Fetal Alcohol Syndrome:

Prenatal ultrasound assessment of fetuses at high risk.

by

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Submitted to the University of Cape Town in fulfilment of the requirements for the degree

M.D.

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Declaration:

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Abstract:

Title: Fetal Alcohol Syndrome:

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Objectives: The incidence of Fetal Alcohol Syndrome has reached endemic proportions in areas of the Western Cape, South Africa. This study aimed to assess the effects of heavy drinking on the incidence of preterm delivery, intrauterine growth restriction (IUGR), fetal alcohol syndrome (FAS), congenital abnormalities, Apgar scores, Doppler waveform studies and fetal distress in labour. We hypothesised that it is possible to identify ultrasound markers of FAS in utero.

Methods: This prospective, blinded, matched cohort study compared two groups of pregnant mothers. The study group, who drank heavily in pregnancy, and the control group, who abstained or drank lightly while pregnant. Women were recruited early, and detailed ultrasound examinations were conducted at regular intervals. Data concerning their delivery and perinatal outcomes was collected and their babies examined at birth and at one year of age.

Results: After attrition there were 60 subjects and 60 controls. There were significant

differences with respect to preterm delivery, FAS, and IUGR. There was no difference in the incidence of fetal distress, congenital abnormalities, Apgar scores or Doppler velocimetry. Examination of the facial features showed that the orbits of the fetuses in the subject group were more widely spaced, and their fetal frontal lobe was marginally larger. Measurement of the distance from fetal upper lip to nose proved to be technically unreliable.

Conclusions: This study confirmed the high risks of heavy drinking while pregnant with respect to timing of delivery, growth and development of the fetus. We identified ultrasound markers for FAS, namely, widely spaced orbits and a larger fontal lobe. We recommend that women planning pregnancy be counselled as to these risks. As the sample size was small, we suggest further investigations into these ultrasound markers for FAS in future studies.

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Acknowledgements.

Collaboration with Indiana University, U.S.A.

This study was partially funded by the Foundation for Alcohol Related Research (FARR), a South African based national organisation under the leadership of Professor Denis Viljoen, currently also Head of Department of Human Genetics at the South African Institute for Medical Research in Johannesburg. Collaboration exists between FARR and the National Institute on Alcohol Addiction and Alcoholism (NIAAA) in the U.S.A. The research was supported by the NIAAA (grant number R37 AA02342024S1). FARR and Industry Association for Responsible Alcohol Use (ARA) assisted in the provision of facilities and staffing for the project.

The ultrasound machine used was supplied by General Electric Medical Systems, Milwaukee, U.S.A, at no cost, and we are indebted to them as this allowed completion of the study.

I gratefully acknowledge...

Professional Sister Anna-Susan Marais, the research assistant for this study,

who was responsible for its success. She provided nursing, administrative and moral support to both the women recruited into the study and the research staff. I am very grateful for all her efforts.

Professor Denis Viljoen, for initiating this study and offering me this opportunity, and for all his encouragement.

Professor Helen Kay (University of Arkansas, U.S.A), who provided academic and moral support throughout this study via a few hundred e-mails.

Project assistants Debbie Price and Maggie September, and Sadick Naude who transported the patients.

Dr. Roger L Brown, who performed the statistical analysis.

Dr Helen Wainwright, who conducted the post mortem examinations.

Professor Edward Coetzee ,Professor Dave Woods and Professor Zephne van der Spuy, who offered their vast knowledge and expert writing skills in the final phases of the study.

My family, John, Daniel and Rachel.

Introduction.

Alcohol has been recognized as a teratogen from antiquity. Biblical writings warn women to abstain from alcohol while pregnant (Judges 13:7) In 1968 Lemoine et al first described the anomalies comprising unusual facies and prenatal growth deficit in infants born to alcoholic mothers. Jones et al (1973) later coined the term "fetal alcohol syndrome". In an article in the Lancet, eight children, the offspring of alcoholic mothers, are described, and he noted the characteristic pattern of "craniofacial, limb, and cardiovascular defects with prenatal-onset growth deficiency and developmental delay"(Jones et al 1973). Since the publication of these articles, many authors have established that fetal alcohol syndrome is a common cause of mental retardation and physical handicap worldwide (Abel and Sokol 1986).

Fetal alcohol syndrome (FAS) is an entirely preventable condition, but the recognition of the adverse effects of alcohol on the fetus appears to have done little to diminish the incidence of this condition. It remains a considerable public health problem in both developed and under resourced countries.

In the last decade, it has become apparent that the incidence of fetal alcohol syndrome is high in South Africa. This problem is particularly severe in the wine-growing districts of the Western Cape, where the traditional practice of giving labourers alcohol as part of their wage packet resulted in a culture of alcohol abuse. Unfortunately this still persists in some areas despite efforts to change both employer and employee expectations.

The total monetary cost of FAS to society is enormous. The annual cost of FAS in the U.S.A. is estimated to exceed $1 billion. It was recently estimated that the child with FAS costs the USA government $2842 from birth to 21 years of age, and that

prevention of one case of FAS could save the government close to $500 million after 20 years (Klug and Burd 2003). In the context of the Western Cape Province, even if the cost of FAS were discounted to 10% of that of the U.S.A., the annual cost would still amount to $300 million.

Early research by the Foundation for Alcohol Related Research (FARR) in South Africa, and the National Institute on Alchohol Addiction and Alchoholism (NIAAA) in the United States of America (U.S.A.), investigated children living in the rural Western Cape Province, South Africa. They were evaluated at school entry level (age 5 to 9 years), and a high percentage of them were found to have features of FAS. The prevalence was found to be 40.5 to 46.4 per 1000 children, which is 18 to 141 times greater than in the U.S.A. (May 2000).

This vulnerable group of women are close to our academic teaching hospital in Cape Town (Groote Schuur Hospital) and as a consequence a study investigating the fetus by ultrasound examination was both feasible and necessary. A more complete knowledge of the ultrasound features of the fetus with FAS was considered to be of value to the local health care providers who deal with this problem. In theory this would assist both medical staff and those involved in social support services to identify the fetus at high risk for FAS early in life, thereby possibly improving the quality of life for that infant, and providing support for the family of the affected infant.

Although there are many studies looking at the perinatal and neonatal outcome, and the neurodevelopment of the infant with FAS, few assess the fetus. At the time of commencing this study there were no other studies that attempted to diagnose FAS before birth. Subsequently, one such study performed in Tennessee, USA, was published (Wass et al 2001). Research in this field was required both in terms of the local community and the international community.

With careful attention to ethical considerations, this study aimed to examine those fetuses exposed to alcohol in utero, following their progress from early pregnancy to

the end of their first year of life.

Aims and Objectives:

i) Aims:

Although FAS is now a well recognised syndrome, and accepted worldwide, to date there are few ultrasound studies that have been conducted on the unborn fetus. This study aimed to assess the fetus in a population of mothers at high risk for FAS (due to maternal alcohol consumption during the pregnancy), looking particularly at the incidence of congenital abnormalities and fetal growth disturbances. To assess fetal well being, this study aimed to examine changes in liquor volume, and to assess placental function by using the resistance index of the umbilical artery Doppler flow waveform. Doppler waveform studies were also used to assess changes in fetal circulation dynamics to vital organs (such as the fetal brain). The maternal uterine artery flow patterns were also studied.

Pre-natal diagnosis of FAS has not been possible to date, and an attempt was made to identify any ultrasound markers (features visible on ultrasound examination), which may lead the clinician to suspect the diagnosis of FAS prenatally. One would anticipate that these markers are most likely to be found on the fetal face or in the brain, as these are the structures where abnormalities are most commonly seen after birth. This study aimed to broaden our knowledge in these areas, by comparing the fetuses of the mother who drank alcohol in pregnancy to those of non- or light drinkers.

While we cannot assess the exact timing and effect of alcohol consumption with this study protocol, this study aimed to compare the fetuses of mothers who consume large

amounts of alcohol in their pregnancy, to those whose mothers did not drink while pregnant. In this way it may be possible to assess if there were any differences in development or growth between these two groups of fetuses.

ii) Objectives:

Heavy drinking during pregnancy carries an increased risk of adverse pregnancy outcome such as preterm delivery, growth restriction and congenital abnormalities. Mothers who drink heavily while pregnant may deliver an infant with fetal alcohol syndrome (FAS). The hypothesis for this study was that specific ultrasound markers are present that lead the clinician to suspect that the fetus has FAS.

Specific objectives of this study were:

-To identify congenital abnormalities in the alcohol-exposed fetus by prenatal ultrasound assessment, and to confirm these findings post-natally by clinical examination.

-To determine if the characteristic facial features found in the FAS infant can be diagnosed by ultrasound examination and measurement of the fetal face.

-To compare the growth of the fetus of heavy-drinking mothers and those who did not drink heavily, and to assess whether intrauterine growth restriction was present.

-To compare the liquor volume of the fetuses of heavy-drinking mothers, and the control mothers.

-To record Doppler waveform studies of maternal uterine arteries,and the umbilical arteries and the middle cerebral arteries in the fetuses.

-To record details of gestational age at birth, birth-weight, head circumference, length of the infant and weight of the placenta, and to compare the two groups of infants.

-To establish what percentage of women who drank heavily gave birth to a child with FAS, and to confirm this diagnosis when the child is one year of age.

Literature review.

i) Prevalence in the local population.

Studies of prevalence of FAS vary from author to author (Abel et al 1986,Olson et al). May and Gossage reviewed the literature in 2001 and found an overall prevalence of FAS of 0.5 to 2 cases per 1000 births in the U.S. during the 1980's and 1990's (May and Gossage 2001). In South Africa, the prevalence is much higher, and has reached endemic proportions in the offspring of labourers on wine-farms in the Western Cape, where alcohol is still sometimes included as part of the labourers wage packet, the so-called "Dop" system (a "dop" is an Afrikaans colloquial word meaning an alcoholic drink) (Viljoen 1991). A study in a tertiary hospital in Cape Town in 1985 showed the prevalence of FAS to be 1:281 live births. (Palmer 1985). The South African population has the misfortune to have the world record rate of FAS at 39.2-46.4 per 1000 births (Viljoen et al 2002).

A study to assess alcohol usage by pregnant women in underprivileged areas of the Western Cape, South Africa, in 1999 confirmed the high rate of alcohol and tobacco abuse. (Croxford and Viljoen 1999). Women were selected in a randomised manner from the antenatal clinics in the area. Of these women, 42,8% admitted to varying degrees of alcohol ingestion during pregnancy. Twenty-three percent (23,7%) of the sample was heavy drinkers, most of them following a pattern of binge drinking over weekends. Heavy drinking was defined in this study as more than 10 units of absolute alcohol per week, or binges of more than 10 drinks per occasion. These women showed a preference for beer drinking. Combined alcohol and tobacco use occurred in 29,6% of the women interviewed.

Another local study conducted in the Western Cape compared the mothers of 31 children with FAS with a control population (Viljoen et al 2002). These mothers were more likely to have started drinking early in life, were more likely to have members of their family who abused alcohol, were more likely to smoke, and to consume alcohol before and during their pregnancies.

To demonstrate the true impact of alcohol abuse in pregnancy, a study was conducted in the wine growing areas of the Western Cape, South Africa, to evaluate children at school entry age of age 5 to 9 years (May et al 2000). Examination of 992 children by trained dysmorphologists demonstrated high rates of fetal alcohol syndrome. The prevalence was found to be 40.5 to 46.4 per 1000 children- 18 to 141 times greater than in the USA. Children living in the rural areas were more likely to be affected than their urban counterparts.

ii) Etiology and pathogenesis.

Ethanol and its major metabolites readily cross the placenta. The teratogenic effects of alcohol have been extensively studied in animals. Studies performed before 1988 were reviewed in a paper published by Gershoni-Baruch and Nelson (Gershoni-Baruch and Nelson 1988). Anomalies of the musculoskeletal, urogenital and neurological systems were demonstrated, and offspring had low birth weight, poor coordination, and were often spastic or blind.

It is obviously difficult to extrapolate these studies to the human embryo. The minimal amount of alcohol needed to produce FAS or alcohol-related birth defects, is

not yet known. It has been postulated that as little as one drink per day (0.5 ounce of absolute alcohol i.e. one glass of wine or beer) is harmful. A case of FAS has been described in a woman who ingested alcohol-containing cough syrup (Chasnoff et al 1981). A dose-response relationship has been shown by some authors (Hanson et al 1978, Mills et al 1984, Little et al 1977). An average consumption of less than one drink per day was associated with a low risk of intrauterine growth restriction (IUGR) and congenital abnormalities, while ingestion of more than two drinks per day increases the risk substantially.

It is still debatable whether abnormal growth and morphogenesis are due to the unmetabolised ethanol itself, or its more toxic metabolite, acetaldehyde. Other factors that have been implicated in the development of the abnormalities found in FAS are hypoglycaemia and deficiency of zinc. These factors may also explain why FAS is more common in successive children as chronic alcoholism and malnutrition may cause episodes of hypoglycaemia and chronic zinc depletion. (Gershoni-Baruch and Nelson 1988)

Abel and Hannigan (1995) reviewed the literature in 1994 and proposed that there are both permissive and provocative factors that increase the likelihood of FAS in mothers that consume alcohol. "Permissive" factors implied predisposing behavioural, social and environmental characteristics that produce certain biological conditions that increase vulnerability to alcohol. "Provocative" factors are the biological conditions in the fetus that create the internal milieu responsible for increased fetal vulnerability to alcohol.

The key permissive factors were behavioural patterns of alcohol consumption (binge drinking, critical periods of consumption), low socio-economic status, ethnicity (black), cultural factors (e.g. frequency of diagnosis of FAS by practitioners due to stigmatisation) and cigarette smoking. "Provocative" factors include placental dysfunction, endocrine changes (such as high peak blood alcohol levels), circulating

tobacco constituents and undernutrition. The authors hypothesized that these permissive and provocative factors interact with alcohol's hypoxic and oxygen free-radical induced effects, and that this exacerbation results in FAS. More recent studies on the human placenta in mothers who consumed alcohol suggest that ethanol induces oxidative stress and impairs nitric oxide availability in the placental villi (Kay et al 2000). Genetic factors also play a role, as women with the alcohol dehydrogenase genotype, ADH2-1/3, may be at greater risk for having an infant with FAS (Stoler et al 2002). In a study of 404 women in the USA, ADH2-1/3 genotype was found to be more prevalent among black women (46% vs. 2% of whites). More black women who reported high alcohol usage during pregnancy had the ADH2-1/3 genotype than those who reported no alcohol use.

May and his co-workers reviewed the demographic risk factors recently (May 2004). They studied data from three different communities, two from the USA and the third

from South Africa. Apart from binge-drinking, other risk factors identified among women who have given birth to FAS children included advanced maternal age, high gravidity and parity, unmarried status, use of tobacco and other drugs, low socio-economic status indicators (e.g. low education, unskilled job classification), low levels of religious beliefs and co-habitation with a drinking male (May 2004). The South African women were more likely to follow a pattern of binge drinking, and the mothers were smaller in body mass than their American counterparts.

iii) Critical periods for prenatal alcohol exposure.

Attempts to study many of the effects of alcohol exposure on humans during pregnancy are affected by confounding variables. Investigators cannot regulate the

timing or extent of drinking, nor can they control individual differences in response to alcohol. The investigators are also reliant on the mothers giving a truthful and accurate description of their drinking habits. The very nature of the problem must influence the accuracy of records and they may well not reflect the full extent of the alcohol exposure to the fetus.

Despite extensive research, information about timing of exposure and its effects on the fetus remain limited, especially regarding effects on behaviour. Heavy drinking at any time during pregnancy can cause neurodevelopmental, intellectual and behavioural problems (Pierce and West 1986;Abel and Hannigan 1995). Some studies showed that the hippocampus and the cerebellum were the areas of the brain affected by third trimester alcohol exposure in rats (West and Goodlett 1990).

Animal and epidemiological studies strongly suggest that the facial malformation characteristic of FAS result from exposure during the first trimester of pregnancy, and more specifically, during the first two months of gestation. Exposure to alcohol in the third trimester of pregnancy in animals leads to reduction in brain weight and head circumference (Coles 1994).

Ernhart and colleagues (1987) reported the relationship between craniofacial anomalies and first trimester exposure. Greater dysmorphism was subsequently associated with lower intelligent quotients. Other studies found minor physical anomalies in children exposed to periconceptual maternal alcohol. The relationship is less clear when the effect on growth is considered. When alcohol is discontinued by the beginning of the second trimester, children of mothers who consumed alcohol may approach the growth of those who did not. It appears that both early exposure and exposure during the third trimester may effect growth. (Coles 1994). Specifically, smaller head circumference, and by extension brain growth appear to be the most consistent outcomes of exposure during these two periods.

iv) Doppler studies

The Doppler principle of the frequency difference between the incident and reflected sound wave being directly proportional to velocity has been used in obstetric ultrasound examination since 1977, when Fitzgerald and Drumm first reported the changes in umbilical artery waveform during normal pregnancy (Fitzgerald and Drumm 1977). The change in frequency results when the total path length changes between the transmitted and receiving sources. In obstetric practice, the transmitting and receiving sources of the ultrasound wave are stationary, and the change in path length results from movement towards or away from the ultrasound probe. In studies of blood vessels, the column of red blood cells flowing in the vessel causes this movement. The greatest frequency shift occurs when the transmitted ultrasound beam is parallel to the flow axis, thus it is the component or the vector of the blood cell velocity that contributes to the Doppler effect. The vector is determined from the cosine of the beam-vessel angle, and is incorporated into the Doppler equation. The

blood flow velocity waveform demonstrates the velocity of blood cells within the vessel, and indices have been developed to measure peak velocity and down stream resistance. These indices are expressed as ratios. The Resistance Index (R.I.) is the ratio most commonly used in obstetrics, and is used in this study. It is the ratio:

$$(A - B) / A$$

In this ratio, A is the maximum velocity of the waveform, and B is the minimum velocity of the waveform. (ed. Fleischer et al 1991).

McCallum et al (1978) then noted in some high risk pregnancies that umbilical Doppler velocity waveforms characterised by a low diastolic velocity and a high pulsatility index (PI) were associated with poor obstetric outcomes. Many authors showed abnormal umbilical artery Doppler velocimetry patterns to be a good predictor of the small for gestational age infant (ed. Maulik 1997). A high resistance

index (above the 95th percentile) or a systolic/diastolic ratio of >3 were defined as abnormal. Doppler ultrasound provides a non-invasive means of measuring impedance to flow in vessels, including the umbilical artery.

In 1985, Erskine and Richie assessed the effect of maternal consumption of alcohol on umbilical artery blood flow (Erskine and Richie 1985). A small group of patients at gestational age 34 to 36 weeks were given a single moderate dose of alcohol (3g per kg maternal weight), and a control group were given plain soda water. Blood levels of alcohol were then taken and recorded, and Doppler studies were done on the umbilical artery at zero time, and at intervals up to 105 minutes. They recorded the peak alcohol level in maternal serum at 30 minutes after ingestion, but found no difference in Doppler velocimetry waveform patterns in the subject or control group. They therefore postulated that the toxicity of alcohol is not mediated by acute changes in fetoplacental blood flow characteristics.

v) Uterine artery notching.

In the non-pregnant uterus, the uterine artery waveform has high pulsatility, an early diastolic notch, and low diastolic frequency shifts. Uterine artery compliance increases dramatically between 8 and 16 weeks gestation, and continues to increase as pregnancy progresses until 26 weeks gestation. The diastolic notch disappears by 20 to 26 weeks gestation (Fleischer et al 1986, Campbell et al 1987). Retention of the diastolic notch is thought to represent persistence of high impedance flow of the uterine artery circulation. Thaler et al (1992) identified a group of hypertensive women who had both systolic and diastolic notches in the uterine artery waveform in pregnancy, and demonstrated that perinatal outcome was worse than when there was a diastolic notch only. Fleischer et al (1986) confirmed the importance of this notch in a study of 71 patients with hypertensive disorders in pregnancy. Ninety percent (90%)

of women (27 of 30) in their study who developed pre-eclampsia or chronic hypertension with superimposed pre-eclampsia had a uterine artery notch. The finding of a uterine artery notch in these patients had a better sensitivity, and positive and negative predictive value for a normal pregnancy outcome, than blood pressure levels, creatinine clearance, uric acid levels or systolic/diastolic ratios.

Other authors showed that when umbilical artery resistance was normal and both uterine arteries had elevated resistance indices; the group with the uterine artery notch had worse perinatal outcomes (Thaler et al 1992,Trudinger and Cook 1990).

At present there is no literature on the effect of alcohol consumption on uterine artery notching.

vi) Alcohol effects on neonatal outcome

a. Preterm labour.

There is debate in the current literature on an association between alcohol consumption and preterm labour. A large prospective study done in the U.S. on 2714 women who consumed mild or moderate amounts of alcohol (Lundsberg et al 1997) showed that there was an increased incidence of preterm labour (before 37 weeks). They found that even light drinking (less than 0.25 oz of absolute alcohol per day) in month 7 of pregnancy was associated with an odds ratio (OR) of 2.88 of preterm delivery (95%CI, 1.64-5.05), and for mild-to-moderate drinking the OR was 2.96 (95%CI, 1.32-6.67). There are several studies supporting these findings, with another study also finding a three-fold increase in preterm labour in women who drank at least 14 drinks per week during pregnancy (Berkowitz et al 1992).

Other studies, however, failed to show an association between drinking in pregnancy and preterm labour. Peacock et al (1985) examined the relationship between preterm

birth, socio-economic factors, and alcohol consumption in 1513 white women in the U.K. They found no apparent effects of smoking or alcohol in the overall length of gestation. One study even reported a protective effect. (McDonald et al 1992).

b. Intrauterine growth restriction.

Both prenatal and postnatal growth restriction are frequently diagnosed in infants with FAS (Jones 1988, Abel and Hannigan {May} 1995). Some authors found linear growth to be more affected than weight, while others found there to be symmetrical IUGR. (Gershoni-Baruch and Nelson 1988)

Most authors studied the effects of alcohol consumption on the outcome at birth, concentrating their reports on birth weight, length and head circumference. O'Callaghan et al (2003) reviewed studies published before the end of 2002 that examined the effects of alcohol consumption on offspring growth. They found very conflicting outcomes, with as many authors finding reductions in birth weight, head circumference and length as those who found alcohol ingestion to have no deleterious effects on these parameters. In the last ten years, there were some similar studies confirming decreased birth weight or IUGR with moderate and heavy drinking (Cornelius et al 1999,Faden et al 1997,Windham et al 1995,Jacobson et al 1994,Shu et al 1995). O'Callaghan also commented that differences in outcomes between studies may be due to factors such as the duration and timing of alcohol use, and also the amount of alcohol consumed that was considered "moderate" drinking by those conducting the study. Findings for moderate drinking women seemed to be the most inconsistent, and this may be due to the fact that some studies considered one to two drinks per day to be "moderate", whereas current studies consider half to one drink per day to be moderate consumption.

However, some authors (Yang et al 2001) could only demonstrate an association between heavy drinking (fourteen or more drinks per week) and intrauterine growth restriction (IUGR), and found no effect with moderate drinking. They suggested that

IUGR was a heterogeneous outcome with a multifactorial origin, and that there were genetic and environmental factors at play. Others confirmed that alcohol had a less significant effect on birth weight than other risk factors for growth restriction, such as smoking, mother's height and body mass index and ethnic factors. (Faden et al 1997)

Abel and Hannigan (1995) did a comprehensive survey of worldwide epidemiological studies concerning self-reported maternal alcohol consumption and birth weight, and low birth weight and/or prematurity (<37 weeks). They found the effect of smoking is indeed three times greater than the effect of alcohol. They reviewed the literature up until 1994, and concluded that the differences in the literature were due to the inclusion criteria for the amount of alcohol consumed. A threshold of two or more drinks a day was present, above which a decrease in birth weight was noted to be linear. This threshold seemed to be only present among smokers. At lower consumption levels, the incidence in decreased birth weight was lessened for both smokers and non-smokers.

vii) Congenital abnormalities and alcohol consumption in pregnancy.

Alcohol has been implicated in many congenital abnormalities found in the fetus. Ouellette and co-workers evaluated 633 women at their first prenatal visit, and administered a questionnaire. They found that mothers who drank heavily had twice the risk for a baby with a congenital abnormality than mothers who abstained (Ouellette et al 1997). Many of these abnormalities are only visible in the late second trimester, while some cannot be diagnosed prenatally. Those malformations that may be diagnosed sonographically include cardiac malformations, central nervous system abnormalities (e.g.microcephaly, agenesis of the corpus callosum, neural tube defects), facial abnormalities (micrognathia, cleft lip and palate) and truncal and skeletal anomalies (Saunders et al 2002).

One of the most common abnormalities diagnosed in the child with FAS is cleft lip and/or palate. Several studies have found an increased risk of producing offspring

with this abnormality with both alcohol and cigarette smoking (Leite at al 2002, Shaw and Lammer 1999, Munger et al 1996) while others could identify an increased risk for isolated cleft palate, but not for cleft lip (Lorente et al 2000). One study done in Japan could not find a link between alcohol consumption and cleft lip and palate, and thought that those mothers who gave birth to babies with defects drank less alcohol in early pregnancy than the control mothers. (Natsume et al 2000). However significantly more babies in the group who had a cleft lip and palate had a family history of clefts, which may have influenced these findings.

Other specific abnormalities reported in infants exposed to maternal alcohol usage are craniosynostosis (Zegler et al 2002), retinal abnormalities and abnormal retinal function (Hug et al 2000), other ocular manifestations (such as lens opacifications and optic nerve hypoplasia) (Chan et al 1991), renal agenesis or hypoplasia (Moore et al 1997), anal atresia (Yuan et al 1995) and Down syndrome (Bingol at al 1987).

Although maternal consumption of alcohol has been shown to cause structural brain abnormalities in animal studies, (Kotkoskie and Norton, 1989, Ashwell and Zhang 1996, Mattson et al 1994) very little research has been conducted on the human fetus. Wass et al (2001) recently conducted a study examining the impact of prenatal alcohol exposure on the frontal cortex in utero. They found the frontal cortex was smaller in fetuses whose mother consumed moderate to large amounts of alcohol while pregnant. To date there have been no other prospective studies to establish if any of the features of the FAS facies were visible in utero.

More recent studies done using magnetic resonance imaging (MRI) have demonstrated that exposure to alcohol causes displacements of the corpus callosum, increased grey matter densities in both hemispheres in the perisylvian regions, and grey matter assymmetry in the temporal lobes. Reduced brain growth in portions of the frontal lobe was also observed. The cerebellum may have decreased volume and minor structural abnormalities. (Riley et al 2004).

viii) Advice given to pregnant mothers regarding alcohol consumption.

There is still no consensus in medical circles as to "safe" levels of alcohol consumption in pregnancy. In 1996 the Royal College of Obstetricians and Gynaecologists released guidelines for patients regarding alcohol consumption during pregnancy (RCOG guidelines 1996). They recommended that mothers be "careful" about alcohol consumption, and that they limit consumption to one standard drink a day (namely, half pint of ordinary strength beer, lager or cider, one-quarter pint strong beer or lager, one small glass of wine, one single measure of spirits, one small glass of sherry). They could find no adverse effects in growth or IQ levels at consumption below 120g or 15 units per week.

However, this was not universally accepted, and in 1998 Guerri et al (1999) commented on these guidelines, quoting studies by Day et al (1994) and Goldschmidt et al (1996). These authors had found growth and IQ effects at consumption levels of one drink per day, lower alcohol amounts than were recommended to be "safe" by the RCOG guidelines. They also felt that the increased risk of binge drinking had not been adequately addressed. They suggested that pregnant women be advised to abstain from alcohol.

Chaudhuri undertook a more recent review of the literature of the teratogenic effects of alcohol (Chaudhuri 2000), and also recommended abstention during pregnancy. This was later supported by a recent study that showed that even low sporadic doses of alcohol consumption may increase the risk of a congenital abnormality, and that this risk increases with increasing levels of alcohol exposure. (Martinez-Frias et al 2004). In this epidemiological study conducted in Spain the records of mothers reporting any alcohol in pregnancy were examined to ascertain possible risks for congenital abnormalities. Those women who consumed low but increasing sporadic levels of alcohol while pregnant had an increased risk of congenital abnormalities in their offspring, as well as those who consumed increasing daily amounts of alcohol,

compared to those who did not drink while pregnant..

While there is still doubt as to whether consuming small amounts of alcohol is safe, it is probably best that mothers should be advised to avoid drinking alcohol while pregnant.

Methods:

This matched cohort study was conducted between July 1999 and April 2002. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town before commencement of the study. (See Appendix 5)

There were 5 phases in the study.

1.Recruitment

2.Ultrasound evaluation of the fetus during the pregnancy

3.Collection of data regarding the delivery and perinatal period

4.Examination of the infant after delivery, and at one year of age.

5.Statitical analysis.

1.Recruitment:

Two groups of women were recruited, the subjects (mothers who drank heavily while pregnant), and the control group, who abstained or drank little while pregnant. All women were recruited from the same midwife obstetric unit ("MOU") situated in the Cape Town municipal area. All women were recruited from Hanover Park MOU. An MOU is a primary care prenatal and delivery facility, which forms an integral part of the Peninsula Maternal and Neonatal Service (the P.M.N.S). Professional midwives staff the MOU, with no permanent medical staff on the premises. Women who are considered to have a high-risk pregnancy (fetal or maternal indications) are referred to a secondary or tertiary teaching hospital for further antenatal care and delivery.

During the planning phase of this study, it was decided that the ultrasonologist (the author, L.M.) would be blinded to the results of the recruitment interview, and would not know the amount of alcohol consumed by the women. In this way the ultrasonologist would not be aware of which patients were the control group, and which were the subject group. The research assistant (R.A) was therefore carefully selected for her experience in the field of alcohol research, and her knowledge of midwifery. A professional nursing sister with a background in midwifery, Sister Anna-Susan Marais was selected for this role. She interviewed women in the MOU as they attended the antenatal clinic for the first time in the current pregnancy (the so-called "booking visit").

The subject group, who drank heavily, were recruited in one of two ways. In the first method the nursing staff at the antenatal clinic, who knew the women from previous pregnancies, would refer the woman to the research assistant as a possible subject. Subjects were also recruited from the women attending the booking clinic that day. They were asked if they were willing to be interviewed in private, and if they consented they were interviewed to ascertain if they consumed heavy amounts of alcohol. If, during the interview, it was established that the woman consumed heavy amounts of alcohol, they were offered recruitment into the study. If the subject was recruited, the control woman was selected by examining the records of the next women in the queue, and recruiting her if she fitted the matching criteria. The "control" was matched as closely as possible to the subject with regard to smoking, maternal weight (within 10 kg), ethnic group, and gestational age at booking (within 4 weeks). If the next patient in the queue did not meet these criteria, the records of the next patient in the queue were examined, and so on. Many possible "controls" were rejected until a good match was found. All interviews were conducted by the research assistant.

The selected woman was approached by the research assistant and asked if she would be willing to participate in an interview. If she consented, the research assistant would interview the woman for a period of approximately 40 minutes. A questionnaire was administered. This was carefully designed to include a detailed history of the woman's medical and obstetric past, as well as details of her diet and possible substance abuse (including smoking). The lifestyle questionnaire included questions

about personal relationships, education level, religious beliefs, exercise, sleep habits and eating habits. (see Appendix 6)

Once the interviewer considered the woman to be relaxed and to have a rapport with her, she asked about drinking habits, being careful to appear non-judgemental and impartial. The woman was asked what type of alcohol she consumed (e.g. beer, home-made beer, wine, mixed drinks, or spirits), how much she consumed in a typical week, and whether she ceased drinking once she discovered she was pregnant, or at any stage during the pregnancy

The woman's drinking habits were assessed and the research assistant decided if the woman fulfilled the requirements for a heavy drinker. "Heavy drinking patterns" fulfilled the following criteria, in keeping with other research in this area (Rosett 1981), where one standard drink was equated to 15 ml of absolute alcohol. This translated to 2 drinks per day or 14 drinks per week or 5 drinks per occasion (a "binge") with 2 such episodes occurring in a month or 6 binges in 3 months. As many patients in this study consumed beer, a 750ml bottle of beer was assessed to be equivalent to 2.5 drinks, with the result that two such bottles consumed would constitute a binge. Similarly, a 750ml bottle of wine would be equivalent to 5 standard drinks.

If the woman fulfilled the criteria of "heavy drinking' in pregnancy, she was asked for consent to participate in the study. After full disclosure as to the nature of the research, what the study would entail, and what the woman's expectations were, those willing signed consent to participate in the study (see Appendix 7). All women were counselled about the risks of drinking during pregnancy and encouraged to abstain.

Exclusion criteria were: women less than 18 years of age, women suffering from diabetes mellitus, epilepsy, cardiac conditions needing treatment, strictly observant Moslem women (who abstain from alcohol) and women who present to the clinic later

than 26 weeks gestation (determined by menstrual dates or initial ultrasound examination).Moslem women were excluded from the study because their traditional clothing would immediately allow the sonologist to identify them as belonging to the control group.

The woman's records reflected that she had been recruited for a research trial, but the medical and nursing staff was not informed as to the nature of the study, and, to avoid any prejudice, they were not informed about subject or control status. There were no recommendations made to the clinician concerned regarding the woman's antenatal care or delivery. The woman was seen at regular intervals throughout the pregnancy by the research assistant. At each visit to the ultrasound department she was interviewed by the R.A. about alcohol consumption, counselled about the risks of alcohol consumption during pregnancy, and was encouraged to abstain.

2.Ultrasound evaluation of the fetus during pregnancy

Women were given appointments to attend the Ultrasound Department in the Department of Obstetrics and Gynaecology, Groote Schuur Hospital at the relevant gestational ages. They were transported free of charge from their homes to the hospital for these visits. The research assistant did not reveal any information to the ultrasonologist about the patient's drinking habits, so that the ultrasonologist did not know which woman was a subject (i.e. a heavy drinker) and which woman was recruited as a control.

All women were examined by the same ultrasonologist, the author of this study (L.M.), at every visit. They were examined using a General Electric 500 Logic

ultrasound unit. All ultrasound examinations were performed trans-abdominally using a curvilinear abdominal probe, 3.5 MHz frequency probe. Doppler waveform sampling was performed using colour flow and pulsed wave Doppler flow. The woman was requested to lie supine on an examining couch, coupling gel was applied to her abdomen and an obstetrical ultrasound examination was performed. Measurements were recorded on paper at every visit, and were later entered into a computer data sheet to aid data analysis.

The fetus was seen at the following gestational ages:

1. 10-14 weeks, or as soon as possible after recruitment, and

2. 20-24 weeks, for those women who booked early enough,

3. 28 weeks

4. 36 weeks

If there were any abnormal findings at the 28-week visit, an additional ultrasound examination was performed at 32 weeks.

As the ultrasonologist was blinded to subject or control status of the patient, counselling regarding the risks and dangers of alcohol use in pregnancy was done by the research assistant, and not by the ultrasonologist. The women were fully counselled at every ultrasound visit.

The ultrasonologist was only informed of the subject or control status of the women after they had delivered, after which time the ultrasonologist had no further physical contact with them.

1.Assessment at 10-14 weeks

This ultrasound examination was only performed on those women who booked early

enough, and was performed for four reasons:

a) To determine the accurate gestational age of the fetus

b) To measure the nuchal translucency, a screening test for Down syndrome and other chromosomal defects

c) To exclude gross structural abnormalities

d) To exclude multiple pregnancy

The fetal gestational age was assessed by the measurement of the crown-rump length. Internationally accepted charts were used to correlate fetal size with gestational age in weeks (Altman and Chitty 1997).

The nuchal translucency measurement was recorded, and a risk assessment for chromosomal abnormalities was given to the woman. The ultrasonologist is registered with the Fetal Medicine Foundation as a competent first trimester scanner, and has the software package, available to registered users, to give the woman a statistical risk based on current research by that organisation. The women was then informed of the risk for Down syndrome calculated by the software, and was offered amniocentesis to exclude a chromosomal defect should the risk be high (the Fetal Medicine Foundation software will report the risk as being high if the risk is greater than 1:300).

If a multiple pregnancy was diagnosed, the woman was excluded from the study.

2. Assessment at 22-24 weeks

At this visit the ultrasonologist performed 3 tasks:

1. Detailed measurement of the fetus, using internationally acceptable landmarks and reference points (Altman and Chitty 1997)

2. Detailed fetal abnormality scan

3. Doppler flow studies of the fetal umbilical vessels

The following measurements were taken

1. Biparietal diameter (BPD)

2. Head circumference (HC)

3. Abdominal circumference (AC)

4. Femur length (FL)

5. Cerebellar diameter

6. Length of humerus

7. Length of foot

8. Interocular measurements (detailed later)

9. Intracranial measurements (detailed later)

10. Liquor volume i.e. amniotic fluid index (A.F.I.)

11. Umbilical artery Doppler Resistance Index (R.I.).

A detailed fetal anatomical scan was performed. At this visit the fetus was systematically examined for structural abnormalities involving any of the major systems, as well as minor abnormalities of the face, hands and feet. The following check list was completed to ensure no omissions were made:

1. Head: cavum septum pellucidum, lateral ventricles, posterior fossa and

cerebellum

2. Face: profile and frontal views
3. Palate
4. Ears
5. Spine: sagittal and coronal views
6. Heart: four-chamber view, outflows, and aorta
7. Diaphragm
8. Stomach
9. Kidneys and pelvic-ureteric junction
10. Umbilical cord insertion
11. Bladder
12. Hands
13. Feet
14. Umbilical cord vessels.

As part of the routine 22 week detailed anatomical ultrasound assessment, the fetus was also examined for chromosomal markers (such as clinodactyly,pelvi-ureteric junction obstruction etc).

The maternal uterine arteries were sampled using Doppler flow waveforms and R.I. to record the presence or absence of persistent notching. An umbilical artery Doppler resistance index was also recorded.

3.Assessment at 28 weeks

At this visit the fetal measurements, done at 22 weeks, were repeated.

In addition to this, a detailed examination was done to record fetal Doppler flow velocity in the following vessels:

1.The middle cerebral vessel

2. The umbilical artery.

Doppler flow waveform studies were completed by examining and sampling the maternal uterine arteries bilaterally.

4. Assessment at 36 weeks

As at the 28-week visit, the fetal measurements and all Doppler flow measurements were repeated.

Many authors have published charts depicting the normal longitudinal growth of the fetus. Since publication of their findings, most centres, including our own, now use those published by Altman and Chitty in 1997 (Altman and Chitty 1997).The callipers were placed from the outer table of the skull bone to the inner table of the skull bone for measurement of the BPD. Abdominal circumference was measured with callipers placed on the outer skin border, using the ellipse calliper function on the ultrasound unit's keyboard. Femur length was measured from end to end, with the markers of the calliper placed along the entire length of the femur, ensuring that the image was not distorted which would result in the femur appearing bowed or shortened.

Cerebellar diameter was measured at the widest point in the transverse plane, taken at the level of the biparietal diameter.

Measurement of the fetal foot was performed from the ventral surface of the foot, taken in the longest length measurable from heel to big toe.

A detailed ultrasound examination of the fetal face and brain was performed at intervals during the pregnancy to establish if there were any features suggestive of fetal alcohol syndrome.

1.Measurement of the fetal orbits: distance between inner and outer orbital margins.

The fetal orbits were examined in the coronal view, and two measurements were taken at each visit. The first was the distance between the inner margins of the orbits, the "inner interorbital" distance. The second was the distance between the outer orbital margins, using a line that bisected the orbits horizontally, the "outer interorbital" distance. Each measurement was recorded in millimetres, with measurements rounded off to the nearest millimetre (see Figure 1.)

If an adequate view of the fetal face could not be achieved for technical reasons, this was documented, and the measurement was not recorded.

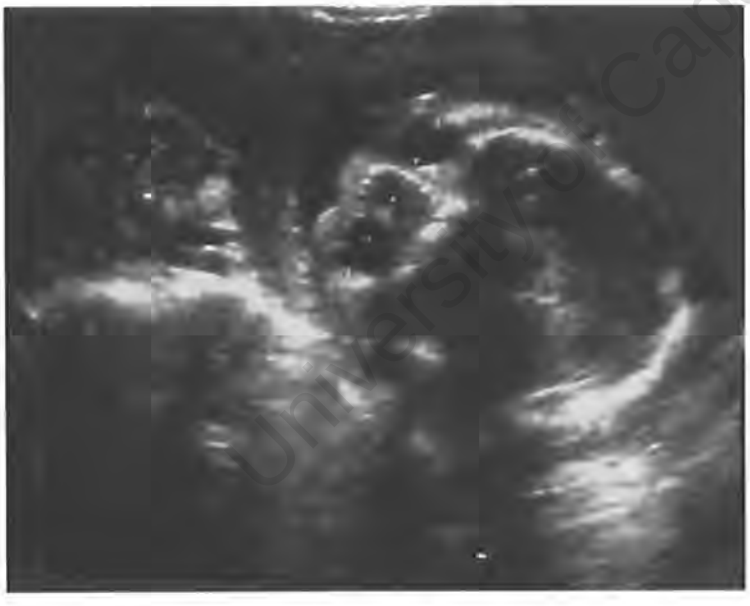


Figure 1: Measurement of the orbits

2.Measurement of the fetal frontal lobe and anterior intracranial anatomy.

The intracranial measurements were performed to document the size of the fetal forebrain, in views that had easily discernable landmarks, and were repeatable. The fetal frontal lobe was assessed using two measurements. The first measured the distance between the inner surface of the calvarium and the posterior border of the cavum septum pellucidum, in the midline (measurement 1)

The second measurement was from the inner surface of the calvarium to the posterior margin of the thalami (measurement 2). See Figure 2.

Each measurement was recorded in millimetres, again, with measurements rounded off to the nearest millimetre.

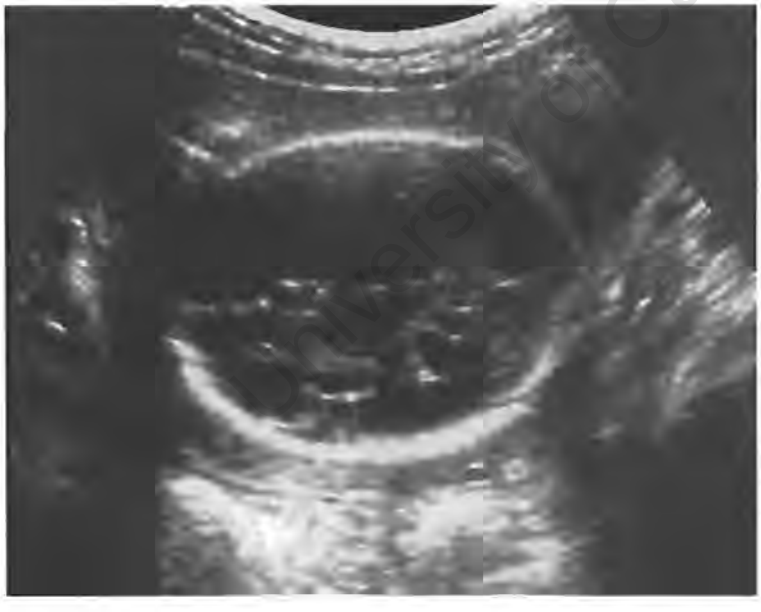


Figure 2: Measurement of fetal brain ("measurement 1").

An attempt to measure the fetal upper lip (from mouth to nose) was made in the planning stages of the study, but it was found to be technically difficult. It was often not possible to demarcate this anatomical area exactly, as the area between the nostrils was indistinct on the frontal and saggital views. The measurement could not be

obtained with any repeatability by the same ultrasonologist. Also, the correct views were not always possible in later gestations due to the fetal position, and the physiological decrease in liquor with increasing gestational age.

Liquor volume is difficult to quantify, so the amniotic fluid index (AFI) is now universally accepted and used in most centres. This was used in the study, and was measured from 20 weeks of gestation onwards. The ultrasound probe is kept at a right angle to the patient's spine, and sweeping movements are made in a horizontal or vertical direction. The uterus is divided into four equal quadrants. The largest vertical pool of liquor seen in each quadrant of the amniotic cavity is measured as centimetres. The AFI is the accumulative total of all four quadrants. Normal AFI ranges from 10 to 25 centimetres, depending on the gestational age, as liquor volume decreases with increasing gestation.

3.Delivery and perinatal period:

The research assistant was notified of the delivery of the baby by the labour ward staff at the respective clinic or hospital. To ensure that the woman did not experience any prejudice, the staff performing the delivery were not informed about her drinking habits, and were not given any information about the subject or control status of the woman.

Data were collected concerning all aspects of the delivery, and a copy of the woman's discharge summary was made. The following information was collected:

1. Date of delivery
2. Duration of 1st, 2nd and 3rd stage
3. Method of delivery
4. Analgesia given
5. Gender of baby
6. Weight of baby
7. Head circumference (occipito-frontal)
8. Resuscitation, if needed
9. Apgar 1 (at 1minute)
10. Apgar 2 (at 5 minutes)
11. Placental weight (gross)
12. Duration of ruptured membranes
13. Induction or spontaneous labour.
14. Delivery result (alive, stillbirth, neonatal death etc.)
15. Any medical illnesses during pregnancy (anaemia, hypertension, diabetes)
16. Small for Gestational Age (SGA)
17. Fetal distress, as diagnosed by delivery team.

3.1 Definition of terms:

i) Small for gestational age (SGA) was defined as birth weight less than 10^{th} percentile, as defined by gestational age curves published by Lubchenco (Lubchenco et al 1966). (see Appendix 8). Although these charts are somewhat outdated, the neonatologists in our neonatal units still use these charts, and they were therefore selected for this study.

ii) Anaemia was defined as haemoglobin of 10g/dl or lower at any stage during the pregnancy.

iii) Fetal distress was defined as any abnormal fetal heart rate tracing in labour as recorded by the obstetrical team. As there was no intervention in the woman's management in labour, this diagnosis made by the delivery team was accepted at face value.

iv) Chronic hypertension was defined as a diastolic pressure greater than 90mmHg before 20 weeks gestation on more than one occasion.

v) Gestational hypertension was defined as diastolic blood pressure greater than 90mmHg on more than one occasion after 20 weeks gestation,with normal diastolic pressures prior to 20 weeks.

vi) Pre-eclampsia was diagnosed when both gestational hypertension and proteinuria was present.

vii) Patients were labelled diabetic if they developed diabetes during pregnancy. Those with type I diabetes, or pre-existing type II diabetes, were not included, as they would not have been followed by the MOU's.

4.Follow up of the baby after delivery.

Once a mother had been discharged from the hospital or clinic after delivery, contact between the mother and the research assistant was maintained telephonically, or by periodic visits to the patient's home if there was no telephone at her home. The mother was asked to bring her baby back to be examined when the baby was 6 weeks old. An appointment for this visit was made at 6 weeks of age, or as soon as possible after the baby had reached that age.

At this six-week visit, the baby was examined by an independent dysmorphologist who was experienced in the examination of newborns and infants for features of FAS. The dysmorphologist was blinded as to whether the mother was a subject or a control. This information was not revealed to the dysmorphologists at any time during this study.

A physical examination was performed, looking for any structural abnormality, as well as any minor features that may be compatible with FAS. A detailed record of these findings was recorded (see example attached as Appendix 9). The baby was weighed, and measurements were taken of the baby's head circumference and length. The baby was examined for neurological development, and a thorough examination of all the systems was performed.

During the study, one of two dysmorphologists examined every baby; both had been selected for their experience in the field of neonatology and fetal alcohol syndrome. Due to the fact that the ultrasonologist was blinded as to subject or control status of the women, the ultrasonologist was not present during these examinations. This would prevent any communication with the dysmorphologist that may allow examiner bias. Subtle features of FAS were searched for, including abnormal palmar creases, hypertrichosis, clinodactyly, and abnormal facial features (short palpebral fissures, strabismus, epicanthic folds, nasal bridge, anteverted nostrils etc). Although findings

were documented systematically, the final decision to diagnose the baby as FAS or not rested with the examiner, as it was considered a "gestalt" diagnosis.

After a complete physical examination was performed the results were documented as one of three options:

1. The baby displayed typical FAS features on examination,

2. The baby appeared normal and displayed no FAS features, or

3. The decision was deferred until one year of age, if a confident decision could not be made based on the examination at that time.

Babies who were diagnosed as FAS, or who were deferred, were called back for a second examination when the baby was between one and three years of age. This repeat examination aimed to confirm the diagnosis previously made, and to re-consider the diagnosis if the decision had originally been deferred.

Table I: Clinical manifestations of Fetal Alcohol Syndrome (Viljoen 1991)

1. Growth disturbance.
2. Central nervous system anomalies.
3. Facial dysmorphism -epicanthic folds, anteverted nares, small nasal bridge, smooth philtrum, ptosis, rotated ears, and prognathism.
4. Other organ manifestation.

5. Statistical analysis

Data collected were recorded on paper and later transferred to Excel computer files. These files were then analysed with the help of a medical statistician.

All data collected were used in the statistical analysis. However, data collected on those women whose pregnancies were terminated for fetal abnormalities were not used in the analysis of birth weight, preterm labour, fetal distress, Apgar scores or the presence of FAS at birth.

Initially descriptive analyses were conducted on the demographic variables across subject conditions (drinkers versus non-drinkers). Both parametric t-tests, non-parametric Mann-Whitney U-tests, and exact proportional difference tests were conducted on the scaling of the variable being studied. Both SAS Version 9.13 (2002) and StatXact 5 (Mehta and Patel 2002) were used. Analysis of the neonatal outcomes across subject conditions used the general linear model along with the covariate of smoking status for difference in birth weight. Since Apgar measures were ordinal level data, we used a rank transformation general linear model procedure (Conover and Iman 1976), which also allowed the inclusion of the smoking status covariate.

Changes in the proportional neonatal outcomes across subjects were assessed using logistic regression, which allowed for the inclusion of the smoking status covariate. Finally, the ultrasound measurements were analysed using fixed occasion longitudinal models and multivariate, multilevel longitudinal models. A probability of <0.05 was accepted as significant.

Ethical considerations.

The need for this study to be ethically sound was paramount to the research team. It was obvious from the early planning stage that we would have to make it clear to the subjects selected that the use of alcohol in pregnancy was not advisable, and that every attempt would be made to encourage the women to stop drinking.

There were many ethical considerations during this study. They are reviewed under the following headings.

1. Recruitment and interviews
2. Obtaining informed consent
3. Counselling women about the dangers of alcohol consumption throughout the study and offering appropriate counselling and support
4. Ensuring confidentiality
5. Performing invasive and non-invasive investigations.

1.Recruitment and interviewing

Women were selected from those attending the antenatal clinics at our midwife obstetric units for the first time in the current pregnancy (the so-called "booking visit"). Women were either recruited at random, or after nursing staff at the clinic indicated to the research assistant (R.A) that the woman might be consuming alcohol while pregnant. All discussions between nursing staff and the R.A. were conducted in private and confidentiality was assured. Other women in the vicinity could not overhear the conversation or be aware of the interview.

Once the woman's folder was selected, she was asked to accompany the R.A. into a separate room, where the interview could be conducted in private.

If the woman consented to participate in the study, a sticker was placed on her folder reading: "MATERNAL INFANT STUDY". No reference was made to the fact that the study involved research into alcohol consumption in pregnancy. There was also no reference to the subject or control status of the woman, either in her clinic folder or on her appointment card.

2.Obtaining informed consent.

Careful counselling of the woman who agreed to participate in the study was performed at several intervals during the study. This counselling was essential as we needed to be certain that all participants fully understood the reason and the nature of the study, and also that they consented to all the procedures that would be necessary during the study.

Disclosure of information derived from the ultrasound examination occurred only if the woman indicated that she wished to be fully informed of all findings. Some women declined invasive testing to exclude chromosomal abnormalities such as the maternal biochemical screen for Down syndrome, and amniocentesis. These women felt that the increased anxiety levels they would experience would outweigh the benefits of knowing the information prenatally. The autonomy of the individual was therefore always respected. An example of this would be when the ultrasonologist (L.M) observed minor variants from normal fetal anatomy which may be markers of Down syndrome (e.g. a choroid plexus cyst). This information was only revealed to the woman if she indicated she wanted full disclosure of the findings. It was explained to the woman that the information might influence the management decision in the pregnancy.

The women in both the control and subject group were informed how the study would be performed, when they would be requested to attend the hospital for ultrasound

examinations, what transport arrangements would be made, and how expenses would be covered.

3. Informing women of the dangers of alcohol consumption during the study.

The ethical considerations of this aspect of the study were challenging. There was a responsibility to inform the subjects of the potential dangers of alcohol consumption on their unborn child at every visit. The R.A. reinforced this message every time she had contact with the woman. This was done in a non-judgemental manner, with a neutral explanation of the current thinking that indicates that alcohol consumption has adverse effects on the unborn child throughout pregnancy, from conception to delivery. All women who were recruited as subjects (those who had excessive alcohol consumption) were offered support, counselling and assistance in stopping alcohol abuse from the time of recruitment until after delivery, and at all follow up visits.

4.Ensuring confidentiality.

Confidentiality of the records regarding the woman's alcohol consumption habits was easy to achieve, as the examiner was blinded to subject or control status of the woman. There was no indication on the woman's antenatal records that she consumed, or had consumed alcohol while pregnant nor was this information available to medical or nursing staff involved in the woman's delivery, unless they

independently obtained this information, or the woman showed evidence of alcohol use/abuse.

All records relating to this study were kept off-site from the antenatal clinics and delivery centres. An exception of this was if any abnormal ultrasound findings were obtained, in which case the clinician involved in the woman's care was informed of these findings. Patient records were only released to the ultrasonologist once the woman had been delivered and the neonate had been examined by the dysmorphologist.

5.Performing invasive and non-invasive procedures.

Ultrasound examination is a non-invasive method of assessing the fetus. Current opinion, supported by extensive research, is that ultrasound examination carries no risk to mother or fetus, provided acoustic exposure duration and intensity are kept within accepted limits, and ultrasound examinations done transvaginally in the first trimester are kept to a minimum (Duck 1999). There were therefore no ethical implications in performing ultrasound examinations, which are routinely carried out in our service on all women who "book" before 24 weeks gestation. There is also no documented or postulated increased risk to women who are examined by ultrasound on more than one occasion during pregnancy.

Patients who are 39 years of age or older at conception are routinely offered amniocentesis to exclude chromosomal abnormalities in our practice. Data on the prevalence of fetal anomalies indicates that for the age of 35 years and older the risk of a chromosomal anomaly exceeds the risk of amniocentesis. However in the Western Cape cost benefit factors dictate that we can offer this service only to women

39 years of age or over. Younger women would be counselled and may elect to have the amniocentesis, but would then have to pay for this investigation (approximately R2000). In our clinical practice, the procedure is performed at 16 to 21 weeks of gestation. All patients were extensively counselled about the risks of this procedure by trained genetic counsellors. They were encouraged to bring their partners with them to this counselling session. Those patients who wished to have the procedure, and were fully aware of the risks and benefits, were referred for the procedure.

Ethics Board Approval.

Ethical approval was obtained from the Research Ethics Committee of Faculty of Health Science of the University of Cape Town before commencement. (Reference 038/99,approved 6 May 1999.)

RESULTS.

Results1: Demographics and neonatal outcomes.

Between July 1999 and April 2002, a total of 125 women were recruited to the study. Of these, 5 women were later excluded from the study. Two of these women defaulted the study and were lost to follow up (one left the area and could not be traced, the other decided not to participate after one visit). One woman was diagnosed as having an anembryonic pregnancy at her initial visit, and was therefore excluded.

A further two women were excluded from the study after delivery, once it became clear that they had not given an accurate history of their true alcohol consumption. Both these women, who were recruited as controls, later admitted that they had consumed more heavily in the first trimester than they had initially reported. As they did not consume enough alcohol to be termed a "heavy " drinker (by the definition used in this study), they could not be used as a subject. They were withdrawn before statistical analysis was done, and their babies were not examined by the dysmorphologist.

With these exclusions a total of 120 women were analysed in the final analysis: 60 subjects and 60 controls. Each ultrasound examination was 40 to 50 minutes in duration. At completion of the study, there had been 278 ultrasound examinations recorded. These examinations were all performed on the same ultrasound machine by the same examiner (L.M.). Women were seen as close to the pre-selected gestational ages as possible (i.e. .at 24,28,and 36 weeks gestation). The number of women seen at each gestational age is represented graphically in Figure 3. This figure demonstrates the clustering of ultrasound examinations done around the pre-selected gestational ages.

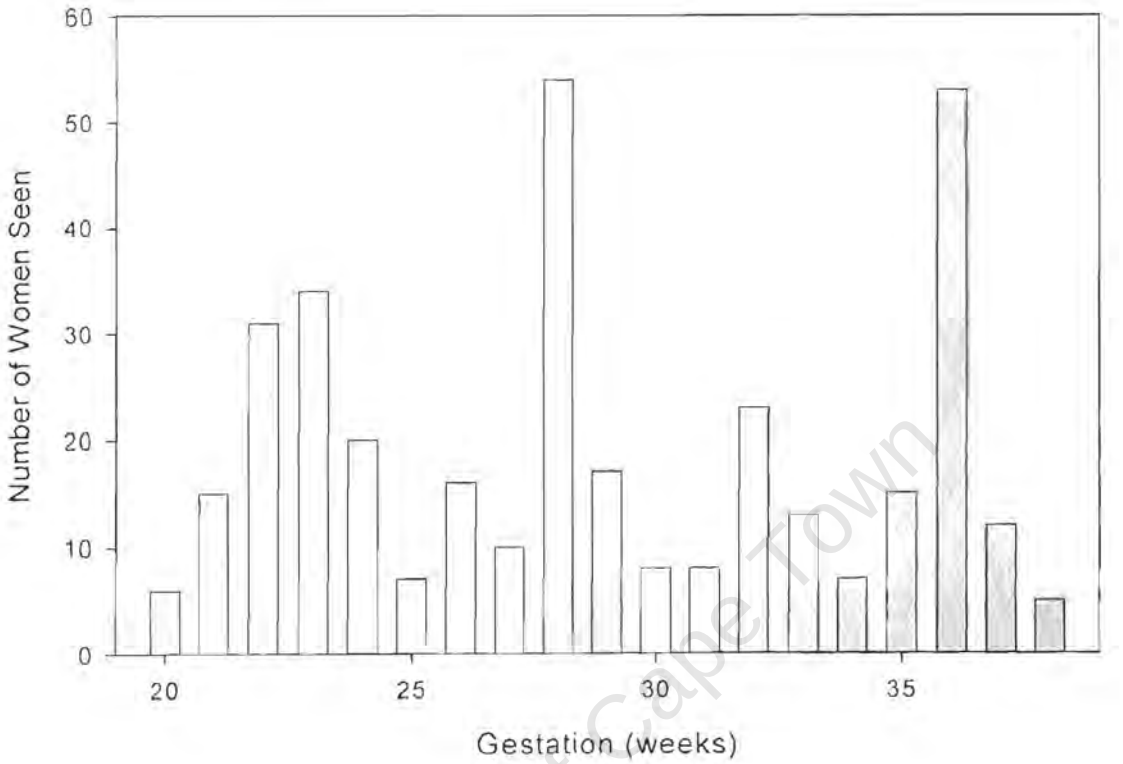


Figure 3. Number of women seen for ultrasound assessment vs. gestational age.

1. Demographics of women at booking:

Results of the demographics of the women who participated in the study are represented in Table II.

Table II: Maternal demographics

	Subjects	Controls	p-value
Age* (years)	25.4 (SD 5.71) Range: 18-41years	25.18 (SD 5.23) Range: 18-41years	0.82
Gravidity ^	2 (range 1-8)	2 (range1-7)	0.80
Parity^	1 (range 0-5)	1 (range0-6)	0.53
Booking weight (kg)*	57.05 (SD 10.68)	62.80 (SD 15.0)	0.01
Body mass index*(kg/m^2)	25.95 Range: 16.1-33.7	25.19 Range: 17.6-40.4	0.41
Height (cm)*	157.7(SD 6.11)	158.9(SD 7.06)	0.30
Smoker #	91.7%(55/60)	60%(36/60)	0.0001
Anaemia #	8.3%(5/60)	1.7%(1/59)	0.20
Hypertension #	11.7%(7/60)	6.7%(4/60)	0.52
Diabetes #	1.7%(1/60)	1.7%(1/60)	1.00

KEY: SD= standard deviation. * = Arithmetic mean contrasts (t-tests), ^ = Mann-Whitney U-test, # = Exact proportional contrasts.

The mean age was 25.2 years (+/_ 5.2) for controls and 25,4 years (+/-5.7) for subjects. This was not statistically significant.

Mean height was 159.0cm (+/-7.1cm) for controls and 157.7cm (+/-6.11cm) for subjects. No differences were found.

The initial booking weight for controls was slightly higher than subjects (62.8 kg vs. 57.1 kg). (p= 0.01).

Body mass index (weight in kg/ height in metres squared) means were 25.1 for the control women and 25.9 for the subject women. No statistical difference was found using t-testing.

Gravidity and parity were analysed (Table II). Means were calculated and rounded off to nearest whole number e.g. 2.23 rounded off to 2. Mean gravidity for both subjects and controls was 2. Mean parity was 1 for both subjects and controls. No difference was found between the subject and control women.

All women recruited for the study were of mixed ancestry (referred to in South Africa as "Cape Coloured"). The ethnic groups that contributed to this ancestry was Khoi, San, black African, white and Malay. They lived in the same geographical area (surrounding the clinic at which they were recruited), and belonged to the lower and middle-income groups.

Menstrual dates (last menstrual period) as reported by the patient were correct, and correlated with early ultrasound assessment of gestational age, in 66.6% of controls but only 53.3% of subjects.

Sixty (60) percent of the controls smoked during pregnancy, compared to 91.7% of subjects. (p : 0.0001)

2.Alcohol consumption in pregnancy.

To fulfil the inclusion criteria for this study, the subject women were all "heavy" drinkers, as defined in "methods". When this data was analysed at the conclusion of the study, we found that these women consumed between 9 and 140 drinks per week (one drink equal to 15 ml absolute alcohol), with 43,1% (25/58) consuming more than 20 drinks per week.

Nearly all our women consumed beer, but a few consumed wine or spirits, either alone or in addition to beer.

After the women were recruited on the study, and had been advised about the risks of alcohol consumption while pregnant, 29% (17/58) declared that they had stopped drinking. None of these women stopped drinking before the end of the first trimester of pregnancy, and most stopped between 20 and 26 weeks (see Appendix 1).

3.Maternal illnesses in pregnancy

Anaemia, diagnosed by a haemoglobin concentration of 10 g/dl or less, was present in 1.7 % of controls, and 8.3% of subjects. Other maternal diseases recorded were hypertension (6.6% of controls and 11.7% of subjects) and diabetes (1.7% of controls and 1.7% of subjects). None of these differences were significant.

4.Delivery and perinatal outcome:

When analysing perinatal and neonatal outcomes, there were statistically significant differences between the two groups in the following variables:

a. Preterm labour, higher incidence in subjects (p =0.005)

b. Mean birth weight, less in subjects (p=0.008)

c. Intrauterine growth restriction, higher incidence in subjects (p=0.021)

d. Confirmed FAS diagnosed at birth, higher incidence in subjects (p=0.017)

e. Placental weight, less in subjects (p=0.038)

There was no statistical difference between the two groups in the following variables:

f. Apgar scores (p=0.74)

g. Incidence of fetal distress (p=0.166)

h. Congenital abnormalities. (P=0.233)

These findings are represented in Table III.

	Subjects	Controls	p-value	p-value controlling smoki
Birth weight*	2653 (SD 649.77)	2958(SD 585.19)	0.008	0.365
Preterm delivery #	29.3% (17/58)	8.5% (5/59)	0.005	0.1636
Fetal distress #	3.4% (2/58)	8.5% (5/59)	0.1452	0.7115
Apgar 1^	9 (range 2-10)	9(range 6-10)	0.74	0.85
Apgar 5 (5 mins)^	9 (range 8-10)	9 (range 7-10)	0.74	0.89
Congenital abnormality #	6.6% (4/60)	6.6% (4/60)	1.00	1.00
IUGR #	16.1% (9/56)	3.4% (2/59)	0.021	0.1884

Table III: Pregnancy outcomes.

* = Arithmetic mean contrasts (t-test), ^ = Rank transformation test, # =Proportional contrasts using exact logit model, SD =standard deviation, range=minimum to maximum.

a) Preterm labour:

Twenty-nine percent (29%) of the subjects delivered preterm infants, defined as a delivery before 37 weeks gestation. There were 58 women in this group, as one woman had a termination of pregnancy for a fetal abnormality, and one woman was lost to follow up in the third trimester. Of the 58 women analysed for this outcome, 7 (12.1%) women delivered between 28 and 33 weeks, and 10 (7.2%) women delivered between 34 weeks and 37 weeks.

Only eight percent (8%) of the control women had preterm deliveries. (p=0.005). In this group there were 59 women, as one woman had a termination of pregnancy for a fetal abnormality and was therefore not analysed for this outcome. Only one women (1.7%) of the control group delivered before 34 weeks.

b) Birth weight:

Birth weight of the babies born to mothers who consumed alcohol was less than the birth weight of the babies born to those mothers who did not drink heavily while pregnant. The mean birth weight of the controls was 2985g (SD 585) and the mean birth weight of the subjects was 2653g (SD 649). P-value was 0.008. However, the p-value when controlling for smoking was 0.215.

c) Intrauterine growth restriction (IUGR):

IUGR was defined as a birth weight of less than the 10^{th} percentile for gestational age. (Lubchencho et al 1966.) Of the control group, 3.4% of neonates had IUGR, but 16.15% of the subjects delivered growth-retarded neonates. (p=0.021)

d) Fetal Alcohol Syndrome (FAS) at birth:

When comparing the finding of FAS diagnosed at birth in the subject and control group, there was a significant difference, with a p value of 0.017.When examining the babies of the control group, there were no babies who were diagnosed as FAS at birth. Ninety-three percent (93.0%) of babies were considered normal, while 7.0% of babies were deferred for later re-assessment, as a decision could not be reached.

In the subject group, 62.7% of babies were considered normal. However 11.9% of babies were considered to have FAS at birth, and a further 25.4% were deferred for a later decision.

These findings will be discussed in more detail later.

c) Placental weight:

Mean placental weight at birth of the women who consumed alcohol was 529.8g (S.D.132.2), while those who did not consume alcohol was 570.1g (S.D. 108.0) (p =0.038).

f) Fetal distress:

There was no difference in the comparison between the two groups with regard to the incidence of fetal distress. The incidence of fetal distress in both groups was low. Eight percent of controls were reported as having fetal distress while 3% of subjects had fetal distress. (p=0.145).

g) Mode of delivery:

Eighty-six (86.7%) of controls delivered vaginally, while 79.6% of subjects delivered vaginally.

h) Apgar scores:

There was no difference in Apgar scores at one minute (Apgar 1) or at 5 minutes after birth (Apgar 5) between the two groups. The mean Apgar 1 in the subjects was 9 and in the control group 9. The mean Apgar 5 in the subjects and in the controls was 9..

i) Congenital abnormalities:

Congenital abnormalities, either major or minor, were recorded after examination prenatally by ultrasound, and post-natally by the dysmorphologist. Combining those found prenatally and those diagnosed after birth, 6.6% of mothers had a fetus with a congenital abnormality in both the subject and control groups. Congenital abnormalities are represented in Table IV. Only 4 of the 8 abnormalities were diagnosed by ultrasound before birth, as many of the minor abnormalities found in these babies cannot be diagnosed by ultrasound examination (e.g.laryngomalacia).

In the subject group, one woman (ID number ND106) underwent a termination of pregnancy due to the ultrasound findings of a spina bifida and dysplastic kidney. Termination was done at 20 weeks gestation. Post mortem examination confirmed these findings. Post mortem findings and photographs are attached as Appendix 9.

TABLE IV: Congenital abnormalities found at birth

Woman ID number	Congenital abnormality	Outcome	Ultrasound findings
	CONTROL GROUP		
EB1	VSD	Healthy	No abnormality found
MV68	Hydrocephalus	Pregnancy terminated. Post mortem non-contributory due to maceration.	Hydrocephalus found at 19 weeks. Small, flattened cerebellum. No spinal defect.
MP124	Laryngomalacia	Healthy, treated as outpatient	No abnormality found
JM113	Cryptorchism	Awaiting surgical repair	No abnormality found
	SUBJECT GROUP		
MG46	Trisomy 21, Hydronephrosis	No surgery required, no other abnormalities found	Hydronephrosis diagnosed at 26 weeks gestation.
CM97	Capillary haemangioma	Healthy	No abnormality found
ND106	Spina bifida, renal dysplasia right kidney, hydrocephalus	Pregnancy terminated. Post mortem performed.	Spina bifida commencing at S2, dyplastic right kidney, rockerbottom feet, diagnosed at 19 weeks. Amniocentesis result: 46XY.
FJ125	Para umbilical hernia	Awaiting repair	No abnormality found

5.Ultrasound markers associated with increased risk of chromosomal defects:

Only 3 of the women (1 subject and 2 controls) booked early enough (before 14 weeks gestation) to have a nuchal translucency (NT) measurement performed on the fetus. All these measurements were within the acceptable range, giving the women a negative screen for Down syndrome.

All women were screened for ultrasound markers of chromosomal aneuploidy, and the following were found:

1.Clinodactyly: This is defined as a deviation of one or more fingers, usually the fifth finger in Down syndrome infants. (Romero et al.1988). This was detected on ultrasound examination in 9/60 subjects and 4/60 controls.

2. Pelvic-ureteric junction obstruction (PUJ): This is defined as an anteroposterior diameter of the pelvis as >4mm at 15-19 weeks, or >5mm at 20-29 weeks (Pilu and Nicolaides, pub 1999). This was present in 2/60 subjects and 4/60 controls.

3. An echogenic focus in the left ventricle of the fetal heart: This was present in the fetus of one of the mothers in the control group.

4.Choroid plexus cysts: One mother in the control group had choroid plexus cysts detected in her fetus.

5.Echogenic bowel: This was not present in either group.

One baby in our study had Trisomy 21,which was only diagnosed postnatally. This baby had one marker for Trisomy 21 on ultrasound examination pre-natally, namely a PUJ obstruction. The women presented to the booking clinic late in the second trimester and her first ultrasound visit was at 26 weeks gestation. As is routine practice in our clinic, amniocentesis was not offered due to the advanced gestation of the pregnancy.

Results 2: Growth of the fetus.

Growth of the fetus in utero was assessed by measuring standardised growth parameters, namely biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL), at regular intervals during the pregnancy. These measurements were recorded, and graphs were constructed plotting growth against gestational age.

2.1. BPD

Growth of the biparietal diameter is represented in Figure 4.

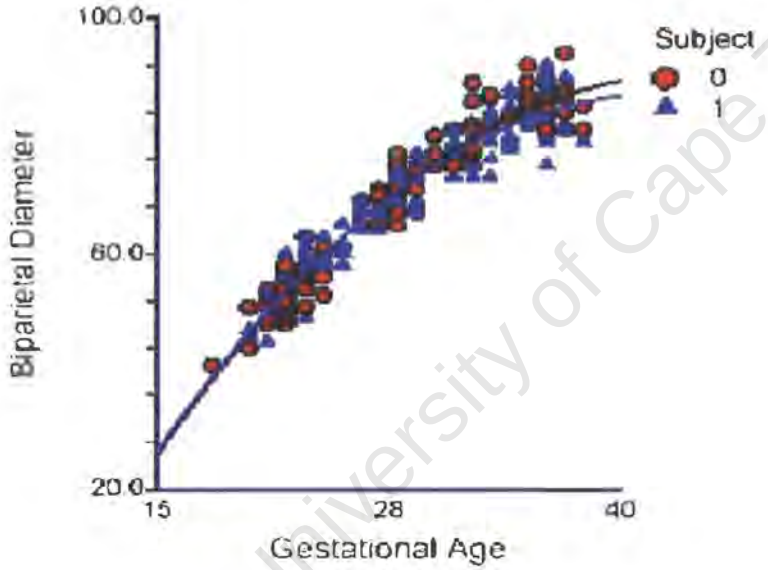


Figure 4: Growth of BPD against gestational age in weeks.

KEY: Subject women = △

Control women = o

BPD in mm

Gestational age in weeks.

When using the trajectory model (continuous growth measurements creating growth curves), there was no significant difference between growth of the BPD in subjects versus controls. When the effect of smoking was excluded, there was only a marginal difference ($p<0.1$), with the subject group having slightly smaller BPD measurement than the controls.

When analysing the data using the fixed occasion model (modelling differences at fixed time periods, for example at 24 weeks gestation), the subject BPD was statistically significantly larger at 24 weeks gestation ($p=0.032$). In the subject and smoking status covariate, this difference was no longer significant when controlling for smoking, but smokers had a smaller BPD at 36 weeks.

2. 2. HEAD CIRCUMFERENCE (HC)

The longitudinal growth of the head circumference is represented in Figure 5.

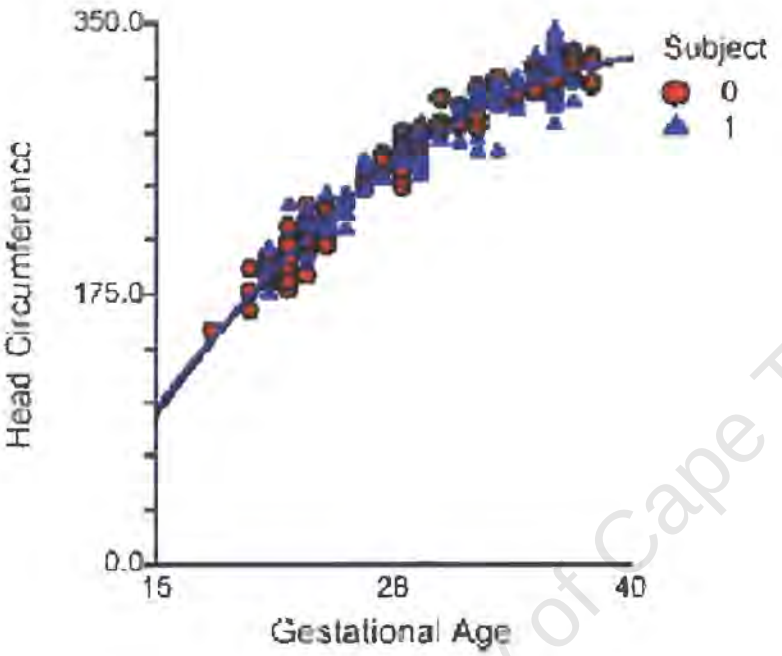


Figure 5. Growth of HC against gestational age in weeks

KEY: Subject women= △

Control women= O

HC in mm

Gestational age in weeks

When the HC of the controls was compared to the HC of the subjects, the HC of the subjects was larger, with the p value =0.026. Once the effect of smoking was excluded, the subject group still had larger HC at 24 weeks (p =0.034). However,by 36 weeks gestation, the HC were significantly smaller in the subjects than the controls (p= 0.032).

Table V: BPD and HC measurements at fixed occasions.

Outcome measure	Gestation	Control	Subject
BPD	24 weeks	53.6 (S.D.4.2)	57.5(S.D.7.1)
HC	24 weeks	202.3(S.D.17.1)	215.8(S.D. 33.0)
BPD	28 weeks	71.1 (S.D. 5.2)	73.6(S.D.4.7)
HC	28 weeks	266.7(S.D.18.7)	273.2(S.D.17.6)
BPD	36 weeks	87(S.D.36)	80.8(S.D.4.77)
HC	36 weeks	318.5(S.D.7.98)	310.7(S.D.22.7)

2.3. ABDOMINAL CIRCUMFERENCE (AC)

Growth of the AC is represented in Figure 6. Using a fixed occasion model, the subjects had a marginally significantly larger AC at 24 weeks (p=0.05). Once the effect of smoking was excluded, the subjects still displayed larger AC measurements at 24 weeks, but at 36 weeks, the AC was significantly smaller in the subject group.

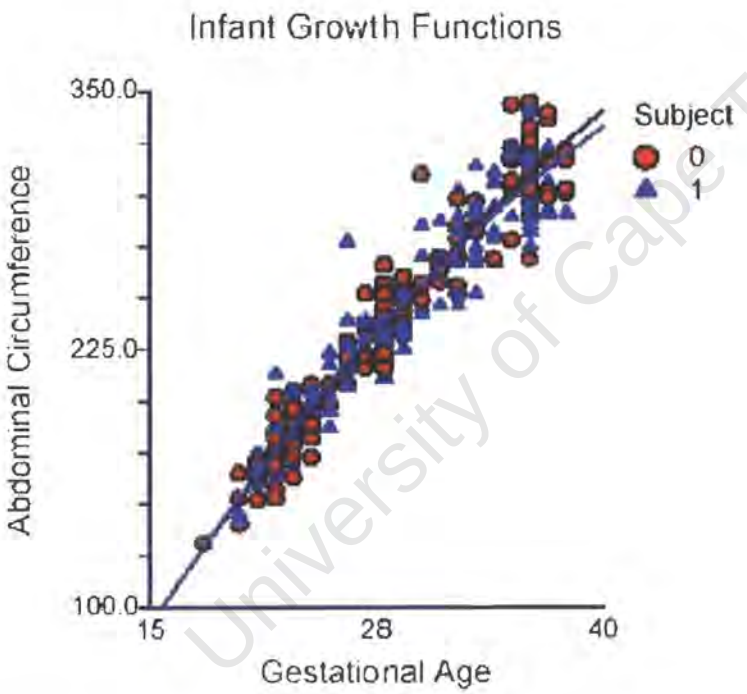


Figure 6. Growth of AC versus gestational age in weeks.

Key: Subjects = △

Controls= O

AC in mm

Gestational age in weeks

2.4. FEMUR LENGTH (FL).

Growth of the femur length when plotted against gestational age is represented in Figure 7.

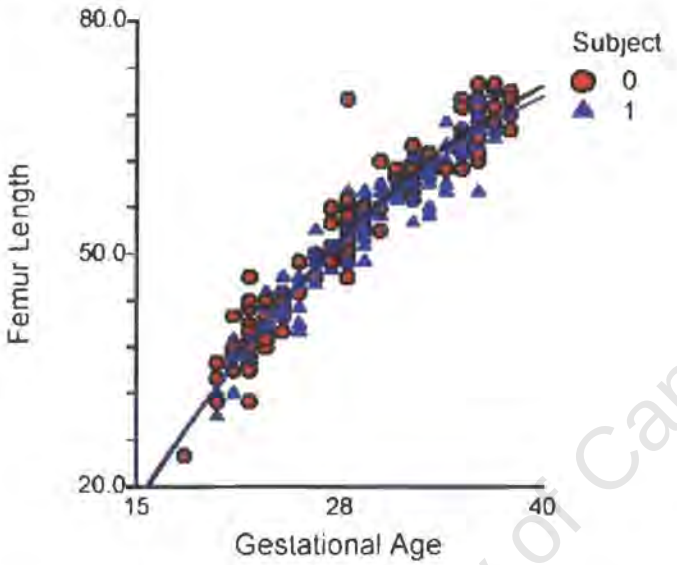


Figure 7. Growth of FL versus gestational age in weeks

KEY: Subjects = △

Controls = O

FL in mm

Gestational age in weeks

There were no significant differences in growth of the femur length between the two groups. Smoking did not have any effect on the growth of the femur length.

There was no difference between the two groups in the length of the humerus or the length of the foot.

Results 3: Doppler Flow Studies.

3.1. Maternal uterine arteries:

The maternal uterine arteries were sampled at 28 weeks gestation. The waveform was recorded and observed for the presence of a diastolic notch. Both right and left arteries were sampled, and the woman was reported to have a positive notch if either or both arteries demonstrated notching.

There were no significant differences in the prevalence of uterine artery notching in the two groups. Thirteen percent (3/23) women in the subject group, and 13%(4/30) in the control group had a uterine notch at 28 weeks. These results are shown in Table VI. Results of uterine artery waveform studies from women who did not have an ultrasound examination at *exactly* 28 weeks gestation (i.e. if they were seen at 29 or 30 weeks) were also analysed, as persistence of uterine artery notching is significant at any gestation after 26 weeks. In this group there were also no differences, with 15.3%(9/59) of the subjects and 13.5%(8/59) having a uterine notch recorded.

Table VI: Doppler studies at 28 weeks gestation.

	Subjects	Controls	p-value
Uterine artery notch in either uterine artery	**13.0%(3/23)**	**13.3%(4/30)**	**1.00**
Umbilical R.I.	**0.57(0.20)**	**0.56(0.17)**	**0.69**
MCA R.I.	**0.818(0.022)**	**0.870(0.024)**	**0.12**

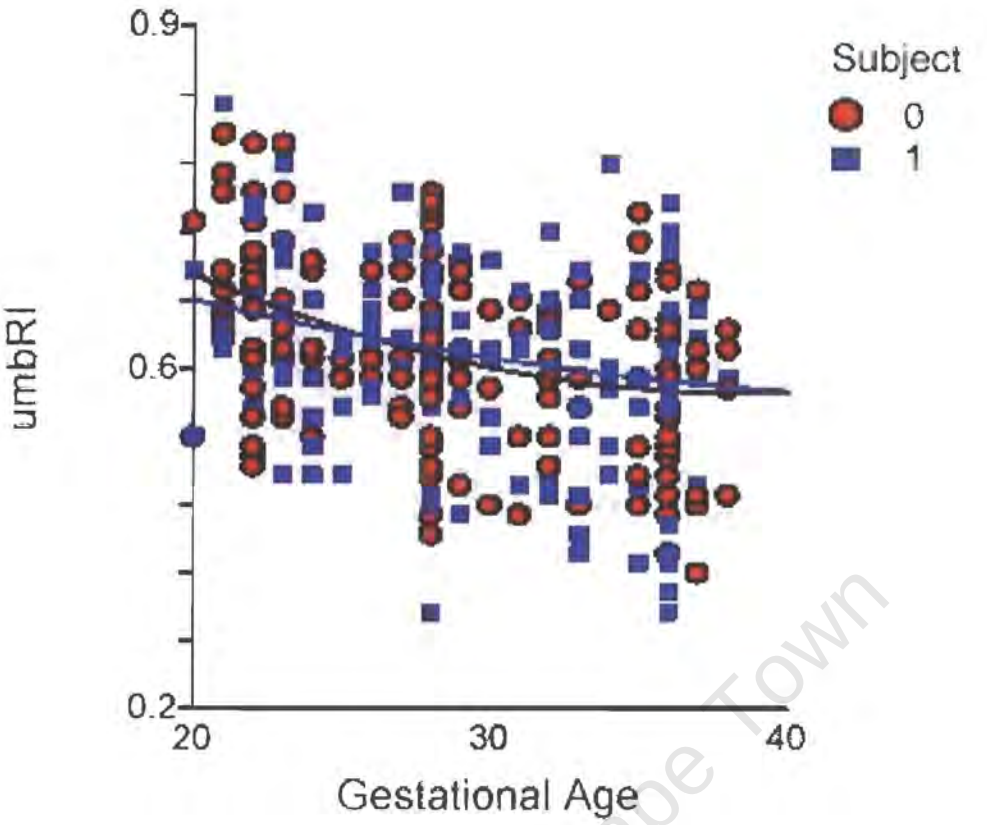


Figure 8. Doppler Flow of Umbilical artery: Resistance Index (R.I.)

KEY: Subject = □

Control = O

There was no demonstrable difference in Doppler flow in the fetal umbilical or middle cerebral arteries. Recorded values are shown in Table VI. Changes in Doppler flow with advancing gestational age are represented in graphic form in Figure 8 and 9.

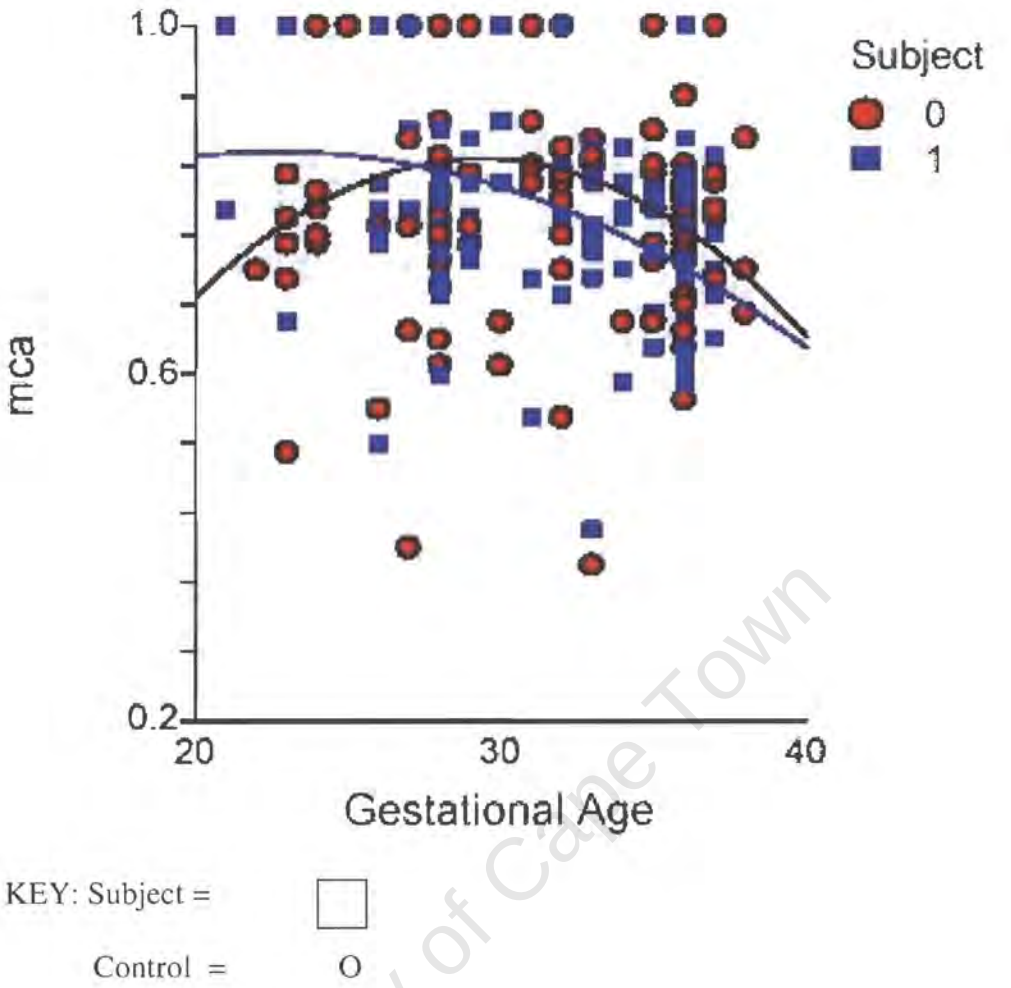


Figure 9.Doppler Flow of middle cerebral arteries (R.I.).

In conclusion, no significant differences were found in the Doppler flow studies between the subject and control group.

Results 4: Facial and intracranial measurements.

All 120 women involved in the study had the interorbital and cerebellar measurements of their fetuses recorded at each visit. The measurement of the intracranial measurements (i.e. the frontal lobe measurements) were only commenced later in the study period, and as a consequence that only 56 women were analysed for this variable. Of these 56 women, 26 women were subjects, and 30 were controls.

The distance between the inner margins of the orbits was significantly different between the subject and control group. At 24 weeks of gestation, the fetuses of the mothers who consumed alcohol in pregnancy had more widely spaced orbits i.e. the distance between the orbits was greater. These findings remained significant ($p<0.05$) once the effect of smoking was excluded, as smoking did not appear to effect this measurement. These findings are represented in Table VII.

There was no significant difference between the two groups when analysing the distance between the outer margins of the orbits. Smoking did also appear not to influence this reading. Analysed as a ratio, the ratio of inner margins of the orbits to outer margins was greater in the subject group at 24 weeks gestation ($p=0.024$).

The examination of the fetal intracranial structures revealed significant findings at 28 weeks gestation. The distance from frontal calvarium to the cavum septum pellucidum (measurement 1) was marginally larger in the fetuses of the subjects than in the fetuses of the control mothers ($p=0.034$). These findings were not statistically different in earlier gestations.

There was no significant difference in the distance from frontal calvarium to the thalami (measurement 2) in the two groups of patients.

When these results were expressed as a ratio, namely measurement 1/measurement 2,the ratio was significantly smaller in the subject group, with these findings being most significant statistically in later gestation (32 weeks). (p=0.0002).

There was no statistical difference between the transverse cerebellar measurements of the fetuses whose mothers consumed alcohol, and those who did not. However, if we considered smoking per se. at 36 weeks smokers had significantly smaller cerebella, with a p value of 0.0002.

Table VII: Results of facial and intracranial measurements.

Outcome measure	Gestation (Weeks)	Subject	Control	P value
BPD	24	57.8 (7.2)	53.7 (4.2)	0.032
HC	24	215.8 (4.4)	202.3 (17.1)	0.034
Cerebellum	24	24.7 (3.5)	22.5 (2.7)	N/S
Inner orbit	24	14.9 (2.1)	14.1(1.9)	0.0006
Outer orbit	24	38.5 (3.4)	35.7 (3.4)	N/S
Intracranial 1	28	34.4 (3.1)	33.4 (3.7)	0.034
Intracranial 2	28	56.6 (3.3)	54.8 (4.3)	N/S

KEY:

Inner orbit=distance between inner orbital margins

Outer orbit=distance between outer orbital margins.

Intracranial measurement 1=distance from frontal calvarium to cavum septum pellucidum

Intracranial measurement 2=distance from frontal cranium to posterior border of thalami

NS= not statistically significant

All measurements in mm

Results 5: Examination of babies at birth and one year.

An analysis of neonatal outcomes and infants at one year of age showed that there were significant differences in the results obtained.

5.1. Examination of babies at birth:

Fifty-seven (57) babies of the control group were examined by the dysmorphologist at birth, or before one month of age if examination at birth was not possible. In the subject group, 59 babies were examined at, or close to birth. When comparing the finding of FAS diagnosed at birth in the subject and control group, there was strong statistical significance between the incidences of FAS in the two groups ($p = 0.017$).

In the subject group, 62.7% (37/59) of babies were considered normal. However 11.9% (7/59) of babies were considered to have FAS at birth, and a further 25.4% (15/59) were deferred for a later decision due to uncertainty of the diagnosis.

When examining the babies of the control group, there were no babies who were diagnosed as FAS at birth. Ninety-three percent (93.0%) (i.e.53/57) of babies were considered normal, and had no features of FAS. However, 7.0% (4/57) of babies were deferred for later re-assessment. In these "deferred" babies, the dysmorphologist could not be certain of the diagnosis of FAS, as there were some features suggestive of FAS, but a confident diagnosis could not be made at this time.

5.2. Examination of babies at one year of age or older:

The babies were examined as close to one year of age as possible. Results of this examination are represented in Table VIII and in figure 10.

In the subject group a total of 54 babies were examined at one year of age. Of the total 59 babies seen at birth, there were 5 babies not included in this arm of the study. Of these, two babies were lost to follow-up, and one baby, who had been diagnosed as FAS at birth, died in the neonatal period from complications relating to preterm delivery. A further two babies died before one year of age.

Of the 54 examined at one year, 72.0% (39/54) were considered not to have FAS. Eleven percent (6/54) of these babies had FAS diagnosed at this visit, and a further 16.7% (9/54) were deferred until the child was older, as a confident decision could not be made at this age. If one includes the 3 babies diagnosed as FAS who died before 1 year of age, 15% (9 of the total 60) of the babies born to the subject mothers were found to have FAS.

In the control group, 57 babies were examined. All babies in the control group who were seen at birth were examined again at one year of age, or as close to one year as possible. There were no defaulters.

Ninety-six (96.0) percent of the babies in this group were considered not to have FAS at birth, while 3.6% were deferred because a confident decision could not be made. No babies were diagnosed with FAS in the control group.

TABLE VIII: Results of examination of baby by dysmorphologist at birth and one year.

AGE OF BABY WHEN EXAMINED	FAS diagnosed at BIRTH	Number	%	FAS diagnosed at ONE YEAR OF AGE	Number	%
CONTROLS	**Yes**	**0**	**0%**	**Yes**	**0**	**0%**
	Deferred	**4**	**7.0%**	**Deferred**	**2**	**3.6%**
	No	**53**	**93.0%**	**No**	**55**	**96.5%**
	Total	**57**		**Total**	**57**	
SUBJECTS	**Yes**	**7**	**11.9%**	**Yes**	**6**	**11.1%**
	Deferred	**15**	**25.4%**	**Deferred**	**9**	**16.7%**
	No	**37**	**62.7%**	**No**	**39**	**72.2%**
	Total	**59**		**Total**	**54**	

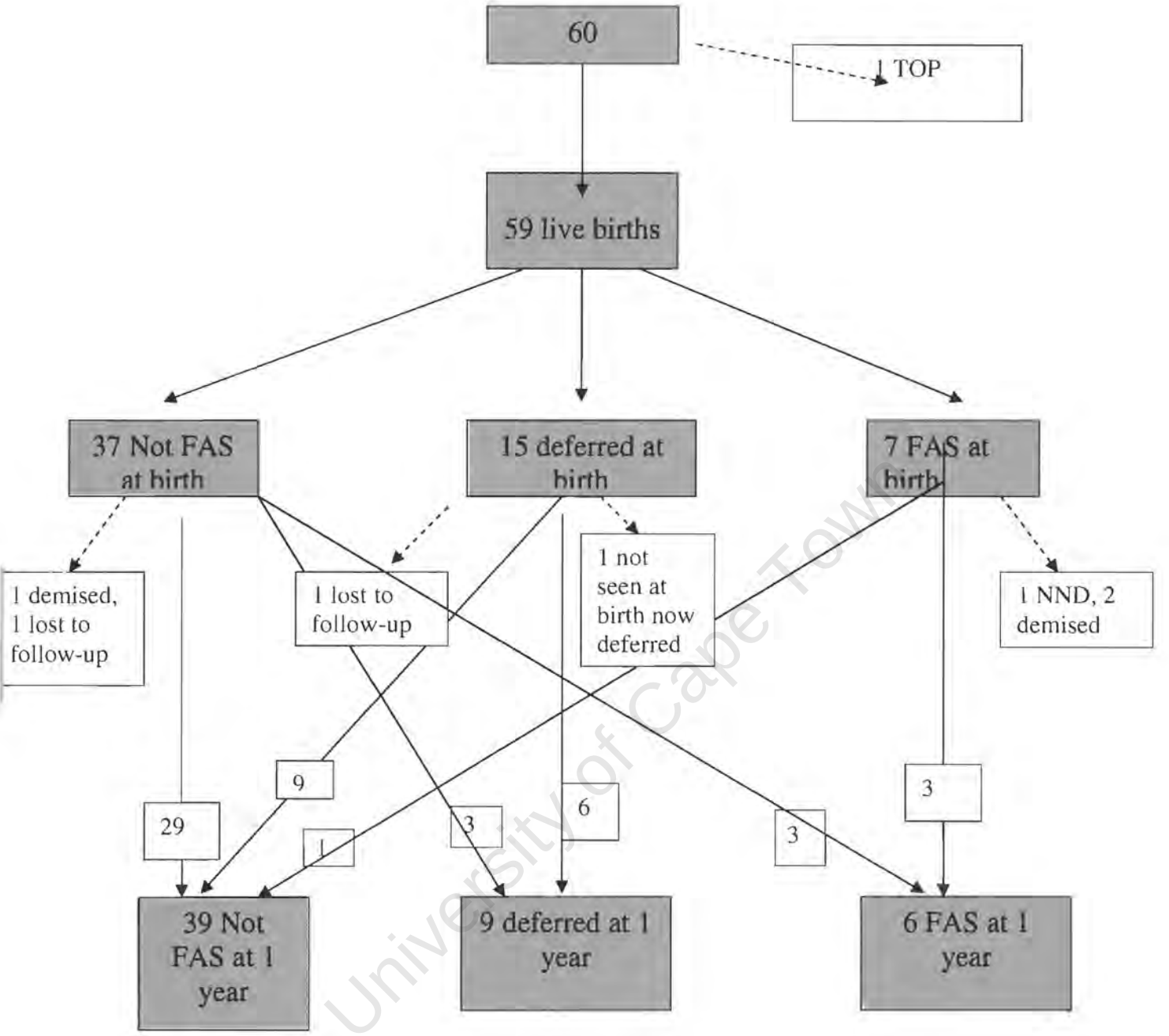


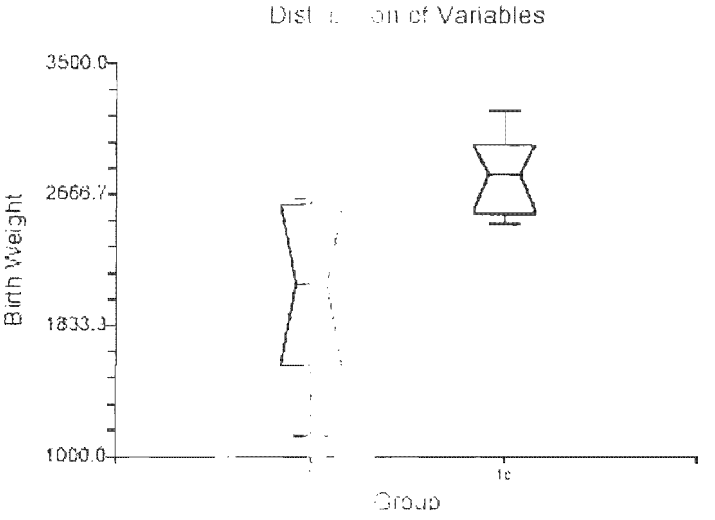
Figure 10: Examination of babies born to subject mothers at one year of age.

Results 6: Subjects who produced a baby with FAS vs. their controls.

Once the study was completed and the babies had been examined at birth and one year, a comparison was made between those babies found to have FAS, and their matched controls. The first analysis was done on the neonatal outcomes of those babies who were diagnosed as FAS infants by the dysmorphologist. There were 9 infants in this group, 6 alive at one year of age. When compared to their matched controls, there were differences in the incidence of preterm delivery (higher in the FAS babies), the incidence of IUGR (higher in the FAS babies), and the incidence of oligohydramnios prenatally (higher in the FAS babies). As a consequence of the preterm delivery and IUGR, the birth weight was also less in the FAS babies. The difference in congenital abnormalities was not statistically significant. These findings are represented in Table IX.

Table IX: Pregnancy outcome in mothers producing an infant with FAS vs. controls.

Outcome	FAS n=9	Controls n=9	P value
Preterm delivery	55.6% (5/9)	11.1% (1/9)	0.057
Congenital abnormality	11% (1/9)	0%	0.052 N/S
IUGR	44% (4/9)	0%	0.033
Oligohydramnios	55% (5/9)	0%	0.010
Birth weight (grams)	2068.9 (S.D.565.9)	2782.2 (S.D.250.5)	0.003



Key: Group 1 =FAS babies

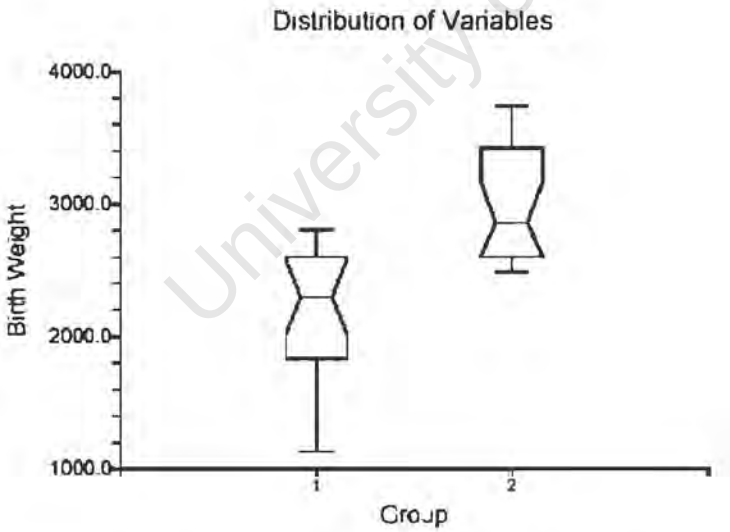
Group 1c=controls

Figure 11: Comparison of birth weight of FAS babies and controls.

Due to the small number of babies who were diagnosed with FAS, an analysis was also done to include those babies who were exposed to alcohol in utero, and who were placed into the "deferred" group because the dysmorphologist could not make a confident decision. These babies had some features suggestive of FAS, but the diagnosis of FAS could not be confidently made. As the dysmorphologist did not know the drinking histories of the mothers, they would defer the decision until the infant was older, and would refer the infant for further assessment and follow up. There were 8 infants deferred at one year of age from the subject mothers. These were then added to the group of 9 infants who were diagnosed as FAS, making a total of 17 infants. The neonatal outcomes of these infants were then compared. Once again the FAS infants had a higher incidence of preterm delivery, IUGR, oligohydramnios and a lower birth weight. These findings are represented in Table X. Difference in birth weight between the two groups is represented in Figure 12.

Table X: Pregnancy outcome in those mothers producing a confirmed and a possible FAS infant vs. controls.

Outcome	FAS & possible FAS (n=17)	Controls (n=17)	P value
Preterm delivery	52.9% (9/17)	5.9% (1/17)	0.003
Congenital abnormality	17.6% (3/17)	5.9% (1/17)	0.349 N/S
IUGR	35.3% (6/17)	0%	0.0091
Oligohydramnios	47% (8/17)	6% (1/17)	0.009
Birth weight (grams)	2211.7 (S.D. 484.1)	3012.9 (S.D. 451.5)	0.0001



Key: Group 1=FAS babies plus babies deferred at one year

Group 2=controls

Figure 12: Comparison of birth weights in FAS and deferred babies, and their controls.

An analysis was also done on the growth measurement data of the two groups (FAS plus possible FAS vs. controls). There were 17 women in the subject and control group. There were an insufficient number of women in the subject group who underwent an ultrasound examination at 24 weeks gestation due to the fact that they booked late in the pregnancy. For this reason, growth data was not assessed at this gestation.

Growth parameters were analysed at 28 weeks and 36 weeks. Only measurements at the exact gestation were analysed (e.g.27 or 29 weeks was not accepted for the 28 week gestation analysis). Only 6 of the 17 subject group women were seen at 36 weeks, as over half (52.9%) had delivered before this gestation. There were significant differences between the two groups at 36 weeks gestation with respect to the BPD and the AC measurements. The BPD was smaller in the subject group ($p=0.002$) at 36 weeks. The AC was also smaller at 36 weeks in the FAS plus possible FAS group ($p=0.007$). There were no differences in the measurements of the BPD, HC, AC or FL at 28 weeks, or the HC or FL at 36 weeks. These results are represented in Table XII.

TABLE XII :Growth of fetuses with FAS or possible FAS vs. their controls.

28 weeks	**Subjects n=9**	**Controls n=10**	**P value**
BPD	70 (variance 3.7)	71 (variance 9.3)	0.20
HC	260.7 (variance 52.2)	264.4 (variance 68.5)	0.32
AC	233 (variance 131.6)	264.4 (variance 68.5)	-
FL	52.8 (variance 15.3)	51.9 (variance 2.98)	-
36 weeks	**Subjects n=6**	**Controls n=9**	**P value**
BPD	83.2 (var 2.56)	87.4 (var 7.02)	0.002
HC	308.6 (var 213.8)	317.6 (var 64.7)	0.25
AC	297.1 (var 2.2)	316.4 (var 213.7)	0.007
FL	65.6 (var 1.46)	67.1 (var 6.36)	0.16

Case report: Woman AR9.

This woman (identified as AR9) was recruited at 19 weeks gestation, when she attended the antenatal clinic for the first time in the pregnancy. Her case report is selected here, as she delivered a stillborn baby with features of FAS.

History:

AR9 was a 33-year-old married woman, who lived on a farm near the clinic. Both she and her husband were farm labourers, earning a combined income of R146 per week. She had limited education (grade 3), and was therefore barely literate.

Obstetric history revealed that she was gravida 6, para 5. All five previous children were reportedly normal, and all pregnancies had been uneventful and had culminated in normal vaginal deliveries.

Her past medical history indicated that she had had numerous skin grafts for a burn she sustained to her abdomen, but was otherwise non-contributory. She had a history of "clubfeet" in her family, but none of her offspring were affected. She smoked, using loose tobacco only, which she smoked as cigarettes, at times using up to two 100g packets per day.

Her alcohol history revealed that she had started consumption at the age of 17 years, and consumed alcohol (beer and wine) only on Fridays and Saturdays. She usually drank 750 ml of beer and 2 litres of wine every Friday and every Saturday of the month. She stopped drinking wine and drank only beer after she discovered she was pregnant, which was at approximately 10 weeks gestation. She believed that wine was more harmful to the baby than beer.

She denied any substance or drug abuse.

Ultrasound examinations:

She attended for ultrasound examinations on 3 occasions, at 19 weeks, 22 weeks and 28 weeks gestation.

Table XI: Measurements taken at each visit.

Date	02/09/1999	30/09/1999	11/11/1999
Gestation	19 weeks	22 weeks	28 weeks
Presentation	Cephalic	Cephalic	Breech
Fetal heart	Present	Present	Present
BPD (mm)	44	56	73
HC (mm)	162	211	275
AC (mm)	135	195	255
FL (mm)	28	39	53
Liquor AFI	15	21	22
Placenta	Normal	Normal	Normal

Cerebellum mm	20	25	33
Lateral ventricles	6:17	9:28	9:36
Humerus (mm)	28	36	48
Foot (mm)	25	41	52
Interocular Orbit 1(mm): Orbit 2(mm):	11 31	14 37	Not possible Not possible
Uterine artery	No notch	No notch	No notch
Umbilical artery R.I.	0.52	0.62	0.51
Middle cerebral artery R.I.	0.72	0.72	0.75
Comments	Small face and mandible noted, no fetal abnormalities	(No comments)	Kidneys appear prominent, but normal morphology.

Delivery and outcome:

The woman unfortunately went into preterm labour, and delivered a stillborn infant at home on 30/11/1999 at 31 weeks gestation. The fetus weighed 1830g. The woman consented to a post mortem examination of the fetus.

Complete post mortem report is attached as appendix 10. The major findings were that of a preterm male, of gestational age approximately 33 weeks according to foot length, with evidence of fetal alcohol syndrome. There was no microcephaly, but evidence of delayed cerebral maturation. There was no IUGR. There was incomplete lobation of the right lung, a thymic node in the neck, and optic coloboma. The fetus had short limbs for gestation. Post mortem photographs are attached.

Discussion

Although the pathologist who performed the post mortem considered the facies of this fetus to be typical of FAS, there were some features that were not typical of FAS (e.g. presense of orbital coloboma and absense of IUGR.).This case report has been included mainly to illustrate to the reader how the study was performed with regard to recruitment, frequency of visits, ultrasound reports at each visit etc.,and cannot be considered a "typical" FAS baby.

Discussion.

Our study clearly showed a significant effect of heavy drinking on the onset of labour, although there is conflicting opinion in the literature regarding the effect of alcohol on preterm labour. Almost 30% of the women in our subject group delivered before 37 completed weeks gestation. Gestational age in this study was taken from menstrual dates if they correlated with ultrasound measurements, or by ultrasound messurements if menstrual dates were unknown or incorrect. All women were seen before 26 weeks gestation, at which time an accurate gestational age can be ascertained from ultrasound parameters (Fleischer pub 1991). This high incidence of preterm delivery may be due to the fact that we studied heavy drinkers, whereas many other authors recruited patients with mild or moderate consumption. Thus, the dangers of drinking in pregnancy do not relate only to the incidence of congenital abnormalities and neuro-developmental delay, but also to the risk of delivering a preterm infant, with all the concomitant neonatal complications. Clinicians need to counsel pregnant women about these risks.

Both prenatal and postnatal growth restriction are frequently diagnosed in infants with FAS. (McDonald and Armstrong 1992). Some authors found linear growth to be more affected than weight, while others found there to be symmetrical IUGR. (Jones et al 1988). There are however many studies suggesting that alcohol had no effect on birth weight, and that the effects of smaller birth weight were due to the influence of smoking or preterm labour. (Gershoni-Baruch and Nelson 1988, Viljoen et al 2003). Abel and Hannigan found the effect of smoking is indeed three times greater than the effect of alcohol. (Godel et al 1992) They also reviewed the literature up until 1994, and concluded that the differences in the literature were due to the inclusion criteria for the amount of alcohol consumed. A threshold of an average of two or more drinks a day was present, above which a decrease in birth weight was noted to be linear. This threshold seemed to be only present among smokers. At lower consumption levels, the incidence in decreased birth weight was lessened for both smokers and non-smokers.

More recent studies (Abel and Hannigan 1995) could demonstrate no association between moderate drinking and IUGR, and others confirmed that alcohol had a less significant effect on birth weight than other risk factors, such as smoking, mother's height and body mass index and ethnic factors. (Yang et al 2001) We found it difficult to find women who drank heavily but did not smoke, suggesting that this group may have had other factors (viz. smoking) influencing the size of the fetus. The birth weight of the fetuses of the drinking mothers was lower than those of the control group. The effect of preterm delivery on this result should, however, be considered. Twenty-nine percent (29%) of the babies in this group were delivered before 37 completed weeks of gestation, compared to only 8% of the controls, which would result in the mean birth weight being lower in the subject group. Once we excluded the effect of smoking, however, the subject group no longer had significantly smaller infants at birth, suggesting that smoking, rather than alcohol, may have been the cause. Our study therefore demonstrated that the effect of alcohol consumption on IUGR and low birth weight was not significant when the effect of smoking was excluded, agreeing with other authors as mentioned.

While poor nutritional status of the mother may influence the birth weight of her baby, we found there was no significant difference in the Body Mass Index (B.M.I.) of the women in our 2 study groups. However, B.M.I may not be a reliable indication of the mother's nutritional status in pregnancy, especially as the B.M.I. was calculated using the weight recorded at the booking visit, not the mother's weight before the pregnancy commenced. For some women in the study this weight was recorded as late as 25 weeks gestation. There was also a large range of recorded B.M.I's; in the subject group the lowest was 16.1 and the highest 33.7. May et al (2004) found that the South African women of mixed ancestry that they studied were smaller when compared to women in the U.S.

They found the women who produced a FAS baby in the U.S. had a mean B.M.I. of 29.7,whereas their South African counterparts had a B.M.I. of 24.9. They postulated that women of smaller B.M.I. might be at greater risk due to their size, as they have less body mass to metabolise the alcohol they consumed. Similarly, our women with a B.M.I of 25.9 would be at a higher risk than women with a greater body mass.

No significant differences were found in the incidence of congenital abnormalities in the two groups. This is partly due to the natural low incidence of congenital abnormalities in the population (Holmes 1976), and partly due to the small numbers of women sampled in this study. A larger, multicentered study involving a larger sample would be more useful to investigate an association between alcohol intake and congenital abnormalities. For the purposes of this study, however, we felt that this would require more than one research assistant and ultrasonologist, and the advantages of good patient compliance, concise data collection, and neonatal assessment from a small experienced team would be lost.

Of interest, none of the fetuses in our study were found to have echodense (or hyper echoic) bowel. MacGregor et al (1995) followed up 45 cases in the U.S. with an ultrasonographic diagnosis of isolated hyperechoic bowel. They found that 76% of these babies had no detectable abnormalities at birth, but one fetus of the 45 was diagnosed as FAS after birth. Although our patient numbers are small, none of our babies later diagnosed with FAS had this finding prenatally.

It was interesting to note that one of our subjects delivered a baby with Down syndrome. Unfortunately, this woman did not book at the antenatal clinic until she was 24 weeks pregnant, and therefore could not be offered early screening. She was first seen for an ultrasound examination at 24 weeks gestation. At this advanced gestation, fetal karyotyping was not offered to the woman, as is routine

medical practice in our local setting. Although the advanced maternal age of the woman (she was 39 years old) placed her at increased risk for Down syndrome, we wondered whether there was any association in the literature between maternal alcohol consumption and Down syndrome. One paper was found that evaluated five babies that had FAS associated with Trisomy 21 (Bingol et al 1987). These babies phenotypically had features of both Trisomy 21 and FAS, and the authors also noted that all these babies had mothers who were chronic alcoholics, and maternal grandmothers who were also alcoholics. They suggested that there might be an increased incidence of Trisomy 21 in children of second-generation mothers. However, Torfs et al (2000) conducted a comparison between mothers who produced a fetus with Down syndrome and those who produced fetuses with no birth defects, and examined the effect of environmental factors, such as smoking, caffeine intake, and alcohol abuse. They found that high alcohol intake in the first month of pregnancy was associated with a reduced risk for Down syndrome.

It was interesting to note that the mothers of the fetuses that were diagnosed as FAS at birth were all over 23 years of age, with 3 of the 8 mothers being 30 years of age or older at the time of delivery. Although this is a small group of mothers, this finding may support other authors who have shown that older mothers are more likely to produce a baby with FAS (Jacobson et al 1996, May et al 2004).

The incidence of fetal distress was lower in the subject (3.4%) than in the controls (8.5%), but this was not statistically significant (p=0.166). This is not surprising, as alcohol exposure would more likely cause a chronic disorder in the neonate rather than an acute intrapartum event such as an abnormal heartbeat.

Doppler studies of these women did not demonstrate any interesting differences between the two groups of women. Doppler flow graphs constructed did not differ from those published by other authors. Middle cerebral artery resistance index was found to be 1.00 in some fetuses, as has been shown by other authors (Kurmanavicius et al 1997).

The typical facial features of a child with fetal alcohol syndrome are now well recognized by paediatricians and dysmorphologists. They include short palpebral fissures with epicanthic folds, micropthalmia, midfacial hypoplasia, micrognathia, and a long, smooth upper lip. (Viljoen 1991, Danis et al 1991). However, there are very few studies done on the fetus. Indeed, the diagnosis of fetal alcohol syndrome is not made before birth, but is made postnatally when the diagnosis is suspected on clinical grounds. There are many different features that raise suspicion of FAS; these range from the typical facial features, to growth restriction, neurodevelopmental delays, other physical abnormalities, and central nervous dysfunction. (Gershoni-Baruch and Nelson 1988, Jones et al 1973, American academy of Paediatrics 2000). Once a history of maternal alcohol consumption during pregnancy is elicited, the diagnosis of FAS can be made. Although the diagnosis of FAS has not been made prenatally, it would be interesting to ascertain whether there are any ultrasound features or "markers" that would raise suspicion that the fetus was adversely affected by maternal alcohol usage.

In a study conducted by Wass et al (2001), the frontal lobe of the fetal brain was measured, looking at differences between fetuses of mothers who drank alcohol during pregnancy and those who did not. In contrast to our study, these authors included women who consumed different amounts of alcohol while pregnant, whereas our study looked specifically at heavy drinkers. These authors found that the frontal lobe appeared to be disproportionately small in fetuses exposed to alcohol, compared to a global effect on the brain, i.e. the fetuses were not microcephalic. Other authors have also concluded that the frontal lobe may be the most severely affected portion of the brain in microcephaly. Persutte (Persutte 1998) commented that anatomic shortening of the frontal lobe precluded microcephaly, and that careful measurement of the frontal lobe may be a tool for the identification of fetuses at risk for microcephaly. Another group (Pilu et al 1998) performed Doppler flow studies on the brains of fetuses with microcephaly and found decreased flow to the undersized cerebral hemispheres, and poor flow in the anterior cerebral arteries specifically.

Our study did not confirm the findings of Wass et al. In fact the frontal lobe was marginally *larger* in the fetuses exposed to alcohol in utero in our study. These findings were not significant until the third trimester. There was no significant difference at 24 weeks gestation, but differences reached statistical significance when the fetus was seen at 28 weeks. We were also surprised to find that the fetuses in the subject group had *larger* head circumferences at 24 weeks; even once the effect of smoking was excluded. By 36 weeks, however, the head circumferences of the fetuses in the subject group were smaller than the control group, as one would expect. It may be possible that larger frontal lobes may be consistent with wider interorbital diameter, as was present in the fetuses that were exposed to alcohol. The larger frontal lobes may also be influenced by the fact that the head circumference was larger in the subject fetuses at this gestation. Both this study, with 26 subjects and the study by Wass, with 70 subjects, examined small numbers of patients. Larger studies involving bigger patient numbers would confirm or refute these findings.

Once the study was completed, we analysed the fetuses born to the subject group mothers who were diagnosed as having FAS, or having possible FAS. We compared these babies to their matched controls. In this group there were striking differences in the fetal measurements at 36 weeks gestation. The AC and BPD measurements were both significantly smaller in the babies with definite or possible FAS. It would be interesting to conduct this study on a much larger scale, perhaps involving different centres and ultrasonologists, to obtain a larger number of babies who were diagnosed with FAS at birth. These babies could then be retrospectively analysed to confirm or refute these growth disturbances. Although this study had small patient numbers, it would seem prudent in clinical practice to have a high index of suspicion for IUGR in women who give a history of alcohol use in pregnancy.

To our knowledge there have been no other studies published that examine the

fetal face prenatally to identify changes associated with alcohol usage by the mother. In this study we hoped to identify some of the facial features known to be present in the baby with FAS in the fetal face. We were particularly interested in the length from upper lip to nose, which we hoped would be longer in the fetuses exposed to alcohol, as is seen in the infant with FAS. However, attempts to establish if the fetal upper lip was longer in fetuses exposed to alcohol were unsuccessful for technical reasons. In early gestations the area was very small and repeatable measurements could not be obtained. In later gestations (the 36 week visit) the position of the fetus and the relative lack of amniotic fluid made visualisation of this part of the face difficult. With the advent of new technology in the form of 3D ultrasound , the examination of the fetal face and upper lip may be possible.

This study showed that the facial features of hypertelorism and small orbits, which are seen on the child with FAS, might also be seen in the fetus as early as 24 weeks. These findings support the original hypothesis of this study, namely that ultrasound markers may be present that would lead the clinician to suspect that the fetus had FAS before delivery. While these findings are exciting, we feel that larger numbers of women need to be studied to refine these measurements and to establish sensitivity of these tests. While a suspicion of FAS can be made when there are widely spaced orbits, we are far from being able to make a definitive diagnosis pre-natally.

As with all clinical studies, there were several factors that need to be considered when analysing the results obtained.

The first limitation was the small number of women recruited for the study. We decided to limit the numbers to allow the same research assistant and ultrasonologist to examine all the women recruited. This was a time-consuming study, as each woman required lengthy counselling and interviews, and attended ultrasound examinations at several visits during the pregnancy. Questionnaires

were deliberately thorough and repetitive in nature. The research assistant interviewed the woman every time she attended the hospital for the ultrasound examination to ascertain whether the woman was still drinking alcohol, and to encourage her to abstain.

Limiting the study to small numbers had two main benefits. Firstly it would ensure that there was no inter-observer bias, as each ultrasound measurement would be compared to a measurement taken by the same examiner at an earlier gestational age, using the same ultrasound machine. Secondly, it allowed the research assistant to conduct all the interviews herself ,thereby establishing a rapport with the woman, and increasing the likelihood that the woman would continue to attend appointments, and give an accurate and honest account of her drinking habits.

The disadvantages of limiting numbers were that statistical significance was not achieved with some findings due to the small number of women analysed. For example,the results of the larger abdominal circumference of the fetuses of the subject group was unexpected and difficult to explain, and may be due to the sample size being too small for statistical significance. Statistical significance was however reached on most of the variables measured, even with such small sample sizes. Initially, we planned to recruit a slightly larger sample of women to allow for those women who decided not to participate, or who did not comply with the appointments made for their ultrasound examinations, but we were pleased to find that the attrition rate was very low, the women were reliable in keeping their scheduled appointments, and they made themselves available for follow-up examinations.

As with all research into alcohol and substance abuse, there are some problems that arise. These problems centre on ethical issues, and the reliability of the drinking history given by the subject. One of the biggest challenges of this study was to ensure that the woman's care was not compromised by her participation in the study. We needed to ensure that each woman was extensively counselled at

several intervals in the study about the dangers of alcohol to her unborn child. We realised that this may result in the woman in fact curtailing or even stopping her alcohol intake during the study period. This decrease in her consumption may have resulted in the findings of our study not being as significant as we had anticipated, as the women recruited as "heavy drinkers" may have in fact consumed less alcohol after they had been recruited into the study. This so-called Hawthorne phenomenon (Campbell et al 1995), where the outcome studied may be affected by the mere fact that a study is being conducted, is an unavoidable part of alcohol-related research. Rosett studied a small group of mothers who consumed large amounts of alcohol while pregnant, and found that those who reduced their alcohol consumption before the third trimester showed less growth restriction than those who continued to drink heavily (Rosett at al 1980). We accepted this limitation before commencing the study as we felt that it would be the only way the study could be conducted in an ethical and responsible way.

In fact, only 29% of our subject group did stop drinking during the pregnancy, despite frequent and extensive advice given to them. Even though this may have played a role in the final outcome, most of these women only stopped drinking late into the second trimester, by which time the alcohol exposure may have already affected the developing fetus. Women in the subject group were all heavy drinkers throughout the first trimester, the crucial time for organogenesis. Almost half of them consumed more than 20 drinks per week. Nearly all the women consumed beer. The beer they consumed is home-brewed, and sold in 750ml glass bottles. The exact alcohol content of this beer is unknown, and would probably vary according to the supplier. For the purposes of this study, we considered this beer to have the same alcohol content as commercially produced beer i.e. 750 ml was equivalent to 2.5 drinks.

Another limitation was that this study relied on the history given to us by the women. Other authors have noted this inherent problem of alcohol-related research. Lundsberg et al (1997) commented that under-reporting of alcohol use was a significant obstacle to their data collection, but with biochemical markers of

alcohol exposure having limited use, they still felt that interviewing remained the mainstay of data collection on alcohol usage in pregnant women. Wherever possible in our study, collateral information was obtained, usually from the nursing staff that attended the patients at the antenatal clinics. However, in most cases we were reliant entirely on the honesty of the women. Overall we felt that the women were truthful concerning their alcohol intake, possibly due to their good rapport with the research assistant. There were, however, two women who informed us later in the study period that they had not been truthful about the timing or amount of alcohol consumed. These women admitted that they had consumed larger amounts of alcohol than they had reported at the recruitment interview, and therefore no longer fulfilled the criteria for the control group into which they had been recruited. We elected to exclude them from the study before entering their data into the study spread sheets.

Our main concern before commencing this study was that it would be difficult to identify subjects who admitted to heavy alcohol consumption during pregnancy, and that they would not be willing to participate in the study, and attend regularly. We were surprised to find that this was not the case.

A strength of this study was the fact that two groups of women were carefully recruited in early pregnancy, and the women in each group were matched woman-to-woman with respect to socio-economic status, ethnic group, maternal weight and gestational age at booking, as well as for smoking habits. Also, due to the fact that the research assistant visited the antenatal clinic frequently, nursing and support staff who were familiar with the study aided data collection.

Another strength of the study was the fact that the ultrasonologist and dysmorphologist were blinded to the subject or control status of the women, and were therefore unbiased in their findings.

It became apparent during the study that the incidence of preterm delivery was higher in the subject group. This resulted in a further limitation, namely that a number of the subject group delivered before they reached 36 weeks gestation, which was the gestational age at which the final ultrasound was scheduled in the pregnancy. Thus abnormal findings that may have been significant in later gestations, particularly growth disturbances and depletion in amniotic fluid levels, were not observed, as the women did not attend this final prenatal visit.

It is interesting to note the pattern of drinking in the population we studied. Almost all of our subjects (96.6%) drank in a "binge" pattern, consuming little or no alcohol during the week, but drinking heavily on Friday and Saturdays. This confirms the findings of the same population group in South Africa reported in early 2004 (May et al 2004). They studied women who had given birth to a baby with FAS. These mothers were interviewed on a large range of maternal risk factors. It was found that 94.9% of these mothers drank over weekends only. It is possible that the high incidence of FAS found in our study could be related to this drinking pattern, as it is known that heavy, sporadic drinking is a prime risk factor (Viljoen et al 2002,May et al 2004.). Even though we found a high incidence of FAS in our drinking group, our study sample was small. With 9 babies diagnosed with FAS in our subject group, and 8 still deferred for a later decision, it did not seem prudent to compare the demographics of mothers who delivered FAS babies with the mothers of the normal babies, as the numbers would be too small.

The diagnosis of FAS can be difficult to make in the newborn baby. This is partly due to the fact that the neurodevelopmental, cognitive and behavioural problems that form part of the diagnosis of FAS are impossible to assess at birth. Also, many women underreport their alcohol consumption (Ernhart et al, 1988). Clinicians often believe that alcohol exposure is more of a problem amongst minority groups, and therefore under diagnose FAS in other ethnic groups (Stoler and Holmes 2004). Physicians may also be unfamiliar with the characteristic features if FAS, and are unprepared to deal with FAS and its implications.

Despite the fact that the newborns and one-year old babies in this study were examined by dysmorphologists with a particular interest and experience in the diagnosis of FAS, there were still a large number of cases in which the definitive diagnosis of FAS could not be made. Dysmorphologists used a "gestalt " method of diagnosis, relying on a checklist of abnormalities, and allowing the examiner to decide for himself whether the FAS phenotype was present. In cases where a definite diagnosis could not be made, the decision was deferred until a later date, and the attending clinician was advised to correlate the findings with the alcohol history given by the mother (the dysmorphologist was not given this history, as he was blinded to allow impartiality). If one postulates that the babies in the subject group, whose diagnosis was deferred again at one year, would have a high probability of being affected by FAS, it would mean that in total 18 of 61 patients, or 29.5%, of mothers who drank heavily in pregnancy produced a baby with FAS.

Recently, some authors have attempted to make the diagnosis of FAS more accurate and precise, and base it on a specific diagnostic code, rather than the "gestalt" method of diagnosis used in this study. Astley and Clarren (2001) demonstrated that a "4-digit diagnostic code" was more precise, and allowed less individual interpretation by the examiner. They used the four key diagnostic criteria as 1) growth deficiency, 2) the FAS facial phenotype, 3) brain dysfunction and 4) gestational alcohol exposure. These authors compared the "gestalt" method of diagnosis with their method, and found that the facial phenotype of those receiving a gestalt diagnosis of FAS was highly variable, but those diagnosed using their 4-digit code showed less variability. They propose that their method, or a similar method, may allow examiners in the future to have a standardised code for the diagnosis of FAS. At the time of this study, no such method has gained universal acceptance or recognition.

Another important diagnostic question relevant to our study was whether the FAS facial phenotype diminished with age. In a study of 54 patients, Spohr and Steinhausen (1987) reported a reduction in cranio-facial features characteristic of

FAS (epicanthic folds, blepharophimosis, ptosis, short, upturned nose, high arched or cleft palate, and retrognathia) on follow-up examination .The change in the appearance of the facial phenotype with age has been confirmed by other authors (Majewski, 1993; Streissguth et al, 1985). This phenomenon may have also influenced our study findings, as the features of FAS are difficult to diagnose at birth, and at one year of age. Facial features may be more obvious when the child is older, and a repeat examination of these infants at 3-4 years of age would be useful.

This study did not attempt to ascertain if there was a "safe" level of alcohol consumption in pregnancy, as it recruited heavy drinkers only, but the findings of this study confirm the risks to the fetus of preterm labour and FAS at birth. A recent study conducted in the U.S followed up mothers who had previously given birth to a child with FAS, and found that half of them were at risk for producing further children damaged by prenatal alcohol exposure. (Astley et al 2000). These mothers were still in the reproductive age and were either actively drinking or at risk of drinking. The investigators felt strongly about the opportunity to provide these mothers with support, and primary prevention intervention. Patients who consume excessive amounts of alcohol should be offered increased fetal surveillance with serial ultrasound examinations to measure growth and decide on timing of delivery. Neonatologists should be informed of the possible diagnosis of FAS, so the baby could be referred to an expert dysmorphologist for an early diagnosis of the syndrome.

Conclusions.

This study compared the growth, development and neonatal outcomes of fetuses whose mothers drank heavily while pregnant to those whose mothers drank lightly, or abstained.

We found that the incidence of preterm delivery was higher in the mothers who consumed alcohol, when compared to the control group.

The fetuses delivered to mothers who drank heavily also had lower birth weights, and were more likely to have intra-uterine growth restriction.

The fetuses exposed to alcohol had larger head circumferences at 24 weeks gestation when compared to fetuses that were not exposed to alcohol in utero, but by 36 weeks gestation the head circumferences were significantly smaller than those fetuses not exposed to alcohol.

There were some differences in the facies and intracranial structures of the fetuses of mothers who consumed alcohol while pregnant. Fetuses exposed to alcohol had more widely spaced orbits at 24 weeks gestation.

The fetal frontal lobe was marginally larger in fetuses exposed to alcohol at 24 weeks gestation, but this was not significant at later gestations.

Twelve percent of babies born to mothers who drank heavily while pregnant were diagnosed as FAS at birth. By one year of age 14.7% were diagnosed as FAS, and a further 16.7% had some features suggestive of FAS.

There was no difference between the drinking and non-drinking mothers with respect to the incidence of fetal distress, Apgar scores at birth and 5 minutes, the presence of congenital anomalies, or Doppler flow studies of the maternal uterine arteries or umbilical arteries.

Almost one-third (29%) of mothers who drank heavily while pregnant stopped drinking after they received counselling about the dangers of alcohol to the unborn child.

Ethical and moral issues complicate alcohol-related research, and may impact on the findings of the research.

Women in this population group followed a pattern of "binge-drinking" which is known to be more risky to the developing fetus than a steady but sustained alcohol consumption.

Recommendations.

While the findings in this study were significant, a larger number of women need to be studied to confirm the results found. Although it is ideal to have one ultrasonologist examine all fetuses, thus eliminating inter-observer bias, using more ultrasonologists would allow larger numbers to be studied. It would not have been possible to conduct this study retrospectively with bigger numbers, because measurements of the fetus need to be carefully timed for correct gestational aging, and eliciting an adequate history of alcohol consumption would be difficult after a long period of time had passed.

The finding of possible prenatal ultrasound markers for FAS (widely spaced orbits, smaller orbits, and larger frontal lobes) are exciting, and also needs to be confirmed studying a larger sample of the population. If these findings were confirmed, it would enable the clinician to identify babies at high risk of FAS before birth, and allow early intervention and support of the mother and child, which has been shown to improve the long-term outcome and functioning of FAS individuals.

Efforts to educate farm-owners about the dangers of alcohol and pregnancy should continue, and attempts to outlaw the practice of giving farm labourers alcohol as part of their pay package should persist. Although this will not solve the problem in the short term, a slow but gradual change in the habits and lifestyles of farm workers could eventually allow the incidence of FAS in these areas to decline.

This study confirms the risks of drinking alcohol during pregnancy found by many authors, namely, the increased risk of preterm labour and intrauterine growth restriction, and the diagnosis of FAS in the neonate. Women who

consume large amounts of alcohol should be offered a detailed anatomical fetal assessment at 22 weeks to exclude fetal abnormalities, and increased fetal surveillance with serial ultrasound examinations to measure growth.. Neonatologists should be informed of the possible diagnosis of FAS in order for the baby to be referred to an expert dysmorphologist for an early diagnosis of the syndrome. Those fetuses that were found to have features suggestive of FAS in utero found in this study, i.e. widely spaced orbits, smaller orbits. and a larger frontal lobe are at particularly high risk. If a definitive diagnosis cannot be made at birth, the baby should be reassessed at one year of age by a dysmorphologist experienced in the field. Careful neurodevelopment assessment should be done, and the progress of the infant should be followed until school-going age and beyond.

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APPENDIX 1.

PATIENT ID	Alcohol consumed	Amount per Week	Binge pattern?	Reduced amount when pregnant?	Stopped drinking when discovered pregnant?	Gestatio when stopped?
VL2	beer	24	yes	No	no	-
RS4	beer	24	yes	No	no	-
AB6	beer and whisky	15 beer,2 whisky	yes	Yes,stopped whisky	no	-
RJ7	beer	15	yes	Yes	yes	20 weeks
MP8	beer	10	yes	Yes	yes	18 weeks
AR9	Beer and wine	15	yes	Yes, 10/week	no	-
LR13	Beer and cider	10	yes	Yes,reduced amount,but occ binge	no	-
AS15	beer	18	yes	no	no	-
NC16	Beer and brandy	13	yes	no	no	-
RW17	Beer and brandy	10	yes	Yes,5/week,occ binge	no	-
EV18	beer	24	yes	no	no	-
KK19	Beer and whisky	20	yes	no	no	-
LP21	Brandy, tequila	12	yes	Yes,occ binge	no	-

	and wine					
JR23	beer	12	yes	No	no	-
SH25	beer	10	yes	no	no	-
EJ27	Beer	21	yes	no	no	-
HR30	Beer and brandy	15	yes	Yes,4/week	no	-
ER32	wine	140	no	no	no	-
BB35	Beer and wine	26	yes	Yes,10/week	no	-
Cv36	beer	27	yes	Yes,reduced ,unspecified	no	-
KS37	beer	10	yes	no	no	-
RK39	beer	23	yes	Yes,10/week	no	-
DJ40	beer	12	yes	yes	yes	22 weeks
SP41	beer	18	yes	no	no	-
PP45	beer	9	yes	yes	yes	16 weeks
MG46	Beer,brandy	34	yes	no	no	-
PP47	Beer and schnapps	35	yes	Yes,reduced,occ binge	no	-
MS52	beer	36	yes	Yes,reduced	no	-
JP54	beer	33	yes	no	no	-
JG57	tequila	16	yes	yes	yes	12 weeks
EM58	beer	18	yes	Yes.9/week	no	-
VS59	beer	18	yes	no	no	-

AF62	Beer and vodka	46	yes	yes	yes	23 weeks
MK67	beer	18	yes	no	no	-
EH72	beer	24	yes	yes	yes	16weeks
VM76	beer	48	yes	no	no	-
FW77	Beer and tequila	17	yes	Yes,reduced,occ binging	no	-
CO80	beer	12	yes	yes	yes	16 weeks
SB82	Beer and brandy	>50	no	yes	yes	22 weeks
IB89	beer	30	yes	yes	yes	20 weeks
CC90	beer	30	yes	Yes,increased,added brandy	no	-
BF91	beer	12	yes	yes	yes	24 weeks
RP94	beer	15	yes	yes	yes	16 weeks
SS96	beer	12	yes	no	no	-
CM97	beer	21	yes	yes	yes	22 weeks
LS98	beer	48	yes	Yes,reduced	no	-
NW99	brandy	10	yes	Yes,reduced,occ binge	no	-
CW104	Beer and vodka	25	yes	Yes,reduced	no	-
JR105	Beer,vodka,brandy	42	yes	no	no	-
ND106	beer	36	yes	yes	yes	20 weeks
JP107	beer	25	yes	yes	yes	25weeks

YF110	beer	2o	yes	no	no	-
TF111	beer	17	yes	Yes,reduced	no	-
SV118	beer	15	yes	yes	yes	24 weeks
CH119	beer	6	yes	no	no	-
ND120	beer	18	yes	yes	yes	23 weeks
MK123	beer	18	yes	no	no	-
FJ125	beer	18	yes	Yes,reduced	no	-

Appendix 2: ultrasound measurements

patient	GA	BPD	HC	AC	FL	cerebellum	humerus	foot	interoc in	interoc out	intracran in	intra
MB5	18	41	152	131	24	16	26	26	12	28	-9	-9
MB5	22	51	185	174	38	21	36	40	13	34	-9	-9
MB5	32	77	283	269	57	32	52	59	-9	-9	-9	-9
MB5	38	85	310	301	66	-9	59	68	-9	-9	-9	-9
AB6	23	58	212	183	41	23	41	41	12	40	-9	-9
AB6	32	82	295	288	61	42	53	62	-9	-9	-9	-9
AB6	37	90	[illegible]	323	67	39	60	66	-9	-9	-9	-9
RJ7	26	69	255	227	46	31	43	48	16	45	-9	-9
RJ7	32	80	287	302	61	42	53	62	21	54	-9	-9
RJ7	36	83	[illegible]	341	66	43	60	-9	-9	-9	-9	-9
EB1	22	54	[illegible]	184	40	-9	39	44	15	36	-9	-9
EB1	28	73	[illegible]	239	54	-9	-9	-9	-9	-9	-9	-9
EB1	36	86	[illegible]	345	68	-9	57	-9	-9	-9	-9	-9
VL2	21	53	[illegible]	167	37	21	32	38	15	36	-9	-9
VL2	27	64	[illegible]	239	51	32	43	51	-9	-9	-9	-9
VL2	33	76	[illegible]	295	62	35	53	62	-9	-9	-9	-9
RS4	24	61	[illegible]	205	42	-9	41	42	13	37	-9	-9
RS4	30	75	[illegible]	285	59	40	53	64	-9	-9	-9	-9
MP8	27	69	[illegible]	216	50	31	45	54	17	41	-9	-9
MP8	32	73	[illegible]	272	57	37	53	59	-9	-9	-9	-9
MP8	36	83	[illegible]	301	67	-9	-9	-9	-9	-9	-9	-9
AR9	22	56	[illegible]	195	39	25	36	41	14	37	-9	-9
AR9	28	73	[illegible]	265	53	33	48	52	-9	-9	-9	-9
DP10	23	57	[illegible]	198	41	31	42	38	13	39	-9	-9
DP10	28	75	[illegible]	277	56	35	53	59	17	44	-9	-9
DP10	35	89	[illegible]	344	69	42	60	67	-9	-9	-9	-9

patient	GA	BPD	HC	AC	FL	cerebellum	humerus	foot	interoc in	interoc out	intracran in	intr
LM11	23	56	217	186	41	24	36	45	16	37	-9	-9
LM11	28	73	73	233	52	32	46	61	16	46	-9	-9
LM11	32	81	308	285	60	30	52	61	-9	-9	-9	-9
LM11	36	83	317	320	65	37	56	76	-9	-9	-9	-9
AB12	24	56	213	196	43	25	42	42	16	40	-9	-9
AB12	29	67	256	242	54	-9	-9	49	16	47	-9	-9
AB12	35	82	5	36	66	-9	62	69	-9	-9	-9	-9
LR13	26	66	51	277	49	30	45	48	13	44	-9	-9
LR13	32	80	7	29	63	43	52	58	22	52	-9	-9
LR13	36	85	5	29	67	-9	64	72	-9	-9	-9	-9
TF14	23	57	1	184	39	-9	40	41	14	39	-9	-9
TF14	28	71	9	223	52	33	49	56	19	46	-9	-9
TF14	36	85	4	303	65	-9	60	68	21	53	-9	-9
AS15	26	67	1	0	47	30	45	50	16	44	-9	-9
AS15	32	75	1	277	59	42	55	65	22	52	-9	-9
AS15	36	80	1	4	66	-9	-9	-9	22	57	-9	-9
NC16	21	45	3	28	32	18	31	30	12	33	-9	-9
NC16	31	78	7	330	57	33	50	61	-9	-9	-9	-9
NC16	33	81	3	274	60	40	54	63	11	36	-9	-9
NC16	37	87	1	5	71	44	59	63	13	42	-9	-9
RW17	26	69	7	3	48	29	-9	49	14	44	-9	-9
RW17	33	82	1	5	61	30	55	63	18	51	-9	-9
RW17	37	82	7	5	68	37	61	63	-9	-9	-9	-9
EV18	23	55	1	0	42	25	37	42	13	36	-9	-9

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out
KK19	22	52	1	10	37	22	35	42	15	33	-9	-9
KK19	28	-9	2	21	47	-9	43	52	21	42	-9	-9
KK19	33	76	-9	2	56	-9	54	-9	-9	-9	-9	-9
CV20	24	58	2	17	42	30	37	41	14	37	-9	-9
CV20	28	67	2	23	49	31	45	57	15	42	-9	-9
CV20	36	82	2	2	62	40	57	-9	15	42	-9	-9
LF21	21	49	1	1	39	-9	38	41	11	35	-9	-9
LF21	28	70	2	2	55	32	51	56	-9	-9	-9	-9
GC22	24	61	1	2	45	26	44	45	15	41	-9	-9
GC22	29	73	1	2	56	36	50	-9	17	47	-9	-9
GC22	36	86	1	2	69	47	61	70	-9	-9	-9	-9
JS23	22	54	1	1	37	-9	-9	36	-9	-9	-9	-9
JS23	28	70	1	2	53	32	43	54	-9	-9	-9	-9
JS23	36	84	1	2	64	-9	-9	-9	17	51	-9	-9
RM24	21	52	1	1	42	23	37	33	13	33	-9	-9
RM24	27	69	1	2	56	25	49	46	16	46	-9	-9
RM24	35	86	1	2	69	35	52	71	-9	-9	-9	-9
SH25	22	51	1	1	39	-9	38	36	12	34	-9	-9
SH25	28	69	2	2	53	29	46	52	-9	-9	-9	-9

SH25	37	81		66	34	56	70	-9	-9	-9	-9
AF26	23	56		39	30	39	38	15	39	-9	-9
AF26	28	75		54	-9	50	54	15	47	-9	-9
EJ27	25	60		41	27	39	45	14	42	-9	-9
EJ27	29	73		49	36	47	53	17	45	-9	-9
EJ27	34	78		58	40	53	65	-9	-9	-9	-9

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out
HK28	22	57	219	202	47	-9	45	45	17	38	-9	-9
HK28	30	80	302	310	62	35	-9	70	-9	-9	-9	-9
HK28	36	90	-9	341	72	38	-9	70	-9	-9	-9	-9
SP29	24	61	230	196	44	25	41	45	12	40	-9	-9
SP29	30	77	282	257	56	36	53	-9	-9	-9	-9	-9
SP29	37	84	327	340	72	-9	62	-9	-9	-9	-9	-9
HR30	22	56	211	170	36	26	36	35	12	34	-9	-9
HR30	28	75	-9	238	53	30	49	52	18	45	-9	-9
HR30	33	86	312	291	62	-9	55	9	16	47	-9	-9
MA31	24	61	231	189	44	25	41	41	14	42	-9	-9
MA31	28	72	277	239	53	34	53	56	14	45	-9	-9
MA31	32	78	299	270	60	42	54	65	-9	-9	-9	-9
MA31	38	85	329	317	71	39	62	68	-9	-9	-9	-9
ER32	22	52	-9	165	36	-9	34	-9	-9	-9	-9	-9
ER32	29	67	252	225	51	26	48	52	-9	-9	9	-9
ER32	32	73	267	246	54	29	48	-9	-9	-9	-9	-9
ER32	37	73	267	267	55	29	50	-9	-9	-9	-9	-9
PS33	22	53	204	173	38	23	39	41	8	24	-9	-9
PS33	28	71	274	252	55	30	54	56	9	-9	9	-9
PS33	36	86	315	326	68	42	63	76	25	57	-9	-9
LH34	23	63	233	205	44	26	-9	47	13	41	9	-9
LH34	32	78	298	279	58	42	52	64	-9	-9	-9	-9

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out	
BB35	24	60	217	193	44	27	40	42	19	40	-9	-9	(
BB35	33	79	-9	270	59	-9	52	-9	-9	-9	-9	-9	(
BB35	36	83	284	282	64	-9	55	-9	-9	9	-9	-9	(
CVJ6	24	63	234	193	40	27	42	45	18	41	-9	-9	(
CV36	33	83	314	314	62	34	56	74	-9	-9	-9	-9	(
CV36	35	87	332	340	67	38	-9	76	26	67	-9	-9	(
KS37	26	68	255	277	48	30	46	52	-9	-9	9	-9	(
KS37	32	78	283	276	60	33	49	62	-9	-9	-9	-9	(
KS37	37	86	-9	302	65	-9	59	72	-9	-9	-9	-9	(
JB38	22	57	190	173	41	20	41	41	16	37	-9	-9	(
JB38	28	70	262	223	55	31	49	51	-9	-9	-9	-9	(
JB38	33	80	315	323	69	46	58	68	21	54	-9	-9	(
RK39	25	69	239	217	47	-9	44	50	15	44	-9	-9	(
RK39	34	87	315	294	64	36	56	60	-9	9	-9	-9	(
RK39	36	88	324	304	68	-9	62	73	-9	-9	-9	-9	(
DJ40	23	49	194	173	39	20	38	38	11	35	-9	-9	
DJ40	31	73	272	246	58	30	53	51	-9	9	-9	-9	(
DJ40	36	82	311	302	65	33	61	70	-9	9	-9	-9	(
SP41	26	67	244	215	50	29	44	50	17	45	-9	-9	(
SP41	29	76	279	252	58	35	51	58	17	46	-9	-9	(
SH42	23	57	215	189	39	23	38	43	15	38	-9	-9	
SH42	28	77	273	241	53	-9	-9	55	17	47	-9	-9	(
SH42	32	89	310	298	61	37	55	-9	-9	-9	-9	-9	(
SH42	35	92	320	317	65	42	-9	-9	-9	-9	-9	-9	(

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out	
CA43	23	9	224	189	42	24	40	41	15	39	-9	-9	
CA43	29	73	283	248	56	27	53	62	14	45	-9	-9	
CA43	33	82	314	291	63	36	55	9	22	57	-9	9	
DS44	24	53	206	187	42	25	41	38	15	37	-9	-9	
DS44	32	75	284	252	61	33	53	57	20	47	-9	-9	
DS44	37	86	313	301	69	34	61	75	-9	-9	-9	-9	
PP45	23	61	221	205	45	25	-9	47	16	39	-9	-9	
PP45	28	74	278	254	58	-9	-9	59	21	47	-9	-9	
PP45	35	87	329	340	70	42	66	76	-9	-9	-9	-9	
MG46	23	63	226	192	43	26	37	47	15	38	-9	-9	
MG46	29	77	272	260	52	36	46	57	-9	-9	-9	-9	
MG46	36	87	312	312	64	38	54	-9	-9	-9	-9	-9	
PP47	23	61	229	180	43	26	41	45	13	42	9	-9	
PP47	30	75	283	252	58	31	52	-9	17	47	-9	-9	
PP47	37	81	299	293	67	36	60	-9	18	38	-9	-9	
LH48	22	54	198	177	40	22	35	37	13	35	9	-9	
LH48	28	70	-9	242	70	32	46	55	-9	-9	-9	-9	
LH48	36	90	-9	323	68	37	61	75	-9	-9	-9	-9	
JH50	23	-9	224	187	38	24	39	41	15	38	-9	-9	
JH50	28	74	271	223	53	28	46	47	-9	-9	-9	-9	
JH50	32	82	308	256	60	-9	48	-9	-9	-9	-9	-9	
JH50	35	87	318	278	61	-9	54	-9	-9	-9	-9	-9	

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out	um
MS51	22	49	189	177	36	21	36	38	14	34	-9	-9	0.7
MS51	27	71	256	238	51	30	47	55	17	49	9	-9	0.8
MS51	33	82	299	282	62	36	56	63	-9	-9	-9	-9	0.4
MS52	25	58	217	195	40	23	37	44	14	39	-9	-9	-9
MS52	29	67	257	232	49	-9	44	53	16	42	-9	-9	0.5
MS52	36	75	294	285	58	41	49	66	-9	-9	-9	-9	0.5
AA53	21	51	182	168	37	21	30	33	15	34	9	-9	0.7
AA53	28	71	262	245	51	29	46	57	17	47	-9	-9	0.7
JP54	23	56	216	196	42	24	38	35	18	40	-9	-9	0.6
JP54	28	70	262	221	53	30	49	55	20	46	-9	-9	0.5
JP54	35	83	310	307	67	-9	59	65	-9	-9	-9	-9	0.6
TJ55	22	52	198	153	38	-9	38	34	14	37	-9	-9	0.6
TJ55	31	75	285	264	61	32	-9	54	-9	-9	-9	-9	0.6
JG57	24	56	207	182	40	23	39	40	-9	9	9	-9	0.5
JG57	28	67	245	226	52	25	45	52	17	44	-9	-9	0.4
JG57	36	84	312	301	68	31	57	70	-9	-9	-9	-9	0.4
EM58	20	48	176	145	32	20	29	32	13	30	-9	-9	0.6
EM58	28	67	271	227	52	9	45	-9	15	42	-9	-9	0.5
EM58	32	75	298	277	60	39	50	59	20	50	-9	-9	0.6
EM58	35	84	328	301	63	44	-9	68	-9	-9	-9	-9	0.4
VS59	25	64	242	207	48	27	43	54	19	40	9	-9	0.5
VS59	32	80	306	267	59	42	-9	64	9	-9	-9	-9	0.5
VS59	35	90	330	314	67	44	61	-9	-9	-9	-9	-9	0.6

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out
NM60	23	55	221	194	42	26	38	46	13	36	-9	-9
NM60	27	35	260	223	50	30	45	51	-9	-9	-9	-9
FA61	22	56	210	193	38	24	39	43	15	37	-9	-9
FA61	27	71	263	235	51	30	49	57	-9	9	-9	-9
AF62	24	61	229	195	47	28	41	43	19	40	-9	-9
AF62	28	76	270	239	54	30	49	45	-9	-9	-9	-9
AF62	34	88	310	306	67	37	63	69	9	-9	40	66
RC63	22	59	-9	182	44	26	41	34	-9	-9	-9	-9
RC63	28	71	269	216	57	-9	50	52	9	-9	-9	-9
RC63	32	78	290	269	64	34	56	61	-9	9	41	63
BG64	22	51	182	165	35	21	37	36	14	34	-9	9
BG64	25	61	233	198	45	-9	9	40	17	42	-9	9
BG64	31	76	267	267	60	-9	54	58	19	50	-9	-9
PM65	22	51	187	163	38	21	36	36	14	35	-9	-9
PM65	28	65	247	221	50	28	45	50	15	46	9	-9
PM65	23	74	277	252	56	32	50	61	16	49	-9	-9
CH66	22	55	201	186	43	24	38	41	14	38	26	45
MK67	25	61	227	187	43	26	42	43	17	42	-9	-9
MK67	28	72	264	242	54	31	47	58	19	51	-9	-9
MK67	32	73	291	282	62	35	-9	61	22	51	-9	-9
WA69	22	54	207	169	35	22	-9	36	16	38	27	45
WA69	27	70	263	215	49	30	46	56	18	29	34	54
WA69	38	87	325	303	68	-9	57	-9	-9	-9	48	74

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out
SM70	23	56	213	174	44	-9	39	42	15	39	-9	-9
SM70	27	67	265	220	51	29	44	-9	23	47	38	57
SM70	37	[illegible]	324	317	69	-9	59	9	9	-9	-9	-9
SM71	24	[illegible]	240	200	44	-9	-9	45	16	42	32	47
SM71	[illegible]	[illegible]	265	239	52	-9	46	54	18	46	-9	-9
EH72	[illegible]	[illegible]	250	218	49	-9	46	47	15	40	-9	-9
EH72	30	79	274	245	55	-9	49	58	17	44	-9	-9
JK73	21	[illegible]	193	164	35	-9	-9	34	12	33	26	41
JK73	32	66	306	283	62	-9	-9	62	-9	-9	-9	-9
LM74	25	-9	233	208	49	9	41	52	18	43	-9	-9
LM74	21	81	297	258	58	-9	52	57	24	49	-9	-9
MD75	21	54	186	161	35	20	35	34	12	35	28	45
MD75	26	60	243	229	50	27	43	-9	-9	-9	30	50
MD75	33	87	316	297	61	40	57	64	-9	-9	38	67
MD75	37	94	333	337	71	-9	64	68	24	53	45	72
VM76	23	58	220	184	41	24	39	43	15	37	24	44
VM76	31	79	293	269	59	35	50	63	-9	-9	39	61
VM76	35	92	339	318	66	41	59	71	-9	-9	43	68
FW77	23	-9	211	185	38	-9	38	41	13	38	-9	-9
FW77	31	78	295	270	57	-9	52	57	-9	-9	39	60
FW77	36	86	314	290	68	-9	60	71	-9	-9	-9	-9
TB78	23	56	210	179	39	20	35	35	20	36	24	44
TB78	34	80	304	269	61	33	-9	66	-9	-9	40	63
TB78	37	87	321	299	67	46	58	71	-9	-9	47	63

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out	t
SF79	21	51	189	168	38	20	37	38	13	33	-9	-9	(
SF79	28	67	255	230	51	33	47	53	16	42	30	53	(
SF79	37	81	316	302	67	34	59	-9	-9	-9	42	69	(
CO80	24	61	221	190	42	23	38	39	19	39	27	47	(
CO80	28	74	261	239	49	32	44	56	19	46	34	58	(
CO80	36	92	345	335	66	48	58	73	-9	9	47	73	(
BD81	21	48	185	152	38	21	34	37	12	32	26	42	(
BD81	29	72	268	232	55	33	52	58	-9	-9	37	57	(
BD81	33	81	297	285	62	42	58	-9	16	48	40	65	(
BD81	36	87	317	304	66	46	62	-9	-9	-9	-9	-9	(
SB82	20	47	-9	142	29	19	29	32	14	31	-9	-9	(
SB82	30	75	-9	242	55	29	47	52	22	46	33	56	(
SB82	34	85	314	279	62	45	54	69	-9	-9	42	67	(
JB83	20	44	163	140	31	-9	28	-9	11	31	19	35	
JB83	28	66	253	232	51	26	44	52	14	42	29	52	(
JB83	36	84	304	301	68	41	56	62	20	57	32	57	(
AJ84	21	52	200	169	38	22	36	37	15	37	26	43	-
AJ84	27	66	251	235	54	30	50	55	19	44	31	52	(
AJ84	35	85	309	323	70	43	61	75	19	52	42	65	(
AA85	24	57	217	172	40	21	38	43	15	37	27	49	(
AA85	28	72	266	233	52	35	46	59	16	43	35	56	(
AA85	36	87	325	307	65	37	55	77	21	52	41	67	(

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out
ED86	23	55	201	190	38	24	35	-9	15	33	-9	-9
ED86	28	72	260	266	55	37	45	-9	-9	-9	29	52
ED86	36	37	313	300	67	39	57	-9	25	57	38	65
JV87	30	81	192	165	36	-9	34	38	12	34	21	39
JV87	28	73	231	251	51	33	50	52	18	46	32	55
JV87	36	90	316	325	65	-9	61	75	24	56	-9	-9
CM88	22	-9	203	173	35	19	37	41	16	35	21	44
CM88	28	69	257	239	51	29	50	49	17	44	29	56
IB89	23	60	229	192	42	-9	40	45	14	36	24	49
IB89	28	77	274	251	54	40	47	60	19	44	34	51
IB89	36	78	310	313	67	39	55	-9	-9	-9	39	63
CC90	22	58	210	193	44	26	39	45	16	33	26	45
CC90	29	74	269	239	55	33	52	60	-9	-9	35	58
CC90	35	88	320	316	66	35	59	66	25	54	38	66
BF91	22	60	232	213	43	27	40	46	-9	-9	27	46
BF91	29	74	285	238	57	31	49	57	21	50	36	59
BF91	35	82	303	289	64	42	58	66	21	55	35	63
CJ92	22	61	195	170	40	19	38	36	15	37	21	40
CJ92	28	69	259	224	51	27	45	53	20	51	31	50
CJ92	36	87	316	300	66	-9	58	71	-9	-9	44	68
JW93	22	57	178	170	31	19	34	34	13	32	24	38
JW93	28	77	253	208	47	-9	43	43	18	44	-9	-9
JW93	31	75	284	270	58	32	52	61	20	47	32	57
JW93	36	85	314	302	67	41	61	68	19	53	39	64

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracr in	intrac out
RP94	23	54	201	181	39	23	41	44	17	37	-9	-9
RP94	29	73	263	236	55	34	50	61	18	45	29	52
RP94	33	85	300	288	66	40	60	70	-9	-9	-9	-9
AR95	24	62	238	199	45	25	46	49	16	40	27	49
AR95	26	70	261	227	53	-9	-9	56	-9	-9	-9	-9
AR95	32	83	-9	268	64	40	-9	-9	-9	-9	37	62
SS96	23	57	222	186	40	20	37	41	12	37	26	42
SS96	27	67	249	230	48	27	47	47	16	44	29	51
SS96	34	80	299	282	59	32	57	58	18	18	40	62
CM97	23	56	209	186	41	23	39	44	14	38	28	48
CM97	28	69	253	226	53	31	46	53	15	44	32	54
CM97	32	78	275	251	61	34	53	60	20	46	36	61
CM97	34	79	295	287	61	35	55	63	22	52	-9	9
LS98	24	-9	202	160	41	16	35	38	13	39	-9	9
LS98	28	-9	252	232	52	9	45	52	19	42	-9	-9
LS98	36	94	321	306	67	9	56	68	-9	9	41	66
NW99	25	63	235	202	46	22	42	46	17	38	38	52
NW99	28	70	260	230	52	26	45	-9	17	43	32	55
NW99	36	94	309	319	65	41	-9	69	21	51	45	65

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracran in	intracr out
AS102	22	[illegible]	203	177	39	21	36	39	-9	-9	27	46
AS102	28	[illegible]	272	222	52	31	48	56	19	45	37	60
ML103	20	-9	177	153	34	20	31	34	14	31	-9	-9
ML103	29	73	272	260	55	31	46	55	20	46	35	56
ML103	35	[illegible]	305	303	65	43	57	70	-9	-9	40	62
CW104	21	[illegible]	192	170	37	20	34	38	13	33	23	40
CW104	30	[illegible]	284	270	59	36	-9	62	18	45	38	61
CW104	35	[illegible]	329	323	66	45	60	-9	-9	-9	41	69
JR105	24	[illegible]	221	205	44	23	41	44	17	39	26	48
JR105	29	[illegible]	277	232	53	32	52	57	17	46	32	57
JR105	36	[illegible]	323	300	68	41	64	-9	-9	-9	43	68
JR105	[illegible]	[illegible]	325	291	71	-9	9	-9	-9	-9	-9	-9
JP107	[illegible]	[illegible]	219	173	44	24	39	36	14	39	28	50
JP107	[illegible]	[illegible]	250	216	50	-9	44	50	18	45	34	58
JP107	[illegible]	[illegible]	283	252	59	36	54	61	20	47	37	63
JP107	36	[illegible]	313	275	65	39	57	64	24	56	44	71
NP108	[illegible]	[illegible]	192	166	35	22	34	35	15	34	26	42
NP108	29	[illegible]	275	252	55	34	51	56	19	46	40	62
NP108	36	[illegible]	335	333	67	44	63	74	-9	-9	48	78
SN109	23	[illegible]	207	182	38	22	39	41	12	39	12	39
SN109	30	[illegible]	286	249	53	33	51	59	18	44	9	-9
SN109	35	[illegible]	330	307	63	39	-9	-9	-9	-9	42	70

patient	GA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracran in	intracr out
YF110	21	50	182	160	32	20	35	31	16	35	24	40
YF110	28	73	267	238	49	32	47	57	16	44	34	58
TF111	22	53	210	187	36	24	32	41	18	37	25	45
TF111	28	73	270	236	53	32	41	56	18	47	36	56
TF111	35	93	318	320	63	40	56	72	-9	-9	47	67
CP112	21	48	186	163	35	21	33	34	12	35	25	40
CP112	29	74	268	238	53	36	50	51	18	45	32	58
CP112	35	95	314	297	66	44	60	75	21	52	40	66
AJ114	22	49	191	168	37	20	37	39	13	33	24	45
AJ114	28	69	263	226	52	32	51	57	19	41	40	57
AJ114	36	94	318	314	66	36	59	-9	23	56	38	64
RS115	22	51	201	173	37	20	35	28	14	34	23	43
RS115	28	67	263	233	52	30	47	55	18	42	29	54
RS115	36	84	312	306	65	44	57	-9	19	49	41	71
SS116	21	49	191	170	37	23	37	37	13	34	22	42
SS116	28	71	269	232	51	34	47	55	9	-9	32	56
SS116	35	94	307	319	64	42	57	70	23	53	40	66
AW117	23	54	204	150	38	22	39	40	15	33	27	46
AW117	29	71	257	223	52	29	47	57	18	41	32	53
AW117	36	93	303	308	67	39	58	71	22	51	37	62
SV118	24	59	223	196	43	29	36	43	14	39	28	46
SV118	28	70	252	230	52	32	45	51	18	45	34	56
SV118	36	93	320	300	65	46	57	66	-9	-9	39	65

iA	BPD	HC	AC	FL	cerebellum	hum	foot	interoc in	interoc out	intracran in	intracr out	umb RI	MCA RI	AFI
3	56	207	170	40	22	37	39	16	38	27	46	-9	-9	14
6	67	247	221	47	-9	45	44	19	46	33	53	0 54	-9	14
6	86	318	300	66	46	59	-9	-9	-9	39	66	0.53	0.69	5
4	59	-9	195	45	25	41	44	16	41	28	47	0 54	-9	12
8	73	268	226	53	30	47	56	15	43	39	61	0.64	0 82	10
5	84	305	301	65	-9	56	70	22	52	-9	-9	0.63	0 63	7
3	57	217	196	39	23	38	41	15	35	31	50	0 68	-9	12
8	70	264	245	53	31	47	56	19	45	36	57	0.71	1	12
8	-9	312	322	70	41	60	-9	9	-9	-9	-9	0.53	-9	5
1	53	201	173	38	23	37	41	15	35	28	44	0 6	-9	16
8	73	276	241	51	34	48	60	16	47	31	56	0 61	1	14
6	89	317	300	70	42	61	-9	24	56	43	68	0.6	0 77	9
2	55	208	186	35	23	37	39	13	35	25	43	0.55	-9	14
6	67	251	221	48	28	45	50	19	42	31	53	0.61	1	16
1	81	294	287	58	33	54	68	16	49	41	65	0 57	1	13
2	50	183	173	37	20	33	34	13	32	24	44	0 63	-9	12
8	67	249	239	47	29	45	46	13	41	31	41	0 47	0.81	6
2	78	290	270	59	34	54	59	21	47	36	60	0.48	0.86	5
6	85	309	311	66	-9	61	71	20	57	44	60	0.59	0.83	0
3	59	216	189	44	25	39	46	-9	-9	29	50	0 73	-9	10
6	66	252	239	50	26	47	51	15	41	9	-9	0 59	1	16
3	84	307	282	62	38	57	66	17	53	35	62	0 36	0.86	14
6	85	316	304	64	40	60	-9	25	54	39	69	0 67	0 87	8
3	58	211	174	39	23	36	40	12	33	24	40	0.62	-9	14
8	72	264	221	50	33	47	55	15	41	34	54	0 6	1	18
6	83	318	292	63	41	59	69	-9	-9	44	67	0 55	0 74	7
4	59	9	195	45	25	41	44	16	41	28	47	0 54	-9	12
8	73	268	226	53	30	47	56	15	43	39	61	0 64	0 82	10
5	84	305	301	65	-9	56	70	22	52	-9	-9	0.63	0 63	7

Appendix 3. Demographics and outcome.

PATIENT	AGE	GRAVA	PARA	initial wt	height	smoker	birthweight	NVD/CS	apgar1	apgar2	subject
MB5	27	2	1	51	151	y	2520	nvd	9	9	n
EB1	28	3	1	129	159	n	3530	nvd	8	10	n
DP10	29	3	2	72	168	y	4240	nvd	8	9	n
LM11	30	2	1	59	159	y	2610	nvd	8	9	n
AB12	35	1	0	67		y	2800	nvd	9	9	n
TF14	24	1	0	49	151	y	2580	nvd	8	9	n
CV20	22	1	0	65	161	y	3200	nvd	8	9	n
GC22	26	2	1	60	168	n	3440	nvd	9	9	n
RM24	24	1	0	68	162	n	3100	nvd	9	10	n
HK28	27	1	0	97	154	n	3710	cs	9	10	n
SP29	32	4	2	69	150	y	3260	nvd	9	9	n
MA31	21	1	0	46	154	y	3060	nvd	9	9	n
PS33	25	3	1	60	155	n	3140	nvd	9	9	n
LH34	24	2	1	51	170	y	2480	nvd	9	9	n
JB38	21	1	0	55	155	y	3100	nvd	9	-9	n
SH42	31	5	3	55	155	n	3740	nvd	9	10	n
CA43	25	3	2	74	167	y	3500	nvd	9	10	n
DS44	22	1	0	59	169	n	3120	nvd	9	9	n
LH48	25	2	1	54	153	n	3500	nvd	8	9	n
JH50	26	3	2	63	157	y	2400	nvd	9	10	n
MS51	27	2	1	83	157	n	3900	nvd	8	9	n
AA53	19	1	0	56	145	y	2700	cs	8	9	n
TJ55	29	2	1	110	165	y	2880	nvd	9	9	n
JG57	20	1	0	55	163	y	2900	nvd	8	9	n
NM60	25	2	1	72	157	y	2760	nvd	9	9	n
FA61	28	1	0	49	156	y	2920	nvd	9	9	n
BC63	24	2	1	63	166	n	3700	nvd	9	9	n
BG64	25	1	0	60	161	y	2940	cs	9	10	n
PM65	27	4	2	61	164	n	3200	nvd	9	9	n
CH66	24	3	4	44	145	y	1800	nvd	9	10	n
MV68	19	2	1	49	149	y	220	vvd	-9	-9	n
WA69	30	2	1	51	149	y	2820	nvd	9	9	n
SM70	21	2	0	70	172	y	2775	nvd	10	10	n
JK73	29	1	0	61	163	n	3400	cs	2	8	n
LM74	20	1	0	50	161	y	2500	nvd	9	10	n
AB6	28	1	0	63	157	y	3590	nvd	8	9	y
RJ7	20	1	0	45	155	y	3250	nvd	9	9	y
VL2	19	2	1	50	155	y	2800	nvd	9	9	y
RS4	31	4	3	85		y	2520	cs	9	10	y
MF8	0	1	0	46	148	y	2440	nvd	9	10	y
AR9	35	6	5	58		y	1830	nvd	-9	-9	y
LR13	34	2	1	57		y	3960	nvd	9	9	y
AS15	30	2	1	67	158	y	3020	nvd	9	9	y
NC16	22	2	1	53	161	y	2710	nvd	9	9	y
RW17	24	1	0	54	157	y	2540	nvd	8	9	y
EV18	34	5	1	64	157	y	1130	nvd	6	7	y
KK19	32	4	3	54	154	y	2100	nvd	8	9	y

LF21	24	1	0	73		y	1680	cs	8	9	y
JS23	21	1	0	50	161	y	2580	nvd	7	9	y
SH25	27	2	0	47	161	y	2300	nvd	10	10	y
AF26	36	1	0	70	162	y	1240	cs	8	10	y
EJ27	38	7	6	54	147	y	2520	nvd	8	9	y
HR30	20	1	0	51	168	y	2585	nvd	9	9	y
ER32	30	3	2	50	156	y	1500	cs	7	9	y
BB35	29	3	2	56	160	y	1660	cs	9	9	y
CV36	34	1	0	65	168	y	3640	nvd	9	10	y
KS37	25	2	1	63	154	y	2560	nvd	9	9	y
RK39	25	3	2	57	156	n	3640	nvd	9	10	y
DJ40	26	2	1	50	158	y	3500	nvd	9	9	y
SP41	35	5	3	52	149	y	2280	cs	8	9	y
PP45	29	3	1	78	161	y	3380	nvd	9	9	y
MG46	29	4	3	68	164	y	2970	nvd	9	9	y
PP47	25	3	2	51	151	y	2520	nvd	8	9	y
MS52	28	2	0	43	146	y	2080	nvd	9	10	y
JP54	25	3	1	41	145	y	2600	cs	9	10	y
EM58		1	0	59	159	n	3500	nvd	8	9	y
VS60	28	1	0	52	159	y	3400	cs	9	10	y
AF62	27	1	0	55	163	y	3500	nvd	8	9	y
MK67	23	2	1	51	159	y	2600	nvd	3	8	y
SM71	25	2	1	47	156	y	1840	cs	3	9	y
EH72	36	4	3	87	167	y	2780	nvd	9	9	y

Patient	AGE	GRAVA	PARA	initial wt	height	smoker	birthweight	NVD/CS	apgar1	apgar2	subject
SM100	[illegible]	5	3	58	155	y	1785	cs	6	9	?
AS102	[illegible]	3	1	64	160	y	2100	nvd	8	9	n
ML103	[illegible]	[illegible]	0	69	156	n	2840	cs	8	9	n
NP108	[illegible]	1	0	59	157	n	3100	nvd	7	9	n
Sn109	[illegible]	3	1	74	176	y	2540	nvd	9	9	n
CP112	[illegible]	1	0	65	154	y	2820	nvd	9	9	n
AJ114	[illegible]	2	1	61	161	y	3140	cs	8	9	n
RS115	[illegible]	1	0	54	149	n	2550	nvd	9	10	n
SS116	[illegible]		0	65	151	y	3290	nvd	8	9	n
AW117	[illegible]	1	0	53	164	y	2420	nvd	8	9	n
PK121	[illegible]	3	2	50	151	n	3220	nvd	8	9	n
BW122	[illegible]	4	2	54	154	y	2920	nvd	8	9	n
NW29	[illegible]	2	1	52	160	y	2680	nvd	8	9	y
CW104	[illegible]	3	2	70	160	y	3180	nvd	8	9	y
JR105	[illegible]	2	0	65	154	y	2900	cs	8	9	y
ND106	[illegible]	2	1	60	173	y	-9	nvd	-9	9	y
JP107	[illegible]	3	2	34	146	y	2220	cs	8	9	y
YF110	[illegible]	4	1	52	156	y	1655	nvd	8	9	y
TF111	[illegible]	1	0	49	159	y	2600	nvd	6	8	y
SV118	[illegible]	2	1	47	153	y	2640	nvd	8	9	y
CH119	[illegible]	1	0	54	150	n	3000	nvd	8	9	y
ND120	[illegible]	4	3	45	160	y	2230	nvd	9	9	y
AC101	[illegible]	6	5	47	163	y	2900	nvd	8	9	
NP124	[illegible]	3	2	85	160	n	2780	cs	8	10	n
MK123	[illegible]	1	0	59	167	y	2800	nvd	9	9	y
FJ125	[illegible]	2	0	46	155	y	2700	nvd	9	9	y

patient	smoker	birthwt	preterm	cong abn	IUGR	oligohydramnois	subject
EV18	y	1130	y	n	n	n	1
KK19	y	2100	y	n	y	y	1
EH22	y	1500	y	n	y	y	1
KS37	y	2560	n	n	n	y	1
MK67	y	2600	n	n	n	n	1
SV118	y	2640	n	n	n	y	1
BB35	y	1660	y	n	y	y	1
JF54	y	2600	y	n	n	n	1
AR9	y	1830	y	y	y	n	1
VL2	y	2800	n	n	n	n	2
MP8	y	2440	y	n	n	y	2
SH25	y	2300	n	y	y	y	2
HJ27	y	2520	n	n	n	n	2
SP41	y	2280	y	n	n	n	2
SM71	y	1840	y	n	n	n	2
EH72	y	2780	n	n	n	n	2
CM97	y	2020	y	y	y	y	2
AB12	y	2600	n	n	n	n	1c
TF14	y	2580	n	n	n	n	1c
LH34	y	2480	y	n	n	n	1c
AA53	y	2700	n	n	n	n	1c
CJ92	y	3200	n	n	n	n	1c
LM 4	y	2500	n	n	n	n	1c
JB36	y	3100	n	n	n	n	1c
JB83	y	2860	n	n	n	n	1c
WA89	y	2820	n	n	n	n	1c
AA85	y	3020	n	n	n	n	2c
JV87	y	3740	n	n	n	n	2c
MB5	y	2520	n	y	n	n	2c
GC22	n	3440	n	n	n	n	2c
JK73	n	3400	n	n	n	n	2c
SH42	n	3740	n	n	n	y	2c
HK28	n	3710	n	n	n	n	2c
LM11	n	2820	n	n	n	n	2c

Appendix 4. Comparison of FAS plus possible FAS vs controls.

Key :1=confirmed FAS, 2= possible FAS, 1c=controls of subjects confirmed FAS, 2c=controls of subjects with possible FAS.

Appendix 5

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
Faculty of Medicine
Anzio Road, Observatory, 7925
Queries : Martha Jacobs
Tel : (021) 406-6492 Fax: (021) 406-6390
E-mail : Martha@medicine.uct.ac.za

07 May 1999

REC REF : # 038/99

Prof D Viljoen
Human Genetics

Dear Prof Viljoen

PRENATAL ASSESSMENT OF FETUSES AT HIGH RISK FOR FETAL ALCOHOL SYNDROME IN A SOUTH AFRICAN POPULATION

I have pleasure in informing you that the above study(including Protocol, Patient Information sheet in English and Questionaire) has been **formally approved** by the Research Ethics Committee on 06 May 1999.

Included is a list of Research Ethics Committee Members who have formally approved your protocol

Please quote the above Reference number in all correspondence.

Yours sincerely,

PROFESSOR FOLB
CHAIR: RESEARCH ETHICS COMMITTEE

Queries: Martha Jacobs
Research Ethics Committee
Room 212 Werner and Beit
UCT Medical School
Anzio Road, Observatory, 7925
Tel: (021) 406-6492 Fax: (021) 406-6390
E-Mail: martha@medicine.uct.ac.za

APPENDIX 6

MATERNAL ANTENATAL QUESTIONNAIRE

Interviewer: ..... Date of first interview:

Clinic: ..... ___/___/_____

Province: .....

PART 1: INFORMATION OBTAINED FROM INTERVIEWEE:

1. Name: .....
2. D.O.B.: ___/___/_____ 3. Folder number: .....
4. Marital status:

Married	common law	single	single+living together	Other .....

5. Address: .....

.....

.....

6. Telephone: (Home) ..... (Work) .....
7. Religious affiliations: .....
8. Ethnic group: .....
9. Maternal education: .....
10. **Father of baby**: Name: .....

Highest educational level achieved: .....

11. **Family income**: i. Income: .....

ii. Source of income: .....

12. OBSTETRIC HISTORY G: ..... P: .....

a) **Previous Obstetric History**

i) Hospital admissions: .....

ii) Problems: .....

.....

b) **Current Obstetric history**

i) Estimated gestation: .....

ii) LMP: .....

iii) Vaginal bleeding: .....

iv) Hypertension: .....

v) Morning sickness: **Yes** **No**

If Yes, Duration: ..... Frequency: .....

vi) Additional information: .....

.....

13. Previous medical history

a) Operations: .....

b) Serious illnesses: .....

14. Family history

a) Any genetic disorders in the paternal/maternal family? **Yes** **No**

b) Disorder: .....

c) Relationship of interviewee to affected person: .....

15. Medication usage

a) Are any regular medications used? **Yes** **No**

b) Drug(s): .....

c) Dosage: .....

16. Smoking

a) Does the patient smoke? **Yes** **No**

b) How many cigarettes per day ..... / day

Or

How many packets of tobacco in a week? No of packets: .....

Size of packet: .....

17. Alcohol History

a) How old were you when you first started drinking alcohol? ..... years

If interviewee has never drunk alcohol, ASK:

i) Is there any particular reason why you have never drunk any alcohol?

.....

.....

If interviewee has stopped drinking, ASK:

ii) When did you stop? .....

iii) Why did you decide to stop drinking? .....

.....

b) What type of alcohol do you usually drink? .....

.....

c) When do you usually drink? .....

.....

d) How much do you usually drink on each occasion? .....

.....

.....

e) Just before and around the time you became pregnant, what did you usually drink in a typical week? *(Start with Friday and ask for details for each day)*

(If interviewee does not drink every week, record drinking pattern for a week when she does drink and then note how many times in a month she does drink.)

	BEER		WINE		SPIRITS		OTHER (specify)	
	No. of Drinks	mls/ drink	No. of Drinks	mls/ drink	No. of Drinks	mls/ drink	No. of Drinks	mls/ drink
FRIDAY								
SATURDAY								
SUNDAY								
MONDAY								
TUESDAY								
WEDNESDAY								
THURSDAY								

Number of weeks in a month when Interviewee drinks: .....

f) Has your drinking pattern changed in any way since ..... (month of conception) **YES** **NO** *If NO, skip to* ***Question17(j)***

g) When did your drinking habits change? .....

h) How did your drinking habits change? .....

i) Why did you change you drinking pattern? .....

.....

j) Have there been times during your pregnancy (even before you knew you were pregnant) when you went to a party or were upset etc and when you may have drank more than is typical for you (as you have just described to me)?

YES **NO**

If YES, ASK:

i) When did this happen? .....

ii) Please describe to me what and how much you drank? .....

.....

iii) About how many times has this happened? .....

iv) COMMENTS: .....

.....

k) Do you usually eat when you are drinking? **YES** **NO**

If YES, Specify: a) .....

.....

l) Over what period of time do you usually drink? *(Calculate this by asking the question in stages, eg. "When do you start drinking on a Friday?", "When have you usually had enough to drink?", etc.)* ..... hours

COMMENTS: .....

.....

.....

18. Drug History

Have you ever used any drugs, such as marijuana (dagga), mandrax or anything else? **YES** **NO**

If YES, ASK:

a) What have you used? .....

b) When last have you used any _____? .....

c) How often do you usually use _____? .....

COMMENTS: .....

.....

19. **Awareness**

a) Is the patient aware of any factors which may be harmful to the growth or well-being of her baby? **YES** **NO**

b) Which factors are harmful? .....

c) Is the patient aware of any factors which may improve the baby's health prior to delivery? **YES** **NO**

d) Which factors are beneficial? .....

PART 2: INFORMATION OBTAINED FROM MEDICAL SOURCES

1. **EDD** by dates: ___/___/____ by palpation ___/___/____ by U/S___/___/____
2. Height: ..... 3. Preconception weight: .....
4. Booking visit:

   Gestational age: ..... Weight: .....

   BP: ..... Hb: .....
5. VDRL: ..... 6. Hypertension: .....
7. Vaginal bleeding: ..... 8. Proteinuria: .....
9. U/Sound findings: Date performed ___/___/____ Gestational age .....

   Comments .....

   .....
10. Medication/supplements dispensed by clinic: .....
11. Additional relevant history.....

.....

12. Assessment .....

.....

Appendix 1

UCT Medical School
Observatory
7925
Cape Town
South Africa
Tel +27 21 406 6210
Fax +27 21 447 7943
e-mail: farr@anat.uct.ac.za

FOUNDATION FOR ALCOHOL RELATED RESEARCH

Association Incorporated Under Section 21

Reg.No.97/00190/08

University of Cape Town Medical School
Wayne State University

COLLABORATIVE MOTHER AND INFANT DEVELOPMENT STUDY
PRENATAL PREGNANCY SURVEY
INFORMED CONSENT--PRENATAL SURVEY

Principal and Co-Principal Investigators:
Sandra W. Jacobson, Denis Viljoen, Joseph L. Jacobson, Julie Croxford

Introduction/Purpose of Study

I have been invited to participate in the University of Cape Town Medical School Pregnancy Survey, which is being conducted jointly with Wayne State University, Detroit, Michigan, USA. The purpose of the prenatal survey is to recruit women to participate in a study on how infants develop, who have been exposed to varying levels of alcohol during pregnancy.

Procedures and Amount of Time Involved

I will be interviewed one time for 30-45 minutes during my prenatal clinic visit about my alcohol and tobacco use and educational and family background, in order to see if I will be invited to participate in the Collaborative Mother and Infant Development Study.

Potential Risks and Benefits of the Study

No risks are anticipated to the women during this screening phase of the study. Potential benefits of the screening study include early detection of medical problems and referral of the women to a medical clinic, if any such problems are found. Potential benefits to others include increased knowledge about the drinking habits of women in this region.

Confidentiality

I understand that all information obtained about me and my family will be kept strictly confidential and will not be used in any way that can reveal my identity. No names or other form of identification will be used in the data to be collected. The study sponsors have obtained a writ of confidentiality from the federal government which says that I cannot be forced to release any other confidential information for criminal, civil, or administrative proceedings.

Voluntary Participation/Withdrawal

I understand that my participation is voluntary and that I may withdraw from the study at any time without losing my medical care. If I have any questions about my rights as a subject, I can contact Dr. Adnan S. Dajani, Chairman of the Wayne State Human Investigation Committee (011-313 577-1628). If I have any questions about the study, I can contact Dr. Denis Viljoen or Sister Julie Croxford, University of Cape Town Medical School, Cape Town, South Africa (021- 4066337) or Dr. Sandra W. Jacobson, Psychology Department, Wayne State University, Detroit, MI 48202, USA (011-313-875-8550).

Consent to Participate in the Research Study

The procedures to be followed in this screening study have been explained to me orally, and I have had a chance to ask questions about the research procedure, possible risks, and the likelihood of any benefits to me. All my questions have been answered. I hereby consent and voluntarily agree to participate in the screening phase of the study. I have been given a signed copy of this form.

_____ _____

Parent's signature Date

_____ _____

Witness' signature Date

Appendix 3

CASE RECORD

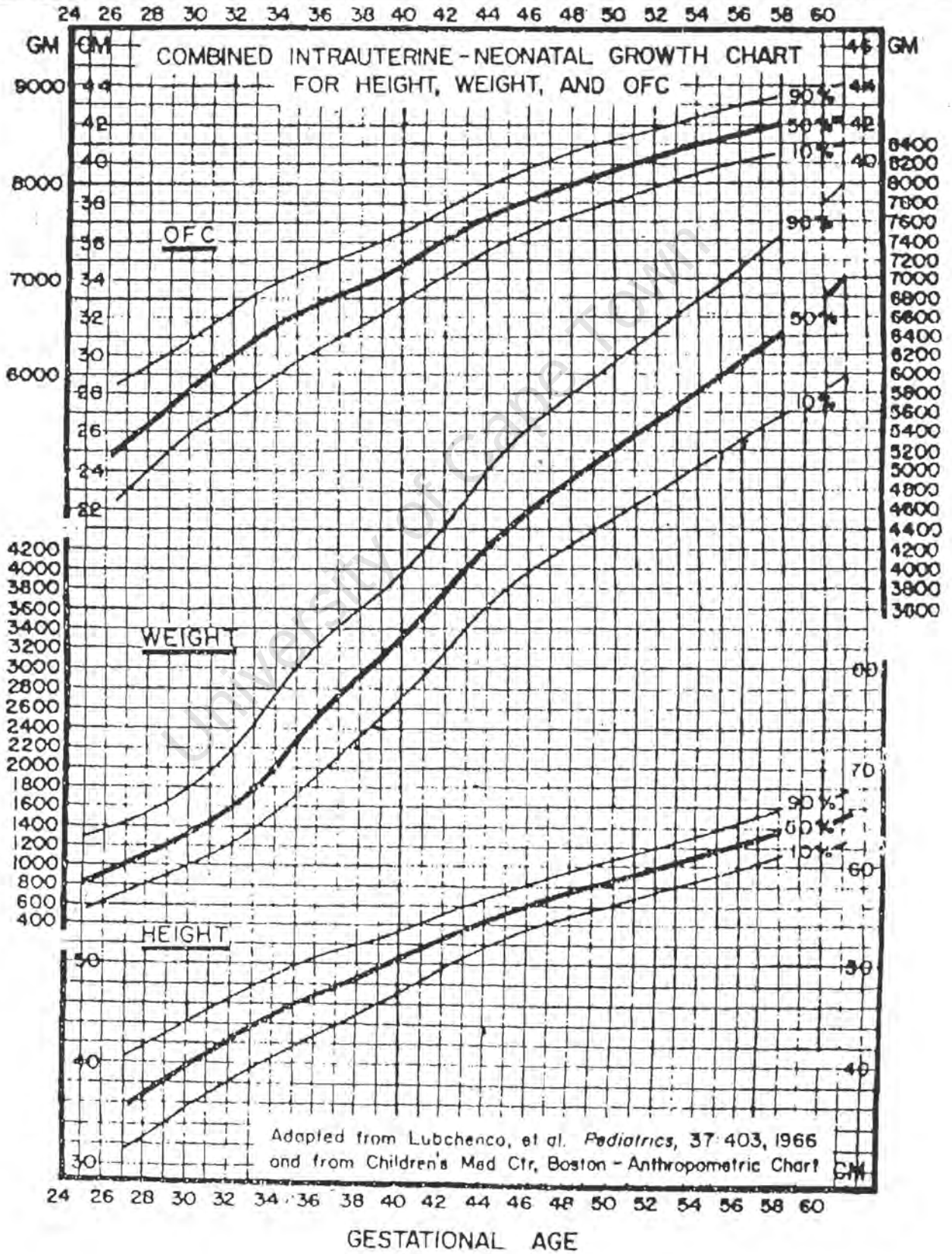
DATE

WARD

NAME

HOSP. NO.

ADDRESS



BINDING MARGIN

Appendix 9

PHYSICAL EXAMINATION

Name: _____ Number: _____

Schools Name: _____

Date of Examination: ____/____/____ Examiner: _____

Date of Birth: ____/____/____ Age: _____years/months

Sex: _____

Ht	_____	Ht	%_____	☐ Exam HT
Wt	_____	Wt	%_____	☐ Exam WT
OFC	_____	OFC	%_____	☐ Exam OFC
ICD	_____	ICD	%_____	☐ Exam ICD
IPD	_____	IPD	%_____	☐ Exam IPD
PFL	_____	PFL	%_____	☐ Exam PFL

Other Measurements _____ ☐ OTHMEAS

Mental status/behaviour _____ ☐ HPERACT

Neurological _____ ☐ FINEMOTR

Cranium _____

Face: General _____ ☐ HYPOFACE

Ears _____ ☐ RREARS

Eyes _____ ☐ PALPFISS

Nose _____ ☐ STRABISM

Mouth _____ ☐ PTOSIS

Neck _____ ☐ EPICANTH

Thorax _____ ☐ NALSBRDG

Heart _____ ☐ ANTENARE

Abdomen _____

Arms _____ ☐ LONGPHIL

Hands: General _____ ☐ SMTHPHIL

Creases _____ ☐ NRRWVRML

Dermal Patterns _____ ☐ PROGNATH

Legs _____ ☐ HEARTMUR

Feet _____ ☐ SUPINATE

Skin _____ ☐ CLINDACT

Hair _____ ☐ CAMPDACT

Other/comments: _____ ☐ PALMCR

☐ HYPRTRIC

_____

_____

Asymmetry: No / **Yes (specify):** _____

_____

Mothers Name: _____

Address: _____

Telephone Number: _____

DIAGNOSIS

Abnormalities compatible with FAS (check ALL that apply)

- ☐ 1. Growth deficiency
- ☐ 2. Structural abnormality
- ☐ 3. Cognitive/behavioural abnormalities
- ☐ 4. No abnormalities compatible with FAS observed
- ☐ 5. No significant abnormalities of any kind observed

Does the Child have FAS?

- ☐ 1. No
- ☐ 2. Yes
- ☐ 3. Deferred

Does the Child have another diagnosis?

- ☐ 1. No
- ☐ 2. Yes (please specify)

a)_____
b)_____
c)_____
d)_____

Is special follow-up or testing recommended?

- ☐ 1. No
- ☐ 2. Yes (please specify)

_____
_____
_____
_____

Notes:

_____
_____
_____
_____
_____
_____

DEPARTMENT OF ANATOMICAL PATHOLOGY

Groote Schuur Hospital
University of Cape Town

Histopathology Laboratory
Tel: 021 404-3134
Fax: 021 404-2386

HOSPITAL : GROOTE SCHUUR HOSPITAL
WARD : H41 LABOUR WARD (MD)
CLINICIAN: DR BOTHA

LABORATORY NUMBER: PN000204B/01

Date of Death : 26/12/2001
Date Received : 27/12/2001
Date of Autopsy :
Authorised : 11/02/2002

PATIENT : [redacted]
FOLDER : [redacted]
DOB : 26/12/2001
RACE/SEX : Unknown Unknown

** POST MORTEM REPORT **

VIDE:

SNOMED CLASSIFICATION:
T10106 - M21630, T65200 - M33120, T71020 - M23070,M33300, T89000 - D5304,E5512,F35300, TX1600 - M33320,
Foramen magnum
Meningomyelocele
Ileum, NOS
Retention, meconium
Left kidney
Congenital renal dysplasia (T-71000)
Retention of fluid, NOS
Fetus, NOS
Fetal alcohol syndrome (E-5512)
Ethyl alcohol
Stillbirth, immature, male (500-999 GMS.)
Cerebral ventricle, NOS
Hydrocephalus, NOS (T-X1600)

CLINICAL DETAILS
The mother was a 20 year old, G2 P1, VDRL - Neg, AH - O Pos, alcoholic and smoker.

She had an u/s examination where a small spina-bifida, lemon-shaped head, small chin, extra digit on hand and renal agenesis was diagnosed. There was a TOP performed at 20 weeks, birth weight 240g.

Date of Birth : 26.12.2001
Date of Death : MISC
Date of PM : 27.12.2001

POST MORTEM FINDINGS

EXTERNAL EXAMINATION
The body was that of an abnormal immature male fetus.

Continued ..

HOSPITAL : GROOTE SCHUUR HOSPITAL SPECIMEN NUMBER: PN000204B/01
WARD : H41 LABOUR WARD (MD)

PATIENT : [redacted]
FOLDER : [redacted]

The external measurements were as follows:-

CH	278mm	Normal @ 22 wks/175 days =	270
CR	190		186
HC	186		
FL	40 -L; 38 -R		39.5
W	460g		400g

There were fused palpebral fissures. There was hypertelorism. The nose was of normal length and there was a long smooth philtgrum. The ears were low set with pinna flattened against the head. There was a large anterior fontanelle with splayed sagittal sutures. There was plantar flexion of the toes and the right foot was rockerbottom. There was abdominal distension. There was a sacral meningomyelocoele measuring 17 X 13mm and situated 1mm above the anus.

RESPIRATORY SYSTEM
The left lung weighed 5.5g and the right 7g. The lungs were normally lobated.

CARDIOVASCULAR SYSTEM
There was normal systemic venous drainage.
There was a PFO and DA.
The pulmonary vessels were normal.
The great vessels arose normally from the arch of the aorta.

GASTROINTESTINAL SYSTEM
The oesophagus was patent.
The caecum was in the right iliac fossa.
The liver, gall bladder and pancreas were normal.

GENITOURINARY SYSTEM
There was right hydronephrosis with the right kidney measuring 33mm in length and the nomral left kidney 26mm.
There was a RPUJ obstruction.
The ureters and bladder were normal.
The testes were abdominal.
There were 2 umbilical arteries.

LYMPHORETICULAR SYSTEM
The thymus and spleen were normal.

ENDOCRINE SYSTEM
Normal adrenals.

CENTRAL NERVOUS SYSTEM
The olfactory bulbs were present. The external gyral was estimated at 17 weeks. The operculum was unexpectedly closed. The brain measured 64mm in length. The brain was photographed for further morphometric assessment. The sacral meningomyelocoele, which measured 17 X 13mm, was bisected longitudinally with Dr Fieggen.

ORGAN WEIGHTS

Brain :	58.5g	Normal @ 22 wks/157 days =	61g
Thymus :	0.8		1.0

Continued ..

HOSPITAL : GROOTE SCHUUR HOSPITAL SPECIMEN NUMBER: PN000204B/01
WARD : H41 LABOUR WARD (MD)

PATIENT : [redacted]
FOLDER : [redacted]

Heart	4	3.4
Lungs	5.5 -L; 7 -R	11
Liver	24.5	23
Spleen	0.5	0.8
Kidneys	5	4.2
Adrenals	2	2.2

PLACENTA
The fixed trimmed placenta weighed 195g and measured 120 X 95 X 30mm. The cord measured 240mm and was inserted 40mm from the nearest margin. The membranes were complete. The placenta was congested on section.

RADIOLOGY
There were 12 pairs of ribs. The long bones were normal. The meningomyelocoele commenced at S2. There was calcification of the frontal and occipital bones.

HISTOLOGY

Placenta : The 3 cord vessels were normal. There was chorionitis. Section of the chorionic plate showed deposits of squames suggestive of amnion nodosum. Amniocytes were vacuolated.
Sections of the placenta show focal syncytial knotting, trophoblast inclusions, sparse perivillous fibrin and chorangiosis.

Organs : The rib had an irregular junction with poorly oriented trabeculae.

The eye was normal.

Sections of the right kidney showed hydronephrosis with dilated calyceal system and thinned cortex. In addition there were foci of cystic renal dysplasia. The left kidney was normal.

The adrenal, larynx, parathyroid, colon, tongue, thymus, pancreas, spleen and lung were normal.

The thyroid had colloid in the follicles, with some colloid showing increased eosinophilia.

The ileum showed meconium ileus.

Sections of the liver showed prominent extramedullary haemopoiesis. There was no fibrosis and iron stain was negative.

The myocardium was normal.

The cervical spinal cord was normal. Sections for the NTD showed diordered neural tissue in the dermis below the epidermis. There was tethering of the cord below the defect with a nodule of disordered nerves attached inferiorly (A13).

Continued ..

HOSPITAL : GROOTE SCHUUR HOSPITAL SPECIMEN NUMBER: PN000204B/01
WARD : H41 LABOUR WARD (MD)

PATIENT : [redacted]
FOLDER : [redacted]

Sections of the brain showed a normal pituitary. There was a dilated aqueduct and 3rd ventricle. The lateral ventricles were also dilated. There was haemorrhage in the periventricular white matter and in the posterior horn of the lateral ventricle with macrophages, presumably related to termination.
Further assessment of the brain as regarding the effects of fetal alcohol exposure will be performed later.

FINAL POSTMORTEM SUMMARY
20 year old, G2 P1, VDRL - Neg, alcoholic and smoker. She had an ultrasound examination and a small neural tube defect, lemon-shaped head, small chin, extra digit on hand, and renal agenesis was diagnosed. TOP was performed at 20 weeks.

The major findings at autopsy were :
- Abnormal immature male fetus.
- Gestational ate 22 weeks according to foot length.
- Facial dysmorphism with hypertelorism, long smooth philtrum suggestive of fetal alcohol syndrome/exposure
- Large anterior fontanelle with splayed sutures due to hydrocephalus secondary to a tethered cord.
- Dilated 3rd ventricle, aqueduct and lateral ventricles.
- Sacral meningomyelocoele resulting in plantar flexion of the toes.
- Right hydronephrosis due to RPUJ obstruction.
- Right renal cystic dysplasia.
- Meconium ileus.
- Abnormal appearance of brain wth closed operculum.

COMMENT : Neural tube defect and hydronephrosis are not listed under common malformations of fetal alcohol syndrome. The possibility of co-existent folate deficiency should be considered.

AUTHORISING PATHOLOGIST : Wainwright H Dr.
REPORTING PATHOLOGIST(S): Dr H Wainwright

REPORT PRINTED ON : 13/02/2002 07:23

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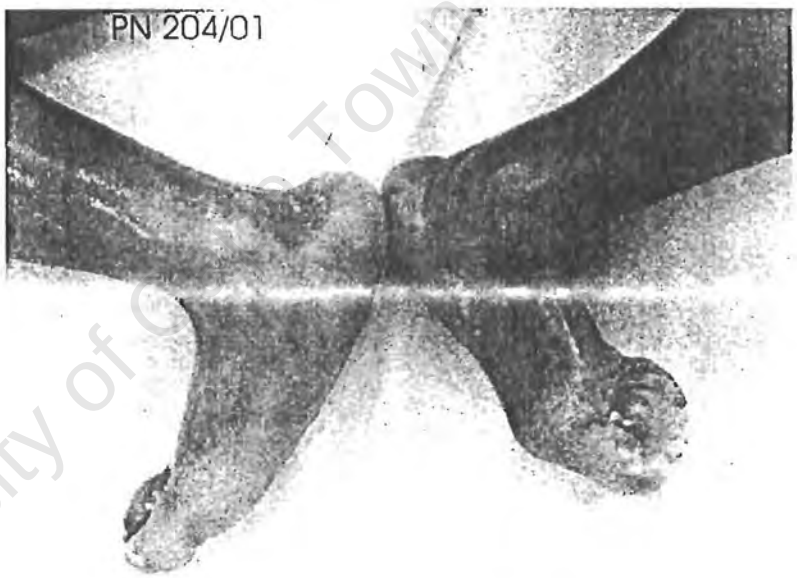

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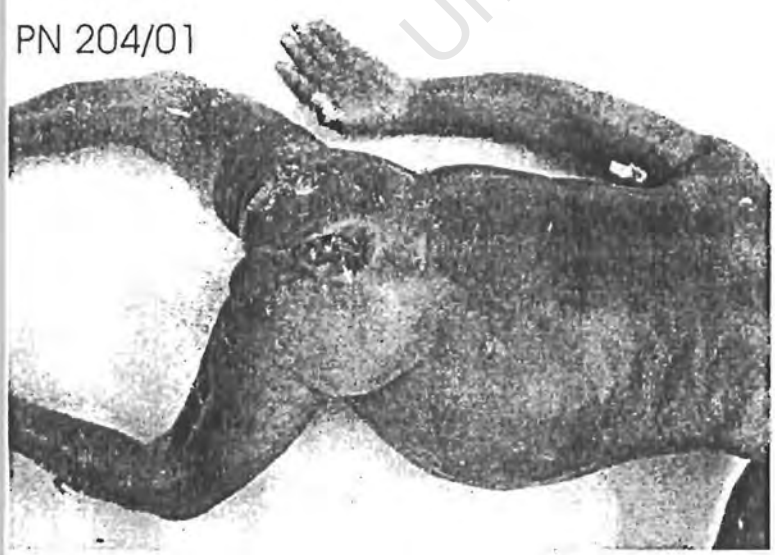

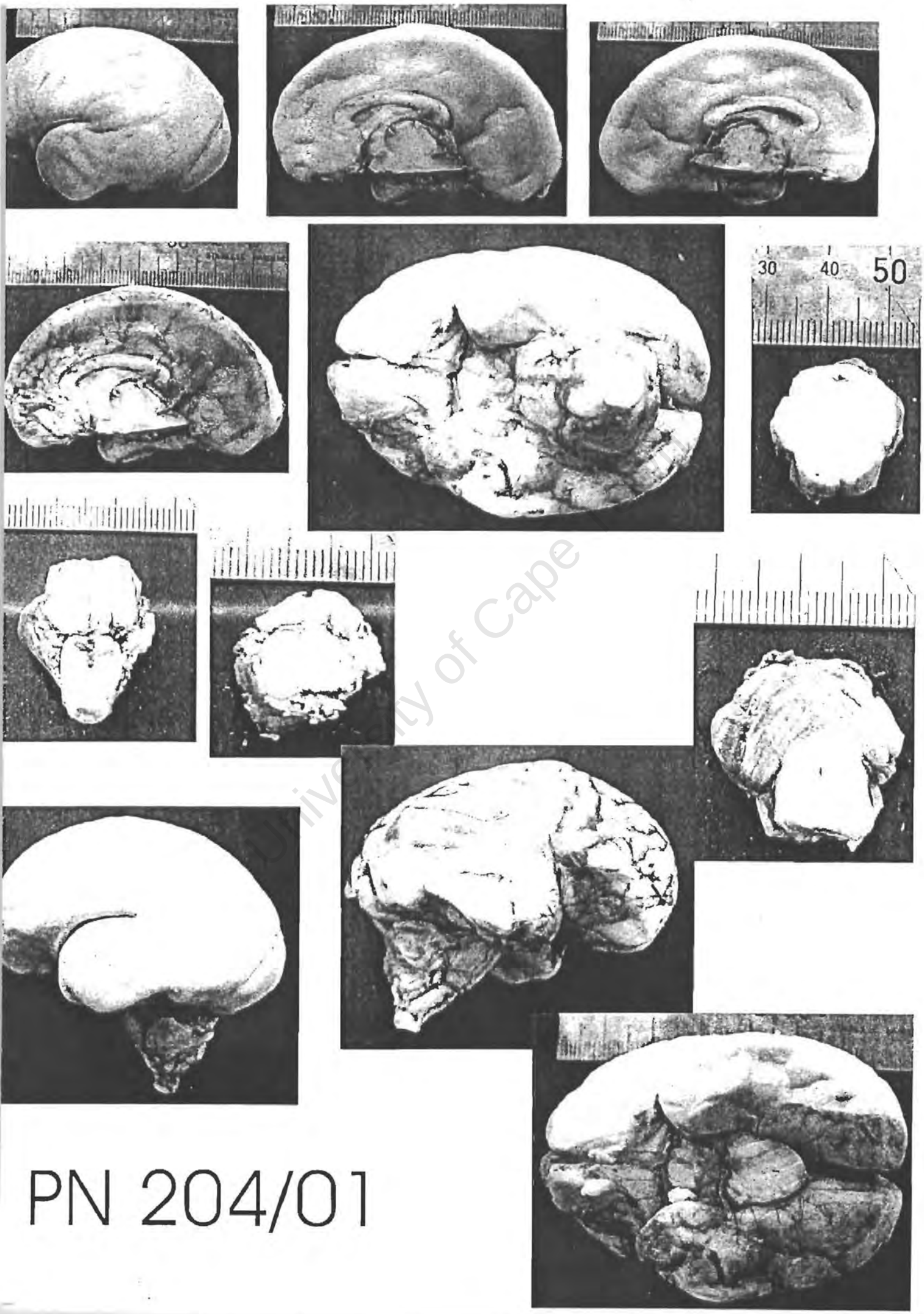

PN 204/01

DEPARTMENT OF ANATOMICAL PATHOLOGY

Appendix 2

Groote Schuur Hospital
University of Cape Town

Histopathology Laboratory
Tel: 021 404-3511
Fax: 021 404-2386

LOCATION : HANOVER PARK MOU
CLINICIAN: Greenfield, D, Dr

LABORATORY NUMBER: PN000189V/99

ADDRESS : Sister in charge
Hanover Park MOU
35 Surran Road
HANOVER
7764

Date of Death : 30/11/1999
Date Received : 01/12/1999
Date of Autopsy :
Authorised : 16/02/2000

[redacted]
FOLDER : 99101708
DOB : 30/11/1999
RACE/SEX : Coloured Male

FASAR-9.

** POST MORTEM REPORT **

VIDE:

SNOMED CLASSIFICATION:
T89000 - D5304,E5512,F35280, TX8040 - M20190,
Fetus, NOS
Fetal alcohol syndrome (E-5512)
Ethyl alcohol
Stillbirth, premature, male (1000-2499 GMS.)
Optic nerve, NOS
Coloboma

PROVISIONAL ANATOMICAL DIAGNOSIS
- FAS
- Premature male
- Gestational age 33 weeks according to footlength.

CLINICAL DETAILS
Maternal History: Age : 32 years, G4 P3, Booked, VDRL - Neg,
Gest 32/52
Habits : ++ Alcohol/Smoker

Delivery: Mode : BBA at Home
Apgars :
Birth Weight: 1830g

Date of Birth: 30.11.1999
Date of Death: Dead on arrival
Date of PM : 01.12.1999

Continued ..

LOCATION : HANOVER PARK MOU SPECIMEN NUMBER: PN000189V/99

PATIENT : [redacted]
FOLDER : [redacted]

POST MORTEM EXAMINATION

External examination

The body was that of a premature male infant. There was a large anterior fontanelle. The eyes were deeply set with downslanting palpebral fissures and a deep bridge of nose. The nose was short with patent nostrils. There was a smooth prominent long upper lip. The palate, gum margin, and tongue were normal. The hands, feet, creases and nails were normal. The breasts, male genitalia and anus were normal.

The external measurements were as follows :

CH	410mm	Normal for G Age of 33 weeks =	416mm
CR	295		293
HC	306		
FL	66 -L		
	67 -R		65
W	1780g		1663g

Thoracic circumference = 237mm
Abdominal = 240
Intercanthal distance = 22

Respiratory System

Lungs : The right lung was bilobed with a partial cleft in the right upper lobe. There were extensive pleural haemorrhages bilaterally.

Cardiovascular System

Venous drainage : Normal
Great vessels : Arose normally from the arch of the aorta
Heart : Epicardial haemorrhages. No VSD.
Foramen Ovale and Ductus Arteriosus : Patent

Gastrointestinal System

Liver : Congested
Gallbladder : Present
Pancreas : Normal
Gut : Clear liquor was present in the stomach. The was inspissated meconium in the terminal ileum and R. colon.

Position of caecum - right iliac fossa.

Genitourinary System

Kidneys : Normal with prominent fetal lobulation.
Ureters : Normal
Bladder : Normal

Reproductive organs : Normal testes.

Continued ..

LOCATION : HANOVER PARK MOU SPECIMEN NUMBER: PN000189V/99

PATIENT : [redacted]
FOLDER : [redacted]

Lymphoreticular System
Spleen : Normal
Thymus : Petechial haemorrhages. A nodule ?lymph node was present in the neck.

Endocrine System
Adrenals : Congested on section.

Central Nervous System
The gyral pattern was in keeping with 26 weeks gestation. The surface had congested meninges. A superior temporal gyrus was present.
On sectioning the fixed brain no obvious abnormality was seen.

ORGAN WEIGHTS

Brain	:	260g	Normal for 33 wks gestation =	227g
Heart	:	13.0		12.7
Lung R	:	25.5		
Lung L	:	20.5		
T	:	16.0		37
Liver	:	75.5		69
Adrenals	:	5.0		4.9
Kidneys	:	19.0		16.1
Spleen	:	4		4.6
Thymus	:	8.0		6.5

Lung/Body ratio : 0.025 (n > 0.015)

Brain/liver ratio : 3.4 (n 2.5 - 3,0)

Placenta

Membranes :incomplete
Cord insertion : 40mm from the edge.
Cord length : 380mm
Plate measures : 160 X 135 X 25mm
Weight : 285g
Serial section showed a marginal haemorrhage and pallor.

Radiology
Ossification centres present : Calcaneus and talus.
Short limbs on X-Ray.

HISTOLOGY
Placenta:
normal. There was stem villous fibrosis, perivillous fibrin deposition and acute congestion.
No cause for the premature rupture of membrnaes was found.

Continued ..

LOCATION : HANOVER PARK MOU SPECIMEN NUMBER: PN000189V/99

PATIENT : [redacted]
FOLDER : [redacted]

ORGANS

Sections of the liver showed more congestion of the left lobe than the right, EMH and normal bile ducts. There was no fibrosis seen on connective tissue stain (BSR). There was sparse iron in zone 1.
No iron was present in the spleen which had normal white pulp and a trabecular pattern.
The head of the pancreas was normal with sparse EMH. Occasional large islets were seen in the tail.
The colon and terminal ilem had inspissated meconium.
The oesophagus and proximal small intestine were normal.
Sections of the lung showed pleural and interstitial haemorrhage, dilated lymphatics, pulmonary oedema and sparse squames.
The myocardium, parathyroid and marrow were normal. The thymus had interstitial and petechial haemorrhages.
There was also haemorrhage in the kidneys and adrenals. There were 6-8 generations of glomeruli. Adrenal fat stain showed sparse fat in the deep fetal cortex. There were absent colloid stores in the thyroid and thymic nodules.
The rib had a straight junction and mild crossbranching.
Section of one eye (7) showed a small optic nerve coloboma. The retina and lens was normal.
The pituitary and cervical cord were normal.
Sections of the spinal cord were normal. There was a filum terminale with a large central canal.
Sections of the cerebral cortex showed oedema of both cortex and white matter. Betz cells were seen. (A22). The meninges were congested. No hypoxic change was seen in the hippocampus.
Sections of the cerebellum show delayed maturation with an external granular layer of 1/2 and Purkinje cells without nucleoli indicating maturation of 28-30 weeks. The pons and medulla were normal.
Myellin stains showed myelination of the medial leminiscus in the medulla (aexpected at 26 Weeks), but not of the pyramids in the pons (expected 36 weeks).

FINAL POSTMORTEM SUMMARY

32 year old, G4P3, booked, VDRL - Neg, gestational age 32 weeks alcohol and smoker. She delivered prematurely at home - birth weight 1830g, a male infant with fetal Alcohol Syndrome.

The major findings at autopsy were :

- Premature male.
- Gestational age 33 weeks according to footlength.
- Evidence of typical Fetal Alcohol Syndrome.
- No microcephaly.
- Delayed cerebral maturation:- External gyral pattern of 26 weeks.
  Cerebellar maturation 28-30 weeks.
- No IUGR.
- Incomplete lobation of R lung.
- Short limbs.
- Thymic nodule in the neck.
- Optic verve coloboma.

Continued ..

LOCATION : HANOVER PARK MOU SPECIMEN NUMBER: PN000189V/99

PATIENT : [redacted]
FOLDER : [redacted]

AUTHORISING PATHOLOGIST : Wainwright H Dr.
REPORTING PATHOLOGIST(S): Dr. H Wainwright

REPORT PRINTED ON : 16/02/2000 08:24