, if one of the feto-placental units escaped the effect of hypertonic saline, pregnancy was sustained because progesteronegenesis continued under the support of placental luteotrophic function.

When these purely academic studies were extended to include clinical trials, it appeared (40) that by the seventies this academic input might elevate the "salting out technique" (which during the fifties had been locked in disrepute), into a widely used routine procedure. In evaluating the prospects of PG therapy, a brief survey of this "renaissance" of the salting out technique might be valuable. For the problems with this method in the early sixties were not unlike those experiences with the PGs today.

Nothing looked more simple in the sixties than to exchange 200ml amniotic fluid with 200ml 20% NaCl. Yet it turned out to be not so very simple. The outcome of the earlier studies (specifically the Japanese experience (41)) provided a warning that this simple method is only safe in the hands of obstetricians trained in intraamniotic manipulations. Also, the mechanism of effect of hypertonic saline had been a source of controversity, which only tapered off somewhat with advances in steroid chemical assays (42)(Figure 31).

Apparently, history repeats itself. There are many ways for injecting PGs and not all of them are effective and acceptable (20, 27). Also the mechanism of the abortifacient action of PGs is still debated by some investigators, who expressed the insufficiently supported opinion that P-withdrawal does not proceed PG-induced abortions.

Apparently, more experience, more time, and certainly much more technical accuracy is needed for a resolution. This can be facilitated by improving the quality of evidence used in documentation. For, those investigators, who in carefully conducted clinical trials examined the PG-provoked changes in P with specific and sensitive assay methods, did confirm (43) the reported P-withdrawal (23, 44) in cases of therapeutic success and the absence of this withdrawal in cases of failure.

A controversial issue is best resolved by collaborative teamwork. Since the PG induced P-withdrawal is the theoretic key to effective abortifacient therapy it seemed desirable to subject our own data to an independent scrutiny. Since the Upjohn Laboratories are now using the same radioimmunoassay procedure and the same antigen, as was used in our study (36), it seemed appropriate to request a reexamination of the same 30 plasma samples. This study revealed a similar P-withdrawal in the individual patients and a similar average P-withdrawal in the group during the IAT (46% as compared to our 50%), which was statistically significant ($P < 0.01$).*

Table 3. Summary of 1000 Consecutive Saline Inductions.

1000 CONSECUTIVE SALINE INDUCTIONS *

	%
Success	99.6
Failure	0.4
Repeated Instillation	1.4
Curettage, Placental Residue	9.9
Complications	**%**
Fever	2.3
Amnionitis	0.1
Hemorrhage	2.3
Transfusion	0.3
Readmission	0.2
Cervical Tear	0.1
Perineal Tear	0.1
Hypofibrinogenemia	0.3
Amniotic Fluid Embolism	0.1

Average IAT: 25 hours. The patients were 68% nulliparous and in 74% 16-20 weeks pregnant.

*Already analyzed cases from: Kerenyi, T., Mendelman, N. and Sherman, D.: "5000 Consecutive Saline Inductions", Amer J Obstet Gynec. In Press.

* The author is grateful to Mr. Dan Brink and Miss Nancy Hopkins of the Upjohn Clinical Research Laboratory for the progesterone assays.

A recent study of 5000 consecutive hypertonic saline induced abortions (of which 1000 cases are already analyzed, Table 3) yielded a 99.6% success rate in 25 hours, with impressively low complication rates (45). In spite of this good outcome, however, PGs could compete favorably with the salting out method, if the "PG impact" does live up to expectation in extensive field trials. In second trimester patients this treatment might reduce the IAT to about 12 hours and reduce the complication rates beyond those experienced with saline.

In the management of first trimester abortions, PG treatment must compete favorably with the reliable and only ten minutes long surgical procedure, dilatation and curettage (D & C). This anticipation seems unrealistic, as long as one is impressed by the speed of D & C and its near certain guarantee of complete abortion. However, there is reason to believe that while D & C does resolve the acute problems of unwanted pregnancies, it creates chronic problems specifically in those women who are repeatedly exposed to it. Reference is made here to the Hungarian Experience described in:

THE RELATIONSHIP BETWEEN INTERRUPTIONS OF PREGNANCY AND PREMATURITY
Hungarian Public Health Statistics 1970
(20% Representation; 37,489 Pregnancies)

Patient's History	Prematurity Rate, %
No previous abortions	8.6
Only spontaneous abortions	9.3
1 interruption	13.0
2 interruptions	16.6
3 or more interruptions	20.6

This statistical analysis revealed that while spontaneous abortions in the patient's history only increased the prematurity rate moderately over the international average, pregnancy interruptions increased it markedly and proportionately with the number of incidences. Since the overwhelming majority of interruptions were resolved by D & C, it would appear that this simple surgical procedure is not without serious consequences. The casual relationship between D & C and increased prematurity rate has not been clearly established. However, evidence has been presented (46), suggesting that rapid cervical dilatation frequently creates the clinical syndrome: "incompetent cervix," which is known to play a significant role in the etiology of prematurity. If this relationship is verified, then PG therapy may be justifiable in first trimester patients, in spite of being a lengthy procedure. However, further studies must guarantee a predictable and high AbS and a complete absence of side effects.

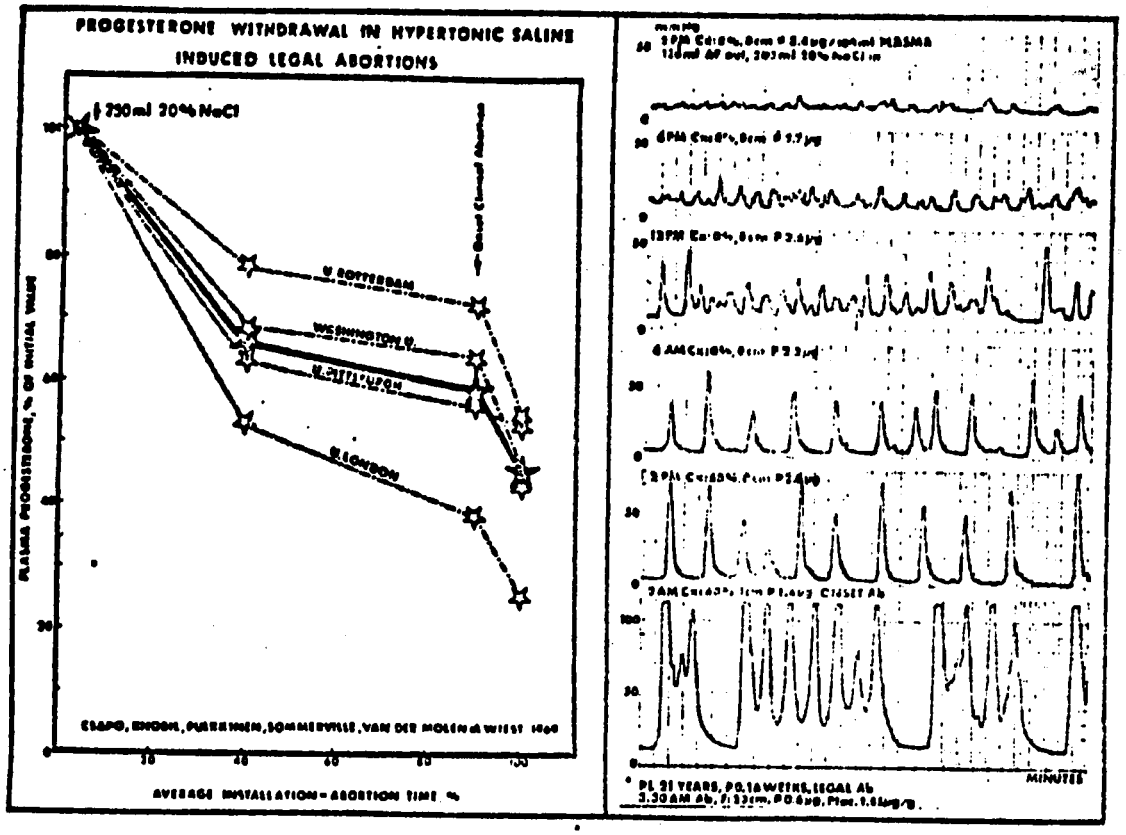


Figure 31. Hypertonic saline induced P-withdrawal, evolution of IUP and abortion. Left: a group of 6 patients were treated with 250ml 20% NaCl and 24 sequential samples were collected for P assays during the IAT. Four independent investigators measured P with reliable methods and invariably observed the P-withdrawal prior to abortion. Right: illustrates the saline induced characteristic evolution of IUP. Note that over 100mm Hg develops before clinical abortion.

Since in both, hypertonic saline and PG-induced abortion, uncertainties developed in the literature, concerning the reality of the P-withdrawal and thus its biological significance, it seems desirable to present here evidence showing that this regulatory imbalance does in fact occur in both instances, in cases of complete abortion. If P-withdrawal is a reality, it can provide to the field of abortifacient therapy not only a sound theoretical background, but it can also be diagnostic and prognostic. For, rapid and reliable assays (when they become available) can inform the clinician 3-6 hours after the saline or PG impact whether treatment will be successful.

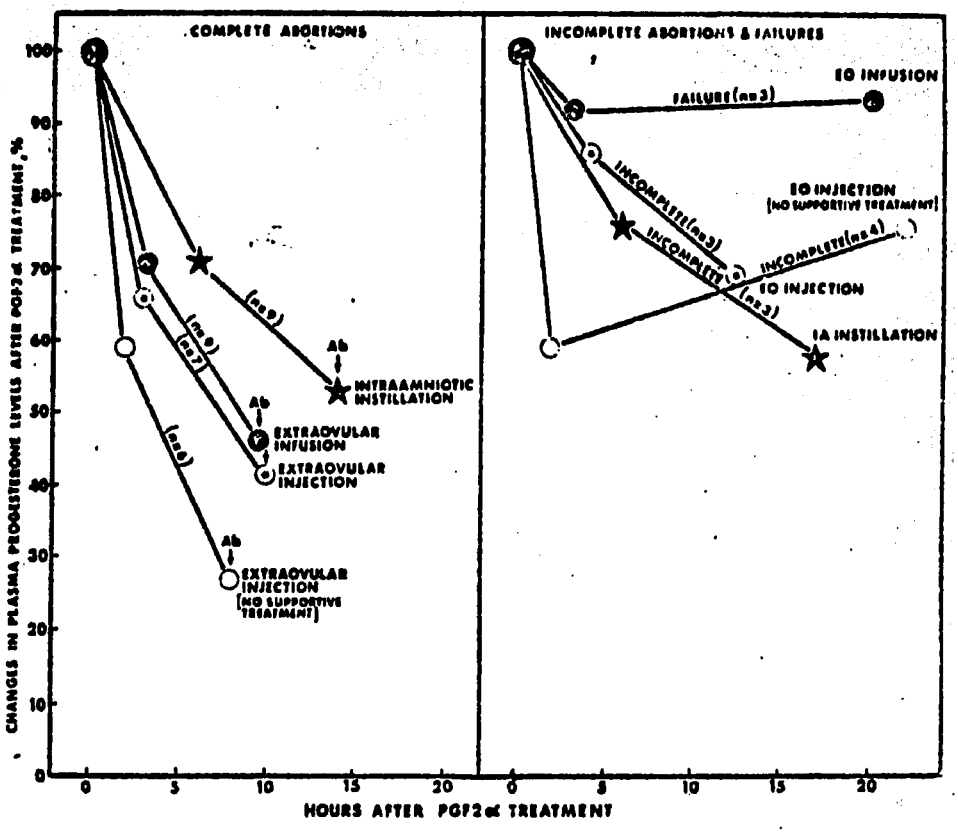


Figure 32. The PG-induced P-withdrawal. Left: illustrates the PG-induced P-withdrawal in 31 cases of PG-induced complete abortions. The 99 samples were obtained sequentially; before and 2-6 hours after the start of PG treatment and at the time of the abortion of the fetus (but before the discharge of the placenta). Note that without regard of the form of treatment, e.g. whether intraamniotic impact, or massive extraovular infusion or extraovular impact, the P levels are decreasing, if the successful treatment culminates in complete abortion. However, note also at Right: that in cases of treatment failure (extraovular infusion) there is no P-withdrawal and in cases of incomplete abortion, the P-withdrawal is limited.

The sequential P measurements,carefully conducted in 44 patients with reliable ("protein binding" and "radioimmunoassay") methods,substantiate the present position, that PG abortifacient therapy is effective, if it provokes a P-withdrawal (Figure 32). If this regulatory imbalance is not observed during the IAT, investigators should carefully examine their method of plasma collection and assay techniques, in appreciation of the fact that this imbalance is an outstanding theoretical and practical issue.

The opinion that PGs when properly applied are clinically effective and acceptable postconceptional agents rather than hopes "around the corner", might be tangibly illustrated by a case report. The clinical merits of the intraamniotic PG impact in midtrimester patients is already in the process of impressive documentation and, therefore, needs no elaboration here.

A 35 years old, P2, 16 weeks pregnant, diabetic Negro was referred to our study suite for legal abortion with psychiatric indications. At the age of 15 she weighed 350 pounds and at admission 455 pounds (!) Her uterus could not be palpated and thus gestational age could not be verified. However, her pregnancy test was positive.

In view of her excessive abdominal thickness, transabdominal puncture was ruled out and with it hypertonic saline treatment. Curettage was contraindicated and laparatomy seemed risky. It would be of interest to know how her pregnancy would have been terminated by others, not equipped for PG therapy.

Under sterile precautions and sedation (Demerol, Vistaril and Campazine), a condom rubber-tipped catheter was introduced into the uterine cavity. By 300ml applied volume through this "stretch balloon" the uterus was distended to increase the resting pressure to 35mm Hg. The low level oxcillation in IUP icreased slightly upon stretch. The "oxytocin test" (1000mU, i.v.) only provoked a transient 10mm Hg contracture. The extraovular 10mg PG F2α impact induced contracture of 130mm Hg, which gradually decreased to a steady 80mm Hg level. Cyclic IUP increased gradually but moderately and therefore a second 10mg PG F2α impact was delivered extraovularly at 4 hours. Two hours later the sustained balloon-stretch was releaved by withdrawing 270ml fluid. At 8 hours after the first PG impact the IUP measured 50mm Hg, and at 11 hours, when cervical progress was evident, 78mm Hg. At 12 hours the membranes ruptured and the patient aborted completely. The fetus was 14cm (100g), the placenta 95g. The patient was discharged in good health 24 hours after abortion.

This unusual patient received all the benefits of theoretic considerations and aborted completely in 12 hours without surgery, in spite of her unique disadvantage (455 pounds weight). It is as yet uncertain what contribution was made to success by the applied stretch. However, the PG impact did resolve a clinical situation, which might have been difficult if not impossible to cope with otherwise.

At the start, the author's intention was to examine the prospects of PG therapy throughout the entire postconceptional range. This intention was guided by the belief that the basic character of uterine function and the nature of contribution of PGs to this delicately controlled process do not change at midterm. Only the degree of the regulatory imbalance and its clinical expressions are changing.

Having examined the uterine model, the factors in control of contractile function, and the mechanism of PG action on the myometrium, this belief was strengthened, rather than weakened. It seemed feasible to follow the regulatory changes throughout gestation and define the nature of the terminal imbalance, triggering the initiation and promoting the progress of spontaneous labor.

To the obstetrician and the therapist, normal pregnancy, spontaneous abortion, interrupted pregnancy by fetal death in utero, missed abortion, premature labor, normal parturition, dysfunctional labor, atony, etc., are clinical entities to be resolved by different managements. To the uterine physiologist and regulatory biologist they are normal, or abnormal, expressions of the same basic contractile and regulatory functions, to be examined and resolved at the level of the myometrial cell, when the normal process might be therapeutically promoted or the imbalance corrected. It is, of course, appreciated that the feto-maternal endocrine system has a decisive influence on uterine function. However, the terminal step in abortion, precocious or term delivery, is the regulatory imbalance, created in the myometrial cells themselves. It is, therefore, at this level where the normal and abnormal contractile functions have to be defined and it is also at this level where PGs have a documented and significant regulatory effect.

However, as the pages accumulated, the original plan had to be abandoned. Following the chapters of this article critically, the reader earned his rest. The prospects of PGs in perinatology will be separately considered in Part II of this Review.

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