HYDERGINE THERAPY OF UTERINE INERTIA*

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General Considerations

NORMAL labour is characterized by a co-ordinated pattern of uterine contractions and complete dilatation of the cervix within a reasonable length of time. *Caldeyro* and *Alvarez* (1) in their study of normal labour found that during a contraction the intra-uterine pressure ranged between 30 and 50 mm. of mercury. According to them, the intra-uterine pressure between contractions, i.e. the resting or basal tone of the uterus, was usually 8 to 12 mm of mercury. Their uterine tracings and recordings showed that a normal contraction pattern started in the fundus and was of greater intensity in that region as compared to the lower segment. Thus the characteristic of normal labour, as demonstrated by these workers, is active participation of all parts of the uterus with strong synchronized contractions starting in the fundal region.

In contrast to this, primary uterine inertia is characterized by a prolonged and painful first stage of labour with incomplete dilatation of the cervix after 24 to 48 hours of ineffectual incoordinate contractions. Clinically, this state is apparent in patients who show signs of emotional tension and fear. In these cases, both the intensity of contractions and the resting tone of the uterus between contractions, may show a great deal of variation. Moreover, the contraction waves of fundal origin, and the normal gradient of activity from the upper to the lower segment are lacking. Instead, an abnormally weak or strong anti-peristaltic contraction pattern persists. These abnormal contractions are associated with slow and painful dilatation of the cervix. Labour becomes virtually arrested after a trying first stage and many of the patients become hysterical, uncooperative and difficult to manage.

MacRae (2) defined primary uterine inertia as a first stage of labour, which, in the absence of cephalo-pelvic disproportion has lasted 48 hours or more. He recognized six types. In his experience, the atonic uterus and the hypertonic uterus with cervical achalasia were the most common. He defined cervical achalasia as non-relaxation of the cervix despite continued severe contractions of the uterus. In his series, the condition was encountered in 3.2 percent of obstetrical cases and was more common in the emotionally hyperactive primipara. He stressed the high incidence of maternal morbidity and the high foetal loss. Asphyxia and intra-uterine infection were responsible for the foetal wastage in these cases.

Jeffcoate (3) considered the hypertonic type of inertia to be the more common and alluded to the functional aspect of this disturbance.

Arthur (4) encountered primary uterine inertia in 1.5 percent of his confinements. He correlated this disorder with disturbance of function, although he

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believed that the delay in dilatation of the 'hanging' cervix might be further complicated by excess fibrous tissue in that organ.

The records of *Caldeyro and Alvarez* (5) on abnormal labour support Jeffcoate's findings. They encountered the hypertonic type of inertia more frequently and found this type to be characterized by increased resting tone of the uterus, severe backache in the mother and hypoxia in the foetus. They described the contractions in this type of inertia as abnormal, irregular and of low intensity. Their uterine tracings showed a loss of fundal dominance of the contraction pattern and the majority of the contraction waves started in the lower segment and spread in an anti-peristaltic fashion to the upper segment. They showed that in this condition cervical dilatation did not progress.

On the other hand, *Williams* (6) claimed that the intra-uterine pressure of hypertonic uterine inertia varied a great deal. He showed that the uterine action was erratic and unpredictable and that there was a tendency for the organ to manifest tetanic spasm.

Reist (7) elaborated on the role played by sympatho-adrenal overactivity in the production of this disorder. He believed that emotional tension with its attendant sympatho-adrenal overactivity was also responsible for the syndrome which he described as 'fixation of the soft parts'. Clinically, this was manifested by a flaccid, relaxed and persistent anterior lip of cervix which had ceased to dilate. This lip often became incarcerated.

Reist (7) reminds us that the appearance of vaginismus on vaginal examination is an external manifestation of emotional tension and sympatho-adrenal overactivity. He points out that this syndrome consists of spasm of the vulvar introitus, internal rotation of the thighs and an attempt to withdraw from the obstetrician's examining hand. Morever, according to Reist, this same sympatho-adrenal overactivity is responsible for the various forms of primary uterine inertia and its attendant cervical spasm or 'fixation' of the cervix. Thus primary uterine inertia and external vaginismus are clinical manifestations of the same functional disorder.

Innervation of the Uterus

The anatomical sensory and motor innervation of the uterine fundus is located in the thoracic sympathetic fibres and the motor and sensory supply of the cervix is traced to the sacral parasympathetic system. This would imply that sympatho-adrenal overactivity must limit its effects to the uterine fundus as the cervix is supposed to be under purely parasympathetic control. The work of *Cleland* (8) and others refutes this implication. Cleland (8) showed that a paravertebral nerve block of the eleventh and twelfth thoracic segments completel abolished the pain of uterine contractions and cervical dilatation. Thus both uterus and cervix are subserved by the same sympathetic afferents whose pain fibres reach the cord with the eleventh and twelfth thoracic nerves.

Kaiser and *Harris* (9) demonstrated that in the pregnant female an injection of exogenous adrenalin will excite a spasm of both cervix and fundus and will disrupt the contraction pattern of normal labour. They noted that this disruption resembled the disordered contractions of uterine inertia in emotionally dis-

turbed patients In these cases, endogenous adrenalin is believed to be secreted excessively.

Schofield (10) reported that stimulation of the hypogastric nerves in the rabbit excited contractions of both the cervix and the cornua. These effects could be reproduced by the injection of either adrenalin or noradrenalin.

Therefore, in summary, it appears that uterine inertia and cervical spasm is a functional disorder of the entire uterus. It is associated with emotional tension and sympatho-adrenal overactivity. The excess of endogenous adrenalin secretion exerts its effect on both cervix and fundus and results in a disorganized pattern of ineffectual contractions during labour. In this situation the first stage of labour is unduly prolonged and cervical dilatation does not progress. These factors are responsible for the high incidence of foetal asphyxia and maternal morbidity encountered in this condition.

Treatment

Many forms of therapy have been advocated for primary uterine inertia and cervical spasm. The conservative school have relied on rest, heavy sedation and intravenous fluids in the hope that these measures would result in a normal pattern of contractions and dilatation of the cervix. It is realized that rest and sedation are effective in allaying fear and apprehension and thus decrease the stream of central sympathetic impulses playing on the uterus and cervix. However, the prolongation of labour attendant upon this form of therapy is detrimental to both mother and child. Uterine anti-spasmodics such as papaverine have direct effect on smooth muscle, and thus suppress uterine contractions. Uterine stimulants such as pitocin are not without danger to both mother and child Moreover, although the oxytocic property of pitocin does increase the intensity of the uterine contractions, it has no effect on the incoordinate character of the contraction pattern. (*Jeffcoate* (3))

The reports of *Sauter* (11), *Gill* and *Farrar* (12) and *Baskin* and *Crealock* (13) on the use of dihydroergotamine (DHE) in primary uterine inertia and cervical spasm stimulated our interest in the hydrogenated ergot alkaloids. *Rothlin* (14) showed that in animals DHE had no oxytocic action. His experiments demonstrated that hydrogenation of the ergot molecule either completely abolished or markedly suppressed its oxytocic properties and, at the same time, greatly enhanced its latent adrenolytic and sympatholytic actions. We (15) used DHE in a series of 50 cases and obtained good results. However, it was our impression that the drug did have a mild but definite oxytocic action when administered intravenously in effectual dosages. Although there were no maternal or foetal complications attributable to the drug, the slowing of the foetal heart in 60 per-cent of the cases did cause us some concern.

For this reason, we have supplanted DHE with Hydergine in a recent series of 100 cases. Hydergine is an equiproportional mixture of dihydroergocornine, dihyrdoergocristine and dihydroergokryptine, derivatives of the three alkaloids comprising the ergotoxine group. It is marketed in 1 ml. ampoules containing 0.3 mg. of the alkaloidal mixture. Hydergine has a central action on the vasomotor center which results in a vasodilatation and a lowering of the vascular

tone in the peripheral vessels. It also has a central vagal stimulating action, and thus, a slow pulse rate is characteristic of Hydergine therapy. Peripherally it exerts an adrenolytic and sympatholytic action and in this way it resembles DHE. However, Hydergine has an additional direct action on the smooth muscle of the peripheral vessels which results in vasodilatation. In this way, it differs from DHE which exerts a mild vasoconstricting action directly on the smooth muscle of these vessels. Hydergine is recommended for the treatment of peripheral vascular disease and hypertension whereas, DHE is recommended for the treatment of migraine cephalalgia.

Rothlin (14) showed that hydrogenation of ergot alkaloids either completely abolished or markedly suppressed their oxytocic action. Because of the difference in the direct smooth muscle effect between the two drugs, we believe that the oxytocic action was more thoroughly eliminated in the case of Hydergine. In addition, it has been shown experimentally that the adrenergic blocking action of Hydergine is more profound on the blood vessels of visceral organs as compared to the somatic. Small doses of Hydergine which readily block the vasoconstrictor action of epinephrine on the renal and superior mesenteric beds do not significantly alter the femoral blood flow response to intra-arterial epinephrine. (*Gruhzit* (16).)

The indication for the use of Hydergine was clinical evidence of arrested labour in a tense, emotionally hyperactive patient who showed no obvious cephalo-pelvic disproportion. In a large number of our cases, the tension mounted to a pitch of hysterical screaming. These patients performed writhing movements during the contractions and complained of great discomfort between their pains. The actual contractions were noted to be of poor quality and character and unduly painful. Dilatation of the cervix did not progress in these patients and vaginal examination usually revealed a hard tense cervix which had reached the stage of 6 cm. or more of dilatation. Occasionally, the obstetrician reported a soft hanging lip of cervix which on repeated vaginal examination showed no change or progress. A few of the cases were outwardly calm and co-operative but their covert tension was revealed by the manifestation of marked vaginismus to vaginal examination.

The drug was used in various dilutions. Fifty of the cases received the Hydergine in a dilution of 1 ampoule in 10 ml. of water; sixteen in a dilution of 1 ampoule in 5 ml. of water; twenty-six in a dilution of 1 ampoule of Hydergine in 500 ml of 5 percent glucose solution, five in a dilution of 1 ampoule in 20 ml. of water, and the remaining three patients had the drug administered in a dilution of 1 ampoule in 1000 ml. of 5 percent glucose solution. The drug was administered slowly over a period of 5 to 8 minutes in the patients receiving the 1 in 5 to 1 in 20 dilutions A drip rate of from 60 to 120 drops per minute was used for the 1 in 500 to 1 in 1000 dilutions and the infusion was stopped as soon as the desired effect was obtained. All the patients received the drug intravenously.

There were 100 cases in the Hydergine series. In 64 percent of these, the cervix dilated fully within 20 minutes from the time the Hydergine injection was started. Furthermore, the majority of the cases in this group, 37 to be exact,

were fully dilated within 10 minutes. Of these there were 54 multiparas whose average duration of labour before Hydergine therapy had been 13 hours—(the shortest was 4 and the longest 30 hours). Ten of the patients were primiparas whose average duration of labour had been 25 hours—(the shortest was 17 and the longest was over 48 hours). It is significant that there was external evidence of tension and emotional overactivity in approximately four-fifths of this group where the response to Hydergine therapy was dramatic. Moreover, there were 7 posterior presentations in this group. Of the remaining 36 percent of the Hydergine series, 19 became fully dilated within ½ hour following the drug administration and the other 17 patients required anywhere from 80 minutes to 5 hours. However in these 36 cases where the results were considered to be equivocal, there were 10 posterior presentations, 4 cephalo-pelvic disproportions and 4 cases where the drug was tried in an attempt to expedite a normally progressing labour. It is again significant that in over two-thirds of these patients there was no evidence of emotional overactivity. Therefore, this 36 percent of the Hydergine series did not fulfill the criteria which, in retrospect, we considered necessary for successful Hydergine therapy.

Complications

There were four instances where the foetal heart slowed to between 80 and 90 beats per minute. In one instance there was a spasm of the uterus for the duration of two pains. In this case the foetal heart rate slowed to 90. This may have been a coincidence because *Williams* (6) found that there was a tendency for uterine spasm to occur in the hypertonic type of inertia.

There were no foetal deaths or maternal complications which could be ascribed to the use of Hydergine The drug had no appreciable effect on the maternal blood pressure. The absence of maternal hypotension was probably due to two factors:—(1) recumbency of the patients, (2) the tendency for Hydergine to exert a more profound effect on the visceral vascular bed as compared to the somatic (16).

Discussion

We were impressed with the relative safety of Hydergine as compared to DHE and Pitocin. The beneficial effect of this therapy was most evident in the primary uterine inertia of the hypertonic type. The clinical criteria for the successful administration of Hydergine were: (1) evidence of emotional overactivity, (2) evidence of arrested labour in the course of trying first stage, (3) evidence that cervical dilatation had progressed to at least 6 cm., (4) evidence of either non relaxation of the cervical os despite hard pains, or of a persistent, soft anterior lip of cervix, (5) absence of definite cephalo-pelvic disproportion. In 64 percent of our series, where the results were good, the majority of the patients fulfilled these criteria. The cephalo-pelvic disproportion was probably minimal in the 7 posterior presentations which responded rapidly to Hydergine.

Some patients were apparently calm and co-operative but the progress of their labour manifested all the other criteria of primary uterine inertia. These cases were better able to suppress the external component of sympatho-adrenal

overactivity. However, the presence of vaginismus on vaginal examination revealed their covert tension and their response to Hydergine therapy was also good. Because one case of mild uterine spasm was encountered when the drug was used in a dilution of 1 ampoule (0.3 mg.) of Hydergine in 10 ml. of water, we feel that the more dilute solutions of the drug such as 1 ampoule in 500 ml. of 5% glucose solution are indicated.

In the 36 percent of our series where the results of Hydergine therapy were considered either equivocal or poor, there was a high incidence of complicating factors such as disproportions and posterior presentations. Furthermore, the majority of this group did not show any clinical evidence of emotional tension.

Summary and Conclusions

HYDERGINE THERAPY OF 100 CASES OF UTERINE INERTIA

A	64%	EXCELLENT RESULTS	cervix fully dilated within 20 minutes.

BREAKDOWN

(1) 37 of the 64 dilated in 10 minutes.

(2) Four-fifths of the 64% showed evidence of emotional overactivity.

B.	36%	EQUIVOCAL RESULTS	cervix fully dilated in from 1 to 5 hours.

BREAKDOWN

(1) 19 dilated in 1 hour.

(2) 17 dilated in from 80 minutes to 5 hours.

(3) Two-thirds of the 36% showed NO clinical evidence of emotional over-activity.

(4) 14 cases showed definite evidence of cephalo-pelvic disproportion.

One hundred obstetrical patients were treated with Hydergine. The drug was used intravenously in various dilutions. In 64 percent of the cases the results obtained were dramatic. In the remaining 36 percent the poor results were attributed to: (1) the high incidence of complicating factors, (2) the random selection of the earlier cases.

The one case of uterine spasm may have been a coincidence. However, because of this, we have resorted to the use of intravenous drip infusion of a solution of 1 ampoule of Hydergine diluted in 500 ml. of 5% glucose solution.

Hydergine should be reserved for patients who manifest all of the clinical criteria of primary uterine inertia and cervical spasm. We feel that definite evidence of cephalo-pelvic disproportion is a contra-indication or this therapy. In our experience the drug is of no value in expediting normal abour.

We are not prepared to say whether the sympatholytic and adrenolytic actions of Hydergine produce their effects predominantly on the cervix or on the entire uterus. Whatever and wherever its mode of action, the net result is a more efficient type of uterine contraction and rapid dilatation of the cervix. With this accomplished, the foetal wastage and the maternal morbidity in these difficult and trying labours is materially reduced.

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Resumé et Conclusions

Thérapeutique avec Hydergine de 100 cas d'inertie Utérine

A. 64%	Résultats Excellents	le col de l'utérus complètement dilaté en 20 minutes.

Détails

(1) 37 des 64 dilatés en 10 minutes.

(2) 4/5ième des 64% ont montré évidence d'un excès d'activité émotionnelle.

B. 36%	Résultats Equivoques	le col de l'utérus dilaté dans un espace variant de 1 à 5 heures

Détails

(1) 19 dilatés en 1 heure.

(2) 17 dilatés dans un espace variant de 80 minutes à 5 heures.

(3) 2/3 des 36% n'ont pas révélé une évidence clinique d'un excès d'activité émotionnelle.

(4) 14 cas ont révélé une évidence nette de disproportion céphalo-pelvienne.

Cent cas obstétricaux ont reçu le traitement à l'Hydergine. La drogue en solutions variées a été employée par injections intraveineuses. Dans 64% des

cas les résultats obtenus ont été frappants. Dans les autres 36% les résultats médiocres ont été attribués à (1) l'incidence élevée de facteurs amenant des complications, (2) aux choix au hasard des cas précédents.

Il se peut que le seul cas de spasme utérin ait été une coincidence. A cause de ceci, toutefois, nous avons eu recours à l'infusion intraveineuse goutte à goutte d'une solution contenant une ampoule d'Hydergine diluée dans une solution de 500 ml. de glucose à 5%.

On devrait réserver l'hydergine pour les patients qui manifestent tous les critères cliniques de l'inertie utérine primaire et du spasme utérin. Nous sommes d'opinion que l'évidence nette de disproportion céphalo-pelvienne est une contre-indication pour ce traitement. Suivant notre expérience la drogue n'a aucune valeur pour accélérer les douleurs qui accompagnent l'accouchement.

Nous ne savons pas encore si les actions sympatholytiques et adrénolytiques produisent leurs effects principalement sur le col de l'utérus ou sur tout l'utérus. Quelle que soit et où que soit son mode d'action, le résultat net est un genre plus efficace de contraction utérine et une dilatation plus rapide de l'utérus. Ces conditions présentes, les déchets foetaux et la morbidité chez la mère, pendant des accouchements difficiles et pénibles, sont considérablement réduits.

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