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ENDOCRINOLOGY OF PARTURITION AND LABOUR INHIBITION

(17th Sir Kedarnath Das Memorial Oration)

P. K. Devi,* M.S., F.R.C.S., F.A.M.S.,

At the outset, I would like to express my sense of deep gratitude to the Bengal Obstetric and Gynaecological Society for having conferred on me the honour and privilege of delivering the 17th Kedarnath Das Memorial Oration this year. The subject that I have selected, I am sure would have interested deeply the great man, to honour whose memory we have met here today, since in addition to being an eminent educationist and teacher, clinician and surgeon, he was deeply concerned with developing obstetrics as a science as well as an art. One of the important regions in obstetrics which concerns all of us who practice obstetrics, is a clearer understanding of the factors which determine the duration of pregnancy and the initiation of labour in the human, since derangements in this period in the form of premature births or postdate pregnancy can lead, not only to increase in perinatal deaths but also affect the physical and mental well being of those babies who survive after being forced to brave the perils of this world too early or too late by a few precious days. The first part of this presentation will be devoted to a brief review of the current knowledge regarding the factors which lead to the initiation of labour with special reference to the foetal and maternal endocrine systems and in the second part some of our own work regarding the arrest or inhibition of premature labour will be presented.

In 1963, thirty-five eminent invited biologists debated for three days the ancient obstetric mystery "The initiation of labour". The debate was closed on the following pessimistic note "That the relevant remarks of Hippocrates (400 B. C.) remain reasonably comprehensive". (Page, 1963).

It appears that a decade later, in 1973 such pessimism is unwarranted as the following review of the subject will attempt to project. Out of several thousand mammalian species, reproductive biology has been extensively studied in farm animals, rodents, rabbits and recently in primates, including man. The process of

* *Professor of Obstetrics & Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh.*

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reproduction is characterised by differences in its several components in different species of animals, such as restricted sexual season, non-spontaneous ovulation, spontaneous multiple ovulation with limited implantation, delayed implantation and even ovulation during pregnancy. It is important to keep in mind these biological and endocrinological peculiarities in different species of animals when comparisons are made between animal models and the human being.

A phenomenon which has long intrigued biologists is the species specificity which characterises the duration of pregnancy and the way in which this species specific timing is maintained has been the subject of extensive speculation and experimentation. There is no doubt that during the course of evolution, nature has favoured a gestational length at which the development of the foetus is mature enough to cope with extrauterine existence and yet not large enough to cause mechanical problems during the process of delivery. The concept and scope of foetal autonomy in determining the period of gestation has been furthered by animal models where inbreeding or cross breeding has clearly demonstrated foetal genetic influence on length of gestation. For example the gestation length is 340 days when a stallion and mare are crossed, but increases to 355 days when a jackass and mare are crossed to produce a mule. Similarly, prolongation of pregnancy with anomalous development of foetal pituitary and adrenals are observed with cross breeding in cattle. By a series of elegant experiments in the sheep, Liggins and co-workers (1967, 1968) established beyond doubt the influence of the foetus in regulating the onset of parturition in that species of animal. By appropriate manipulation of foetal adrenal function parturition in these animals could be delayed or advanced by five to seven weeks. Foetal hypophysectomy leading to adrenal hypoplasia, or bilateral foetal adrenalectomy delayed the onset of parturition. Conversely, stimulation of foetal adrenal by ACTH administration provoked delivery. These workers further postulated that the action of the foetal adrenal on parturition is probably mediated by the glucocorticoid effect of cortisol which disturbs the local progesterone activity and removal of the "Progesterone Block". Administration of large doses of progesterone to the sheep or its foetus did not reverse the action provoked by cortisol thereby showing that parturition is not related to blood progesterone levels but to local direct effect at the placental site. The foetal role in initiation of labour in the human is supported by the well known observation that pregnancy tends to be prolonged in anencephaly without hydramnios. The role of cortisol in initiation of labour has been supported in the human further by Mati *et al.*, (1973) who successfully induced labour in a small series of postdate pregnancies by intra-amniotic injection of Betamethasone. The role of the foetal pituitary-adrenal axis in determining the onset of labour was stressed by Turnbull and Anderson (1970) who found significant differences in the weights of foetal adrenals in infants after premature delivery without apparent cause from those delivered after sudden antepartum haemorrhage, etc There is no doubt that within the complex regulatory process that governs gestational length, the foetus itself makes an important contribution to timing its own delivery.

However, complete foetal autonomy in this process is questioned on the basis of

certain other observations. For example in the human, intrauterine death of the foetus is followed by an unpredictable and varying period of uterine inactivity. Studies in rabbits, mice and monkeys have demonstrated that if the foetuses are surgically removed in such a way as to spare the placentae, then the placentae are delivered at a time characteristic of the gestation period of that particular species, thereby showing that the foetus is not indispensable to the initiation of labour. Perhaps the foetal endocrine system exerts a modifying influence on an endogeous process for which we need to look at the maternal organism and the placenta.

Briefly the maternal and placental endocrine factors concerned with initiation of labour are, (a) placental progesterone and oestrogens, (b) oxytocin and oxytocinase, (c) other endogenous substances which act on the myometrium, especially when under the influence of steroids.

Experimental studies have classified all viviparous animals into two groups with pronounced differences. (A) Those who abort if oophorectomy is carried out during pregnancy—showing thereby that the hormones necessary for the maintenance of such pregnancies are derived mainly from the corpus luteum. The placenta of such animals cannot synthesize significant amounts progesterone or oestrogens. After oophorectomy it is possible to maintain gestation by exogenous progesterone and oestrogen. Examples of such animals are the rat, the rabbit and the dog. (B) The second group of animals, including the human, are those that do not abort after oophorectomy if carried out at somewhat varying periods of time during pregnancy. These animals have a relatively longer gestation period (112-330 days) showing that during the process of evolution, a complex foetoplacental unit has become necessary for the production of hormones for maintaining pregnancy. In comparative studies of several species of animals, it has been shown that the placenta as in the human, synthesizes oestrogens from precursors produced mainly by the foetal adrenals, whereas progesterone is derived from maternal cholesterol. A difference in the control of production of the two hormones is important to note. With advancing pregnancy, oestrogen synthesis dependent on foetal growth and well-being increases more rapidly than progesterone synthesis giving rise to an alteration in oestrogen-progesterone ratio which may contribute to increasing sensitivity of the myometrium to oxytocin as gestation progresses. The exact role of progesterone in the initiation of labour or the maintance of pregnancy has been difficult to study because of problems in interpretation of available data. The two major difficulties in assigning a dominant role to progesterone have been (i) failure to observe any significant decline, either in peripheral plasma levels of progesterone or urinary pregnanediol prior to the onset of labour and (2) failure to reverse myometrial activity or prolong pregnancy by exogenous massive administration of progesterone.

Recent discoveries of the binding of steroids in plasma and tissues can perhaps explain these two major hurdles. Progesterone is bound firmly to the same globulin fraction which binds cortisol (transcortin) and albumin as well as other less well characterised proteins. During pregnancy, progesterone having more affinity competes effectively with cortisol for binding sites on the transcortin molecule. Transcortin is also present

extravascularly and has been demonstrated in uterine homogenates in rats, which have also other specific proteins for binding oestrogens. So far there have been no definite studies on the interaction of various hormones especially progesterone, oestrogens and glucocorticoids at the tissue level, especially in the myometrium. But it is quite clear that peripheral blood levels of hormones may not reflect possible biological activity at tissue or uterine level and thus no correlation is likely to be obtained between changes in hormone levels and onset of labour. The progesterone-oestrogen factor can be accepted to build up myometrial activity and induce a state of "labour readiness", after which a variety of stimuli, (mechanical, neurological or chemical) can induce labour (Ryan 1971).

It is not possible to ignore the influence of oxytocin, catecholamines and prostaglandins on the one hand and on the other, the effects of distension or stretch, amniocentesis foetal death and other factors which influence uterine activity. They must necessarily fit into place once the steroid protein interactions at tissue levels are better understood. It is unlikely that a single theory for initiation of labour can be evoked to explain the mechanism of either maintenance of pregnancy or initiation of labour in all species of animals, especially in view of the differences already documented in the endocrinology of pregnancy in the different types of mammals mentioned earlier. In the human also "Labour readiness' is probably achieved first by a process of gradual evolution involving both foetal and maternal factors, at the end of which a variety of stimuli, mechanical (amniocentesis), chemical (cortisol, oxytocin) or neurological can initiate the actual process of labour.

The mechanism of onset of premature labour is as yet even less well understood. Sociological, nutritional and obstetric complications which specially predispose to premature labour have been well documented. Biochemical changes in the cervix during pregnancy and myometrial sensitivity have been related to endocrine factors in causing premature labour in that premature labour presents as endocrine related interference with the physiological process of normal pregnancy. Thus, the approach to prevention or inhibition of premature labour can only be rationalised when the mechanism of initiation of normal labour is better understood.

The use of agents to inhibit uterine activity and arrest premature labour is of special interest, because of its role in decreasing perinatal mortality and morbidity and the importance of this subject needs no further emphasis. The use of progesterone, with or without oestrogens has not been successful for reasons mentioned earlier.

Scommegna *et al.*, (1970) reported that intravenous infusion of pregnenolone sulphate decreased uterine activity in 12 women when given at the onset of labour and attributed this effect not to increased placental progesterone output, but to a direct effect on the myometrium and recommended the possible use of this agent with ethanol to arrest premature labour. In 1951 Van Dyke and Ames showed that alcohol (ethanol) inhibits the release of A.D.H. or vasopressin from the posterior pituitary gland. That this inhibition also affects oxytocin was shown by Fuchs and co-workers (1963, 1966) who then demonstrated that the milk ejection reflex dependent on oxytocin release can be blocked by ethanol in the rabbit as well as in the human. The onset of labour

could also be postponed in the rabbit by ethanol infusion. A number of studies have since been reported to illustrate the success of ethanol infusion in inhibiting labour in the human. Since the diagnosis of onset of labour in early stages is only clinical, it is important to include controls to prove the efficacy of the agent used in these trials.

TABLE I

I.V. Ethanol in Arrest of Premature Labour

Year	Authors	Criteria of success	Success rate	No. of cases
1965	Fuchs	3 days	60%	25
1967	Fuchs et al.	3 days	67%	68
1970	Mehra et al.	3 days	68%	50
1970	Wakhloo	24 hrs.	51.4%	35
1972	Mahendru	7 days	60%	25
1972	Zlatnik & Fuchs	3 days	80%	21

The dose of ethanol usually recommended is 15 ml./kg. of 9.5% Solution in the first two hours and then 1.5 ml/kg. of the same solution for 24 hours. Ethanol passes the placental barrier freely but is quickly metabolised by the foetus as well, hence no adverse effects are observed. Some side effects like nausea, vomiting, drowsiness, flushing, etc. were noticed in a few cases in the first two hours but these did not warrant discontinuation of drip in any case. In most of the successful cases after ethanol infusion, no further treatment is necessary and the uterus remains quiescent for varying periods of time and labour did not occur until after an interval of days or weeks or even months. Thus, the triggering factor in the onset of labour in such cases is a temporary and reversible one rather than any permanent change in endocrine or other environmental factors (Fuchs, 1971). The follow up of the successful cases to delivery confirmed that there was no retardation of foetal growth subsequent to arrest of labour as shown by vaginal cytology, oestriol excretion and pregnancy outcome.

In 1946, Ahlquist proposed the concept that two types of receptors are found in smooth muscle, the alpha receptor, the stimulation of which resulted in smooth muscle contraction in most organ systems and the beta receptor, the stimulation of which resulted in inhibition of smooth muscle activity. The concept of alpha and beta receptor sites is a functional rather than an anatomic one and these have been evaluated further by the use of several pharmacological agents which have selective ability to block one or stimuate another.

Among the well known drugs with specific beta adrenergic activity which have been tried clinically to inhibit myometrial activity are isoxsuprine, ritodrine and orciprenaline. These drugs are generally characterised by quick action when given intravenously and can be followed by oral administration for maintenance effects. Their action is purely local on the myometrium and since they also act on other smooth muscles, especially of the vascular system, side effects like tachycardia, hypotension, etc. are seen in varying degrees. These side effects hence control and limit the doses and usefulness of these agents for obstetric use. These drugs are quickly metabolised and no adverse effects have been reported on the

foetus if the drug fails to inhibit labour. The general principles governing the administration of these drugs are the same i.e. initially administration is by intravenous drip, first a test dose is given for a few minutes, and then the maximum therapeutic dose is achieved by gradual increment over twenty to thirty minutes. Cessation of uterine contractions generally occurs in the first half hour, but the drip is continued for six to eight hours or more and replaced by oral therapy. Maternal pulse and blood pressure are monitored frequently, especially in the first half hour and the drip rate adjusted so that the maternal pulse does not exceed 120-140 per/minute. If contractions recur the drip can be restarted. The newer agents like Ritodrine or salbutamol are reported to have less side effects and more selective action on the myometrium.

The results of treatment with this group of drugs as reported in the literature and our own studies are presented in Tables II, III and IV.

Work is in progress at our centre to combine a beta adrenergic agent with ethanol so that the peripheral and central effects of the two agents can be combined effectively to inhibit labour. The maximum success has so far been obtained only when the cervical dilatation is 5 cms or less and it remains to be seen whether results can be improved in this group as well as in patients seen later in labour.

The practical applicability of the use of

TABLE II

Isoxsuprine in Arrest of Premature Labour

Year	Authors	Criteria of success	Success rate	No. of cases
1961	Bishop & Wontersz	7 days	40%	120
1965	Allen & co-workers	7 days	61%	186
1968	Malhotra & Joseph	7 days	71.4%	35
1969	Dass	7 days	72%	25
1972	Mahendru	7 days	24%	25

TABLE III

Results of Treatment For Arrest of Premature Labour

	Control	Ethanol	Isoxsuprine
Failure	24	10	19
Successful	1	15	6

(Successful if labour was arrested and pregnancy continued more than a week).

TABLE IV

Riodrine and Orciprenaline in Arrest of Premature Labour

Year	Author	Drugs	Criteria of success	Percentage success	Total No. of cases
1972	Wesselius-De Casparis et al.	Ritodrine I.V. + oral	5-8 days	77%	35
1970	Baillie et al.	Orciprenaline I.V.	upto 36 weeks	70%	30
1973	Mathur et al.	Orciprenaline I.V.	3 days	66%	18
1973	Liggins & Vaughan	Salbutamol I.V.	24 hrs. 7 days	85% 40%	88

these drugs to the problem of prematurity is of some interest. The prematurity rate in most hospitals in India (birth weight below 2250 gms.) ranges around 20-25%. The causes of low birth weight is analysed in 220 consecutive cases in Table V. This shows that if a drug which will positively and safely inhibit labour were available to-day, it would be suitable for use only in about 26% of cases of low birth weight.

TABLE V

Labour Inhibition in Relation to Low Birth Weight

Material: 220 consecutive live births weighing 2250 gms or less.	
Less than 37 weeks: (suitable)	58 (26%)
Over 37 weeks (unsuitable):	65 (30%)
Complications e.g. Toxaemia, APH Medical problems, major malformations, etc.	62 (27%)
Premature rupture of membranes (unsuitable) or late in labour	35 (17%)

In 30% of cases from this group, where low birth weight beyond 37 weeks of gestation could be classified as small-for-date rather than premature, drugs to inhibit labour would be contraindicated. However, it is possible that some women with mistaken dates or exact duration of gestation not known have been included in this and the obstetrician would need a quick and objective test to determine the exact foetal maturity before instituting treatment in such cases. In this connection Zlatnick and Fuchs, (1972) have pointed out that palpation findings and assessment of birth weight of the foetus by the clinician are often greatly biased by the dates given by the patient.

Other indications for the use of these drugs would be in hypertonus of the uterus, especially associated with foetal distress as illustrated by the use of orciprenaline in dextrose prior to caesarean section. In such cases Type II Dips and foetal bradycardia could be corrected by inhibiting uterine activity and improving placental blood flow so that perinatal mortality following caesarean section for foetal distress can be improved considerably. In general inhibition of labour is not advocated after premature rupture of membranes. There are, however, reports that corticosteroids can promote lung maturity in the foetus and thus prevent respiratory distress syndrome in premature neonates. Liggins and Vaughan (1973) have used Salbutamol after premature rupture of membranes so as to postpone labour by at least 24 hours, so as to allow of corticosteroid administration to the mother and hopefully reduce the incidence of respiratory distress syndrome in such babies, as these drugs could be also used in selected cases for prophylaxis against premature labour. Thus, the scope for the use of labour inhibiting agents is already being further explored in many directions.

The object of this presentation is to highlight the new information regarding foetal, genetic and hormonal effects as well as mechanism of action of maternal and placental hormonal factors in the control of length of gestation. Studies in comparative endocrinology of pregnancy and parturition in experimental animals has made significant contributions to the understanding of this age old problem in the human and would pave the way for therapeutic advances in the management of aberrations in gestational length and resulting problems in the field of future obstetric practice. This presentation is dedicated with all humility to the memory of that great master, Sir Kedernath Das.

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