STRESS AND FETAL LUNG MATURITY

Henry Gordon Dobbie

B.Sc. (Hons), M.B.Ch.B., M.R.C.O.G.

M.D. THESIS

UNIVERSITY OF GLASGOW

The Department of Midwifery, Glasgow University.

Queen Mother's Hospital, Glasgow.

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Declaration

I declare that the preparation and writing of this Thesis has been carried out by myself.

The research described in this Thesis was carried out by myself except where the contribution of others is acknowledged.

Henry Gordon Dobbie

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Summary

It has been the clinical impression for many years that certain 'stressful' pregnancy complications appear to be associated with a generally improved neonatal outcome. The reason for this is unclear but is has been proposed that a hostile intrauterine environment may, perhaps as a result of relative hypoxia, promote the release of hormones such as cortisol and catecholamines. These hormones may facilitate the maturational processes, particularly in the lung, and so help to prepare the fetus for extrauterine life.

Certainly, and despite advances in neonatal care, respiratory problems remain the most common cause of death in normally-formed live-born babies (Chamberlain et al 1975), being responsible for about 1500 deaths in England and Wales alone in 1980 (HMSO 1980). Even if the baby survives, however, the need for prolonged ventilatory support may lead to the development of bronchopulmonary dysplasia and other causes of chronic respiratory insufficiency (Levine and Dubowitz 1982, Tarrow-Mordi and Wilkinson 1986). Other problems such as intraventricular haemorrhage, patent ductus arteriosus and pneumothorax are also related to respiratory immaturity (Greenhough and Roberton 1985, Whittle et al 1986).

The improvements in neonatal care have resulted in survival rates of over 88% for babies weighing greater than 1000 g in some units (Greenhough and Roberton 1985). In view of the excellent survival rates for the small baby, the obstetrician when faced with a difficult management problem not unnaturally has a low threshold for preterm delivery often, as is increasingly the trend, without prior assessment of fetal lung maturity. With more and more small babies receiving assisted ventilation, knowledge of the natural development of the respiratory system in the human fetus is essential.

The aims of this thesis were:

1 To evaluate certain obstetric factors, considered to influence fetal lung maturity.

2 To investigate what controls respiratory maturity in the human fetus.

3 To evaluate human fetal adrenal cortisol and medullary activity from mid-trimester until term.

The basis of the study centres on the concept of fetal stress in utero being the interlinking factor between the various obstetric problems and fetal lung maturity. However, many of the current ideas regarding human fetal lung development have been derived from animal experiments, the results of which may not be applicable to the human. A timetable of events can, however, be defined using a combination of animal and human data and a review of the current literature is contained in Chapters 2 and 3.

Chapter 2 outlines what is currently known of the normal development of the human fetal lung. The anatomical, physiological and biochemical development are discussed and the evidence presented suggesting an important role for the fetal stress hormones cortisol and the catecholamines. A number of animal studies have suggested that corticosteroids can cause an induction of the enzymes involved in surfactant synthesis and that the catecholamines, especially adrenaline, facilitate the release of surfactant (the surface-active lung phospholipids) and the clearance of lung fluid at birth, all helping to optimise neonatal lung function. These animal expriments are supported by clinical studies suggesting a reduction in the incidence of respiratory problems following treatment of the pregnant mother with corticosteroids and various Beta sympathomimetic drugs.

Various factors, both physiological and pathological, considered to influence fetal lung maturity in the human are discussed in Chapter 3, with regard to both clinical and biochemical lung maturity. In addition, the available evidence linking the obstetric factors with the human fetal adrenocortical and sympathoadrenal responses is presented.

A total of 381 babies were investigated in this study, of which 189 were born at or prior to 35 weeks' gestation. Lung maturity was assessed clinically by the occurrence of the respiratory distress syndrome and the requirement for neonatal ventilation and biochemically by measurement of amniotic fluid phospholipids. The fetal stress responses were assessed by measuring, in blood sampled from the umbilical artery at birth, the cortisol, noradrenaline and adrenaline levels and pH. These measurements were also made in maternal venous blood at time of delivery. The physiological factors investigated were: gestational age, labour and route of delivery and multiple pregnancy and the pathological factors: the condition of the baby at birth and the obstetric complications, intrauterine growth retardation, premature rupture of the membranes, vaginal bleeding, hypertension and preterm labour.

For each of the physiological and pathological factors, the clinical and biochemical lung maturity and the fetal adrenocortical and sympathoadrenal responses were investigated.

It is generally believed that certain obstetric complications can protect the fetus from developing RDS. However, from this study there is little evidence to support this, and in addition none of the obstetric complications studied had any consistent influence on fetal cortisol or catecholamine levels.

Despite much indirect evidence in the literature this study was unable to confirm the proposed effect of stress on fetal lung maturity.

The adrenocortical and sympathoadrenal responses have been extensively studied in the human fetus at birth from 24 to 41 weeks' gestation. Although there is a marked increase in UAC levels with gestation, especially from 34 weeks, the changes in sympathoadrenal responses are not so clear cut. There was a tendency for the levels of both NAD and AD to rise with gestation and there is some evidence to suggest that the ratio of NAD/AD does decrease with increasing gestation, suggesting an increased AD response to stress in the term compared to the preterm fetus.

Interestingly neither the adrenocortical nor the sympathoadrenal responses seemed to influence the clinical outcome for the baby.

It cannot be assumed that a fetus under chronic stress will necessarily have accelerated fetal lung maturity, a history of obstetric complications producing stress is often found in babies who die from RDS. Indeed from this study those babies who developed RDS, required ventilation or died were significantly more acidotic than those babies who had no respiratory difficulties.

The study therefore does not support the view that stress, either the physiological stress of labour or the pathological stress of certain obstetric complications accelerates fetal lung maturity. In addition to this it does not appear that the stress products cortisol or catecholamines have a major role to play in influencing neonatal lung function. Gestational age and the condition of the baby at birth would seem to be of paramount importance.

CHAPTER 1

The Importance of Fetal Pulmonary Maturity

Despite advances in neonatal care respiratory problems remain the most common cause of death in normally formed live born babies (Chamberlain et al 1975), being responsible for about 1500 deaths in England and Wales alone in 1980 (HMSO, 1980).

The change from placental to pulmonary respiration which occurs at birth is the most important adaptation that a fetus makes to extrauterine existence. The failure of this normal pulmonary adaptation at birth can result from two main causes, although there may be some overlap between them. Firstly, delayed clearance of lung fluid at birth can result in transient tachypnoea of the newborn (Avery et al 1966). Fortunately this tends to be self limiting and rarely causes major problems. In contrast, however, a deficiency of the lung surfactant which lines the terminal air spaces results in the development of the respiratory distress syndrome (RDS) or hyaline membrane disease (HMD) (Avery and Mead 1959). Lung surfactant is a collection of different phospholipids which coat the alveoli and reduce their surface tension, preventing them from collapsing during expiration and facilitating air entry during inspiration. When surfactant is deficient as in RDS (Adams et al 1965, Boughton et al 1970), the alveoli collapse during expiration and a high intrathoracic pressure is then needed to open the lungs. RDS is a serious disease and if surfactant deficiency is severe a deteriorating cycle of events occurs - due to collapse of the alveoli the fetus becomes hypoxic and acidotic and this in turn reduces pulmonary blood flow, all of which will inhibit surfactant production and cause more alveoli to collapse.

Even if the baby survives, the need for prolonged ventilatory support may lead to the development of broncho-pulmonary dysplasia and other causes of chronic respiratory insufficiency (Levene and

Dubowitz, 1982). Unfortunately mechanical ventilation is frequently associated with complications. Pnuemothorax and pulmonary interstitial emphysema, both examples of air leak, occur in 30-50% of infants given mechanical ventilation and weighing under 1500 g at birth. Around one third of these very small infants develop chronic lung disease (Tarrow-Mordi and Wilkinson 1986). Another complication of ventilatory support is intraventricular haemorrhage which may lead to cerebral dysfunction. In addition behavioural problems may result from prolonged enforced separation from the mother.

The development of RDS is related to the stage of fetal lung maturation at time of birth, which explains why preterm babies are more likely to develop RDS.

In our own experience at the Queen Mother's Hospital during 1979 (3303 total births), using a clinico-pathological classification, 11 out of 26 (42%) first week deaths, and 8 out of 13 (62% later neonatal deaths (8th to 62nd day), were due primarily to immaturity at birth, principally respiratory immaturity; RDS was present in 16 of all the babies dying from immaturity.

These deaths, perinatal and late neonatal, constitute the 'tip of the iceberg' of prematurity which besides carrying risks of residual impairement (Leader BMJ 1979, Leader BMJ 1980, Levene and Dubowitz 1982, Greenhough and Roberton 1985) poses a very considerable burden on both expensive facilities and skilled personnel.

The improvements in neonatal care in recent years have resulted in survival rates of over 88 per cent for babies weighing greater than 1000 g, in some units (Greenhough and Roberton 1985). In view of the excellent survival rates for the small baby, the obstetrician when faced with a difficult obstetric problem, not unnaturally has a low threshold for preterm delivery often, as is increasingly the trend,

without prior assessment of fetal lung maturity. Thus as more and more babies are being born who require mechanical ventilation, knowledge of the natural development of the respiratory system in the human fetus is essential. Many of the current ideas regarding fetal lung development, however, have been derived from animal experiments, the results of which are not necessarily appropriate to the human.

The information which is available in the human has been obtained in the face of obstetric pathology making it difficult to evaluate the individual influences of stress, drugs, labour and mode of delivery.

It has been the clinical impression for many years that certain pregnancy complications appear to be associated with an unusually low incidence of neonatal RDS. The reason for this is uncertain. However, it has been proposed that a hostile intrauterine environment stresses the fetus and in some way accelerates the normal lung development.

In this thesis, current ideas on the normal development of the human fetal lung and how this may be modified by certain obstetric factors are discussed. The role that fetal stress, both physiological and pathological, plays in the development of fetal, and thus neonatal lung development, is investigated.

CHAPTER 2

The Development of Fetal Lung Maturity

This chapter will review the current knowledge regarding the anatomical, physiological and biochemical development of the fetal respiratory system.

The methods available to assess fetal lung maturity prior to birth will also be discussed.

The Development of fetal lung maturity

2.1 Anatomical Development (Strang 1977)

2.1.1 Embryonic phase (3-6 weeks) The rudimentary respiratory tract first appears about 3-4 weeks after fertilization, arising from the ventral portion of the foregut as a single bud, which quickly divides into two. These two subdivisions grow rapidly, with further divisions pushing into the underlying mesoderm, from which cartilaginous rings, lymphatics and capillaries will eventually form. About six weeks after fertilization the trachea, main and subsidiary bronchi are well developed.

2.1.2 Pseudoglandular phase (7-17 weeks) This is a very active phase of development, with further extensive branching of the respiratory tree continuing until completion by about the 16th week. Cartilage formation, together with the development of a more definitive pulmonary vascular system, commences at this time. Microscopically the lung appears to comprise glandular tissue, with goblet cells and cilia being observed.

2.1.3 The canalicular phase (18-24 weeks) During this time the rather tall cells of the preceding phase become more cuboidal and, subsequently, the walls of the terminal bronchioles become thinner. A capillary plexus begins to develop around the terminal bronchioles to form a rudimentary gas-exchange system.

2.1.4 The terminal sac phase (24 weeks to term) The terminal bronchioles now begin to subdivide into three or four respiratory bronchioles from which develop the clusters of saccules that are a feature of the fetal lung at about 30-32 weeks. Even earlier in the

terminal sac phase, the space between capillaries and potential air spaces is small enough to enable effective gas exchange in some babies born at 24-26 weeks. As the fetus approaches term, minute alveoli appear in the terminal saccules - a process which becomes markedly accelerated once the baby is born and which continues rapidly until about two years of age.

Important epithelial changes also occur during this phase, the cells of the terminal air passages thinning out and the specialized Type II cells, the pneumocytes, appearing. These latter cells are found in the human as early as 24 weeks (Campiche et al 1963) and they are characterized by their ability to manufacture surfactant which appears as osmiophilic granules within lamellar bodies in the cytoplasm.

2.2 Physiological Development

2.2.1 Fetal Breathing Movements

Breathing movements occur in the human fetus in utero from early pregnancy and they have been studied extensively with the introduction of real time ultrasound scanning (Lewis & Boylan 1979). The fetal breathing movements are not continuous but episodic with periods of breathing interspersed with periods of 'apnoea'. In each 24 hour period fetal breathing occurs about 30 per cent of the time in the human (Patrick et al 1980).

The function of fetal breathing movements in utero is obscure but presumably they have the function of preparing the fetus for extrauterine life. Trudinger (1981) has noted an increase in the incidence of neonatal respiratory problems amongst later fetuses with a rapid irregular breathing pattern. In contrast they found a positive relationship between a slow regular breathing pattern,

considered to be a mature pattern, and a mature L/S ratio.

It has also been found that FBM diminish or cease 24-36 hours before the onset of established labour (Boddy et al 1974) and this may reduce the flow of fluid known to occur from the trachea (Scarpelli 1967) and help retain surfactant in the fetal alveoli prior to birth. It is interesting that infusion of noradrenaline (NAD), but not adrenaline (AD), causes inhibition of FBM in rhesus monkeys (Murata et al 1981). NAD is the predominant catecholamine in the human fetus and extremely high levels are reached following vaginal delivery (Falconer and Lake 1982).

Therefore, although the exact role of FBM is uncertain it would seem to have a part to play in the normal development of the fetal lung.

2.2.2 Clearance of Lung Fluid

The rapid absorption of fluid from the respiratory tract which occurs at the time of the first breath is important in achieving optimal lung function.

Clearance of lung fluid is thought, at least partly, to be due to the thoracic squeeze which occurs during a normal vaginal delivery (Karlberg 1960). Defective clearance of lung fluid will leave the neonate with less compliant lungs and therefore increase the work of breathing. The thoracic squeeze effect on clearance of lung fluid may not be the whole story however. In newborn rabbits the lowest lung water content is found following labour, irrespective of mode of delivery (Bland et al 1980).

In the human, neonatal lung volumes have been assessed by the crying vital capacity (CVC - expressed as ml/cm of chest circumference) and by the more invasive measurements of thoracic gas volume.

Chiswick & Milner (1976) and Brice & Walker (1977) have shown that neonates born by caesarean section have significantly lower CVC than those born vaginally during the first 48 hours after birth. In addition Boon et al (1981) noted that babies delivered by emergency caesarean section (ie after the onset of labour) formed an intermediate group. Milner et al (1978) found significantly higher thoracic gas volumes in those babies delivered vaginally compared with those delivered by caesarean section. The above studies suggest that both labour and passage down the birth canal promote clearance of lung fluid.

Exactly how labour itself causes clearance of lung fluid is uncertain. However, animal work has suggested that the catecholamines especially AD may play an important role.

Intravenous infusion of AD into fetal lambs at concentrations similar to those found in labour causes absorption of lung fluid (Brown et al 1981, Lawson et al 1978). AD was much more effective than NAD in this respect, suggesting that the absorption of fluid is moderated via Beta receptors (Walters & Olver 1978). The sensitivity of the response to AD seems to increase throughout gestation and is maximal at term (Brown et al 1981, Walters & Olver 1978).

Brown et al (1981) using chronically catherised fetal lamb preparations noted a correlation between endogenous AD concentration and lung liquid absorption during labour. However no such correlation of lung liquid absorption was found with NAD and the fact that the process is blocked by propranolol is a clear indication that Beta receptors are involved.

Enhorning et al (1977) noted significantly less fetal pulmonary fluid in rabbit fetuses infused with a Beta mimetic drug, isoxsuprine compared with controls. In the human, data concerning control of clearance of lung fluid is sparse. However, Faxelius et al (1983) have found a correlation between cord catecholamine levels and clearance of lung fluid after vaginal delivery but not after elective caesarean section.

It would seem, therefore, that the catecholamines may have an important role to play in the clearance of lung fluid, thus helping to achieve optimal lung function.

Experiments in goats have suggested that vasopressin, the levels of which rise acutely during labour, may induce lung liquid absorption (Perks & Cassin (1982). The significance of thses observations is as yet not clear.

2.3 Biochemical Development

Avery & Mead (1959) demonstrated that babies suffering from RDS (ie where there were no other obvious causes for the baby to have respiratory problems) had deficient surfactant in their lungs.

2.3.1 Physical properties of surfactant

Pattle in 1955 noted that surfactant could reduce surface tension to very low levels. He found tiny air bubbles from lung tissue did not shrink and disappear as rapidly as expected. As early as 1947 Gruenwald suggested that surface tension and RDS might be related. By the La Place equation $\Delta P = \frac{2T}{R}$, (where P = difference between air pressure and intrathoracic pressure; T = wall tension in the alveolus; R = radius of alveolus), if the surface tension (T) in the alveoli were not extremely low, a very high pressure (P) would be required to maintain expansion when the radius of the alveoli (R) has reached its

minimum at the end of expiration, (ie because the alveolar surface tension is low, collapse of the alveolus is prevented as it reduces in size).

Clements et al (1961) using a modified Wilhelmy balance and Enhorning (1977) using a pulsating bubble technique, concluded that normal alveolar stability was due to the ability of pulmonary surfactant to cause a change in surface tension as the surface of the alveolus (and therefore the radius) changes. On expiration, as the alveolus decreases in size the molecules of surfactant are packed closer together thus reducing the surface tension as the radius decreases and allowing re-expansion of the alveolus at a lower pressure during inspiration (Harvey & Parkinson 1981). Morley et al (1978) have suggested that surfactant forms a rigid structure which holds the lungs open at the end of each breath.

It has further been demonstrated that surfactant may also have a role to play in the clearance of lung fluid (Guyton & Moffatt 1981).

2.3.2 Chemical composition of surfactant

Lung surfactant is composed of several phospholipids of varying importance in combination with proteins (Table 2.1).

The phospholipid molecule contains a hydrophilic part (the phosphatidyl radical) and a hydrophobic part (the long chain fatty acids). Many molecules of phopholipids line the alveoli with the hydrophobic end in the air, the alveolar surface then takes on the properties of the phospholipid molecule (Harvey & Parkinson 1981). The major component of lung surfactant phospholipid is dipalmitoyl-phosphatidyl choline (lecithin). The next most important phospholipid is phosphatidyl glycerol (PG) (Hallman et al 1976) which has been shown to be at least as surface active as surfactant lecithin (Pfleger et al 1972). Other, and at present state of knowledge, less important

phospholipids include phosphatidyl inositol (PI), phosphatidyl ethanolamine (PE) and phosphatidyl serine (King & Clements 1972, Pfleger et al 1972).

2.3.3 Control of surfactant synthesis

The type II alveolar epithelial cells are generally believed to be responsible for the production of surfactant (Niden 1967).

The phospholipids of lung surfactant appear to recycle between lamellar bodies and alveolar spaces (Fig 2.1).

Clements et al (1984) suggest that lamellar body contents when secreted from tubular myelin, generate a monolayer at the gas-liquid interface. Surfactant molecules from the monolayer may form vesicles, and return to the type II cells. The control of the surfactant system is as yet uncertain and likely to be more complex then previously thought as more information becomes available (Clements et al 1984).

The biosynthesis of phospholipids by the type II pneumocytes has been studied in detail by a number of investigators (Gluck et al 1972[A]; Farrell & Avery 1975; Rooney et al 1976).

Two biosynthetic pathways for phosphatidyl choline have been described by Gluck, one being active in the very immature fetus and involving progressive methylation of phosphatidyl ethanolamine and the other, functioning in the mature fetus involving the incorporation of activated choline into diacylglycerol. It is now considered that the methylation pathway is unimportant in the lung (Van Golde 1976).

Although most early work on surfactant concentrated on phosphatidyl choline it became obvious that other components are at least as important. Hallman et al (1976) described two acidic phospholipids, phosphatidyl glycerol (PG) and phosphatidyl inositol (PI) found in amniotic and tracheal fluid. PG but not PI seemed to be almost invariably associated with mature fetal lungs. The

biosynthetic pathways of these two phospholipids appeared to be linked, the concentration of PG rising while that of PI fell.

The enzymes involved in catalysing the synthesis of the phospholipids may be under the influence of endogenous corticosteroids. Doell & Kretchmer (1964) observed that the activity of gut invertase could be increased using hydrocortisone. Since lung is a gut derivative it seemed possible that its enzymes might also be similarly affected and this has been shown to be true by Farrell & Zachman (1973) and Rooney et al (1976). A number of animal studies have tended to confirm the hypothesis of steroid induction of the lung enzymes involved in surfactant synthesis.

a) Animal studies

Liggins (1969), while studying premature delivery of fetal lambs infused with corticosteroids, observed partial aeration of lungs at an earlier than expected gestation in lambs born vaginally after treatment with dexamethasone. He suggested that this may be the result of steroid induced accelerated appearance of surfactant activity. De Lemos et al (1970) treated one of twin fetal lambs (8 sets of twins) with hydrocortisone and noted acceleration of lung maturation in the steroid treated lambs. Further evidence for accelerated appearance of pulmonary surfactant in the fetus was provided by Kotas and Avery (1971), where lung maturation in the fetal rabbit was assessed by pressure/volume curves, dry weight and surface tension properties and by Wang et al (1971), Chiswick et al (1973), Motoyama et al (1971), who noted an accelerated appearance of osmophilic bodies in fetal lungs following steroid injection. These findings are supported by research demonstrating that fetal lungs of rabbits, lamb and humans all contain the specific glucocorticoid receptor considered necessary for hormonal resposiveness (Ballard &

Ballard 1972 and 1974).

Clinical and biochemical studies in the human have tended to support the animal experiments, however the evidence that glucocorticoids have a beneficial effect on lung development in humans is by no means clear cut.

b) Human Clinical Studies

Following the observation in animal lungs that corticosteroids may cause accelerated appearance of surfactant (Liggins 1969), Liggins and Howie (1972) performed a controlled trial of betamethasone therapy to mothers threatening preterm labour or those undergoing elective preterm delivery in the hope of reducing the incidence of RDS. In babies less than 32 weeks' gestation who had been treated for at least 24 hours before delivery RDS occurred less often in treated babies than in controls. Howie and Liggins (1977) reported the results of a larger controlled trial and confirmed that giving antepartum betamethasone to mothers threatening preterm labour, reduced the incidence of RDS and in addition reduced the incidence of intraventricular haemorrhage. However, no benefit was derived from treatment if the baby was delivered within 24 hours or more than 7 days from the start of treatment of if the gestational age was greater than 34 weeks. Most subsequent work has tended to confirm the findings of Liggins & Howie, (Ballard & Ballard 1976), of the beneficial effects of betamethasone (Block et al 1977, Schutte et al 1980, Kennedy 1974) and also of dexamethasone (Caspi et al 1976) and hydrocortisone (Morrison 1978). Unfortunately not all these studies were double blind or had adequate controls.

In a prospective randomised study of corticosteroids in the management of PROM Garite et al (1981) failed to demonstrate any advantage of steroid treatment over conventional expectant management.

In 1981 a large double blind randomised trial (Collaborative Group on Antenatal Steroid Therapy 1981) while confirming the findings of Liggins and Howie noted that the reduction in incidence of RDS in the treatment group was attributable to differences among singleton female infants with no effect observed in males. In addition non Caucasians seemed to respond but Caucasians did not. The study concluded that steroid therapy should be used selectively and with caution.

c) Human - Biochemical studies

Surprisingly little work has been carried out on this subject. Liggins and Howie (1972 and 1974) could find no consistent change in the L/S ratio of amniotic fluid samples taken before and after betamethasone treatment. However, Spellacy et al (1973) performed amniocentesis at 2 weekly intervals in pregnant women between 28 and 32 weeks' gestation. One group was given oestrogen therapy, a second group corticosteroid and a third group, the controls, no treatment. There was a significantly greater rise in L/S ratio in the women receiving glucocorticoid treatment.

Although other small studies have tended to confirm a corticosteroid induced rise in L/S ratio, the effect seems to occur mainly after 32 weeks' gestation (Diedrich et al 1978, Ekelund et al 1976, Zuspan et al 1977).

d) Placental transfer of cortisol

The proposed influence of exogenous corticosteroids on fetal lung maturity raises the possibility that corticosteroids from the mother may add to fetal cortisol to influence fetal lung maturity.

Leon and Murphy (1976) showed a significant correlation between maternal and umbilical cord venous cortisol concentrations but not

between maternal venous and umbilical arterial blood concentrations. However, there is a dispute concerning an umbilical arterial/venous cortisol concentration gradient, which might imply a fetal secretion of cortisol. Although several groups of workers (Murphy & Diaz d'Aux 1972, Leong & Murphy 1976) found higher umbilical arterial than umbilical venous cortisol concentrations, Cawson et al (1974) could detect no umbilical arterio-venous difference and Smith and Shearman (1974 A and B) found higher umbilical venous levels.

More recently Poulakka (1982) noted that the fetal ACTH levels tended to be lower in umbilical venous than umbilical arterial blood.

Although there is a concentration gradient across the placenta for total cortisol levels, over 90% of maternal cortisol is protein bound (Sandberg and Slaunwhite 1959) and not available for transfer. There is an increase in corticosteroid binding globulin (CBG) during pregnancy and the increased cortisol levels during labour and delivery may not exceed this rise in CBG (Slaunwhite and Sandberg 1959). However even if this did happen, the placenta via the enzyme 11-B hydroxysteroid dehydrogenase, metabolises 80-85% of the cortisol produced by the mother to inactive cortisone (Murphy et al 1974, Levitz et al 1978). This may be a mechanism whereby the fetus is protected from maternal cortisol levels at critical stages in its development, as cortisol is known to be an enzyme inducer (Liggins 1976).

It is likely therefore that most of the free cortisol in the fetal circulation originates from the fetal adrenal gland, the contribution of maternal cortisol being of lesser importance. It has been estimated that at least 75% of the cortisol in fetal plasma at term is of fetal origin (Beitins et al 1973). However, it may be that due to the large increase in maternal cortisol during labour the capacity of the 11-B hydroxysteroid dehydrogenase responsible for the

conversion of cortisol to cortisone may be overcome and that a larger part of the fetal cortisol is of maternal origin in the later stages of labour and delivery.

In addition to the above studies on the effect of exogenous corticosteroids on the human fetal lung there is some evidence to suggest a corticosteroid deficiency in RDS. Naeye et al (1971) in a series of 387 consecutive autopsies on human neonates, demonstrated that adrenal glands were 19% lighter in infants with HMD compared with those without HMD, the difference being a greater number of adrenal cortical cells in those infants who did not develop RDS. These workers also showed that anencephalics with little or no adrenal cortex had 45% less osmiophilic granules in pulmonary type 11 alveolar cells as did 'normal' controls. Further evidence supporting a corticosteroid deficiency in RDS was provided by the measurement of cortisol in cord blood at delivery. Murphy (1974 A), Murphy (1974 B), Sybulski and Maughan (1976) have shown significantly lower levels of cortisol in cord blood in infants who subsequently developed RDS compared with unaffected infants of similar gestational age. However, the results of these studies were far from being clear cut. Murphy (1974 A) omitted clinical details of the infants, eg method of delivery, known to affect cortisol levels. In the series reported by Murphy (1974 B) one third of the babies with RDS were equal or greater than 35 weeks, including 3 at 40 weeks' gestation, calling into question the accuracy of the diagnosis of RDS or the gestational ageing, or both. Furthermore, when method of delivery was taken into account, small numbers were involved (10 with RDS and 8 without), although there was still a significant difference in control levels ($P = 0.05$) between the two groups. In addition Sybulski and Maughan (1976) concluded that whether or not RDS developed, appeared to depend more on the degree of prematurity than upon cortisol levels at

delivery.

Several groups of investigators have shown that neonates suffering from RDS have significantly higher cortisol levels than infants of the same gestational age with no RDS (Klein et al 1973, Reynolds 1973, Baden et al 1972). In addition Reynolds (1973) demonstrated that infants with and without RDS were equally responsive to ACTH administration by producing elevated corticosteroids, suggesting no lessened responsiveness in those with fatal HMD.

Therefore, there is some evidence to suggest an endogenous corticosteroid deficiency antenatally in babies who subsequently develop RDS but nothing to suggest that postnatal adrenal hypofunction plays a role in the pathogenesis of HMD.

Exogenous corticosteroid treatment antenatally seems to influence fetal lung maturity and it might be reasonable to propose that the effect of stress on fetal lung maturity is mediated via endogenous cortisol production.

In addition to the glucocorticoids, other hormones are thought to play a role in surfactant synthesis. Hitchcock (1979) has shown that thyroxine can promote lung maturation in fetal rabbit lungs and in vitro (Gross & Wilson 1982) and in vivo (Gross et al 1983) studies have suggested that the effects of glucocorticoid and thyroxine hormones are synergistic. Redding et al (1979) were the first to suggest treatment with thyroxine to accelerate lung maturation and the results of Mashiach et al (1979) tend to suggest that it may have some benefit. Thyroxine, however, does not cross the placenta and therefore requires to be given intraamniotically. A way round this may be to use TRH which readily crosses the placenta (Rooney et al 1979).

It has also been proposed that Prolactin may have a role to play in controlling surfactant production (Hauth 1978). Prolactin levels were found to be lower in babies developing RDS compared to babies of similar gestation with no respiratory problems.

The importance of thyroid hormones and prolactin in the control of surfactant synthesis has as yet to be ascertained.

2.3.4 Control of surfactant release

Although the production of surfactant in the type II pneumocyte may be controlled, at least partly by fetal adrenocortical hormones, it has been suggested that the release of this surface active material into the alveolar space may be controlled by a different mechanism (Chiswick et al 1973, Mescher et al 1975).

Evidence is now accumulating that the catecholamines may have an important role in preparing the fetus for extrauterine existence, especially with regard to lung function (Olver 1981). Most of this evidence has been obtained directly from animal experimentation and indirectly from clinical observation in humans where Beta sympathomimetic drugs have been employed in an attempt to arrest preterm labour.

The catecholamines are thought to be important in the clearance of lung fluid as discussed previously (p 37). In addition however to dehydrating fetal lungs there is also evidence to suggest that the catecholamines may cause an increase in surfactant release (Lawson et al 1978, Abdellatif & Hollingsworth 1979).

a) Animal research

In these experiments exogenous adrenaline was infused into fetal sheep and neonatal rabbits with a resulting increase in lung surfactant secretion. This effect was blocked by propranolol (Abdellatif & Hollingsworth 1979) implying that it was mediated via Beta receptors. This theory is supported by observations made on rabbit fetuses infused with the Beta sympathomimetic drugs isoxsuprine and terbutaline. The lungs of fetal rabbits treated with these drugs retained more air on deflation (ie were more stable) than those of control rabbits (Wyszogrodski et al 1974, Corbet et al 1977, Bergman and Hedner 1978). These observations were considered to be due to enhanced release of surfactant.

Enhorning et al (1977) as well as finding greater surface activity and higher L/S ratios in isoxsuprine treated animals compared with controls, also noted significantly less fetal pulmonary fluid in treated animals. These authors also found a significant decrease in lamellar inclusions in type 11 pneumocytes, further evidence of enhanced surfactant release by Beta adrenergic stimulation.

In vitro studies (Dobbs & Mason 1979) of isolated type 11 cells from rat lungs have shown a release of disaturated phosphatidylcholine on Beta adrenergic stimulation with Terbutaline. A similar study by Kanjanapone et al (1980) found that in addition to increased release of surfactant following isoxsuprine treatment there was also an increase in choline incorporation into disaturated phosphotidylcholine indicating increased surfactant synthesis in the treated group.

There is therefore evidence to suggest that, at least in some animal species, exogenous catecholamines cause a decrease in lung fluid, and an increase in surfactant synthesis and release.

b) Human clinical research

A number of workers have noted a reduced incidence of RDS in preterm babies whose mothers were treated with 'B' mimetic drugs in an attempt to suppress preterm labour (Kero et al 1973, Boog et al 1975, Hastwell 1977, Bergman & Hedner 1978). In two of these studies (Boogs et al 1975 and Bergman & Hedner 1978), which were both retrospective, a significant reduction in the incidence of RDS was found after treatment with a 'B' mimetic, although, in the study by Boog et al the difference was only statistically significant for infants weighing under 2300 grams.

c) Human biochemical research

Cabero et al (1979) provided some evidence to suggest that the same response occurs in humans as in animals after Beta mimetic treatment. In their study ritodrine was given orally to pregnant women between 33-35 weeks' gestation, following which there was a 70% increase in the palmitic acid concentration of amniotic fluid at the end of the treatment period. There is therefore some evidence that exogenous catecholamines and Beta sympathomimetics can influence lung function. However, little work has been done to show that in situations of stress endogenous catecholamines can bring about a similar improvement in lung function.

In animals, Brown et al (1981), using chronically catheterised fetal lamb preparations noted a correlation between endogenous AD concentration and lung liquid absorption during labour. However no such correlation of lung liquid absorption was found with NAD.

In humans, Woodman et al (1978), noted a significant correlation between the ratio of NAD/AD and the L/S ratio, and Artal et al (1982) found that mature lung profiles (ie L/S ratio 2.0 + presence of PG) correlated significantly with progressively rising metanephrine

levels.

The ability of exogenous catecholamines to influence fetal lung maturity in animal experiments raises the possibility that transfer of maternal catecholamines to the fetus in conditions where the mother is under stress, eg during vaginal delivery, would help to optimise neonatal lung function. Available evidence (see below), however, does not lend support to the idea of placental transfer of catecholamines from mother to the fetus.

d) Placental transfer of catecholamines

Catecholamines in physiological concentrations do not appear to cross the placenta, whereas pharmacologic concentrations of poorly metabolised sympathomimetic drugs do have the potential of crossing the placenta in significant amounts (Phillipe 1983). Sandler et al (1963) in a small study where labelled NAD was injected into mothers prior to elective abortion of non viable fetuses, detected small amounts in umbilical venous blood but negligible amounts in fetal heart blood.

In vitro studies of the human placenta have demonstrated that catecholamines cross the placenta in very limited concentrations (Morgan et al 1972, Saarikoski 1974). both these studies have demonstrated the presence of catechol-o-methyltransferase and monoamine oxidase in the placenta which metabolises the catecholamines to inactive metabolites. The placenta would seem therefore to act as a barrier to the transfer of catecholamines from mother to fetus. The demonstration of higher catecholamines in the plasma of the fetus compared with the mother (Poulakka et al 1983, Jones and Greiss 1982, Messow-Zahn et al 1978, Inglis et al 1981), and in the umbilical artery compared with the umbilical vein, further support the idea of functional separation of the fetal and maternal sympatho adrenal

systems.

2.3.5 Amniotic fluid phospholipids and RDS

Helmy and Hack (1962) were first to discover lecithin in amniotic fluid and a flow of fluid from the fetal lung into the amniotic fluid has been demonstrated by several workers (Scarpelli 1967, Dawes et al 1972, Rethmeier & Egberts 1975). Although Graven (1968) had suggested that the amniotic fluid lecithin concentration might be used in the prediction of RDS it was Gluck et al (1971) who made the major advance with the introduction of the L/S ratio. They investigated the concentrations of the phospholipids, lecithin and sphingomyelin in the amniotic fluid, from 18 weeks' gestation until term. Although the sphingomyelin concentration remained low and fairly constant throughout pregnancy there was a sudden increase in lecithin concentration around 35 weeks. They found that the ratio of lecithin to sphingomyelin concentration remained low and fairly constant throughout pregnancy whereas was a sudden increase in lecithin concentration around 35 weeks, which resulted in a rise in the L/S ratio. They found that the L/S ratio was a reliable predictor of RDS. Since it was introduced the L/S ratio has been used successfully throughout the world as a predictor of RDS (Lemons & Jaffe 1973, Donald et al 1973, Wagstaff & Bromham 1973, Gluck & Kulovich 1973, Whitfield and Sproule 1974). Harvey and Parkinson (1981) reviewed 42 papers from the world literature and found that when the L/S ratio ≥ 2.0 the incidence of RDS was 1.5% when L/S ratio < 2.0 there was a 53% incidence of RDS. (Liquor specimens obtained within 72 hours of delivery.)

Although generally reliable the L/S ratio has certain disadvantages.

1 A high percentage of false negative results (ie an L/S ratio below the critical value but no RDS (Harvey & Parkinson 1981, Whittle et al 1981[B], Whitfield & Sproule 1974, Worthington & Smith 1978).

2 Occasional false positive results (Ie unpredicted RDS occurring despite an adequate L/S ratio (Worthington & Smith 1978).

3 It is unreliable when the amniotic fluid has been collected vaginally (Wagstaff et al 1974, Van Graff & Gunston 1978, Drombroski et al 1981).

4 It is unreliable when the amniotic fluid is contaminated by blood or meconium (Gluck et al 1974, Van Graff & Gunston 1978).

5 Some workers have questioned the reliability of the L/S ratio when the pregnancy is complicated by diabetes. Whitfield and Sproule (1974) noted the association of maternal diabetes with 11 out of 21 cases of RDS occurring despite 'safe' L/S ratios. Other workers have confirmed the unreliability of the L/S ratio in predicting lung maturity in diabetic pregnancies (Dahlenbrug et al 1977, Mueller-Heubach et al 1978).

In an effort to overcome these limitations of the L/S in predicting RDS, Kulovich et al (1979) developed an amniotic fluid phospholipid profile. This method employed two dimensional thin layer chromatography of the amniotic fluid and in addition to the L/S ratio this technique determines the presence of phospotidyl glycerol (PG) and phosphotidyl inositol (PI) as well as the less important phospholipids, phospotidyl ethanolamine (PE) and phosphotidyl serine

(PS).

This method has proved reliable in the assessment of fetal lung maturity in diabetic pregnancies (Cunningham et al 1978, Kulovich & Gluck 1979) and the presence of PG is unaffected by contamination of the amniotic fluid (Strassner et al 1980, Hallman & Teramo 1981). PG has also shown to be reliable when the liquor was collected vaginally at spontaneous rupture of the membranes (Whittle et al 1981, 1982, Brame & McKenna 1983).

Since the introduction of the amniotic fluid phospholipid profile Whittle et al (1981)[B] have shown that only the L/S ratio and the presence or absence of PG are important indicators of the risk of RDS, and that this modified profile offers an improvement in the predictive accuracy over the L/S ratio alone both in singleton (Whittle et al 1981[B],1982) and in multiple pregnancies (Dobbie et al 1983).

2.4 Factors which control and modify fetal lung maturity

Clearly the maturation of the fetal lungs is a complex process involving a number of different systems. The overall control of the process is uncertain for a number of reasons. Most information has been derived from animal experimentation which may not be necessarily applicable to man and the investigation of lung maturation in man is made more complex by a number of issues. Firstly should the best indicator of fetal/neonatal lung maturity be the presence of adequate surfactant levels in amniotic fluid/pharyngeal aspirate or should the neonatal respiratory performance be of greater importance? Secondly, difficulty in the diagnosis of RDS is often encountered. Thirdly other compounding factors such as mode of delivery, condition at birth and the vigor of neonatal resuscitation may also influence neonatal functional maturity. Finally, attempts to derive a 'normal' timetable

for fetal lung maturity necessitates the study of prematurely born babies who, by definition, are not normal either because of the time of their birth or underlying maternal pathology.

The role of the stress products cortisol and the catecholamines has a scientific basis in animals but is less clear in the human (pp 35-38, 40-50).

For many years obstetricians have had the impression that certain pregnancy complications appear to be associated with an unusually low incidence of neonatal RDS. Why this should be is unclear but it was proposed that 'fetal stress' arising from a hostile intrauterine environment was a likely underlying factor.

A possible mechanism whereby stress, both physiological and pathological, may influence fetal lung maturity in man is outlined in Figure 2.2. The rise in fetal cortisol and catecholamine levels as a direct result of fetal stress resulting in increased surfactant production and release, and increased absorption of lung fluid leading to optimal neonatal lung function.

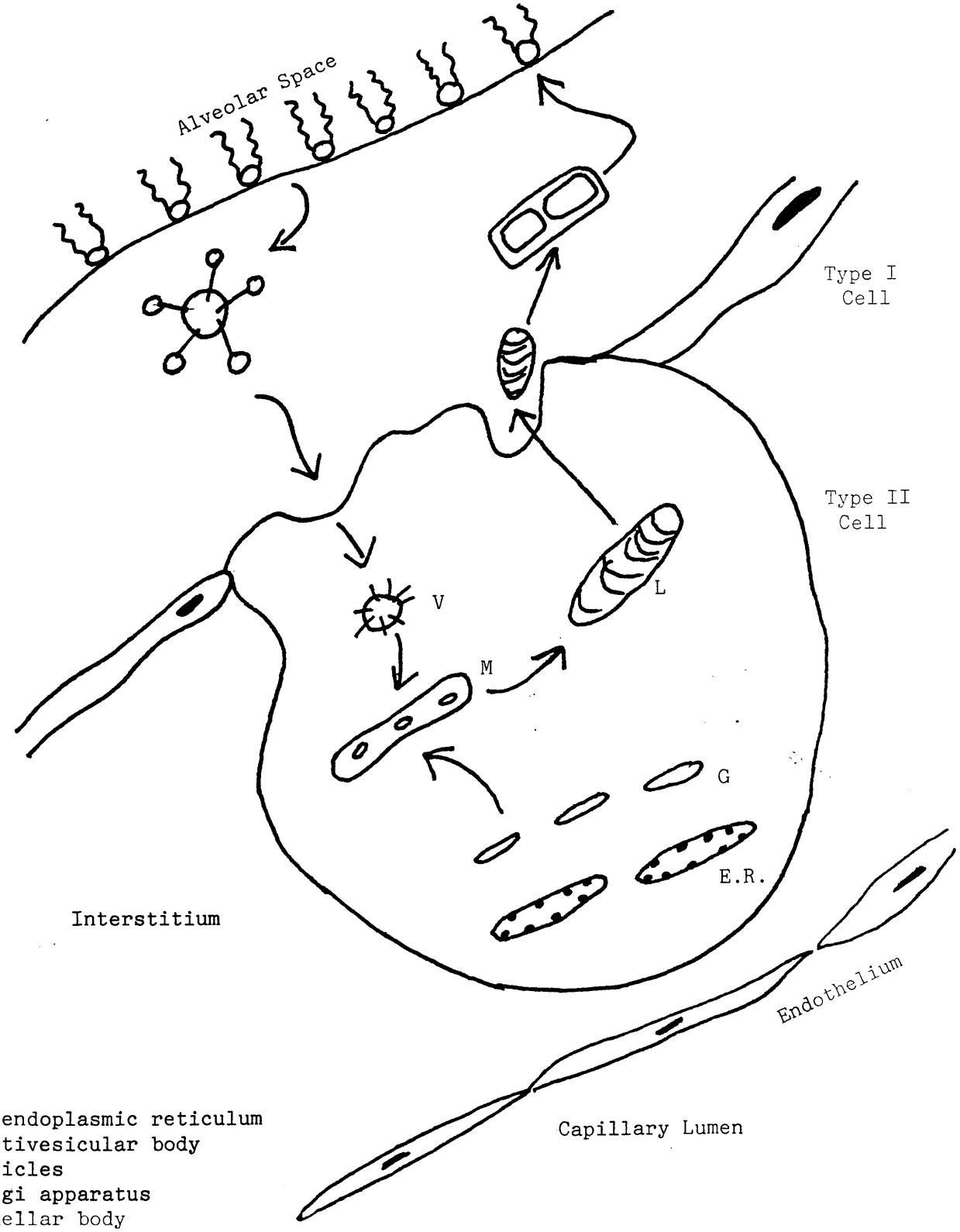
Chapter 3 will discuss the effect of various physiological and pathological factors thought to influence fetal lung maturity and will present the evidence for changes in the fetal stress products cortisol and the catecholamines as a result of these factors.

TABLE 2.1 Chemical Composition of Surfactant

The phospholipid % composition of alveolar lavage fluid in the mature newborn rabbit	
Phosphotidyl choline	79%
Phosphotidyl glycerol	6%
Phosphotidyl inositol	6%
Phosphotidyl ethanolamine	5%
Sphingomyelin	1%
Phosphotidyl serine	1%

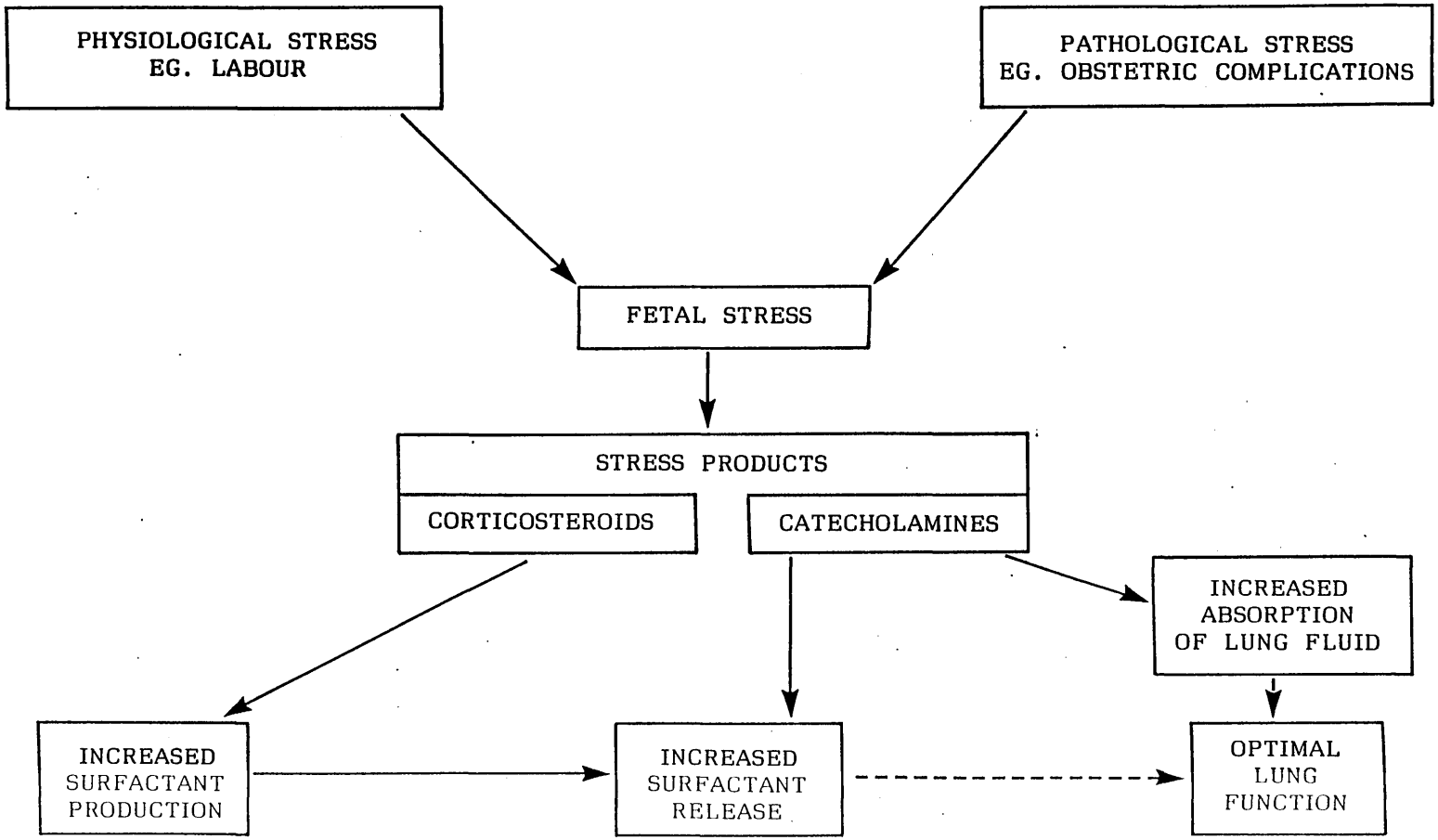
Data from Hallman 1981

Fig. 2.1. Turnover of Lung Surfactant - from Clements et al (1984)



E.R. = endoplasmic reticulum
M = multivesicular body
V = vesicles
G = Golgi apparatus
L = Lamellar body

Fig. 2.2 Stress and Lung Maturity



Chapter 3

Factors Which May Influence Fetal Lung Maturity

Much clinical and biochemical evidence has suggested that certain obstetric factors predispose to the development of RDS, while others somehow cause an acceleration of the normal timing of fetal lung maturity (Table 3.1). The evidence, discussed below, has often been less than convincing and occasionally even conflicting.

These obstetric factors may influence fetal lung maturity by the mechanism outlined in Figure 2.2, whereby the fetal stress products cortisol and catecholamines represent the final common pathway facilitating optimal neonatal lung function. The evidence available in the literature supporting changes in the levels of fetal cortisol and catecholamines as a result of these obstetric factors is discussed.

3.1 Physiological Factors

3.1.1. Gestational Age

a) Clinical Outcome

One of the most important factors associated with the development of RDS is preterm delivery. The earlier the gestational age at birth, the higher the incidence and severity of the condition. This has been demonstrated in many studies (Dunn 1965, De Sa 1969, Cohen et al 1960, Usher et al 1971, Jones et al 1975). However, the observation that some preterm liveborn babies have mature lungs and survive while others of exactly the same gestational age develop RDS and die demonstrates clearly that other factors are involved in the pathogenesis of RDS. This is most dramatically seen in multiple pregnancies where some siblings develop RDS and die while their cosiblings do not (Pender 1972, Lemons & Jaffe 1973, Wilkinson et al 1982, Pritchard & McDonald 1976, Dobbie et al 1983).

b) Surfactant

Gluck & Kulovich (1973) observed, in uncomplicated pregnancies, that the L/S ratio rose gradually as gestational age advanced, reaching mature levels between 34 and 36 weeks. Similar studies have reported changes in the concentrations of the other amniotic fluid phospholipids with advancing gestational age (Kulovich, Hallman & Gluck 1979). Whittle (1984) reported a personal series where the PI/S and PG/S ratio was observed in a large group of babies where the gestational ages were accurately known. The quantity of PI seemed to remain fairly constant after rising from low levels prior to 29 weeks, while the concentration of PG rises steadily towards term. However, gestational age is not the only determinant of surfactant concentration. This is well demonstrated in multiple pregnancies in which the babies are of the same gestational age and have been subjected to similar obstetric complications. Dobbie et al (1983) have shown that the correlation of L/S ratio between pairs of twins is poor and, although much improved, is not perfect for PG.

c) Fetal cortisol

1) Adrenal mass

The fetal adrenal cortex occupies 0.5% of total body volume compared with mature adult cortex which occupies 0.01% of total body volume. There is an increase of relative fetal adrenal mass throughout pregnancy. This increase, however, is most marked between 32-36 weeks (Buster 1980).

2) Umbilical cord plasma cortisol

Smith and Shearman (1974 A & B)) showed a rise in total umbilical cord plasma corticosteroids throughout gestation with a surge at 35-37 weeks, followed by a gradual decline thereafter both with vaginal

delivery and with caesarean section. In the caesarean section study, however, there were very few cases born less than 35 weeks and unusually they found umbilical venous levels to be higher than umbilical arterial levels which is in contrast to many studies. Gestational age was assessed 'within the usual clinical limits' and therefore may not have been very accurate.

Goldkrand et al (1976) studying babies delivered vaginally, found significantly higher cord cortisol levels at less than 36 weeks gestation compared with greater than $37\frac{1}{2}$ weeks. However, Roopnarinesingh et al (1977) found no significant change in mean cord plasma cortisol values with advancing gestational age after 33 weeks gestation and Pokoly (1973) found that a small group of preterm babies delivered by elective caesarean section had similar cortisol levels as term babies delivered by caesarean section, and they therefore did not demonstrate therefore a rise of fetal cortisol as term approached. Murphy (1982) noted a slight fall in cord plasma cortisol from 15 to 20 weeks and then a rise to 35 weeks followed by a further rise between 37 weeks and 40 weeks. These changes occurred in both elective caesarean section group and vaginally delivered groups. Gestational age was based on last menstrual period in the 'mature' babies and on neonatal assessment in the preterm group.

3) Amniotic fluid cortisol

Murphy et al (1975) and Fencl and Tulchinsky (1975) have shown that amniotic fluid cortisol rises with gestational age, Murphy et al noting a late surge just before term.

4) Fetal lung cortisol-cortisone metabolism

Murphy (1979) has shown that with advancing gestational age, the fetal lung's ability to convert cortisol to cortisone diminishes, resulting in increased intracellular cortisol bioavailability. This process may be related to maturation of the fetal lung.

The consenses of opinion would seem to indicate that as gestation advances there is an increase in fetal corticoids.

d) Fetal catecholamines

In the fetus catecholamines are produced in the adrenal medulla, adrenergic nerve endings and in the extra medullary paraaortic chromaffin tissue. The largest masses of extramedullary chromaffin tissue (the origins of Zukerkandl) are situated at the origin of the inferior mesenteric artery and have a higher concentration of catecholamines than any other major organ, including the brain and adrenal medulla (Greenberg & Lind 1961). The extra adrenal chromaffin tissue has been shown to be identical developmentally and structurally to the phaechromocytes of the adrenal medulla (Coupland 1952).

In a study of the function of the extra adrenal chromaffin tissue West et al (1953) noted that by 20-22 weeks the tissue was cytologically mature and thereafter underwent no change until they begin to fibrose after birth. Pharmacologically the extra adrenal chromaffin tissue contains appreciable quantities of NAD, the concentration of which increases from 16 weeks until term. The study had certain drawbacks. It employed a biological assay for the catecholamine measurement and examination of the fetal tissue took place 30 hours after death in several cases. Histologic studies by Hervonen (1971) have shown an intimate relationship between the phaechromocytes of the extramedullary chromaffin tissue and the well developed capillary sinusoidal networks of the human fetus,

emphasizing the resemblance of this tissue to other endocrine glands.

Unlike the adrenal medulla, the extramedullary chromaffin tissues are poorly innervated and show no response to splanchnic nerve stimulation (Muscholl & Vogt 1964, Hervonen 1971).

Compared to the extramedullary chromaffin tissue, the adrenal medulla is much later in attaining structural maturity. Its chromaffin tissue being scanty and immature during fetal life. It contains much smaller amounts of NAD than the extramedullary chromaffin tissue, with AD only appearing in appreciable amounts after birth (West et al 1953). After birth the adrenal medulla grows rapidly and by the end of the first year, resembles the adult gland.

Niemineva and Pekkarinen (1952) noted that in the adrenals of human fetuses (Fetal weight range 230-4270 gm), $^{3}/_{4}$ of the catecholamine content was NAD, whereas Greenberg and Lind (1961) found equal concentrations of NAD and AD in the adrenals of fetuses weighing 37-635 grams. Experiments with rabbits (Brundin 1966) and rats (Margolis 1966) seem to confirm the finding in humans by West et al (1953) that AD only increases near term and early postnatal life.

Although it is generally assumed that a high proportion of NAD in the adrenal medulla is indicative of immaturity and that the percentage of AD increases slowly with age, there have been few studies of the catecholamine content during fetal and neonatal life (Comline & Silver 1966).

The maturation of the fetal adrenal appears to involve two main factors. Firstly the development of splanchnic innervation to the adrenal medulla and secondly the ability of the adrenal cortex to secrete corticosteroids (Artal 1980).

Several histological studies have shown that the adrenal medullary cells are richly innervated, from 14 weeks' gestation, with preganglionic nerves which synapse with phaechromocytes (Coupland & Weakley 1970, Hervonen 1971, Turkel & Itabashi 1974). Neural impulses are relayed in centres in the posterior hypothalamus to the adrenal medulla via the splanchnic nerves, stimulation of which causes a significant release of catecholamines from the adrenal medulla (Artal 1980). The gestational age at which the adrenal medulla becomes sensitive to splanchnic nerve stimulation, in the human, is unknown. There does appear to be an interspecies variation in the timing of the response. In the fetal lamb the adrenal medulla becomes responsive to nerve stimulation at 80-100 days' gestation (equivalent to 24-28 weeks in humans), whereas in the fetal calf there is only a slow and small increase in the response of the adrenal medulla to nerve stimulation throughout gestation. It is felt that the human fetus resembles the fetal calf in this respect (Comline & Silver 1966).

The adrenal medulla, situated in close proximity to the cortex is exposed to increasing glucocorticoid secretion as gestation advances. the glucorticoids are known to regulate the activity of phenylethanolamine-N-methyl transferase (PNMT) (Wurtman and Axelrod 1966). This enzyme is necessary for the n-methylation of NAD thus converting it to AD, and is mainly located in the adrenal medulla. The extramedullary chromaffin tissue, in contrast, contains only small amounts of this enzyme (Gehnser & Studnitz 1969). Therefore, as gestation advances the adrenal medulla is exposed to increasing concentrations of glucocorticoids encouraging the n-methylation of NAD and resulting in increasing concentrations of AD.

There have been few studies measuring catecholamines throughout gestation in humans. Studies on amniotic fluid catecholamine concentrations have demonstrated increasing amounts of both AD and NAD

throughout gestation (Phillipe and Ryan 1981, Divers et al 1981)[A]. However, while Phillipe et al found that NAD predominated over AD, Divers et al found the opposite to be true. Woodman et al (1978) discovered on increase in the NAD/AD ratio in amniotic fluid between 37 and 43 weeks' gestation and they suggested that in late pregnancy the fetus excretes NAD in increasingly greater amounts than AD. Lagercrantz and Bistoletti (1973) found that preterm infants had lower UA and UV catecholamine levels than term infants after both uneventful deliveries and intrauterine asphyxia. However, the percentage of AD relative to the total catecholamine concentrations was essentially the same in both term and preterm infants. A recent paper (Newnham et al 1984) measured UA, NAD and AD concentrations in 36 preterm fetuses and found significantly greater AD levels in preterm than term fetuses.

3.1.2 Labour and Mode of delivery

a) Clinical outcome

Although Donald et al (1973) and Garbert et al (1973) could find no evidence that the mode of delivery had any bearing on the subsequent development of RDS, several large retrospective surveys have shown that delivery by caesarean section predisposes the neonate to RDS and death from hyaline membrane disease (Cohen et al 1960, Usher et al 1971) Fedrick and Butler (1972) examined the data of the 1958 British Perinatal Mortality Survey and found an increased chance of dying from hyaline membrane disease (HMD) if the baby was delivered by elective caesarean section compared with delivery by caesarean section after the onset of labour or vaginal delivery. Unfortunately in the other studies quoted above, which link caesarean section with an increased incidence of RDS, no distinction was made between elective caesarean section and caesarean section performed during

labour. The evidence presented by Fedrick and Butler was based on the necropsy diagnosis of HMD and therefore there could be little confusion over diagnosis.

b) Surfactant

Labour has been considered to facilitate the normal adaptation of the lungs at birth. This may be achieved by promoting both clearance of lung fluid (p 36) and release and increased production of surfactant. Cabero et al (1976) and Craven et al (1976) found higher L/S ratios and higher lecithin concentrations during labour compared with before the onset of labour, suggesting that labour causes a significant increase in surfactant. Studies in which serial liquor samples were obtained during labour (Whittle et al 1977 and 1981, Whittle & Hill 1980) have demonstrated that in some labours the L/S ratios rise, in some they stay the same and in some they decrease. There was a tendency to short labours in the labours where a rise in L/S ratio occurred. Whittle et al (1981) have demonstrated reduced fetal heart rate variability in long labours in which the L/S ratio fell and postulated that the fetus under stress retained its surfactant producing high concentrations in the lung passages, thus resulting in optimal lung function.

c) Cortisol

Many studies have shown that in term pregnancies the levels of corticosteroids in umbilical cord blood is significantly higher following vaginal delivery compared with elective caesarean sections (Cawson et al 1974, Weekes et al 1976, Goldkrand et al 1976, Talbert et al 1977, Isherwood et al 1981).

Umbilical cord ACTH levels have also been found to be higher after vaginal delivery compared with elective caesarean section (Arai

et al 1976, Poulakka et al 1982, Sybulski & Maughan 1976). Whether the high levels of corticosteroids observed are due to the stress of labour itself or to the process of initiation of labour in a similar manner to the sheep has been the subject of much debate. The finding of higher cortisol levels in cord blood after vaginal delivery of spontaneous onset compared with induced labour has led some workers to favour the initiation of labour theory (Cawson et al 1974, Goldkrand et al 1976). However, supportive evidence for higher cord corticosteroid levels in spontaneous compared with induced labour has not been forthcoming (Isherwood et al 1981, Weekes et al 1976, Sybulski & Maughan 1976, Pokoly 1973).

Ohrlander et al (1976), using fetal scalp blood samples found that the initial plasma cortisol levels did not differ between spontaneous and induced labours but rose equally in both during labour.

It would seem more likely therefore that the higher levels of cord cortisol observed in vaginal delivery compared with elective caesarean section is a result of the stress of labour rather than a cause of its initiation.

d) Catecholamines

Several studies of the term human fetus have now demonstrated significantly higher cord blood catecholamine levels in those babies undergoing the stress of vaginal delivery compared with those delivered by elective caesarean section (Inglis et al 1981, Falconer & Lake 1982, Poulakka et al 1983, Irestedt et al 1982, Jones and Greiss 1982). Although not all studies have found this (Eliot et al 1980). When vaginal delivery was achieved by instrumental manipulation, eg obstetric forceps, this has been associated with significantly higher

concentration of umbilical arterial NAD than normal vertex deliveries (Falconer & Lake 1982). The highest cord catecholamine levels have been noted in babies undergoing vaginal breech deliveries (Falconer & Lake 1982, Poulakka 1982, Blouquit et al 1979). The high levels of circulating catecholamines in the human term fetus after vaginal delivery seem to return to normal resting adult levels within 12-48 hours (Eliot et al 1980,Leonetti et al 1980). In a study of fetal catecholamine release in preterm delivery Newnham et al (1984) found similar cord catecholamine concentrations in infants delivered vaginally and by caesarean section (both elective caesarean section and after labour).

3.1.3. Twins

a) Clinical Outcome

RDS appears to be more frequent in twins than in singletons and this increase cannot be entirely accounted for by the higher prematurity rate of twins over singletons (Myrianthopolous et al 1971).

The second born of twins appears to be at greater risk than the first born for the development of RDS (Farr 1975, Verduzco et al 1976, Kenny et al 1977, Neligan et al 1969, Rokos et al 1968). However, Usher (1967) and Silverman and Nisihara (1957) found no difference in incidence of RDS in first or second born twins.

The higher incidence of RDS in second born twins has been attributed to perinatal asphyxia (Rokos et al 1968, Verduzco et al 1976). However Kenney et al (1977) in a study of premature twins felt the role of birth asphyxia in the development of RDS was minor and generally overemphasized.

b) Surfactant

Parkinson et al (1980) noted that twins had significantly lower pharyngeal L/S ratio than singletons born between 29 and 35 weeks. Obladen and Gluck (1977) have shown that twins with and without RDS have markedly different phospholipids, although several reports have shown a good correlation of amniotic fluid phospholipids between cotwins and no statistical difference between twin one and twin two (Spellacy et al 1977, Sims et al 1976, Parkinson et al 1980, Norman et al 1983). However, in sporadic reports of individual twin pregnancies in which only one twin is affected it seems that the second born almost always has the more immature phospholipids and develops RDS (Caspi et al 1975, Gluck et al 1974, Dobbie et al 1983). Also there appears to be a similar relationship to birth order and lung maturity in triplets (Lemons & Jaffe 1973, Pender 1972, Weller et al 1976, Dobbie et al 1983), quadruplets, (Weller et al 1976, Wilkinson et al 1982), and quintuplets (Pritchard & McDonald 1976). The reason for this is obscure and is generally attributable to birth asphyxia. However, Weller et al (1976) postulated that there may be a link between pulmonary maturation of the presenting infant and the onset of labour.

c) Cortisol

Goldkrand (1978) found similar cord cortisol levels in three sets of twins compared with singletons. Norman et al (1983) found that amniotic fluid glucocorticoids were similar in twin one and two before labour, but that during labour concentrations of glucocorticoids were significantly increased in twin one compared with twin two.

d) Catecholamines

Poulakka et al (1983) studying 7 sets of twins found a 10-fold increase in noradrenaline concentration in twin two compared with twin one.

3.1.4 Genetic Factors

a) Clinical outcome

Several workers have now suggested that genetic factors may be important in determining which babies develop RDS. Males account for a disproportionate number of deaths compared with females (Farrell & Wood 1976) and black preterm neonates appear to have a lower incidence of fatal HMD/RDS than whites (Fujiwara & Froelick 1966, Farrel & Wood 1976).

b) Surfactant

In a study of healthy pregnant Nigerian women, Olowe and Akinkugbe (1978) found that the L/S ratios were significantly higher for a given gestational age than those obtained from a North American community. Indeed it is apparently rare to find RDS in Nigerian babies.

Myrianthopoulos et al (1971) and Verduzco et al (1976) found a significantly higher concordance rate among monozygotic than dizygotic twin pairs for the occurrence of RDS. In addition Dobbie et al (1983) noted an improved correlation for the L/S, PG/S and PI/S ratios between co-twins for monozygotic compared with dizygotic twin pairs, again suggesting that genetic factors are of some aetiologic importance in the development of RDS.

c) Cortisol

Although Furuhashi et al (1982) found significantly higher cord serum cortisol levels in male compared with female neonates, Murphy (1982) and Roopnarinesingh et al (1977) could find no sex differences in cord serum cortisol levels.

d) Catecholamines

Padbury et al (1981)[B] provided evidence suggesting that fetal catecholamines play a significant role in the sex difference of pulmonary maturity. they found significantly more AD in the fetal adrenal gland of the female rabbit fetus and the ratio of AD to total catecholamine content in the adrenal gland was greater in the female fetus. They also found a greater number of adrenergic receptors in the fetal lung of the female fetus.

However, in humans Padbury et al (1981) were unable to find any sex differences in plasma noradrenaline or adrenaline levels or in responsiveness.

3.2 Pathological factors - obstetric complications

3.2.1 Preterm rupture of membranes (PROM)

There is some evidence to suggest that premature rupture of the membranes in preterm pregnancy protects against development of RDS in the neonate. However, despite considerable research there is no general agreement regarding this.

a) Clinical outcome

Mead (1980) in a review of the management of patients with premature rupture of the membranes considered that there was approximately equal evidence to support or refute the claim that PROM accelerates fetal lung maturity.

Of the retrospective studies supporting a beneficial effect of PROM, Alden et al (1972) demonstrated an increased survival rate if PROM were present but the incidence of RDS was unaffected. Lee et al (1976), Yoon & Harper (1973), Chiswick & Burnard (1973), Sell & Harris (1977) all showed a decreased incidence of RDS with PROM for more than 24 hours. Lee et al (1976) noted the effect to be limited to neonates weighing between 1500-2500 g and was not beneficial under 1500 g. This is in contrast to Miller et al (1978) who found a relationship between increased duration of ruptured membranes and a decreased incidence of RDS only in the 1000-1500 g weight group and the incidence of RDS was unaffected when birth weight was greater than 1500 g. Thibeault & Emmanoulides (1977) found only a decreased incidence of RDS after 48 hours of ruptured membranes, whereas Berkowitz et al (1976 & 1978) found a beneficial effect after 16 hours. Berkowitz et al (1976) found a decreased incidence of RDS in neonates at equal or less than 32 weeks' gestation but not between 32-36 weeks. This contrasts with Lee et al (1976) and Berkowitz et al (1978) who found a statistically significant decrease in RDS only in neonates of 31 weeks or older gestational age.

In a prospective study of 133 cases Worthington et al (1977) found a statistically significant decrease in the incidence of RDS in newborn infants of equal or greater than 28 weeks and birth weight greater than 1000 g. However, they found no relation between duration of ruptured membranes and protection from RDS and suggested that fetal lung maturity occurs before membrane rupture. In contrast Richardson et al (1974) suggested that the incidence of RDS is inversely proportional to the duration of membrane rupture. Another two smaller prospective studies, Bauer et al (1974) - 17 cases and Cohen et al 1976) - 12 cases, support the theory of acceleration of fetal lung maturity following PROM.

Although the above retrospective and prospective surveys seem to suggest a beneficial effect from PROM this has not been a universal finding. Several retrospective surveys - Quirk et al (1979), Dimmick et al (1976), Barrada et al (1977), Schreiber & Beneditti (1980), Dluholcky et al (1976), including two large studies by Jones et al (1975) and Bada et al (1976) failed to show benefit from prolonged rupture of the membranes in the reduction of HMD.

Similarly prospective studies by Christensen et al (1976) and Taeusch et al (1979) failed to show any protective effect of prolonged rupture of membranes.

The literature regarding the effect of premature rupture of the membranes on the incidence of RDS remains confusing, with approximately equal evidence on either side. Retrospective studies have many disadvantages, eg difficulty in determining the time of ruptured membranes, confusion between RDS and respiratory infection and inaccuracy in gestational ageing. There are few prospective studies and most involve small numbers.

b) Surfactant

Biochemical studies involving measurement of the surface active phospholipids in the amniotic fluid do give a clearer picture and tend to support the idea of a beneficial effect of PROM. Gluck et al (1972)[B] and Gluck and Kulovich (1973) noted an earlier appearance of a mature amniotic fluid L/S ratio in pregnancies complicated by PROM compared with normal pregnancies. Richardson et al (1974) measured L/S ratios (liquor obtained by amniocentesis) serially in a number of cases with spontaneous PROM and showed an 'acceleration' or increasing L/S ratio independent of gestational age, implying an acceleration of lung maturity. Kulovich and Gluck (1979), Obladen et al (1979) and Bustos et al (1979) observed an earlier appearance of PG in

pregnancies complicated by PROM compared with normal pregnancies. Whittle et al (1983) observed the early appearance of PG, prior to a mature L/S ratio in complicated pregnancies. The early appearance of PG was particularly striking in amniotic fluids obtained after PROM, although the duration of membrane rupture before sampling did not correlate significantly with the presence of either PG or a mature L/S ratio. In a study of vaginal pool phospholipids in the management of PROM Brame and MacKenna (1983) found 36 patients in whom PG was initially absent and later appeared, (average number of days required for PG appearance was 3 to 9). None of these babies developed RDS. In addition Rajegowda et al (1975) noted the absence of RDS following PROM in one sib of a set of twins in two cases.

c) Cortisol

Preterm rupture of the membranes has been associated both with a reduced incidence of RDS and elevated cord blood and amniotic fluid cortisol levels (Murphy 1974[B], Bauer et al 1974, Cohen et al 1976), although this has not been a universal finding (Sybulski 1977).

d) Catecholamines

Blouquit and co-workers (1979), in a small series, found significantly raised cord catecholamine levels in pregnancies complicated by PROM (12 cases) compared with normal pregnancies (20 cases).

3.2.2 Hypertension in Pregnancy

a) Clinical outcome

Although some studies have shown a reduced incidence of RDS when the mother has hypertension (both toxaemia and essential hypertension) Chiswick & Burnard 1973, Lee et al 1976), a large retrospective review by Jones et al (1975) failed to show any relationship between toxaemia and the occurance of RDS. In addition Lee et al (1976) only found a reduced incidence of RDS when the birth weight was greater than 1500 g or gestational age greater than 32 weeks.

b) Surfactant

The early appearance of a mature L/S ratio (Gluck & Kulovich 1973, Aubry et al 1976) or more recently PG (Bustos et al 1979, Kulovich & Gluck 1979, Yambao et al 1981), has been proposed as evidence of acceleration of fetal lung maturity when hypertension complicates pregnancy. However, some studies disagree. Doran et al (1976) failed to find a mature L/S ratio in advance of normal in hypertensive pregnancies and Skjaeraasen (1979) noted a significantly delayed surfactant synthesis after 37 weeks' gestation.

c) Cortisol

Raised cortisol levels in umbilical cord blood has been noted in pregnancies complicated by hypertension compared with normal pregnancies, by some workers (Goldkrand 1978) but not by others (Roopnarinesingh et al 1977).

d) Catecholamines

Several workers have measured maternal plasma catecholamines in women who developed pregnancy induced hypertension. Some groups found higher maternal catecholamines in pregnancy induced hypertension

compared with normal pregnancies (Sammour et al 1980, Davey & MacNab 1981, Poland & Lucas 1980). Others, however, found the opposite (Tunbridge & Donnai 1981, Natrajam et al 1982). Sammour et al (1980) also found higher cord blood catecholamines in pregnancies complicated by preeclampsia compared with normal pregnancies.

3.2.3 Intrauterine Growth Retardation

a) Clinical outcome

It is a commonly held opinion that intrauterine growth retardation (IUGR) protects the fetus from developing RDS, chronic intrauterine stress in some way enhancing lung maturation, but objective evidence for this is scanty.

Procaindy et al (1980) compared 19 small for gestational age infants with 19 appropriately grown, matched for gestation, apgars, prolonged rupture of the membranes, delivery, survival rate, steroids, sex and twinning and found a higher evidence of HMD and intraventricular haemorrhage in the appropriately grown infants.

b) Surfactant

Biochemical evidence of acceleration of fetal lung maturity in growth retarded fetuses is confusing. Gunston and Davey (1978) measuring total amniotic fluid phospolipids, could find no evidence that IUGR accelerates pulmonary maturity in the fetus and the finding of early pulmonary maturity does not indicate IUGR.

Some workers have found lower L/S ratios in IUGR pregnancies than a normal reference group (Doran et al 1976, Skjaeraasen 1979, Dyson et al 1975, Dewhurst et al 1973). Others, however, have found higher concentrations of phospholipids in the amniotic fluid of IUGR fetuses (Fairbrother et al 1975, Sher et al 1981).

In a retrospective survey of 82 pregnancies resulting in the birth of a baby weighing less than 2.7 kg, Gross et al (1981) found a significantly higher percentage of PG and L/S ratio in a small for gestational age group than an appropriately grown control group. However, although there was a similar incidence of maternal complications in both groups, the gestational age was significantly greater in the small for gestational age group implying that the 'acceleration of lung maturity' noted was not necessarily due to IUGR.

c) Cortisol

IUGR and meconium stained liquor have both resulted in elevated cord cortisol levels compared with normal pregnancies (Sybulski 1977).

Whether elevated cortisol levels in obstetric complications cause an acceleration of fetal lung maturity is debatable, as no good correlation has been found between the L/S ratio and amniotic fluid or cord blood corticosteroids (Sivakumeran et al 1975, Whittle & Hill 1980), although there is an increasing trend in both amniotic fluid corticosteroids and L/S ratio as term approaches (Sivakumaran et al 1975). Norman et al (1983) made the interesting observation that during labour there was a rise in amniotic fluid glucorticoids which accompanied a rise in L/S ratio in twin one but not twin two.

There is therefore evidence which suggests that treatment of the pregnant woman and hence the fetus with exogenous corticosteroids can cause enzymatic induction resulting in elevated lung surfactant and a decreased incidence of RDS. Whether conditions which chronically stress the fetus can achieve accelerated maturation of the fetal lung via endogenous corticosteroids, remains debatable.

d) Catecholamines

Divers et al (1981) discovered significant elevations of catecholamines and catecholamine metabolites in pregnancies resulting in IUGR babies compared with normal infants, suggesting an increase in adrenergic activity in IUGR as a response to chronic stress in utero.

3.2.4 Antepartum Haemorrhage

The evidence that maternal antepartum haemorrhage causes acceleration of fetal lung maturity is unconvincing.

a) Clinical outcome

Rogers and Greenwald (1956) reported an increased incidence of antepartum haemorrhage in pregnancies complicated by HMD and in 2 large retrospective surveys, either maternal bleeding was associated with an increased incidence of RDS (Cohen et al 1960) or no protective effect of APH could be shown (Jones et al 1975).

b) Surfactant

Although one particular group of research workers (Gluck et al 1972 [B], Gluck & Kulovich 1973, Gould et al 1977) claimed an acceleration of fetal lung maturity in association with chronic retroplacental bleeding, only small numbers were involved.

c) Cortisol

No work appears to have been carried out on the fetal cortisol response to maternal haemorrhage.

d) Catecholamines

Although no work appears to have been carried out in humans on the catecholamine response of the fetus to maternal haemorrhage, experiments in animal models have given us insight into the possible outcome. Artal et al (1979)[A] using chronically instrumented pregnant ewes and their fetuses, found that a maternal blood volume depletion of 30% was needed to induce significant changes in fetal homeostasis. This reduction of maternal blood volume resulted in a 21-fold rise in NAD and a 150-fold rise in AD in the fetal circulation. The maternal catecholamines which were also raised returned rapidly to normal in the recovery period in the ewe but remained elevated for much longer in the fetus. This may be a reflection of reduced placental perfusion or an inability of the fetus to metabolise the high levels of catecholamines.

3.2.5 Birth Asphyxia

a) Clinical outcome

Although chronic stress in utero has been linked with acceleration of lung maturity in many conditions, acute perinatal stress in the form of birth asphyxia is thought to be a risk factor leading to or aggravating RDS. Birth asphyxia has been implicated in two ways, firstly by causing a decrease in pulmonary vascular perfusion leading to ischaemia (Chu et al 1967) and secondly as a result of acidosis at cellular level causing a decrease in production of phospholipids (Merritt & Farrell 1976).

The incidence of RDS has been shown to be higher among infants with abnormal fetal heart rate patterns (Martin et al 1974, Hobel et al 1972). Several authors consider that asphyxia plays a central role in RDS (James 1959, De Sa 1969, Bruns et al 1961). In addition, Jones et al (1975) noted that low apgar scores were associated with an

increased incidence of RDS.

b) Surfactant

Worthington and Smith (1978) noted that all infants with an L/S ratio greater than 2 who developed RDS had evidence of asphyxia. This confirmed a previous report by Donald et al (1973). An explanation for the effects of acidosis on the RDS was provided by Merritt and Farrell (1976) and Smith and Torday (1974). These workers showed that in rat and rabbit lung preparations, metabolic acidosis decreased lecithin biosynthesis in vitro.

However, recent work by Thibeault et al (1984) suggests that acidosis is not such a major factor in the development of RDS as has been thought.

c) Cortisol

It has been shown that intrauterine hypoxia and acidosis in the full term human fetus results in an increase in endogenous secretion of cortisol (Martinsen et al 1982).

d) Catecholamines

Comline et al (1965) studying the factors responsible for stimulation of the adrenal medulla during asphyxia in the fetal lamb, found that both direct stimulation by hypoxia and indirect stimulation via splanchnic nerves caused secretion of catecholamines by the fetal chromaffin tissue.

In early gestation the direct response predominated, however, as gestation advanced and the fetus matured the indirect response became more important and this coincided with the secretion of significant amounts of adrenaline. They also found that hypoxia was the main

stimulator of fetal chromaffin tissue, with acidosis, and hypercarbia having little effect on catecholamine secretion during fetal life.

In the human fetus several workers have demonstrated significantly raised catecholamine levels in the presence of low apgar scores or low cord pH (Nylund et al 1979, Nakai and Yamada 1978, Blouquit et al 1979, Bistoletti et al 1983, Padbury et al 1982, Messow-Zahn et al 1978, Falconer & Lake 1982). Similar catecholamine responses in the preterm human fetus have also been demonstrated (Newnham et al 1984).

FHR tracings indicative of fetal distress, eg moderate/severe variable decelerations and late decelerations have been associated with significantly raised concentrations of catecholamines (Bistoletti et al 1983, Padbury et al 1982). Hervonen and Korkala (1972) demonstrated that human fetal chromaffin tissue could respond to hypoxia. They studied the effect of hypoxia on the catecholamine content of human fetal abdominal paraganglia and adrenal medulla using extra uterine perfusion techniques on second trimester previable fetuses obtained at hysterotomy. They found that the adrenal medulla did not respond to hypoxia as clearly as the paraganglia. They concluded that in hypoxia release of catecholamines by the paraganglia was caused by direct stimulation of the paraganglionic cells as no functional nerve endings could be demonstrated at this gestational age during fetal life. They considered that the effect of hypoxia on medullary chromaffin cells was mediated by the preganglionic innervation and it may be that this alternative catecholamine secretion mechanism would be dominant at term. However, during the second trimester, the direct hormonal regulation of the paraganglia seems to be dominant.

3.2.6 Maternal Diabetes

a) Clinical outcome

Epidemiological studies have shown that babies born to diabetic mothers are more prone to develop RDS (De Sa 1969, Farrell & Avery 1975).

b) Surfactant

Gluck and Kulovich (1973) and Gluck et al, (1972)[B] were the first to report a delay in the normal L/S ratio maturation in diabetic pregnancies. Class A, B and C diabetics showed a 1-2 week delay in maturation whilst class D and E diabetics showed an accelerated maturation. Whitfield et al (1972 and 1973) suggested that the normal terminal rise in L/S ratios did not occur in diabetic pregnancies and in some cases there was a fall in L/S ratio when serial liquor samples were taken. These original observations have been confirmed by other workers (Polishuk et al 1973, Aubry et al 1976, Singh et al 1974). However, Dahlenburg et al (1977) found a similar rise in L/S ratio in class A,B,C diabetics compared with non diabetics and little correlation with gestational age and L/S ratio in classes D,F and R diabetics, but almost one third of those with an L/S ratio greater than 2 developed RDS. The occurrence of RDS in association with an L/S ratio equal or greater than 2 has often been reported in diabetic pregnancies (Donald et al 1973, Farrell 1976, Gabert et al 1973, Dunn et al 1974, Mueller-Heubach et al 1978). Cunningham et al (1978) found reduced or absent PG in diabetic amniotic fluids between 34 and 37 weeks' gestation, RDS occurring in 6 diabetic mothers delivered preterm with L/S ratios equal or greater than 2 - PG was absent in 5 of the cases. Kulovich and Gluck (1979) noted a significant delay in the appearance of PG in pregnancy induced (Class A) diabetics. They also felt that the appearance of PG marks the 'final' maturation of

surfactant, and that after the appearance of PG a diabetic pregnancy of any class can be safely delivered free of RDS.

Recent studies, however, (James et al 1984) question the assumption that there is a delay in fetal lung maturation in diabetic pregnancies.

c) Cortisol

No significant differences in cord blood or amniotic fluid cortisol has been found in diabetic compared with normal pregnancies (Sybulski 1977, Goldkrand 1978).

d) Catecholamines

While Stern et al (1968) found a diminished catecholamine excretion rate in newborn infants born to diabetic mothers, other researchers (Young et al 1979, Artal et al 1982) found higher umbilical arterial (UA) and umbilical venous (UV) catecholamines in diabetic compared with normal mothers indicating an excessive sympatho adrenal activity at birth in infants of diabetic mothers. Hertel et al (1982) found that while there was no statistically significant difference in the UA, NAD and AD levels in infants of diabetic compared with normal mothers at birth, by 2 hours post partum the NAD and AD levels were significantly higher in infants of diabetic mothers compared with controls.

There is therefore evidence in the literature for changes in the fetal stress hormones cortisol and catecholamines in each of the factors thought to influence fetal lung maturity, (Table 3.1) and this lends support to the idea of a final common pathway linking stress and lung maturity as outlined in Figure 2.2.

TABLE 3.1 Factors considered to influence fetal lung maturity

Factors Enhancing Lung Maturity	Factors Predisposing To RDS
LABOUR	ELECTIVE CAESAREAN SECTION
PROM	BIRTH ASPHYXIA
HYPERTENSION	DIABETES
IUGR	2nd TWIN
FEMALE	MALE

CHAPTER 4

Aims of the Study

Aims of the Study

1 To evaluate the effect of obstetric factors on neonatal lung maturity.

The factors studied are gestational age (Chapter 6), method of delivery (Chapter 7), multiple pregnancy (Chapter 8), condition of the infant at birth (Chapter 9) and various obstetric complications (Chapter 10).

2 To investigate the control of respiratory maturational processes (Chapters 11, 12 and 13).

3 To evaluate human fetal adrenal cortical and medullary activity from mid-trimester until term (Chapters 6 and 7).

CHAPTER 5

Materials and Methods

5.1 Subjects

A total of 381 babies was investigated in this study. Figure 5.1 shows the distribution of gestational ages and Figure 5.2 shows the birthweights in the study. The study concentrated on the babies most likely to develop respiratory difficulties, namely those born prior to 36 weeks' gestation. A group of 'term' babies (36-41 weeks) was also investigated in order to determine more clearly the influence of gestational age on the various parameters measured, and also to establish an adequate 'normal' data base where some of the parameters, namely the fetal catecholamines, had not been adequately assessed.

There were 189 babies in the preterm group (24-35 weeks) - 91 delivered vaginally, 51 by elective caesarean section and 47 by caesarean section following the onset of labour.

In the 'term' group there were 192 babies - 118 delivered vaginally, 45 by elective caesarean section and 29 by caesarean section following the onset of labour.

In the vaginally delivered groups the method of delivery is shown in Table 5.1, and the type of anaesthesia employed in Table 5.2

The indications for elective caesarean section are shown in Tables 5.3 and 5.4 and type of anaesthesia employed in Table 5.5.

The indications for caesarean section following the onset of labour are shown in Table 5.6 and the type of anaesthesia employed in Table 5.7.

Since multiple pregnancies are often complicated by preterm birth it is not surprising that the preterm group included 25 sets of twins and 3 sets of triplets. The term group included 36 sets of twins for comparison with the preterm twins.

Table 5.8 shows the twin pregnancies by gestational age and method of delivery.

The 3 sets of triplets were born at 26 weeks (vaginally), 31 weeks (caesarean section following labour) and 33 weeks (caesarean section following labour).

In the investigation of respiratory problems, although the simple division of cases into preterm and term appeared adequate, it was obvious that the preterm babies required to be further categorised, based on the likelihood of them developing respiratory problems.

The groups were established arbitrarily into Group I ($\leq$ 29 weeks) when functional respiratory immaturity was almost certain; Group II (30-33 weeks), when respiratory immaturity was still common but associated with fewer problems; and Group III (34-35 weeks) when the respiratory maturational processes were clearly active and respiratory problems unlikely.

So that the numbers were large enough for meaningful statistical analysis, all of the babies, singletons, twins and triplets have been grouped together except when a direct comparison between singleton and twins was made. Where this was done (Chapter 8) there was little difference between singleton and twins in clinical outcome, amniotic fluid phospholipids or the fetal stress hormones in the preterm group (26-35 weeks) of babies studied.

5.2 Collection of blood and amniotic fluid samples

5.2.1 Umbilical cord blood

Immediately after delivery and before separation of the placenta a portion of umbilical cord was isolated between 2 clamps, the baby's end of the cord always being clamped first as Padbury et al (1981)[A] have shown in the fetal lamb a rapid increase in both NAD and AD

subsequent to cord clamping. At least 5 ml of blood was obtained first from the umbilical arteries and then the umbilical vein. One ml of blood was used for pH and blood gas measurement. The remaining blood was spun down under ice using a centrifuge (3,000 revs/min for 5 minutes). The supernatant was then drawn off and divided into 2 portions, one for cortisol and one for catecholamine assay, and stored at -70 C until assayed (within 6 weeks of collection).

5.2.2 Maternal blood

Immediately after delivery of the baby 5 ml of blood was withdrawn from an antecubital fossa vein. The blood was again spun down under ice, separated into 2 portions for cortisol and catecholamine measurement and stored at -70 °C until assayed.

5.2.3 Amniotic fluid specimens

Amniotic fluid samples were collected within 24 hours of delivery. Amniotic fluid was obtained by aspiration under direct vision from a pool of amniotic fluid high in the vagina if membranes had ruptured spontaneously or immediately after artificial rupture of the membranes. At caesarean section amniotic fluid was obtained by needle aspiration of the intact sacs. If an amniotic fluid sample could not be obtained or if it was heavily contaminated with blood a gastric aspirate was obtained from the baby immediately after birth.

Before analysis, the amniotic fluid was centrifuged at 3,000 rpm for 5 minutes and stored at -20 °C after centrifugation.

5.3 Catecholamine assay

Samples for catecholamine assay were stored at -70 °C, all were assayed within 6 weeks of collection.

Plasma noradrenaline (NAD) and adrenaline (AD) levels were measured by the radioenzymatic method of Da Prada and Zurcher (1976).

This assay depends on the methylation of catecholamines by catechol-o-methyl transferase (COMT) with the transfer of a labelled methyl group from s-adenosyl-l-methionine (SAM) to the catecholamine, ie

$$NAD + SAM(H^3) \xrightarrow{COMT} H^3 \text{ NORMETANEPHRINE}$$

Certain modifications to the method of Da Prada and Zurcher were included (Ball et al 1981).

1 Plasma was used without deproteinization but containing ethyleneglycolbisamino-ethylathertetra acetate (3 n mols/litre).

2 Plasma (100 µℓ) with and without internal standard was added to incubates containing Tris (1 mol/litre), magnesium chlorate (75 m mol/litre) benzyloxamine (dopa decarboxylase inhibitor; 0.5 m mol/litre), 20 µℓ of catechol O-methyltransferase solution and 3.6 Ci of s-adenosyl-l-(methyl- H) methionine (5-15 Ci/mmol). The total incubation volume was 150 µℓ and pH 8.4.

3 The 3-methoxy derivatives were extracted into 1 ml of ether in the presence of tetraphenylboron and both extracted into 50 µℓ of hydrochloric acid (0.1 mol/Litre). This could be applied directly to thin layer chromatography and the individual metabolites separated and identified under ultraviolet light.

The separated amines are then quantified using estimators of radioactivity.

The limit of detection calculated as twice the blank value was 0.1 n mol/litre for NAD and AD. The intrassay coefficient of variation for NAD was 8.6% and AD 11.2%.

This radioenzymatic method for the measurement of catecholamines is extremely sensitive and requires a small sample size.

5.4 Cortisol assay

Total cortisol in umbilical cord and maternal venous plasma was measured using the commercially available Amerlex Cortisol Radioimmuno assay Kit (Amersham International plc, Amersham UK). This assay covers the approximate range 0-1700 n mol/litre. Where levels greater than 1700 n mol/litre were found, measurement was made following dilution of the samples.

5.5 Amniotic fluid analysis

5.5.1 The lung phospholipid profile

The amniotic fluid was centrifuged at 3,000 rpm (about 1100 g) for 5 minutes; when analysis was delayed the amniotic fluid was stored at -20 C after centrifugation.

The technique of two-dimensional thin-layer chromatography has been described (Kulovich et al 1979). The phospholipids are extracted from 3-4 ml amniotic fluid, using a chloroform-methanol mixture as in the routine L/S ratio technique (Borer & Gluck 1971). Cold acetone is used to precipitate the surface-active phospholipids, and this precipitate is resuspended in 30 µl chloroform, 15 µl of which is then injected onto a thin layer of silica. The thin layer is made from a slurry of silica gel H with 5% ammonium sulphate and spread onto a 20 x 20 cm borosilicate glass plate. A standard two-dimensional chromatography technique is used. The first solvent system comprises chloroform, methanol, water, glacial acetic acid (65, 25, 4, 8, v/v/v/v), and the solvent front is allowed to develop to 10 cm from the origin. Theplate is removed from the chromatography tank, dried at 70 C for 5 minutes, turned at right-angles and placed in the second solvent system of tetrahydrofuran, methylal, methanol, 2N ammonium hydroxide (40, 28.5, 7.8, 4.2, v/v/v/v).This new solvent front is also allowed to develop for 10 cm; the plate is removed,

dried at 100 °C and then charred at 250 °C. Figure 5.3 shows the separation of the phospholipids. The L/S ratios, phosphatidylglycerol/sphingomyelin (PG/S) ratios, and phosphatidyl-inositol/sphingomyelin (PI/S) ratios were estimated using densitometry (Kulovich et al 1979).

5.5.2 The lecithin and phosphatidylglycerol concentrations

The lecithin and phospatidylglycerol concentrations were determined by a phosphate analysis technique following 2 dimensional thin layer chromatography (TLC).

The phosphate assay was based on the technique of Kankara et al (1971) and is described below.

a) Recovery of phospholipids from TLC

The phospholipids were scraped from the plate into clean tubes ready for digestion, and the gel blank was made from an area of silica gel scraped off from below the origin, where both solvents had been in contact with the gel but not with the lipid extract (Figure 5.4). The concentration of phosphorus in the gel blank is directly proportional to the area of silica removed, regardless of the presence of phospholipid, therefore a constant area of silica gel is removed for each phospholipid spot and for the blank. This area is equivalent to the area of the largest phospholipid spot present which is usually lecithin.

b) Digestion

2 ml 5M H_2SO_4 was added to each tube. The digestion was carried out at 180 °C for 2 hours. The tubes were cooled. 0.1 ml of 30% H_2SO_4 was added to each tube, and digestion continued at 180 °C for a further 2 hours.The volume in each tube by the end of the digestion was only 0.5ml.

c) Colour Development

9.5 ml double-distilled water was added to each tube and a set of standards, containing from 0 to 0.3 moles of inorganic phosphate in 10 ml of 1M H_2SO_4, prepared.

2 ml of freshly prepared mixture of equal volumes of 5% w/v ammonium molybdate and Fiske-Subba Row Reagent were added to each tube.

The contents of each tube were mixed using a vortex mixer. The tubes were placed in a boiling water bath for 7 minutes. The tubes were then centrifuged for 2 minutes at 370g to precipitate the silica gel. A spectrophotometer (Pye Unicam, SP600) was used and the optical density determined at 830 nm in standard 3 ml cuvettes. Reagent blanks, the gel blank, and the eluted lipids were assayed simultaneously.

A typical standard curve is shown in Figure 5.5. The phosphate content was determined for each lipid from such a curve after allowance had been made for the amount of silica gel containing the lipid.

5.6 Blood and gases

Measurements of pH and Po_2 on umbilical arterial, umbilical venous and maternal venous blood were performed on a Corning 178 pH/Blood Gas Analyzer. Utilizing its microprocessor the '178'

calculates bicarbonate ion concentration, total Co2 and base excess. The Corning 178 automatically calibrates itself.

5.7 Gestational Age

Gestational age, determined from the menstrual history and clinical assessment of the uterine size at the first antenatal clinic in all cases was confirmed by an early ultrasound scan (< 20 weeks) in 95% of cases.

5.8 Respiratory Distress Syndrome

Evaluation of the newborn was by the paediatric staff, the diagnosis of RDS being based on the clinical features (tachypnoea, grunting, sternal recession and rib retraction) present for at least 24 hours and the radiological appearance of the lung field (diffuse granularity with a superimposed air bronchogram).

On the basis of the ventilatory support required to maintain satisfactory oxygenation, RDS was assessed as mild when only enriched ambient oxygen was required, moderate when constant positive airways pressure (CPAP) was needed, and severe when intermittant positive-pressure ventilation (IPPV) had to be used.

5.9 Method of anaesthesia

For elective caesarean section under general anaesthesia, Ranitidine 150 mg orally is given the night before and morning of operation.

Prior to induction of anaesthesia, left lateral tilt is employed, and oxygen 3 litres min via a Hudson mask for 3 minutes if given. Induction of anaesthesia is achieved with Atropine 0.5 mg IV, Thiopentone 3-4 mg/kg and Suxamethonium 1.5 mg/kg. Anaesthesia is

maintained with 50% nitrous oxide and oxygen plus 0.5% Halothane until delivery.

At emergency caesarean section Cimetidine 200 mg IM is given at time of decision to operate.

Epidural anaesthesia was induced via an epidural catheter inserted into the epidural space at L3-L4. For elective epidural caesarean section 15-25 ml of 0.5% plain Bupivicaine is used to obtain an anaesthetic level of T5. For emergency epidural caesarean section 20-30 ml of 2% Lignocaine and Adrenaline (0.2 ml 1:1000 in 20 ml) is used.

For labour analgesia 6-10 ml of 0.25% plain Bupivicaine is used to obtain an anaesthetic level of T10.

5.10 Statistical Methods

Note, in the Probability Plots described below;

*	represents 1 observation
+	represents 10 observations
a number	represents the number of observations at that point.

5.10.1 Catecholamines

Neither the fetal nor the maternal catecholamine levels were normally distributed. Figures 5.6, 5.7 and 5.8 show the distribution and probability plots for umbilical arterial NAD, AD and NAD/AD ratios, and Figures 5.9, 5.10 and 5.11 show the maternal NAD, AD and NAD/AD ratios. Figures 5.12-5.17 show the distribution and probability plots following logarithmic transformation of the catecholamine levels.

Comparison of catecholamine levels between various groups were made using Student's T test following logarithmic transformation of

the catecholamine levels, where a normal distribution was obtained - Log UA NAD, AD and NAD/AD ratios (Figures 5.12, 4.13 and 5.14). Where there was still doubt regarding the normality of the distribution - maternal NAD and AD and NAD/AD ratios (Figures 5.15, 5.16, and 5.17), a Mann Whitney test was used).

5.10.2 Cortisol

Figures 5.18 and 5.19 show the distribution and probability plots for umbilical arterial and maternal venous cortisol levels.

Comparisons of cortisol levels between groups was made using Student's T test for maternal venous cortisol levels. However, the UA cortisol data showed a slightly skewed distribution and a Mann Whitney test was used.

5.10.3 Amniotic Fluid Phospholipids

The distribution and probability plots for the L/S and PG/S ratios are described in Figures 5.20 and 5.21. Neither the L/S, nor PG/S ratios were normally distributed and comparisons of ratios between groups were made using the Mann-Whitney test.

The distribution and probability plots for the lecithin concentrations and phophatidylglycerol concentrations are shown in Figures 5.22 and 5.23.

Comparisons of levels between groups were made using Student's T test.

5.10.4 Clinical parameters

Comparison of the occurrence of clinical parameters (eg occurrence of RDS, death etc) between groups was made using the method of Chi- square (χ^2), except when the numbers concerned made this test

inappropriate. In this circumstance Fisher's test of exact probability was used.

Statistical analysis was performed on the Glasgow University main frame computer, employing a Minitab statistical package.

Table 5.1 Vaginally Delivered Group - Method of Delivery

	Number
Term (36-41 weeks)	
SVD	78
Forceps	13
Rotational Forceps	10
Breech	17
	118
Preterm (24-35 weeks)	
SVD	48
Forceps	28
Rotational Forceps	4
Breech	11
	91

Table 5.2 Vaginally Delivered - Type of Anaesthesia

	Number of Babies	
	Term	Preterm
Pethidine Alone	30	15
Pudendal Block	6	8
Epidural Block	57	40
Nil	25	28
	118	91

Table 5.3 Indications for Elective Caesarean Section

Term (36-41 weeks) Group

	Number of Babies
Breech Presentation	15
Placenta Praevia	8
Suspected Cephalopelvic Disproportion	2
Suspected Intrauterine Growth Retardation	1
Previous Caesarean Section	13
Maternal Disease	2
Other	3
	45

Table 5.4 Indications for Elective Caesarean Section

Preterm (24-35 weeks) Group

	Number of Babies
Fetal Distress	4
Placenta Praevia	1
Suspected IUGR	11
Severe Maternal Hypertension	25
Rhesus Sensitized	7
Other	3
	51

Table 5.5 Type of Anaesthesia for Elective Caesarean Section

	Number of Babies
Term (36-41 weeks)	
Epidural	36
General Anaesthesia	9
Preterm (24-35 weeks)	
Epidural	16
General Anaesthesia	35

Table 5.6 Indications for Caesarean Section Following the Onset of Labour

	Number of Babies
Term (36-41 weeks) Group	
Failure to Progress in Labour	6
Fetal Distress	11
Suspected Cephalo Pelvic Disproportion	8
Other	4
	29
Preterm (24-35 weeks) Group	
Failure to Progress in Labour	2
Fetal Distress	3
Preterm Breech in Labour	15
APH	2
Abruption	6
Placeta Praevia	4
Intra Partum Bleeding	3
Severe Maternal Hypertension	2
Previous Caesarean Section	2
Rhesus Sensitized	1
Intrauterine Infection	1
Multiple Pregnancy	6
	47

Table 5.7 Type of Anaesthesia for Caesarean Section Following the Onset of Labour

	Number of Babies
Term (36-41 weeks) Group	
Epidural	17
General Anaesthesia	12
Preterm (24-35 weeks) Group	
Epidural	12
General Anaesthesia	35

Table 5.8 Twin Pregnancy by Gestational Age and Method of Delivery

Delivery	Gestation (Weeks)			
	28-29	30-33	34-35	36-39
Vaginal	4	5	4	28
Elective C/S	0	1	3	3
Emergency C/S	1	2	4	5
	5	8	11*	36

* + One twin pregnancy where first twin delivered vaginally but second delivered by emergency C/S.

TOTAL 61 sets of twins

Figure 5.1

Gestational Age (Weeks) Distribution

EACH * REPRESENTS 2 OBSERVATIONS

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
24.	1	*
25.	3	**
26.	6	***
27.	4	**
28.	11	******
29.	21	**********
30.	13	*******
31.	17	*********
32.	19	**********
33.	25	************
34.	36	******************
35.	33	*****************
36.	24	**********
37.	25	************
38.	56	****************************
39.	36	******************
40.	35	*****************
41.	16	********

Figure 5.2

Birthweight (Kg) Distribution

BW

EACH * REPRESENTS 2 OBSERVATIONS

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.5	8	****
1.0	38	*******************
1.5	45	**********************
2.0	85	**
2.5	68	**********************************
3.0	63	********************************
3.5	51	**************************
4.0	17	*********
4.5	4	**
5.0	1	*

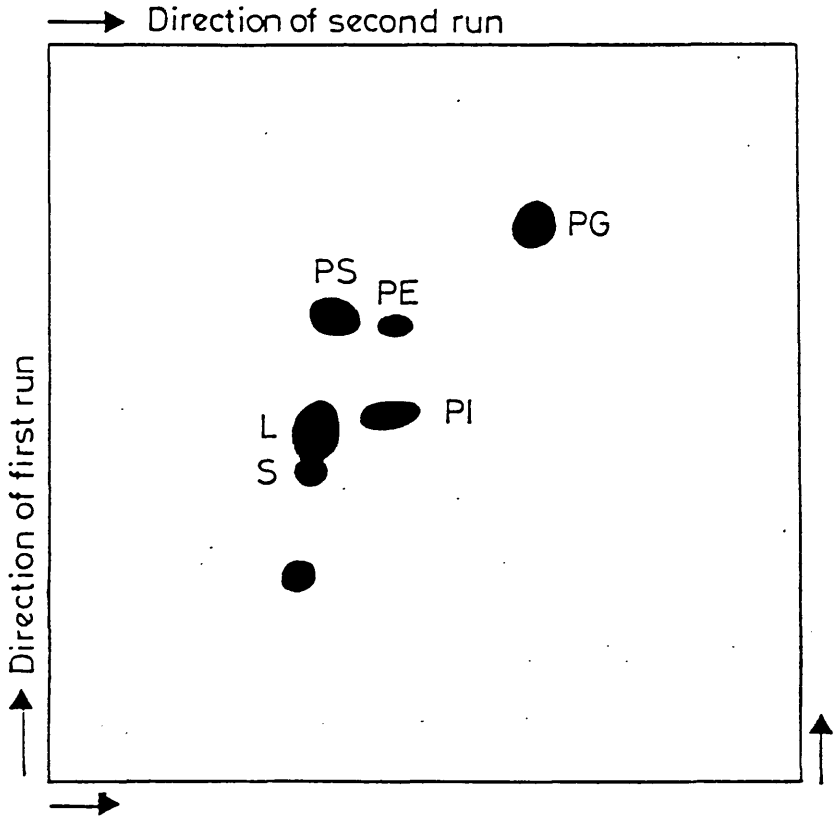


Figure 5.3 Phospholipid profile after two-dimensional thin-layer chromatography. L=Lecithin. S=Sphingomyelin. PI=Phosphatidylinositol. PS=Phosphatidylserine. PE=Phosphatidylethanolamine. PG=Phosphatidylglycerol.

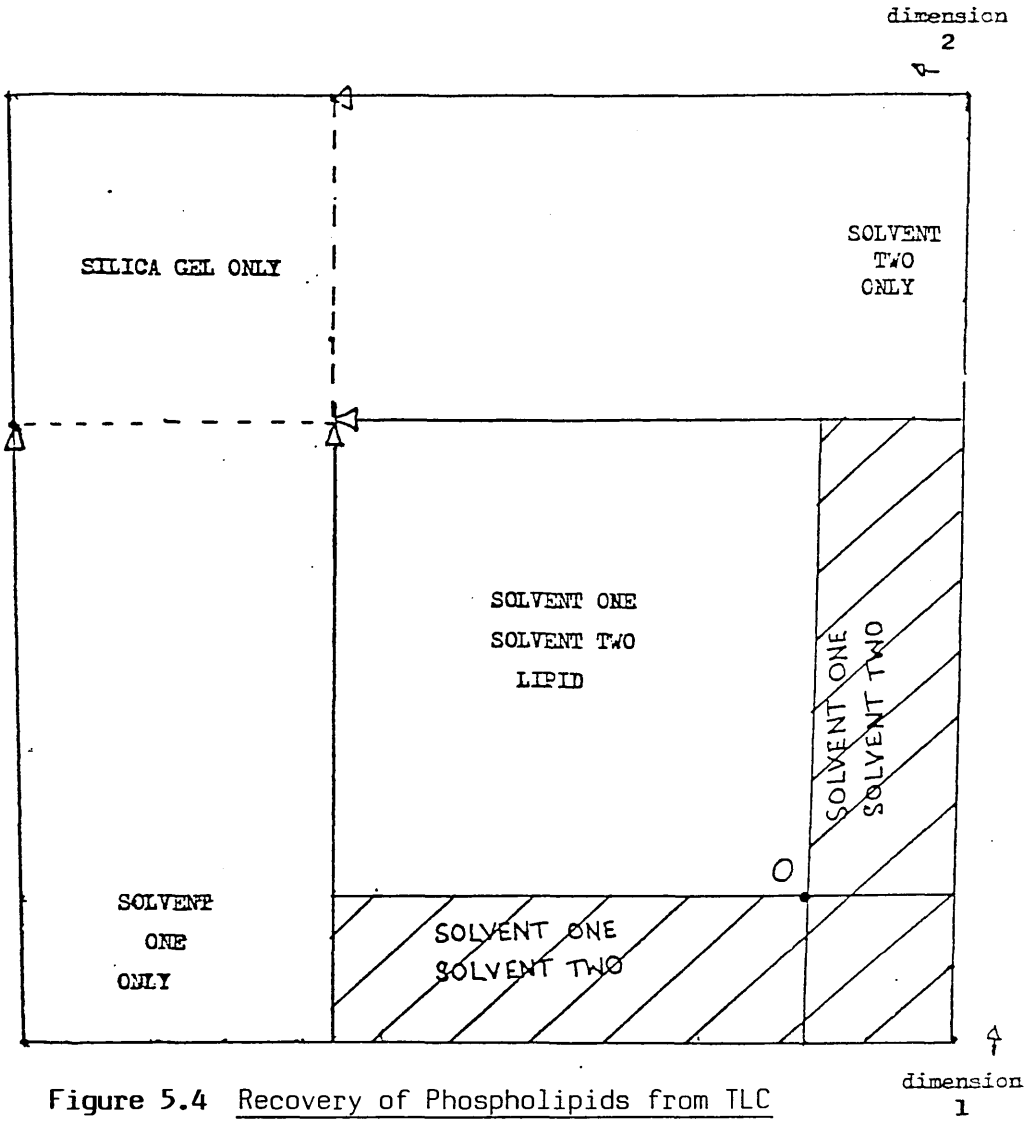


Figure 5.4 Recovery of Phospholipids from TLC

Removal of the Gel Blank

The gel blank was made from an area of silica gel scraped off from below the origin, where both solvents had been in contact with gel but not with the lipid extract.

The hatched area represents the silica gel in contact with both solvents and not with the lipid extract.

Figure 5.5 A Typical Standard Curve

The phosphate content was determined for each lipid from such a standard curve.

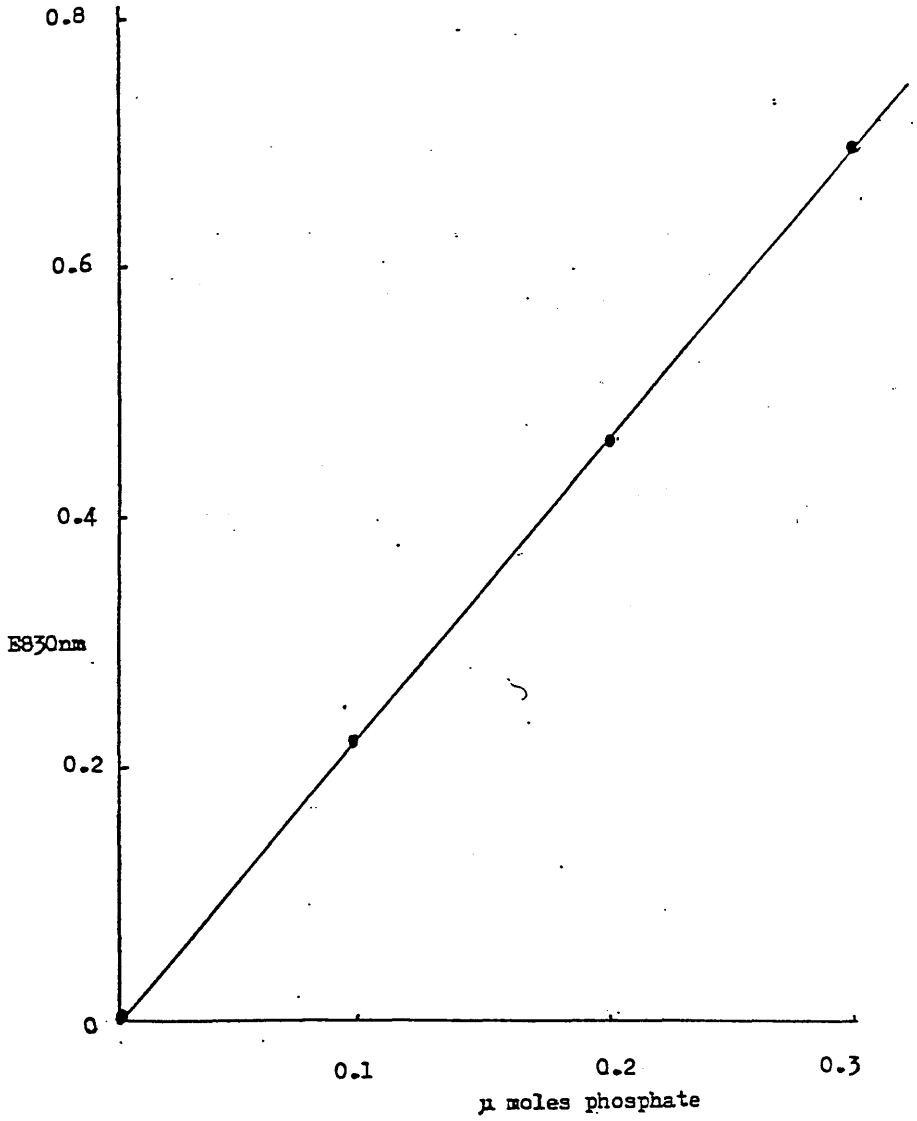


Figure 5.6 Distribution and Probability Plot for UA NAD (nmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	163	**********
20.	94	**********
40.	34	*******
60.	18	****
80.	3	*
100.	6	**
120.	0	
140.	2	*
160.	2	*
180.	0	
200.	2	*
220.	1	*
240.	0	
260.	0	
280.	0	
300.	1	*

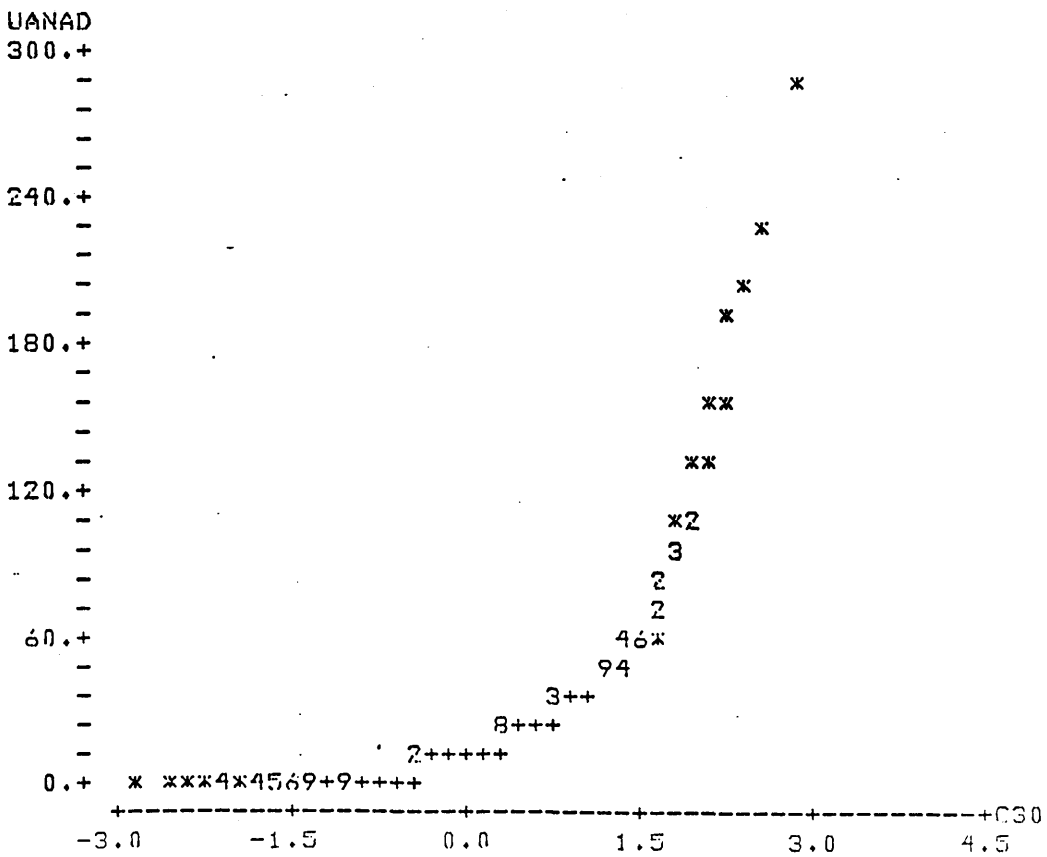


Figure 5.7 Distribution and Probability Plot for UA AD (nmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	107	**********
2.	92	**********
4.	52	**********
6.	29	******
8.	24	*****
10.	4	*
12.	0	
14.	1	*
16.	0	
18.	0	
20.	0	
22.	0	
24.	0	
26.	0	
28.	1	*
30.	1	*

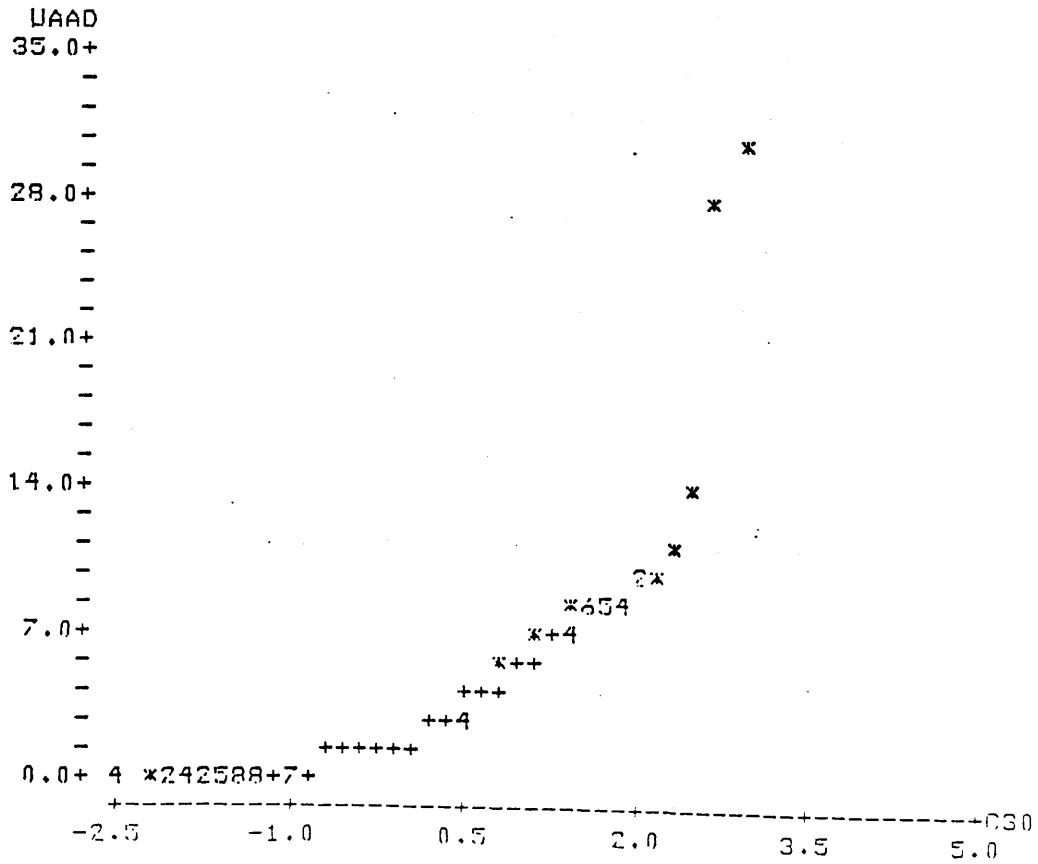


Figure 5.8 Distribution and Probability Plot for UA NAD/AD Ratio

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	140	**********
10.	138	**********
20.	13	***
30.	6	**
40.	2	*
50.	6	**
60.	1	*
70.	2	*
80.	0	
90.	0	
100.	1	*
110.	2	*

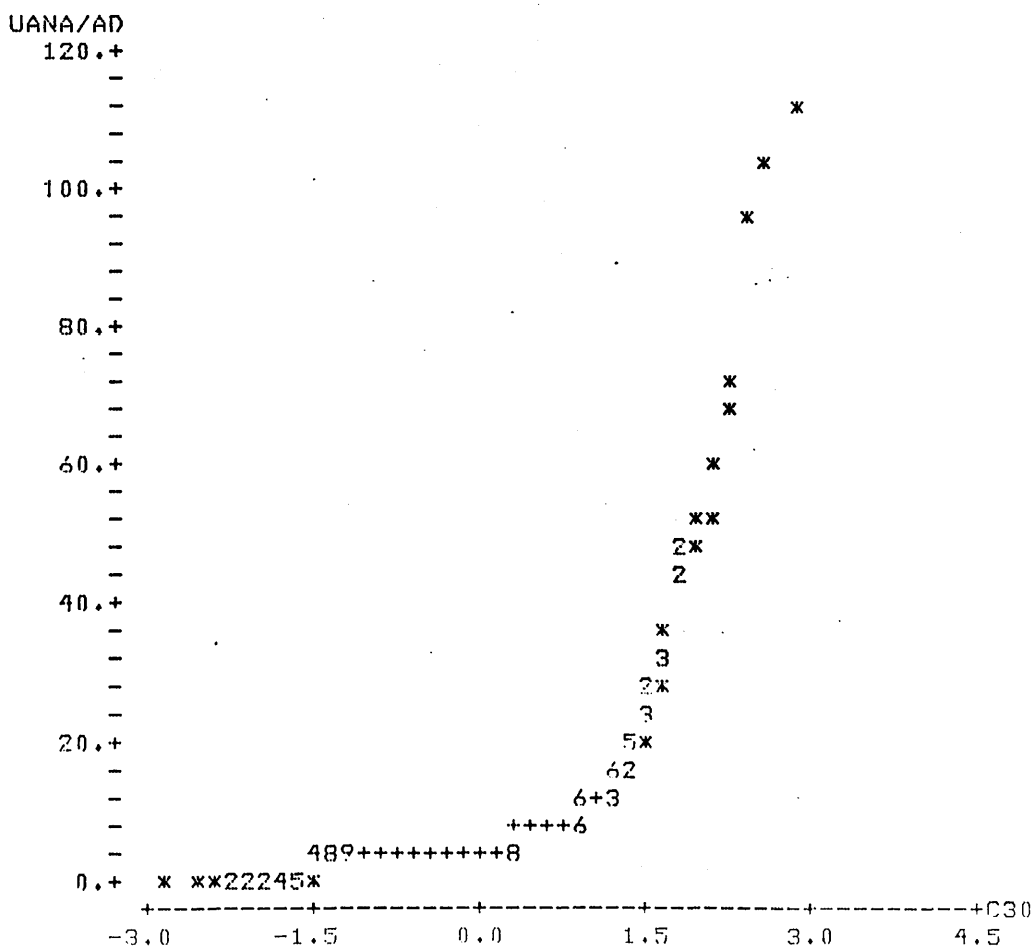


Figure 5.9 Distribution and Probability Plot for MV NAD (nmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	7	**
1.	105	**********
2.	152	**********
3.	34	********
4.	7	**
5.	0	
6.	1	*
7.	2	*
8.	0	
9.	0	
10.	1	*

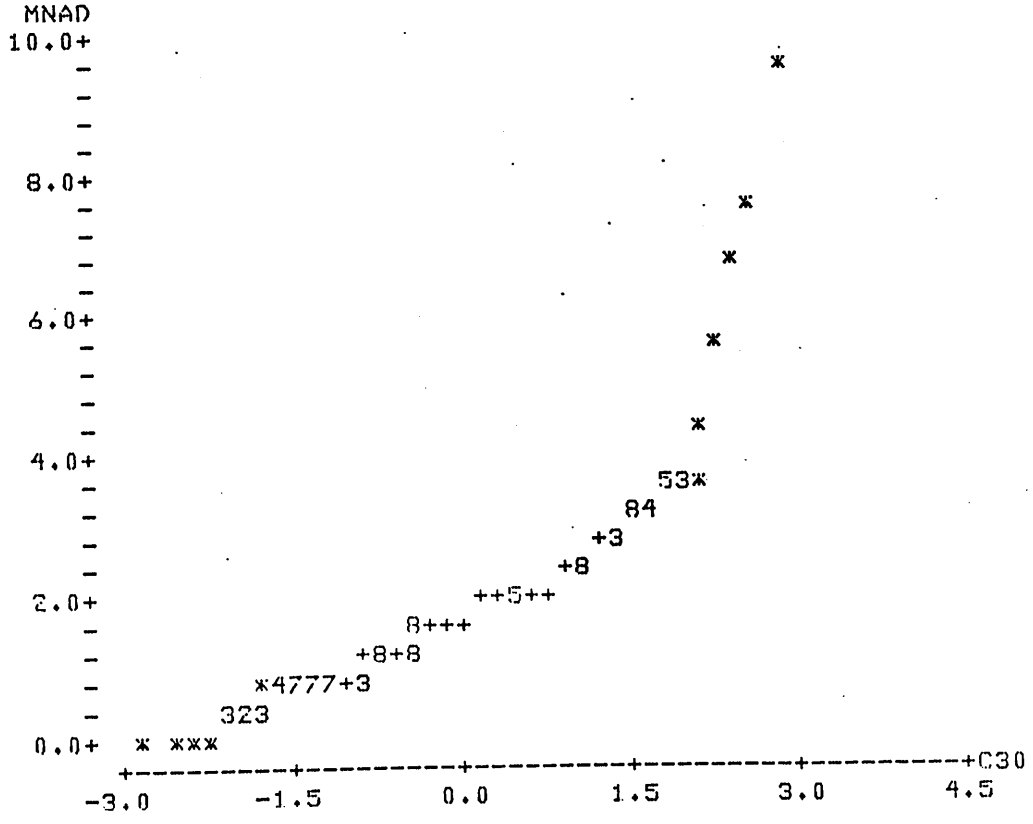


Figure 5.10 Distribution and Probability Plot for MV AD (n mol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.0	39	********
0.5	156	**********************************
1.0	77	*****************
1.5	8	**
2.0	2	*
2.5	2	*
3.0	0	
3.5	0	
4.0	2	*

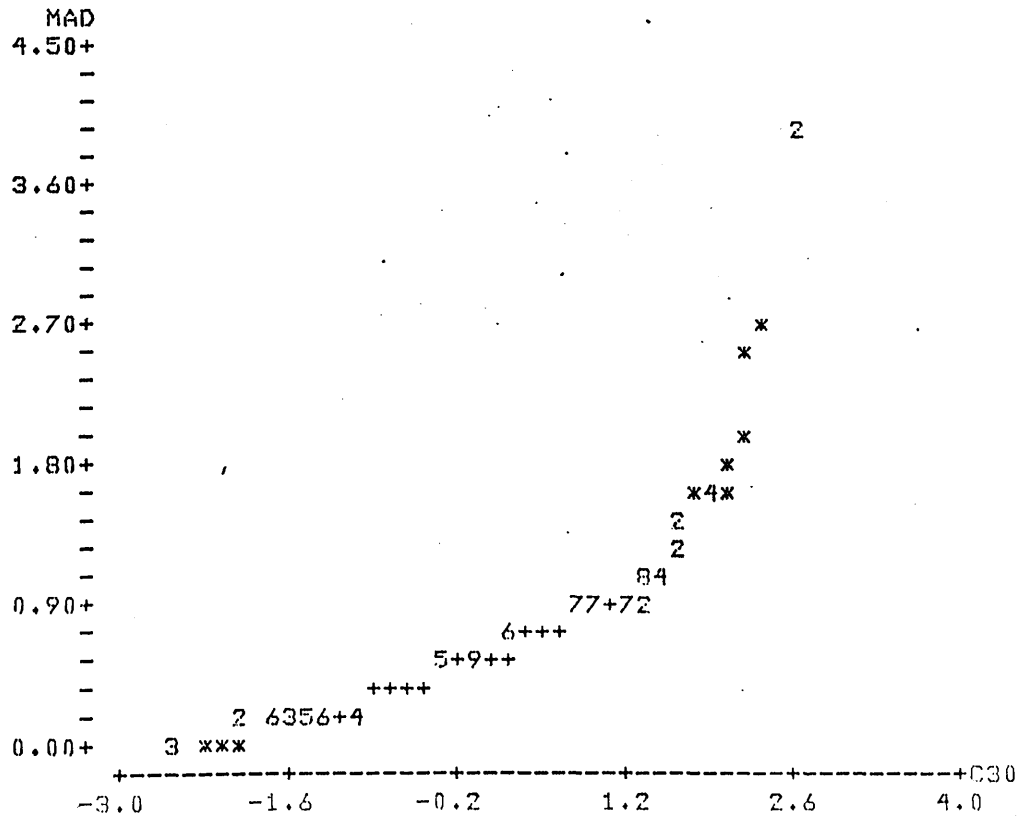


Figure 5.11 Distribution and Probability Plot for MV NAD/AD Ratio

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	108	**********
5.	144	**********
10.	17	****
15.	4	*
20.	9	**
25.	1	*
30.	0	
35.	0	
40.	0	
45.	0	
50.	0	
55.	0	
60.	0	
65.	0	
70.	2	*

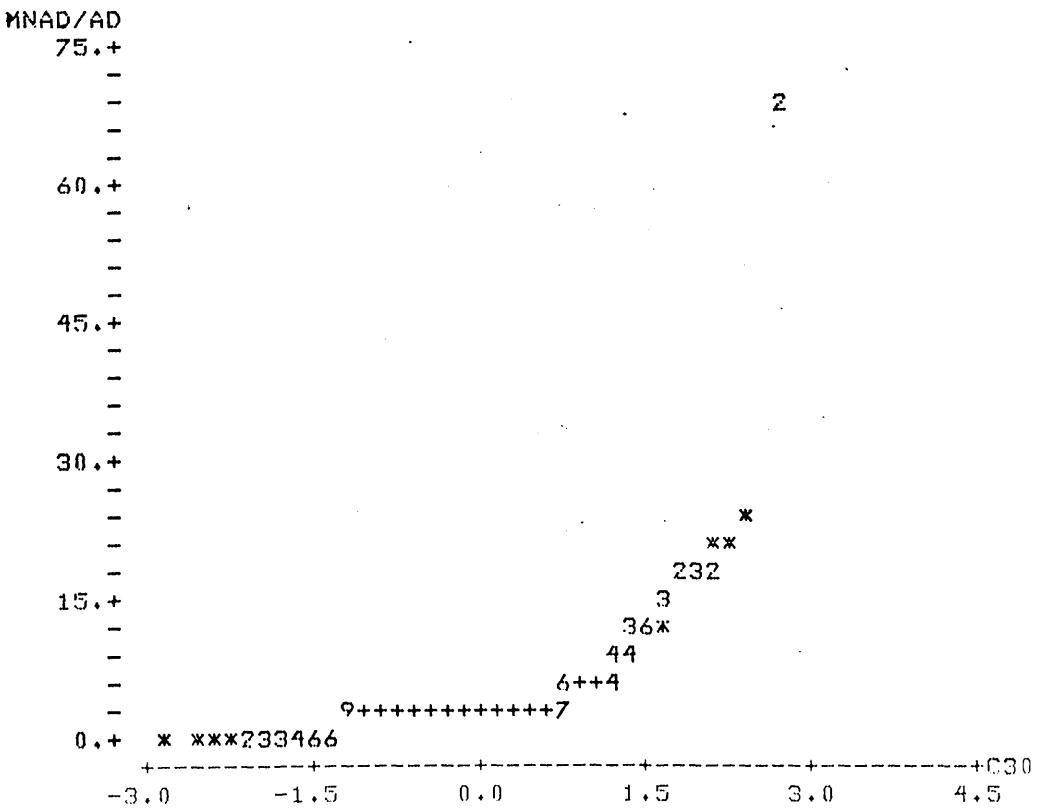


Figure 5.12

Distribution and Probability Plot for Log_{10} UA NAD

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
-0.6	1	*
-0.4	0	
-0.2	2	**
0.0	10	**********
0.2	16	**********
0.4	32	**********
0.6	41	**********
0.8	34	**********
1.0	38	**********
1.2	44	**********
1.4	43	**********
1.6	31	**********
1.8	18	**********
2.0	8	********
2.2	5	*****
2.4	3	***

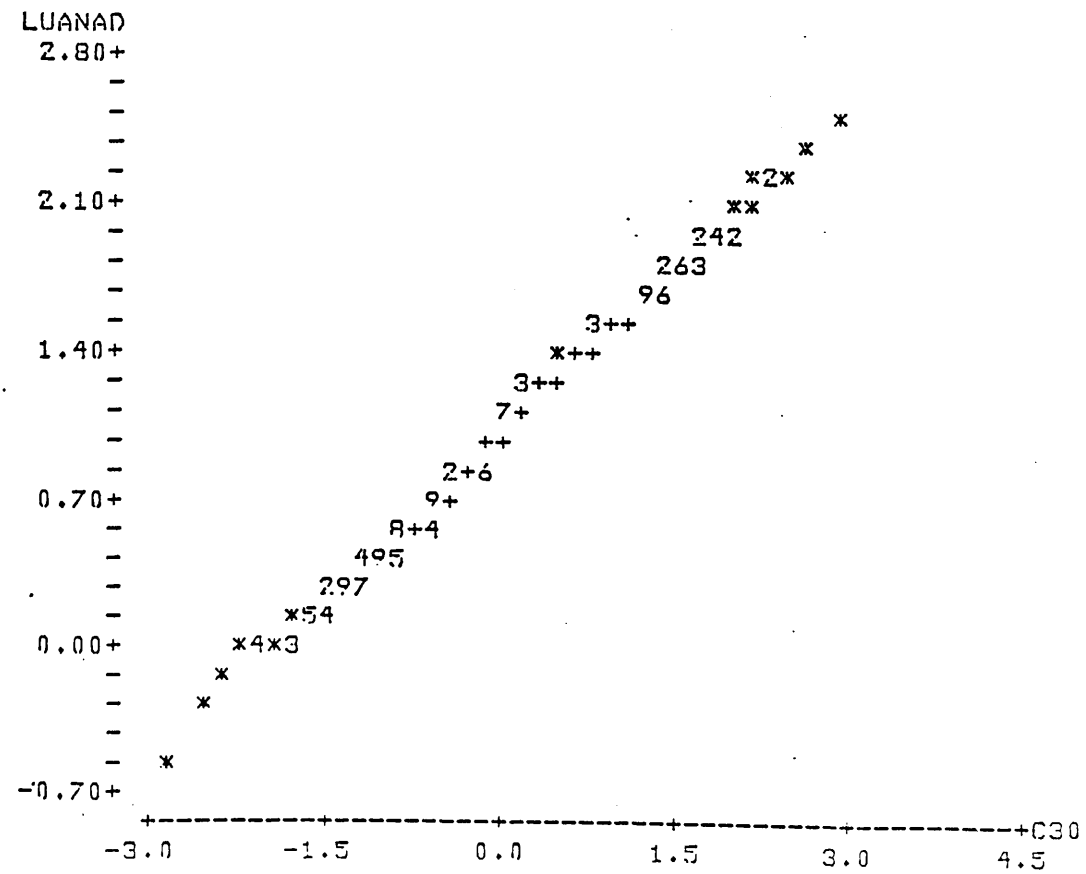


Figure 5.13 Distribution and Probability Plot for Log_{10} UA AD

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
-1.0	5	***
-0.8	3	**
-0.6	5	***
-0.4	34	******************
-0.2	32	*****************
0.0	50	**************************
0.2	34	******************
0.4	40	*********************
0.6	53	****************************
0.8	34	******************
1.0	18	*********
1.2	1	*
1.4	2	*

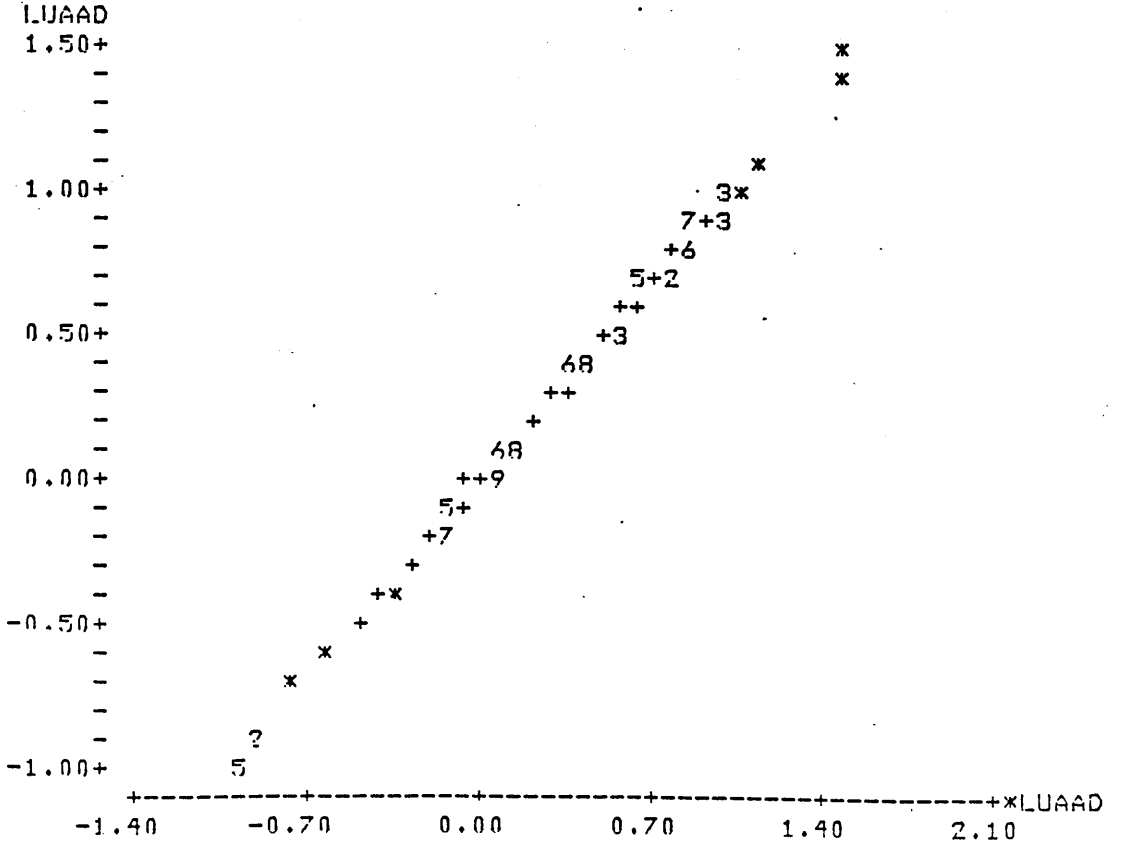


Figure 5.14 Distribution and Probability Plot for Log_{10} UA NAD/AD Ratios

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
-0.2	3	**
0.0	4	**
0.2	11	******
0.4	34	**********
0.6	92	**********
0.8	79	**********
1.0	46	**********
1.2	16	********
1.4	9	*****
1.6	9	*****
1.8	5	***
2.0	3	**

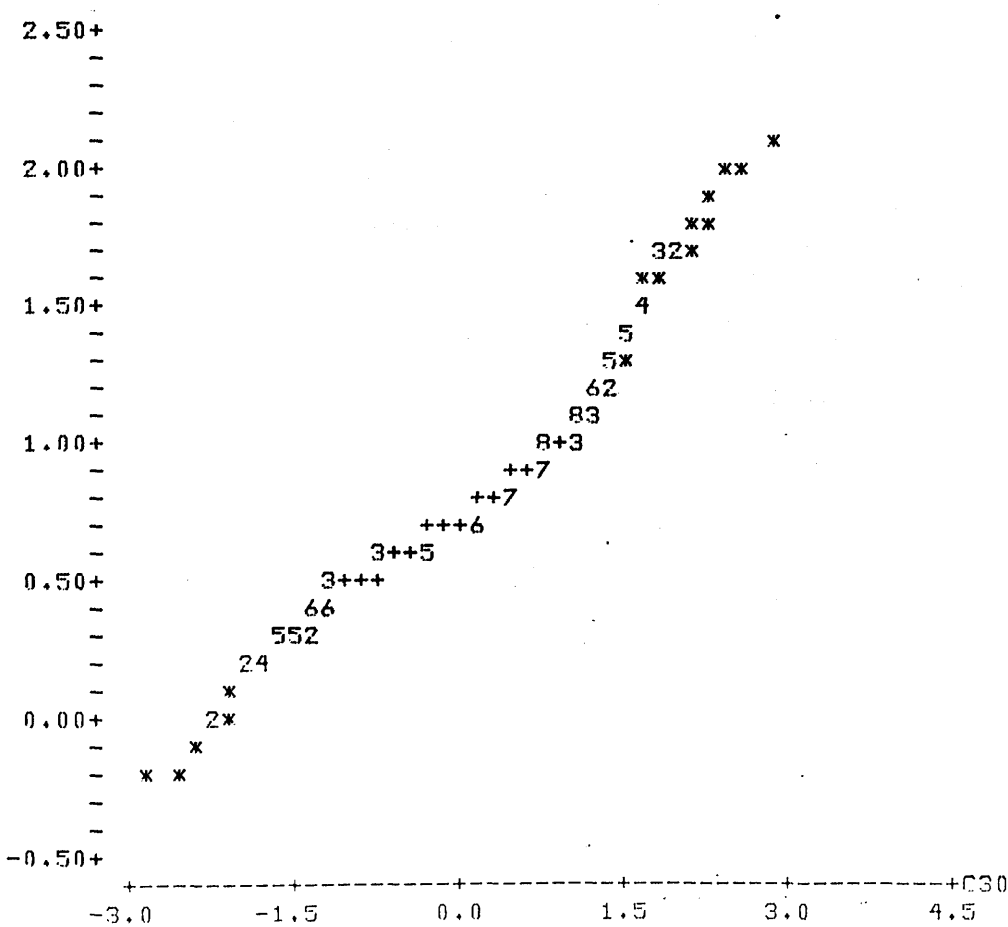


Figure 5.15 Distribution and Probability Plot for Log_{10} MV NAD

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
-1.4	1	*
-1.2	0	
-1.0	2	*
-0.8	1	*
-0.6	1	*
-0.4	4	*
-0.2	18	****
0.0	59	**********
0.2	124	**************************
0.4	80	**********
0.6	15	***
0.8	3	*
1.0	1	*

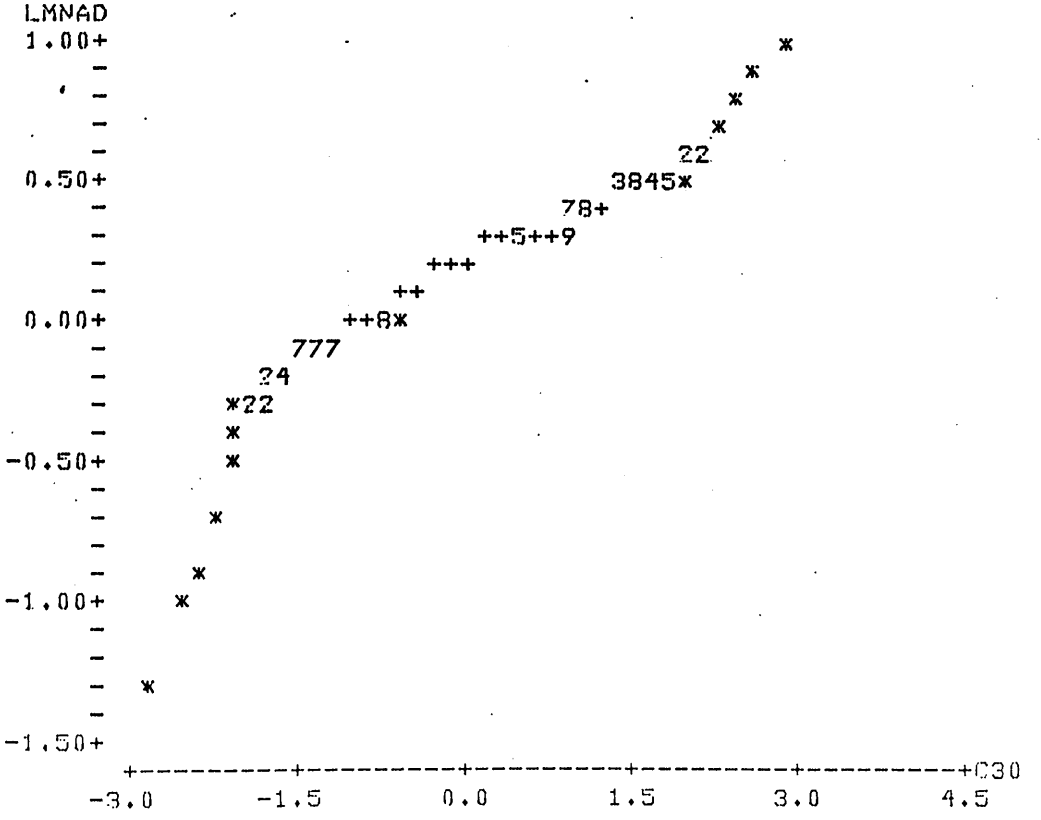


Figure 5.16 Distribution and Probability Plot for Log_{10} MV AD

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
-1.6	3	**
-1.4	1	*
-1.2	2	*
-1.0	15	********
-0.8	7	****
-0.6	29	**********
-0.4	78	**********
-0.2	67	**********
0.0	70	**********
0.2	9	*****
0.4	3	**
0.6	2	*

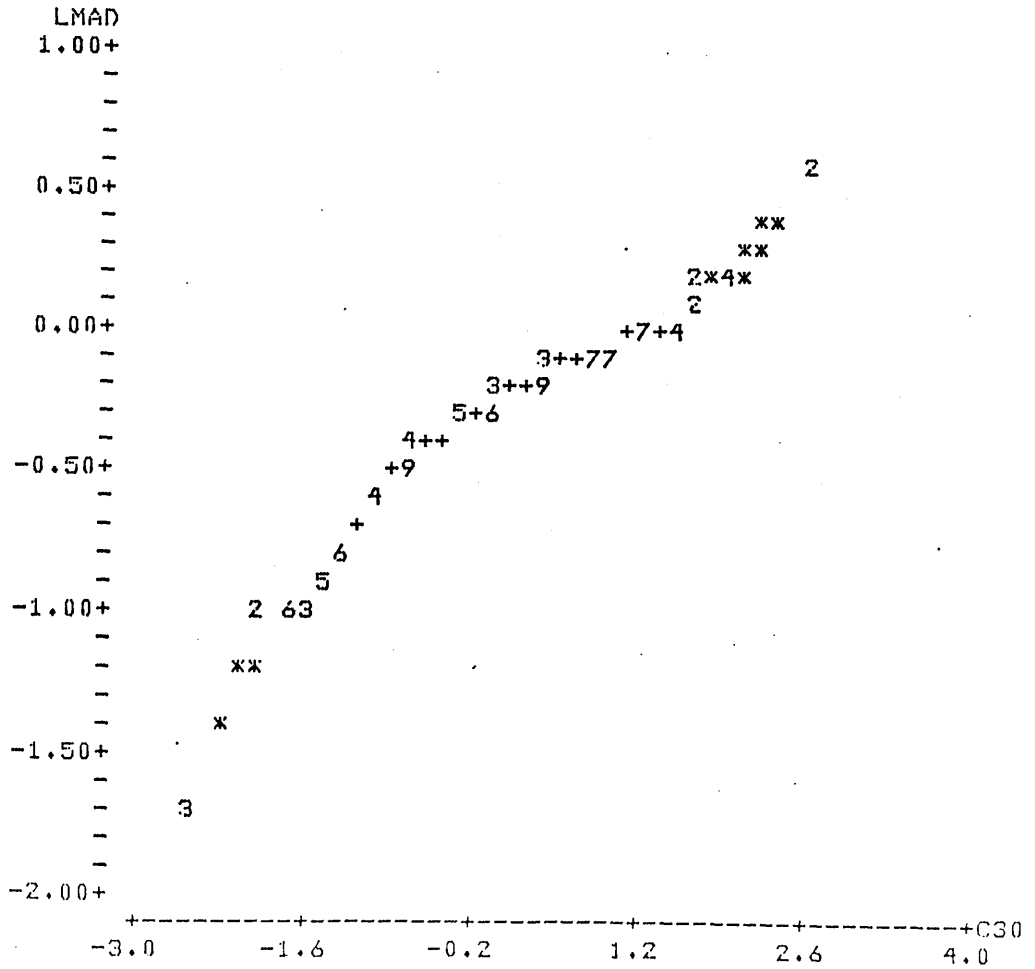


Figure 5.17 Distribution and Probability Plot for Log_{10} MV NAD/AD Ratio

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
-0.6	1	*
-0.4	1	*
-0.2	2	*
0.0	16	****
0.2	39	*********
0.4	118	**************************
0.6	58	************
0.8	18	****
1.0	16	****
1.2	11	***
1.4	3	*
1.6	0	
1.8	2	*

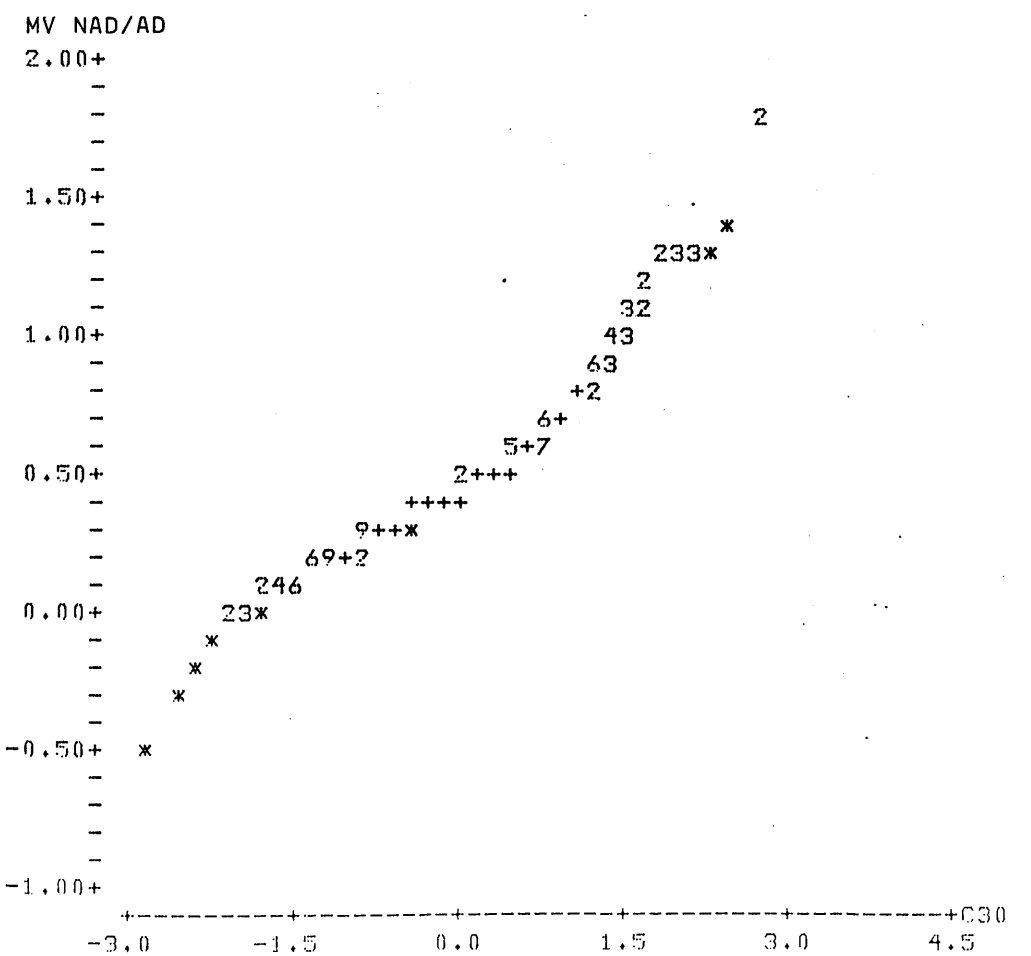


Figure 5.18 Distribution and Probability Plot for UA Cortisol (nmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	2	*
100.	36	**********
200.	58	**********
300.	55	**********
400.	32	**********
500.	40	**********
600.	24	**********
700.	16	********
800.	7	****
900.	2	*
1000.	4	**

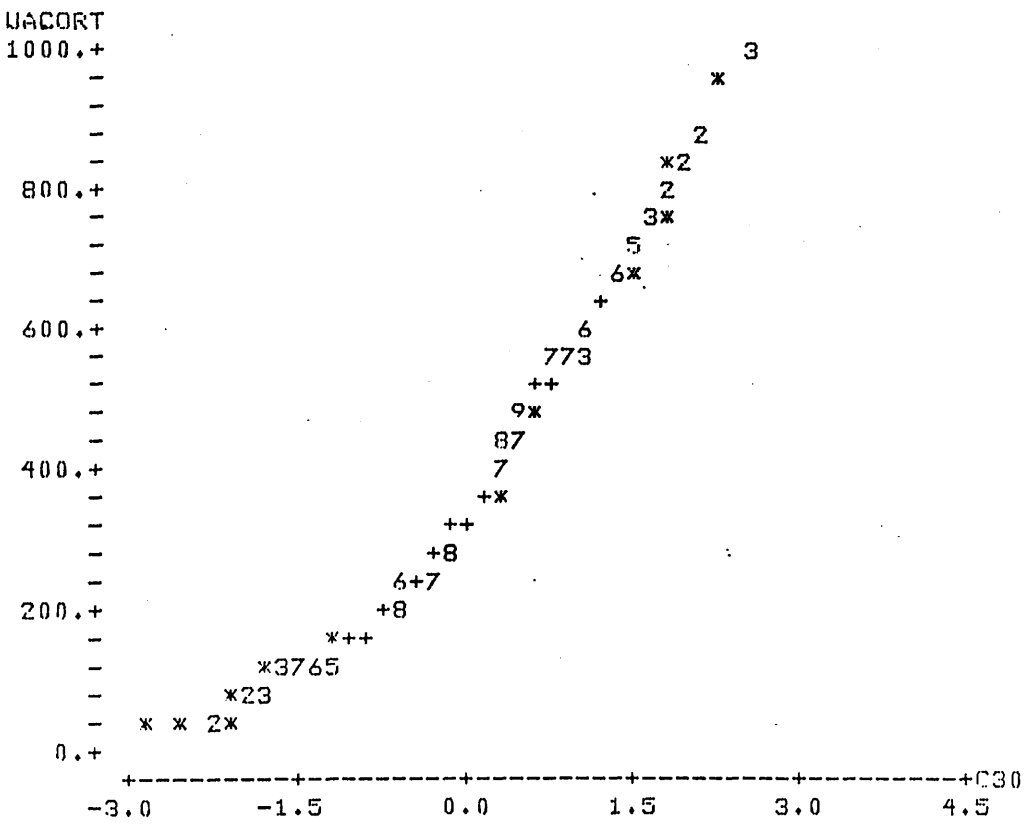


Figure 5.19 Distribution and Probability Plot for MV Cortisol (nmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	2	*
400.	15	*********
800.	48	**************************
1200.	92	**
1600.	73	*************************************
2000.	37	*******************
2400.	16	*********
2800.	7	****
3200.	4	**
3600.	1	*

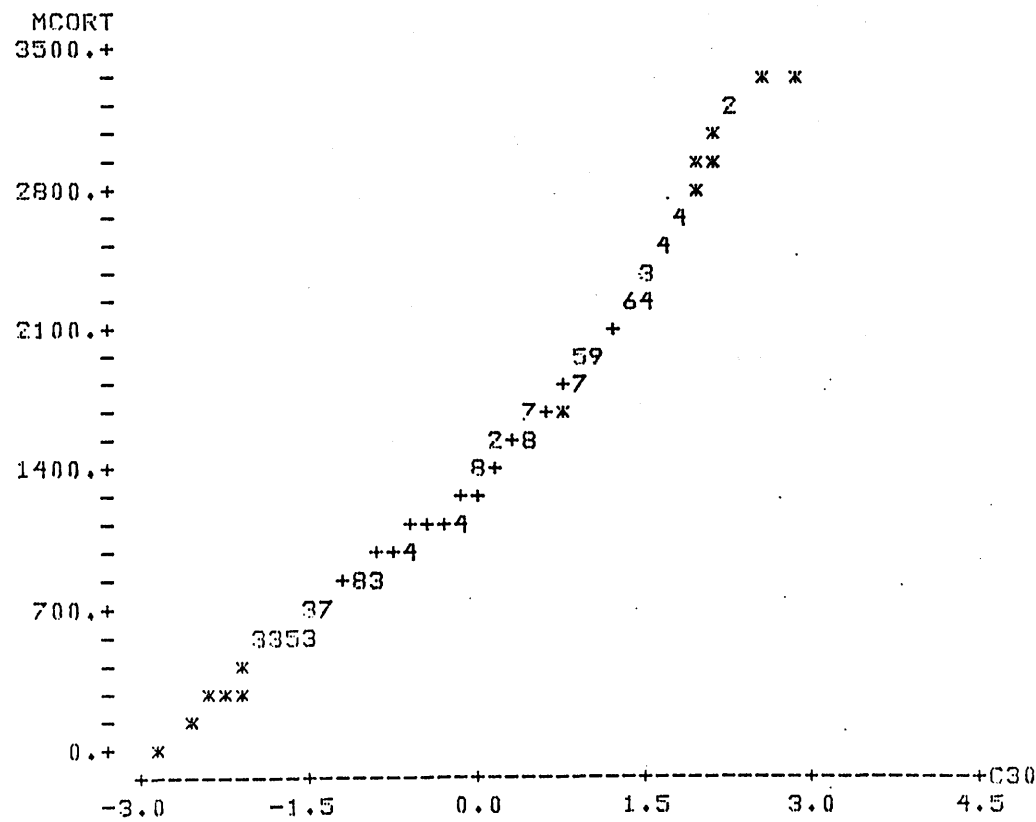


Figure 5.20 Distribution and Probability Plot for L/S Ratios

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	1	*
1.	67	**********
2.	100	**********
3.	60	**********
4.	44	**********
5.	18	**********
6.	19	**********
7.	4	**
8.	2	*
9.	3	**
10.	0	
11.	1	*
12.	0	
13.	2	*

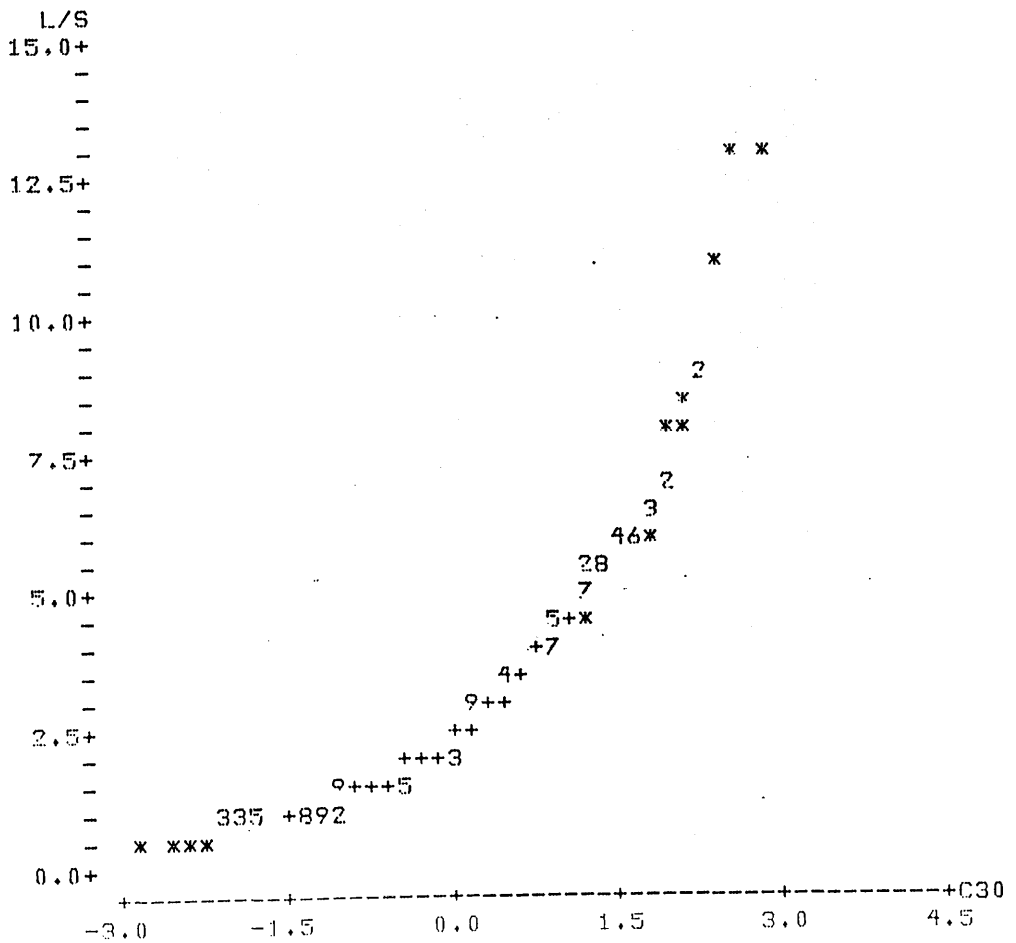


Figure 5.21 Distribution and Probability Plot for PG/S Ratios

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	38	********
1.	132	**************************
2.	50	**********
3.	15	***
4.	10	**
5.	0	
6.	0	
7.	0	
8.	0	
9.	1	*

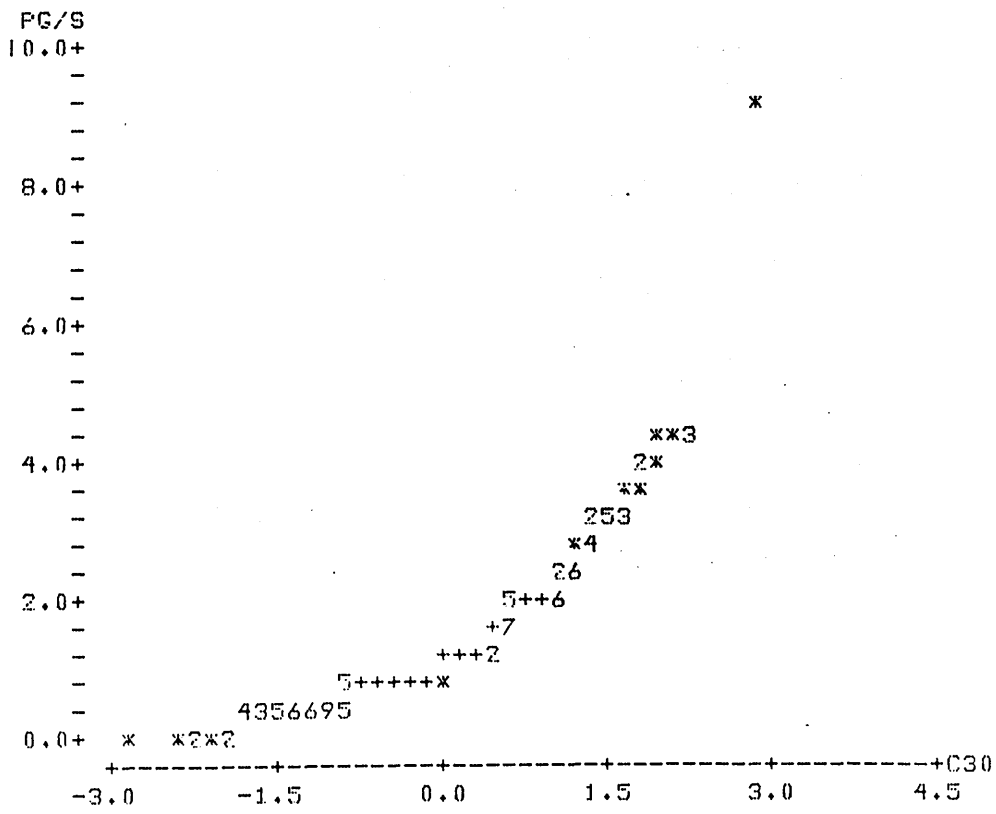


Figure 5.22 Distribution and Probability Plot for Lecithin Concentrations (µmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	1	*
10.	21	**********
20.	59	**********
30.	37	**********
40.	31	**********
50.	13	*******
60.	9	*****
70.	4	**
80.	1	*

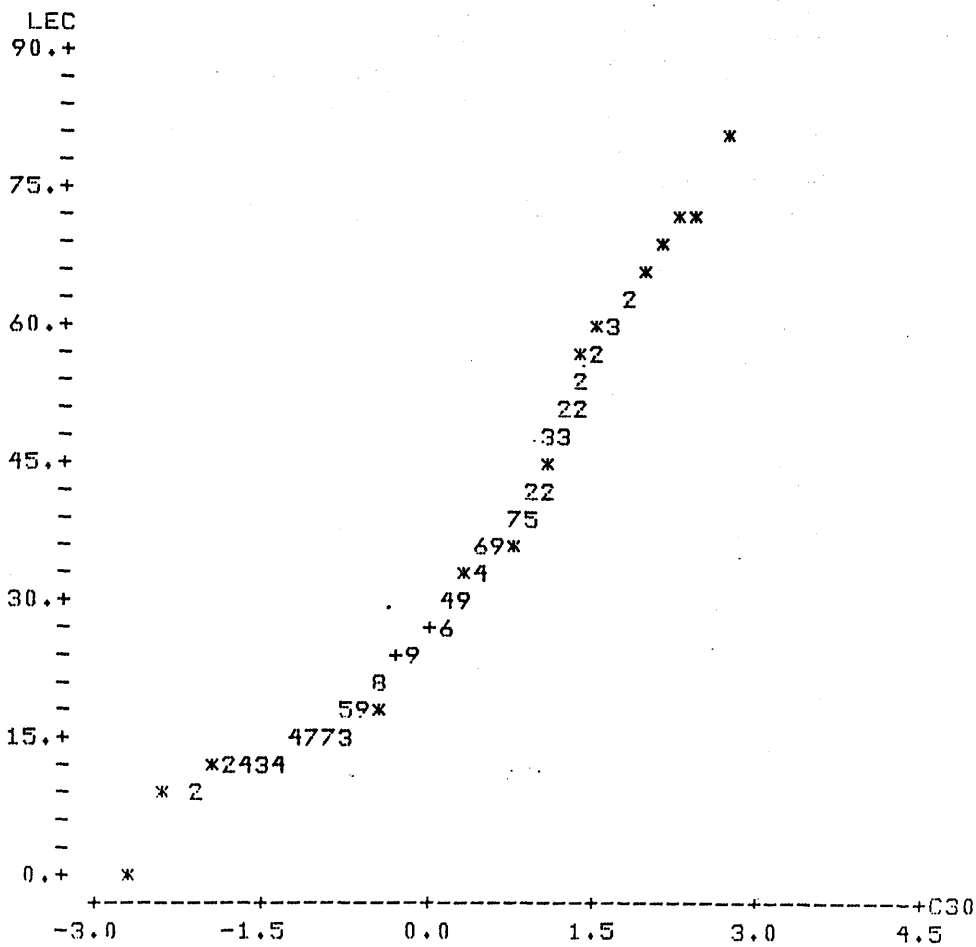
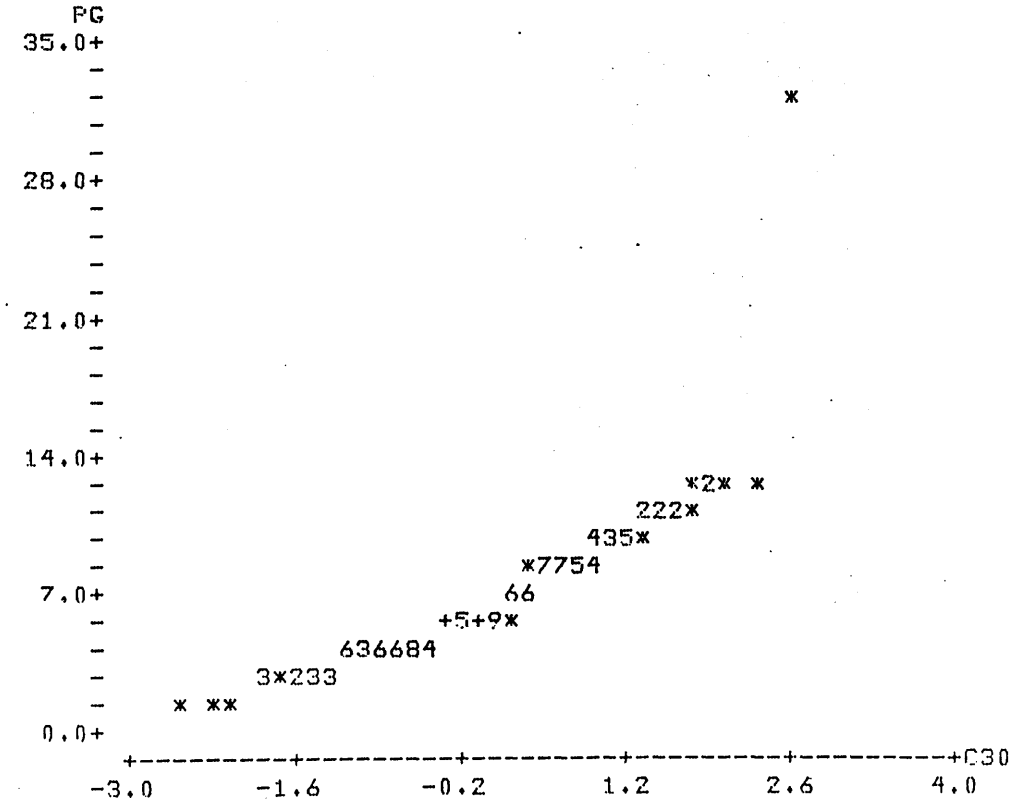


Figure 5.23 Distribution and Probability Plot for PG Concentrations (µmol/ℓ)

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.	1	*
2.	11	**********
4.	36	************************************
6.	44	**
8.	27	***************************
10.	18	******************
12.	8	********
14.	0	
16.	0	
18.	0	
20.	0	
22.	0	
24.	0	
26.	0	
28.	0	
30.	0	
32.	1	*



CHAPTER 6

Influence of Gestational Age

6.1 Introduction

The earlier the gestational age at birth, the higher the incidence and severity of neonatal respiratory problems. This has been demonstrated in many studies (p 56). Amniotic fluid surfactant also appears to increase with gestational age (p 57). However, gestational age per se is not the sole factor determining functional lung maturity, as some babies may have adequate surfactant levels and have no respiratory problems, while others of a similar birthweight and gestational age have deficient lung surfactant and develop severe respiratory problems requiring artificial ventilation.

In the investigation of the control of fetal lung maturity, as outlined in Figure 2.2, knowledge of the effect of gestational age on the fetal stress products cortisol and catecholamines is important. Fetal cortisol appears to increase with gestation in the human fetus (p 57), however the influence of gestation on the levels of catecholamines in the human fetus is sparse and conflicting (p 61).

Animal experiments have suggested that AD is much more important than NAD in enabling the fetus to adapt to an extrauterine existence (p 37) and that the conversion of NAD to AD in the fetal adrenal, possibly under the control of rising corticosteroid levels, increases as the gestation advances.

This chapter will investigate the influence of gestational age on

1 Cliical outcome, amniotic fluid phospholipids and the fetal stress hormone levels.

2 The relationship between fetal NAD and AD levels.

3 The relationship between fetal NAD and AD and fetal cortisol.

In addition, the possibility that maternal levels of cortisol and catecholamines may be able to influence fetal levels of the stress hormones is also investigated.

6.2 Results

6.2.1 Influence of Gestational Age on Clinical outcome

Table 6.1 illustrates that neonatal mortality drops dramatically as gestation increases.

The incidence of respiratory problems was about 78% in babies at or less than 29 weeks, about 38% for babies born between 30 and 33 weeks, but only 16% and 1% for those at 34 to 35 and 36 to 41 weeks respectively. The frequency of other morbid events such as patent ductus arteriosus, intracranial haemorrhage (as diagnosed by ultrasound) and apnoeic attacks also fall as gestation advances.

6.2.2 Influence of Gestation on Amniotic Fluid Phospholipids

There is a gradual increase in L/S ratio (Figure 6.1) and lecithin concentration (Figure 6.2) with increasing gestational age. The PG/S ratio (Figure 6.3) and PG concentration (Figure 6.4) rise after 36 weeks. Only those cases where PG was present were included in Figures 6.3 and 6.4.

6.2.3 Influence of Gestation on Umbilical Arterial Cortisol

There is a marked increase in umbilical arterial cortisol (UAC) with gestational age from around 34 weeks (Figure 6.5).

A similar increase in UAC is found after correcting for method of delivery (Figures 6.6, 6.7 and 6.8).

In contrast to UAC there appears to be no increase with gestational age in maternal venous cortisol levels at delivery (Figure 6.9).

The UAC levels in the term (36-41 weeks) and preterm (24-35 weeks) groups are directly compared in Table 6.2 and demonstrate significantly higher UAC levels in term compared with the preterm baby, for all methods of delivery.

6.2.4 Source of Cortisol in Umbilical Cord Blood

Current evidence suggests that fetal cortisol levels are largely uninfluenced by maternal levels (p 44). This section describes the relationship between maternal and fetal cortisol levels for those babies delivered vaginally and those delivered by elective caesarean section.

a) Maternal-Fetal Concentration Gradients

There was a significant maternal-fetal concentration gradient in the term (36-41 weeks) and preterm (24-35 weeks) groups in both methods of delivery (Tables 6.3 and 6.4).

The maternal venous cortisol (MVC) levels were significantly higher after the stress of vaginal delivery compared with elective caesarean section in both the term and preterm groups.

b) The Correlation between Maternal Venous and Umbilical Cord Cortisol

In the vaginally delivered group MVC levels correlated significantly with umbilical venous (UVC) levels at each gestational age group except between 36-37 weeks (Table 6.5).

The MVC and UAC levels correlated prior to 34 weeks. There was no correlation in the 34-35 week groups and a weak correlation in the 38-41 week group which surprisingly reached statistical significance

(Table 6.5).

In the elective caesarean section group there was no correlation between MVC and UAC or UVC levels at any gestational age group (Table 6.6).

c) Umbilical Arterio-Venous Concentration Gradient

In the vaginally delivered group, a significant umbilical arterio-venous difference only occurred from 34 weeks' gestation (Table 6.7).

In contrast, in the elective caesarean section groups, there was a significant umbilical arterio-venous concentration difference at all gestations, except the small group (6 cases) at $\leq$ 29 weeks (Table 6.8).

d) The Correlation between Umbilical Arterial and Umbilical Venous Cortisol

There is an excellent correlation between UAC and UVC regardless of gestational age or mode of delivery (Table 6.9).

e) Placental Clearance of Cortisol

The clearance of cortisol ($\frac{UA-UV}{UA} \times 100$) in different gestational age groups is shown in Table 6.10, and demonstrates an increased clearance of cortisol after 34-35 weeks' gestation.

6.2.5 Influence of gestational age on umbilical arterial catecholamines

a) Umbilical arterial NAD

The mean (SD) for Log_{10} UA NAD at each week of gestational age from 25 to 41 weeks is shown in Figure 6.10. There appears to be an

increase of umbilical arterial NAD with gestation.

The mean (SD) for umbilical arterial NAD at each week of gestation is shown in Figure 6.11 for those babies delivered vaginally, Figure 6.12 for those born by elective caesarean section and Figure 6.13 for those delivered by caesarean section following the onset of labour. There appears to be a trend to increasing NAD levels with advancing gestational age in those babies delivered vaginally. However, there is no apparent change in the mean umbilical arterial NAD concentration in those babies delivered by elective caesarean section or by caesarean section following the onset of labour.

The mean umbilical arterial NAD concentration is compared between the term group (36-41 weeks) and the preterm group of babies (24-35 weeks) for each of the three methods of delivery (Table 6.11).

The preterm group delivered vaginally had significantly lower mean umbilical arterial NAD concentrations than the term group. Following delivery by elective caesarean section or by caesarean section after the onset of labour, there was no significant difference in mean umbilical arterial NAD between term and preterm babies.

b) Umbilical Arterial AD

The UAAD levels, shown in Figure 6.14 are seen to rise around 34 weeks' gestation. Figures 6.15, 6.16 and 6.17 demonstrate that this rise in UAAD levels is confined to those babies delivered vaginally. There is no apparent change in mean UAAD concentration as gestation advances in those delivered by caesarean section.

The mean umbilical arterial AD concentration of the term and preterm groups of babies for the 3 methods of delivery is shown in Table 6.12. In the preterm group those babies delivered vaginally had a significantly lower mean umbilical arterial AD concentration than

those babies born in the term group. In contrast there was no significant difference in the mean umbilical arterial AD concentration between the term and preterm groups of babies who were delivered by elective caesarean section or by caesarean section following labour.

There was no change with gestation in mean maternal venous NAD or AD at delivery (Figures 6.18 and 6.19).

c) Influence of gestational age on the relationship between noradrenaline and adrenaline

The relationship between umbilical arterial AD and NAD for the term (36-41 weeks) and preterm (24-35 weeks) groups of babies is shown in Figure 6.20. A linear relationship is demonstrated for both the term and preterm groups.

The slopes of the regression lines indicate that the NAD/AD ratio increases with increasing NAD levels. The regression lines for the term and preterm babies are statistically significantly different ($p < .05$ using F test of Equality of Regression). This indicates that as the NAD level increases the ratio of NAD/AD would be greater in the preterm than the term babies.

The babies are further divided into gestational age groups and their respective regression lines shown in Figure 6.21. The babies born between 34-35 weeks have a regression line almost identical to that at 36-41 weeks. However, the regression lines of those babies born between 30-33 weeks and 25-29 weeks again suggest that for a given NAD level the ratio of NAD/AD is highest in the preterm baby.

The mean (SD) umbilical arterial NAD/AD ratio at each gestational age from 25 to 41 weeks is shown in Figure 6.22. There is no obvious trend with gestational age. There is a much wider variation in NAD/AD levels in the babies born prior to 35 weeks compared to those born after this gestation.

The mean (SD) umbilical arterial log NAD/AD ratio in term (36-41 weeks) and preterm (24-35 weeks) groups of babies for the 3 different methods of delivery are shown in Table 6.13. There was no significant statistical difference in the NAD/AD ratios between the term and preterm groups.

d) The Influence of gestational age on the relationship between UAC and the UA NAD/AD ratio

The relationship between UAC levels and the UA NAD/AD ratio is shown in Figure 6.23 and shows that there is no correlation between the two. However, when the babies were divided into a preterm group (25-35 weeks) and a term group (36-41 weeks), those babies with the lowest UAC levels in conjunction with the highest NAD/AD ratios were found in the preterm group (Figure 6.24). There was no correlation between UAC and UA NAD or UA AD levels (Table 6.14).

6.2.6 Source of catecholamines in umbilical cord blood

Current evidence suggests that the fetal catecholamines are largely uninfluenced by maternal levels. This section describes the relationship between maternal and fetal levels for those babies delivered vaginally and those delivered by caesarean section.

a) Maternal-fetal concentration gradients

There was a significant maternal-fetal concentration gradient for both NAD and AD, the highest levels being in the fetus. This was true for both the term and preterm groups of babies irrespective of method of delivery (Tables 6.15, 6.16, 6.17, 6.18).

The mean UA NAD/AD ratio was significantly higher than the mean MV NAD/AD ratio (Table 6.19).

The MV NAD and AD levels found after vaginal delivery were not

significantly different to those observed following elective caesarean section (Tables 6.15, 6.16, 6.17, 6.18).

b) The correlation between maternal venous and umbilical cord catecholamines

There was no correlation between MV catecholamines and umbilical cord catecholamines, except a weak correlation between MV aned UV AD in term vaginal delivered group and between MV and UA AD in the preterm group (Table 6.20).

c) Umbilical Arterio-venous concentration gradients

There was a significant umbilical arterio-venous concentration gradient for both NAD and AD, in the term and preterm groups for both methods of delivery (Tables 6.15, 6.16, 6.17, 6.18).

d) The correlation between umbilical arterial and umbilical venous catecholamines

There was a significant umbilical arterio-venous correlation for NAD and AD in the term and preterm groups of babies for both methods of delivery (Table 6.21).

e) Placental clearance of catecholamines

The placental clearance ($\frac{UA-UV}{UA}$ x 100) for NAD and AD by gestational age is shown in Table 6.22.

The placental clearance for NAD was similar throughout gestation, however clearance of AD seemed to rise as gestational age advanced.

A linear relationship was demonstrated between the arterio-venous concentration difference and the umbilical arterial concentration of NAD in both the term and preterm groups (Figure 6.25), the slopes of the lines being almost identical.

A linear relationship was also demonstrated between the arterio-venous AD concentration difference and the umbilical arterial concentration of AD in both the term and preterm groups (Figure 6.25). Again the slopes of the lines were almost identical.

Figures 6.25 and 6.26 demonstrate that the clearance of NAD and AD was directly proportional to their respective umbilical arterial concentrations and over the concentration ranges found in this study the process was non-saturable.

6.3 Discussion

Effect of gestational age on clinical and biochemical lung maturity and fetal stress hormones

Gestational age has a pronounced effect not only on mortality and morbidity but also on amniotic fluid phospholipids and umbilical arterial cortisol levels. The neonatal mortality and incidence of RDS falls as the amniotic fluid phospholipids and umbilical arterial cortisol levels rise. The rise in UAC, which occurs irrespective of method of delivery, parallels the rise in amniotic fluid phospholipids. In addition the incidence of RDS falls dramatically after 34-35 weeks, the time of the main UAC surge. It is therefore not unreasonable to postulate that endogenous cortisol secretion may play a role in the synthesis of fetal lung phospholipids.

The catecholamines however did not demonstrate such clear cut changes with gestational age. Figures 6.10 and 6.14 (all cases) and Figures 6.11 and 6.15 (all vaginal deliveries) suggest an increase in umbilical arterial NAD and AD with increasing gestational age. In contrast there seemed no evidence to suggest such a trend when the babies were delivered by elective caesarean section or caesarean section following labour. However, the relatively small numbers at each week of gestation age, especially prior to 30 weeks, makes

interpretation difficult. Separating the babies into a preterm (24-35 weeks) and a term (36-41 weeks) group, (Tables 6.11 and 6.12) the mean umbilical arterial NAD and AD levels were significantly lower in the preterm compared with the term babies who were delivered vaginally. No such differences were seen when the babies were delivered by caesarean section either electively or following labour.

These findings are in broad agreement with Lagercrantz and Bistoletti (1973) who, in a small series of 9 preterm babies and employing a fluorometric method for catecholamine measurement reported lower catecholamine values in preterm than term infants at birth. In contrast, Newnham et al (1984) observed significantly greater mean arterial plasma AD concentration in preterm than term fetuses, with NAD similar in the 2 groups.

The reason for the discrepancy when comparing the catecholamine levels in the preterm and term babies between this study and the work of Newnham et al is not immediately obvious. However, the study by Newnham et al(1984) involved a much smaller series (36 preterm babies) and this combined with the wide range of catecholamine levels found in the human fetus may account for this discrepancy.

It is generally assumed that a high proportion of NAD in the adrenal medulla is indicative of immaturity and that the percentage of AD increases slowly with age (Comline & Silver 1966). However no obvious trend in the NAD/AD ratio with gestational age could be demonstrated, (Figure 6.22) and there was no significant difference in the mean NAD/AD ratio between the term and preterm babies (Table 6.13). In babies born prior to 35 weeks there was a much wider scatter of NAD/AD values and it would appear that the higher NAD/AD ratios occurred prior to this gestation.

Figures 6.21 and 6.22 demonstrate that as the umbilical arterial NAD concentration increases the ratio of NAD/AD increases and that for

a given NAD concentration the preterm baby tends to have a relatively lower AD concentration than at term. This may reflect a poorer AD response to stress in the preterm baby.

AD would seem to be relatively more important than NAD in the adaptation of the fetus to an extrauterine environment. It is thought to play a major role in lung maturation - both the release of surfactant and the absorption of lung fluid, cardiovascular changes and glucose homeostasis. The preterm neonate with a relatively poorer 'AD response' would be placed at a disadvantage in adjusting to extrauterine life.

As gestation advances the adrenal medulla is exposed to increasing levels of glucocorticoids which encourages the 'N' methylation of NAD and AD. However, there was no correlation between the umbilical arterial cortisol and the NAD/AD ratio (Figure 6.23). Nevertheless the highest NAD/AD ratios and the lowest UAC concentrations were found in those babies born prior to 35 weeks (Figure 6.24). It may be that those babies with a high NAD/AD ratio and a low UAC are biochemically immature and may be placed at a disadvantage when attempting to adapt to an extrauterine environment.

Source of fetal cortisol

The large maternal-fetal concentration gradient across the placenta would suggest that maternal cortisol levels could influence cord levels, especially with the high maternal levels associated with vaginal delivery.

However, more than 90% of maternal cortisol is bound to corticosteroid binding globulin (CBG) and therefore unavailable for transfer (Sandberg & Slaunwhite 1959). This CBG is elevated during pregnancy (Slaunwhite & Sandberg 1959). In addition to this the placental 'barrier' to the transfer of cortisol is re-inforced by the

presence of 11B-hydroxysteroid dehydrogenase in the placenta and fetal membranes which promotes oxidation of maternally transferred free cortisol to cortisone (Murphy et al 1974).

It is possible, however, that the high levels of maternal cortisol noted during vaginal delivery could overcome the 'placental barrier' and thereby influence fetal cord levels. In this regard it is interesting that there is no correlation between maternal venous cortisol levels and umbilical cord levels at elective caesarean section, when the maternal venous cortisol levels are relatively low. In contrast during vaginal delivery there was a significant correlation of maternal venous and umbilical venous cortisol in all gestational groups except between 36-37 weeks.

The strongest correlation between maternal venous and umbilical cord cortisol levels were found in the preterm group of babies. This may help to explain the lack of umbilical arterio-venous cortisol gradient in the preterm babies born vaginally prior to 34 weeks. There is a significant umbilical arterio-venous cortisol gradient only after 33 weeks and this arterio-venous gradient increases with gestation (Table 6.7). This may reflect not only an increase in endogenous fetal secretion of cortisol but also an increase in corticosteroid binding globulin and in placental 11B oxidoreductase as gestation advances.

The maternal venous cortisol levels were significantly lower in the elective caesarean section group compared with those mothers delivered vaginally (Table 6.3 and 6.4). These lower cortisol levels may explain the lack of correlation between maternal venous and umbilical cord cortisol levels, in contrast to the vaginally delivered group (Table 6.5, 6.6). The relative lack of maternal influence on cord cortisol levels in the elective caesarean section group may also be reflected in the significant umbilical arterio-venous cortisol

levels found in all but one of the gestational age groups. In this group, however, there were only 6 cases (Table 6.8). In the vaginally delivered babies the lack of an arterio-venous cortisol gradient in those born prior to 34 weeks (Table 6.7)and the correlations between maternal venous and umbilical cord cortisol levels (Table 6.5) suggest that maternal cortisol levels can influence fetal cord blood levels especially in the preterm baby.

Source of fetal catecholamines

In contrast to plasma cortisol the plasma catecholamine levels in the fetus were significantly higher than those in maternal venous blood (Tables 6.15, 6.16, 6.17 and 6.18). The significantly higher catecholamine levels in the umbilical artery than in the umbilical vein (Tables 6.15, 6.16, 6.17 and 6.18), the significant correlations between umbilical arterial and umbilical venous catecholamines (Table 6.21) and the lack of correlation between maternal venous and cord blood catecholamine levels (Table 6.20) all suggest that the fetus is the predominant source of cord blood catecholamines. In vitro studies have demonstrated the presence of catechol-o-methyltransferase and monoamine oxidase in the human placenta which metabolise the catecholamines into inactive metabolites (Morgan et al 1972). It would seem likely therefore that there is functional separation between the fetal and maternal sympathoadrenal systems.

Falconer et al (1982) have shown that the clearance of NAD by the term placenta was directly proportional to the umbilical arterial NAD concentration and that over the concentration range which they encountered the process was non-saturable. This has been confirmed and has also been shown to be true for the preterm placenta (Figure 6.25).

It would also appear that there is a substantial placental clearance for AD (Figure 6.26). This substantial clearance and inactivation of catecholamines by the placenta may help protect the fetus from the high circulating levels of NAD and AD.

6.4 Conclusions

1 Gestational age has a marked influence on

a) Neonatal lung function - the incidence of RDS and mortality increases with decreasing gestation age below 34-35 weeks.

b) Lung surfactant - the important surface active phospholipids lecithin and PG increase with gestational age.

c) UAC increases with gestational age, especially after 34 weeks

2 Gestational age appears to have some effect on fetal catecholamine levels.

Fetal NAD and AD seems to increase with gestation but only in those babies delivered vaginally.

The higher NAD/AD ratios were found in preterm babies.

3 There was no obvious relationship between UAC and UA NAD/AD ratios.

4 The maternal and fetal sympathoadrenal systems appear to function independently.

5 Fetal cortisol levels may be influenced by the high MVC levels associated with vaginal delivery, especially in the preterm baby.

Table 6.1 Influence of Gestational Age on Clinical Outcome

Gestation (Weeks)	Number	Mean Birthweight (kg)	Died	RDS	VENTIL	PDA	ICH	Apnoeic Attacks
≤ 29	46	1.09	46%	78%	70%	35%	45%	56%
30-33	74	1.72	9.5%	38%	32%	12%	20%	20%
34-35	69	2.16	4%	16%	11.6%	0%	-	4%
36-41	192	3.05	1%	1%	1%	0%	-	0%

VENTIL - Requirement for artificial ventilation

PDA - Patent ductus arteriosus

ICH - Intracranial haemorrhage

Table 6.2

Umbilical Arterial Cortisol (nmol/ℓ)

Term compared with Preterm Delivery

Delivery	Term (SD) (36-42 weeks)	Preterm (SD) (24-35 weeks)	Significance
Vaginal	533 (185) (n = 74)	314 (180) (n = 63)	$p < .0000$
Elective Caesarean Section	353 (134) (n = 35)	239 (116) (n = 43)	$p < .0002$
Labour and Caesarean Section	474 (250) (n = 22)	235 (149) (n = 37)	$p < .0003$

Table 6.3

Maternal Venous versus Umbilical Cortisol (nmol/ℓ)

Term Group (36-41 weeks)

			(Mean) Cortisol	(SD)*	
Vaginal Delivery	Maternal Venous	(n = 83)	1572	(502)	$p < .0000$
	Umbilical Artery	(n = 74)	533	(180)	$p < .0000$
	Umbilical Vein	(n = 95)	396	(135)	
Elective Caesarean Section	Maternal Venous	(n = 34)	1179	(431)	$p < .0000$
	Umbilical Artery	(n = 35)	353	(134)	$p < .0000$
	Umbilical Vein	(n = 37)	276	(95)	$p < .007$

$p < .0001$

* (SD = Standard Deviation)

Table 6.4

Maternal Venous versus Umbilical Cord Cortisol (nmol/ℓ)

Preterm Group (24-35 weeks)

			(Mean) Cortisol	(SD)*	
Vaginal Delivery	Maternal Venous	(n = 68)	1681	(658)	$p < .0000$
	Umbilical Artery	(n = 63)	315	(185)	NS
	Umbilical Vein	(n = 73)	287	(162)	
Elective Caesarean Section	Maternal Venous	(n = 45)	1067	(397)	$p < .0000$
	Umbilical Artery	(n = 43)	239	(116)	NS
	Umbilical Vein	(n = 44)	202	(80)	

$p < .0000$ (Maternal Venous vs Umbilical Artery)

$p < .0000$ (Maternal Venous vs Umbilical Vein)

$p < .0000$ (Maternal Venous, Vaginal Delivery vs Maternal Venous, Elective Caesarean Section)

* (SD = Standard Deviation)

Table 6.5

Correlation between Maternal Venous and Umbilical Cord Cortisol

Vaginal Deliveries

Gestation (weeks)	MVC v UAC r	p	MVC v UVC r	p
≤ 29	0.568 (n = 21)	< .01	0.646 (n = 21)	< .01
30-33	0.52 (n = 18)	< .05	0.59 (n = 22)	< .01
34-35	0.43 (n = 20)	NS	0.674 (n = 22)	< .001
36-37	-0.03 (n = 24)	NS	0.22 (n = 29)	NS
38-41	0.4 (n = 41)	<.02	0.54 (n = 50)	< .001

r = correlation coefficient

Table 6.6

Correlations between Maternal Venous and Umbilical Cord Cortisol

Elective Caesarean Section

Gestation (weeks)	MVC r	v UAC p	MVC r	v UVC p
≤29	-0.67 (n = 5)	NS	0.384 (n = 5)	NS
30-33	0.3 (n = 19)	NS	0.435 (n = 19)	NS
34-35	-0.15	NS	0.06	NS
36-37	I N S U F F I C I E N T D A T A			
38-41	0.14 (n = 28)	NS	0.12 (n = 29)	NS

r = correlation coefficient

Table 6.7

The Influence of Gestational Age on

Umbilical Arterio-Venous Cortisol Difference

Vaginal Deliveries

Gestation (weeks)		UA mean (SD)	UV mean (SD)	*p
≤ 29	(n = 20)	225 (134)	242 (150)	NS
30-33	(n = 22)	286 (182)	260 (156)	NS
34-35	(n = 20)	440 (174)	369 (157)	<.0006
36-37	(n = 24)	482 (173)	347 (347)	<.0000
38-41	(n = 50)	558 (180)	419 (145)	<.0000

*p Paired 'T' Test

Table 6.8

The Influence of Gestational Age on

Umbilical Arterio-Venous Cortisol Difference

Elective Caesarean Section

Gestation (weeks)		UA mean (SD)	UV mean (SD)	*p
⩽ 29	(n = 6)	220 (83)	201 (59)	NS
30-33	(n = 19)	205 (87)	175 (64)	< .007
34-35	(n = 18)	280 (142)	230 (95)	< .005
36-37	I N S U F F I C I E N T		D A T A	
38-41	(n = 33)	351 (138)	272 (94)	< .0000

*p Paired 'T' Test

Table 6.9

Umbilical Arterio-Venous Cortisol Correlation

by Gestational Age and Method of Delivery

Gestation (Weeks)	Vaginal		Elective Caesarean Section	
	r	p	r	p
≤ 29	0.9 (n = 20)	<.001	0.38 (n = 6)	NS
30-33	0.88 (n = 22)	<.001	0.88 (n = 19)	<.001
34-35	0.86 (n = 20)	<.001	0.9 (n = 18)	<.001
36-37	0.7 (n = 25)	<.001	INSUFFICIENT DATA	
38-41	0.6 (n = 49	<.001	0.86 (n = 33)	<.001

Table 6.10

Influence of Gestational Age on

Placental Clearance of Cortisol

$\frac{UA-UV}{UA} \times 100$ All Vaginal Deliveries

Gestation (weeks)	Cortisol Clearance
$\leq$ 29	8%
30-33	5%
34-35	18%
36-37	26%
38-41	24%

Table 6.11

Umbilical Arterial Noradrenaline (nmol/ℓ)

Term (36-41 weeks) compared with Preterm (24-35 weeks) Delivery

Delivery	Term mean (SD)	Preterm mean (SD)	Significance*
Vaginal	35.8 (38) (n = 104)	17.4 (24) (n = 66)	<.0002
Elective Caesarean Section	13.8 (22) (n = 42)	10.6 (15) (n = 44)	NS
Emergency	11 (10) (n = 28)	24 (54) (n = 40)	NS

* 'T' Test performed using logarithmic transformed values of NAD

Table 6.12

Umbilical Arterial Adrenaline (nmol/ℓ)

Term (36-41 weeks) compared with Preterm (24-35 weeks) Delivery

Delivery	Term mean (SD)	Preterm mean (SD)	Significance*
Vaginal	4.5 (3.7) (n = 96)	2.5 (2.5) (n = 66)	<.0000
Elective Caesarean Section	2.0 (1.7) (n = 37)	1.9 (2.2) (n = 44)	NS
Emergency Caesarean Section	1.9 (1.7) (n = 27)	2.5 (4.9) (n = 39)	NS

* 'T' Test performed using logarithmic transformed values of AD

Table 6.13

Umbilical Arterial Noradrenaline/Adrenaline Ratio
Term (36-41 weeks) compared with Preterm (24-35 weeks) Delivery

Delivery	Term mean (SD)	Preterm mean (SD)	Significance *
Vaginal	8.6 (7.7) (n = 96)	9.4 (15.1) (n = 66)	NS
Elective Caesarean Section	5.9 (3.3) (n = 37)	10.7 (21) (n = 44)	NS
Labour and Caesarean Section	7.5 (7.4) (n = 27)	13.3 (21) (n = 39	NS

* 'T' Test performed using logarithmic transformed values

Table 6.14

Correlation of Umbilical Arterial Cortisol and Umbilical Arterial Noradrenaline and Adrenaline

			r	
UAC	v	NAD	0.264	NS
UAC	v	AD	0.3	NS

Table 6.15

The Relationship between Maternal Venous and Cord NAD (nmol/ℓ) Levels

Term (36-41 weeks) Deliveries

			NAD (mean (SD))				
Vaginal Delivery	MV	(n = 96)	1.83	(0.6)	p <.0000	p <.0000	NS
	UA	(n = 104)	35.8	(38.9)			
	UV	(n = 110)	9.12	(8.9)	p <.0000		
Elective Caesarean Section	MV	(n = 40)	1.69	(0.75)	p <.0000	p <.001	
	UA	(n = 42)	13.8	(22.1)			
	UV	(n = 44)	3.26	(2.39)	p <.0000		

Table 6.16

The Relationship between Maternal Venous and Cord NAD Levels (nmol/ℓ)

Preterm (24-35 weeks) Group

			NAD (mean (SD))				
Vaginal Delivery	MV	(n = 66)	1.48	(0.7)	$p < .0000$	$p < .0000$	NS
	UA	(n = 66)	17.36	(24)			
	UV	(n = 72)	6.77	(10.8)	$p < .0000$		
Elective Caesarean Section	MV	(n = 38)	1.82	(0.9)	$p < .0000$	NS	
	UA	(n = 46)	10.18	(15)			
	UV	(n = 45)	3.82	(8.2)	$p < .0000$		

Table 6.17

The Relationship between Maternal Venous and Cord AD Levels (nmol/ℓ)

Term Group (36-41 weeks)

			AD (mean (SD))				
Vaginal Delivery	MV	(n = 84)	0.66	(0.4)	$p < .0000$	$p < .0000$	NS
	UA	(n = 96)	4.57	(3.74)			
	UV	(n = 100)	1.48	(1.16)	$p < .0000$		
Elective Caesarean Section	MV	(n = 33)	0.66	(0.47)	$p < .0000$	NS	
	UA	(n = 37)	1.97	(1.65)			
	UV	(n = 39)	0.85	(0.75)	$p < .0000$		

Table 6.18

The Relationship between Maternal Venous and Cord AD Levels (nmol/ℓ)

Preterm Group (24-35 weeks)

			AD (mean (SD))				
Vaginal Delivery	MV	(n = 66)	0.57	(0.3)	p <.0000	p <.0002	NS
	UA	(n = 66)	2.49	(2.52)	p <.0004		
	UV	(n = 72)	1.22	(1.5)			
Elective Caesarean Section	MV	(n = 35)	0.83	(0.85)	p ≤.006	NS	
	UA	(n = 44)	1.86	(2.2)	p <.01		
	UV	(n = 43)	1.01	(1.5)			

Table 6.19

Comparison of the NAD/AD Ratio in Umbilical Arterial and Maternal Venous Blood

	(mean) NAD/AD Ratio	SD	*p
Maternal Venous (n = 285)	4.49	6.72	p <.0000
Umbilical Arterial (n = 309)	9.25	13.9	

* 'T' Test using logarithmic transformed values

Table 6.20

Plasma Catecholamines

Maternal Venous - Umbilical Cord Correlations

Term Group (36-41 weeks)

Vaginal Delivery			r	p
MV NAD	v	UA NAD	-.07	NS
MV NAD	v	UV NAD	.18	NS
MV AD	v	UA AD	.13	NS
MV AD	v	UV AD	.43	< .001
Elective Caesarean Section				
MV NAD	v	UA NAD	.12	NS
MV NAD	v	UA NAD	.18	NS
MV AD	v	UA AD	.19	NS
MV AD	v	UV AD	.31	NS

Preterm Group (24-35 weeks)

Vaginal Delivery				
MV NAD	v	UA NAD	-.02	NS
MV NAD	v	UV NAD	.04	NS
MV AD	v	UA Ad	.07	NS
MV AD	v	UV AD	.18	NS
Elective Caesarean Section				
MV NAD	v	UA NAD	-.08	NS
MV NAD	v	UV NAD	-.2	NS
MV AD	v	UA AD	-.47	< .01
MV AD	v	UV AD	-.31	NS

Table 6.21

Plasma Catecholamines
Umbilical Arterial-Venous Correlations

Term Group (36-41 weeks)

			r	p
Vaginal Delivery				
UA NAD	v	UV NAD	0.75	<.001
UA AD	v	UV AD	0.64	<.001
Elective Caesarean Section				
UA NAD	v	UV NAD	0.77	<.001
UA AD	v	UV AD	0.59	<.001

Preterm Group (24-35 weeks)

Vaginal Delivery				
UA NAD	v	UV NAD	0.74	<.001
UA AD	v	UV AD	0.45	<.001
Elective Caesarean Section				
UA NAD	v	UV NAD	0.82	<.001
UA AD	v	UV AD	0.6	<.001

Table 6.22

Placental Clearance of Catecholamines

by Gestational Age

	NAD	AD
All Cases	71% (n = 326)	62% (n = 322)
≤ 29 weeks	67% (n = 33)	44% (n = 32)
30-33 weeks	64% (n = 63)	51% (n = 63)
34-35 weeks	64% (n = 54)	66% (n = 54)
36-41 weeks	75% (n = 174)	65% (n = 160)

Figure 6.1

Influence of Gestational Age on the L/S Ratio

(Mean (SD) at Each Week of Gestation)

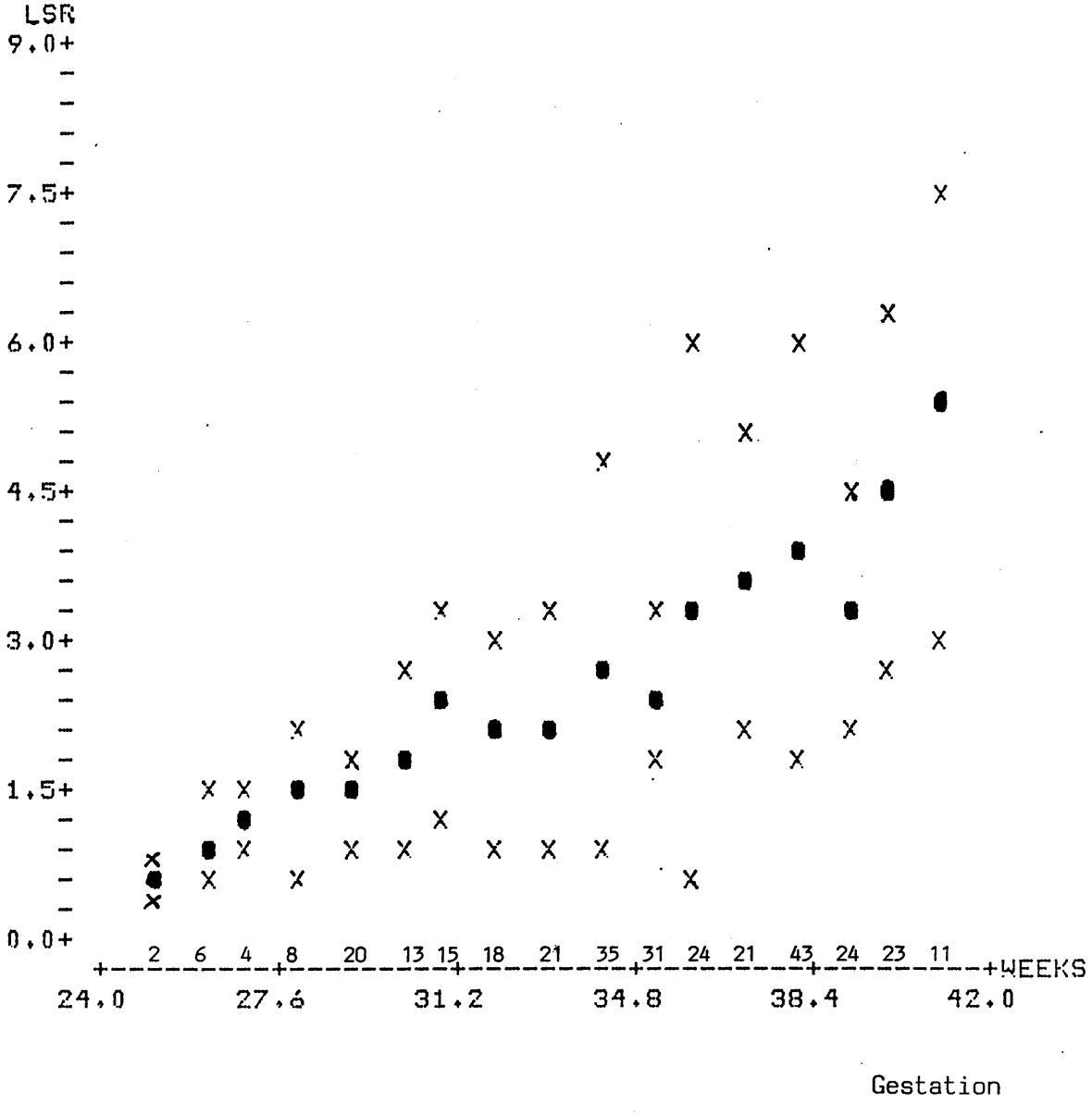


Figure 6.2

Influence of Gestational Age on Amniotic Fluid Lecithin Concentration

(Mean (SD) at each week of gestation)

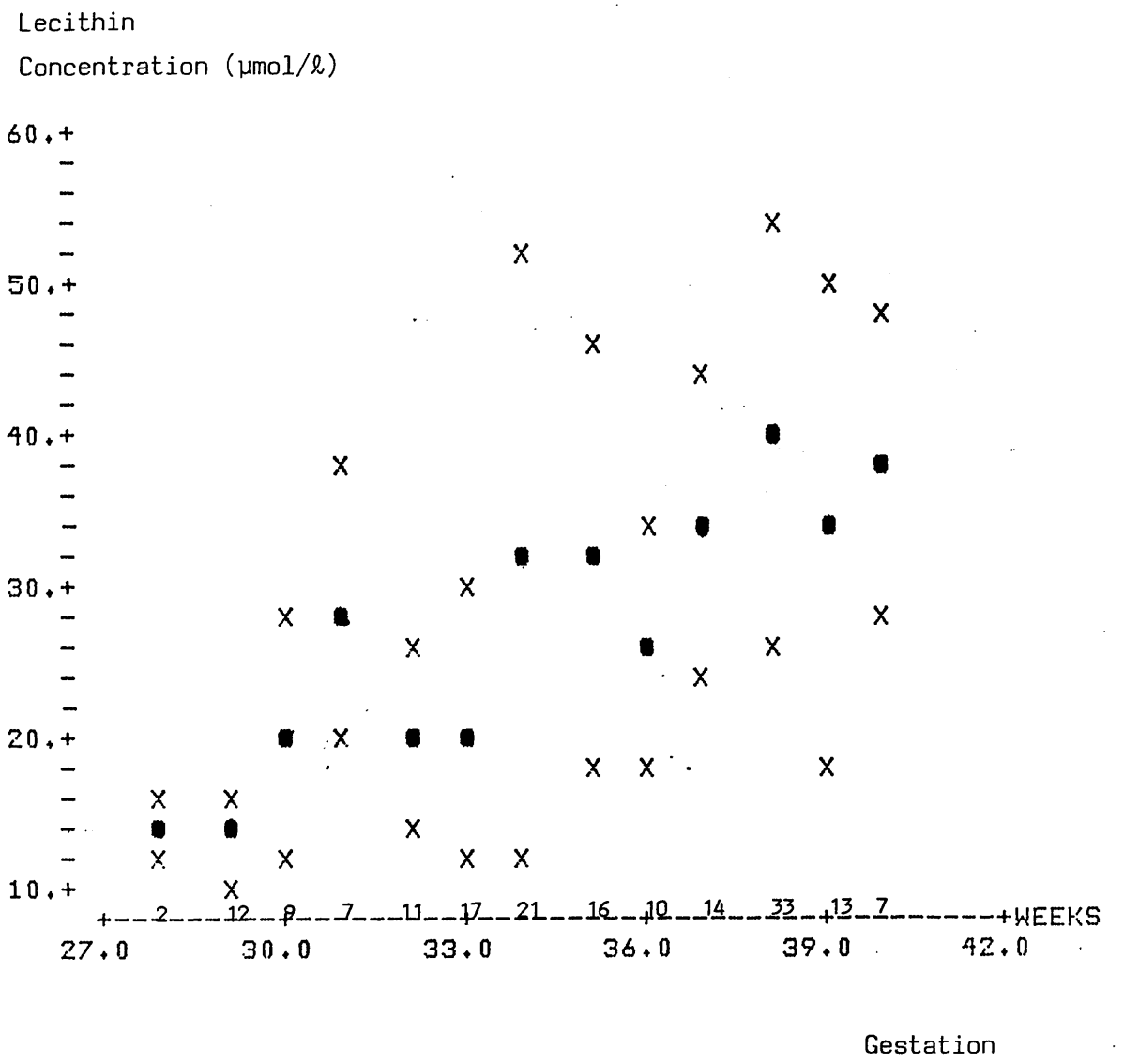


Figure 6.3

Influence of Gestational Age on the PG/S Ratio

(Mean (SD) at each week of gestation)

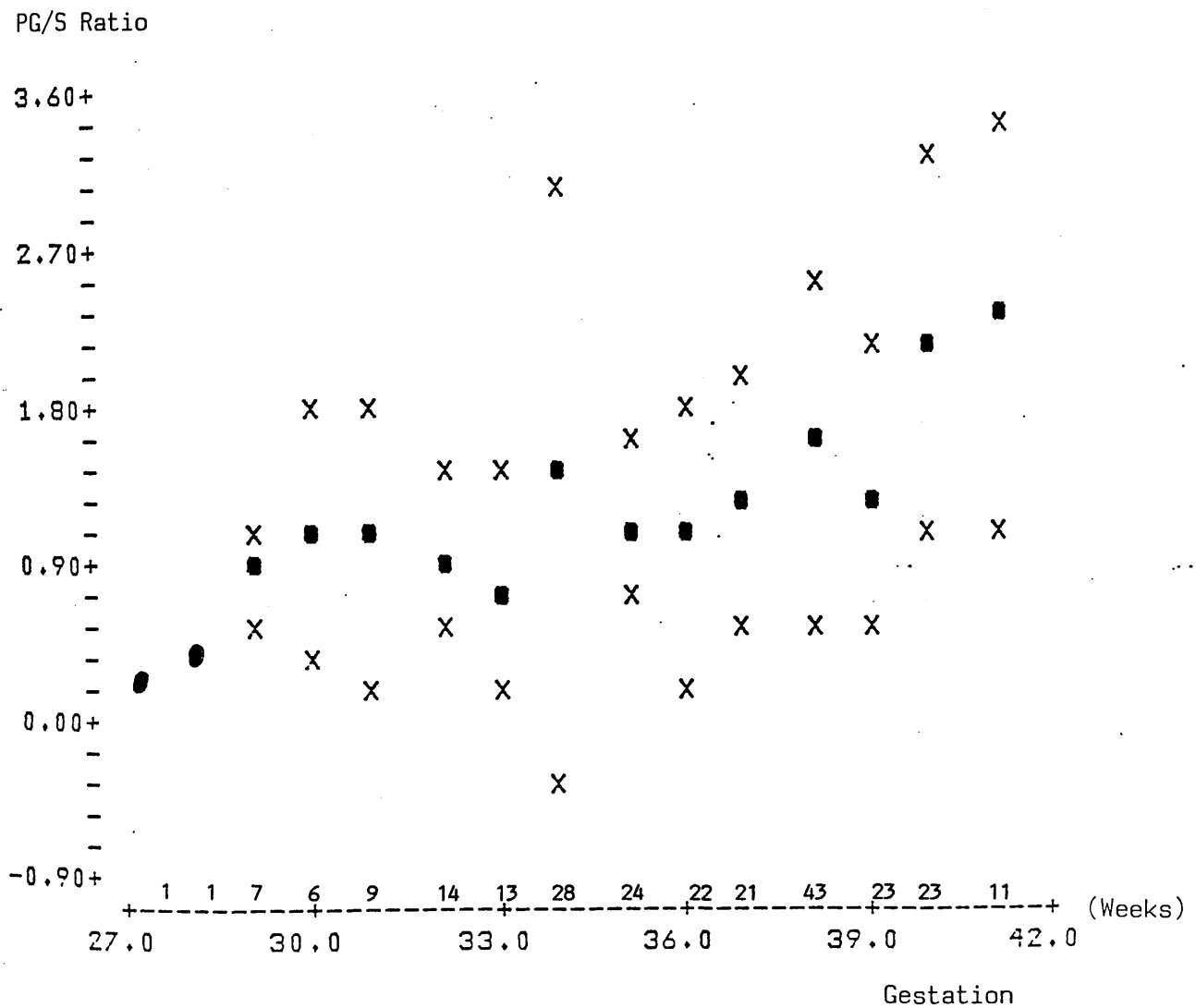


Figure 6.4

Influence of Gestational Age on the Amniotic Fluid PG Concentration

(Mean (SD) at each week of gestation)

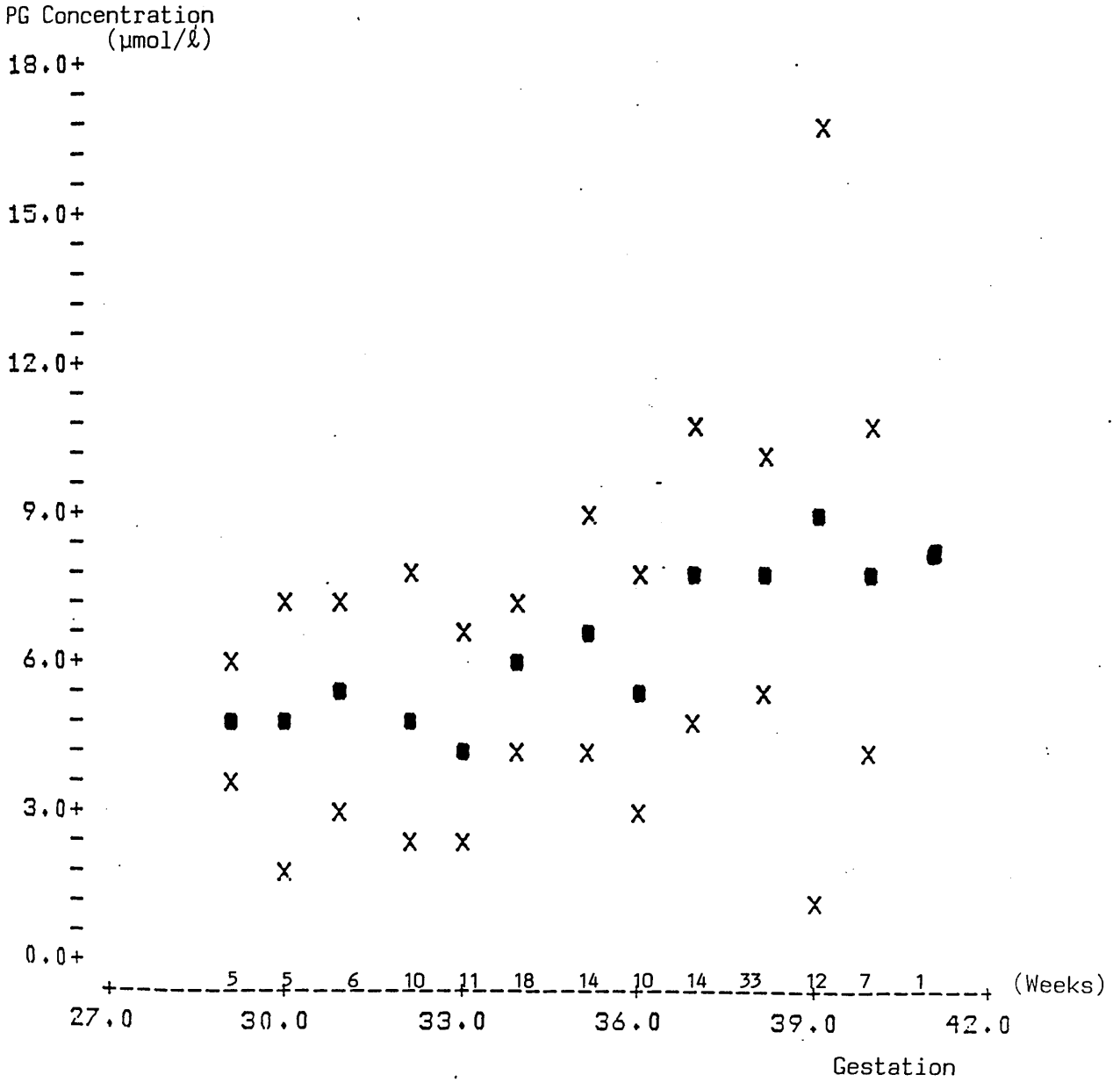


Figure 6.5

Umbilical Arterial Cortisol ((n.mol/ℓ) against Gestational Age in Weeks All Cases Mean (SD)

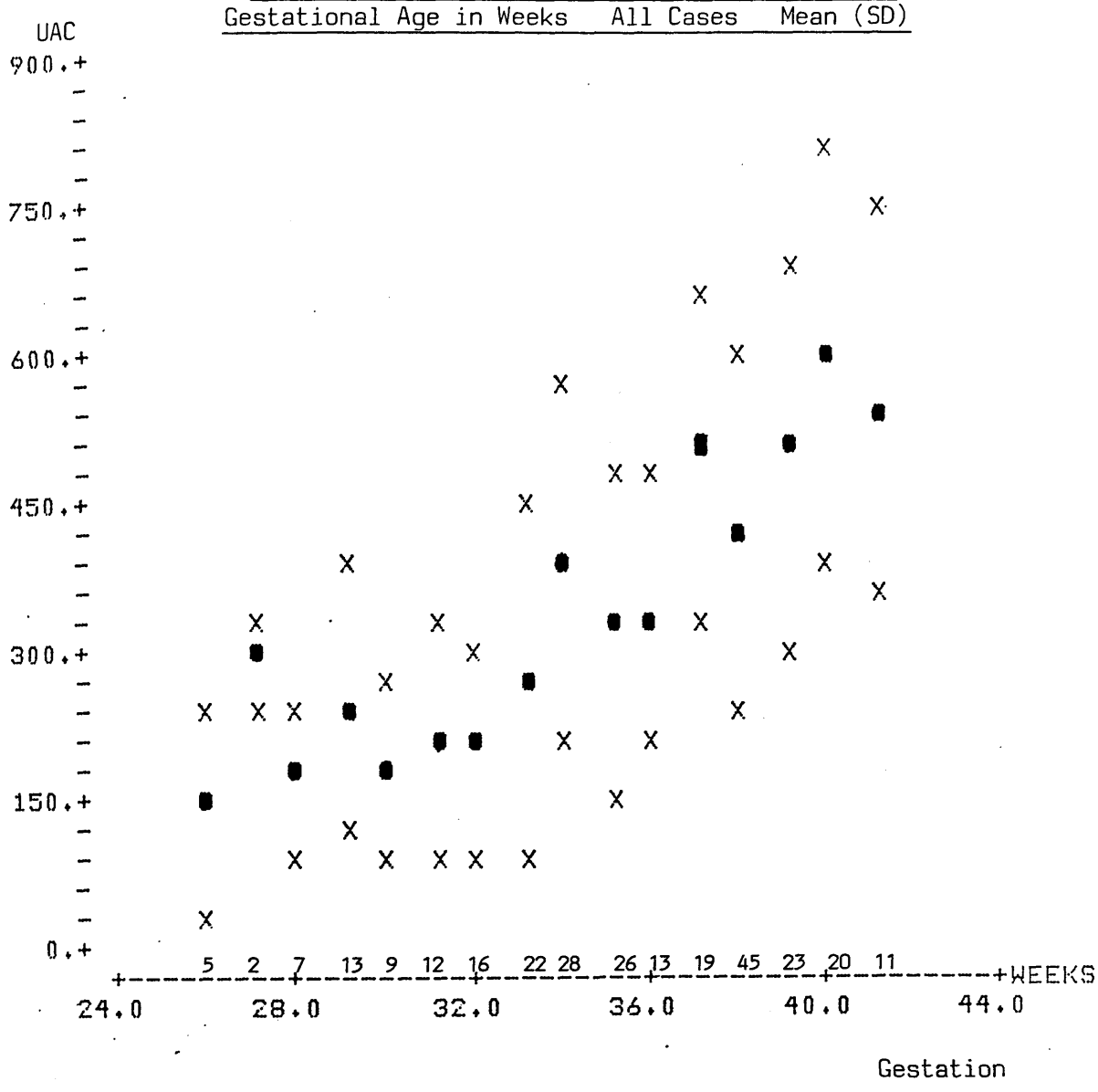


Figure 6.6

Umbilical Arterial Cortisol (nmol/ℓ) against

Gestational Age in Weeks All Vaginal Deliveries Mean (SD)

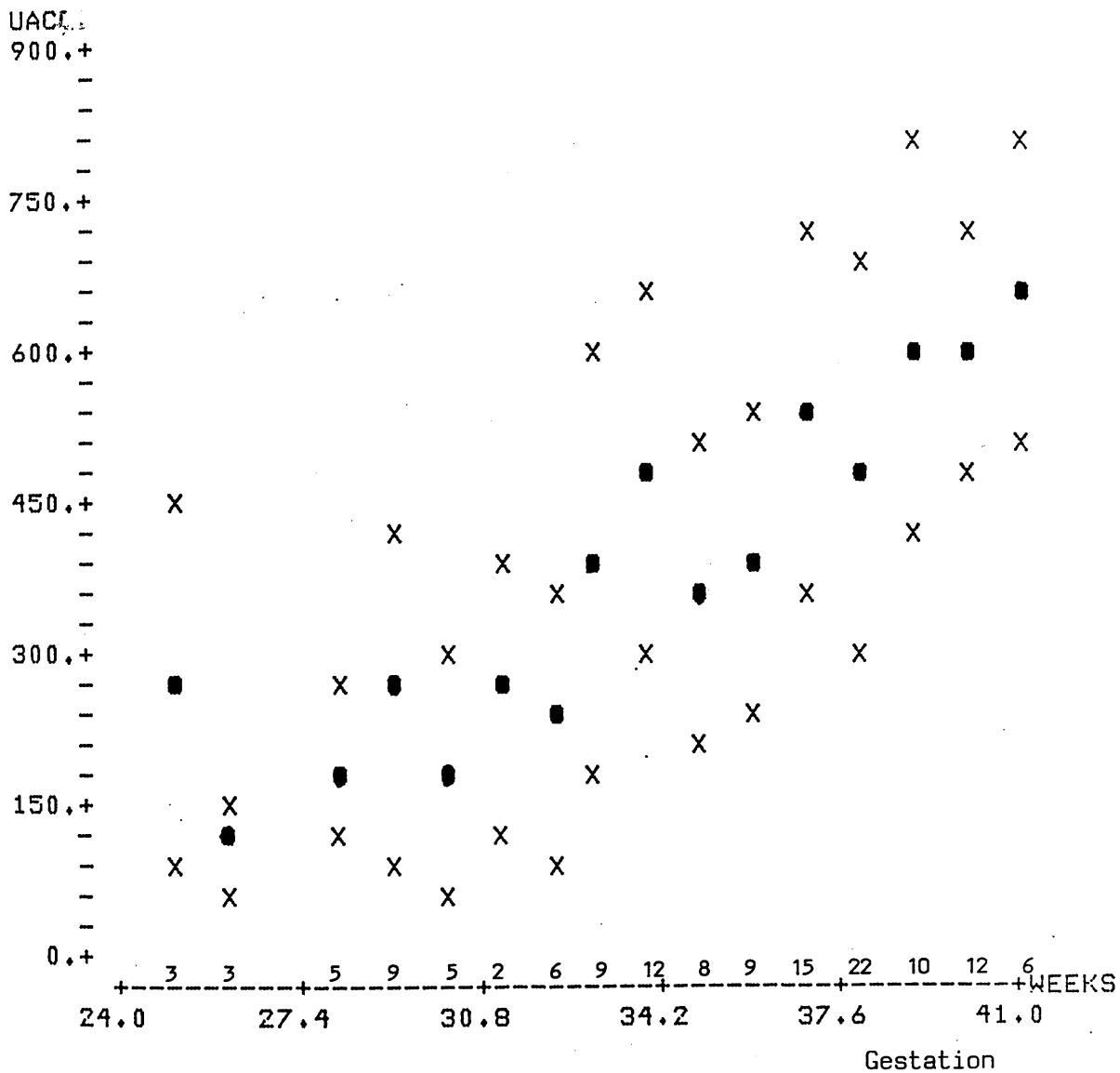


Figure 6.7

Umbilical Arterial Cortisol (nmol/ℓ) against
Gestational Age in Weeks Elective Caesarean Section Mean (SD)

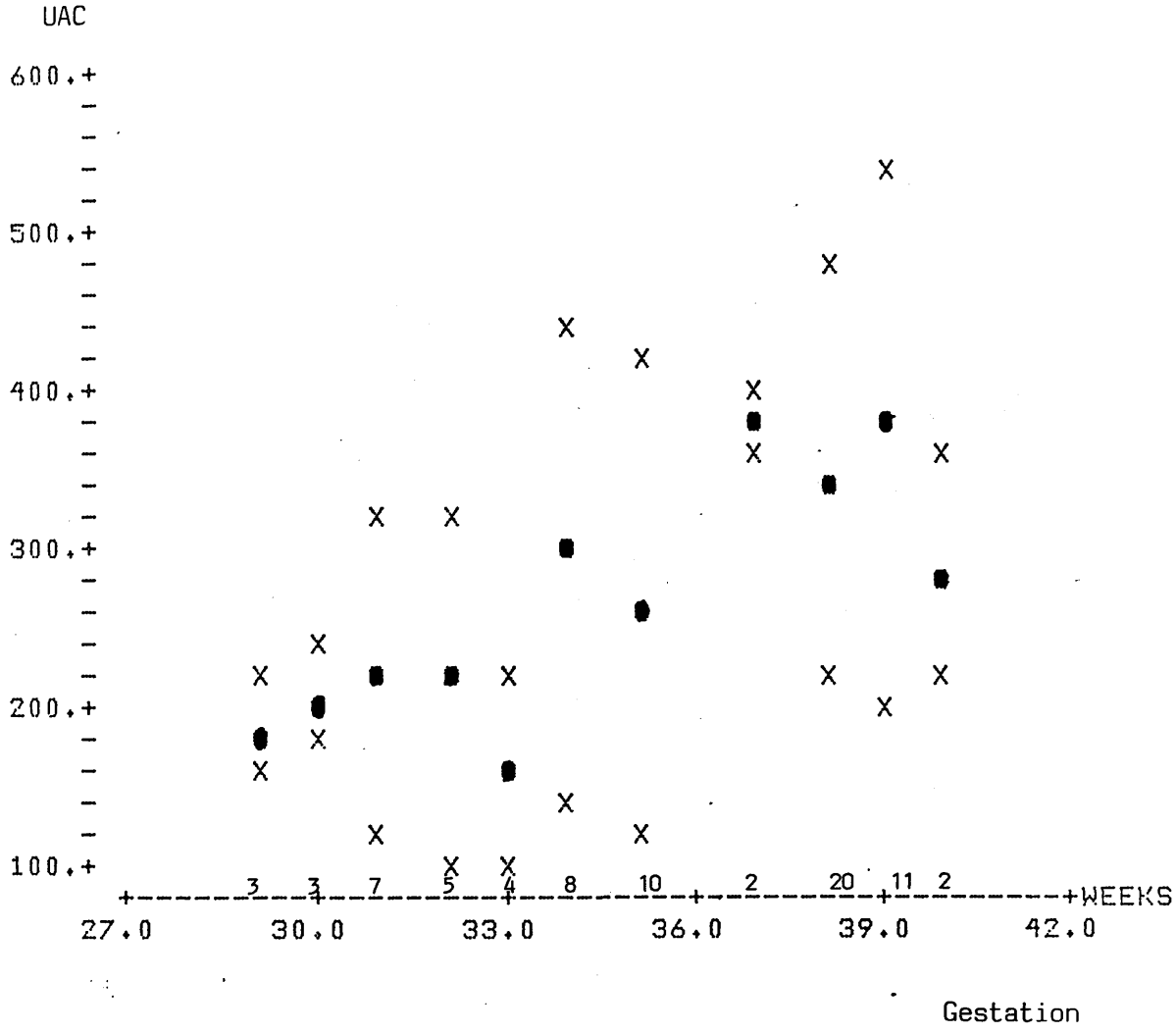


Figure 6.8

Umbilical Arterial Cortisol (nmol/ℓ) against Gestational Age in Weeks Labour and Caesarean Section Mean (SD)

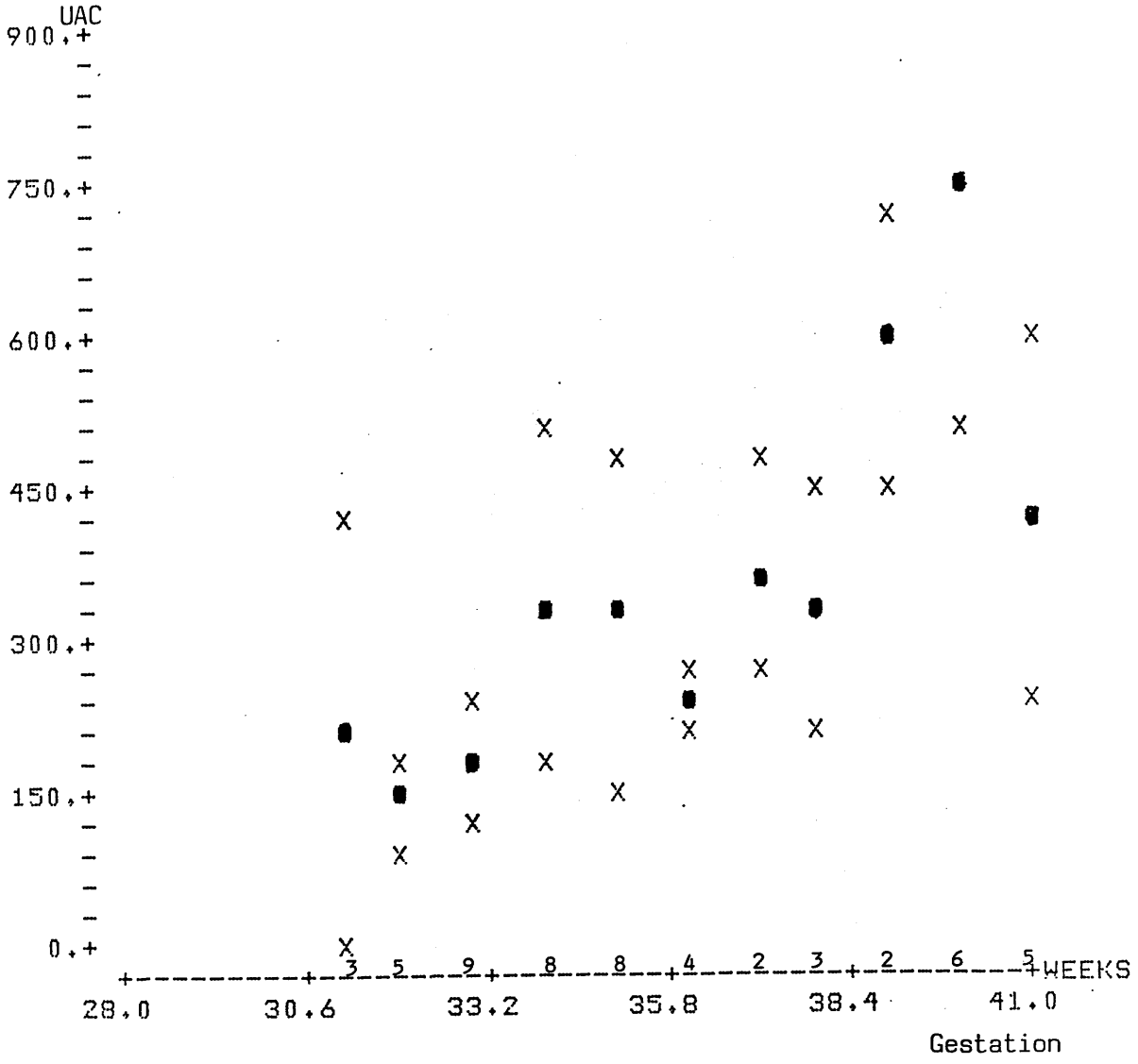


Figure 6.9

Maternal Venous Cortisol (nmol/ℓ) against Gestational Age Mean (SD)

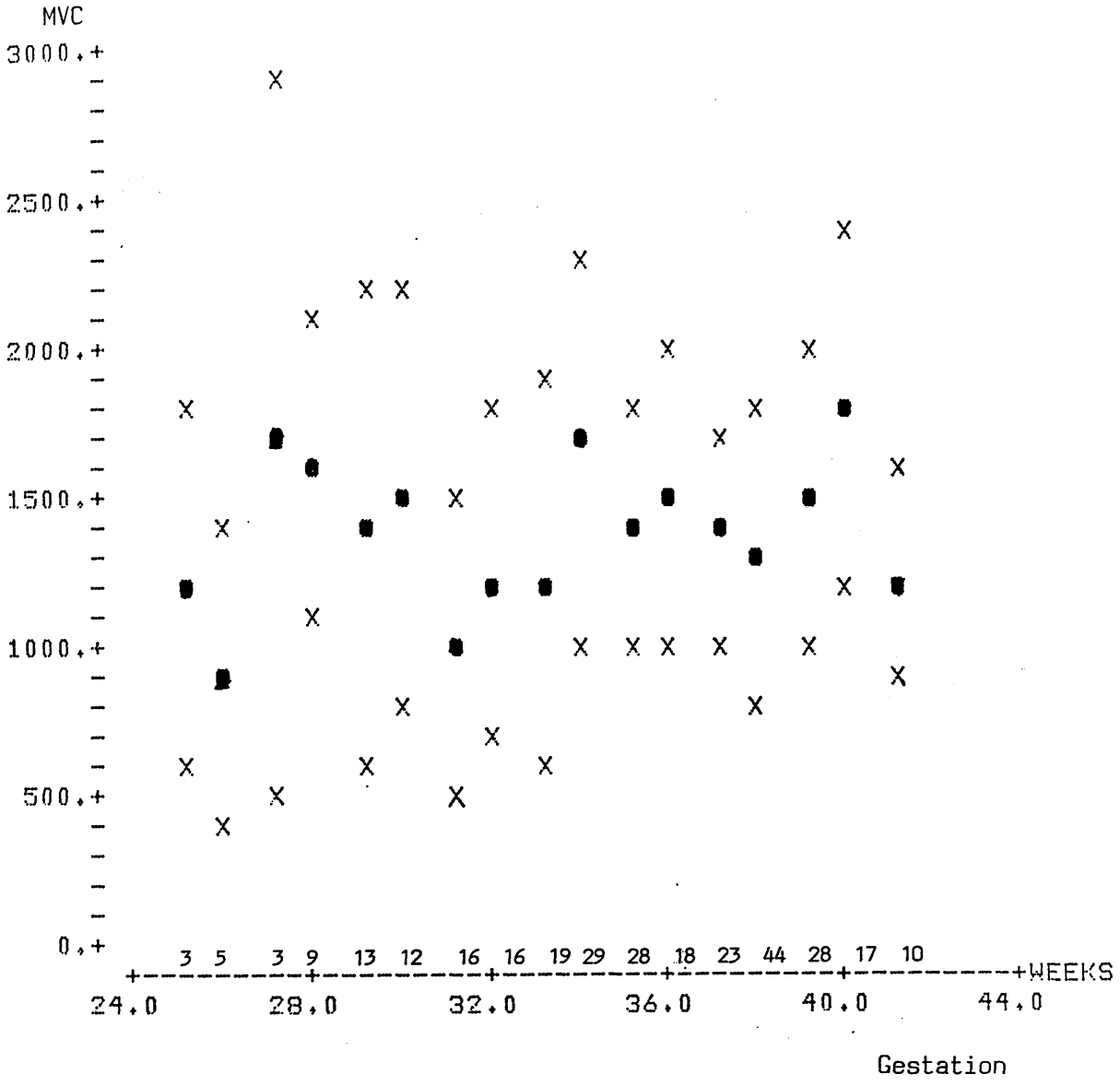


Figure 6.10

Umbilical Arterial Log_{10} Noradrenaline (nmol/ℓ) against Gestational Age in Weeks All Cases Mean (SD)

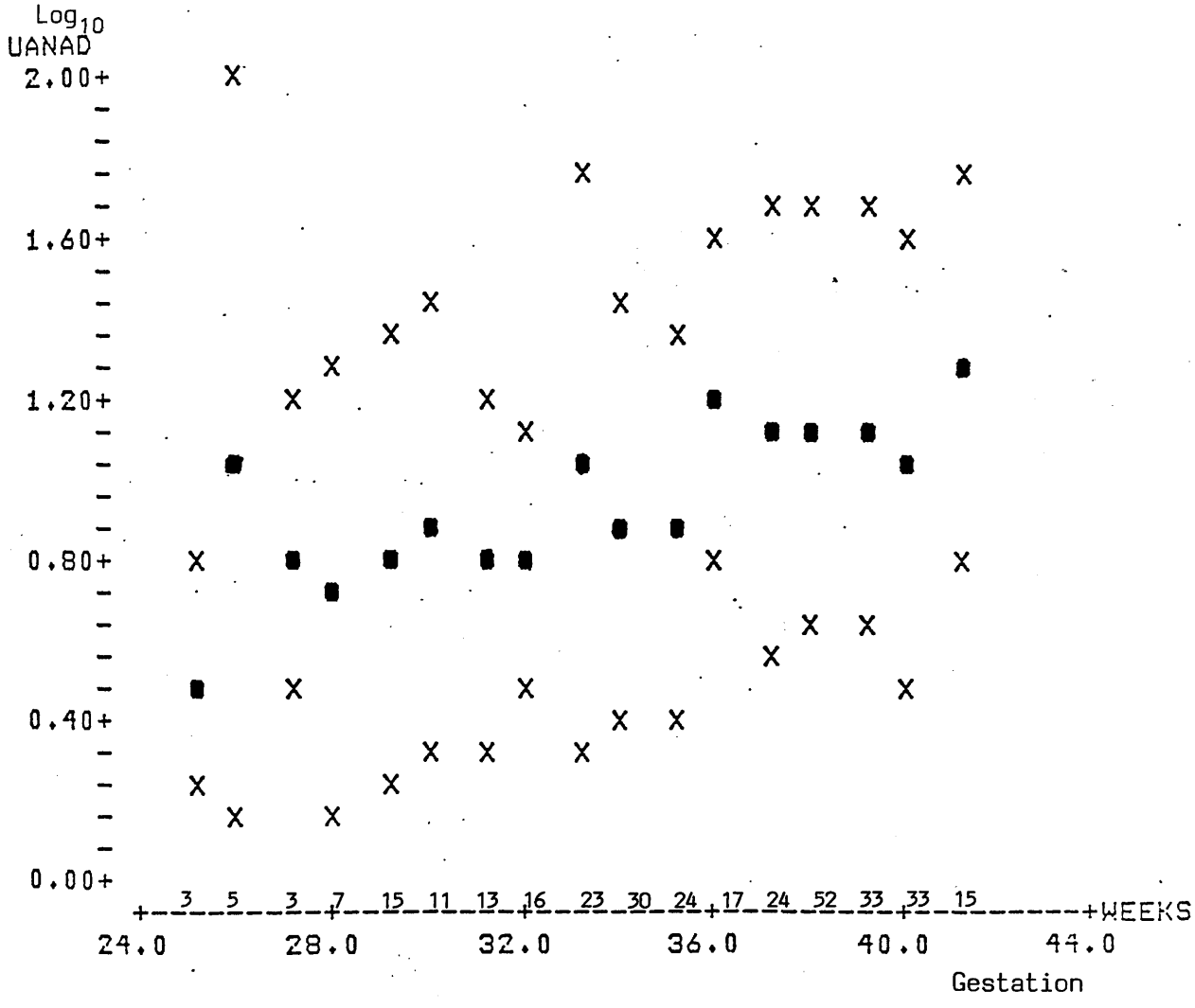


Figure 6.11

Umbilical Arterial Log_{10} Noradrenaline (nmol/ℓ) against
Gestational Age in Weeks All Vaginal Deliveries Mean (SD)

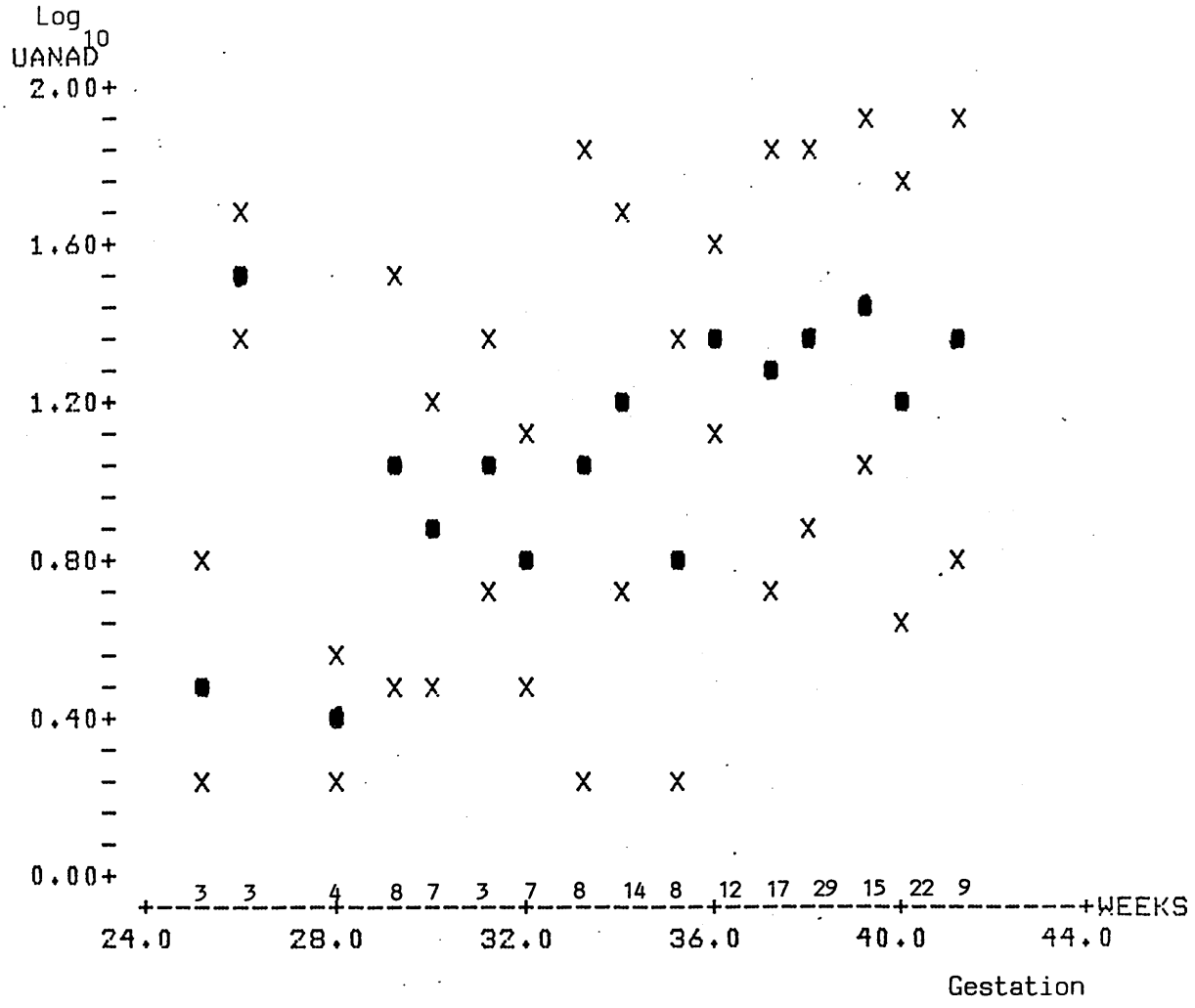


Figure 6.12

Umbilical Arterial Log $_{10}$ NAD (nmol/ℓ) against Gestational Age in Weeks Elective Caesarean Section Mean (SD)

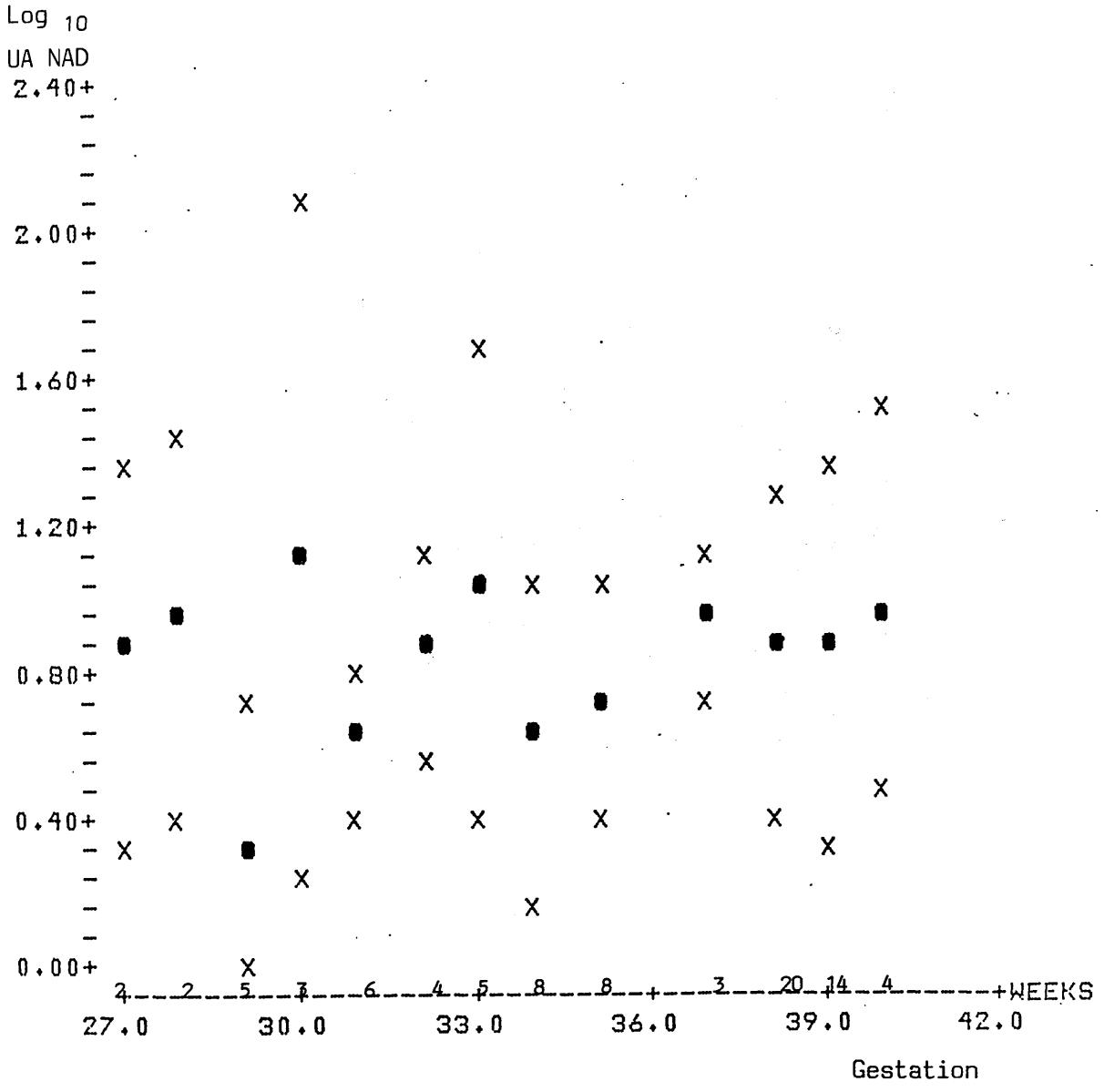


Figure 6.13

Umbilical Arterial Log_{10} NAD (nmol/ℓ) against

Gestational Age in Weeks Caesarean Section Following Labour Mean (SD)

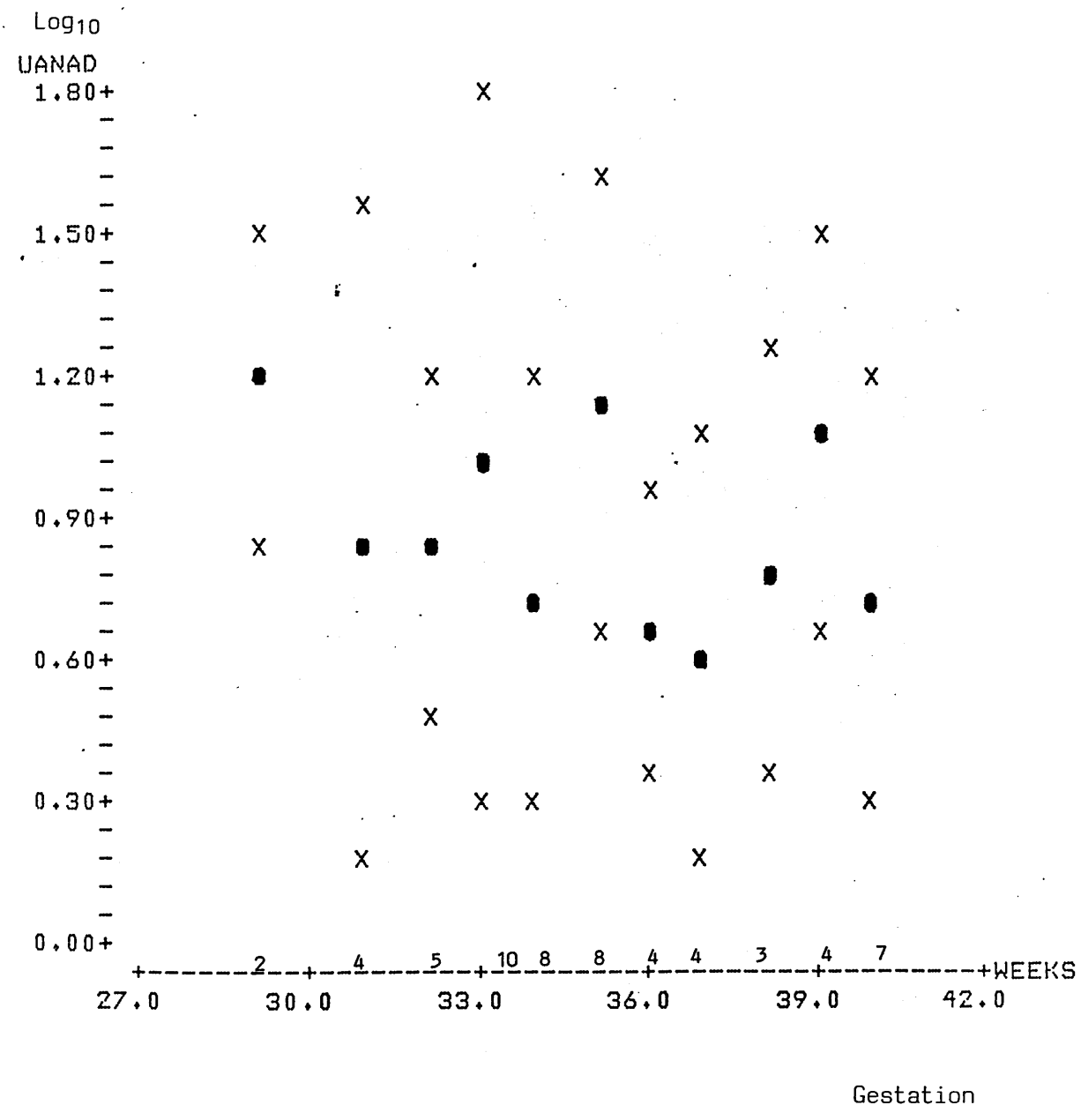


Figure 6.14

Umbilical Arterial Log_{10} Adrenaline (nmol/ℓ) against Gestational Age in Weeks All Cases Mean (SD)

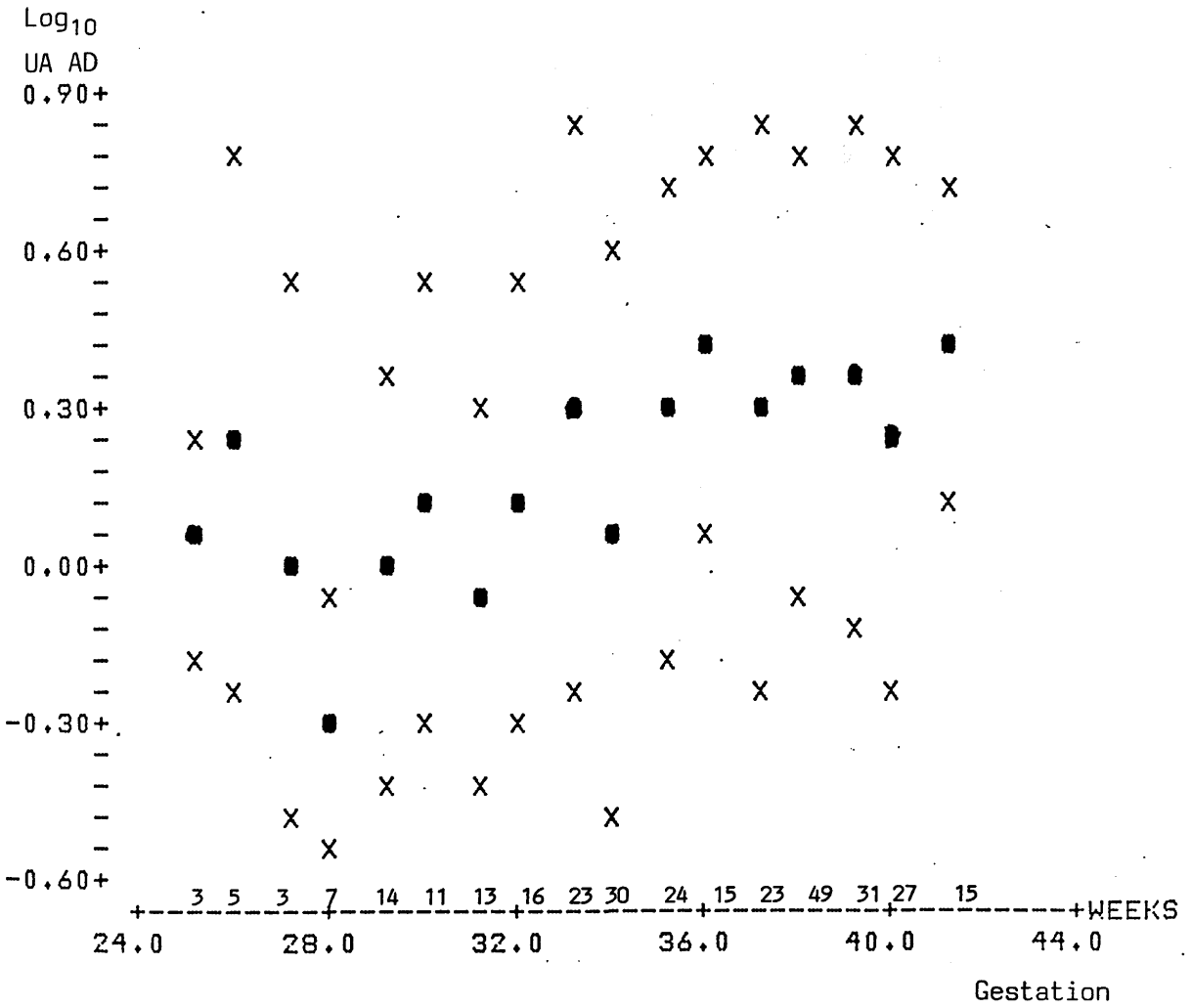


Figure 6.15

Umbilical Arterial Log_{10} Adrenaline (nmol/ℓ) against Gestational Age in Weeks All Vaginal Deliveries Mean (SD)

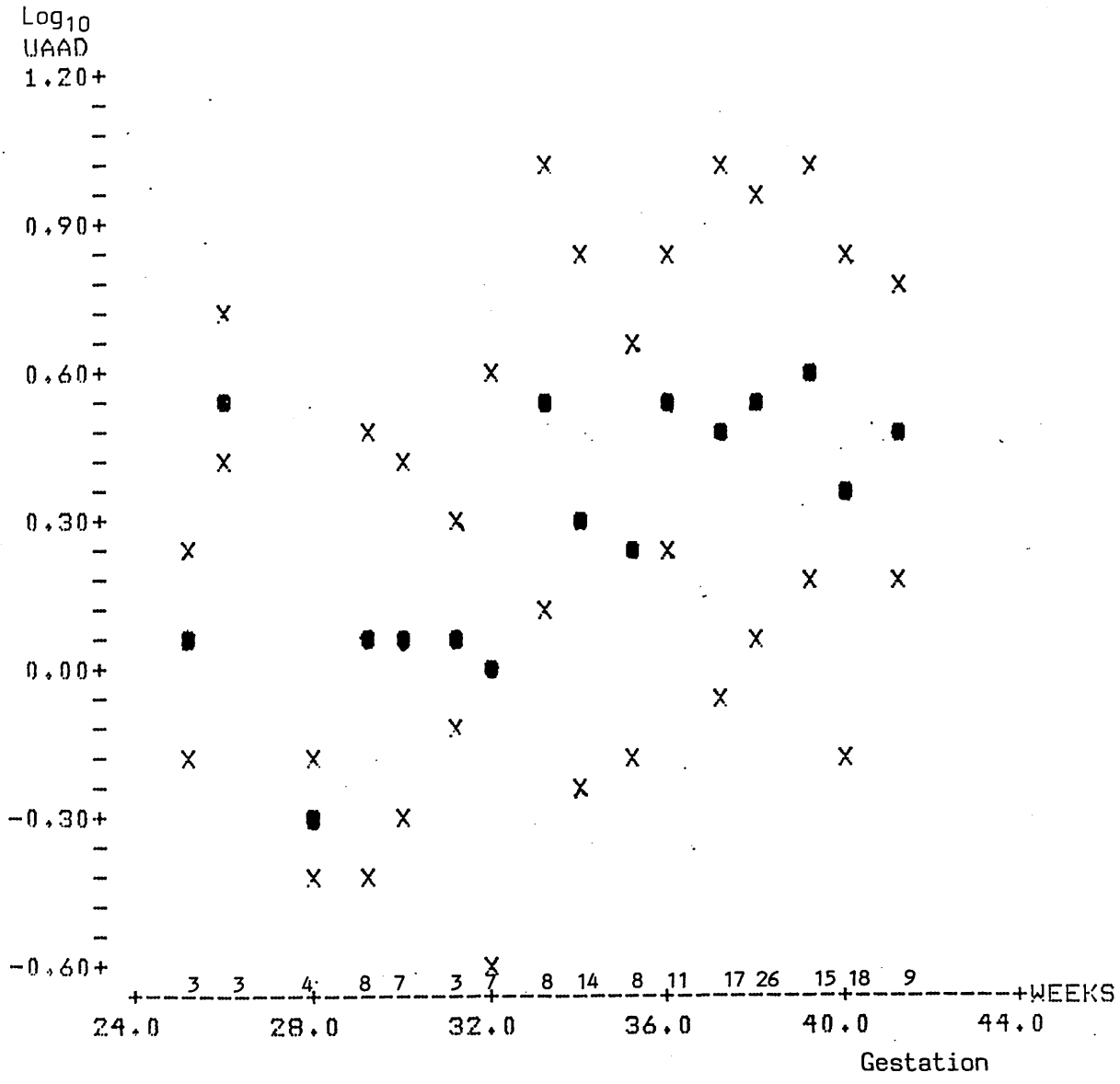


Figure 6.16

Umbilical Arterial Log_{10} Adrenaline (nmol/ℓ) against Gestational Age in Weeks Elective Caesarean Section Mean (SD)

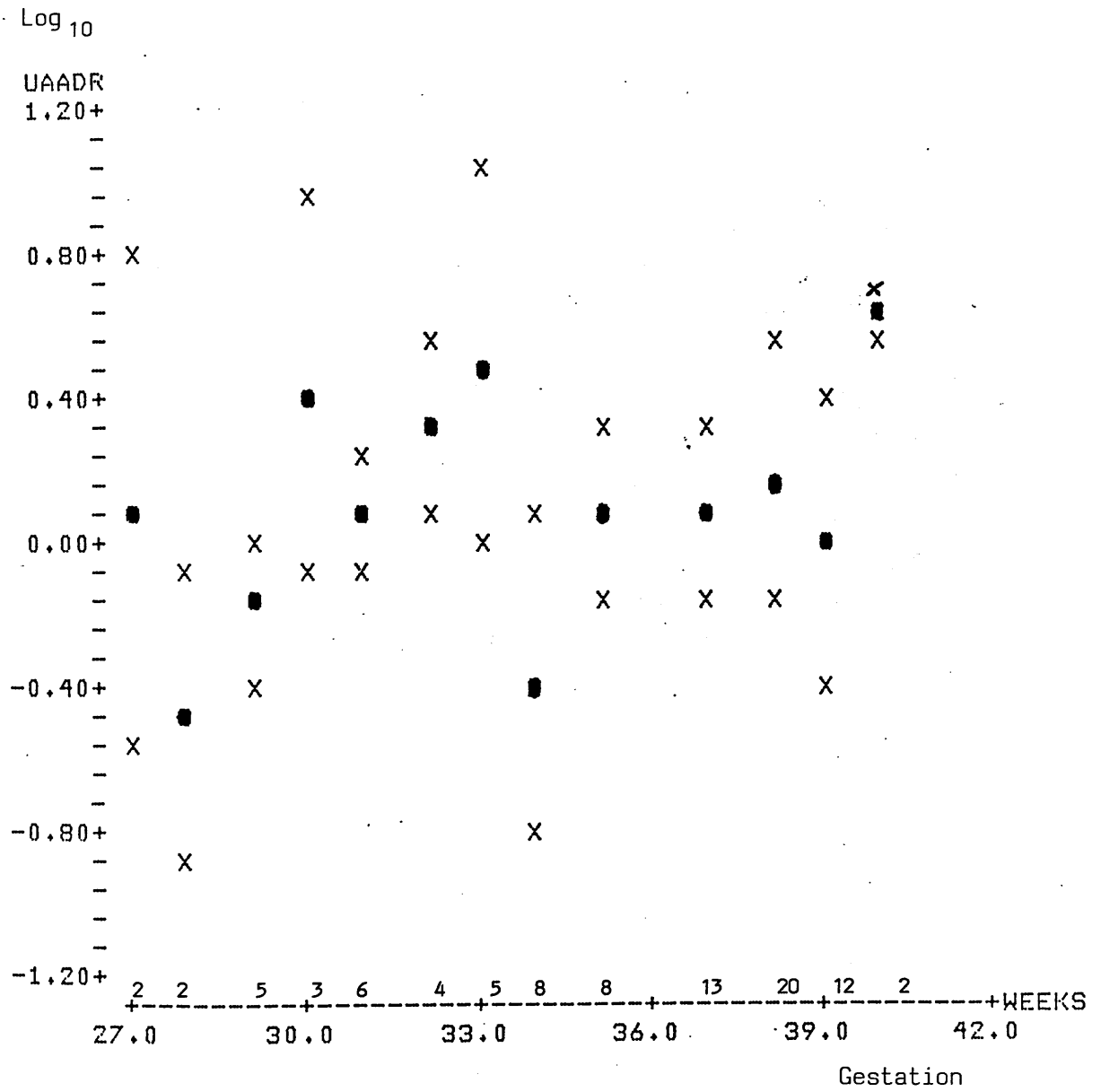


Figure 6.17

Umbilical Arterial Log_{10} Adrenaline against

Gestational Age in Weeks Labour and Caesarean Section Mean (SD)

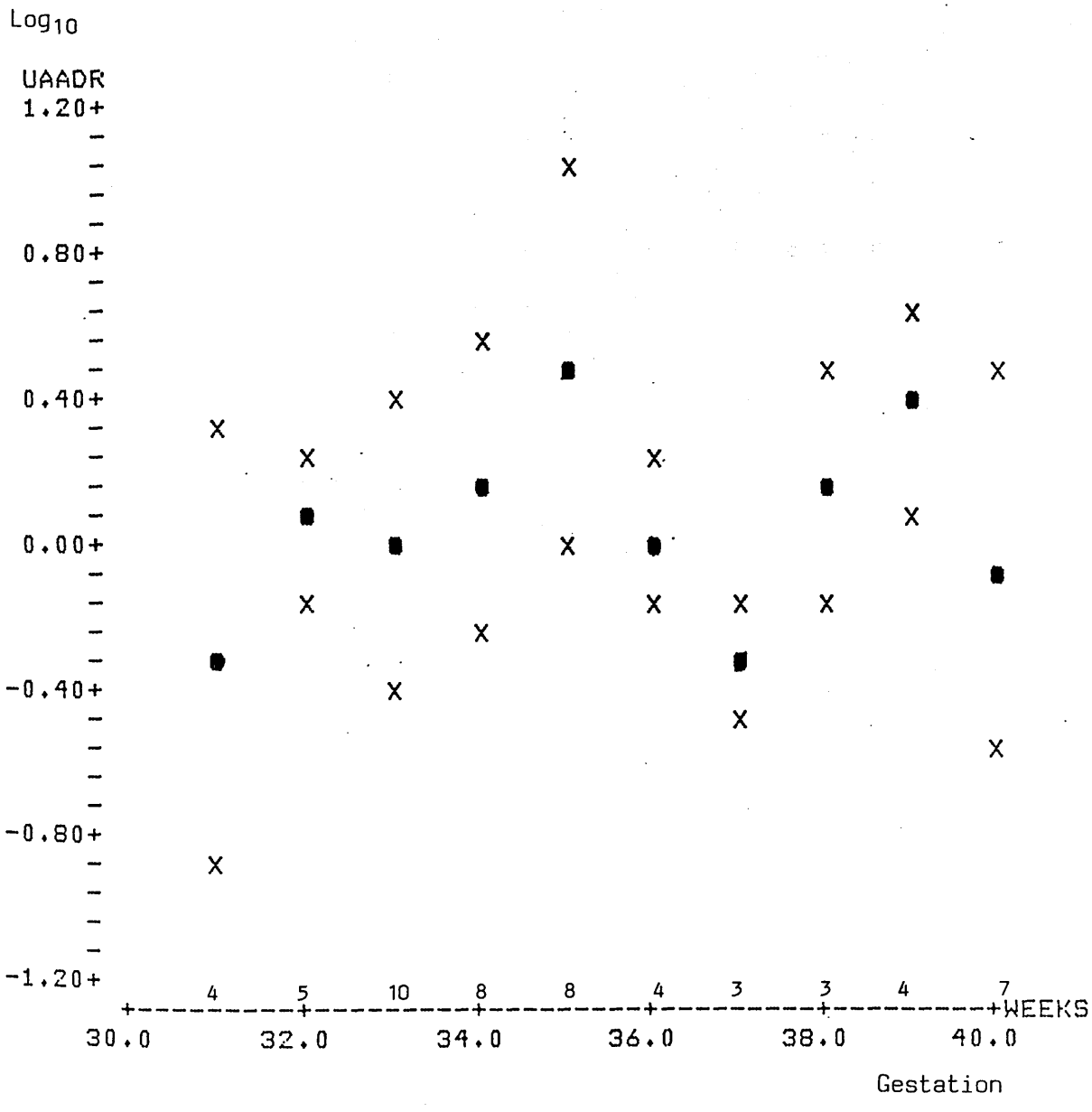


Figure 6.18

Maternal Venous Log_{10} Noradrenaline (nmol/ℓ) against Gestational Age in Weeks All Cases Mean (SD)

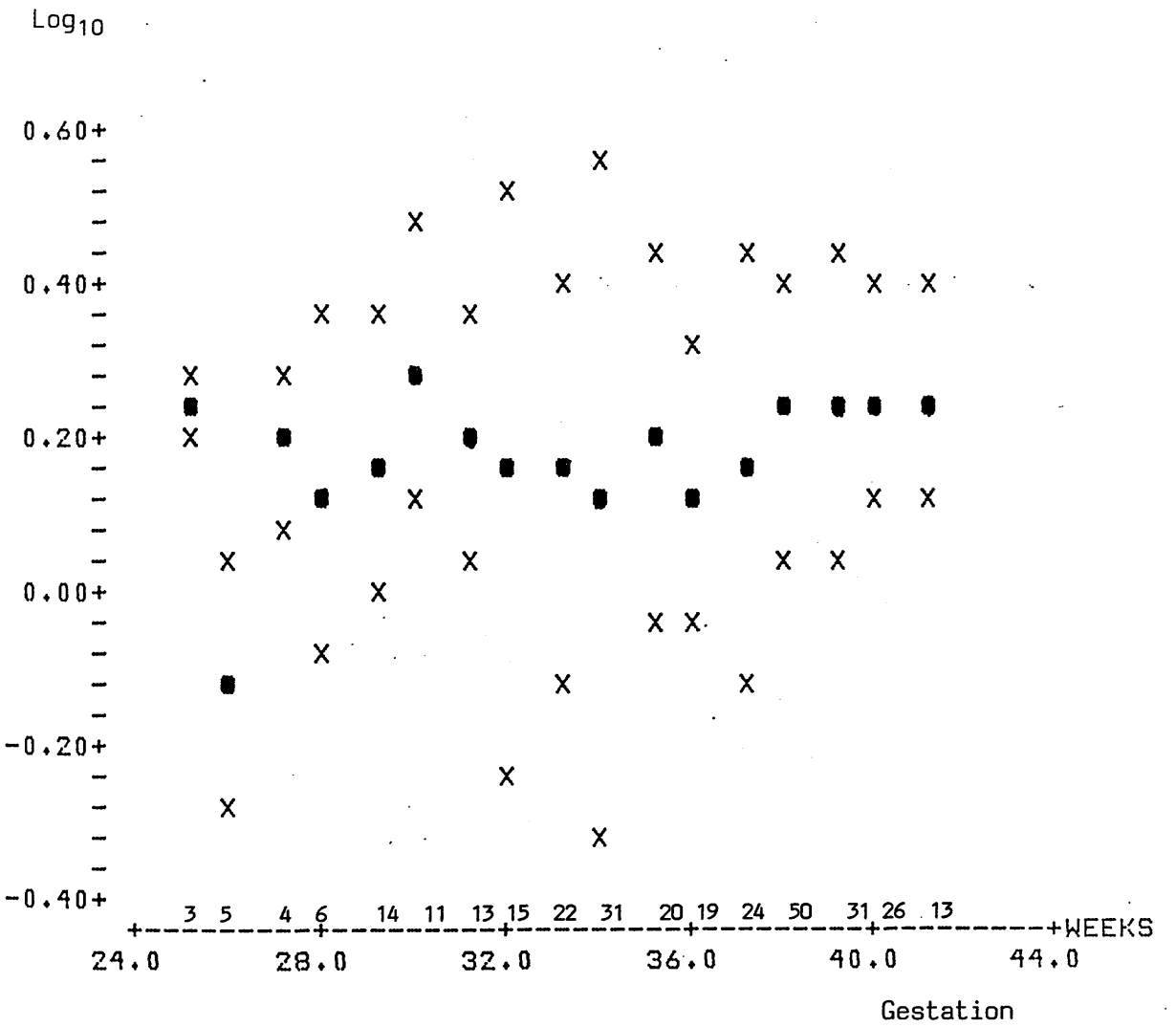


Figure 6.19

Maternal Venous Log_{10}Adrenaline (nmol/ℓ) against Gestational Age in Weeks All Cases Mean (SD)

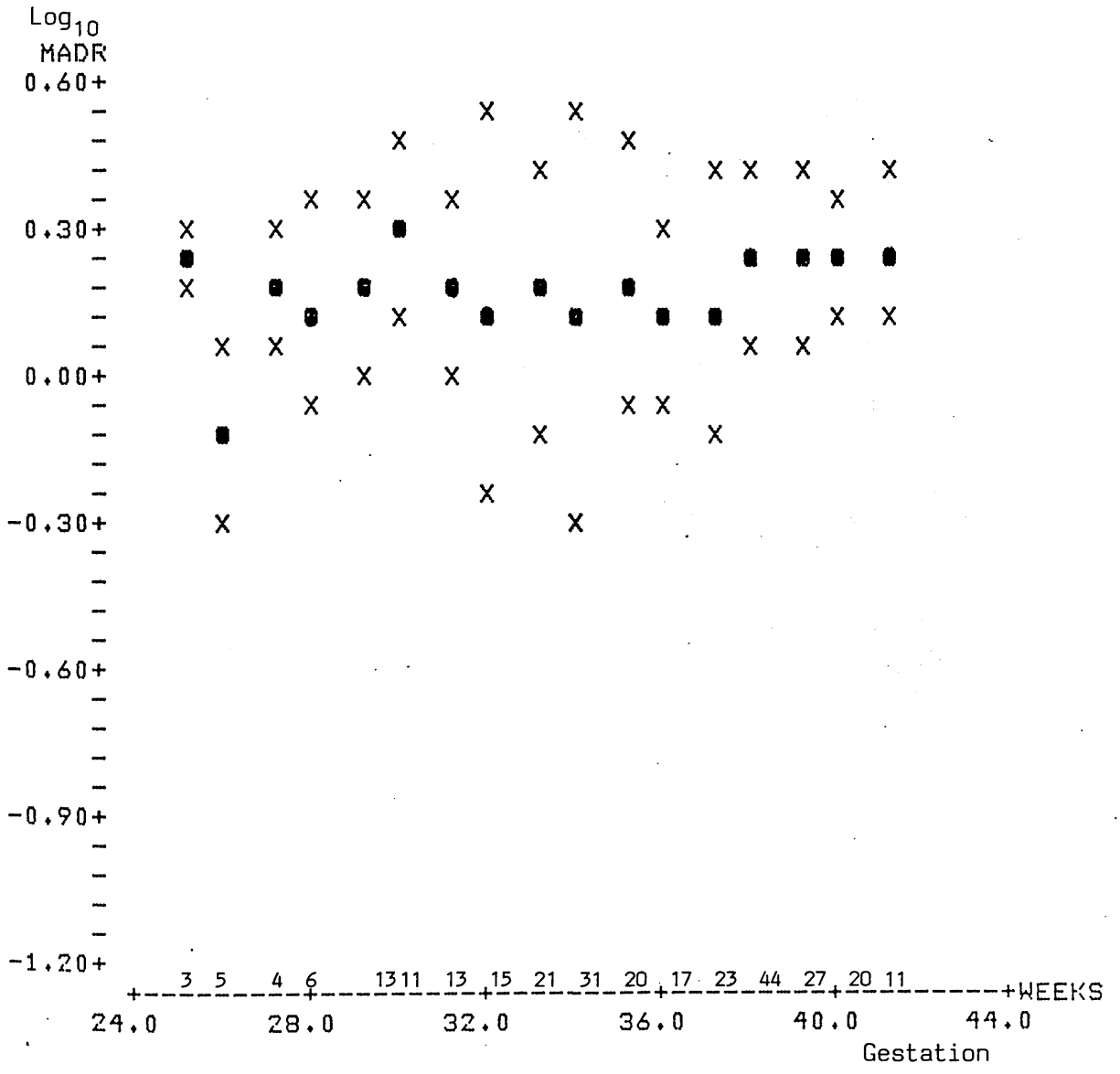


Fig 6.20

Relationship between UA AD & UA NAD for term (36-41 weeks) & preterm (25-35 weeks)

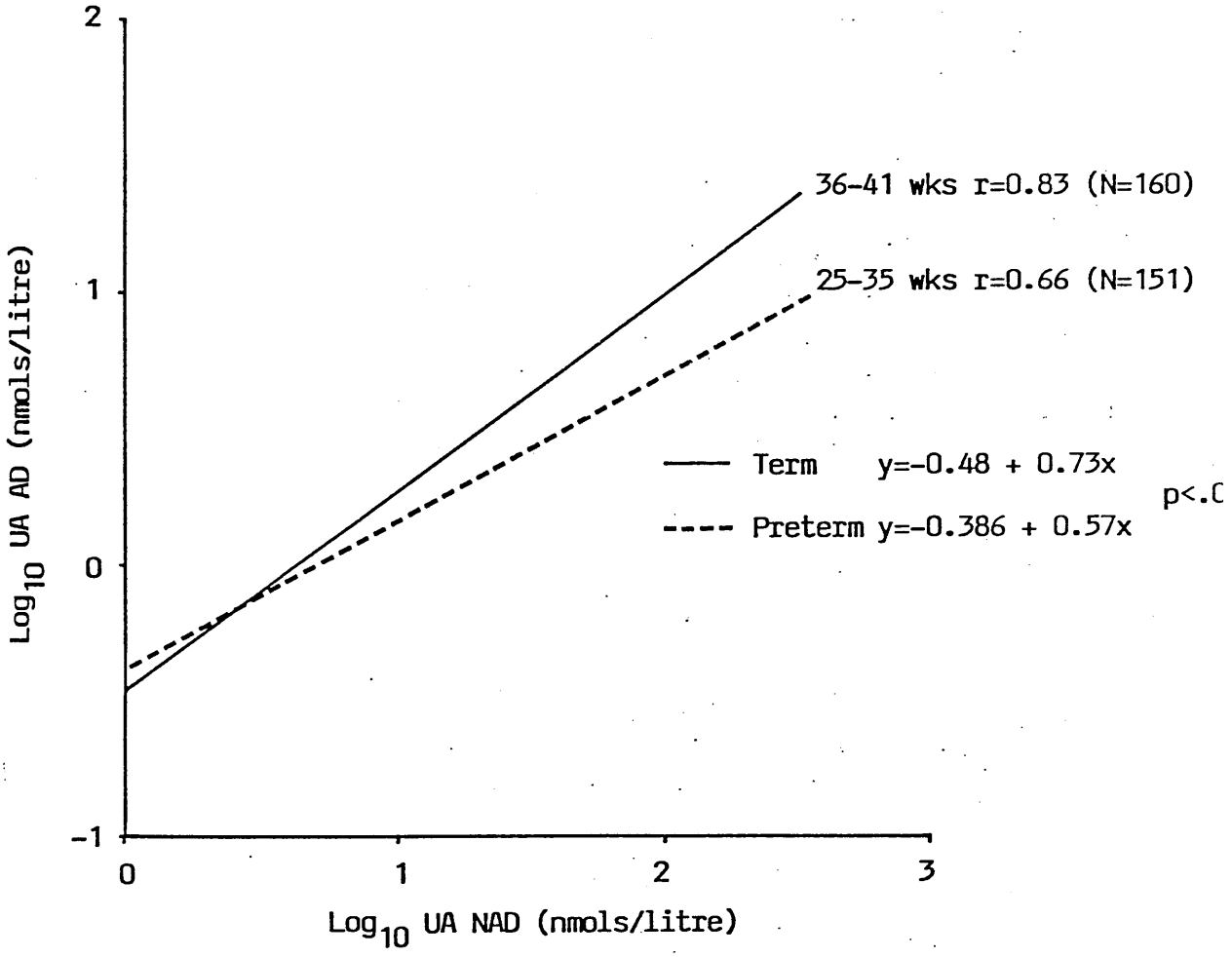


Fig. 6.21

Relationship between UA NAD & UA AD by gestational age groups

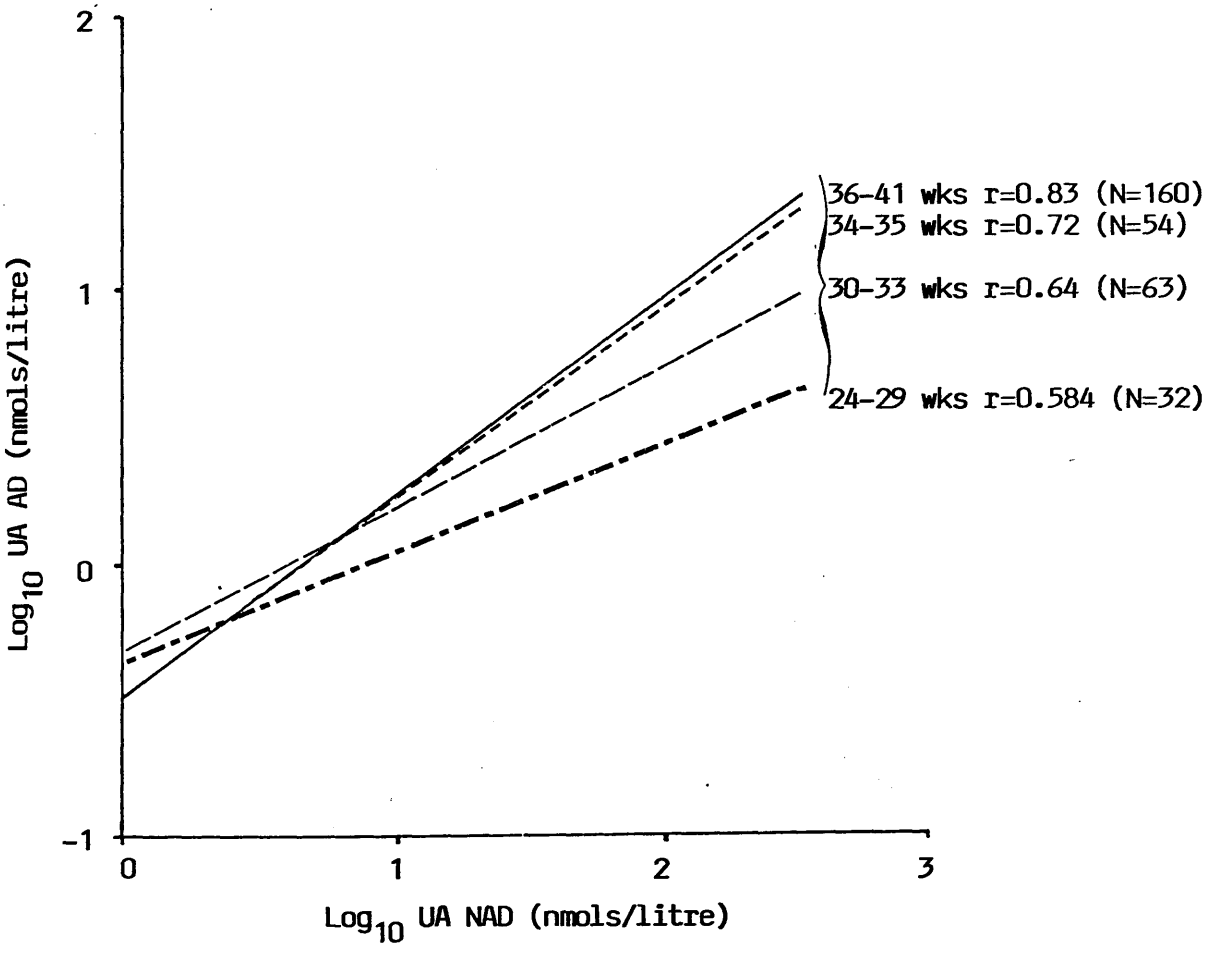


Figure 6.22

Umbilical Arterial NAD/AD Ratio against
Gestational Age in Weeks All Cases Mean (SD)

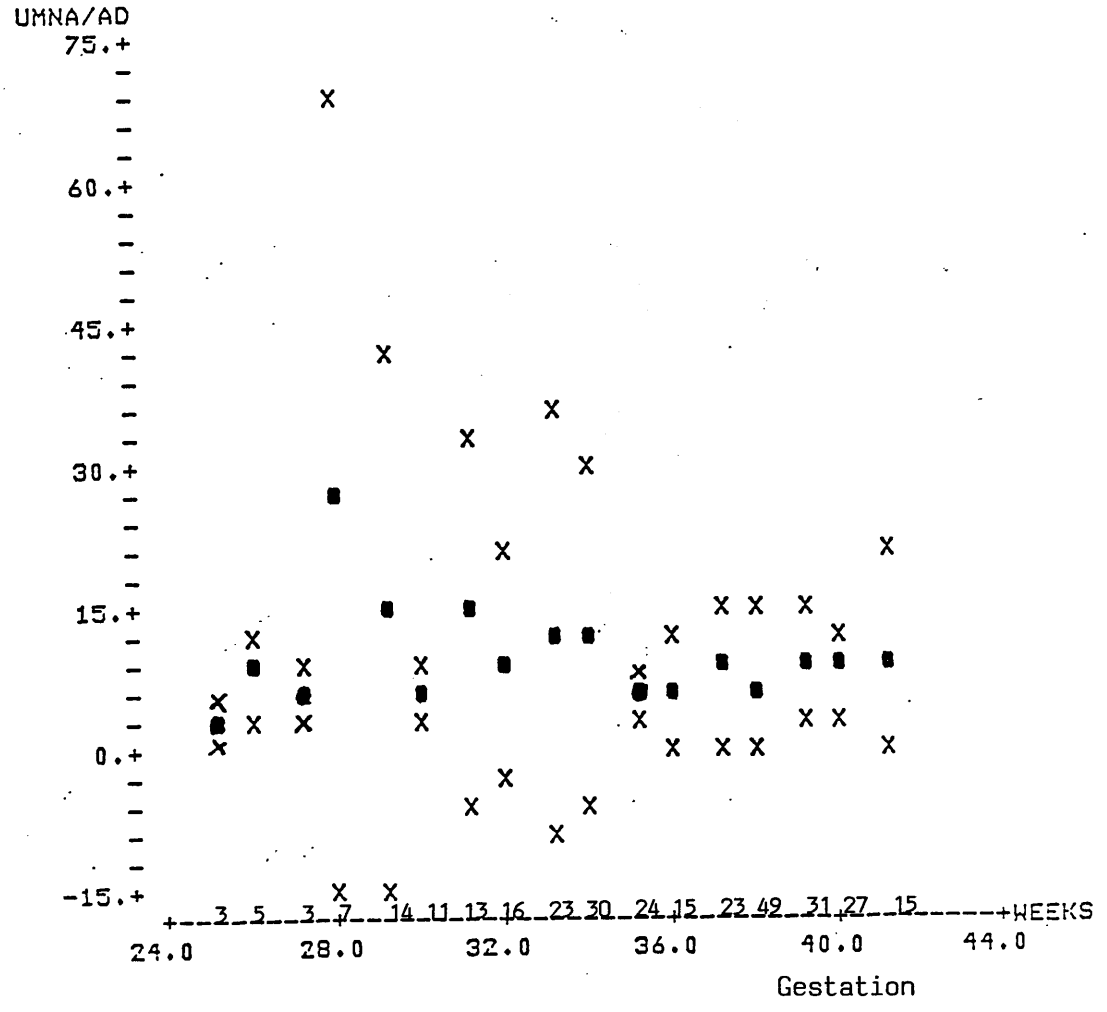
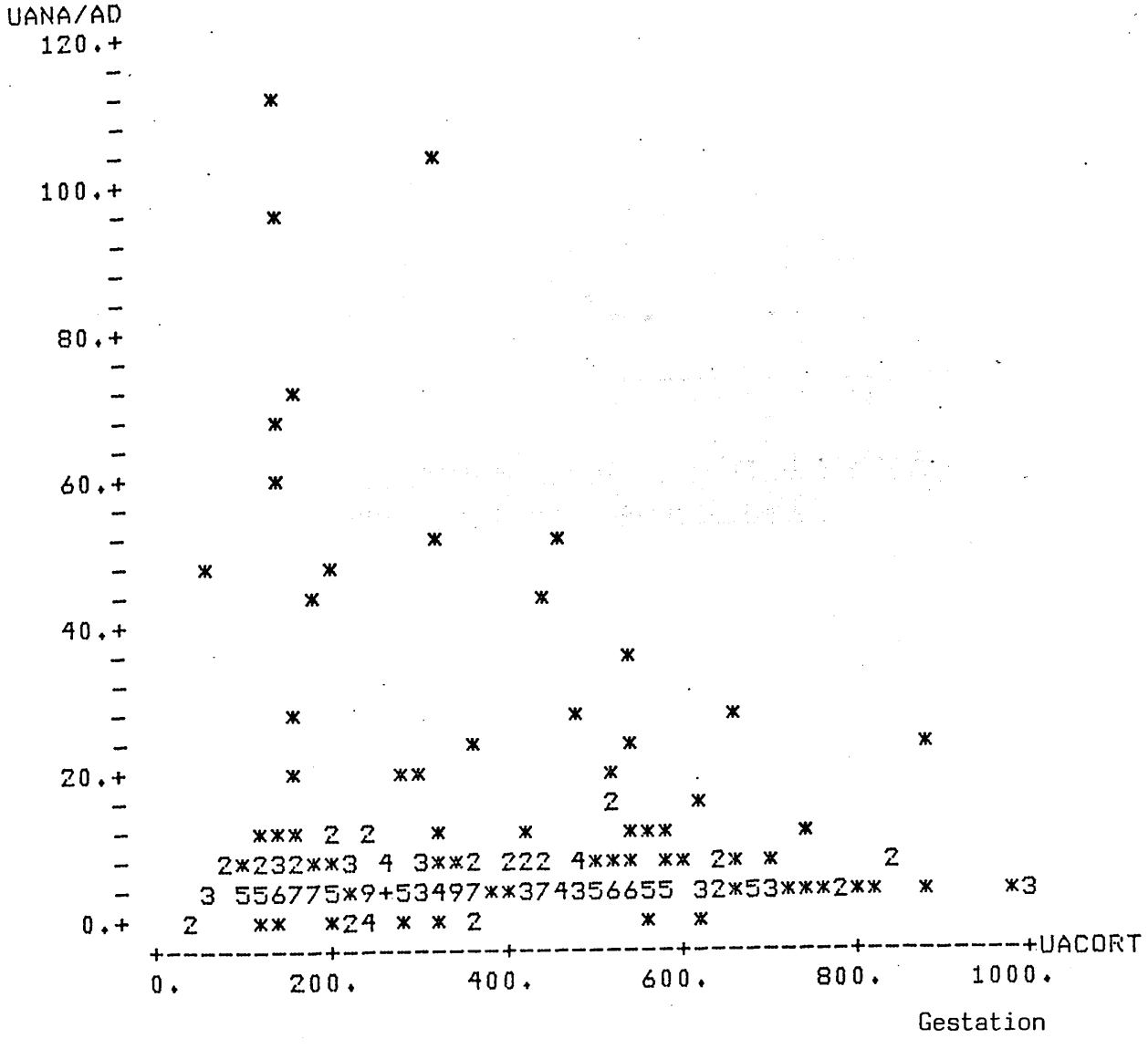


Figure 6.23

The Relationship between the Umbilical Arterial NAD/AD Ratio and Umbilical Arterial Cortisol (nmol/ℓ) All Cases

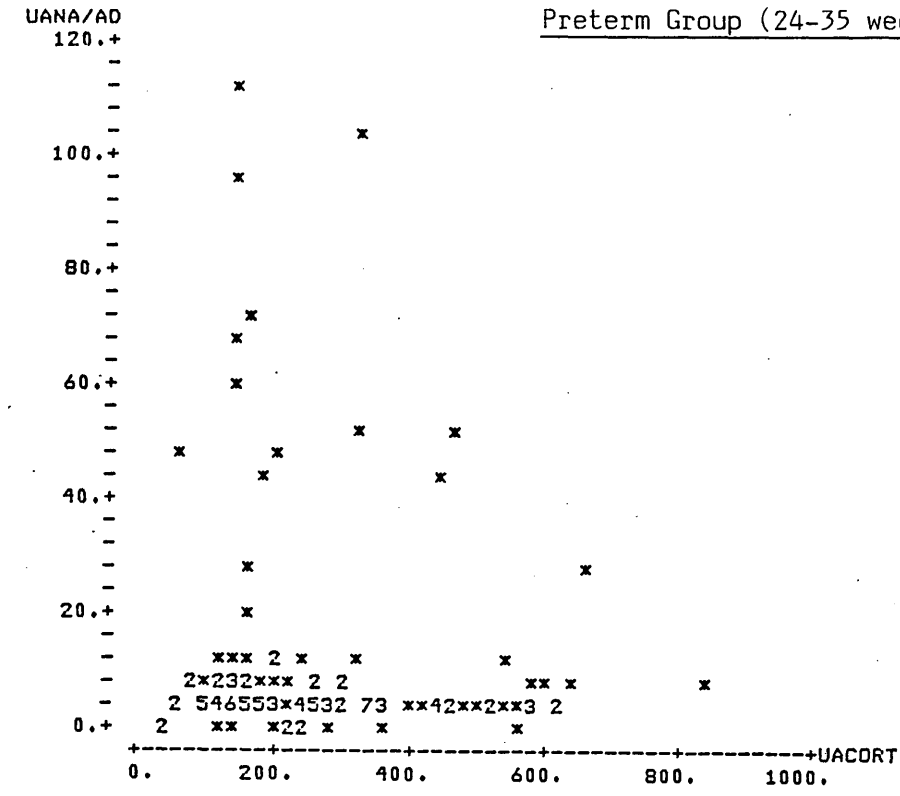


* = 1 observation

number = number of observations at that point

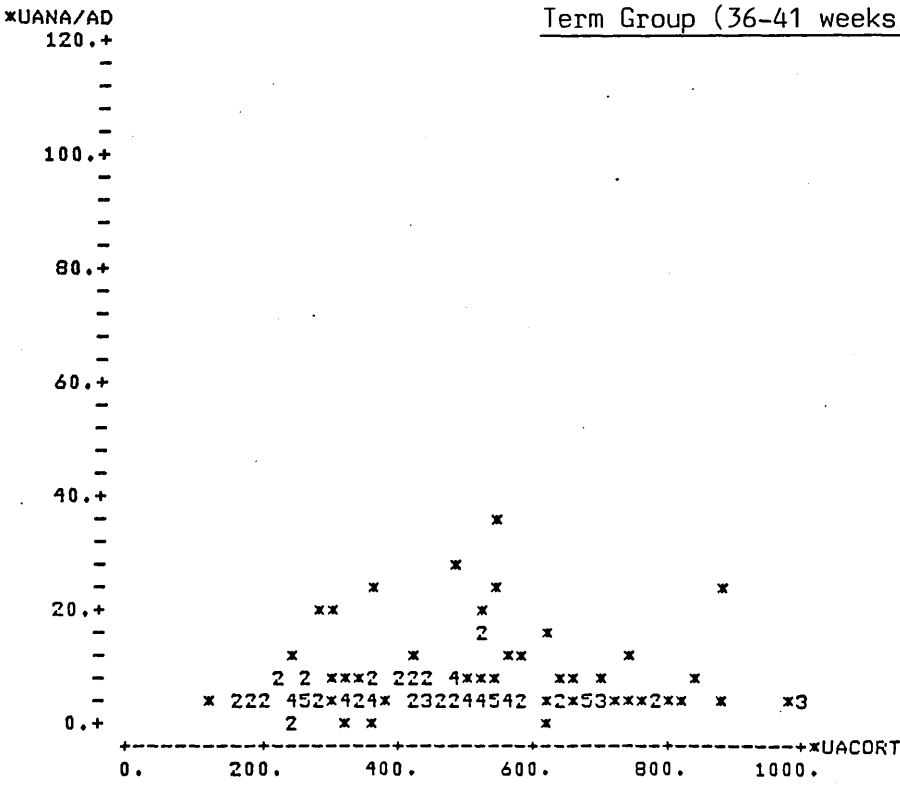
\+ = 10 observations

Figure 6.24



Preterm Group (24-35 weeks)

The Relationship between the Umbilical Arterial NAD/AD Ratio and Umbilical Arterial Cortisol (nmol/ℓ)



Term Group (36-41 weeks)

Figure 6.25

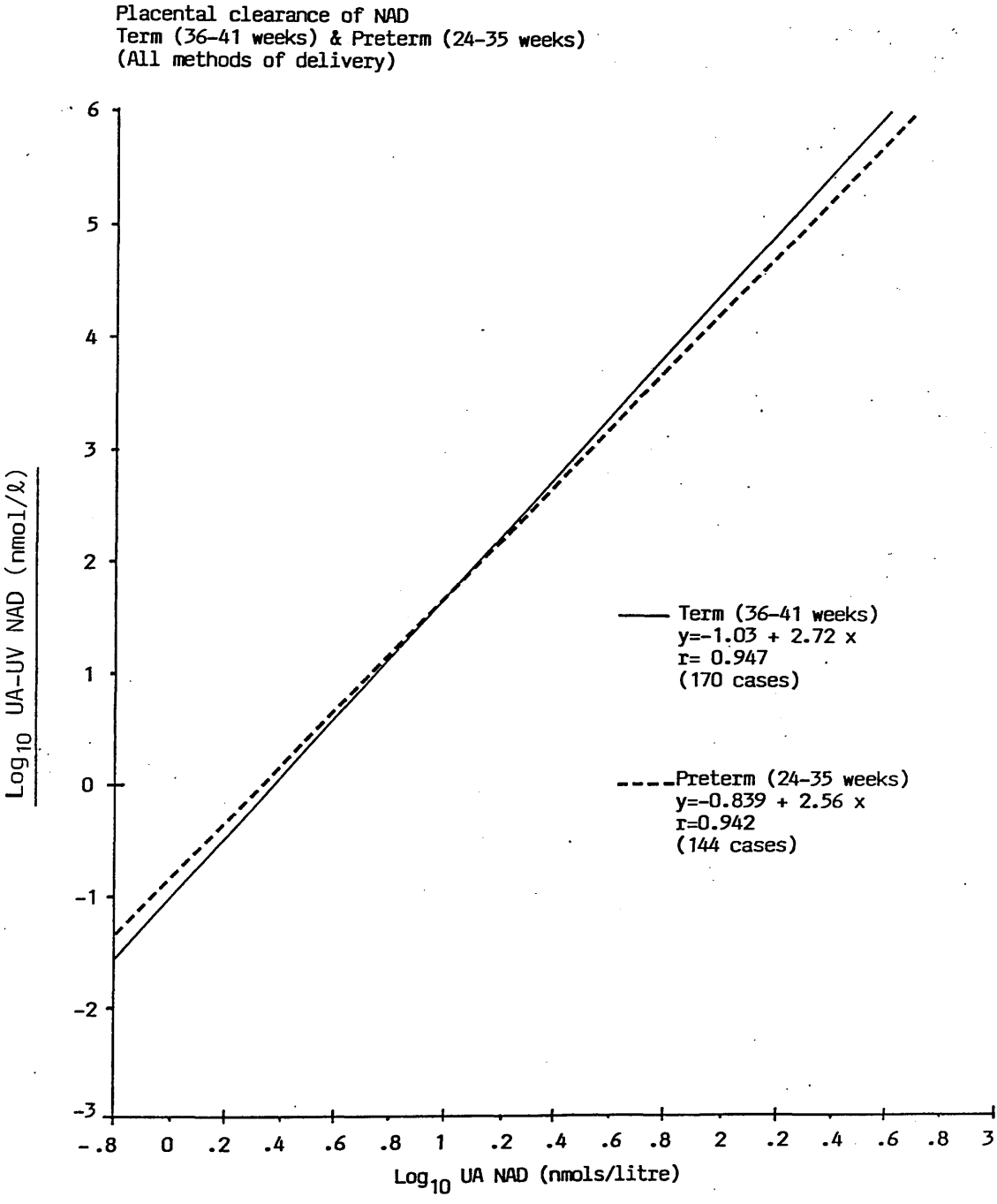
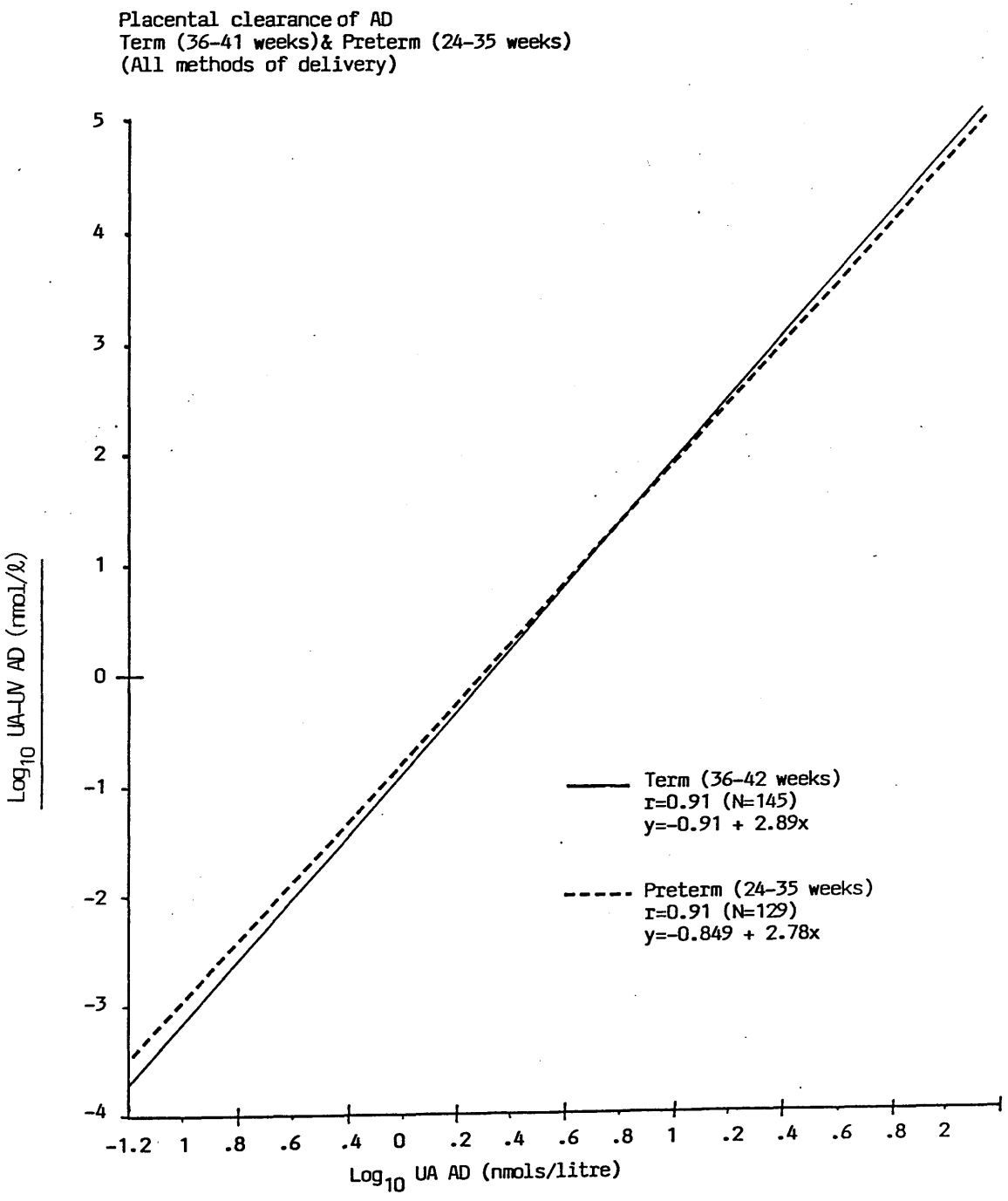

Placental clearance of NAD
Term (36-41 weeks) & Preterm (24-35 weeks)
(All methods of delivery)
Log10 UA-UV NAD (nmol/ℓ)
6
5
4
3
2
1
0
-1
-2
-3
-.8
0
.2
.4
.6
.8
1
.2
.4
.6
.8
2
.2
.4
.6
.8
3
Log10 UA NAD (nmols/litre)
Term (36-41 weeks)
y=-1.03 + 2.72 x
r= 0.947
(170 cases)
Preterm (24-35 weeks)
y=-0.839 + 2.56 x
r=0.942
(144 cases)

Figure 6.26


Placental clearance of AD
Term (36-41 weeks)& Preterm (24-35 weeks)
(All methods of delivery)
Log10 UA-UV AD (nmol/l)
5
4
3
2
1
0
-1
-2
-3
-4
-1.2
1
.8
.6
.4
0
.2
.4
.6
.8
1
.2
.4
.6
.8
2
Log10 UA AD (nmols/litre)
Term (36-42 weeks)
r=0.91 (N=145)
y=-0.91 + 2.89x
Preterm (24-35 weeks)
r=0.91 (N=129)
y=-0.849 + 2.78x

7.1 Introduction

Fedrick and Butler (1972) found that babies delivered by elective caesarean section were at greater risk of dying from RDS than those babies delivered either vaginally or even by caesarean section if this was preceded by labour. This observation seemed to imply that labour may protect the baby from RDS, although the mechanisms responsible remain to be elucidated. However (as discussed in Chapter 2) it is possible that the increase in cortisol and/or catecholamine levels associated with labour promotes both clearance of fluid from lung and increases production and release of surfactant.

In this chapter the effect of labour and mode of delivery on neonatal outcome, amniotic fluid phospholipids and umbilical arterial cortisol and catecholamines in those babies born $\leq$ 35 week's gestation, will be assessed. Because of the substantial effect of gestational age on these parameters (Chapter 5) the babies were also divided into gestational age groups as discussed in Chapter 5, depending on the likely occurrence of RDS.

As the term group of babies (36-41 weeks) had a very low incidence of respiratory problems, study of neonatal outcome and A.F. phospholipids was confined to those babies born $\leq$ 35 weeks. However the effect of mode of delivery on UAC and UA catecholamines was studied in the term babies and their response compared with the preterm group.

7.2 Results

7.2.1 Clinical outcome

In order to reduce confusion over the diagnosis of RDS and to make it easier to detect differences between babies with and without respiratory problems, only those babies with moderate and severe RDS (ie requiring artificial ventilation - CPAP or IPPV) were included in the RDS groups.

24-35 weeks (Table 7.1)

Although there were no significant differences between the birthweights and gestational ages of the babies by route of delivery (Table 7.1), Figures 7.1 and 7.2 illustrate that more of the smaller and younger babies were delivered vaginally (11% were < 28 weeks in the vaginally delivered group compared with 6% in elective caesarean section group).

Neonatal death was less common in the labour plus caesarean section group although this was not statistically significant. However, the incidence of RDS in this group was statistically lower than when the baby was delivered by elective caesarean section.

≤ 29weeks, 30-33weeks, 34-35 weeks (Tables 7.2, 7.3 and 7.4)

Although neonatal death and RDS were more common in those babies delivered by elective caesarean section, there were no statistically significant differences between the different routes of delivery after allowance for gestational age.

7.2.2 Amniotic fluid phospholipids

24-35 weeks (Table 7.5)

There were no statistically significant differences in mean L/S ratio, PG/S, ratio, lecithin concentration, PG concentration and in

the percentage of babies with PG present in their amniotic fluid, between the 3 different routes of delivery.

24-29 weeks, 30-33 weeks, 34-35 weeks (Tables 7.6, 7.7 and 7.8)

There were no significant differences in amniotic fluid phospholipids between the 3 modes of delivery after allowance for gestation age.

7.2.3 Umbilical arterial cortisol

a) Method of delivery

24-35 weeks (Table 7.9)

The mean UAC levels were statistically significantly higher following vaginal delivery compared with delivery by caesarean section.

The babies delivered by elective caesarean section had a significantly lower mean UApH compared to those delivered vaginally.

A similar picture of higher UAC levels in vaginal delivery compared to caesarean section was also found in the term group of babies (Table 7.10).

24-29 weeks, 30-33 weeks, 34-35 weeks (Tables 7.11, 7.12 and 7.13)

Except in the 24-29 weeks group when the numbers were small, those babies born vaginally had higher UAC levels than those born by elective caesarean section, after allowance for gestational age.

b) Type of vaginal delivery

The effect of type of vaginal delivery on UAC levels for the 24-35 week group is shown in Table 7.14. There was no significant difference in mean UAC between the 3 types of vaginal delivery.

In the term group of babies the spontaneous vaginal group had significantly raised mean UAC compared with the vaginal breech group (Table 7.15).

c) Duration of labour

There was no correlation between UAC levels and the duration of labour in the preterm (34-35 weeks) (Table 7.17) or the term (36-41 weeks) group of babies (Figure 7.3 and Table 7.16) delivered by SVD.

d) Type of anaesthesia employed

In the vaginally delivered group, 78 babies were born by spontaneous vertex delivery between 36-41 weeks and 48 between 24-35 weeks. The type of analgesia employed is shown in Table 7.18 and 7.19.

In those babies delivered by elective caesarean section, 45 were born between 36-41 weeks and 51 between 24-35 weeks. The type of anaesthesia employed is shown in Table 7.20 and 7.21.

In those babies delivered by caesarean section following the onset of labour, 29 were born between 36-41 weeks and 47 between 24-35 weeks. The type of anaesthesia employed is shown in Table 7.22 and 7.23.

Apart from a significantly lower mean UAC concentration in those preterm babies delivered spontaneously from mothers given pethidine compared with those given no analgesia in labour, the type of anaesthesia employed did not affect the UAC levels in the preterm or term babies after either vaginal delivery (Tables 7.18, 7.19) or after

caesarean section (Tables 7.20, 7.21, 7.22 and 7.23).

7.2.4 Umbilical arterial catecholamines

a) Method of delivery

24-35 weeks (Table 7.9)

In this group of babies the only significant difference in catecholamine levels in the different delivery groups was a significantly raised UANAD level in those babies delivered vaginally compared with those delivered by elective caesarean section.

This is in contrast to the term group of babies (36-41 weeks) (Table 7.10) where the catecholamine levels were significantly raised following vaginal delivery compared with either elective or emergency caesarean section.

24-29 weeks, 30-33 weeks, 34-35 weeks (Tables 7.11, 7.12 and 7.13)

Method of delivery had little influence on cord catecholamines prior to 34 weeks. However the 34-35 week group showed a similar response to the term group (36-41 weeks) with significantly higher UA NAD and AD levels following vaginal delivery compared with caesarean section.

b) Type of vaginal delivery

The effect of the type of vaginal delivery on UA catecholamine levels for the 24-35 week group is shown in Table 7.14.

Those babies born by vaginal breech delivery tended to have lower catecholamine levels than those delivered by forceps or spontaneous vaginal delivery. However the babies born by the breech had significantly lower mean gestational age and mean birth weights than the forceps or spontaneous delivery group.

In contrast the mean UA AD level in those babies delivered by the breech at term (Table 7.15) was significantly raised compared with the level for the forceps or spontaneous vertex groups.

c) Duration of labour

There was no correlation between UA catecholamine levels and the duration of labour in the preterm (24-35 weeks) (Table 7.17) or the the term group (Figure 7.3) of babies delivered by spontaneous vertex delivery.

d) Type of anaesthesia/analgesia employed

In those babies undergoing spontaneous vertex delivery there were no significant differences in UA catecholamines or pH between the 3 methods of analgesia (Tables 7.18 and 7.19).

The effect of type of anaesthesia on those babies delivered by elective caesarean section is shown in Table 7.20 for the preterm group and Table 7.21 for the term group of babies. In the preterm group the only statistical significant difference was a higher mean UA AD concentration in the epidural compared with the general anaesthetic group. In the term group there was no significant difference in UA catecholamines between those babies delivered under general anaesthesia or under epidural blockade.

The effect of type of anaesthesia on the UA catecholamines of those babies delivered by caesarean section after the onset of labour is shown in Table 7.22 for the preterm group and Table 7.23 for the term group. In the preterm group the fetal catecholamines were significantly lower in those babies whose mothers were given a general anaesthetic. In the term group there were no significant differences in the UA catecholamine levels between those babies delivered under general anaesthesia compared with those born under epidural block.

7.3 Discussion

The reported lower incidence of hyaline membrane disease (Fedrick & Butler 1972), higher thoracic gas volumes following vaginal delivery compared with elective caesarean section (Milner et al 1978) and the increase in phospholipid content of amniotic fluid collected serially in labour (Cabero et al 1976, Craven et al 1976, Whittle et al 1977), all strongly suggest that labour produced optimal conditions for neonatal respiratory function. The mechanism whereby this adaptation to extrauterine existence occurs is uncertain. However animal evidence suggests that endogenous cortisol and catecholamines, elevated by the stress of labour may cause increased synthesis and release of phospholipids and promote clearance of lung fluid. The baby delivered by elective caesarean section, especially if born prior to term may therefore be placed at a disadvantage.

In the preterm group of babies (24-35 weeks) those delivered vaginally had a similar incidence of respiratory problems as those born by elective caesarean section. However significantly more babies developed RDS in the elective caesarean section group compared with the group delivered by caesarean section following labour (Table 7.1). These groups were not stricly comparable however, as although the mean gestational ages and mean birthweights showed no significant difference, the distribution of birthweights and gestational ages were different between delivery groups (Figure 7.1 and 7.2). The lower birthweights and earlier gestational ages occurring in the elective caesarean section group.

In general labour did not appear to confer any particular advantage with respect to respiratory function, the incidence of problems being similar in babies born following either labour or elective caesarean section. However, although the numbers are small, babies delivered by caesarean section following the onset of labour at

≤29 weeks or 30-33 weeks had half the incidence of respiratory complications of those delivered vaginally or by elective caesarean section.

Measurement of the amniotic fluid phospholipids, did not explain the variability in clinical outcome since there were no differences in amniotic fluid phospholipids between the method of delivery in any of the gestational age groups.

The differences seen in the cortisol and catecholamine levels between the different routes of delivery in the term group of babies (Table 7.10) were not so obvious in the preterm groups 24-29 weeks and 30-33 weeks (Table 7.11 and 7.12). This may be due to the smaller numbers involved but more likely it reflects that whereas those babies delivered by elective caesarean section at term were, as a group, relatively uncomplicated, those delivered preterm by this route came from high risk pregnancies. This latter group although not subjected to the physiological stress of labour were under a more severe pathological stress, as reflected by the significantly lower mean umbilical arterial pH in the elective caesarean section group compared with those delivered vaginally between 30 and 33 weeks. Thus, although there was no difference in amniotic fluid phospholipids between the elective caesarean section and the vaginally delivered groups (at 30-33 weeks), hypoxia in the elective caesarean section group may have interfered with surfactant activity either because of decreased surfactant production or extrasavation of fluid into the interstitial space of the fetal lung thus interfering with surfactant activity (Strang 1976). This may explain why twice as many babies in the elective caesarean section group developed RDS than in the vaginally delivered group.

In the term neonate (Table 7.10) the significantly higher cortisol levels in vaginally delivered babies and in those delivered by caesarean section following the onset of labour compared with those delivered by elective caesarean section indicate that both labour and vaginal delivery cause cortisol levels to rise.

In contrast there was no significant difference in the mean NAD or AD levels between those babies delivered by elective caesarean section and those by caesarean section after the start of labour (Table 7.10). Vaginal delivery, however, caused a significant increase in mean NAD and AD levels compared with either method of caesarean section, suggesting that it was the passage down the birth canal which stimulated catecholamine release rather than the stress of labour itself. Vaginal delivery therefore should be advantageous if endogenous fetal cortisol and/or catecholamines are important elements in assuring optimal lung funtion.

However, vaginal delivery in the preterm group of babies did not appear to convey any great advantage, either in terms of clinical outcome or in the maturity of the lung phospholipids.

Whether the fetal endocrine responses to the stress of delivery can be modified by the type of anaesthesia has been investigated. Tables 7.20 to 7.23 demonstrate that there was no significant difference in mean fetal cortisol levels between those babies delivered by caesarean section (both elective and after onset of labour) under epidural block or under general anaesthesia. This was true for both the term and preterm groups of babies. This finding is in agreement with Namba et al (1980) who also found that method of anaesthesia does not influence the fetal cortisol responses.

The literature regarding the fetal catecholamine response to the type of anaesthesia employed at caesarean section is rather conflicting. Falconer and Lake (1982) and Newham et al (1984) found

no difference in fetal mean catecholamine levels at caesarean section between epidural block and general anaesthesia, while Jones et al (1985) noted that the 'lowest levels' were found after caesarean section under epidural. These conclusions, however, were based on small numbers of cases. Irestedt et al (1982) with a large series found significantly higher fetal NAD and AD levels in epidural caesarean sections compared with caesarean section performed under GA. Tables 7.21 and 7.23 show that, in the term group, there was no significant difference in mean catecholamine levels between those babies delivered by caesarean section (both elective and following the onset of labour) performed under general anaesthesia and those under epidural block. In the preterm group of babies, however, (Tables 7.20 and 7.22) the fetal catecholamines tended to be higher in those babies delivered by caesarean section under epidural block than those delivered by caesarean section under general anaesthesia. The reason for these differences in the preterm but not the term group of babies is difficult to explain. The two preterm caesarean section groups of general anaesthesia and epidural block may not be strictly comparable as the distribution of gestational ages and birth weights were not similar in the two groups , the younger and smaller babies predominating in the general anaesthesia group. In addition to this, those babies delivered by caesarean section prior to 36 weeks were a very heterogenous group (see Table 5.4 and Table 5.6).

With vaginal delivery the type of anaesthesia would appear to have little effect on fetal catecholamines (Falconer & Lake 1982, Bistoletti et al 1983). This would be in agreement with Tables 7.18 and 7.19 which show no significant differences in the biochemical parameters between those babies whose mothers were given either pethidine alone or an epidural block. Overall, therefore, it would

appear that the type of maternal analgesia or anaesthesia has little effect on fetal stress products at delivery.

7.4 Conclusions

1 Route of delivery had little effect on incidence of RDS or neonatal survival in the group of babies studied.

2 Route of delivery had little influence on lung surfactant as reflected by amniotic fluid phospholipids.

3 Route of delivery had a marked influence on UAC levels. Those babies born vaginally had significantly raised mean UAC compared with those delivered by caesarean section.

4 Route of delivery had a marked influence on UA catecholamine levels in the term (36-41 weeks) babies, those born vaginally having significantly raised mean UANAD and AD levels compared with those delivered by caesarean section.

In the preterm babies ($\leq$ 35 weeks) the effect of route of delivery on UA catecholamine levels was not so clear cut.

5 The type of maternal analgesia/anaesthesia had little effect on UA cortisol or catecholamine levels.

Table 7.1

The Effect of Method of Delivery on Clinical Outcome of the Neonate - Preterm Group (24-35 weeks)

	Number	Birthweight (kg) mean (SD)	Gestation (weeks)	Death (%)	RDS (%)	Apnoeic Attacks (%)	Patent Ductus (%)	ICH (%)
Vaginal Delivery	91	1.72 (.6)	31.3 (3)	16.5	33	25	16.5	36
Labour and Caesarean Section	47	1.85 (.5)	32.5 (2.2)	10.6	19	21	12.8	36
					p <.05‡			
Elective Caesarean Section	51	1.61 (.7)	32.1 (2.5)	22	37	22	8	29

‡ (Chi-Square)

Table 7.2

The Effect of Method of Delivery on Clinical Outcome of the Neonate - 24-29 weeks

	Number	Birthweight (kg) mean (SD)	Death (%)	RDS (%)	Apnoeic Attacks (%)	Patent Ductus (%)	ICH (%)
Vaginal Delivery	29	1.13 (0.37)	45	69	59	41	43
Labour and Caesarean Section	7	1.38 (0.28)	29	43	43	29	33
		p <.01					
Elective Caesarean Section	10	0.94 (0.26)	60	90	60	20	40

Table 7.3

The Effect of Method of Delivery on Clinical Outcome of the Neonate - 30-33 weeks

	Number	Birthweight (kg) mean (SD)	Deaths (%)	RDS (%)	Apnoeic Attacks (%)	Patent Ductus (%)	ICH (%)
Vaginal Delivery	32	1.79 (9.39)	6	22	16	9	25
Labour and Caesarean Section	21	1.79 (0.4)	5	24	29	19	14
Elective Caesarean Section	21	1.53 (o.57)	19	43	19	9.5	22

Table 7.4

The Effect of Method of Delivery on Clinical Outcome of the Neonate - 34-35 weeks

	Number	Birthweight (kg) Mean (SD)	Death (%)	RDS (%)	Apnoeic Attacks (%)	Patent Ductus (%)	ICH (%)
Vaginal Delivery	30	2.33 (0.3)	0	10	3.3	0	0
Labour and Caesarean Section	19	2.16 (0.4)	10.5	5.3	5.3	0	5.3
Elective Caesarean Section	20	2.04 (0.6)	5	5	5	0	0

Table 7.5

Effect of Method of Delivery on Amniotic Fluid Phospholipids - 24-35 weeks

	Number*	L/S	PG/S	Lecithin Concentration	PG Concentration	% PG
Vaginal Delivery	91	2.1 (1.45)	0.6 (1.1)	25.8 (18.4)	5.4 (2)	54
Labour and Caesarean Section	47	2.2 (1)	0.7 (0.8)	23.7 (10.1)	5.2 (2.2)	68
Elective Caesarean Section	51	2.0 ((1)	0.5 (0.6)	21.5 (8.5)	5.5 (2.4)	59

* NOTE - Not all parameters measured in every baby

Table 7.6

Effect of Method of Delivery on Amniotic Fluid Phospholipids - 24-29 weeks

	Number *	L/S	PG/S	Lecithin Concentration	PG Concentration	% PG
Vaginal Delivery	29	1.2 (0.6)	-	12.9 (2.2)	-	21
Labour and Caesarean Section	7	1.38 (0.3)	-	13.4 (2.3)	-	57
Elective Caesarean Section	10	1.4 (0.6)	-	13.9 (2.8)	-	10

* NOTE - Not all parameters measured in every baby

Table 7.7

Effect of Method of Delivery on Amniotic Fluid Phospholipids - 30-33 weeks

	Number *	L/S	PG/S	Lecithin Concentration	PG Concentration	% PG
Vaginal Delivery	32	1.94 (1.04)	0.49 (0.6)	19.5 (8.7)	5.3 (2.9)	56
Labour and Caesarean Section	21	2.25 (1.2)	0.55 (0.5)	24.3 (8.5)	4.3 (1.6)	71
Elective Caesarean Section	21	1.91 (0.9)	0.58 (0.8)	20.1 (8.4)	4.8 (2.10)	57

* NOTE - Not all parameters measured in every baby

Table 7.8

Effect of Method of Delivery on Amniotic Fluid Phospholipids - 34-35 weeks

	Number *	L/S	PG/S	Lecithin Concentration	PG Concentration	% PG
Vaginal Delivery	30	2.9 (1.8)	1.23 (1.6)	35.7 (22)	5.5 (1.4)	87
Labour and Caesarean Section	19	2.5 (0.9)	0.87 (1)	26.3 (13)	7.1 (2)	68
Elective Caesarean Section	20	2.4 (1.2)	0.6 (0.5)	28.4 (5.4)	6.5 (2.8)	85

* NOTE - Not all parameters measured in every baby

Table 7.9

The Effect of Method of Delivery on Biochemical Aspects of the Neonate

Preterm Group 24-35 weeks — Arterial cord Values Mean (SD)

	Number*	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
Vaginal Delivery	66	314 (185)	17.36 (24)	2.48 (2.5)	7.27 (.09)
		$p < .02$			
Labour and Caesarean Section	40	235 (149)	24.2 (54)	2.5 (2.2)	7.24 (.09)
			$p < .01$	$p < .04$	$p < .007$
Elective Caesarean Section	44	239 (116)	10.6 (15.2)	1.86 (1.6)	7.22 (.1)

* NOTE - Not all parameters measured in every baby

Table 7.10

The Effect of Method of Delivery on Biochemical Aspects of the Neonate

Term Group (36-41 weeks) Arterial Cord Values Mean (SD)

	Number	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
Vaginal Delivery	104	533 (180)	35.8 (38.4)	4.6 (3.7)	7.24 (.08)
			p <.0000	p <.0000	
Labour and Caesarean Section	29	473 (250)	11.8 (10.3)	1.84 (1.7)	7.26 (.1)
		p <.0000	p <.0000	p <.0000	
		p <.05			
Elective Caesarean Section	42	353 (134)	13.8 (22.1)	1.97 (1.7)	7.28 (.06)

Table 7.11

The Effect of Method of Delivery on Biochemical Aspects of the Neonate

24-29 weeks Arterial Cord Values Mean (SD)

	Number *	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
Vaginal Delivery	21	225 (134)	13.5 (14)	1.7 (1.7)	7.23 (0.1)
Labour and Caesarean Section	4	123 (111)	21.8 (23.1)	1.36 (1.24)	7.18 (0.21)
Elective Caesarean Section	6	220 (83)	8.24 (8.5)	1.02 (1.05)	7.17 (0.14)

* NOTE - Not all parameters measured in every baby

No Significant Difference

Table 7.12

The Effect of Method of Delivery on Biochemical Aspects of the Neonate

30-33 weeks Arterial Cord Values Mean (SD)

	Number	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH	
Vaginal Delivery	25	286 (182)	18 (31)	2.8 (3.3)	7.3 (0.05)	p <.003
		p <.01			p <.04	
Labour and Caesarean Section	20	167 (92)	32.4 (74)	1.2 (0.9)	7.26 (.07)	
				p <.006		
Elective Caesarean Section	19	205 (86)	15.3 (21)	3.05 (2.9)	7.21 (0.1)	

Table 7.13

The Effect of Method of Delivery on Biochemical Aspects of the Neonate

34-35 weeks Arterial Cord Values Mean (SD)

	Number	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
Vaginal Delivery	22	440 (174)	19.8 (21.6)	2.8 (2)	7.25 (.09)
Labour and Caesarean Section	16	333 (155)	14.6 (14.8)	4.3 (7.3)	7.24 (.08)
		p <.0037	p <.015	p <.0042	p <.008
Elective Caesarean Section	18	279 (142)	6.7 (6.8)	1.04 (1.05)	7.25 (.1)

Table 7.14

Effect of Method of Vaginal Delivery on Biochemical Aspects of Neonate

Preterm Group (24-35 weeks) Arterial Cord Values Mean (SD)

	Number	Gestation (weeks)	Birthweight (kg)	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
SVD	48	31.7 (2.9)	1.87 (0.59)	327 (175)	15.7 (29)	2.76 (2.9)	7.29 (.07)
					p <.0048		
Forceps	32	31.3 (3.1)	1.69 (0.5)	324 (215)	24.5 (20)	2.62 (2)	7.26 (.09)
		p <.04	p <.0008			p <.007	
		p <.02	p <.007		p <.0027	p <.01	
Vaginal Breech	11	29 (2.4)	1.18 (0.49)	226 (127)	6.5 (6.9)	0.87 (0.5)	7.18 (.12)

Table 7.15

Effect of Mode of Vaginal Delivery on Biochemical Aspects of Neonate

Term Group (36-41 weeks) Arterial Cord Values Mean (SD)

	Number	Birthweight (kg)	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
SVD	76	3.05 (0.6)	572 (177)	32.7 (36.2)	4.07 (2.8)	7.26 (.07)
Forceps	20	2.9 (0.4)	487 (174)	30.9 (28)	3.9 (3)	7.21 (.09)
Vaginal Breech	17	2.7 (0.5)	448 (170)	56.5 (56)	7.4 (6.2)	7.20 (.07)

p <.01 (SVD vs Forceps)

p <.02 (SVD vs Vaginal Breech)

p <.04 (Forceps vs Vaginal Breech)

p <.04 (SVD vs Vaginal Breech)

p <.03 (SVD vs Vaginal Breech)

Table 7.16

Relationship between Duration of Labour and Biochemical Aspects of Neonate

Term Group (36-41 weeks) SVD'S

				r	
	UAC	v	2nd Stage	.013	NS
Log_{10}	UA NAD	v	2nd Stage	.097	NS
Log_{10}	UA AD	v	2nd Stage	.09	NS

Table 7.17

Relationship between Duration of Labour and Biochemical Aspects of the Neonate

Preterm Group (24-35 weeks)

			r	
UAC	v	Duration of Labour	-0.26	NS
Log_{10}UA NAD	v	Duration of Labour	-0.26	NS
Log_{10}UA AD	v	Duration of Labour	-0.34	NS

Table 7.18

Effect of Analgesia on Biochemical Aspects of Neonate

Spontaneous Vertex Delivery - Preterm Group (24-35 weeks)

Arterial Cord Blood Values - Mean (SD)

	Number	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
Pethidine	8	230 (96)	12.2 (188)	2.5 (2.8)	7.28 (.06)
Epidural	13	344 (145)	13.8 (15.2)	2.9 (2.4)	7.29 (.06)
		p <.03			
None	27	356 (194)	18.7 (33.4)	2.9 (3.3)	7.29 (.08)

Table 7.19

Effect of Analgesia on Biochemical Aspects of the Neonate

Spontaneous Vertex Delivery - Term Group (36-41 weeks)

Arterial Cord Blood Values - Mean (SD)

	Number	Cortisol (nmol/ℓ)	Noradrenaline (nmol/ℓ)	Adrenaline (nmol/ℓ)	pH
Pethidine	25	568 (216)	37 (36.7)	4.3 (2.9)	7.28 (.05)
Epidural	25	552 (188)	31.2 (38.7)	4.4 (2.7)	7.24 (.07)
None	28	569 (153)	29.3 (32.2)	3.5 (2.9)	7.25 (.07)

Table 7.20

Effect of Anaesthesia on Biochemical Aspects of the Neonate

Preterm (24-35 weeks) Elective Caesarean Section

Arterial Cord Values - Mean (SD)

		GA (n = 35)	Epidural (n = 16)	
Cortisol	(nmol/ℓ)	254 (122)	202 (96)	NS
NAD	(nmol/ℓ)	8.1 (10.6)	15.3 (21)	NS
AD	(nmol/ℓ)	1.4 (1.7)	2.8 (2.8)	$p < .04$
pH		7.22 (0.1)	7.21 (0.1)	NS

Table 7.21

Effect of Anaesthesia on Biochemical Aspects of the Neonate

Term (36-41 weeks) Elective Caesarean Section

Arterial Cord Values - Mean (SD)

		GA (n = 9)	Epidural (n = 36)	
Cortisol	(nmol/ℓ)	311 (180	360 (128)	NS
NAD	(nmol/ℓ)	10.7 (11.8)	14.5 (24.2)	NS
AD	(nmol/ℓ)	1.9 (1.5)	2.8 (1.7)	NS
pH		7.31 (0.07)	7.28 (.05)	NS

Table 7.22

Effect of Anaesthesia on the Biochemical Aspects of the Neonate

Preterm (24-35 weeks) Labour and Caesarean Section

Arterial Cord Values - Mean (SD)

		GA (n = 35	Epidural (n = 12)	
Cortisol	(nmol/ℓ)	238 (165)	225 (99)	NS
NAD	(nmol/ℓ)	12 (15)	53.3 (88)	$p < .005$
AD	(nmol/ℓ)	2.3 (5.6)	5 (8)	$p < .01$
pH		7.29 (.05)	7.23 (0.1)	NS

Table 7.23

Effect of Anaesthesia on the Biochemical Aspects of the Neonate

Term (36-41 weeks) Labour and Caesarean Section

Arterial Cord Values - Mean (SD)

		GA (n = 12)	Epidural (n = 17)	
Cortisol	(nmol/ℓ)	474 (296)	473 (208)	NS
NAD	(nmol/ℓ)	7.1 (4.9)	14.1 (12.3)	NS
AD	(nmol/ℓ)	1.9 (1.78)	1.8 (1.6)	NS
pH		7.22 (0.1	7.28 (0.05)	NS

Figure 7.1

Distribution of Birthweights (24-35 weeks)

Vaginal Delivery

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.4	1	x
0.6	3	xxx
0.8	3	xxx
1.0	8	xxxxxxxx
1.2	6	xxxxxx
1.4	10	xxxxxxxxxx
1.6	11	xxxxxxxxxxx
1.8	10	xxxxxxxxxx
2.0	14	xxxxxxxxxxxxx
2.2	13	xxxxxxxxxxxx
2.4	5	xxxxx
2.6	3	xxx
2.8	0	
3.0	3	xxx

Labour and Caesarean Section

BW

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
1.0	3	xxx
1.2	3	xxx
1.4	7	xxxxxxx
1.6	3	xxx
1.8	7	xxxxxxx
2.0	7	xxxxxxx
2.2	10	xxxxxxxxxx
2.4	3	xxx
2.6	3	xxx
2.8	0	
3.0	1	x

Elective Caesarean Section

BW

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
0.4	2	xx
0.8	7	xxxxxxx
1.2	14	xxxxxxxxxxxxx
1.6	8	xxxxxxxx
2.0	8	xxxxxxxx
2.4	8	xxxxxxxx
2.8	3	xxx
3.2	1	x

Figure 7.2

Distribution of Gestational Ages (24-35 weeks)

Vaginal Delivery

GEST

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
24.	1	*
25.	3	***
26.	4	****
27.	2	**
28.	7	*******
29.	12	**********
30.	8	********
31.	5	*****
32.	9	*********
33.	10	**********
34.	17	**********
35.	13	**********

Labour and Caesarean Section

GEST

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
26.	1	*
27.	0	
28.	2	**
29.	4	****
30.	2	**
31.	4	****
32.	5	*****
33.	10	**********
34.	11	**********
35.	8	********

Elective Caesarean Section

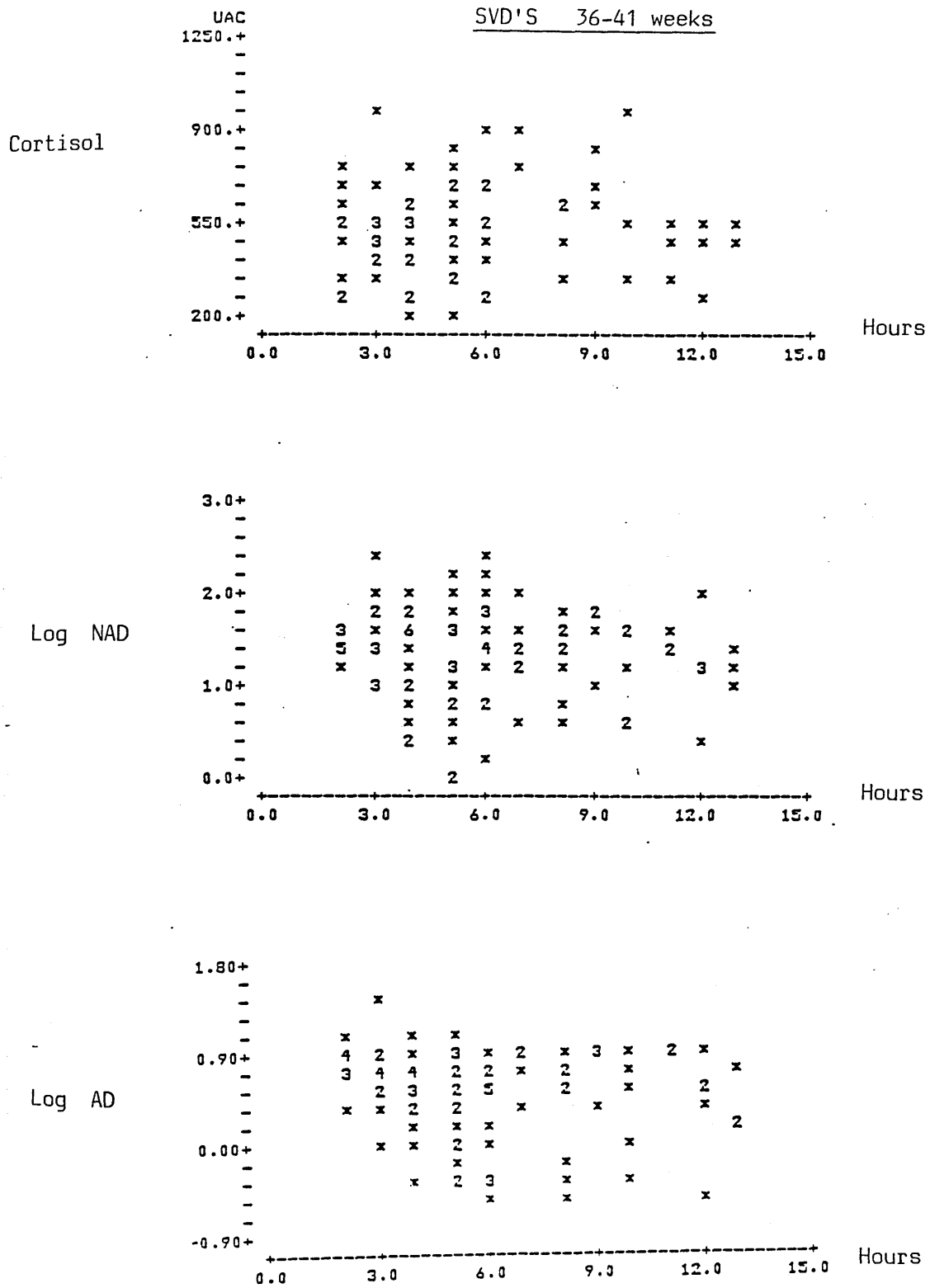
*GEST

MIDDLE OF INTERVAL	NUMBER OF OBSERVATIONS	
26.	1	*
27.	2	**
28.	2	**
29.	5	*****
30.	3	***
31.	8	********
32.	5	*****
33.	5	*****
34.	8	********
35.	12	**********

Figure 7.3

Influence of Duration of Labour on Umbilical Cortisol

NAD and AD (nmol/ℓ)



CHAPTER 8

Multiple Pregnancy

8.1 Introduction

RDS appears to be more frequent in twins than in singletons and this increase cannot entirely be accounted for by the higher prematurity rate in twins over singletons (Myrianthropulous et al 1971). In addition, as discussed in Chapter 3, there is some evidence to suggest that twins have lower surfactant levels than singletons at similar gestational ages. Twin II appears to be at particular risk of developing RDS and this has generally been attributed to increased perinatal asphyxia.

In this Chapter, twins are compared firstly to singletons and secondly twin I is compared to twin II with respect to clinical and biochemical lung maturity and the levels of stress hormones cortisol and the catecholamines.

Some authors have described a similar relationship to birth order and lung maturity in triplets, quadruplets and quintuplets (p 66) and in this Chapter the clinical and biochemical lung maturity and fetal stress hormones are described in 3 sets of triplets.

8.2 Results

8.2.1 Comparison of Twins and Singletons

A total of 61 sets of twins was studied (Table 8.1). As there were no twin pregnancies delivered prior to 28 weeks or after 39 weeks, the gestational age groups considered in this section were 28-29, 30-3, 34-35 and 36-39 weeks. Clinical outcome was considered only in babies born prior to 36 weeks.

Lack of numbers did not permit correction for method of delivery except for the babies born after 35 weeks, when only vaginal deliveries were investigated.

Only from 34 weeks' gestation was there a significant difference in mean birthweight between singletons and twins (Table 8.2).

a) Clinical outcome

The babies born from twin pregnancies seemed to do at least as well as singletons at each gestational age group studied (Tables 8.3-8.5).

b) Amniotic fluid phospholipids

There were few differences in amniotic fluid phospholipids between singletons and twins (Tables 8.6-8.9). However the mean PG/S ratio and mean PG concentration were significantly higher in singletons than twins at 30-33 weeks (Table 8.7) and the mean PG/S ratio significantly higher in singletons than twins in 30-33 and 36-39 week groups (Tables 8.7 and 8.9).

c) Umbilical arterial cortisol

Table 8.10 shows that from 34 weeks' gestation the mean UAC level was significantly higher in singletons than in twins.

d) Umbilical arterial catecholamines

There was no significant difference in mean UA NAD or AD levels between singletons and twins at any gestational age (Table 8.11 and 8.12).

e) Condition of infant at birth

There was no significant difference in mean UA pH between singletons and twins prior to 36 weeks. However, after this gestation the twins were significantly more acidotic as a group compared to singletons (Table 8.13).

8.2.2 Comparison of Twin I and Twin II

In this section the first and second born twins were compared with regard to clinical outcome, amniotic fluid phospholipids, umbilical arterial cortisol and catecholamines.

a) Clinical outcome

(Clinical outcome was only considered in those babies born less than 36 weeks).

The clinical outcome for twins I and II is shown in Table 8.14. Although the incidence of RDS and requirement for ventilation was similar, more deaths occurred in Twin II.

b) Amniotic fluid phospholipids

In the preterm group of babies (28-35 weeks) twin I had significantly higher mean lecithin concentration compared with twin II (Table 8.15). This, however, was the only observation to suggest a deficiency in surfactant in the second twin. There were no significant differences in amniotic fluid phospholipids betweeen twin I and twin II when all twins in study were considered together (Table 8.16) or when only those born $\geq$ 36 weeks were studied (Table 8.17).

The correlation between co-twins for amniotic fluid phospholipids is shown in Table 8.18. Only the PG concentration showed a significant correlation in the term group (36-39 weeks) or in the study as a whole.

The correlations were much improved in the preterm group ($\leq$ 35 weeks). The statistically significant correlations are shown in Figures 8.1-8.5. However, in the one twin pregnancy in the study, where one baby (twin II) developed RDS and its co-twin did not PG was absent in twin II (Table 8.19).

c) Umbilical arterial cortisol

The mean UAC level was significantly higher in twin I compared to twin II when all twins were considered together or when only those born after 35 weeks were considered (Table 8.20). Interestingly, when only one twin developed RDS (Table 8.19) the twin developing RDS had a much higher UAC level).

There was a significant correlation between co-twins for UAC (Table 8.21) (Figures 8.6, 8.7 and 8.8).

d) Umbilical arterial catecholamines

There were no significant differences in mean UA NAD or AD between co-twins (Tables 8.22 and 8.23) but an excellent correlation between twin I and twin II (Table 8.21) (Figures 8.9, 8.10 and 8.11).

e) Umbilical arterial pH

There were no significant differences in mean UA pH between twin I and twin II (Table 8.24) and no significant correlation between co-twins (Table 8.21).

8.2.3. Triplets

There were 3 sets of triplets included in the study (Table 8.25). The triplets born at 26 weeks were grossly immature and all 3 developed severe RDS.

Interestingly in one set of triplets at 31 weeks the first two babies delivered were monozygotic, both had PG and neither developed RDS while the third - a genetically different baby, had no PG and developed RDS. Zygosity was established using 8 blood group systems - ABO, Rh, MNS, PI, KELL, LUTHERAN, DUFFY and KIDD - when twins had the same sex and dichorionic placentation (Corney & Robson 1975). All 3 babies had intact amniotic sacs and were delivered by caesarean

section in a similar condition, as shown by their UA pH values. Despite the similar condition at birth the cord cortisol and catecholamine levels varied considerably, with no obvious relationship to lung maturity.

8.3 Discussion

Twins versus Singletons

RDS appears to be more frequent in twins than in singletons and this increase cannot apparently be entirely accounted for by the higher prematurity rate of twins over singletons (Myrianthopolous et al 1971). In this small study no increase in the incidence of RDS in twins compared with singletons could be demonstrated (Tables 8.21-8.23). However the mean amniotic fluid PG/S ratio and mean PG concentration were significantly lower in twins than in singletons at 30-33 weeks' gestation. There was also a lower percentage occurrence of amniotic fluid PG in twins compared with singletons at 30-33 weeks and 28-29 weeks, although these differences were not statistically significant. This suggestion of a 'poorer' surfactant in twins compared with singletons is consistent with the findings of Parkinson et al (1980) who noted that twins had significantly lower pharyngeal L/S ratio than singletons when born between 29-35 weeks. This may indicate that with large numbers more significant differences between singletons and twins would become apparant.

There were no significant differences in mean UA NAD, AD or pH between singletons and twins in the gestational age groups considered, however there was a significantly raised mean UAC in singletons compared with twins. This difference may reflect the differences in mean birthweight between singletons and twins but may also have some bearing on differences in surfactant noted between the 2 groups.

Twin I versus Twin II

In the study of fetal lung maturity, multiple pregnancies provide an interesting model, the babies acting as their own controls especially with regard to gestational age and intrauterine environment. The second born twin is reported to have double the risk of RDS than the first born (Rokos et al 1968, Farr 1975) and this has mainly been attributed to perinatal asphyxia, (Rokos et al 1968, Verduzco et al 1976). In sporadic reports of individual twin pregnancies where only one twin is affected, it seems that the second born almost always has the more immature surfactant and develops RDS (Caspie et al 1975, Gluck et al 1974, Dobbie et al 1983).

Although in this study more second twins died, the incidence of other complications, including RDS was similar between twin I and twin II. In addition little difference was found in amniotic fluid phospholipids between co-twins (Tables 8.32-8.34) although the lecithin concentration was significantly lower in twin I between 30-33 weeks' gestation.

Measurement of stress related products in cord blood demonstrated excellent correlation for UAC NAD and AD but not pH between co-twins with no differences in arterial catecholamine or pH levels noted between twins. However the UAC level was significantly higher in twin I compared with twin II (after 35 weeks) and this is in agreement with the findings of Norman et al (1983) who found that during labour glucocorticoids increased significantly in the amniotic fluid of twin I compared with twin II.

8.4 Conclusions

Singletons compared to twins

In the group of babies studied:-

1 There was no difference in incidence of respiratory complication.

2 Apart from a lower mean PG/S ratio and mean PG concentration in twins compared to singletons at 30-33 weeks' gestation, there were no other significant differences in lung surfactant.

3 The mean UA cortisol was significantly raised in singletons compared to twins only after 34 weeks' gestation.

4 There was no difference in mean UA NAD, AD or pH.

Twin I compared to twin II

1 No difference in clinical or biochemical lung maturity.

2 Significantly higher mean UA cortisol in twin I only after 35 weeks.

3 No difference in mean UA NAD, AD or pH.

4 Excellent correlations between co-twins for UA NAD, AD and cortisol but not pH.

Table 8.1

Twin Pregnancy by Gestational Age and Method of Delivery

Delivery	Gestation (weeks)			
	28-29	30-33	34-35	36-39
Vaginal	4	5	4	28
Elective C/S	0	1	3	3
Emergency C/S	1	2	4	5
	5	8	11*	36

* + One twin pregnancy where first twin delivered vaginally but second delivered by emergency C/S.

TOTAL 61 sets of twins

Table 8.2

Singleton v Twin Pregnancy

Birthweight (kg) Mean (SD)

Gestation (weeks)	Singleton	Twin	
28-29	1.24 (0.3) (n = 22)	1.12 (0.3)	NS
30-33	1.74 (0.4) (n = 52)	1.77 (0.6) (n = 16)	NS
34-35	2.25 (0.45) (n = 45)	1.98 (0.28) (n = 24)	p <.004
36-39 (Vaginal delivery only)	3.02 (0.55) (n = 29	2.64 (0.43) (n = 56	p <.009

Table 8.3

Singleton v Twin Pregnancy

Clinical Outcome

28-29 weeks

	Singleton (n = 22)		Twin (n = 20)		
Died	36%	(8/22)	30%	(3/10)	NS
RDS	59%	(13/22)	70%	(7/10)	NS
Ventilation	59%	(13/22)	80%	(8/10)	NS

Table 8.4

Singleton v Twin Pregnancy

Clinical Outcome

30-33 weeks

	Singleton (n = 52)	Twin (n = 16)	
Died	10% (5/52)	13% (2/16)	NS
RDS	35% * (18/52)	13% * (2/16)	NS
Ventilation	44% ° (23/52)	6% ° (1/16)	

Fishers Exact Test

* p <0.078 NS

° p <.004

Table 8.5

Singleton v Twin Pregnancy

Clinical Outcome

34-35 weeks

	Singleton (n = 45)		Twin (n = 24)		
Died	4%	(2/45)	4%	(1/24)	NS
RDS	11%	(5/45)	0%		NS
Ventilation	16%	(7/45)	4%	(1/24)	NS

Table 8.6

Singleton v Twin Pregnancy

Amniotic Fluid Phospholipids

28-29 weeks

	Singleton (n = 22) Mean (SD)		Twin (n = 10) Mean (SD)		
L/S Ratio	1.4	(0.6)	1.5	(0.3)	NS
PG/S Ratio	0.7	(0.3)	0.9	(0.05)	NS
AFPG	(7/15)	47%	2/10	20%	NS
Lecithin Concentration*	13.3	(2.2)	INSUFFICIENT DATA		
PG Concentration*	4.6	(1.3)	INSUFFICIENT DATA		

* (µmol/ℓ)

Table 8.7

Singleton v Twin Pregnancy

Amniotic Fluid Phospholipids

30-33 weeks

	Singleton (n = 52) Mean	(SD)	Twin (n = 16) Mean	(SD)	
L/S Ratio	1.94	(0.97)	1.78	(0.76)	NS
PG/S Ratio	1.05	(0.6)	0.47	(0.4)	$p < .008$
AFPG	64%	(35/52)	44%	(7/16)	NS
Lecithin Concentration*	19.9	(8)	21.9	(7.8)	NS
PG Concentration*	5	(2.4)	3	(0.5)	$p < .002$

* (µmol/ℓ)

Table 8.8

Singleton v Twin Pregnancy

Amniotic Fluid Phospholipids

34-35 weeks

	Singleton (n = 45) Mean	(SD)	Twin (n = 24) Mean	(SD)
L/S Ratio	2.5	(1.2)	3	(1.8)
PG/S Ratio	0.9	(0.4)	1.6	(1.9)
AFPG	78%	(35/45)	88%	(21/24)
Lecithin Concentration*	32.7	(19)	29.8	(10.6)
PG Concentration*	5.7	(1.7)	7	(2.4)

(No significant differences)

* (µmol/ℓ)

Table 8.9

Singleton v Twin Pregnancy
Amniotic Fluid Phospholipids

36-39 weeks Vaginal Delivery Only

	Singleton (n = 29) Mean	(SD)	Twin (n = 56) Mean	(SD)	
L/S Ratio	3.5	(1.6)	3.5	(2.3)	NS
PG/S Ratio	1.7	(0.9)	1.0	(0.8)	$p < .008$
AFPG	66%	(19/29)	91%	(51/54)	NS
Lecithin Concentration*	32	(8.3)	38	(16)	NS
PG Concentration*	7.4	(3)	8.1	(5)	NS

* (µmol/ℓ)

Table 8.10

Singleton v Twin Pregnancy

Umbilical Arterial Cortisol (nmol/ℓ) Mean (SD)

Gestation (Weeks)	Singleton	Twin	
28-29	228 (142) (n = 22)	192 (63) (n = 10)	NS
30-33	216 (124) (n = 52)	271 (203) (n = 16)	NS
34-35	388 (171) (n = 45)	248 (116) (n = 24)	p <.002
36-39 *	594 (165) (n = 29)	469 (185) (n = 56)	p <.01

* Vaginal deliveries only

Table 8.11

Singleton v Twin Pregnancy

Umbilical Arterial Noradrenaline (nmol/ℓ)

Mean (SD)

Gestation (Weeks)	Singleton	Twin	
28-29	14.2 (15) (n = 22)	2.6 (0.9) (n = 4)	NS
30-33	14.6 (26) (n = 52)	12.1 (7) (n = 16)	NS
34-35	13.3 (16.7) (n = 45)	17.7 (18) (n = 24)	NS
36-39 *	36.9 (34) (n = 29)	36.2 (42) (n = 56)	NS

* Vaginal deliveries only

Table 8.12

Singleton v Twin Pregnancy

Umbilical Arterial Adrenaline (nmol/ℓ)

Mean (SD)

Gestation (Weeks)	Singleton	Twin	
28-29	1.3 (1.5) (n = 22)	0.5 (0.15) (n = 4)	NS
30-33	2.6 (3) (n = 52)	1.7 (0.9) (n = 16)	NS
34-35	2.2 (1.9) (n = 45)	4.1 (7.9) (n = 24)	NS
36-39 *	4.1 (2.9) (n = 29	5.4 (4.5) (n = 56)	NS

* Vaginal deliveries only

Table 8.13

Singleton v Twin Pregnancy

Condition of Infant at Birth

Umbilical Arterial pH Mean (SD)

Gestation (Weeks)	Singleton	Twin	
28-29	7.21 (0.13) (n = 22)	7.19 (0.12) (n = 10)	NS
30-33	7.26 (0.08) (n = 52)	7.27 (0.1) (n = 16)	NS
34-35	7.25 (0.09) (n = 45)	7.22 (0.1) (n = 24)	NS
36-39 *	7.3 (0.05) (n = 29)	7.2 (0.06) (n = 56)	p <.0000

* Vaginal deliveries only

Table 8.14

Twin I v Twin II

Clinical Outcome 28-35 Weeks

	Twin I		Twin II		
Birthweight (kg) Mean (SD)	1.8	(0.5)	1.7	(0.5)	NS
RDS	4/25	(16%)	5/25	(20%)	NS
Ventilation Requirements	4/25	(16%)	6/25	(24%)	NS
Died	1/25	(4%)	5/25	(20%)	p <.0000 *

* Fishers Exact Test

Table 8.15

Twin I v Twin II

Amniotic Fluid Phospholipids

28-35 Weeks (n = 25)

	Twin I Mean	(SD)	Twin II Mean	(SD)	
L/S Ratio	2.25	(1.1)	2.5	(1.8)	NS
PG/S Ratio	1.39	(1)	1.4	(2.2)	NS
AFPG	64%	(16/25)	56%	(14/25)	NS
Lecithin Concentration *	30.8	(12)	23	(6.8)	p <.01
PG Concentration *	6.3	(3.3)	5.9	(2.2)	NS

* (µmol/ℓ)

Table 8.16

Twin I v Twin II

Amniotic Fluid Phospholipids

28-39 Weeks (n = 61)

	Twin I Mean (SD)		Twin II Mean (SD)		
L/S Ratio	3	(1.9)	2.9	(2)	NS
PG/S Ratio	1.3	(0.9)	1.12	(1.4)	NS
AFPG	79%	(48/61)	74%	(45/61)	NS
Lecithin Concentration *	36	(14)	35	(16)	NS
PG Concentration *	6.8	(3)	8.3	(5.3)	NS

* (µmol/ℓ)

No significant differences

Table 8.17

Twin I v Twin II

Amniotic Fluid Phospholipids

36-39 Weeks (n = 36)

	Twin I Mean (SD)		Twin II Mean (SD)		
L/S Ratio	3.5	(2.1)	3.2	(2.1)	NS
PG/S Ratio	1.2	(0.8)	0.99	(0.68)	NS
AF PG	89%	(32/36)	86%	(31/36)	NS
Lecithin Concentration *	37.6	(14.6)	38.8	(16)	NS
PG Concentration *	7	(3)	9	(5.7)	NS

* (µmol/ℓ)

No significant differences

Table 8.18

Correlation between Co-twins

Amniotic Fluid Phospholipids

	All Twins (28-29 weeks)		Term (36-39 weeks)		Preterm (28-35 weeks)	
	r		r		r	
LSR	0.1	NS	0.07	NS	0.46	p <.05
PGSR	0.37	NS	0.34	NS	0.45	NS
Lecithin Concentration *	0.33	NS	0.2	NS	0.89	p <.001
PG Concentration *	0.67	p <.001	0.67	p <.001	0.9	p <.01

* (μmol/ℓ)

Table 8.19

Twin Pregnancy (33 weeks) Emergency Caesarean Section (Epidural)

Ruptured Membranes

	Weight (kg)	pH (UA)	L/S Ratio	PG	Cortisol'	AD'	NAD'	RDS
I	2.10	7.28	1	Present	190	1.7	8.6	No
II	2.02	7.27	1.97	Absent	330	1.3	5.4	Yes

(Dizygotic twin pregnancy)

' (nmol/ℓ)

Table 8.20

Twin I v Twin II

Umbilical Arterial Cortisol (nmol/ℓ)

Mean (SD)

	Twin I		Twin II		
28-39 weeks (n = 61)	383	(199)	332	(176)	p < .02 *
36-39 weeks (n = 36)	452	(199)	386	(161)	p < .01 *
28-35 weeks (n = 25)	260	(132)	225	(160)	NS

* Paired 'T' Test

Table 8.21

Correlation between Co-twins

Cord Blood Biochemistry

	All Twins (28-39 weeks)		Term (36-39 weeks)		Preterm (28-35 weeks)	
	r		r		r	
UAC	0.69	p <.001	0.58	p <.01	0.83	p <.001
Log UA NAD	0.65	p <.001	0.58	p <.01	0.82	p <.001
Log UA AD	0.73	p <.001	0.58	p <.01	0.9	p <.001
UA pH	0.16	NS	0.14	NS	0.34	NS

Table 8.22

Twin I v Twin II

Umbilical Arterial Noradrenaline (nmol/ℓ)

Mean (SD)

	Twin I		Twin II		
28-29 weeks (n = 61)	20	(30)	29	(37)	NS
36-39 weeks (n = 36)	23.4	(35)	35	(42)	NS
28-35 weeks (n = 25)	13.1	(13)	14	(15.8)	NS

Table 8.23

Twin I v Twin II

Umbilical Arterial Adrenaline (nmol/ℓ)

Mean (SD)

	Twin I		Twin II		
28-29 weeks (n = 61)	3.1	(2.7)	4.7	(6.3)	NS
36-39 weeks (n = 36)	3.7	(2.8)	5.2	(5.3)	NS
28-35 weeks (n = 25)	1.8	(1.7)	3.8	(8.2)	NS

Table 8.24

Twin I v Twin II

Umbilical Arterial pH

Mean (SD)

	Twin I		Twin II		
28-39 weeks (n = 61)	7.23	(.08)	7.21	(.1)	NS
36-39 weeks (n = 36)	7.22	(.09)	7.22	(.07)	NS
28-35 weeks (n = 25)	7.27	(.05)	7.20	(.15)	NS

Table 8.25

TRIPLETS

Clinical and Biochemical Lung Maturity and Stress Hormones

1 Triplet Pregnancy (26 weeks) Vaginal Delivery

	Weight (kg)	pH (UA)	L/S Ratio	PG	Cortisol'	AD'	NAD'	RDS
I	0.94	7.33	1.0	Absent	87	2.6	21.7	Yes
II	0.88	7.26	0.85	Absent	182	3.8	38.6	Yes
III	0.90	7.36	0.70	Absent	78	5.0	40.2	Yes

2 Triplet Pregnancy (31 weeks) Emergency C/S (GA) Membranes Intact

	Weight (kg)	pH (UA)	L/S Ratio	PG	Cortisol'	AD'	NAD'	RDS
I	0.92	7.19	3.54	Present	430	0.8	38.6	No
II	1.32	7.16	4.22	Present	-	0.1	1.8	No
III	1.5	7.17	1.83	Present	135	0.31	20.9	Yes

3 Triplet Pregnancy (33 weeks) Emergency C/S

	Weight (kg)	pH (UA)	L/S Ratio	PG	Cortisol'	AD'	NAD'	RDS
I	1.62	-	2.11	Present	138	3.0	293.6	No
II	1.75	-	1.67	Present	150	0.73	21.6	No
III	1.38	-	5.74	Present	140	3.3	192.4	No

' (nmol/ℓ)

Figure 8.1

Correlation between Co-twins (28-39 weeks)

PG Concentration

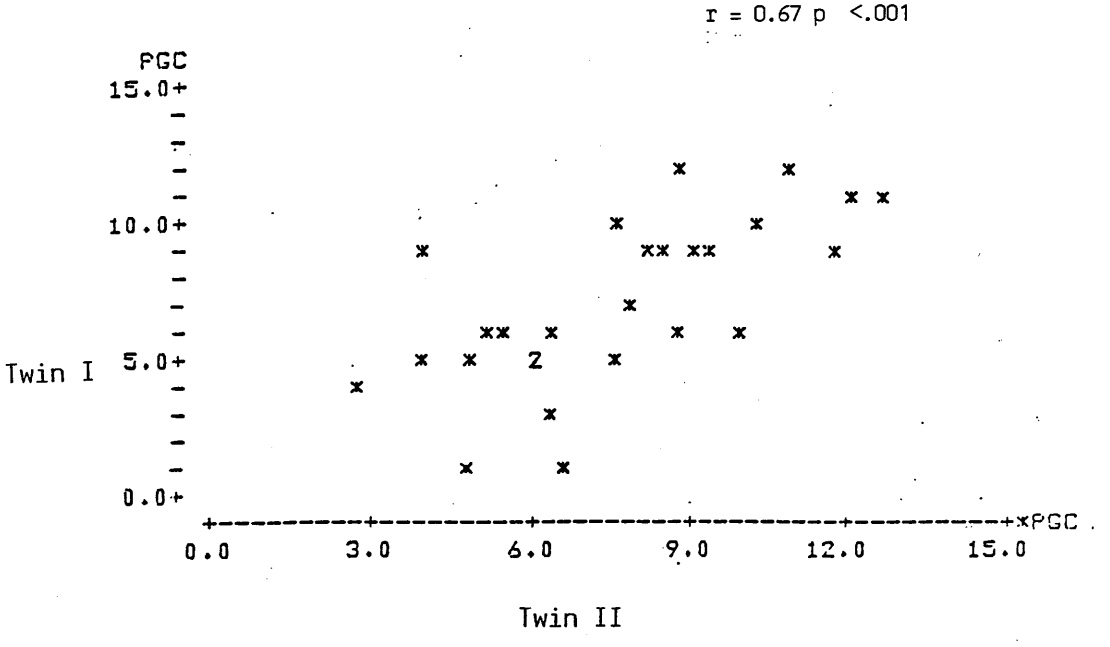
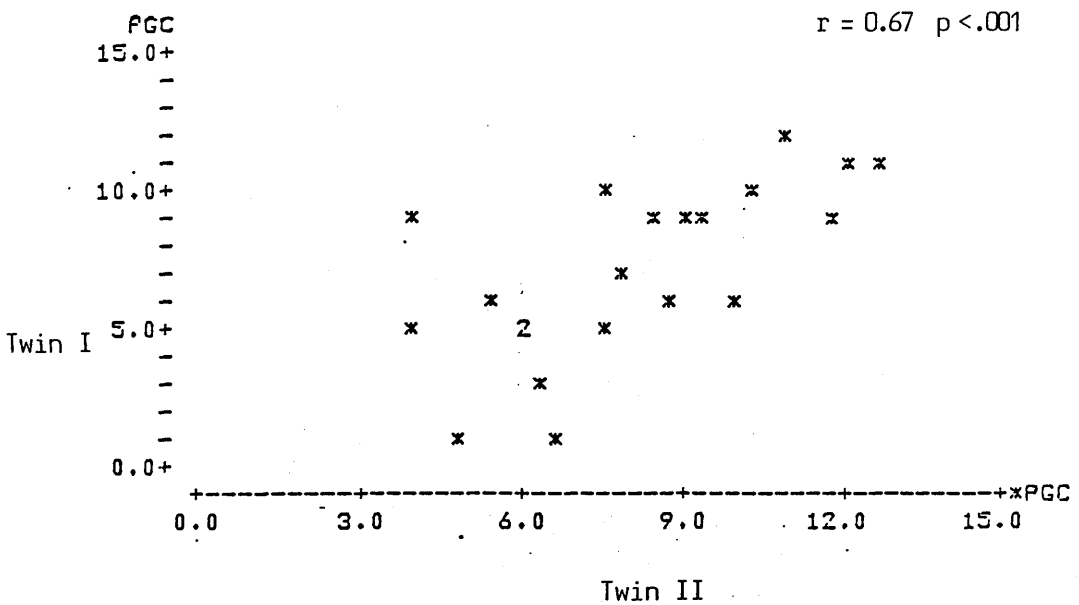


Figure 8.2

Correlation between Co-twins

PG Concentration

Term Twins (36-39 weeksO



Twin II

Figure 8.3

Correlation between Co-twins

L/S Ratio

Preterm Twins (28-35 weeks0

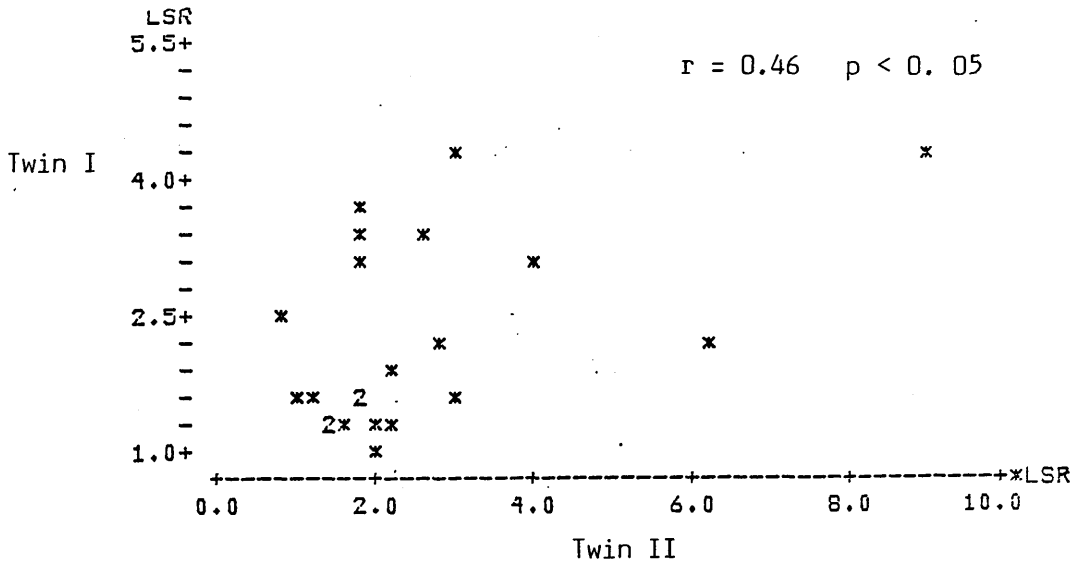


Figure 8.4

Correlation between Co-twins

Lecithin Concentration

Preterm Twins (28-35 weeks)

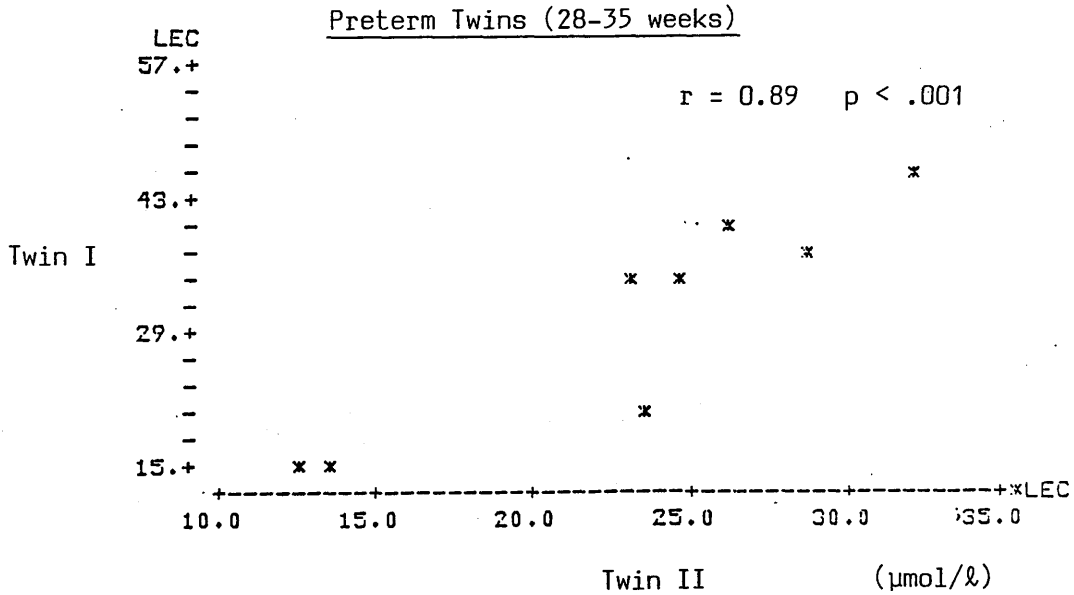


Figure 8.5

Correlation between Co-twins

PG Concentration

Preterm Twins (28-35 weeks)

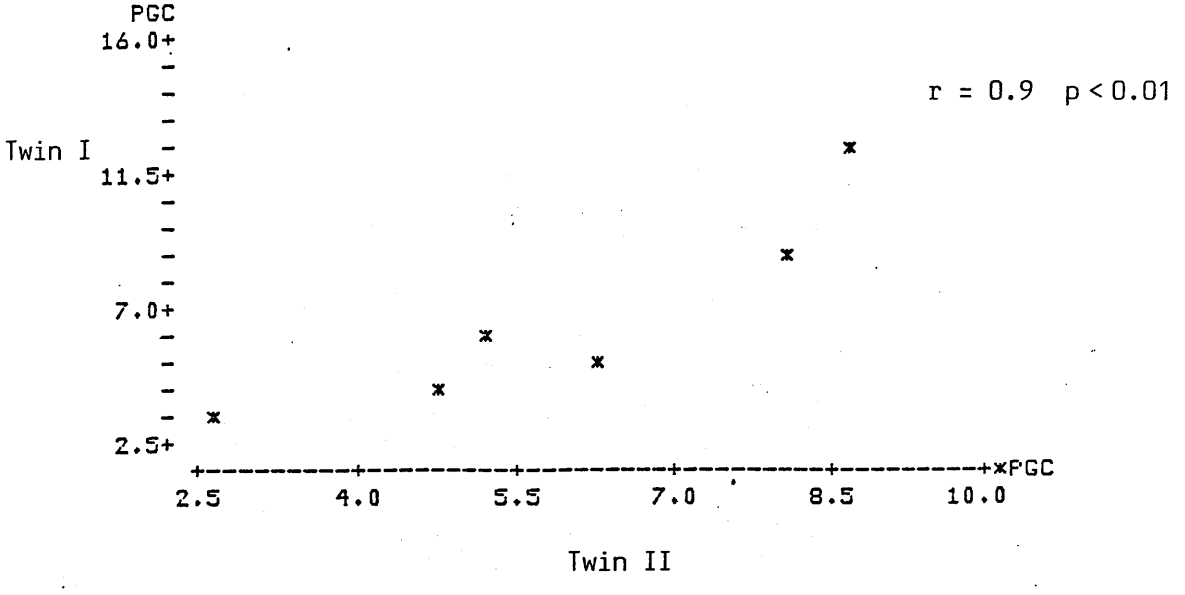


Figure 8.6

Correlation between Co-twins

Umbilical Arterial Cortisol (nmol/ℓ)

All Twins 28-39 weeks

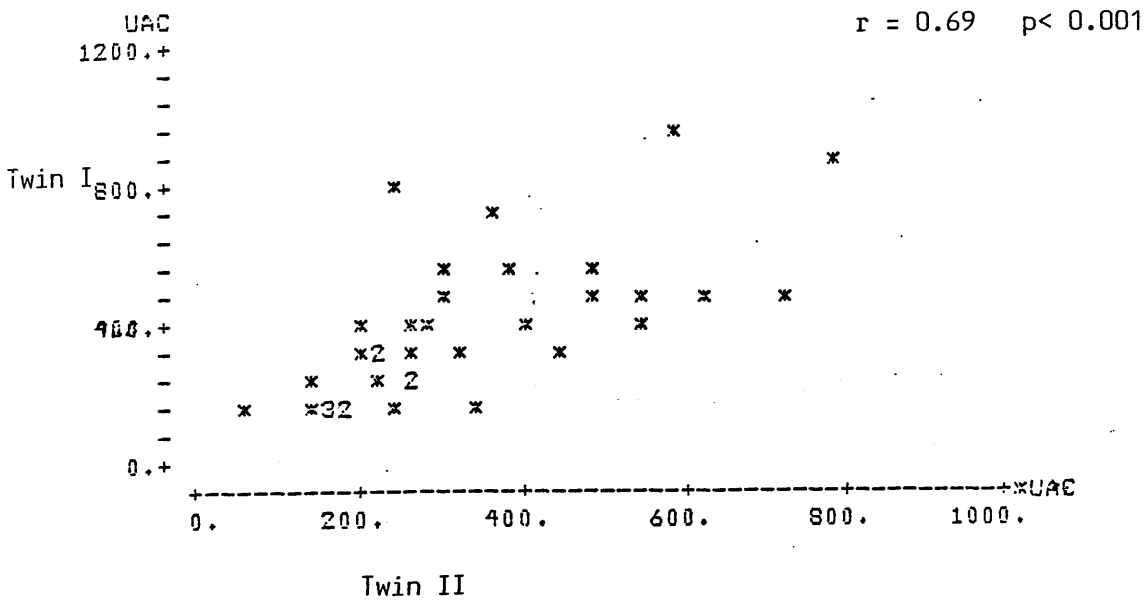


Figure 8.7

Correlation between Co-twins

Umbilical Arterial Cortisol (nmol/ℓ)

Term Twins (36-39 weeks)

r = 0.58 p < 0.01

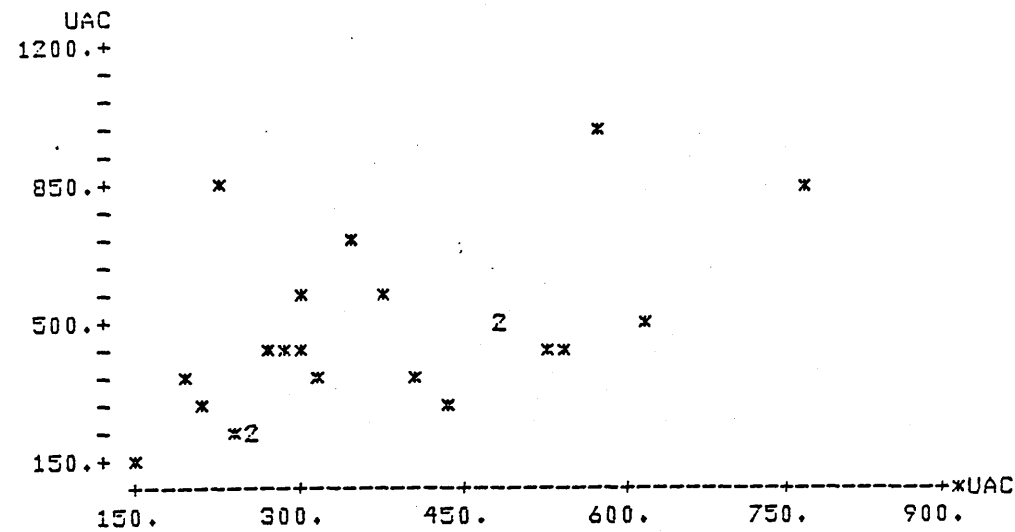


Figure 8.8

Correlation between Co-twins

Umbilical Arterial Cortisol (nmol/ℓ)

Preterm (28-35 weeks)

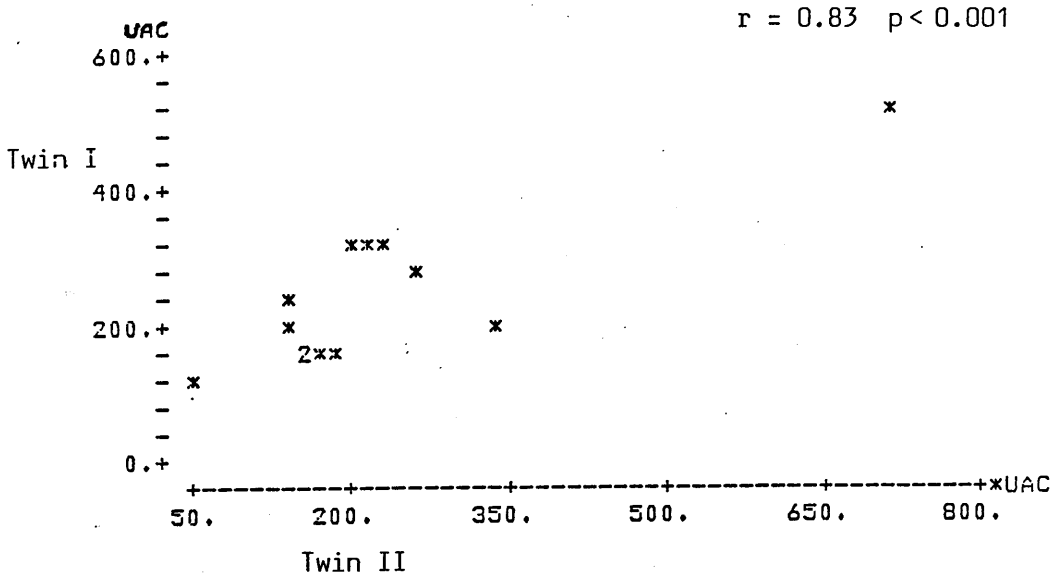
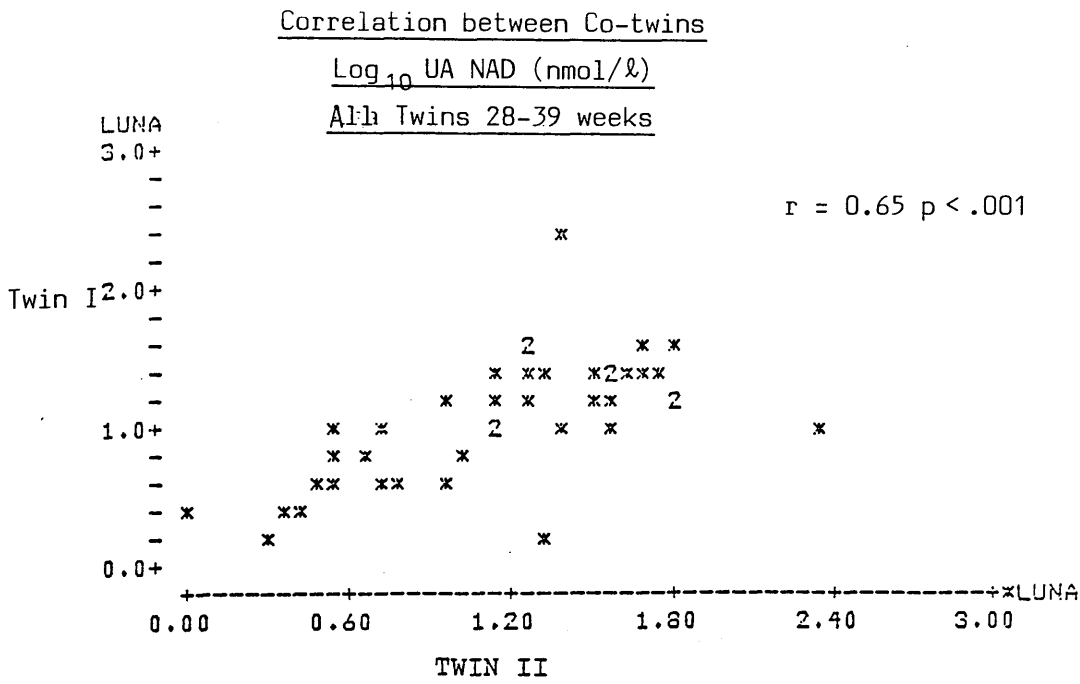


Figure 8.9


Correlation between Co-twins
Log10 UA NAD (nmol/ℓ)
All Twins 28-39 weeks
LUNA
3.0+
2.0+
1.0+
0.0+
Twin I
r = 0.65 p < .001
+---------+---------+---------+---------+---------+LUNA
0.00 0.60 1.20 1.80 2.40 3.00
TWIN II

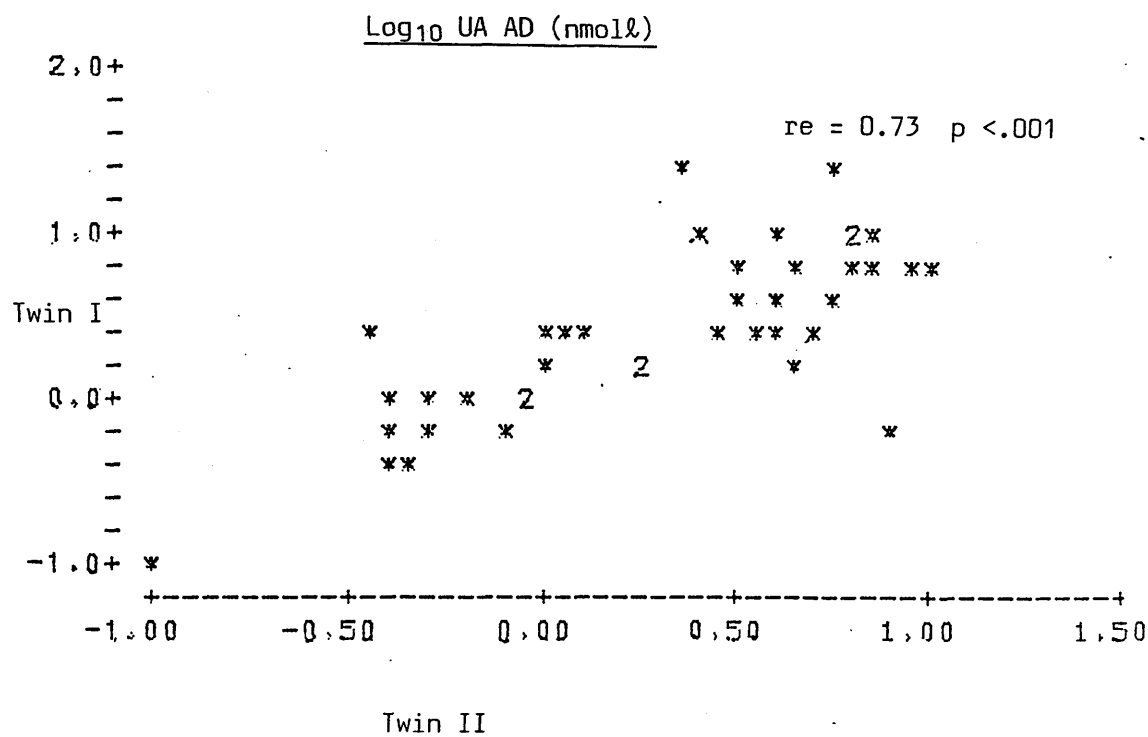
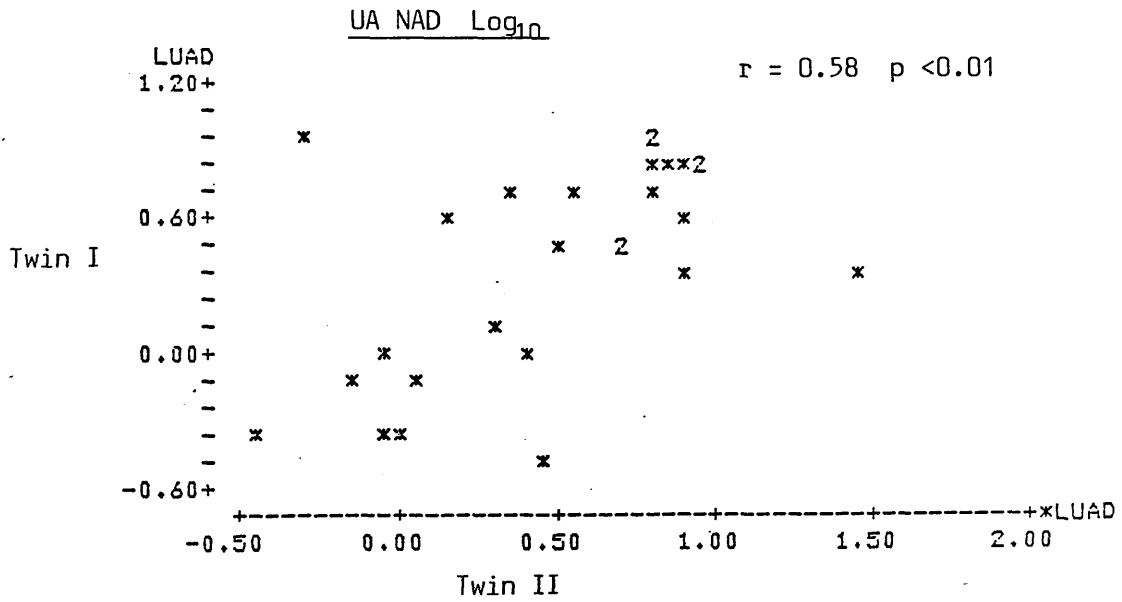

Log10 UA AD (nmolℓ)
2,0+
1,0+
0,0+
-1,0+
Twin I
re = 0.73 p <.001
+---------+---------+---------+---------+---------+---------+
-1,00 -0,50 0,00 0,50 1,00 1,50
Twin II

Figure 8.10

Correlation between Co-twins

Term Twins (36-39 weeks)



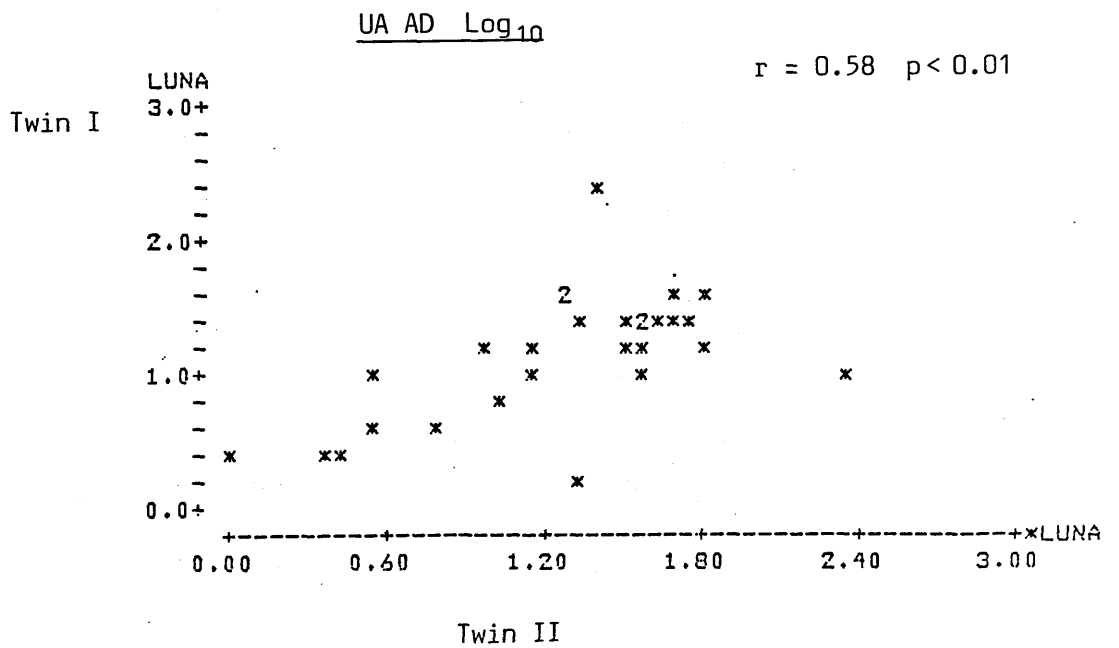
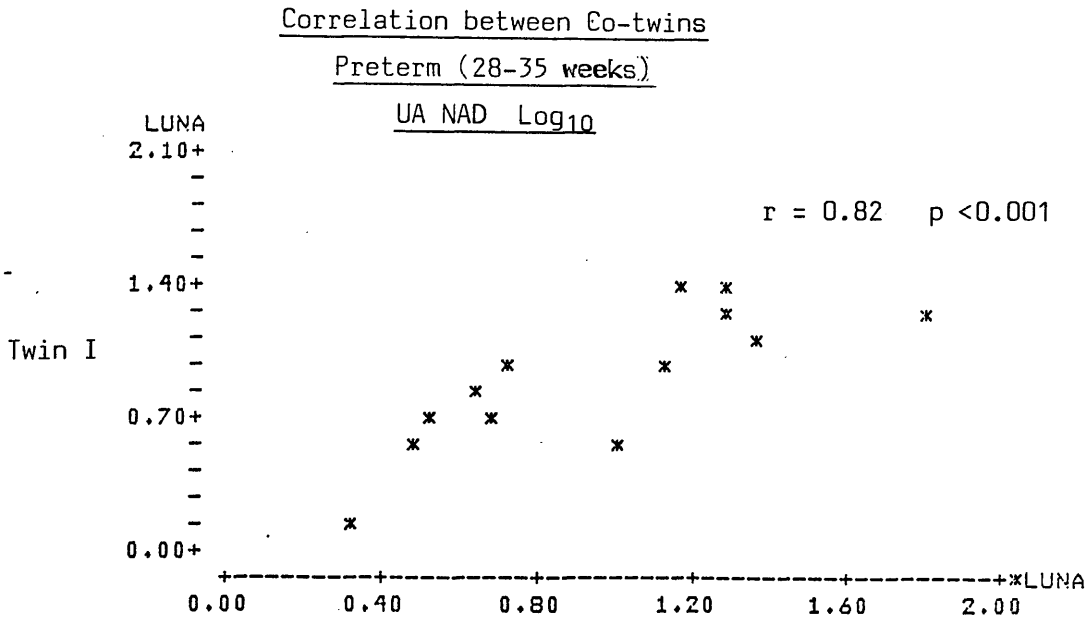
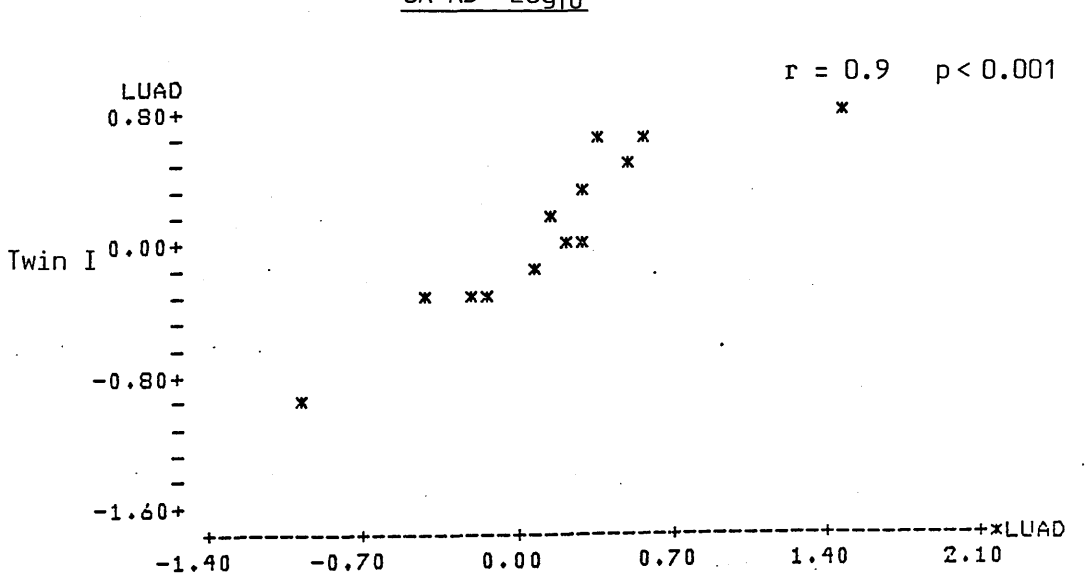


Figure 8.11


Correlation between Co-twins
Preterm (28-35 weeks)
UA NAD Log10
LUNA
2.10+
1.40+
0.70+
0.00+
r = 0.82 p <0.001
Twin I
0.00 0.40 0.80 1.20 1.60 2.00
*LUNA
Twin II


UA AD Log10
r = 0.9 p < 0.001
LUAD
0.80+
0.00+
-0.80+
-1.60+
Twin I
-1.40 -0.70 0.00 0.70 1.40 2.10
*LUAD
Twin II

CHAPTER 9

Condition of the Infant at Birth

9.1 Introduction

The incidence of RDS has been shown to be higher among infants with low apgar scores (Jones et al 1975) and abnormal fetal heart rate patterns (Martin et al 1974, Hobel et al 1972), and several workers (De Sa 1969, Bruns et al 1961) consider that asphyxia plays a central role in the development of RDS.

The possible mechanisms whereby asphyxia may result in RDS was investigated by establishing the relationship between fetal acidosis and clinical outcome, amniotic fluid phospholipids, umbilical arterial cortisol and umbilical arterial catecholamines.

The babies were again divided into gestational age groups:- 24-29 weeks, 30-33 weeks and 34-35 weeks as described in Chapter 4 (Materials and Methods Section).

9.2 Results

9.2.1 Clinical outcome

From 30 weeks onwards, those babies who developed RDS, required ventilation or died were significantly more acidotic than those babies who had no respiratory difficulties (Tables 9.1, 9.2 and 9.3).

9.2.2 Amniotic fluid phospholipids

a) 'Mature' versus 'Immature' amniotic fluid phospholipid profile

At each gestational age group (ie $\leq$ 29 weeks, 30-33 weeks, 34-35 weeks) a mature lung phospholipid profile (L/S $\geq$ 2.0 + PG) was compared to an immature profile (L/S < 2.0 no PG) with respect to UApH (Table 9.4).

In addition to the phospholipid profile, the L/S ratio alone and PG alone were also considered at each gestational age group (Tables 9.5 and 9.6).

There were no significant differences in mean UApH between those babies with 'mature' compared with 'immature' amniotic fluid phospholipids.

b) Correlation between UApH and Amniotic fluid phospholipids

There was no significant correlation between UApH and the L/S ratio PG/S ratio, LECITHIN concentration or PG concentration (Table 9.7).

9.2.3 Umbilical arterial cortisol

There is no obvious relationship between UApH and UAC levels in all cases studied (Figure 9.1) or after allowance for gestational age and method of delivery (Figures 9.2 and 9.3).

9.2.4 Umbilical arterial catecholamines

a) UA NAD

There was no obvious relationship between UApH and UANAD levels in the study as a whole (Figure 9.4). After correction for gestational age and method of delivery (Figure 9.5 and 9.6), only those babies delivered vaginally (SVD's) between 36-41 weeks demonstrated any significant correlation.

b) UA AD

There was no obvious relationship between UApH and UAAD levels (Figure 9.7) even after correction for gestational age and method of delivery (Figure 9.8 and 9.9).

9.3 Discussion

The condition of the baby at birth, as indicated by the UApH had a significant effect on the occurrence of RDS, the requirement for ventilation and the ultimate survival of the infant. However, the study did not confirm previous work that acidosis causes a decrease in the production of phospholipids (Merritt & Farrell 1976, Smith & Torday 1974) as no significant differences in mean UApH were observed between those babies with 'mature' and those with 'immature' phospholipids.

In addition there was no correlation between UAph and L/S ratio PG/S ratio, lecithin or PG concentrations.

However, exudation of plasma proteins from the injured lung, secondary to hypoxia, may interfere with surfactant function and lead to RDS. In addition asphyxia may cause central depression and therefore interfere with the infant's respiratory efforts which result in initial lung expansion. This lung expansion normally helps to clear lung fluid resulting in an abrupt fall in pulmonary vascular resistance.

The lack of correlation between UApH and UAC is in agreement with Farquarson et al (1985) but in contrast to the findings of Martinsen et al (1982) who in a study of 108 full term neonates delivered vaginally, found a significant correlation between cord cortisol levels and UAph. In this latter study, however, in the UApH range in which most babies are born (7.20-7.30) there was a wide variation in UAC levels. The correlation depended on those babies having highest UAC levels when pH was < 7.20, suggesting a threshold response. No such UApH threshold for release of cortisol was found in this present study. Only those babies undergoing spontaneous vertex delivery in the term (36-41 weeks) group showed a significant correlation to UApH.

Several other studies, however, have demonstrated a significant correlation between cord blood NAD and pH in the term (Padbury et al 1982, Falconer & Lake 1982) and in the preterm human fetus (Newham et al 1985). Bistoletti et al (1983) demonstrated a significant difference in mean cord NAD levels between babies with an UApH < 7.25 compared to those with an UApH > 7.26.

In the study by Padbury et al (1982) the relationship between UApH and UANAD became much less obvious when babies with UApH < 7.20 were omitted, again suggesting a threshold response.

Similarly no obvious relationship could be demonstrated between UApH and UAAD. This is in agreement with Bistoletti et al (1983) who, in term vaginal deliveries demonstrated no difference in UAAD levels between babies whose pH was less than 7.26 compared to those whose pH was greater than 7.25. In contrast, however, Padbury et al (1982) in the term fetus demonstrated a significant correlation between UAAD and UApH which no longer held true when babies whose UApH was less than 7.20 were omitted, again suggesting a threshold response. A significant correlation between UApH and UAAD was also demonstrated in the preterm neonate by Newham et al (1985).

It would seem, therefore, that there is evidence from the literature, although not substantially supported by the present study, to suggest that fetal catecholamine and cortisol levels are influenced by fetal acidosis to some extent. However, in the range of pH values in which most babies are born (ie > 7.20) there is a very wide scatter of catecholamine and cortisol values and that it is only when the pH drops to below 7.20 that a significant relationship between pH and fetal stress products occur in most studies.

9.4 Conclusions

The condition of the baby at birth, as reflected by the UA pH had:

1 a pronounced effect on the occurrence of neonatal respiratory problems. Those babies who were more acidotic developed more respiratory problems.

2 no effect on the concentration of amniotic fluid phospholipids.

3 no obvious relationship to fetal UA levels of cortisol NAD and AD.

Table 9.1

Condition at Birth and Clinical Outcome

RDS

Gestation		RDS	No RDS	Significance *
	Number	32	14	
≤ 29 weeks	BW (kg)	1.06 (.3)	1.17 (.4)	NS
	UApH	7.23 (.1)	7.2 (.1)	NS
	Number	21	53	
30-33 weeks	BW (kg)	1.58 (.4)	1.72 (.4)	NS
	UApH	7.22 (.1)	7.28 (.08)	p <.02
	Number	5	64	
34-35 weeks	BW (kg)	2.3 (.2)	2.1 (.4)	NS
	UApH	7.17 (.1)	7.25 (.09)	NS

* Tests of Significance UApH Mann Whitney
BW Student's 'T' Test

Table 9.2

Condition at Birth and Clinical Outcome

Ventilation Requirements

Gestation		Ventilation	No Ventilation	Significance *
	Number	32	14	
≤ 29 weeks	BW (kg)	1.06 (.3)	1.17 (.4)	NS
	UApH	7.23 (.1)	7.2 (.1)	NS
	Number	24	50	
30-33 weeks	BW (kg)	1.7 (.5)	1.8 (.5)	NS
	UApH	7.23 (.09)	7.28 (.08)	p <.008
	Number	8	61	
34-35 weeks	BW (kg)	2.17 (.3)	2.5 (.4)	NS
	UApH	7.11 (.1)	7.26 (.07)	p <.01

* Tests of Significance UApH Mann Whitney

BW Student's 'T' Test

Table 9.3

Condition at Birth and Clinical Outcome

Survival

Gestation		Died	Survived	Significance *
	Number	21	25	
≤ 29 weeks	BW (kg)	0.9 (.3)	1.25 (.25)	NS
	UApH	7.2 (.1)	7.22 (.1)	NS
	Number	7	67	
30-33 weeks	BW (kg)	1.6 (.6)	1.7 (.5)	NS
	UApH	7.15 (.1)	7.27 (.07)	$p < .05$
	Number	3	66	
34-35 weeks	BW (kg)	1.94 (.2)	2.16 (.4)	-
	UApH	7.02 (.1)	7.26 (.08)	-

* Tests of Significance BW - Student's 'T' Test
UApH - Mann Whitney

Table 9.4

Condition at Birth and Amniotic Fluid Phospholipids

L/S Ratio and PG

Gestation		<2 No PG	≥2 + PG	Significance
	Number			
≤ 29 weeks	BW (kg)	I N S U F F I C I E N T D A T A		
	UApH			
	Number	17	18	
30-33 weeks	BW (kg)	1.5 (.4)	1.8 (.4)	NS
	UApH	7.24 (.09)	7.28 (.08)	NS
	Number	7	39	
34-35 weeks	BW (kg)	2.14 (.3)	2.13 (.4)	NS
	UApH	7.21 (.1)	7.25 (.08)	NS

Table 9.5

Condition at Birth and Amniotic Fluid Phospholipids

L/S Ratio

Gestation		< 2	≥ 2	Significance
	Number			
≤29 weeks	BW (kg)	I N S U F F I C I E N T D A T A		
	UApH			
	Number	44	23	
30-33 weeks	BW (kg)	1.65 (.4)	1.75 (.5)	NS
	UApH	7.26 (.08)	7.26 (.1)	NS
	Number	24	42	
34-35 weeks	BW (kg)	2.17 (.5)	2.13 (.4)	NS
	UApH	7.24 (.08)	7.26 (.09)	NS

Table 9.6

Condition at Birth and Amniotic Fluid Phospholipids

PG

Gestation		Absent	Present	Significance
	Number	36	10	
⩽ 29 weeks	BW (kg)	1.04 (.4)	1.32 (.3)	p <.01
	UApH	7.21 (.1)	7.22 (.1)	NS
	Number	29	45	
30-33 weeks	BW (kg)	1.7 (.5)	1.7 (.4)	NS
	UApH	7.25 (.1)	7.27 (.07)	NS
	Number	13	56	
34-35 weeks	BW (kg)	2.19 (.4)	2.15 (.4)	NS
	UApH	7.20 (.1)	7.26 (.07)	NS

Table 9.7

Correlation between UApH and Amniotic Fluid Phospholipids

(24-35 weeks' gestation)

			r
UApH	&	L/S Ratio	0.12
UApH	&	PG/S Ratio	-0.02
UApH	&	Lecithin concentration (μ mol/ℓ)	0.09
UApH	&	PG concentration (μmol/ℓ)	0.18

Figure 9.1

Correlation of UApH and UAC

(All cases in study)

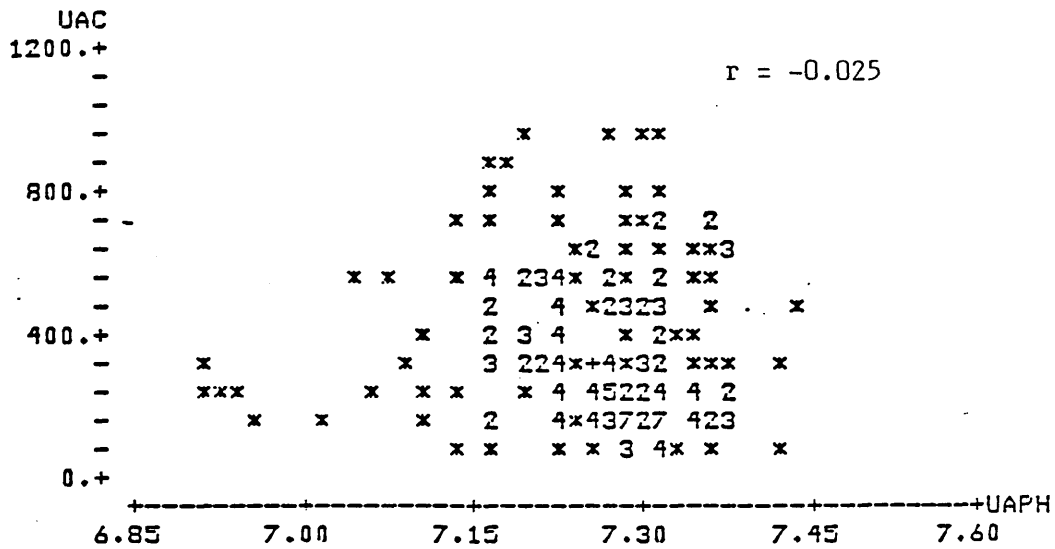
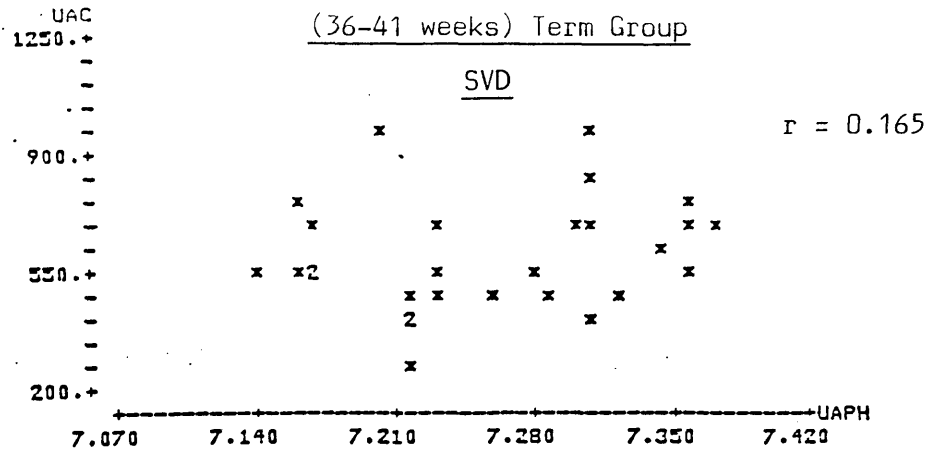


Figure 9.2

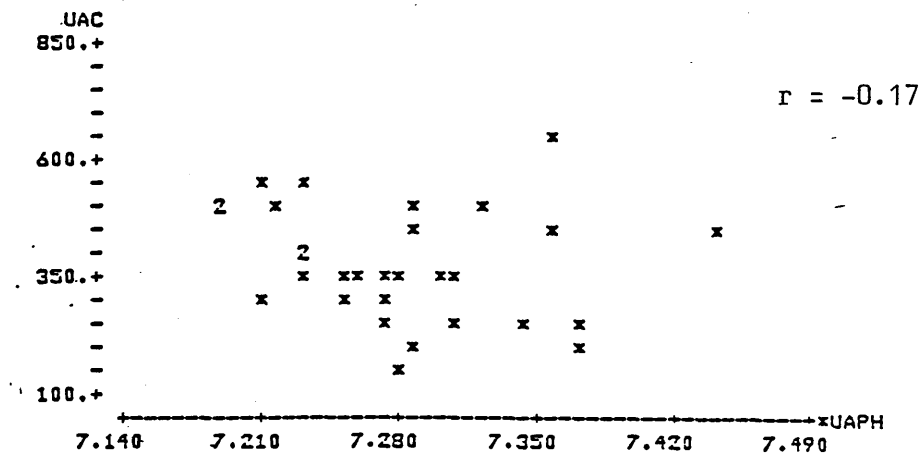
Correlation of UApH and UAC

(36-41 weeks) Term Group

SVD



Elective Caesarean Section



Emergency Caesarean Section

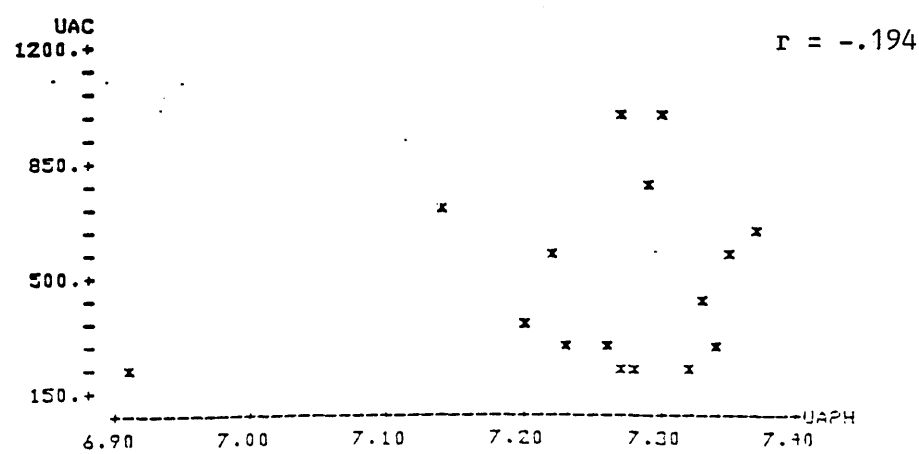
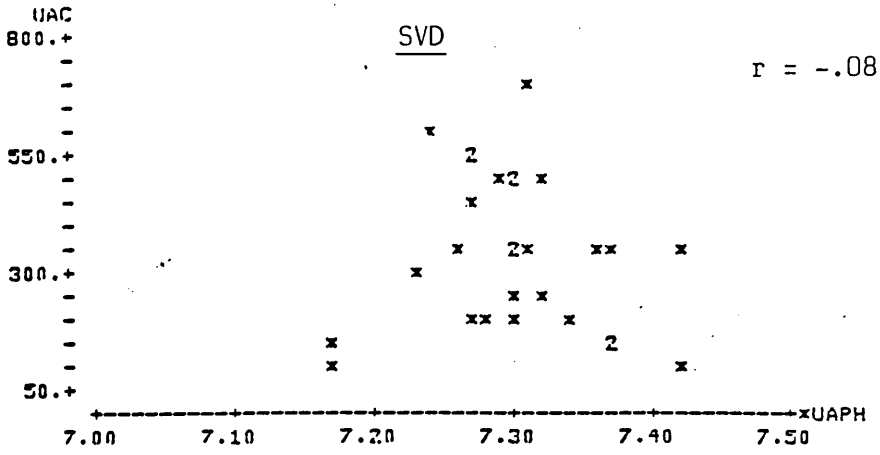


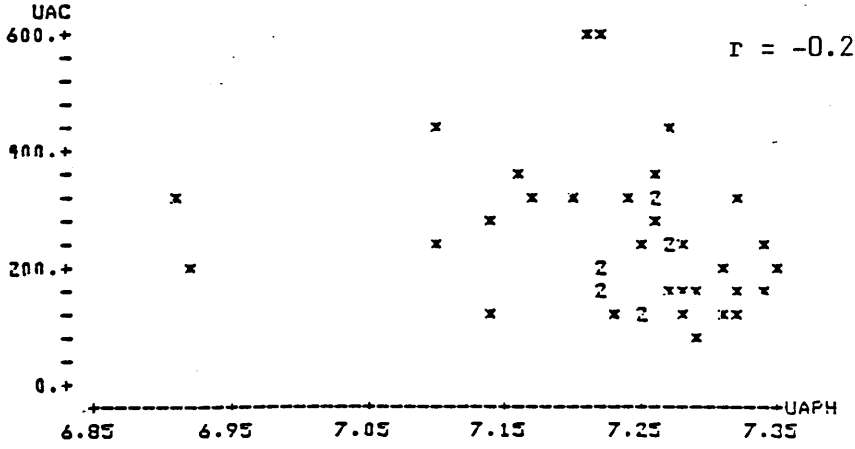
Figure 9.3

Correlation of UApH and UAc

(24-35 weeks) Preterm Group



Elective Caesarean Section



Labour and Caesarean Section

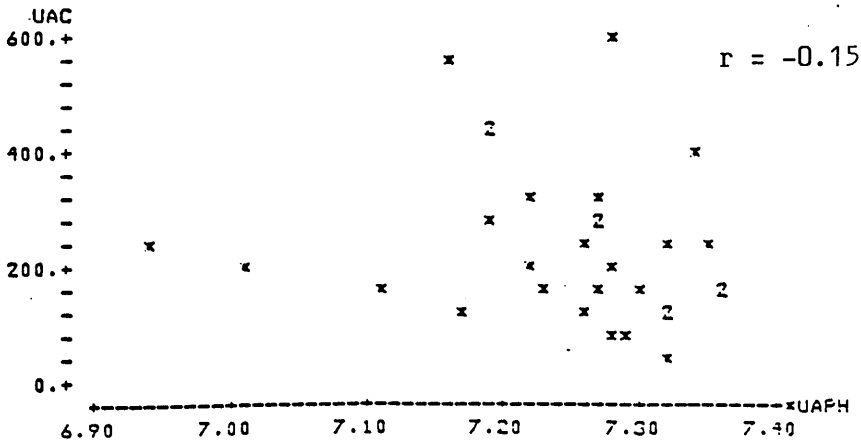


Figure 9.4

Correlation between UApH and Log UA NAD

(All cases)

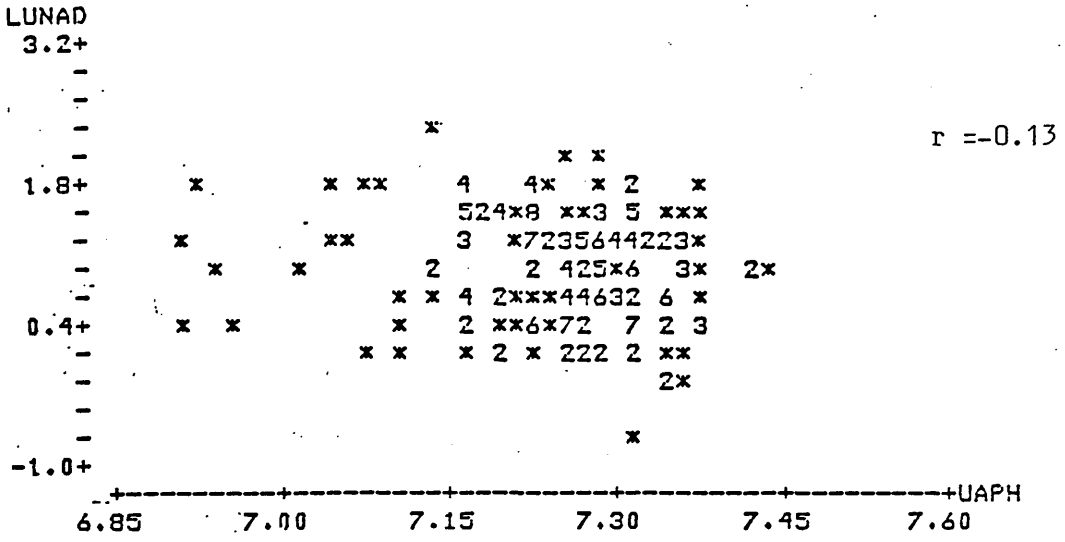
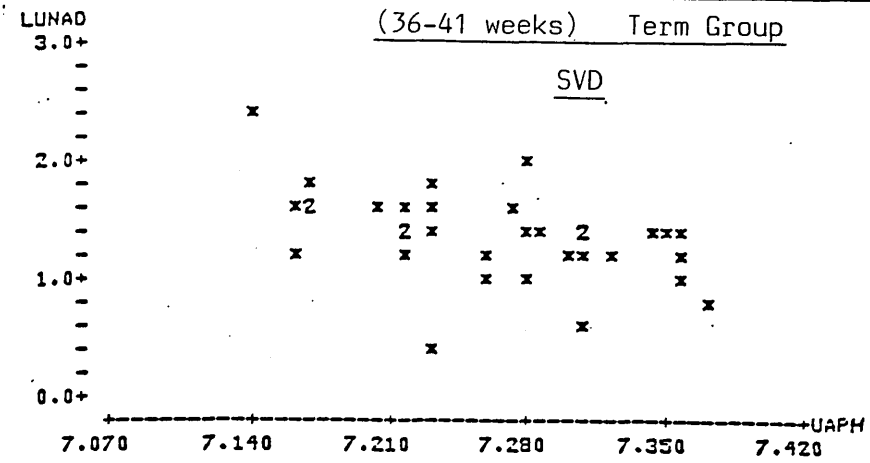


Figure 9.5

Correlation between UApH and Log UA NAD

(36-41 weeks) Term Group

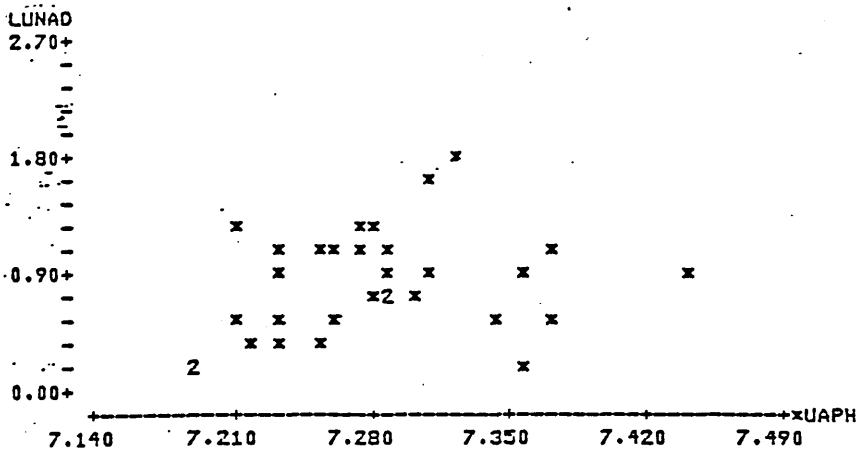
SVD



r = -0.425

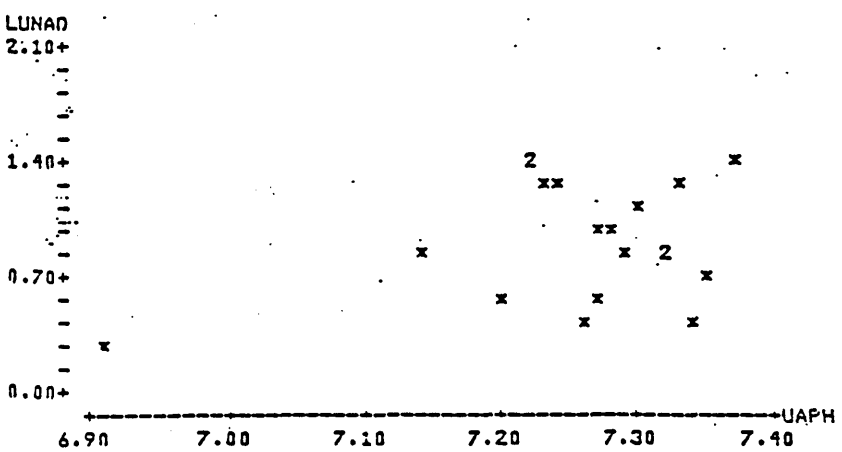
p < .01

Elective Caesarean Section



r = 0.244

Labour and Caesarean Section



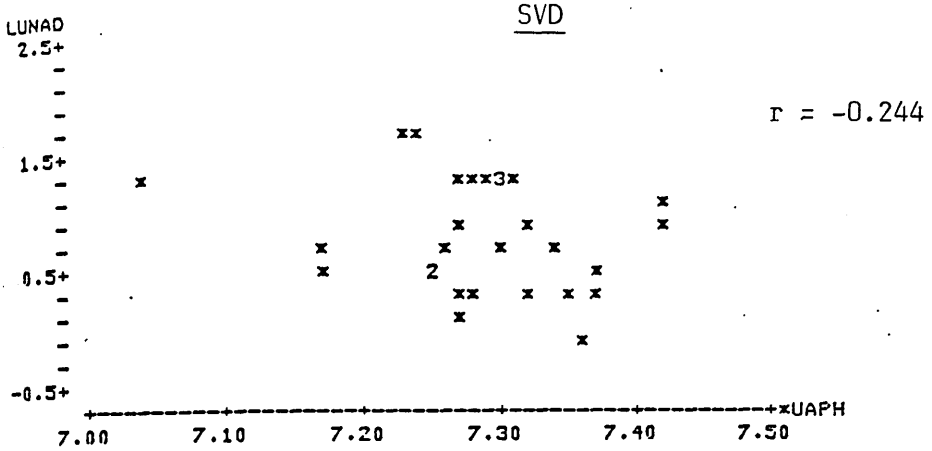
r = 0.298

Figure 9.6

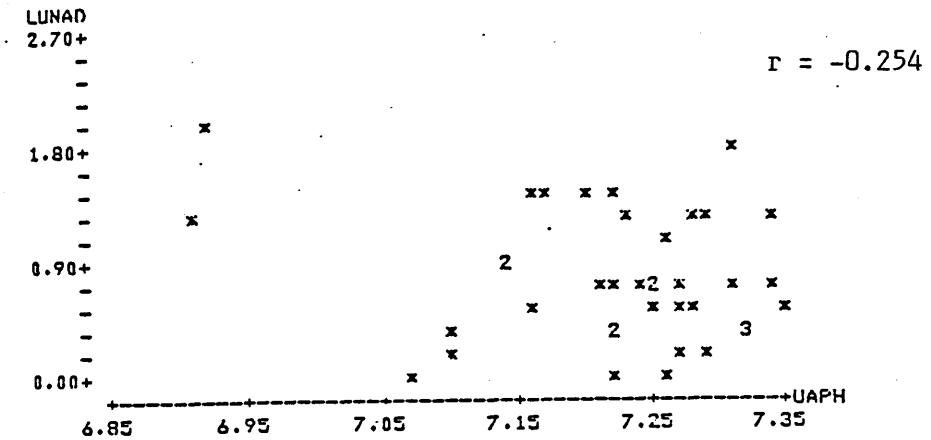
Correlation between UApH and Log UA NAD

(24-35 weeks) Preterm Group

SVD



Elective Caesarean Section



Labour and Caesarean Section

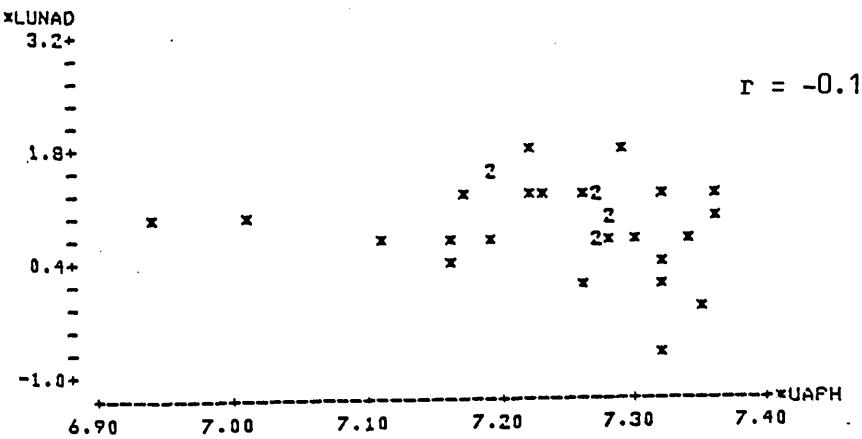


Figure 9.7

Correlation between UApH and Log UA AD

(All cases)

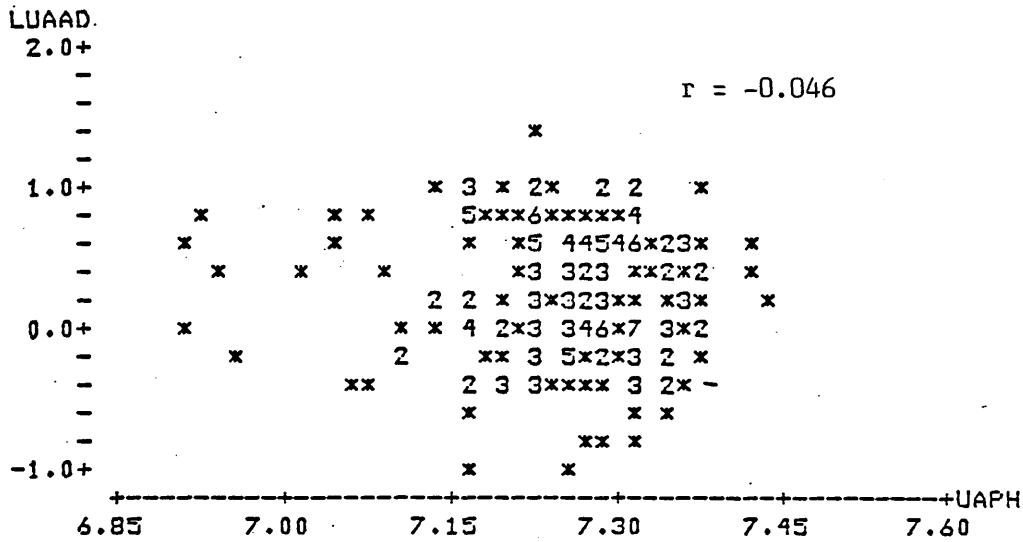
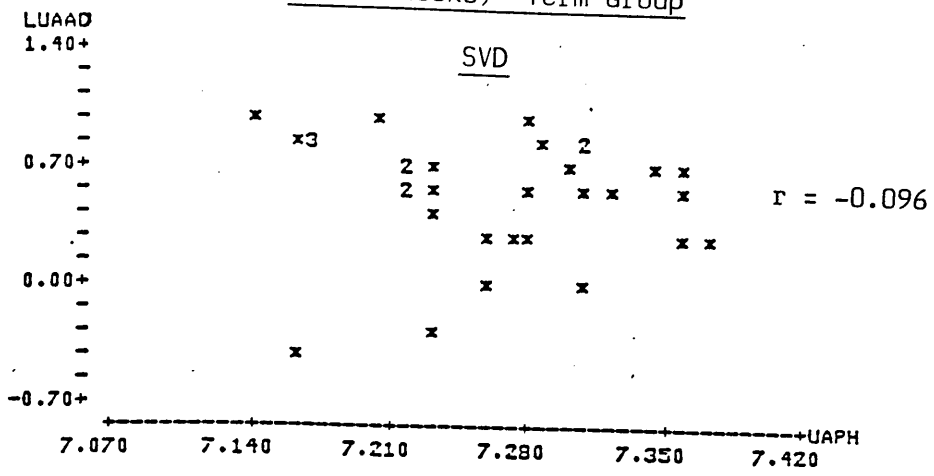


Figure 9.8

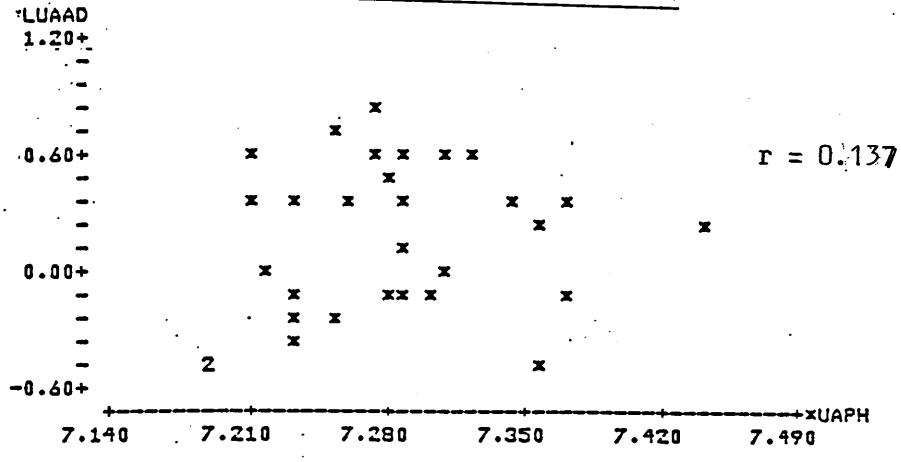
Correlation between UApH and Log UA AD

(36-41 weeks) Term Group

SVD



Elective Caesarean Section



Labour and Caesarean Section

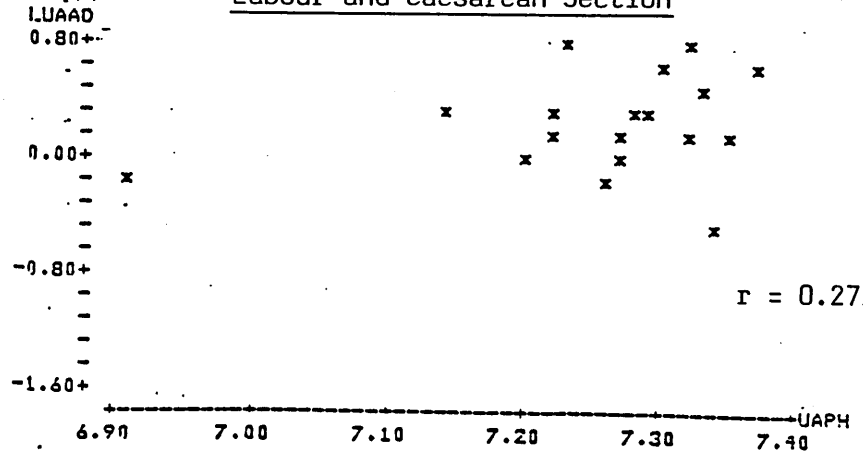
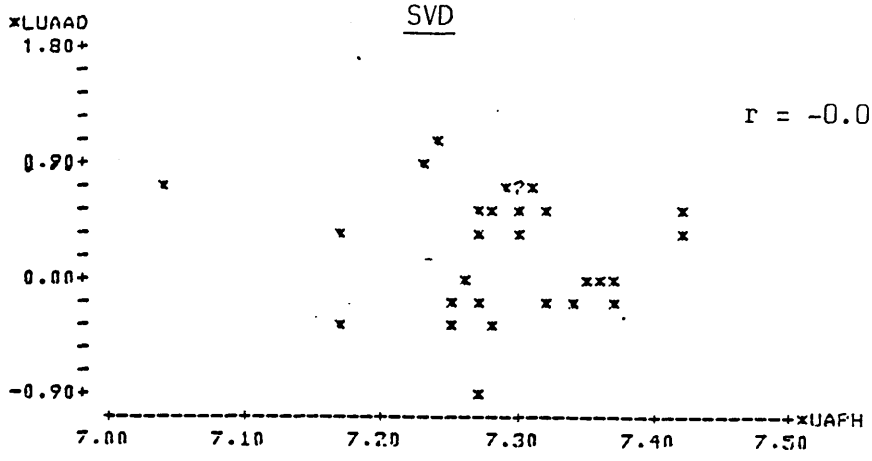


Figure 9.9

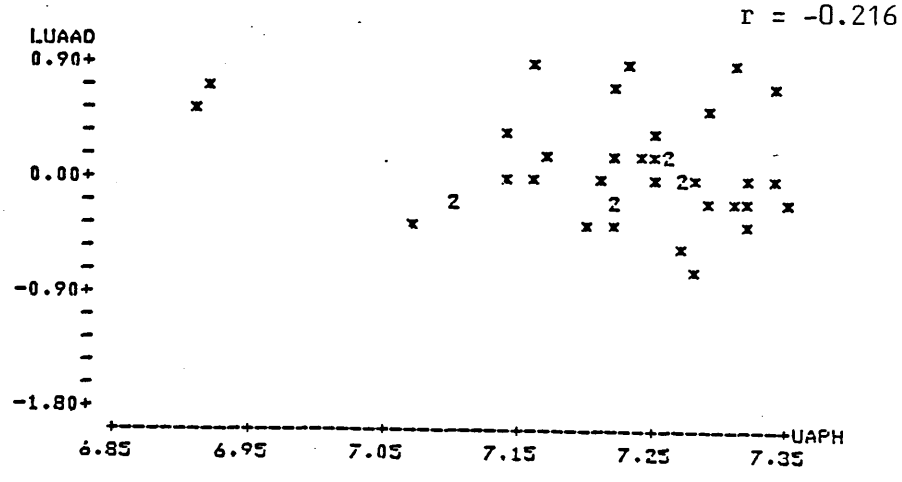
Correlation between UApH and Log UA AD

(24-35 weeks) Preterm Group

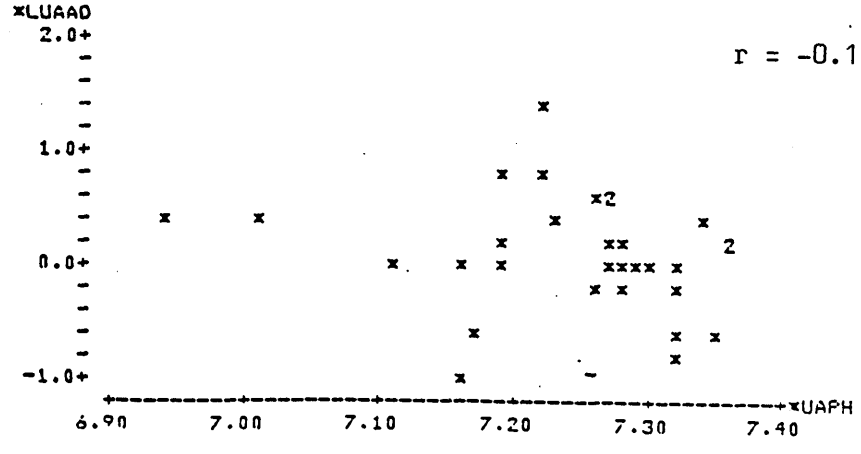
SVD



Elective Caesarean Section



Labour and Caesarean Section



CHAPTER 10

Obstetric Complications

Obstetric Complications

10.1 Introduction

Clinical experience over many years has suggested that certain obstetric complications are associated with a lower incidence of RDS, whilst others are associated with a higher incidence than expected (Chapter 3).

Premature rupture of the membranes - PROM (Chiswick 1973, Yoon and Harper 1973, Lee et al 1976, Sell 1977, Worthington 1977), intrauterine growth retardation - IUGR (Procaindy et al 1980), hypertension (Chiswick and Burnard 1973, Lee at al 1976) and antepartum haemorrhage (Gluck et al 1972) have all been associated with an 'acceleration' of fetal lung maturity whilst neonates of diabetic mothers (Gluck and Kulovich 1973) are thought to be at greater risk of developing RDS.

Exactly how such obstetric stress influences fetal lung maturity is unknown. However, elevated cord blood and amniotic fluid cortisol levels have been found in pregnancies complicated by PROM (Murphy 1974[A], Bauer et al 1974, Cohen et al 1976), pregnancy induced hypertension (Goldkrand 1978) and IUGR (Sybulski 1977). Similarly, elevated cord catecholamine levels have been noted in pregnancies complicated by preclampsia (Tunbridge & Donnai 1981, Sammour et al 1980), by IUGR (Divers et al 1981) and by PROM (Blouquit et al 1979).

In this chapter the effect of various obstetric complications on clinical and biochemical lung maturity and on the levels of fetal cortisol and catecholamines was studied.

The evidence in the literature that premature rupture of the membranes (PROM) causes an 'acceleration' of fetal lung maturity (especially biochemical lung maturity) is more convincing than for other other obstetric complications (Chapter 3). Therefore, the first

part of this chapter considers only PROM. In the second part of the chapter other complications, namely intrauterine growth retardation (IUGR), proteinuric hypertension, vaginal bleeding, abnormal antenatal cardiotocograph and spontaneous onset of labour and vaginal delivery were considered together.

10.2 Results

10.2.1 Premature rupture of membranes(PROM)

The first section of this chapter considers the effect of PROM on clinical outcome, amniotic fluid phospholipids and cord blood biochemical parameters.

Two groups of babies who laboured spontaneously, prior to 36 weeks, were studied. In one group the membranes had been ruptured for less than 24 hours prior to delivery and this group was compared with a group whose membranes had ruptured > 24 hours prior to delivery. Because of the relatively small numbers involved, only 2 gestational age groups were considered, ie 24-29 weeks and 30-35 weeks. Although a higher percentage of babies were delivered by caesarean section in the group whose membranes had ruptured for < 24 hours, this was not statistically significant (Chi square) (Tables 10.1 and 10.2).

a) PROM and clinical outcome

There were no significant differences in mean birthweight or gestational age for those whose membranes had ruptured < 24 hours compared with > 24 hours, in either gestational age group (Tables 10.3 and 10.4).

Duration of rupture of membranes seemed to have no influence on clinical outcome - the occurrence of RDS, requirement for ventilation or mortality (Tables 10.3 and 10.4).

b) PROM and amniotic fluid phospholipids

There was no significant difference in amniotic fluid phospholipids between those babies whose membranes had ruptured < 24 hours compared to those with ruptured membranes ≥ 24 hours in either gestational age group (Tables 10.5 and 10.6).

c) PROM and umbilical arterial cortisol

PROM (> 24 hours) seemed to have no significant influence on UAC levels (Table 10.7).

d) PROM and umbilical arterial catecholamines

PROM (> 24 hours had no influence on mean UA NAD or AD levels (Table 10.8).

e) PROM and umbilical arterial pH

PROM (> 24 hours) had no effect on condition of infant at birth as reflected by the mean UA pH (Table 10.9).

10.2.2 Obstetric complications (other than PROM)

In this section the influence of 5 obstetric complications on clinical outcome, amniotic fluid phospholipids, umbilical arterial cortisol and catecholamines was studied. The 5 obstetric complications considered were, proteinuric hypertension - (a blood pressure of at least 140/90 accompanied by significant proteinuria ≥0.5 g/litre in a 24 hour hour collection), vaginal bleeding, intrauterine growth retardation - (birth weight < 5th centile for gestational age), an abnormal antenatal cardiotacograph - (no acceleration in a 20 minute tracing and/or the presence of decelerations), and a group of babies who had uncomplicated sponteneous onset of labour and vaginal delivery.

Unfortunately it is not possible to obtain a control group of 'normal' babies delivered prior to term, as the delivery of a preterm baby, either electively or spontaneously is not a normal event. Those babies undergoing spontaneous onset of labour and vaginal delivery are probably as close to a 'normal' group as can be obtained.

Some pregnancies were complicated by more than one problem (eg proteinuric hypertension and IUGR) and it was often impossible to assign one major complication to a particular case.

The babies were divided into the following gestational age groups, as previously outlined, $\leq$ 29 weeks, 30-33 weeks, 34-35 weeks. In order to increase numbers in each group and thus allow more meaningful statistical analysis, a third group 30-35 weeks was also included.

Tables 10.10 to 10.13 show the number of babies for each obstetric complication, by gestational age and method of delivery.

Table 10.14 shows the mean birthweight for each complication in each gestational age group studied. It can be seen that the mean birthweight in the IUGR group was consistently significantly lower than that in the preterm labour or vaginal bleeding groups, but similar to the proteinuric hypertension and abnormal CTG groups.

a) Obstetric complications and clinical outcome

The 5 complications assessed seemed to have little obvious effect on whether respiratory problems developed. In each gestational age group, the highest percentage of babies who died was in the group with abnormal CTGs (Tables 10.15 - 10.18).

b) Obstetric complications and amniotic fluid phospholipids

None of the 5 obstetric complications appeared to influence the amniotic fluid phospholipids in any particular way (Tables 10.19 -

10.22). Although an abnormal CTG was associated with a lower percentage of babies with amniotic fluid PG (Table 10.22).

c) Obstetric complications and umbilical arterial cortisol

None of the 5 obstetric complications appeared to affect the cord blood cortisol in any consistently significant way. However after 33 weeks, the preterm labour group and the IUGR group had significantly raised mean UAC concentration compared to the proteinuric hypertension group (Table 10.23).

d) Obstetric complications and umbilical arterial catecholamines

None of the 5 obstetric complications appeared to affect the cord blood catecholamines in any consistently significant way (Tables 10.24 and 10.25).

e) Obstetric complications and condition of infant at birth

The mean UA pH was consistently depressed in babies delivered in response to an abnormal CTG (Table 10.26).

10.3 Discussion

It is believed that certain obstetric complications, eg pre eclampsia, IUGR, PROM, appear to protect the neonate from developing RDS and it has been suggested that they may do so by 'stressing' the fetus. However, in none of the obstetric complications investigated were the levels of so-called stress hormones NAD AD and cortisol consistently different from the others, particularly the 'control' group of spontaneously preterm labouring and vaginally delivered babies.

Of the obstetric complications considered only in pregnancies where there was an abnormal antenatal CTG was there a suggestion of a

different clinical outcome. The higher percentage of babies dying or requiring ventilation were found in this group (Table 10.15 to 10.18). These babies were also in a poor condition at birth as reflected by the mean UA pH which was significantly lower in the abnormal CTG group compared with the other groups (except IUGR group), (Table 10.26). This difference in UA pH however was not reflected in the levels of the other stress products measured, namely cortisol, noradrenaline and adrenaline which have been implicated in influencing neonatal respiratory function.

There was no evidence to suggest any difference in amniotic fluid phsopholipids between those babies undergoing the physiological stress of spontaneous preterm labour and vaginal delivery and the pathological stress of IUGR, proteinuric hypertension or vaginal bleeding. However, those babies who were severely stressed in the abnormal CTG group had the lowest occurrence of AFPG (Table 10.22).

No support could be found from this chapter for the idea of acceleration of fetal lung maturity (either clinical or biochemical lung maturity). However, this is not really surprising, considering the hypothesis of acceleration of fetal lung maturity as a result of obstetric complications implies that we know the normal timing of events in lung development in the human. How is it possible to derive a normal timetable for fetal lung maturation using prematurely born infants who, by definition are not normal, whether because of the time of their birth or underlying maternal pathology. The fact that more than one obstetric complication can, and often does occur in some pregnancies, makes the situation even more confusing and open to misinterpretation.

It would seem therefore that the gestational age and the condition of the infant at birth are more important factors determining neonatal respiratory performance than obstetric complications which themselves led to premature delivery.

10.4 Conclusions

1 None of the obstetric complications studied, (proteinuric hypertension, IUGR, vaginal bleeding, spontaneous preterm labour and vaginal delivery, PROM) appeared to cause an acceleration in either clinical or biochemical lung maturity.

2 None of the obstetric complications studied consistently effected the levels of fetal stress hormones NAD, AD and cortisol in any particular way.

3 The gestational age and the condition of the infant at birth would seem to be at least as important as any obstetric complications which may lead to preterm delivery.

4 The presence of an abnormal CTG seemed positively deleterious to the neonates, who required significantly more ventilatory support.

Table 10.1

Membranes Ruptured < 24 hours

Number of cases by gestational age and method of delivery

Gestation (weeks)	Vaginal	C/S	All
25	3	0	3
26	2	1	3
27	2	0	2
28	3	2	5
29	8	2	10
30	5	1	6
31	3	2	5
32	4	4	8
33	5	7	12
34	12	8	20
35	7	4	11
ALL	54 (64%)	31 (36%)	85

Table 10.2

Membranes Ruptured 24 hours

Number of cases by gestational age and method of delivery

Gestation (weeks)	Vaginal	C/S	All
24	1	0	1
28	2	1	3
29	2	1	3
30	1	0	1
31	1	0	1
32	4	0	4
33	2	0	2
34	3	2	5
35	2	0	2
ALL	18 (82%)	4 (18%)	22

Table 10.3

PROM and Clinical Outcome

24-29 weeks' gestation

	Membranes Ruptured				
	< 24 hours (n = 23)		> 24 hours (n = 7)		
Birthweight (kg) (Mean SD)	1.16	(0.3)	1.15	(0.5)	NS
Gestation (weeks) (Mean SD)	27.7	(1.5)	27.9	(1.7)	NS
RDS	(14/23)	61%	(4/7)	57%	NS
Ventilation	(16/23)	70%	(4/7)	57%	NS
Died	(7/23)	30%	(5/7)	71%	NS

Table 10.4

PROM and Clinical Outcome

30-35 weeks' gestation

	Membranes Ruptured				
	< 24 hours (n = 62)		> 24 hours (n = 15)		
Birthweight (kg) (Mean SD)	2.03	(0.4)	1.98	(0.5)	NS
Gestation (weeks) (Mean SD)	33.1	(1.5)	33.0	(1.5)	NS
RDS	10/62	(16%)	3/15	(20%)	NS
Ventilation	14/62	(23%)	3/15	(20%)	NS
Died	3/62	(5%)	0/15	(0%)	NS

Table 10.5

PROM and Amniotic Fluid Phospholipids

Mean (SD)

24-29 weeks gestation

	Membranes Ruptured				
	< 24 hours (n = 23)		> 24 hours (n = 7)		
L/S Ratio	1.2	(0.4)	2.2	(1)	NS
PG/S Ratio	0.7	(0.4)	INSUFFICIENT DATA		
AFPG *	(7/23)	30%	(1/7)	14%	NS
' Lecithin concentration	13.2	(2.2)	INSUFFICIENT DATA		
' PG concentration	5.2	(1.5)	INSUFFICIENT DATA		

* PG present in amniotic fluid

' (μmol/ℓ)

Table 10.6

PROM and Amniotic Fluid Phospholipids

Mean (SD)

30-35 weeks' gestation

	Membranes Ruptured				
	<24 hours (n = 62)		>24 hours (n = 15)		
L/S Ratio	2.19	(0.9)	2.8	(1.9)	NS
PG/S Ratio	1.09	(.7)	0.95	(.6)	NS
AFPG *	(46/62)	74%	(10/15)	67%	NS
'Lecithin concentration	26.4	(15)	34.2	(26)	NS
'PG concentration	5.4	(2)	6.3	(3)	NS

* PG present in amniotic fluid

'(µmol/ℓ)

Table 10.7

PROM and Umbilical Arterial Cortisol (nmol/ℓ)

Mean (SD)

	Membranes Ruptured		
	<24 hours	>24 hours	
24-29 weeks	192 (108) (n = 23)	318 (203) (n = 7)	NS
30-35 weeks	307 (183) (n = 62)	405 (172) (n = 15)	NS

Table 10.8

PROM and Umbilical Arterial Catecholamines (nmol/ℓ)

		Membranes Ruptured				
		< 24 hours		> 24 hours		
	UA NAD	12.3	(15)	19.3	(9.2)	NS
24-29 weeks		(n = 23)		(n = 7)		
	UA AD	1.11	(0.9)	2.5	(2.6)	NS
	UA NAD	17.2	(42)	17.9	(17)	NS
30-35 weeks		(n = 62)		(n = 15		
	UA AD	2.0	(1.7)	3.3	(3.1)	NS

Table 10.9

PROM and Condition of Baby at Birth (UApH)

		Membranes Ruptured		
		< 24 hours	> 24 hours	
24-29 weeks	UApH	7.22 (.1) (n = 23)	7.26 (.06) (n = 7)	NS
30-35 weeks	UApH	7.27 (.08) (n = 62)	7.28 (.07) (n = 15)	NS

Table 10.10

Proteinuric Hypertension

Gestation (weeks)

Delivery	29	30-33	34-35
Vaginal	-	-	2
Elective C/S	7	14	9
Emergency C/S	-	-	2
	7	14	13

Table 10.11

Vaginal Bleeding
Gestation (weeks)

Delivery	≤ 29	30-33	34-35
Vaginal	9	8	1
Elective C/S	1	2	1
Emergency C/S	4	8	4
	14	18	6

Table 10.12

Abnormal Antenatal Cardiotocograph

Gestation (weeks)

Delivery	≤29	30-35	34-35
Vaginal	1	2	2
Elective C/S	4	8	4
Emergency C/S	1	-	2
	6	10	8

Table 10.13

IUGR

Gestation (weeks)

Delivery	≤29	30-33	34-35
Vaginal	3	1	1
Elective C/S	3	7	10
Emergency C/S	-	2	5
	6	10	16

Table 10.14

Obstetric Complications

Mean (SD) Birthweight (kg) at each gestational age group

Gestation (weeks)	BP + Protein	APH	IUGR	Abnormal CTG	Preterm Labour	Significance
24-29	0.97 (.24)* (n = 7)	1.28 (.3)*+ (n = 14)	0.71 (.2)°+ (n = 6)	0.97 (.2) (n = 6)	1.13 (.4)° (n = 29)	* p < .025 + p < .0005 ° p < .0025
30-33	1.31 (.5)*° (n = 14)	1.85 (.3)*+‡ (n = 18)	1.02 (.17)+x (n = 10)	1.29 (.56)‡ (n = 9)	1.72 (.3)°x (n = 29)	* p < .0025 +, x p < .0005 °, ‡ p < .025
34-35	1.99 (.48)*+ (n = 13)	2.5 (.38)*°‡ (n = 6)	1.67 (.35)x° (n = 16)	1.8 (.46)‡• (n = 7)	2.25 (.3)+•x (n = 27)	* p < .025 +, • p < .05 °, x p < .0005 ‡ p < .01
30-35	1.64 (.6)*+ (n = 27)	2.02 (.4)*•‡ (n = 24)	1.42 (.4)°‡ (n = 26)	1.51 (.57)•x (n = 16)	1.97 (.4)+°x (n = 56)	*, +, x p < .01 °, ‡ p < .0005 • p < .005

Table 10.15

Obstetric Complications and Clinical Outcome

24-29 weeks' gestation

	↑BP + Proteinuria	APH	IUGR	Abnormal CTG	Preterm Labour
RDS	6/7 (86%)	10/14 (71%)	4/6 (67%)	5/6 (83%)	20/29 (69%)
Ventilation	6/7 (86%)	10/14 (71%)	4/6 (67%)	5/6 (83%)	22/29 (76%)
Died	3/7 (29%)	4/14 (29%)*	4/6 (67%)	5/6 (83%)*	13/29 (45%)

* ($p < .04$ Fisher's Exact Test)

Table 10.16

Obstetric Complications and Clinical Outcome

30-33 weeks' gestation

	↑BP + Proteinuria		APH		IUGR		Abnormal CTG		Preterm Labour	
RDS	6/14	(43%)	6/18	(33%)	4/10	(40%)	3/9	(33%)	7/29	(24%)
Ventilation	6/14	(43%)	6/18	(33%)	4/10	(40%)	4/9	(44%)	7/29	(24%)
Died	1/14	(7%)•	1/18	(6%)+	0/10	0%º	4/5	(80%)*‡•	2/29	(7%)*

Fisher's Exact Test

* p <.0015
º p <.0037
\+ p <.0027
• p <.0044

Table 10.17

Obstetric Complications and Clinical Outcome

34-35 weeks' gestation

	↑BP + Proteinuria	APH	IUGR	Abnormal CTG	Preterm Labour
RDS	1/13 (8%)	1/6 (17%)	0%	0%	3/27 (11%)
Ventilation	1/13 (8%)	2/6 (33%)	2/16 (13%)	2/7 (29%)	3/27 (11%)
Died	0%	1/6 (17%)	2/16 (13%)	2/7 (29%)*	0%*

Fisher's Exact Test

* $p < .037$

Table 10.18

Obstetric Complications and Clinical Outcome

30-35 weeks' gestation

	↑BP + Proteinuria		APH		IUGR		Abnormal CTG		Preterm Labour	
RDS	7/27	(26%)	6/24	(25%)	4/26	(15%)	3/16	(19%)	10/56	(18%)
Ventilation	7/27	(26%)	8/24	(33%)	6/26	(23%)	6/16	(38%)	10/50	(18%)
Died	1/27	(4%)•	2/24	(8%)+	2/26	(8%)▫	6/16	(38%)*▫+•	2/56	(4%)*

Fisher's Exact Test

* p <.001
▫ p <.02
\+ p <.03
• p <.006

Table 10.19

Obstetric Complications and Amniotic Fluid Phospholipids - Mean (SD)

24-29 weeks

	↑BP + Proteinuria (n = 7)		APH (n = 14)		IUGR (n = 6)		Abnoral CTG (n = 6)		Preterm Labour (n = 29)	
LSR	1.28	(1.3)	1.3	(.4)	1.25	(.2)	1.23	(.5)	1.22	(.6)
PGSR	0.94		0.55		-		-		0.72	(.04)
AFPG Present	1/7	(14%)	4/14	(29%)	0/6	(0%)	1/6	(17%)	5/29	(17%)
Lecithin Concentration*	14.7	(2.4)	14.3	(2.5)	12.8	(3)	12.6	(2.2)	12.9	(2.2)
PG Concentration*	4		5		-		4		5.13	(1.5)

No significant differences

* (µmol/ℓ)

Table 10.20

Obstetric Complications and Amniotic Fluid Phospholipids - Mean (SD)

30-33 weeks' gestation

	↑BP + Proteinuria (n = 14)		APH (n = 18)		IUGR (n = 10)		Abnormal CTG (n = 9)		Preterm Labour (n = 29)	
LSR	1.9	(.8)	1.9	(.9)	2.37	(1.7)	1.8	(.9)	1.96	(1)
PGSR	1.29	(.4)	0.86	(.7)	1.24	(.4)	1.24	(.5)	0.95	(.5)
Lecithin concentration*	20.9	(8.9)	21.2	(7.7)	28	(11)	19.9	(12)	19.8	(8.9)
PG concentration*	4.76	(.19)	5.4	(2)	5	(1.24)	4.35	(1)	5.5	(2.9)
AFPG present	8/14	(57%)	12/18	(67%	6/10	(60%)	3/9	(33%)	17/29	(59%)

No significant differences

* (μ mol/ℓ)

Table 10.21

Obstetric Complications and Amniotic Fluid Phospholipids - Mean (SD)

34-35 weeks' gestation

	↑BP + Proteinuria (n = 13)		APH (n = 6)		IUGR (n = 16)		Abnormal CTG (n = 7)		Preterm Labour (n = 27)	
LSR	2.75	(1.19)	2.39	(.93)	2.7	(1)	1.8	(.89)	2.88	(1.9)
PGSR	1.02	(.27)	1.35	(.67)	0.97	(.5)	0.88	(.7)	1.49	(1.8)
Lecithin concentration*	28.6	(6.7)	25.3	(16)	32.5	(8)	31.5	(21)	36	(22)
PG concentration*	6.7	(2.9)	9.2	(.35)	7.6	(2.7)	6.4	(2.4)	5.6	(1.5)
AFPG present	12/13	(92%)	3/6	(50%)	13/16	(81%)	4/7	(57%)	23/27	(85%)

No significant differences

* (µmol/ℓ)

Table 10.22

Obstetric Complications and Amniotic Fluid Phospholipids - Mean (SD)

30-35 weeks' gestation

	↑BP + Proteinuria (n = 27		APH (n = 24)		IUGR (n = 26)		Abnormal CTG (n = 16)		Preterm Labour (n = 56)	
LSR	2.3	(1)	2.0	(.9)	2.6	(1.3)	1.8	(.9)	2.4	(1.6)
PGSR	1.1	(.3)	0.9	(.7)	1.1	(.5)	1	(.6)	1.26	(1.4)
Lecithin concentration'	25.4	(8.4)	22.2	(9.6)	30.6	(9)	24.9	(16)	29.2	(19)
PG concentration '	6	(2.5)	6.4	(2.4)	6.6	(2.6)	5.4	(1.9)	5.6	(2.1)
AFPG	20/27	(74%)^{x}	15/24	(63%)	19/26	(73%)^{z}	7/16	(44%)$^{**z x}$	40/56	(71%)**

Fisher's Exact Test

** p <.0416
z p <.0582
x p <.0487

' (µmol/ℓ)

Table 10.23

Obstetric Complications and Umbilical Arterial Cortisol (nmol/ℓ)

Gestation (weeks)	†BP + Proteinuria	APH	IUGR	Abnormal CTG	Preterm Labour
≤ 29	215 (68) (n = 7)	170 (99) (n = 14)	167 (18) (n = 6)	253 (75) (n = 6)	224 (134) (n = 29)
30-33	223 (92) (n = 14)	196 (125) (n = 18)	282 (93) (n = 10)	254 (85) (n = 9)	261 (154) (n = 29)
34-35	226 (63)*+ (n = 13)	310 (140) (n = 6)	338 (149)* (n = 16)	424 (173) (n = 7)	447 (175)+ (n = 27)
30-35	225 (78)*°‡ (n = 27)	234 (138)• (n = 24)	316 (130)° (n = 26)	325 (150)* (n = 16)	354 (188)•‡ (n = 56)

Significance
* p < .025
+ p < .0005
°) •) ‡) p < .01

Table 10.24

Obstetric Complications and Umbilical Arterial Noradrenaline (nmol/ℓ)

Mean (SD)

Gestation (weeks)	↑BP + Proteinuria	APH	IUGR	Abnormal CTG	Preterm Labour
≤ 29	5.3 (7.9) (n = 7)	10 (15.4) (n = 14)	4 (3) (n = 6)	7.6 (6.1) (n = 6)	13.5 (14.2) (n = 29)
30-33	13.7 (16) (n = 14)	7.1 (6.4) (n = 18)	39 (69) (n = 10)	19.7 (29.3) (n = 9)	12.4 (3.4) (n = 29)
34-35	16.4 (20) (n = 13)	5.9 (2.9) (n = 6)	9.8 (9.8) (n = 16)	15.2 (10.4) (n = 7)	19.9 (21.6) (n = 27)
30-35	15.1 (18.2) (n = 27)	6.8 (5.7)* (n = 24)	20 (42) (n = 26)	17.8 (23) (n = 16)	15.9 (18)* (n = 56)

* Significance ('T' Test) (following logarithmic Transformation of NAD values)

$p < .025$

Table 10.25

Obstetric Complications and Umbilical Arterial Adrenaline (nmol/ℓ)

Mean (SD)

Gestation (weeks)	↑BP + Proteinuria	APH	IUGR	Abnormal CTG	Preterm Labour
≤ 29	0.7 (0.5) (n = 7)	1.4 (1.6) (n = 14)	0.8 (0.4) (n = 6)	1.8 (1.4) (n = 6)	1.7 (1.7) (n = 29)
30-33	3.1* (2.9) (n = 14)	1.4* (1.3) (n = 18)	1.8 (1.6) (n = 10)	2.6 (2.1) (n = 9)	2.4 (2.4) (n = 29)
34-35	4.5 (8.6) (n = 13)	1.7 (0.8) (n = 6)	1.7 (1.7) (n = 16)	2.4 (2.2) (n = 16)	2.8 (2) (n = 27)
30-35	3.8 (6.4 (n = 27)	1.4 (1.2) (n = 24)	1.8 (1.6) (n = 26)	2.5 (2) (n = 16)	2.5 (2.2) (n = 56)

* Significance ('T' Test - following logarithmic Transformation of adrenaline values)

$p < .05$

Table 10.26

Obstetric Complications and Condition of Infant at Birth

Umbilical Arterial pH - Mean (SD)

Gestation (weeks)	↑BP + Proteinuria	APH	IUGR	Abnormal CTG	Preterm Labour
< 29	7.2 (.09) (n = 7)	7.18 (.18) (n = 14)	7.27 (.07) (n = 6)	7.04 (.14) (n = 6)	7.23 (.1) (n = 29)
30-33	7.21^{+} (.09) (n = 14)	7.28^{*o} (.06) (n = 18)	$7.2^{o\,x}$ (.06) (n = 10)	$7.14^{*\bullet}$ (.14) (n = 9)	7.31 (.05)$^{\bullet + x}$ (n = 29)
34-35	7.28 (.05) (n = 13)	7.27 (.15) (n = 6)	7.22 (.11) (n = 16)	7.15 (.14) (n = 7)	7.26 (.09) (n = 27)
30-35	7.24 (.08)$^{o\alpha}$	7.28 (.08)$^{*\gamma *}$	7.21 (.09)$^{z}_{\gamma}$	7.15 (.14)$^{**}_{+\delta}$	7.29 (.08)$^{+z\alpha}$

$^{*}_{\bullet}$) p <.05

$^{o}_{\gamma}$) p <.025

$^{z}_{+}$) p <.005

x p <.001

$^{**}_{\alpha}$) p <.01

CHAPTER 11

Fetal Cortisol

Fetal Cortisol

11.1 Introduction

As discussed in Chapter 2, a number of animal studies (Liggins 1969, De Lemos et al 1970, Kotas and Avery 1971), have tended to confirm the hypothesis of corticosteroid induction of enzymes involved in surfactant synthesis. Subsequently a trial of antepartum betamethasone treatment to human mothers threatening preterm labour apparently reduced the incidence of RDS (Howie and Liggins 1977). There is also some evidence in humans to suggest an endogenous deficiency antenatally in babies who subsequently developed RDS (Naeye et al 1971, Murphy 1974[B], Sybulski and Maughan 1976).

Therefore it might be reasonable to propose that the suspected effect of stress on fetal lung maturity may be mediated via endogenous fetal cortisol production and that clinical and biochemical immaturity of the fetal lung would be less frequent when cortisol levels were highest.

This chapter will investigate the influence of fetal cortisol on clinical outcome (RDS, requirement for ventilation and survival), and the relationship between endogenous fetal cortisol and the amniotic fluid phospholipids.

11.2 Results

11.2.1 Fetal cortisol and clinical outcome

The babies were again divided into gestational age groups:

$\leq$ 29 weeks, 30-33 weeks, 34-35 weeks, as described in Chapter 5.

a) RDS

There was no significant difference in mean birthweight (Table 11.1) or in percentage of babies delivered by Caesarean section between those babies with and without RDS (Table 11.2),

Based on experimental and clinical evidence it might be expected that RDS would be less frequent when cortisol levels were highest. However there was no significant difference in mean UAC level in those babies with and without RDS before 34 weeks. In the 34-35 week group the babies with RDS had significantly lower UAC levels (Table 11.3).

b) Ventilation requirements

There was no statistically significant difference in mean birthweight, percentage of infants delivered by Caesarean section or mean UAC level in the babies who required neonatal artificial ventilation to those babies with minimal or no respiratory problems (Tables 11.4, 11.5 and 11.6).

c) Survival

There was no significant difference in mean birthweight between those infants who died or survived in each gestational age group (Table 11.7).

The mean UAC level was significantly lower in those babies who died in the 30-33 week group (Table 11.9). However the numbers are small and a high percentage were delivered by Caesarean section compared to the survival group (Table 11.8).

11.2.2 Effect of fetal cortisol on amniotic fluid phospholipids

a) Correlation between fetal cortisol and amniotic fluid phospholipids

The correlations between UAC and the amniotic fluid phospholipids - L/S ratio, PG/S ratio, lecithin concentration and PG concentration, are shown in Table 11.10 for all cases in study, in Table 11.11 for the Term group[(36-41 weeks) alone and Table 11.12 for the preterm group alone (24-35 weeks). In each table allowance is also made for method of delivery.

Overall (Table 11.10) the correlations were very poor but surprisingly statistically significant between UAC and the L/S, PG/S ratios and lecithin concentration, when all gestations were considered. After correction for gestational age (Tables 11.11 and 11.12) only a few weak correlations remained in the preterm group (24-35 weeks) (Figures 11.1, 11.2 and 11.3).

b) UAC levels in babies with mature and immature amniotic fluid phospholipids

A similar percentage of babies were delivered by Caesarean section in the mature and immature phospholipid groups (Table 11.13).

There was no significant difference in mean birthweight between groups except when PG alone was considered. In this case those babies with PG present had a significantly higher mean birthweight compared to those with PG absent (Table 11.14), in the ≤ 29 week group.

In the 3 situations investigated, phospholipid profile (L/S ratio and PG), L/S ratio alone and PG alone, there were no significant differences in mean UAC between those babies with mature and those with immature amniotic fluid phospholipids, at any gestational age group studied (Table 11.15).

Discussion

The beneficial effects of labour on lung function have often been attributed to increased surfactant synthesis secondary to the cortisol surge associated with labour (Fedrick and Butler 1972, Cabero et al 1976). However this would seem an unlikely theory as it has been shown that exogenous steroids have no effect in preventing RDS unless given at least 24 hours before delivery (Liggins and Howie 1972, Dluholucky et al 1976).

Prior to 34 weeks there was no difference in mean UAC between those babies with and without RDS. However those babies developing

RDS in the 34-35 week group had a significantly lower mean UAC lwevel. This may reflect the small numbers involved (only 5 cases of RDS), however it is interesting that the main UAC surge occurs around 34 weeks (Figure 6.5) and it may be that those babies who develop RDS around this gestational age do not demonstrate this UAC surge.

The surge in UAC at around 34 weeks may result in a steroid induction of the enzymes involved in surfactant synthesis. However, no direct link was found between fetal cortisol levels and biochemical lung maturity as assessed by measurement of the amniotic fluid phospholipids (Tables 11.13, 11.14 and 11.15).

The finding of very weak but surprisingly statistically significant correlations between UAC and L/S, PG/S ratios and lecithin concentration (Table 11.10) suggested that endogenous fetal cortisol might influence surfactant levels. However as Chapter 6 has demonstrated there is a marked rise in both amniotic fluid phospholipids and UAC with gestation. When the term group of babies only were considered (Table 11.11) the correlations between UAC and the amniotic fluid phospholipids were no longer present, suggesting the correlations were not due to a direct effect of UAC on amniotic fluid phospholipids but rather to the compounding effect of gestational age. In the preterm group (24-35 weeks) some weak but significant correlations between UAC and amniotic fluid phospholipids remained (Table 11.2). These weak correlations were almost certainly due again to a gestational age effect as shown in Figures 11.4, 11.5 and 11.6. Therefore although both UAC and the amniotic fluid phospholipids increase with gestational age this does not mean that one necessarily influences the other.

Fetal cortisol, however, may act in a different way by 'priming' the fetal adrenal medulla resulting in increased conversion of NAD to AD, which is the catecholamine most implicated in influencing fetal lung maturity. This aspect will be considered in detail in Chapter 12.

d) Conclusions

1 UAC level did not relate to survival, requirement for ventilation or to the development of RDS before 34 weeks.

2 A significantly lower mean UAC level was found in babies developing RDS in the 34-35 week age group, suggesting a deficiency in the fetal cortisol surge in those babies, which is known to occur at this time.

3 No relationship was found between UAC levels and biochemical lung maturity as reflected by the amniotic fluid phospholipids.

Table 11.1

Comparison of Birthweights in Babies

With and Without RDS

Gestation (weeks)	RDS	No RDS	
≤ 29	1.06 (.3) (n = 32)	1.17 (.4) (n = 14)	NS
30-33	1.58 (.4) (n = 21)	1.77 (.4) (n = 53)	NS
34-35	2.3 (.2) (n = 5)	2.1 (.4) (n = 14)	NS

Table 11.2

Percentage Delivered by Caesarean Section

in Babies With and Without RDS

Gestation (weeks)	RDS	No RDS
< 29	31% (n = 32)	50% (n = 14)
30-33	67% (n = 21)	53% (n = 53)
34-35	40% (n = 5)	58% (n = 64)

Table 11.3

The Effect of Fetal Cortisol on Occurrence of RDS

Gestation (weeks)	UAC (nmol/ℓ) RDS	No RDS	
⩽ 29	193 (94) (n = 32)	280 (189) (n = 14)	NS
30-33	217 (102) (n = 21)	227 (155) (n = 53)	NS
34-35	185 (90) (n = 5)	368 (168) (n = 64)	p <.02

Table 11.4

Birthweight and Ventilation Requirements

Birthweight (kg) Mean (SD)

Gestation (weeks)	Ventilation	No Ventilation	
≤ 29	1.06 (.3) (n = 32)	1.17 (.4) (n = 14)	NS
30-33	1.7 (.5) (n = 24)	1.8 (.5) (n = 50)	NS
34-35	2.17 (.3) (n = 8)	2.15 (.4) (n = 61)	NS

Table 11.5

Ventilation Requirements and

Percentage of Babies Delivered by Caesarean Section

Gestation (weeks)	Ventilation	No Ventilation
≤ 29	31% (n = 32)	50% (n = 14)
30-33	70% (n = 24)	50% (n = 50)
34-35	63% (n = 8)	56% (n = 61)

Table 11.6

The Effect of Fetal Cortisol on Ventilation Requirements

UAC (nmol/ℓ) Mean (SD)

Gestation (weeks)	Ventilation	No Ventilation	
⩽ 29	193 (94) (n = 32)	280 (189) (n = 14)	NS
30-33	198 (101) (n = 24)	238 (156) (n = 50)	NS
34-35	300 (192) (n = 8)	361 (168) (n = 61)	NS

Table 11.7

Died or Survived

A Comparison of Birthweights (kg) Mean (SD)

Gestation (weeks)	Died	Survived	
≤ 29	0.9 (.3) (n = 21)	1.25 (.25) (n = 25)	NS
30-33	1.6 (.6) (n = 7)	1.7 (.5) (n = 67)	NS
34-35	1.94 (.2) (n = 3)	2.16 (.4) (n = 66)	NS

Table 11.8

Died or Survived

Percentage Delivered by Caesarean Section

Gestation (weeks)	Died	Survived	
≤ 29	38% (n = 21)	36% (n = 25)	NS
30-33	86% (n = 7)	55% (n = 67)	NS
34-35	67% (n = 3)	55% (n = 66)	NS

Table 11.9

Effect of Fetal Cortisol on Survival

UAC (nmol/ℓ) Mean (SD)

Gestation (weeks)	Died	Survived	
≤ 29	224 (108) (n = 21)	204 (104) (n = 25)	NS
30-33	155 (35) (n = 7)	229 (143) (n = 67)	$p < .01$
34-35	540 (42) (n = 3)	347 (170) (n = 66)	NS

Table 11.10

Correlation between Fetal Cortisol and Amniotic Fluid Phospholipids

All Gestations

UAC	L/S Ratio	PG/S Ratio	Lecithin Concentration	PG Concentration
All Cases	0.4*	0.4*	0.4*	0.2
All Vaginal	0.43*	0.4*	0.4*	0.3
Elective C/S	0.24	0.28	0.3	0.01
Labour + C/S	0.43**	0.4º	0.3	0.1

* $p < .001$ ** $p < .01$ º $p < .02$

Table 11.11

Correlation between Fetal Cortisol and Amniotic Fluid Phospholipids

Term Group 36-41 weeks' gestation

UAC	L/S Ratio	PG/S Ratio	Lecithin Concentration	PG Concentration
All Cases	0.18	0.3	0.1	0.1
Vaginal	0.2	0.3	0.1	0.2
Elective C/S	0.1	0.4	-0.3	-0.2
Emergency C/S	0.4	0.2	0.1	-0.04

No significant correlations

Table 11.12

Correlation between Fetal Cortisol and Amniotic Fluid Phospholipids

Preterm Group 24-35 weeks' gestation

UAC	L/S Ratio	PG/S Ratio	Lecithin Concentration	PG Concentration
All Cases	0.2	-0.06	0.4*	0.02
Vaginal	0.4*	-0.1	0.4*	0.1
Elective C/S	-0.07	-0.2	0.09	-0.07
Emergency C/S	0.2	0.2	0.3	0.07

* $p < .01$

Table 11.13

Percentage of Babies Delivered by Caesarean Section

in Babies With Immature and Mature Amniotic Fluid Phospholipids

Gestation (weeks)	Phospholipid Profile		L/S Ratio Alone		PG Alone	
	L/S < 2 No PG	L/S ⩾2 + PG	L/S < 2	L/S ⩾2	PG Absent	PG Present
⩽ 29	-	-	-	-	33% (n = 36)	50% (n = 10)
30-33	65% (n = 17)	67% (n = 18)	59% (n = 44)	61% (n = 23)	52% (n = 29)	60% (n = 45)
34-35	57% (n = 7)	49% (n = 39)	62% (n = 24)	53% (n = 42)	69% (n = 13)	54% (n = 56)

Table 11.14

Birthweight (kg) - Mean (SD) in Babies with Immature and Mature Amniotic Fluid Phospholipids

Gestation (weeks)	Phospholipid Profile		L/S Ratio Alone		PG Alone	
	L/S < 2 No PG	L/S ≥ 2 + PG	L/S < 2	L/S ≥ 2	PG Absent	PG Present
≤ 29	-	-	-	-	1.04 (1.4)* (n = 36)	1.33 (.3)* (n = 10)
30-33	1.5 (.4) (n = 17)	1.8 (.4) (n = 18)	1.65 (.4) (n = 44)	1.75 (.5) (n = 23)	1.7 (.5) (n = 29)	1.7 (.4) (n = 45)
34-35	2.14 (.3) (n = 7)	2.13 (.4) (n = 39)	2.17 (.5) (n = 24)	2.13 (.4) (n = 42)	2.19 (.4) (n = 13)	2.15 (.4) (n = 56)

* $p < .01$

Table 11.15

UAC Levels (nmol/ℓ) in Babies with Immature and Mature Amniotic Fluid Phospholipids

UAC Mean (SD)

Gestation (weeks)	Phospholipid Profile		L/S Ratio Alone		PG Alone	
	L/S < 2 No PG	L/S ⩾ 2 + PG	L/S < 2	L/S ⩾ 2	PG Absent	PG Present
⩽ 29	INSUFFICIENT DATA		INSUFFICIENT DATA		218 (130) (n = 36)	188 (99) (n = 10)
30-33	222 (142) (n = 17)	205 (148) (n = 18)	208 (127) (n = 44)	209 (112) (n = 23)	256 (162) (n = 29)	200 (117) (n = 45)
34-35	337 (153) (n = 7)	363 (168) (n = 39)	348 (185) (n = 24)	355 (167) (n = 42)	332 (145) (n = 13)	360 (117) (n = 56)

No significant differences

Figure 11.1

Relationship between Lecithin Concentration (μmol/ℓ) and UAC (nmol/ℓ)

Preterm Group (24-35 weeks) All Methods of Delivery

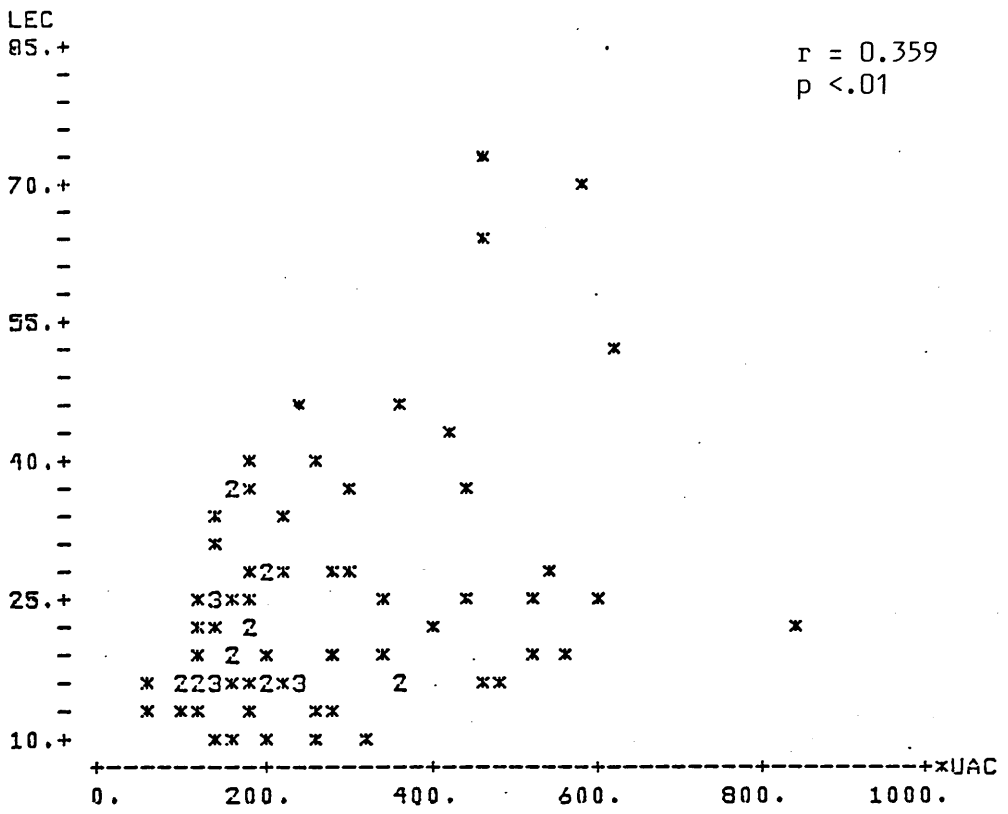


Figure 11.2

Relationship between L/S Ratio and UAC (nmol/ℓ)

Preterm Group (24-35 weeks) Vaginal Deliveries

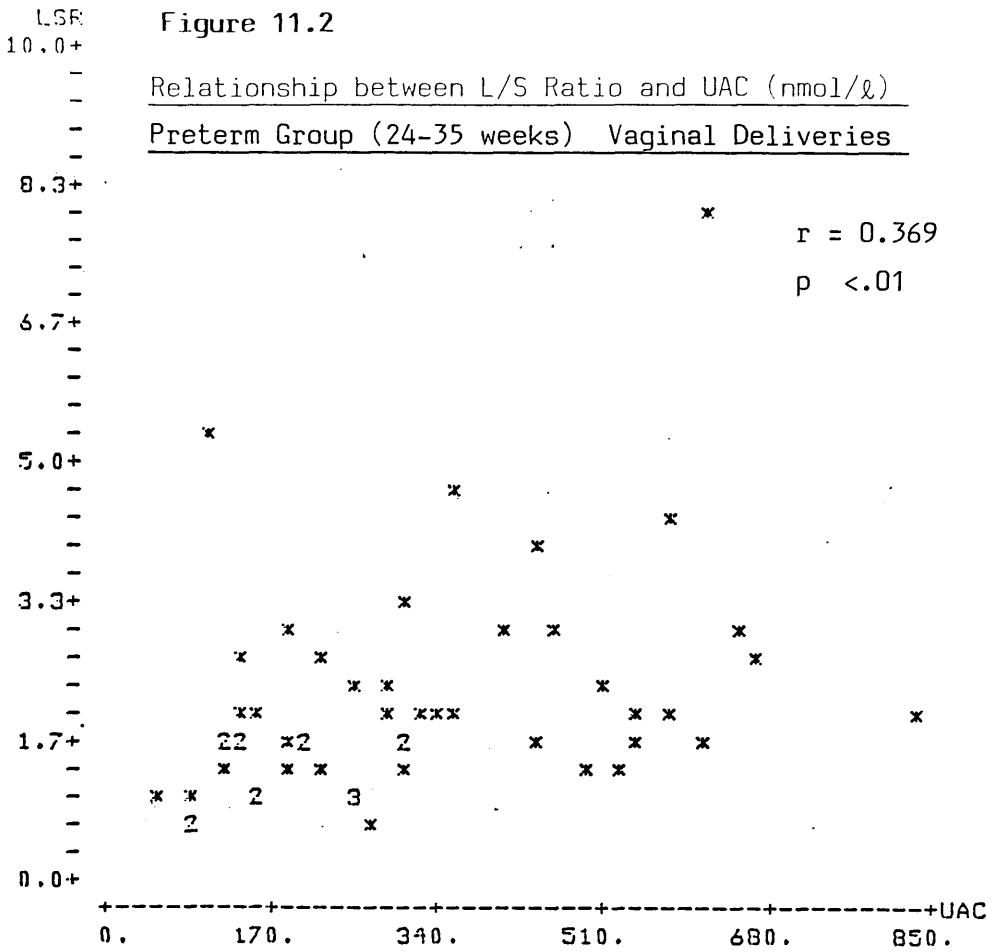


Figure 11.3

Relationship between Lecithin Concentration (µmol/ℓ) and

UAC (nmol/) Preterm Group (24-35 weeks) Vaginal Deliveries

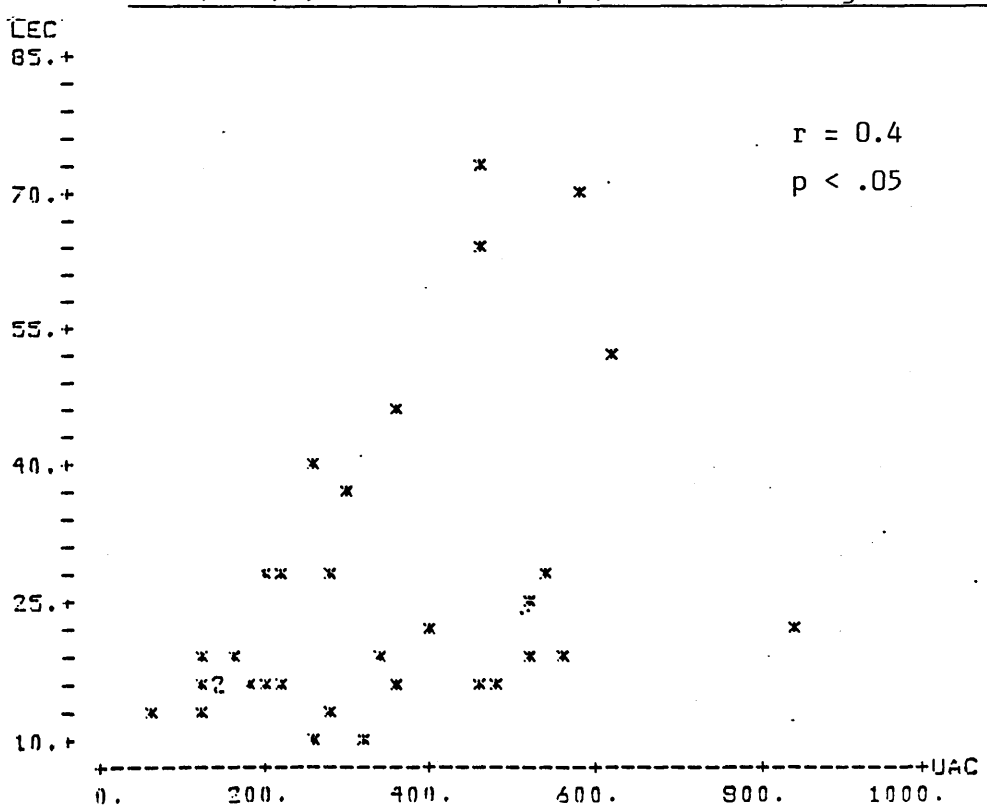
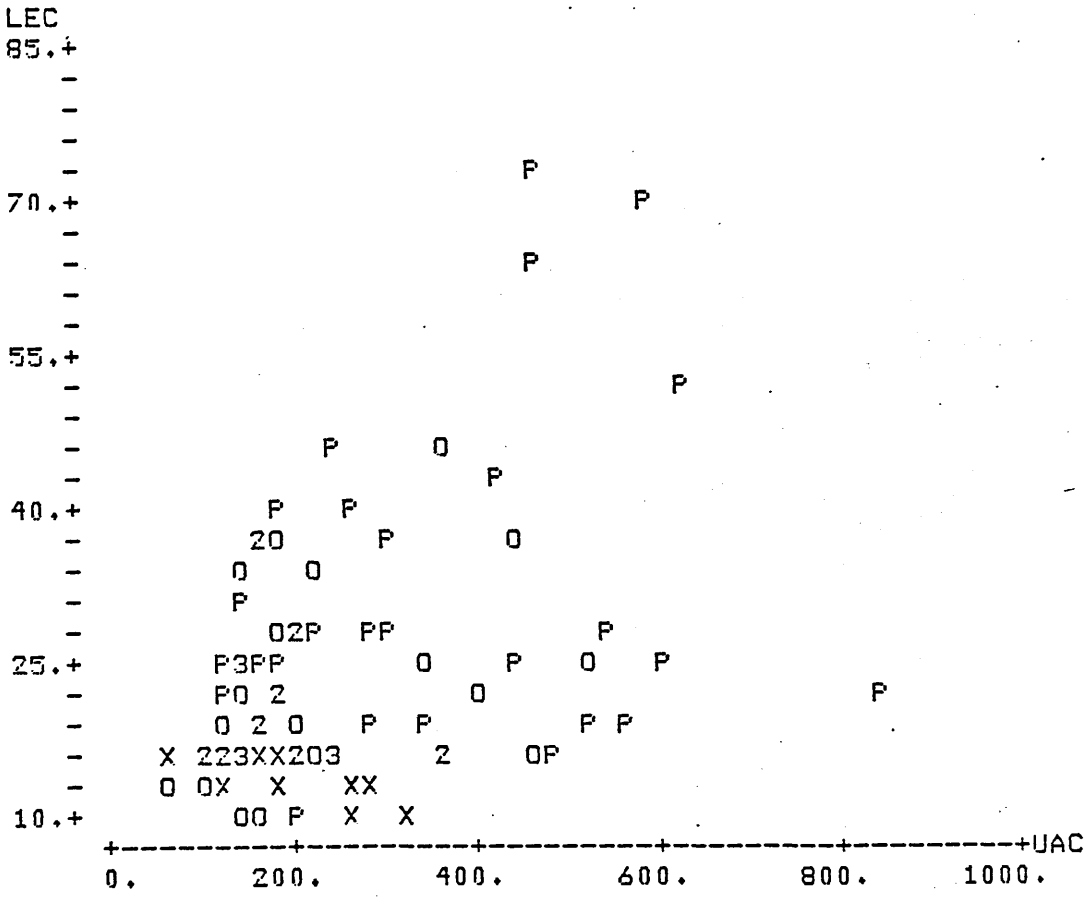


Figure 11.4

Relationship between Lecithin Concentration (µmol/ℓ) and UAC (nmol/ℓ)

Preterm Group (24-35 weeks)

All Methods of Delivery



p = 34-35 weeks' gestation

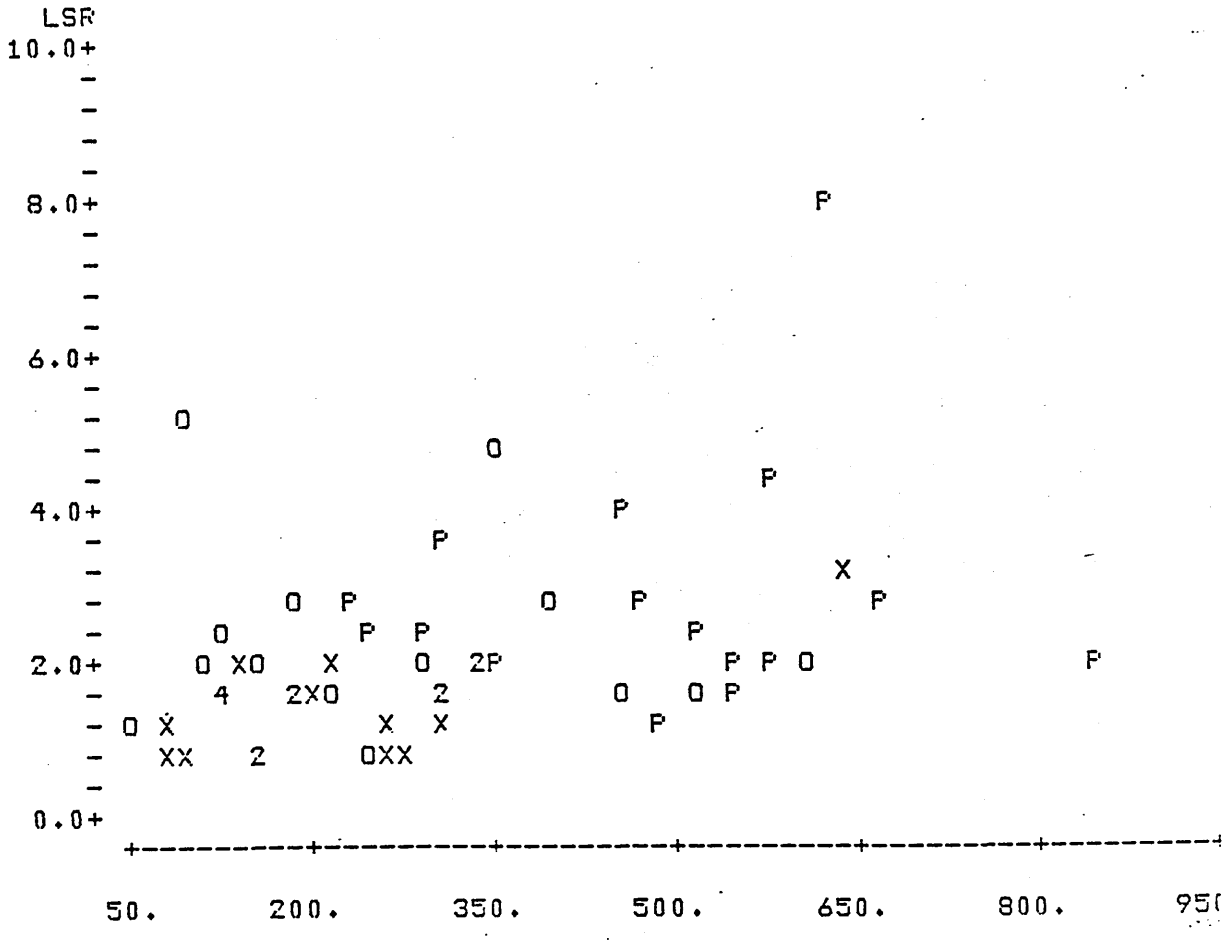
0 = 30-33 weeks' gestation

X = ≤ 29 weeks' gestation

Figure 11.5

Relationship between the L/S Ratio and UAC (nmol/ℓ)

Preterm Group (24-35 weeks) Vaginal Delivery



P = 34-35 weeks' gestation

O = 30-33 weeks' gestation

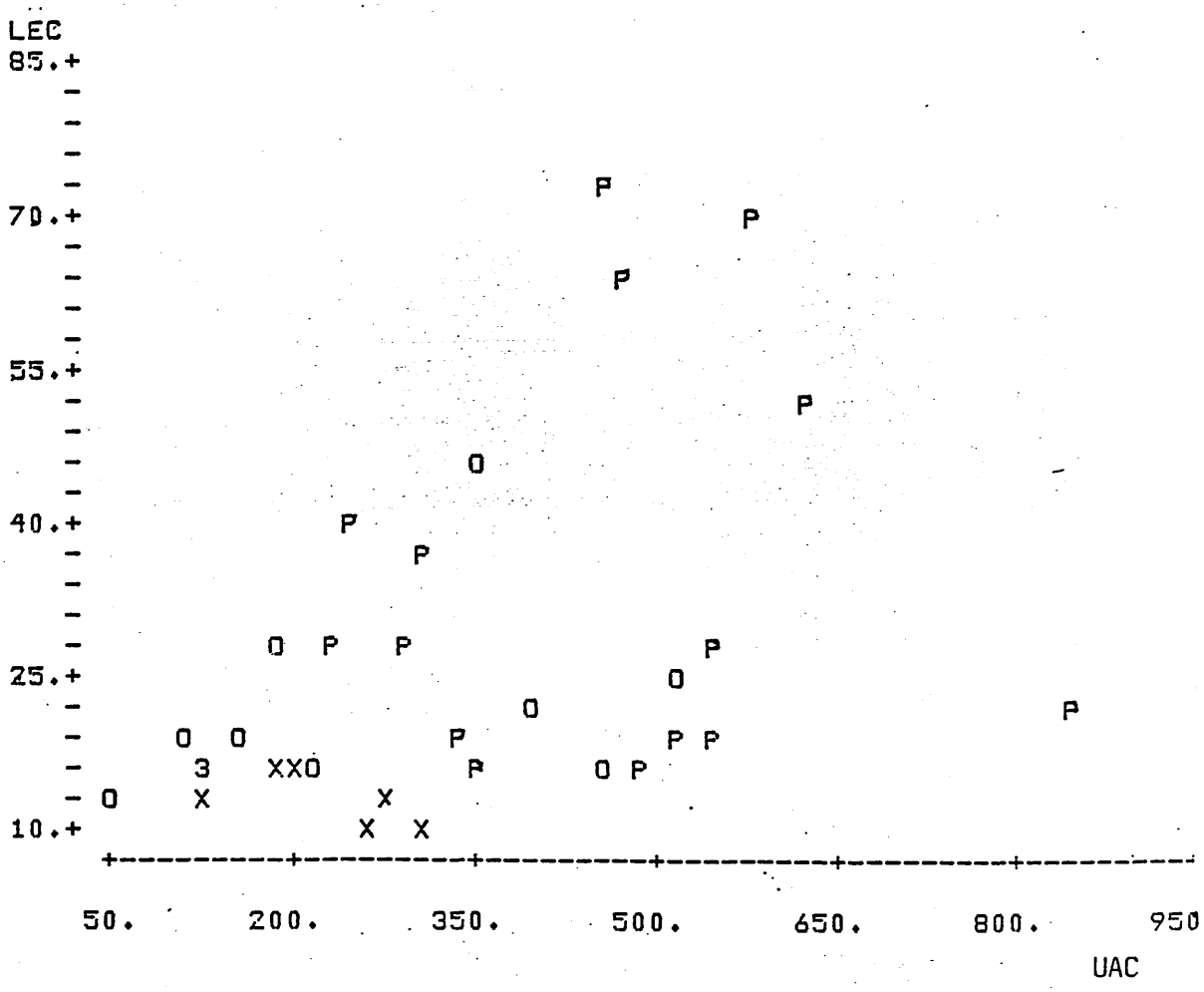
X = ≤ 29 weeks' gestation

Figure 11.6

Lecithin Concentration v UAC

Preterm Group (24-35 weeks)

Vaginal Delivery



P = 34-35 weeks' gestation

O = 30-33 weeks' gestation

X = ≤ 29 weeks' gestation

CHAPTER 12

Fetal Catecholamines

12.1 Introduction

Evidence is now accumulating that the catecholamines may have an important role to play in preparing the fetus for extrauterine existence, especially with regard to lung function (Olver 1981).

Infusion of AD into fetal lambs causes absorption of lung fluid (Lawson et al 1978) and a correlation between endogenous AD concentration and lung liquid absorption has also been noted in animal experiments (Brown et al 1981). In addition to aiding the absorption of fluid from the fetal lungs there is also evidence to suggest that catecholamines may cause an increase in surfactant release (Lawson et al 1978, Enhorning et al 1977, Dobbs and Mason 1979). Those effects have been blocked by propranolol in animal experiments Abdellatif and Hollingsworth 1979), implying that they are mediated via Beta receptors. This theory is supported by observations on rabbit and lamb fetuses infused with Beta sympathomimetic drugs (Wyazogrodski et al 1974, Corbet et al 1977, Bergman & Hedner 1978, Enhorning et al 1977, Brown et al 1981, Walters and Olver 1978). In humans, treatment with Beta mimetic drugs in an attempt to suppress preterm labour and delivery, has been associated with a decreased incidence of RDS (Kero et al 1973, Boog et al 1975). Woodman et al (1978) noted a significant correlation between the ratio of amniotic fluid NAD/AD and L/S ratio and Artal et al (1979) found that mature amniotic fluid phospholipid profiles correlated significantly with rising metanephine levels. Therefore, stress in the form of the physiological stress of labour or the pathological stress of certain obstetric complications may act via endogenous fetal catecholamines to promote optimal lung function as discussed in Chapter 2.

This chapter will investigate the influence of fetal catecholamines on clinical outcome (RDS, requirement for ventilation and survival), and the relationship between endogenous fetal catecholamines and the amniotic fluid phospholipids. In addition, where an attempt was made to suppress labour by use of intravenous Ritodrine the influence of this Beta sympathomimetic drug on clinical outcome and amniotic fluid phospholipids was also considered.

12.2 Results

12.2.1 Fetal catecholamines and clinical outcome

The babies were divided into gestational age groups $\leq$ 29 weeks, 30-33 weeks, 34-35 weeks as outlined in Chapter 5.

a) RDS

There was no significant difference in mean birthweight (Table 11.1) or in the percentage of babies delivered by Caesarean section between those babies with and without RDS (Table 11.2).

NAD

The mean UA NAD concentration was significantly lower in those babies developing RDS $\leq$ 29 weeks (Table 12.1). However this was not found consistently in the other gestational age groups.

AD

There were no significant differences in mean UA AD concentration between the 'RDS' and 'no RDS' groups (Table 12.1).

NAD/AD Ratio

There was some evidence in Chapter 6 to suggest that compared to the term baby, the preterm baby had lower NAD and AD levels and that the ratio of NAD/AD may be higher in the preterm. In particular Figure 6.24 identified a group of preterm babies with high NAD/AD

ratios and low cortisol levels. These babies might be considered biochemically immature and at increased risk of developing RDS. Figure 12.1 shows the relationship between UA NAD/AD ratios, UAC levels and the occurrence of RDS. However, RDS did not occur predominantly in those babies with high NAD/AD ratios and low cortisol levels.

Ritodrine Treatment

One hundred and thirty one babies laboured spontaneously. An attempt was made to suppress labour in 54. In the remainder no treatment was initiated as obstetric complications contraindicated their use or labour was so advanced as to make any attempt at suppression worthless.

There was no significant difference in mean birthweight or the percentage of babies delivered by Caesarean section in those babies treated and not treated with ritodrine (Table 12.2 and 12.3). There was no significant difference in incidence of RDS between the treated and non treated groups (Table 12.4).

b) Neonatal Ventilation Requirements

There was no difference in mean birthweight or percentage of babies delivered by Caesarean section between those babies who required and those who did not require mechanical ventilation (Table 11.4 and 11.5).

NAD

In the $\leq$29 week group those babies who required mechanical ventilation had a significantly lower mean NAD concentration. After this gestation, however, no differences in NAD concentration were found between those babies requiring and not requiring artificial ventilation (Table 12.5).

AD

There were no statistically significant differences in mean UA AD concentration between those babies who required ventilation and those who did not (Table 12.5).

Ritodrine Treatment

There was no significant difference in the requirement for neonatal mechanical ventilation between those babies who had and those who had not been given tocolytic therapy (Table 12.4).

c) Survival

There was no significant difference in mean birthweight or in percentage of babies delivered by Caesarean section between those babies who died and those who survived (Tables 11.7 and 11.8)

NAD

There was no obvious relationship between fetal NAD levels and survival of the baby (Table 12.6).

AD

Similarly AD levels did not relate to the chance of the baby surviving (Table 12.6).

12.2.2 Effect of fetal catecholamines on amniotic fluid phospholipids

a) Correlation between fetal catecholamines and amniotic fluid phospholipids

There were no significant correlations between UA NAD or UA AD and the amniotic fluid phospholipids for all cases in study (Tables 12.7 and 12.8) or after considering them as a term group (Tables 12.9 and 12.10) and a preterm group (Tables 12.11 and 12.12).

b) UA NAD and AD levels in babies with mature and immature amniotic fluid phospolipids

The percentages of babies delivered by Caesarean section have already been shown in Tables 11.13 and the birthweights in each group in Table 11.14, for those babies with mature and immature phospholipids.

At each gestational age group studied, a mature lung phospholipid profile (L/S $\geq$ 2 + PG) was compared to an immature profile (L/S < 2.0 no PG) with respect to UA NAD and AD (Table 12.13 and 12.14).

In addition to the L/S ratio combined with PG, the L/S ratio alone and PG alone (Tables 12.13 and 12.14) were also considered at each gestational age group.

There were no significant differences in UA NAD or UA AD levels between those babies with mature and those with immature phospholipids.

c) Beta sympathomimetic treatment and amniotic fluid phospholipids

There were no significant differences in mean L/S, PG/S ratios or mean lecithin or PG concentrations between the treated and non treated groups at any gestational age (Tables 12.15 - 12.17).

Although the percentage of babies with amniotic fluid PG present was higher in the treated groups in no case did this reach statistical significance (Chi squared).

Discussion

Despite the evidence available from many animal experiments showing the importance of catecholamines specially AD in the achievement of optimal lung function (Chapter 2), the mechanism linking fetal stress with lung maturity as outlined in Figure 2.2, could not be supported in the human from the results of this Chapter.

In contrast to corticosteroids, (Chapter 11) the catecholamines are quick acting and during labour may reach extremely high levels in some babies. These levels are extremely high even in comparison to adult patients with a phaechromocytoma and therefore one might have expected to find some evidence linking them with neonatal respiratory function as suggested by Olver (1981) and others.

However there was no direct link found between the levels of fetal catecholamines and the development of RDS, neonatal ventilation requirements or the biochemical maturity of the fetal lung making it very unlikely that a fetal catecholamine surge has a major influence on neonatal lung function in humans.

It has been suggested that fetal cortisol may act in a different way by 'priming' the fetal adrenal resulting in increased conversion of NAD to AD, which is the catecholamine most implicated in influencing fetal lung maturity (Chapter 6). The glucocorticoids are known to regulate the activity of phenylethanolamine-N-methyl transferase (PMMT) (Wurtmann & Axelrod 1966). This enzyme is necessary for the N-methylation of NAD, thus converting it to AD, and is mainly located in the adrenal medulla. The adrenal medulla, situated in close proximity to the cortex is exposed to increasing concentration of glucocorticoids as gestation advances, thus encouraging the N-methylation of NAD resulting in increasing concentrations of AD. A neonate with a low cortisol level and a high NAD/AD ratio could be considered biochemically immature and at

increased risk of developing RDS. However Figure 12.1 has shown that the development of RDS was not confined to those babies with a combination of high NAD/AD ratios and low cortisol.

It has been suggested that fetal catecholamines have an important role to play in preparing the fetus for extrauterine existence, not just in promoting lung maturity but in glucose homeostatis, cardiovascular changes and via non shivering thermogenesis (Phillipe 1983, Artal 1980).

However a recent paper by Falconer and Poyser (1986) could find little evidence to support sympathoadrenal mediated metabolic responses in the human fetus. Interestingly Jones et al (1985) noted that human fetal platlets showed an impaired alpha 2 adrenoreceptor function with absent aggregatory responses to adrenaline compared to adult platlets. The defect in adrenoreceptor function in the fetus was not thought to be due to changes in the number of fetal platlet alpha receptors nor to changes in receptor affinity for adrenaline, as fetal platlets failed to aggregate to adrenaline from deliveries with high and low cord blood catecholamines. The possibility remains therefore that despite several reviews suggesting an important role for the catecholamines (Phillipe 1983, Artal 1980), the human fetus may not be capable of responding to these very high catecholamine levels because of a deficiency in adrenoreceptor function. This would be in keeping with our findings which show a lack of efect of NAD nd AD on fetal lung maturity.

Treatment of the pregnant mother with intravenous ritodrine in an attempt to suppress preterm labour did not seem to influence he incidence of RDS or the requirement for ventilation, not were there any significant differences in the amniotic fluid phospholipids between the babies of treated and non-treated mothers. Although this was not a randomised controlled trial to test the possible benefit of

Beta mimetic treatment on functional lung maturity there was little to suggest that such drugs will be useful.

It does not appear that the fetal stress hormones, the catecholamines, have a major role to play in influencing neonatal lung function.

12.4 Conclusions

1 The level of fetal catecholamines had no influence on incidence of RDS or requirement for ventilation.

2 There was no obvious relationship between fetal catecholamine levels and biochemical lung maturity as assessed by measurement of amniotic fluid phospholipids.

3 Treatment of the mother with the Beta sympathomimetic drug ritodrine had no influence on clinical or biochemical lung maturity. This was not however a controlled study.

Table 12.1

The Relationship between Fetal Catecholamines and Development of RDS

Gestation (weeks)	UA NAD (nmol/ℓ) Mean (SD) RDS	UA NAD (nmol/ℓ) Mean (SD) No RDS	UA AD (nmol/ℓ) Mean (SD) RDS	UA AD (nmol/ℓ) Mean (SD) No RDS
≤ 29	8.7 (11.3)* (n = 32)	26 (14.9)* (n = 14)	1.29 (1.5) (n = 32)	2.1 (1.3) (n = 14)
30-33	16.3 (22.3) (n = 21)	24 (55) (n = 53)	2.6 (2.9) (n = 21)	2.3 (2.6) (n = 53)
34-35	17.7 (26) (n = 5)	14.1 (17) (n = 64)	2.16 (2) (n = 5)	2.8 (4.5) (n = 64)

* $p < .001$

Table 12.2

Effect of Ritodrine Treatment

Method of Delivery

(24-35 weeks)

	Treated (n = 54)	Non Treated (n = 77)
Vaginal Delivery	69%	62%
Caesarean Section	31%	38%

Table 12.3

Effect of Ritodrine Treatment

Birthweight (kg) Mean (SD)

Gestation (weeks)	Treated	Non Treated
≤ 29	1.14 (.2) (n = 22)	1.14 (.5) (n = 15)
30-33	1.7 (0.4) (n = 20)	1.79 (0.3) (n = 29)
34-35	2.15 (0.2) (n = 12)	2.3 (0.4) (n = 33)

No significant differences

Table 12.4

Effect of Ritodrine Treatment on Occurrence of RDS and Neonatal Ventilatory Requirements

Gestation (weeks)	RDS (%)		Ventilation Required (%)	
	Treated	Not Treated	Treated	Not Treated
≤ 29	(13/22) 59%	(11/15) 73%	(14/22) 64%	(12/15) 80%
30-33	(7/20) 35%	(4/29) 14%	(7/20) 35%	(6/29) 21%
34-35	(0/12) 0%	(4/33) 12%	(0/12) 0%	(5/33) 15%

No significant differences

Table 12.5

The Relationship between Fetal Catecholamines and Neonatal Ventilation Requirements

Gestation (weeks)	UA NAD (nmol/ℓ) Mean (SD) Ventilation Required	UA NAD (nmol/ℓ) Mean (SD) No Ventilation	UA AD (nmol/ℓ) Mean (SD) Ventilation Required	UA AD (nmol/ℓ) Mean (SD) No Ventilation
≤ 29	8.7 (11.3)* (n = 32)	26 (14.9)* (n = 14)	1.29 (1.5) (n = 32)	2.1 (1.3) (n = 14)
30-33	14.8 (21) (n = 24)	26 (57) (n = 50)	2.5 (2.8) (n = 24)	2.3 (2.7) (n = 50)
34-35	14.3 (20.6) (n = 8)	14.4 (16.8) (n = 61)	1.9 (1.6) (n = 8)	2.8 (4.6) (n = 61)

* $p < .001$

Table 12.6

The Relationship between Fetal Catecholamines and Survival

Gestation (weeks)	UA NAD (nmol/ℓ) Mean (SD) Died	UA NAD (nmol/ℓ) Mean (SD) Survived	UA AD (nmol /ℓ) Mean (SD) Died	UA AD (nmol /ℓ) Mean (SD) Survived
≤ 29	12.9 (16.5) (n = 21)	12.9 (12.5) (n = 25)	1.8 (1.7) (n = 21)	1.04 (1) (n = 25)
30-33	21.8 (49) (n = 7)	21.7 (31) (n = 67)	2.3 (2.7) (n = 3)	3.3 (3.3) (n = 67)
34-35	7.35 (1.7) (n = 3)	14.7 (17) (n = 66)	1.6 (.7) (n = 3)	2.8 (4.4) (n = 66)

No significant differences

Table 12.7

Correlation between UA NAD (nmol/ℓ) and Amniotic Fluid Phospholipids

All Gestations

	L/S	PG/S	Lecithin Concentration (μ mol/ℓ)	PG Concentration (μmol/ℓ)
All Cases	0.14	0.01	0.14	-0.02
Vaginal Delivery	0.12	0.04	0.1	-0.05
Elective Caesarean Section	0.13	-0.08	0.1	-0.02
Labour + Caesarean Section	0.08	-0.11	-0.07	-0.1

Table 12.8

Correlation between UA AD (nmol/ℓ) and Amniotic Fluid Phospholipids

All Gestations

	L/S	PG/S	Lecithin Concentration (μmol/ℓ)	PG Concentration (μmol/ℓ)
All Cases	0.12	0.07	0.17	0.03
Vaginal Delivery	0.12	0.09	0.16	-0.09
Elective Caesarean Section	0.01	-0.02	-0.06	-0.02
Labour + Caesarean Section	0.08	0.07	0.7	0.3

Table 12.9

Correlation between UA NAD (nmol/ℓ) and Amniotic Fluid Phospholipids

Term Group (36-41 weeks)

	L/S	PG/S	Lecithin Concentration (μmol/ℓ)	PG Concentration (μmol/ℓ)
All Cases	-0.01	-0.1	0.02	-0.1
Vaginal Delivery	-0.03	0.01	0.02	-0.16
Elective Caesarean Section	0.12	-0.34	-0.4	-0.02
Labour + Caesarean Section	-0.1	-0.3	-0.4	-0.4

Table 12.10

Correlation between UA AD (nmol/ℓ) and Amniotic Fluid Phospholipids

Term Group (36-41 weeks0

	L/S	PG/S	Lecithin Concentration (μ mol/ℓ)	PG Concentration (μmol/ℓ)
All Cases	-0.06	-0.05	-0.03	-0.08
Vaginal Delivery	-0.09	0.06	-0.04	-0.19
Elective Caesarean Section	0.05	-0.34	-0.43	0.12
Labour + Caesarean Section	-0.12	-0.2	-0.26	0.04

Table 12.11

Correlation between UA NAD (nmol/ℓ) and Amniotic Fluid Phospholipids

Preterm Group (24-35 weeks)

	L/S	PG/S	Lecithin Concentration (μmol/ℓ)	PG Concentration (μmol/ℓ)
All Cases	0.08	-0.04	0.03	-0.1
Vaginal Delivery	-0.01	-0.3	-0.06	-0.29
Elective Caesarean Section	-0.01	0.2	-0.13	-0.13
Labour + Caesarean Section	0.3	0.1	0.1	0.15

Table 12.12

Correlation between UA AD (nmol/ℓ) and Amniotic Fluid Phospholipids

Preterm Group (24-35 weeks)

	L/S	PG/S	Lecithin Concentration (μmol/ℓ)	PG Concentration (μmol/ℓ)
All Cases	0.07	0.1	0.08	-0.08
Vaginal Delivery	0.14	-0.15	0.11	-0.3
Elective Caesarean Section	-0.16	-0.33	-0.15	-0.14
Labour + Caesarean Section	0.2	0.3	0.1	0.45

Table 12.13

UA NAD (nmol/ℓ) Levels in Babies with Immature and Mature Amniotic Fluid Phospholipids

UA NAD - Mean (SD)

Gestation (weeks)	Phospholipid Profile		L/S Ratio Alone		PG Alone	
	L/S <2 No PG	L/S ≥2 + PG	L/S <2	L/S≥ 2	PG Absent	PG Present
≤ 29	INSUFFICIENT DATA		INSUFFICIENT DATA		10.6 (11.6) (n = 36)	23.3 (20.8) (n = 10)
30-33	14.8 (22.6) (n = 17)	37.2 (78) (n = 18)	14.5 (28) (n = 44)	36.9 (70) (n = 23)	17 (23.1) (n = 29)	24 (57) (n = 45)
34-35	19.6 (19) (n = 7)	13.8 (17.5) (n = 39)	16.1 (18.2) (n = 24)	14.[illegible] (17) (n = 42)	16.2 (15) (n = 13)	13.9 (18) (n = 56)

Table 12.14

UA AD (nmol/ℓ) Levels in Babies with Immature and Mature Phospholipids

UA AD - Mean (SD)

Gestation (weeks)	Phospholipid Profile		L/S Ratio Alone		PG Alone	
	L/S < 2 No PG	L/S ≥ 2 + PG	L/S < 2	L/S ≥ 2	PG Absent	PG Present
≤ 29	INSUFFICIENT DATA		INSUFFICIENT DATA		1.5 (1.6) (n = 36)	1.1 (.8) (n = 10)
30-33	2.1 (2.7) (n = 17)	2.1 (1.9) (n = 18)	2.2 (2.9) (n = 44)	2.8 (2.5) (n = 23)	2.65 (2.9) (n = 29)	2.2 (2.6) (n = 45)
34-35	3 (1.9) (n = 7)	3 (5.5) (n = 39)	2.2 (2) (n = 24)	3.1 (5.3) (n = 42)	2.9 (1.9) (n = 13)	2.7 (4.8) (n = 56)

Table 12.15

Effect of Ritodrine Treatment

Amniotic Fluid Phospholipids - Mean (SD)

24-29 weeks

	Treated (n = 22)		Non Treated (n = 15)	
L/S Ratio	1.27	(0.5)	1.42	(0.7)
PG Present	(8/22)	36%	(1/15)	7%
PG/S Ratio	0.68	(0.3)	INSUFFICIENT DATA	
Lecithin Concentration (µmol/ℓ)	13.2	(2.5)	12.7	(0.8)
PG Concentration (µmol/ℓ)	4.8	(1.5)	INSUFFICIENT DATA	

No significant differences

Table 12.16

Effect of Ritodrine Treatment

Amniotic Fluid Phospholipids - Mean (SD)

30-33 weeks

	Treated (n = 20)		Non Treated (n = 29)	
L/S Ratio	2.3	(1.1)	1.9	(1.2)
PG Present	(15/20)	75%	(17/19)	59%
PG/S Ratio	0.9	(0.6)	0.8	(0.5)
Lecithin Concentration (µmol/ℓ)	23.6	(8.8)	21.2	(8.9)
PG Concentration (µmol/ℓ)	4.4	(2.5)	5.4	(2.2)

No significant differences

Table 12.17

Effect of Ritodrine Treatment

Amniotic Fluid Phospholipids - Mean (SD)

34-35 weeks

	Treated (n = 12)		Non Treated (n = 33)	
L/S Ratio	3.18	(2)	2.5	(1.4)
PG Present	(12/12)	100%	(24/33)	73%
PG/S Ratio	2.1	(2.5)	0.9	(0.5)
Lecithin Concentration (µmol/ℓ)	34.2	(21.4)	32.2	(21.6)
PG Concentration (µmol/ℓ)	5.3	(0.6)	6.1	(2)

No significant differences

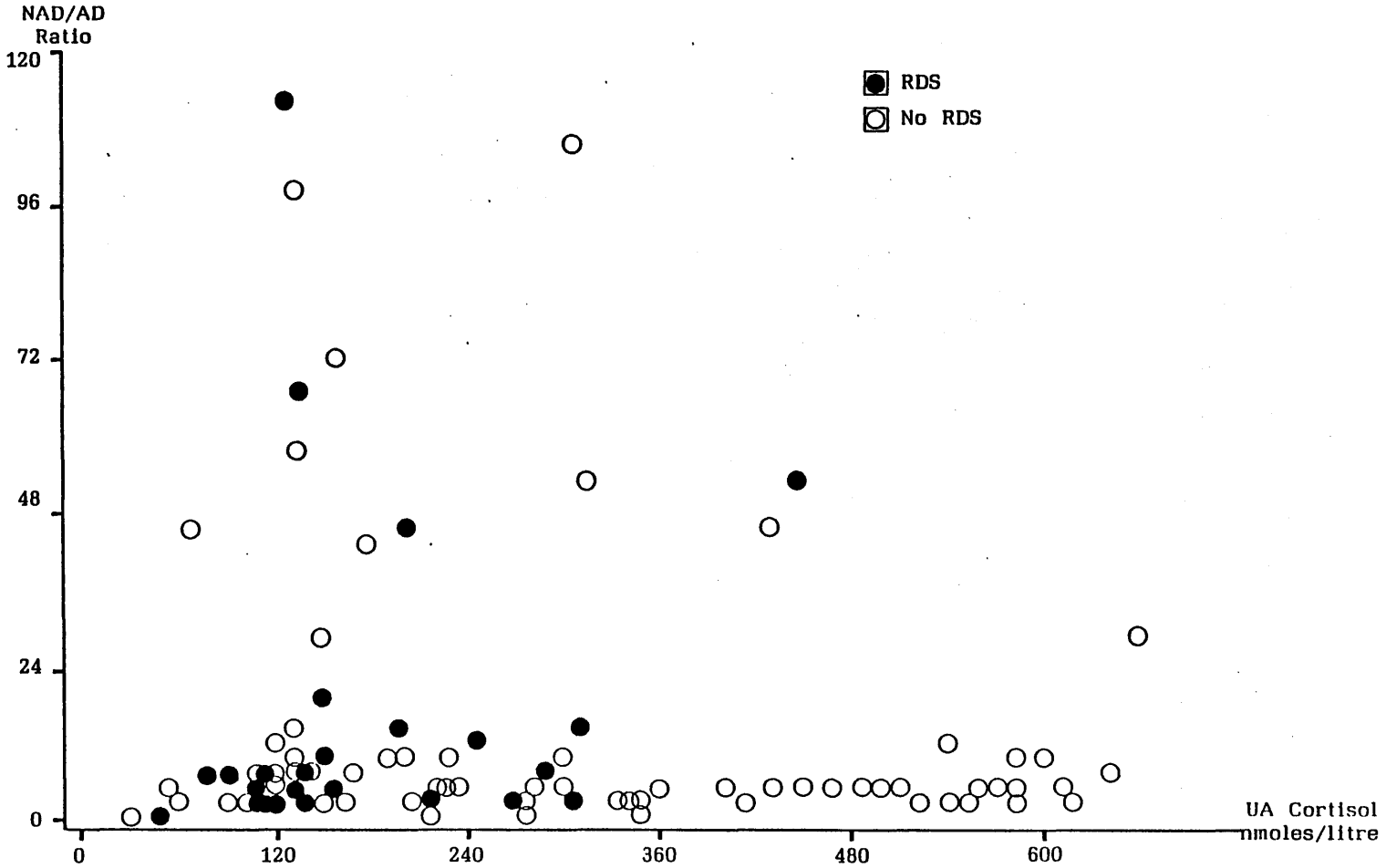


Figure 12.1

The Relationship between UA/NAD Ratio, UA Cortisol and the Occurrence of RDS.

CHAPTER 13

Amniotic Fluid Phospholipids and Clinical Outcome

13.1 Introduction

This chapter will consider the influence of amniotic fluid phospholipids on clinical outcome. Firstly, the clinical outcome (RDS, necessity for ventilation and survival) will be compared between those babies with and without a mature amniotic fluid phospholipid profile. A mature phospholipid profile is defined as an L/S $\geq$ 2.0 + PG. The effect of PG alone or an L/S ratio < 2.0 or $\geq$ 2.0 will also be investigated. Secondly, the amniotic fluid phospholipids will be compared in those babies with or without a favourable outcome (RDS, requirement for ventilation and survival).

As before the preterm babies ($\leq$ 35 weeks) were divided into the following gestational age groups: $\leq$ 29 weeks, 30-33 weeks, 34-35.

13.2 Results

13.2.1 Clinical outcome in babies with immature and mature amniotic fluid phospholipids

a) L/S Ratio + Presence or Absence of PG (The phospholipid profile)

(Only 2 babies had L/S $\geq$2 in $\leq$ 29 week group and therefore this group has been omitted from Table 13.1.)

When the L/S < 2 and no PG was present nearly 60% of babies developed significant respiratory problems and almost one third died between 30-33 weeks (Table 13.1).

In contrast a mature amniotic fluid phospholipid profile (L/S $\geq$2 + PG) was associated with an excellent outcome for the baby both with regard to morbidity and mortality.

b) Consideration of L/S ratio alone (Table 13.2)

When the L/S ratio $\geq$ 2.0 the babies had statistically significantly less respiratory problems and although fewer babies died

when L/S $\geq$ 2.0, this did not reach statistical significance.

c) Consideration of PG alone (Table 13.3)

The presence of PG in the amniotic fluid was associated with considerable advantage to the neonate, in terms of a significantly reduced incidence of respiratory problems and an increased chance of survival.

13.2.2 Amniotic fluid phospholipids in babies with unfavourable and favourable outcomes

a) RDS

The relationship between the amniotic fluid phospholipids and the occurrence of RDS is shown in Table 13.4 in each gestational age group.

When PG was absent a higher percentage of babies developed RDS (statistically significant at 34-35 weeks). In addition, at 34-35 weeks those babies developing RDS had significantly lower mean L/S ratios and lecithin concentrations than those babies with no RDS.

b) Neonatal ventilation requirements

In the $\leq$ 29 week age group the data were identical to Table 13.4. In the 34-35 week (Table 13.5) age group the mean L/S ratio and lecithin concentration was significantly lower in those babies who required ventilation.

Significantly fewer babies had PG present when ventilation was required (Table 13.5) in the 34-35 week group.

c) Survival (Table 13.6)

Fewer amniotic fluids contained PG amongst pregnancies in which the babies died. This was statistically significant in each gestational age group. Of the 31 babies who died only 6 % had PG present compared to almost 70% in those babies who survived in the age

group 24-35 weeks.

In addition, those babies who died had a statistically significantly lower mean L/S ratio and mean lecithin concentration compared to those babies who survived in the 30-33 week gestational age group.

13.3 Discussion

The amniotic fluid L/S ratio has become the standard biochemical method of assessing fetal lung maturity (Gluck et al 1971). However it is rather an insensitive method as although a mature L.S ratio is unlikely before 34 weeks' gestation, the incidence of RDS may be as low as 12.9% at 32-33 weeks and 56% at 30-32 weeks (Howie and Liggins 1977). In an attempt to improve the prediction of neonatal RDS, Gluck and his colleagues (Kulovich et al 1979) developed a more specific test, the lung profile which included as well as the L/S ratio, the percentages of other phospholipids, phosphatidylinositol and PG. While this profile gave a more complete evaluation of the fetal lung, it has been shown that only the L/S ratio and the presence or absence of PG are important indicators of the risk of RDS. The L/S ratio alone, PG alone and the phospholipid profile of L/S ratio + PG have been used in this chapter as a biochemical assessment of fetal lung maturity. The importance of these phospholipids in the development of respiratory problems and indeed the survival of the baby has been confirmed in this chapter. In a recent paper by Whittle et al (1986) the chance of survival is strikingly improved when PG is present regardless of gestational age. In addition there is less need for ventilatory support and the incidence of intraventricular haemorrhage and patent ductus arteriosis is much lower, for babies in whom PG is present.

The occurrence of RDS when amniotic fluid PG was present is

higher in this chapter compared to other published series (Whittle et al 1981). However, as outlined in Chapter 5, in order to avoid confusion over the diagnosis of RDS in cases where only mild respiratory problems (ie not requiring ventilatory support) were present the RDS group in this Chapter only contained those babies requiring artificial ventilation either by CPAP or IPPV.

It is this group in which serious problems of morbidity and mortality occur.

13.4 Conclusions

This Chapter demonstrates clearly the importance of the surface active phospholipids, especially PG, which make up lung surfactant not only in the development of RDS and requirement for ventilation but also for the eventual survival of the baby.

Table 13.1

Clinical Outcome in Babies with Immature and Mature Amniotic Fluid Phospolipid Profiles

Gestation	30-33 weeks		34-35 weeks	
Phospholipid Profile	L/S <2 No PG	L/S ≥2 + PG	L/S <2 No PG	L/S ≥2 + PG
Number	17	18	7	39
Birthweight (kg) Mean (SD)	1.5 (.4)	1.8 (.4)	2.14 (.3)	2.13 (.4)
RDS	59%	0%*	43%	0%+
Neonatal Ventilation	59%	0%*	57%	0%*
Died	29%	0%+	14%	0%

Fisher's Exact Test * $p < .001$ + $p < .01$

Table 13.2

Clinical Outcome in Babies with an Immature and Mature L/S Ratio

Gestation	30-33 Weeks		34-35 weeks	
L/S Ratio	L/S <2	L/S ≥2	L/S <2	L/S ≥2
Number	44	23	24	42
Birthweight (kg) Mean (SD)	1.65 (.4)	1.75 (.4)	2.18 (.5)	2.13 (.4)
RDS	39%	13%*	17%	2%°
Neonatal Ventilation	45%	17%+	21%	2%+
Died	14%	4%	4%	o%

Fisher's Exact Test * p <.001 + p <.02 ° p <.05

Table 13.3

Clinical Outcome in Babies with and without Amniotic Fluid PG

Gestation	≤ 29 Weeks		30-33 Weeks		34-35 Weeks	
PG	PG Absent	PG Present	PG Absent	PG Present	PG Absent	PG Present
Number	36	10	29	45	13	56
Birthweight (kg) Mean (SD)	1.04 (.4)	1.32 (.3)*	1.7 (.5)	1.7 (.4)	2.19 (.4)	2.15 (.4)
RDS	83%	20%**	48%	11%+	31%	2%°
Neonatal Ventilation	83%	20%**	45%	24%	54%	2%**
Died	56%	10%°	21%	2%°	23%	0%

Chi squares + p <.01 Fisher's Exact Test ° p <.01 ** p <.001 Student's 'T' Test * p <.01

Table 13.4

Occurrence of RDS and Amniotic Fluid Phospholipids

Gestation	≤ 29 Weeks				30-33 Weeks				34-35 Weeks			
RDS	RDS		No RDS		RDS		No RDS		RDS		No RDS	
Number	32		14		21		53		5		64	
Birthweight (kg) Mean (SD)	1.06	(.3)	1.17	(.4)	1.58	(.4)	1.77	(.4)	2.3	(.2)	2.1	(.4)
L/S Ratio Mean (SD)	1.3	(.5)	1.4	(.6)	1.6	(.5)	2.2	(1.2)	1.7	(.2)	2.7	(1.5)**
PG/S Ratio Mean (SD)	0.6	(.5)	0.7	(.3)	1	(.6)	0.9	(.6)	Not measured		1.27	(1.28)
PG Present	6%		57%		33%		72%		20%		86% °	
Lecithin (µmol/ℓ) Mean (SD)	13.7	(2.3)	12.8	(2.5)	17.6	(4.3)	22.7	(9)	16.6	(5.4)	33.8	(18)+
PG * (µmol/ℓ) Mean (SD)	Not measured		4.8	(1.5)	5	(3.3)	4.8	(2.1)	Not measured		6.1	(2)

* (Only those cases where PG was present) Chi square ° p <.01 Mann Whitney ** p <.02 + p <.01

Table 13.5

Neonatal Ventilation Requirement and Amniotic Fluid Phospholipids

Gestation	≤ 29 Weeks				30-33 Weeks				34-35 Weeks			
Neonatal Ventilation	Required		Not Required		Required		Not Required		Required		Not Required	
Number	32		14		24		50		8		61	
Birthweight (kg) Mean (SD)	1.06	(.3)	1.17	(.4)	1.7	(.5)	1.8	(.5)	2.17	(.3)	2.15	(.4)
L/S Ratio Mean (SD)	1.3	(.5)	1.4	(.6)	1.7	(.7)	2.2	(1.2)	1.7	(.18)	2.8	(1.5)**
PG/S Ratio Mean (SD)	0.6	(.5)	0.7	(.3)	0.97	(.6)	0.94	(.5)	Not measured		1.7	(1.3)
PG Present	6%		57%		46%		64%		13%		90%+	
Lecithin (µmol/ℓ) Mean (SD)	13.7	(2.3)	12.8	(2.5)	18.4	(6.8)	22.9	(9)	16.6	(5.4)	33.8	(18)**
PG * (µmol/ℓ) Mean (SD)	Not measured		4.8	(1.5)	4.5	(2.6)	4.9	(2.2)	Not measured		6.1	(2)

* (Only those cases where PG was present) Mann Whitney ** p <.01 Fisher's Exact Test + p <.001

Table 13.6

Neonatal Mortality and Amniotic Fluid Phospholipids

Gestation	⩽ 29 Weeks		30-33 Weeks		34-35 Weeks	
Survival	Died	Survived	Died	Survived	Died	Survived
Number	21	25	7	67	3	66
Birthweight (kg) Mean (SD)	0.9 (.3)	1.25 (.23)	1.6 (.6)	1.7 (.5)	1.94 (.2)	2.16 (.4)
L/S Ratio Mean (SD)	1.13 (.6)	1.4 (.5)	1.3 (.4)	2.1 (1)^{o}	1.6	2.7 (1.5)
PG/S Ratio Mean (SD)	0.4 (1 case only)	0.74 (.3)	0.6 (1 case only)	0.9 (.6)	Not measured	0.99 (1.3)
PG Present	5%	36%**	14%	66%**	0%	85%**
Lecithin (µmol/ℓ) Mean (SD)	12.9 (2.5)	13.8 (2.2)	12.9 (2.4)	22.7 (8.5)$^{+}$	Not measured	31.9 (17.8)
PG * (µmol/ℓ) Mean (SD)	3.6 (1 case only)	4.85 (1.4)	2.8 (1 case only)	4.9 (2.2)	Not measured	6.1 (2)

* (only those cases where PG present) Fisher's Exact Test ** p <.01 Mann Whitney + p <.001 ^{o} p <.01

CHAPTER 14

Final Discussion

The aims of this study as outlined in Chapter 4 were:-

1 To evaluate certain obstetric factors, considered to influence fetal lung maturity.

2 To investigate what controls respiratory maturity in the human fetus.

3 To evaluate human fetal adrenal cortical and medullary activity from mid-trimester until term.

14.1 The basis of the study

The basis of the study is outlined in Figure 2.2 and revolves round the concept of fetal stress in utero being the interlinking factor between the various obstetric factors and fetal lung maturity.

Fetal stress is not easily defined, but it relates to the fetal condition which may be found not only in the presence of certain obstetric complications (PROM, IUGR, hypertension, antepartum haemorrhage and acidosis) but also physiologically as a result of labour and particularly vaginal delivery.

It has been the clinical impression for many years that certain 'stressful' pregnancy complications appear to be associated with a generally improved neonatal outcome. The reason for this is unclear but it has been proposed that a hostile intrauterine environment may, perhaps as a result of relative hypoxia, promote the release of hormones such as cortisol and catecholamines. These hormones may facilitate the maturational processes, particularly in the lung and so help to prepare the fetus for extrauterine life. The concept of fetal stress hormones, cortisol and catecholamines being the final common pathway in the modification of lung maturity is derived both from

animal experiments and clinical experience. As discussed in Chapter 2, Farrell and Zackman (1973) have shown that the enzymes involved in catalising the synthesis of the phospholipids can be influenced by corticosteroids. A number of animal studies have tended to confirm the idea of steroid induction of the enzymes involved in surfactant synthesis (Liggins 1969, De Lemos et al 1970, Kotas and Avery 1971, Wang et al 1971, Chiswick et al 1973, Motoyama et al 1971). These findings are supported by research demonstrating that fetal lungs of rabbits, lambs and humans all contain the specific glucocorticoid receptor (Ballard and Ballard 1972 and 1974).

Subsequently, studies in humans have found a reduction in the incidence of RDS following treatment of pregnant mothers with corticosteroids (Liggins and Howie 1972, Howie and Liggins 1977, Ballard and Ballard 1976, Block et al 1977, Schutte et al 1980, Kennedy 1974, Caspi et al 1976, Morrison 1978). Unfortunately not all these studies were double blind or had adequate controls. A few small studies in humans have noted a rise in L/S ratio following corticosteroid treatment (Spellacy et al 1973, Eklund et al 1976, Zuspan et al 1977, Diedrich et al 1978). In addition, there is some evidence to suggest a corticosteroid deficiency in RDS (Naeye et al 1971, Murphy 1974 A and B, Sybulski and Maughan 1976).

Exogenous corticosteroid treatment antenatally seems to influence fetal lung maturity and it might be reasonable to propose as in Figure 2.2 that the effect of stress on fetal lung maturity is mediated via endogenous cortisol production by the fetus.

Although the production of surfactant may be controlled, at least partly, by adrenocortical hormones, it has been suggested that in addition to dehydrating the fetal lungs (Chapter 2) the catecholamines may cause an increase in surfactant release (Lawson et al 1978, Abdellatif and Hollingsworth 1979). These effects of catecholamines

were blocked by propranolol, suggesting a Beta receptor response.

In the human, a number of workers have noted a reduced incidence of RDS in preterm babies whose mothers were treated with Beta mimetic drugs in an attempt to suppress labour (Kero et al 1973, Boog et al 1975, Hastwell 1977).

Therefore available evidence in the literature would suggest that both cortisol and the catecholamines may be important modulators of surfactant synthesis and release. Situations of stress, either physiological or pathological, resulting in a rise in cortisol and the catecholamines should therefore be theoretically beneficial to the human fetus.

The literature regarding the adrenocortical and sympathoadrenal responses to the various physiological and pathological stress factors were reviewed extensively in Chapter 3. It is apparent that knowledge regarding these stress responses is more complete for the term than the preterm human fetus. This is especially true for the sympathoadrenal responses in the preterm human fetus. Two studies involving small numbers have shown conflicting evidence. Lagercrantz and Bistoletti (1973) found that preterm infants had lower cord catecholamine levels compared with the term fetus while Newnham et al (1984) found significantly higher AD levels in 36 preterm compared to a group of term neonates.

During the course of this study the adrenocortical and sympathoadrenal responses of the human fetus were studied from 24 to 41 weeks' gestation in a large number of babies at birth.

Information is even more sparse concerning the preterm babies' stress responses in the face of various obstetric complications (discussed in Chapter 3) and these were studied in detail in Chapter 10.

14.2 What did the study demonstrate?

Chapter 6 Influence of gestational age on clinical and biochemical lung maturity and fetal stress responses

Gestational age had a marked influence on clinical lung maturity - the incidence of RDS, and mortality increasing with decreasing gestational age below 34-35 weeks, and on biochemical lung maturity - the important surface active phospholipids lecithin and PG increasing with gestational age.

Gestational age also had a major influence on the fetal adrenocortical responses. UAC levels increased with gestational age, especially after 34 weeks, and seems to parallel the rise in amniotic fluid phospholipids and suggests that cortisol levels might have an influence on surfactant.

The proposed influence of exogenous corticosteroids on fetal lung maturity (Howie and Liggins 1977) raises the probability that corticosteroids transferred from the mother may add to fetal cortisol to influence fetal lung maturity. It is felt that most of the free cortisol in the fetal circulation originates from the fetal adrenal gland, the contributions of the maternal cortisol being of lesser importance (Chapter 2 p 43). However there was some evidence in this Chapter (p109) suggesting that fetal cortisol levels may be influenced by high maternal venous levels associated with vaginal delivery, especially in the preterm labour.

Cortisol may facilitate maturation of the fetus in another way by 'priming' the fetal adrenal medulla, ie by increasing the conversion of NAD to AD, which is the catecholamine most associated with optimising neonatal lung function.

This could not be substantiated in this study however as there was no obvious relationship between UAC levels and the UA NAD/AD ratio (p 103).

This may be far too crude a method of assessing this however as varying quantities of NAD are probably released from extraadrenal chromaffin tissue and from adrenergic nerve endings which would distort the NAD/AD ratio and may mask a possible relationship with fetal cortisol.

In contrast to cortisol, gestational age did not have such a marked effect on the fetal catecholamines. However, in those babies delivered vaginally, the preterm group (24-35 weeks) had significantly lower NAD and AD levels than the group of babies born in the term group (36-41 weeks). This is in contrast to the finding of higher AD levels in the preterm fetus by Newham and colleagues (1984). However this was a much smaller series of preterm babies (36) compared to the present study, the results of which tend to support the work of Lagercrantz and Bistoletti (1973) who found lower catecholamine levels in 16 preterm babies compared to a group at term.

The highest NAD/AD ratios were found in the preterm group of babies and there was some evidence to suggest that as AD increases the ratio of NAD/AD is greater in the preterm baby (Figures 6.20 and 6.21), implying a poorer adrenaline response in the preterm fetus.

The evidence from this Chapter also suggests that, again in contrast to cortisol, the maternal and fetal sympathoadrenal systems function independently.

Chapter 7 Influence of labour and delivery

The route of delivery had little effect on incidence of RDS, on neonatal survival or on biochemical lung maturity as reflected by the amniotic fluid phospholipids. In contrast to this however, the route

of delivery had a marked influence on the fetal stress hormones. Those babies born vaginally had significantly raised mean UAC levels compared to those delivered by caesarean section. If the cortisol response to labour was of importance in determining fetal lung maturity, one might have expected that those babies delivered by elective caesarean section would have in increased incidence of respiratory problems. This however was not the case.

The route of delivery also had a marked influence on UA catecholamine levels in the term (36-41 weeks) group of babies, those born vaginally having significantly raised mean UA NAD and AD levels compared to those delivered by caesarean section.

In the preterm group of babies (24-35 weeks), the effect of route of delivery on UA catecholamines was not so clear cut and this is in agreement with Newnham et al (1984) who could also find no differnce between vaginal delivery and caesarean section.

In contrast to the babies delivered by elective caesarean section in the term troup, those in the preterm elective caesarean section group were a group under much more stress (as reflected by lower mean UApH) and this may explain the lack of difference in catecholamine levels between elective caesarean section and vaginally delivered babies in the preterm group.

Chapter 8 Multiple Pregnancy

There was no difference in the incidence of respiratory problems and very few differences in amniotic fluid phospholipids between singletons and twins.

There was no significant difference in UA catecholamine levels between singletons and twins and only after 34 weeks was there any difference in mean UAC levels. The mean UAC level was significantly raised in singletons compared to twins after 34 weeks' gestation.

There was no difference in clinical or biochemical lung maturity between first and second born twins and no difference in mean UA catecholamine levels. However after 35 weeks the mean UAC level was significantly higher in first compared to second born twins.

An excellent correlation was found between twin I and twin II for UAC, NAD and AD but not pH.

Chapter 9 Condition of infant at birth

The condition of the baby at birth (as indicated by UApH) had a significant effect on occurrence of RDS, requirement for ventilation and for the ultimate survival of the infant.

Respiratory problems were more common in babies who were acidotic at birth. No obvious relationship could be demonstrated betgween UApH and the amniotic fluid phospholipids or between UA pH and UAC and the UA catecholamines.

Chapter 10 Obstetric complications

None of the obstetric complications studied, (proteinuric hypertension, IUGR, vaginal bleeding, spontaneous preterm labour and vaginal delivery, PROM) appeared to cause an acceleration of clinical or biochemical lung maturity, neither did they affect the levels of fetal stress hormones NAD, AD and cortisol, in any particular way.

Only in pregnancies where there was an abnormal antenatal CTG was there a suggestion of a different clinical outcome. The highest percentages of babies requiring ventilation or dying were found in this group (Tables 10.15 - 10.18). These babies were in a poor condition at birth, as reflected by mean UA pH which was significantly lower in the abnormal CTG group compared with the other obstetric complications (Table 10.26).

Chapter 11 Fetal cortisol and lung maturity

1 UAC level did not relate to survival, requirement for ventilation or to the development of RDS before 34 weeks.

2 A significantly lower mean UAC level was found in babies developing RDS in the 34-35 week age group, suggesting a deficiency in the fetal cortisol surge in these babies, which is known to occur at this time.

3 No relationship was found between UAC levels and biochemical lung maturity as reflected by the amniotic fluid phospholipids.

Chapter 12 Fetal catecholamines and lung maturity

The level of fetal catecholamines had no apparent influence on incidence of neonatal respiratory problems nor on biochemical lung maturity as reflected by the amniotic fluid phospholipids.

Treatment of the pregnant mother with the Beta sympathomimetic drug ritodrine had no influence on clinical or biochemical lung maturity.

Chapter 13 Amniotic fluid phospholipids and clinical outcome

This Chapter demonstrated clearly the importance of the lung surface active phospholipids, especially PG, not only in the development of lung maturity but also for the ultimate survival of the infant.

14.3 Conclusions drawn from the study

1 It is generally believed that certain obstetric complications can protect the fetus from developing RDS, however from this study there is little evidence to support this (Table 8.15-8.18) and in addition none of the obstetric complications studied had any consistent influence on fetal cortisol or catecholamine levels.

2 Despite much indirect evidence in the literature (Chapters 2 and 3) we were unable to confirm the proposed effect of stress on fetal lung maturity as oulined in Figure 2.2. In this Figure a mechanism was proposed whereby fetal stress in utero, either the physiological stress of labour or the more pathological stress of certain obstetric complications could act via the fetal adrenal gland and extra adrenal chromaffin tissue to cause a rise in fetal cortisol and catecholamine secretion.

3 The adrenocortical and sympathoadrenal responses have been extensively studied in the human fetus at birth from 24 to 41 weeks' gestation. Although there is a marked increase in UAC levels with gestation, especially from 34 weeks, the changes in sympatho-adrenal responses are not so clear cut. There was a tendency for the levels of both NAD and AD to rise with gestation and there is some evidence to suggest that the ratio of NAD/AD does decrease with increasing gestation, suggesting an increased AD response to stress in the term compared to the preterm group.

Interestingly neither the adrenocortical nor the sympatho-adrenal responses seemed to influence the clinical outcome for the baby.

4 It cannot be assumed that a fetus under chronic stress will necessarily have accelerated fetal lung maturity, a history of obstetric complications producing stress is often found in babies who

die from RDS. Indeed from this study those babies who developed RDS, required ventilation or died were significantly more acidotic than those babies who had no respiratory difficulties.

The study therefore does not support the view that stress, either the physiological stress of labour or the pathological stress of certain obstetric ocmplications accelerates fetal lung maturity. In addition to this it does not appear that the stress products cortisol or catecholamines have a major role to play in influencing neonatal lung function. Gestational age and the condition of the baby at birth would seem to be of paramount importance.

14.4 The Relationship of the Study to Current Literature

For many years obstetricians have had the impression that certain pregnancy complications appear to be associated with an unusually low incidence of neonatal RDS. However it is doubtful if this can really be substantiated from a detailed review of the literature (Chapter 3). There is almost equal evidence to support or refute the claim that PROM, IUGR, hypertension in pregnancy or antepartum haemorrhage cause a reduction in the incidence of RDS and only in PROM does the evidence tend to support the idea of an acceleration in the normal timing of biochemical lung maturity as reflected by the amniotic fluid phospholipids.

Evidence to support a rise in the fetal stress hormones, purported to influence fetal lung maturity, is sparse. What studies there are tend to be either conflicting or based on small numbers.

The present study failed to find a link between any of the obstetric complications studied and an acceleration of clinical or biochemical lung maturity or a rise in fetal stress hormones peculiar to any one of them. These findings therefore would not be out of step with available literature.

Large epidemiological studies have shown that a baby delivered after the experience of labour is less likely to develop RDS than one delivered by elective caesarean section (Fedrick and Butler 1972). However in the small group of babies studied in this thesis, labour seemed to confer little benefit and it would seem that in the individual baby the method of delivery would be much less important to the baby's morbidity and mortality than the gestational age and condition at time of birth.

The proposed mechanism linking stress and lung maturity outlined in Figure 2.2 was derived mainly from the results of animal experiments.

There is a large body of convincing evidence in animals linking corticosteroids with induction of the enzymes involved in surfactant synthesis and catecholamines with clearance of lung fluid and control of the release of surfactant (Chapter 2). No such relationships were found during the course of this study in the human. Indeed the evidence for the efficacy of exogenous corticosteroid treatment to the pregnant human mother in preterm labour to prevent neonatal RDS is conflicting and has never been fully accepted by all authorities. The results of experiments in animals may not be applicable to the human, eg there are certain important differences in the adrenal cortex between human and non-human. The human fetal adrenal contains a large internal zone, the fetal zone, which comprises about 80% of the mass of the fetal adrenal and regresses rapidly rapidly after birth. Such a fetal zone is not present in the adrenals of sheep, rabbits and rats on whom most experimental work in this field has been performed.

Similarly there may be important differences in the sympatho-adrenal responses between the human and non-human fetus. For example Padbury et al (1981) provided evidence suggesting that fetal catecholamines play a significant role in the sex difference of

pulmonary maturity. They found significantly more adrenaline in the fetal adrenal gland of the female rabbit fetus and the ratio of adrenaline to total catecholamine content in the adrenal gland was greater in the female fetus. They also found a greater number of adrenergic receptors in the fetal lung of the female fetus. However, in humans, Padbury et al (1981) were unable to find any sex differences in plasma noradrenaline or adrenaline levels or in responsiveness.

It has been suggested the fetal catecholamines have an important role to play in preparing the fetus for extrauterine existence, not just in promoting lung maturity but in glucose homeostasis, cardiovascular changes and via non shivering thermogenesis (Phillipe 1983, Artal 1980). A recent paper by Falconer and Poyser (1986) could find little evidence to support sympathoadrenal mediated metabolic responses in the human fetus. Interestingly Jones et al (1985) noted that human fetal platelets showed an impaired alpha 2 adrenoreceptor function with absent aggregatory responses to adrenaline compared to adult platelets. The defect in adrenoreceptor function in the fetus was not thought to be due to changes in the number of fetal platelet alpha receptors nor to changes in receptor affinity for adrenaline, as fetal platelets failed to aggregate to adrenaline from deliveries with high and low cord blood catecholamines. The possibility remains therefore that despite several reviews suggesting an important role for the catecholamines (Phillipe 1983, Artal 1980), the human fetus may not be responding to these very high catecholamine levels because of a deficiency in adrenoreceptor function. This would be in keeping with the findings of this thesis showing a lack of effect of NAD and AD on fetal lung maturity.

The study therefore does not support the view that stress, either the physiological stress of labour or the pathological stress of certain obstetric complications accelerates fetal lung maturity. In addition to this it does not appear that the stress products cortisol or catecholamines have a major role to play in influencing neonatal lung function. Gestational age and the condition of the baby at birth would seem to be of paramount importance.

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