INVITED ARTICLE

CURRENT CONCEPTS IN THE MANAGEMENT OF PRETERM LABOUR

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ABSTRACT

Prematurity remains the major cause of perinatal mortality and morbidity in Singapore. Prevention of prematurity is therefore of vital importance. Epidemiological methods using historical variables have been superseded by ongoing pregnancy factors including work, exercise and cervical dilatation. PGF levels bear a positive correlation to duration and cervical dilatation but are not elevated at onset. PGE production is high in ruptured membranes. Progesterone and relaxin are potent inhibitors before labour. Infection must play an important role in developing countries as organisms not thought of to be pathogenic produce phospholipase A_2. For prediction, cervical assessment and topography are proving important. In view of the dangerous side effects of tocolytic drugs and the difficulty in diagnosis of preterm labour, absence of fetal breathing is a useful index of progressive labour. In those labours that are advanced, whether to allow vaginal delivery or not will be determined by the presentation and condition of the fetus. The complementary role of other drugs to reduce morbidity from hyaline membrane disease and intraventricular haemorrhage is being studied. Fetal acidosis should be avoided and the infant delivered without trauma under optimal circumstances. In utero transfer to a facility with neonatal intensive care carries a better prognosis for the baby.

Keywords: Prematurity, tocolysis, Respiratory distress.

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INTRODUCTION

Preterm birth accounts for a major proportion of perinatal deaths. An Oxford study reported that 85 per cent of neonatal deaths, not due to a lethal abnormality, occurred in infants with gestational ages between 22 and 27 weeks of gestation. Nearly three million preterm infants are born in South East Asia each year. The true incidence of preterm labour (< 37 weeks) is not known because of variations in reporting. The British Perinatal Mortality Survey reported that 3.4 per cent of births occurred at gestations less than 251 days. A united States Medical Centre reported a preterm delivery rate of 7.6 per cent over the previous eleven years. We have also to consider the contribution of preterm birth in relation to perinatal morbidity. Although there has been a significant increase in neonatal survival rate of preterm babies, morbidity is still high, however late neurological handicap is still high. The incidence of late neurological handicap in the group below 34 weeks (750-1500g) has improved in parallel with modern neonatal intensive care. Major handicaps are present in 10-30 percent of very small survivors. This group can be decreased considerably with good neonatal care. For the present, we realise that the incidence of handicap runs parallel with perinatal mortality and is dependent on the adequacy of neonatal care. In developing countries neonatal intensive care is limited and this will only worsen the handicap rate. The important guideline to each practising obstetrician is the standard of neonatal care in his unit. I personally feel that there is little place to deliver infants below 750g in South East Asia. It is mandatory to exclude lethal abnormalities by x-ray or ultrasound when patients are admitted in preterm labour.

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KNOWN ASSOCIATES WITH PREMATURITY

MATERNAL:	PATERNAL:
No prenatal care	Coitus
History of	
– Antepartum haemorrhage	ENVIRONMENTAL:
– Perinatal loss	Stress
– Low birthweight infants	Crowding
– Therapeutic abortion	Work
– Spontaneous abortions	Accidents
Age	FETAL:
Parity	Multiple pregnancy
Height	Fetal abnormalities
Weight	
Psychosocial	PLACENTAL:
Social class	Abruption
Illegitimacy	Previa
Nutritional	
Smoking	
Anaemia	MEMBRANES:
Diabetes	Premature rupture
Pregnancy	
Polyhydramnios	
Heart disease	
Uterine anomaly	GENETICS:
Incompetent cervix	Family history
Uterine irritability	
Infection	

The most important challenge in perinatal medicine is the prevention of preterm birth. However preterm birth is not a single disease and is multifactorial in origin. Unfortunately most authors have included deaths from obstetric complications resulting in elective

deliveries and even included lethal anomalies. It is time perhaps the definition of preterm labour was changed to include only infants born before 34 completed weeks as neonatal death after this is uncommon. We have proposed a model for spontaneous preterm labour including socioeconomic and infective aetiologies. Stress in the environment can induce uterine contractility by an effect of catecholamines whilst infection can 'stress' the decidual cell liberating phopholipase and prostaglandins (Figure 1). The series of events culminating in early delivery has several triggering stimuli. Prediction of these patients at risk of preterm birth by histological factors is not sufficient. Monitoring the pregnancy by clinical, endocrine and biophysical methods have opened new frontiers of prevention.

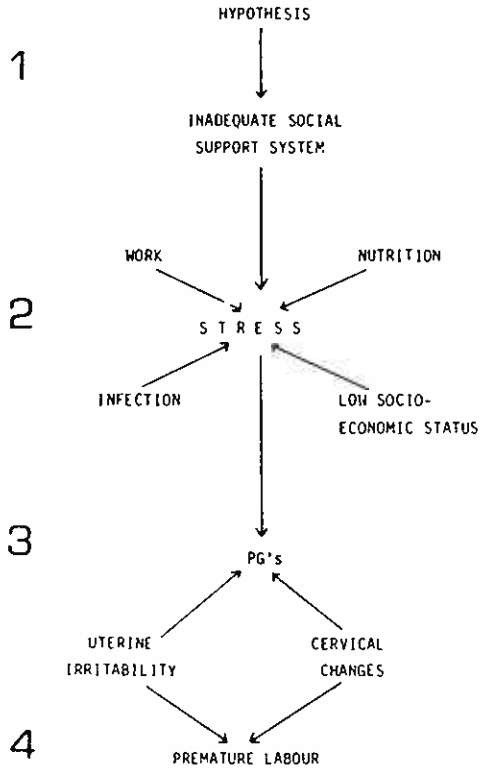

Figure 1
Proposed hypothesis in the evolution of myometrial contractility by environmental and uterine factors.

ENDOCRINE FACTORS

That endocrine factors may hold the key was the fervent belief of Csapo (1) who believed that progesterone deficiency could lead to premature uterine activity. In the early seventies we (2) reported a group of patients who had elevated oestrogen (E_2) levels and suggested a ratio of E_2/P as a predictor of preterm birth. In view of the conflicting reports and the difficulties of radioimmunoassay only a few workers like Hobel (3) in California used these hormonal parameters. Darne et al (4) recently described 13 patients who went into preterm labour with rising salivary E_3/P ratio with intact membranes. It may therefore be possible to use this ratio to predict preterm labour in high risk patients.

Our original studies that a rise in free oestrogen should precede the onset of labour (2) accords with the known physiological effects of increasing receptors and enhancing prostaglandin production and increasing gap junction formation. In contrast to this group of patients in which we also described premature cervical effacement and delivery, is the group described by Darne et al with normal salivary oestradiol to progesterone ratio who present in preterm labour with ruptured membranes. Several organisms have been found to have phospholipase A_2 activity which could lead to prostaglandin synthesis. Especially in South East Asian countries poor hygiene and nutrition may lead to infection and weakening of membranes and spontaneous rupture. Thus bacterial infection might lead to PG production with the onset of labour which bypasses the increase in oestrogen to progesterone ratio that normally occurs before labour. This was recently confirmed by Lamont (5) and Lopez who have independently looked at PGE in the human amnion and shown increased production. However, we have been able to show only low levels of PGF at the onset of preterm labour although levels rise considerably with contractions.

THE ROLE OF OXYTOCIN

Recently Fuchs et al (6) (1984) suggested that an increase in the number of oxytocin receptors of the myometrium may be an important factor in the initiation of labour. Since the onset of preterm labour is not associated with increased circulating levels of myometrial oxytocin it is likely to result from increased myometrial oxytocin receptors sensitising the uterus to the oxytocin level already in circulation.

UTERINE CONTRACTIONS

Although antenatal contractions have been known since Hicks (7) first described them in 1871, only now is their importance being recognised. Woods et al (8) first suggested that increased uterine activity may be associated with preterm birth. Anderson and Turnbull (9) could not substantiate this. Recently, Suranyi and Szolmolya (10) recorded the frequency of major contractions once in pregnancy and correlated activity to preterm birth. Bell (11) has reported that recording contractions of more than 15 mmHg is useful for the prediction of preterm labour and we have studied this in a group of patients at risk using a modified Smyth (12) tocodynometer. A light weight ambulatory monitor has been devised by Michael Katz in California (13). In the presence of uterine contractions, treatment to suppress uterine contractions can be implemented. This method of prophylaxis is illustrated by several case reports.

Successful parturition results not only from contractions by a concomitant relaxation of the cervix. The cervical connective tissue is made up of collagen fibres and elastin which are influenced by hormones in particular oestrogen, relaxin and prostaglandin.

THE CERVIX AND PRETERM BIRTH

Cervical incompetence is generally accepted as a cause of mid trimester abortion and many methods have been devised to deal with this problem.

Cervical cerclage retrospectively studied by several authors including us report success rates of 50-80%. However the results require critical interpretation.

Recent prospective randomised studies (14,15) failed to find statistical significance. The RCOG trial is nearing completion and in nearly 1000 cases the place of cerclage is in doubt. The French worker, Paperniek (16) pays much attention to cervical palpation in pregnancy using a scoring system. Therapeutic sutures are inserted on patients if the cervix opens prematurely.

In patients having more than 5 preterm losses we have advocated "chemical" cerclage using indomethacin (17). In 22 patients given the drug from 18-28 weeks there have been no fetal loss nor pulmonary problems although 2 babies were delivered around 30 weeks.

Medical disorders particularly thyrotoxicosis and SLE cause recurrent preterm birth and our study of sixty SLE patients had a prematurity rate of 12.4%.

DIAGNOSIS OF PROGRESSIVE PRETERM LABOUR

More than 50% of patients admitted to the labour ward will remain undelivered without treatment. However cardiotocographic evidence of contractions with a dilating cervix is equivocal evidence of progressive labour. I have recently had the opportunity to re-examine the original studies of Castle and Turnbull (18) who showed a marked correlation of the absence of fetal breathing and progressive labour in over 100 patients. In the presence of intact membranes there is high specificity as also reported from studies in Dundee and Israel. Ultrasound is a valuable tool to exclude fetal abnormality and the presence of fetal breathing will avoid the unnecessary use of tocolytics.

Tocolysis

The inhibition of preterm labour after the cervix is more than 4 cms dilated is usually unsuccessful. Inhibition of preterm uterine contractility does not necessarily mean the outcome of the pregnancy will be necessarily better. In support of this is a report from Dublin where Boylan and O'Driscoll (19), without using tocolytic therapy, have observed a decline in mortality and morbidity from preterm birth. We feel that in countries like Singapore and Sweden, the use of β-mimetic agents has had a positive effect in lowering the prematurity rate (TambyRaja et al (20)). Ian Chalmers et al (21), at the National Perinatal Epidemiology unit in Oxford, have recently critically evaluated recent placebo controlled trials providing an odds ratio. If the ratio is less than one it suggests that treatment is significantly effective. In the studies reported treatment was better than placebo in delaying delivery over 24 hours and reducing babies born before 37 weeks. There is no evidence however that there is a reduction in perinatal mortality or lowering in the incidence of respiratory distress syndrome.

The side effects of therapy have been well documented. In addition to the β_1 inotrophic, and chronotrophic effects, the metabolic side effects hyperglycemia and hyperinsulinaemia are troublesome. Interest has recently centred on water retention by stimulation of the renin aldosterone system releasing ADH and increasing plasma volume and a fall in colloid osmotic pressure. We therefore administer 5 per cent glucose solutions and follow a strict protocol. In view of reports of maternal deaths we have studied the cardiotoxicity of these agents.

Most authors have reported ECG changes with the retrosternal pain. We (17) have reported 4 patients in whom cardiac enzymes were normal. More recently there have been two additional cases in whom there was persistent tachycardia without chest pain. No doubt the major contributing factors are increased intravascular volume, hypertension and myocardial ischaemia. The reversal of ECG changes on cessation of therapy with the absence of raised cardiac enzymes suggest no long term sequale. Caution is however necessary and there is increasing evidence that patients with viral infections and latent cardiac disease could develop decompensation and failure.

We (22) have evaluated several β receptors in Singapore and realised in randomised trials that the new generation drugs have similar potency and side effects. Salbutamol has been used effectively in our hospital since 1974 in over 900 cases with no maternal death or pulmonary oedema. A few patients had demonstrated cardiac arrythmia. Since there is desensitization or loss of surface receptors, it is possible that receptor loss is prevented or "lost" receptors are allowed to recover during the period that tissue is not exposed to the drug in the intermittent regime. These findings suggest that modification of the present method of administration of beta adrenergic agonists from continuous to intermittent infusion may improve the success of these agents in the prevention of preterm births and also reduce complications. In patients studied the infusion was started at 10 drops per minute (50ug salbutamol/minute) and increased stepwise. If tocolysis is achieved the dose is reduced after 2 hours at 5ug/half hour. Thereafter, the infusion is intermittent for periods of 30 minutes for 4 hours. Oral salbutamol; 4 mg 6 hourly is given and the intravenous infusion further tailed down intermittently.

Oxytocin Inhibitors for Suppressing Preterm Labour

The mechanism of spontaneous labour at term is ill understood. The aetiology of preterm labour is summarised in Figure 2 and show the modalities of prevention. In the majority of cases viz. placental abruption or intrauterine infection treatment is contraindicated. Ackerlund (23) and colleagues have recently reported the use of an inhibitor of oxytocin for the management of preterm labour. Using an analogue of oxytocin (ide amino 2 D Tyr (OE t)-4 Thr 8 orn oxytocin) in 13 patients, successful inhibition of labour occurred in 10 cases.

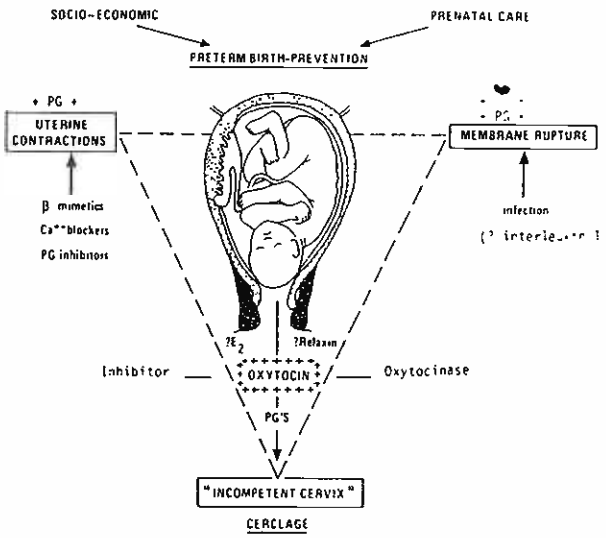

Figure 2
Diagrammatic strategy for intervention in preterm birth.

ACCELERATION OF PULMONARY MATURATION

The use of corticosteroids to induce lung maturation has been well documented since the pioneering work of Liggins and Howie in the early 1970's (24). A significant reduction in the respiratory distress syndrome and in mortality from this syndrome has been shown in infants with intact membranes who have received corticosteroids for more than 24 hours and less than 7 days from delivery as compared to controls. This benefit is more apparent at 28 to 32 weeks of gestation but is of doubtful significance outside this

range of gestational age. For corticosteroids to be effective, the course should be completed 24 hours before delivery. Corticosteroids appear to confer benefits on the fetus for about 7 days. It is current practice to repeat the course of corticosteroid therapy after 7 days although no trials have confirmed the value of this procedure. The regimen is 2 doses of betamethasone 12 mg intramuscularly 24 hours apart with a booster dose of 12 mg weekly up to 34 weeks. Our early endocrine studies which indicate a depression of the fetal adrenal glands together with new evidence of cortisol turning on a genetic switch, make glucocorticoid administration after 32 weeks superfluous.

Despite the clear benefits of using corticosteroids to induce lung maturity, some obstetricians are reluctant to use these agents for fear of the potential deleterious effect on the growth and development of the fetal brain as shown in animal studies (25). However, such effects have not been documented in humans. More recently there has been increasing evidence that pulmonary maturation can be accelerated by the synergistic effects of thyrotrophin, prolactin and cortisol.

TRANSFER OF THE PATIENT

When tocolysis is contraindicated or has failed, one of the most important questions facing the obstetrician is whether or not to transfer the patient to a centre where neonatal intensive care facilities are available, as the survival of very premature infants in neonatal intensive care units greatly exceeds those who are kept in institutions without such facilities. Infants transferred in utero also have a better survival rate than neonates transferred after birth. However, transfer is inappropriate when there is a strong likelihood that the mother will deliver en route.

Pain Relief in Labour

Analgesia in preterm labour should preferably be provided by means of epidural anaesthesia. This removes any possible respiratory depressant effects of opiates on the fetus and may also enhance fetal oxygenation and reduce the incidence of intracranial haemorrhage by abolishing the premature 'bearing-down' effort of the mother before the cervix is fully dilated. If opiates are given then respiratory depression can be prevented by intubation and aided respiration and the use of specific antagonists.

Intrapartum Fetal Monitoring

Electronic fetal heart rate monitoring is of paramount importance in preterm labour because intrapartum asphyxia increases the incidence of respiratory distress syndrome, intraventricular haemorrhage and the need for respiratory support after birth. Changes in the fetal heart rate pattern carry the same significance in preterm labour as in term labour. However, it must be remembered that the deterioration of a mildly abnormal fetal heart rate pattern may occur rapidly. In order to safeguard the premature fetus against hypoxia, scalp blood pH measurement should be used liberally. Borderline pH values of 7.20 to 7.25 must be treated with caution as this may already be hazardous to the premature fetus. About 25% of preterm infants are growth retarded (26). These infants are very likely to become asphyxiated early in labour so the early diagnosis of preterm labour and continuous fetal heart rate monitoring is even more vital in this subset of patients. If cardiotocography is not available, auscultation of the fetal heart should be performed at 15 minute intervals especially during contraction.

Delivery of Preterm Fetus

The past decade has seen an increasing use of caesarean section in the delivery of premature infants. The potential benefits of casesarian section to the fetus include:

Avoidance of birth trauma
Avoidance of intrapartum asphyxia
Reduced intraventricular haemorrhage

However, it must be emphasised that whatever benefits caesarean section may confer on the fetus, it will always represent a potential hazard to the mother. The bulk of medical opinion now states that elective caesarean section does not improve the outcome of the preterm vertex fetus but does confer benefit to the fetus weighing between 1000 and 1500g in breech presentation. In developing countries with inadequate neonatal services, vaginal delivery may be optimal for mother and baby in most instances.

The choice of uterine incision is of particular importance in performing a caesarean section for the preterm infant and this can only be made intraoperatively. If the lower uterine segment is not wide enough to allow atraumatic delivery with a transverse incision, a low vertical incision seems prudent. In the case of malpresentation, especially at an advanced stage of labour, the fetus may be trapped in the contracted portion at a level between the lower and upper uterine segment. A vertical incision across the constriction is then necessary. The temptation to perform a low transverse incision and extend vertically if necessary should be resisted because this frequently leads to unnecessary delay and trauma to an already compromised fetus. The risk of rupture of the low vertical incision in subsequent pregnancy and labour after a low vertical caesarean section has been performed suggests avoiding doing such incisions or operations.

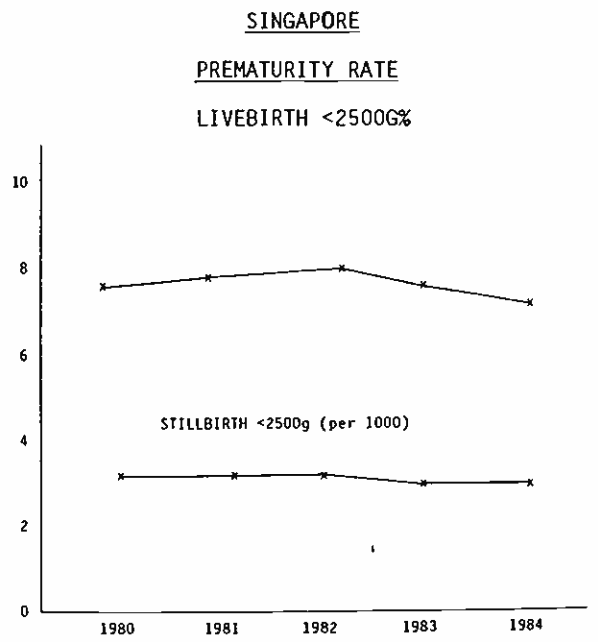

Figure 3
The prematurity and stillbirth rates in Singapore.

The Role of Forceps and Episiotomy

The routine use of forceps in delivering preterm infants has fallen into disfavour since the recent work by Fairweather and Stewart who demonstrated that the use of such forceps to protect the head conferred no benefit (27). Elective 'generous' episiotomy has been

advocated in order to shorten the second stage of labour and to reduce the force compressing on the soft fetal skull. However, its value has not been tested in clinical trials. Although episiotomy is associated with little maternal morbidity or mortality it does cause significant discomfort to the mother. Thus, attempts should be made to establish the necessity of such a procedure.

Neonatal Care

The first few minutes of life are critical in relation to morbidity and mortality rates of the very premature infant. The maintenance of euthermia and the prevention of neonatal hypoxia and hypercapnia are the 2 most important aspects in the resuscitation of these very small infants. Hypothermia may worsen the respiratory distress syndrome. The autoregulatory shifts of blood from peripheral cutaneous vascular beds to central beds may also increase the risk of intracranial bleeding because of the increased pressure on the poorly developed fragile capillaries. Hypoxaemia and hypercapnia have also been shown to impair the proliferation of type II pneumocytes and thus decrease the quantity of surfactant produced. It cannot be overemphasised how vital it is to have an experienced neonatal paediatrician present to resuscitate these premature infants from their first minute of life onwards. The availability of positive ventilation and intensive monitoring have further reduced mortality and morbidity.

The Growth Retarded Preterm Infant in Singapore

In Singapore, the major contribution (nearly 50%) to prematurity arises from stillbirth. Indians and Malays have double the stillbirth rate compared to the Chinese (9.9, 9.9 vs 5.1 in Chinese). The neonatal mortality however for all 3 races for low birth weight is similar. During a recent visit to France, it was realised that Professor Papierniek had noticed the same problem in France and in those of mixed ancestory and black Africans. Despite high socioeconomic standards in France and Singapore, an ethnic prediction to low birth weight and shortened duration of pregnancy is still prevailing. We have suggested that in some ethnic groups the higher stillbirth rate and perinatal mortality may be related to different intrauterine maturation patterns leading to a post mature state in utero! The clinical importance of antenatally monitoring these fetuses cannot be over-stressed. What is of more practical importance is South East Asia is *NOT TO INHIBIT LABOUR* in a baby above 2000g even when dates are reliable.

CONCLUSION

Preterm birth has been the major contributor to perinatal mortality and mortality for a long time. The prediction of preterm labour seems possible by biochemical and biophysical methods in those at high risk. Low risk populations should be educated in the appreciation of excessive contractions. The inhibition of uterine contraction by agents that have less maternal hazards and not crossing to the fetus is being accomplished. A more rational pharmacological approach should appear in the next few years. The cost of neonatal care and long term handicap in the low birth weight survivors demand an improved medical and social approach to the problem. Socioeconomic conditions have often been thought to be a major cause of prematurity in the developing world. Our studies seem to indicate that genetic factors controlling fetal growth interact with poor nutrition in determining the duration of gestation. It may become apparent that different ethnic groups have different lengths of gestation and the norm of 280 days may not be true for all ethnic groups. What is perhaps more important is that chronic malnutrition and hypoglycemia can induce myometrial contractility (28) and will be a perfect model for the growth retarded preterm fetus of South East Asia.

REFERENCES

1. Csapo AI, Pohanka O, Kaihola: Progesterone deficiency in premature labour. Br Med J 1974; 1:137.
2. TambyRaja RL, Anderson ABM, Turnbull AC: Endocrine changes in premature labour. Br Med J 1974; iv:67-71.
3. Cousins LM, Hobel CJ, Chang RJ, Okada DM, Marshall JR: Serum progesterone and estradiol-17β levels in premature and term labour. Am J Obstet Gynecol 1977; 127:612-5.
4. Darne J, McGarrigle HHG, Lachelin GCL: Increased saliva oestriol to progesterone ratio before idiopathic preterm delivery: a possible predictor for preterm labour. Br Med J 1987; 294:270-2.
5. Lamont RF, Dunlop PD, Crowley P, Spelder MJ: Spontaneous preterm labour and delivery at under 34 weeks gestation. Br Med J 1983; 284:454-7.
6. Fuchs AR, Fuch F, Husselein P, Saloff MJ: Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol 1984; 150:734-41.
7. Braxton Hicks contractions quoted by Caldeyo Barcia, Alvarez H (1953). Proc 1st World Congress Fertility and Sterility, New York, pp 217.
8. Wood C, Bannerman RHO, Booth RT, Pinkerton JHM: The predictability of premature labour by observation of the cervix and external tocography. Am J Obstet Gynecol 1965; 19:396-402.
9. Anderson ABM, Turnbull AC: Relationship between length of gestation and cervical dilatation, uterine contractility and other factors during pregnancy. Am J Obstet Gynecol 1969; 105:1207-14.
10. Suranyi S, Szolmolya M: Uterine contractions and preterm birth. J Perinatal Med 1981; 9 (Suppl 1):140-1.
11. Bell R: The prediction of preterm labour by recording spontaneous antenatal uterine activity. Br J Obstet Gynaecol 1983; 90:884-7.
12. Smyth CN: The guard-ring tocodynanometer. J Obstet Gynaecol Br Emp 1957; 64:59-66.
13. Katz M, Gill FM: Initial evaluation of an ambulatory system for home monitoring and transmission of uterine activity data. Obstet Gynaecol 1985; 66:273-7.
14. Rush RW, Isaacs S, McPherson K, Jones Lesley, Chalmer I, Grant I: A randomised controlled trial of cervical cerclage in women at high risk of spontaneous preterm delivery. Br J Obstet Gynaecol 1984; 91:724-30.
15. Lazar P, Gueguen S, Dreypus J, Renaud R, Pontonmier G, Paperniek E: Multicentred controlled trial of preterm delivery cerclage in women at moderate risk of preterm delivery. Br J Obstet Gynaecol 1984; 91:731-5.

16. Paperniek E: Prediction of the preterm baby. In: Clin Obstet Gynecol 1984; 11:315-5
17. TambyRaja RL: Preterm birth – the beginning or the end. Sing. J Obstet Gynaecol 1984; 15:71-82.
18. Castle BM, Turnbull AC: The significance of preterm breathing in preterm labour and its consequences. Proceedings of the 13th Study Group of RCOG 1985:53-9.
19. Boylan P, O'Driscoll K: Improvements in perinatal mortality rate attributed to spontaneous preterm labour without use of tocolytic agents. Am J Obstet Gynecol 1983; 145:781-3.
20. TambyRaja RL, Arulkumaran S, Viegas OAC, Wong YC, Ratnam SS In: Perspectives in perinatal care for Singapore. Sing J Obstet Gynaecol 1985; 16:23-36.
21. King FK, Kierse M, Grant A, Chalmers I (1987). Pooled analysis of the placebo controlled trials of β mimetic agents used in the treatment of preterm labour. In: Bonnar J. ed. Recent Advances in Obstetrics and Gynaecology No. 15. Churchill Livingstone, 1987:70-4.
22. TambyRaja RL, Ratnam SS: The small fetus growth retarded and preterm. Clin Obstet Gynaecol 1988; 9:517-37.
23. Ackerlund M, Stromberg P, Hauksson A, Anderson LF, Lyndrub J, Trojner J, Melin P: Inhibition of uterine contractions of premature labour without oxytocin analogue. Results from a pilot study. Br J Obstet Gynaecol 1987; 94:1040-4.
24. Liggins GC, Howie RW: A controlled trial of antepartum glucocorticoid treatment for prevention of respiratory distress syndrome in preterm infants. Pediatrics 1972; 50:515-9.
25. Epstein MF et at: Maternal betamethasone and fetal growth and development in monkeys. Am J Obstet Gynecol 1977; 127:261.
26. Rush RW et al: Contribution of preterm delivery to perinatal mortality. Br Med J 1976; 2:965-9.
27. Fairweather DVI, Stewart A. How to deliver the under 1500 grams infant. In:Zuspan FP et al. eds. Reid's controversy in obstetrics and gynaecology. Vol 3. Philadelphia: Saunders & Co, 1983:154-64.
28. Binienda, Massmann A, Mitchell MD, Gleed RD, Figueroa JP, Nathanielsz PW: Effects of food withdrawal on arterial blood glucose and plasma 13, 14 de hydro 15 koto prostaglandin $F_{2\alpha}$. Concentrations and nocturnal myometrial electro myographic activity in the pregnant rhesus monkey in the last third of gestation: A Model for preterm labor. Am J Obstet Gynecol 1989; 160:746-50.