1995

Selected pregnancy outcomes related to maternal glucose levels in women without gestational diabetes

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SELECTED PREGNANCY OUTCOMES RELATED TO MATERNAL GLUCOSE LEVELS IN WOMEN WITHOUT GESTATIONAL DIABETES.

A thesis submitted in fulfilment of the requirements for the award of the degree of

MASTER OF SCIENCE (HONOURS)
UNIVERSITY OF WOLLONGONG

by

Robert Moses

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF WOLLONGONG
1995
DEDICATION

To Karen for her understanding, encouragement and patience.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of contents</td>
<td>1</td>
</tr>
<tr>
<td>Glossary</td>
<td>2</td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Literature review</td>
<td></td>
</tr>
<tr>
<td> Historical considerations</td>
<td>6</td>
</tr>
<tr>
<td> Diagnosis of GDM</td>
<td>9</td>
</tr>
<tr>
<td> The risk to the fetus</td>
<td>11</td>
</tr>
<tr>
<td> The effects of minor degrees of glucose intolerance on pregnancy outcomes</td>
<td>15</td>
</tr>
<tr>
<td>Patients and Methods</td>
<td></td>
</tr>
<tr>
<td> Diagnosis</td>
<td>23</td>
</tr>
<tr>
<td> Data collection procedures</td>
<td>25</td>
</tr>
<tr>
<td> Pregnancy and fetal outcome data</td>
<td>26</td>
</tr>
<tr>
<td> Data collection - type and definitions</td>
<td>27</td>
</tr>
<tr>
<td> Exclusions</td>
<td>29</td>
</tr>
<tr>
<td> Statistical methods</td>
<td>30</td>
</tr>
<tr>
<td> Ethical approval</td>
<td>32</td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td> Frequency of assisted delivery</td>
<td>36</td>
</tr>
<tr>
<td> Parity</td>
<td>40</td>
</tr>
<tr>
<td> Pregnancy Induced Hypertension</td>
<td>41</td>
</tr>
<tr>
<td> Rate of induction</td>
<td>43</td>
</tr>
<tr>
<td> Birthweight of the baby - absolute</td>
<td>45</td>
</tr>
<tr>
<td> Birthweight of the baby - relative</td>
<td>48</td>
</tr>
<tr>
<td> Apgar score</td>
<td>50</td>
</tr>
<tr>
<td> Morbidity</td>
<td>51</td>
</tr>
<tr>
<td>Discussion</td>
<td>53</td>
</tr>
<tr>
<td>Conclusion</td>
<td>69</td>
</tr>
<tr>
<td>References</td>
<td>71</td>
</tr>
<tr>
<td>Appendix</td>
<td>86</td>
</tr>
</tbody>
</table>
Glossary

ACOG  American College of Obstetricians and Gynecologists.
ADA  American Diabetes Association.
ADIPS  Australasian Diabetes in Pregnancy Society.
GDM  Gestational diabetes mellitus.
GTT  Glucose tolerance test.
gtt0  The fasting glucose result before a GTT.
gtt2  The 2 hour glucose result of a GTT.
IDDM  Insulin dependent diabetes mellitus.
LGA  Large for gestational age.
MGTT  A GTT where only the gtt2 is measured.
NDDG  National Diabetes Data Group.
NIDDM  Non insulin dependent diabetes mellitus.
PIH  Pregnancy induced hypertension.
RACOG  Royal Australasian College of Obstetricians and Gynaecologists.
SCN  Special care nursery.
SGA  Small for gestational age.
WHO  World Health Organisation.
Disorders of carbohydrate tolerance have an immediate and significant impact on the outcome of pregnancy. Pregnancy in women with established diabetes, either insulin dependent diabetes mellitus (IDDM) or non insulin dependent diabetes mellitus (NIDDM), has frequently been associated with an adverse fetal outcome. The most frequently encountered adverse outcomes are related to diabetic control in the first and the third trimesters. The incidence of congenital malformations and early spontaneous abortions is associated with poor maternal diabetic control at the time of conception and during the first trimester. The incidence of macrosomia is largely determined by maternal diabetic control during the last trimester. However it was noted around fifty years ago that some women who had macrosomic infants developed diabetes shortly after delivery or during a subsequent pregnancy. Thus the concept of a disorder of carbohydrate metabolism or a degree of carbohydrate intolerance intermediate between "normality" and established diabetes came about.

This intermediate state is now known as gestational diabetes mellitus (GDM) which is currently defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" (Metzger, 1991). A diagnosis of GDM identifies a maternal/fetal unit at increased risk of certain complications. For the fetus there are the immediate risks associated with the availability of excessive nutrition during the last trimester. There is now an increasing body of evidence that this abnormal intrauterine nutritional milieu can result in problems in childhood, adolescence and in subsequent generations. There is also the long term risk to the mother of developing NIDDM in future years.
Despite knowledge about the risks associated with a diagnosis of GDM there remains considerable controversy about whether the diagnosis actually exists and, if it does exist, how it should be diagnosed and who should be tested. The Australasian Diabetes in Pregnancy Society (ADIPS) and the American Diabetes Association (ADA) recommend that all women should be tested in all pregnancies. The American College of Obstetricians and Gynecologists (ACOG) recommend that only women with certain risk factors should be tested while the Royal Australian College of Obstetricians and Gynaecologists (RACOG) have no policy about who should be screened but a recommendation about the preferred method of screening!

Hunter et al (1989) in a chapter of a widely read and influential textbook of obstetrics felt that, except for research purposes, all forms of glucose tolerance testing in pregnancy should be stopped as the potential benefits did not compensate for the actual disadvantages. One of the major concerns expressed was related to the distress of being labelled “diabetic”. A less extreme and more reasonably argued approach against GDM as an entity has been advanced by Jarrett (1993) who felt that any unfavourable obstetric outcomes were more likely to have come about on the basis of maternal age and weight rather than any disorder of maternal glucose metabolism. Ales et al (1989) felt that the problem of macrosomia had been overrated and problems only developed if the fetus weighed more than 4500 g.

The proponents of GDM as a medical disorder worthy of immediate and long term care have several serious conceptual and methodological problems to overcome. There is no national or international consensus about the preferred method of testing for glucose intolerance, the dose of glucose to be used and whether the glucose tolerance test (GTT) alone is sufficiently accurate or
reproducible to be the sole diagnostic test. One test is being used to identify different groups of risks in two different people. The GTT criteria currently used for the diagnosis of GDM have been based on either the probability of the mother converting to NIDDM (O'Sullivan et al, 1964) or derived by consensus from non-pregnant criteria (WHO, 1980). No criteria for determining the immediate and long term risks to the fetus have so far been validated.

There has in recent years been an increasing body of evidence from animal experiments and both retrospective and prospective epidemiological data in humans to suggest that many “adult” diseases have some of their origins in disorders of fetal intrauterine nutrition. In addition, minor degrees of glucose intolerance below the diagnostic criteria for GDM have been found to be associated with many of the fetal complications found with unequivocal GDM. These findings have led to the suggestion that there may well exist a continuum of risk for the fetus associated with increasing levels of maternal glucose below the diagnostic level for GDM.

The aim of this study is to examine certain aspects of fetal and maternal outcomes in pregnancies not complicated by GDM and to relate these to the maternal glucose levels. The hypothesis is that there will be a gradation of risk associated with increasing maternal glucose levels.
Literature review - Historical considerations.

It is difficult to pinpoint exactly when it became apparent that some women developed a reversible form of carbohydrate intolerance during pregnancy and that this was associated with an increased fetal death rate and therefore was a substantive clinical problem. As could be reasonably expected the initial studies exploring the relationship between temporary maternal glucose intolerance in pregnancy and an increased rate of fetal morbidity and mortality were both retrospective and inferential.

The concept of a particular kind of diabetes associated with pregnancy and antedating the onset of permanent diabetes in the mother by many years was first given scientific credence by Miller et al in 1944. In a retrospective study they found that the fetal mortality rate in pregnancies where diabetes developed was five times higher than in a non-diabetic control group. One-third of the mothers who developed diabetes during the pregnancy did not require insulin and their fetal mortality was three times the background rate. This group of women could be considered to have what is now known as GDM though the possibility that they had NIDDM discovered during the pregnancy was not explored. That these women had GDM could be inferred from the observation that an increased perinatal mortality rate could be demonstrated in pregnancies 15 to 20 years before the onset of clinically recognised diabetes. In addition, the perinatal mortality rate increased the closer the women came to the eventual diagnosis of diabetes.

Islet cell hypertrophy is a feature of stillborn fetuses of mothers with established diabetes. In 1952 it was demonstrated that islet cell hypertrophy
could be found in stillborn infants of mothers without diabetes who subsequently developed NIDDM (Van Beek, 1952). In 1958 Jackson et al reported that the overall stillbirth rate in prediabetic women was 14% rising to 29% during the 5 years before the diagnosis of diabetes.

Also in 1958 Carrington et al presented their data of the results of testing for carbohydrate intolerance in pregnancy and the treatment of women with abnormalities - a seminal paper which could be considered the forerunner of modern diagnosis and treatment. Women with high risk pregnancies, with criteria that are now universally recognised as historical risk factors for GDM, had a GTT at various stages during pregnancy. Those women with abnormal results were treated with diet and, in a few instances, with insulin. Those women diagnosed and treated early had no fetal deaths while those women who were diagnosed at a late stage or around the time of delivery had an infant mortality rate of 25.6%. The observation that the “difference between treated and untreated patients indicate that early diagnosis is important” was as valid then as it is now.

The term “gestational diabetes” appeared in the authoritative medical literature in 1961 (O’Sullivan). In a retrospective survey the results of glucose tolerance testing in 8344 high risk patients delivered between 1954 and 1959 in Boston, USA, were presented. Using diagnostic criteria, which in some centres is still used today with only minor modifications, the overall incidence in the women tested was 0.73%. No mention was made of fetal outcome in this paper. Three years later the validity of the diagnostic criteria for predicting the conversion to NIDDM were presented (O’Sullivan et al, 1964).
The possibility of an increased perinatal mortality rate associated with GDM was prospectively addressed in an observational study for the first time in 1973 by O'Sullivan et al. A perinatal mortality rate of 6.4% in 187 pregnancies complicated by GDM was more than four times the rate of 1.5% in 259 control patients. In another observational study Pettitt et al (1980) found that the rates of perinatal mortality, macrosomia, toxaemia and Caesarean section varied directly with the maternal glucose concentration 2 hours after a 75 g glucose load administered in the morning without fasting. They concluded that the “distribution of third-trimester glucose levels were unimodal and continuous” and therefore it was “not possible to identify a specific level of glucose intolerance that can be designated as gestational diabetes”.

The selected papers outlined above, progressing from retrospective reviews to the delineation of gestational diabetes and to prospective observational studies have clearly outlined the extent and seriousness of the problem of GDM. It would now not be ethically possible to repeat any observational study unless the glucose level for non-intervention was set at such a low level as to make any unfavourable fetal outcome extremely improbable. While advances in obstetric and perinatal management continue to make pregnancy and childbirth an increasingly low risk event, the lessons from history can only be forgotten or ignored with extreme peril.
Literature review - Diagnosis of GDM.

There is little consensus about the ideal way of diagnosing GDM. This is due to methodological differences between the established criteria, difficulties in determining criteria sympathetic to the fetal outcome and very real differences in the glycaemic responses of the populations being tested.

The results of glucose tolerance testing in pregnancy will vary depending on the period of gestation (Forest et al, 1983; Hatem et al, 1988) the racial group (Phillipou, 1993) and perhaps the ambient temperature (Schmidt et al, 1994; Moses et al, 1995). When dealing with fine diagnostic margins between normality and GDM the GTT has been criticised for a lack of reproducibility (Catalano et al, 1993).

Current clinical practices regarding testing, screening and the diagnosis of GDM vary considerably (Nelson - Piercy et al, 1993; Hunter et al, 1990). The screening tests currently employed use different glucose loads, may be used fasting or non-fasting, may rely on a one or two hour glucose sample and have variable cut off points for further testing (Cousins et al, 1991). The definitive oral GTT, to mention a few, may use the O'Sullivan criteria (O'Sullivan et al, 1964), the modification of Carpenter and Coustan (Carpenter et al, 1982), the National Diabetes Data Group (NDDG) criteria (NDDG, 1979), the WHO criteria (WHO, 1980) or in Australia the Mercy Hospital criteria (Abell et al, 1975) or the ADIPS criteria (Martin, 1991).

The diagnostic criteria for GDM have concentrated on glucose measurement for historical reasons, ease of measurement and reproducibility between laboratories. It is now apparent that variations in insulin sensitivity and insulin resistance as well as disorders of fat and amino acid metabolism can all be an
intrinsic part of the GDM syndrome (Ratner, 1993). Alternative diagnostic criteria using amniotic fluid insulin (Persson et al, 1989) and maternal glycosylated proteins (Morris et al, 1986) have been suggested. Buchanan et al (1994) have suggested the use of fetal ultrasound measurements to identify higher risk subgroups.

Ultimately the most suitable means of defining a disease must be based upon the morbidity associated with that condition. The diagnosis of GDM has so far been almost exclusively based upon measurement of maternal glucose levels. For practical reasons this is likely to remain the situation for the immediate future. The maternal glucose level, and the method of testing, which most accurately defines the risks to the fetus have yet to be determined.
It has become increasingly apparent that many adult diseases have their origins in infancy or as a result of factors operating in the intrauterine environment. Maternal undernutrition or specifically, protein/calorie malnutrition, may result in a fetus who is either small for gestational age (SGA) or who has a disturbance of anthropometry. Excessive fetal nutrition, perhaps as a consequence of maternal diabetes, may lead to a large for gestational age (LGA) fetus or a macrosomic fetus with excessive fat accumulation.

Interest in the linkage between ischaemic heart disease and birth weight became an issue for the first time towards the end of the eighties. Barker et al (1989a) examined the relationship between birthweight and cardiovascular mortality in 5654 men born between 1911-1930 in Hertfordshire, England. Men with the lowest weights at birth (and at one year) had the highest death rates from cardiovascular disease. In England, past trends in infant mortality, taken as a surrogate for infant health and nutrition, correlated well with subsequent trends in ischaemic heart disease (Osmond, 1987). It could be postulated that the decline in cardiovascular deaths in other Western countries which began in the sixties could be related more to changes in infant morbidity at the turn of the century than to subsequent health interventions (Barker, 1989b).

The Hertfordshire report was the first part of an increasing body of epidemiological evidence linking low birthweights with adult onset hypertension (Barker et al, 1990), NIDDM (Hales et al, 1991), and high cholesterol concentrations (Barker et al, 1993). Thinness at birth, either determined by a low ponderal index or a relative reduction in abdominal circumference was associated with insulin resistance (Phillips et al, 1994) and
the features of Syndrome X (Barker et al, 1993).

The epidemiological data outlined above also sit comfortably with the thrifty gene hypothesis of NIDDM (Hales et al, 1992). A significant impediment to a more generalised extrapolation of these findings has been the fact that the results have so far been confined to Caucasiens living in one country. However corroborative data are now becoming available from different ethnic groups in the USA (Valdez et al, 1994). Animal experiments (Swenne et al, 1987), at least as far as the development of diabetes is concerned, have suggested that protein-calorie malnutrition may be an important aetiological factor.

If on one hand reduced fetal nutrition leading to low birthweights can be linked to serious adult diseases, then on the other hand fetal overnutrition can also have deleterious effects. Maternal diabetes mellitus, either established before the pregnancy and poorly managed during the pregnancy, or gestational diabetes in the last trimester are examples par excellence of this particular problem. In the Pima Indians the risk of subsequent diabetes was 'U' shaped with a higher rate for both low and high birthweight infants (McCance et al, 1994). According to the Pedersen hypothesis (Pedersen et al, 1977), elevated maternal glucose levels cross the placenta and lead to an increased fetal insulin secretion. Fetal insulin is a potent growth factor and promotes fat storage of this excessive metabolic fuel resulting in a high rate of macrosomia. This fuel mediated teratogenesis (Freinkel, 1980) leads to an increased risk of several childhood, adolescent and adult onset disorders.

Using Wistar rats it has been demonstrated that the degree of fetal islet cell hyperplasia at birth was correlated with the severity of the maternal diabetes
As young adults the pups born from mothers with diabetes were often heavier and had impaired glucose tolerance on stimulation (Bihoreau et al, 1986; Gaugier et al, 1990). The mechanism of this insulin resistance appeared to vary depending on the severity of the maternal diabetes (Aerts et al, 1988). Females of the second generation had a high risk of developing GDM, an observation which led to the question as to whether GDM was an acquired condition (Aerts et al, 1979). The metabolic consequences of a pregnancy complicated by GDM can be detected in at least the third generation (Van Assche et al, 1991).

Prospective long-term longitudinal studies of humans over several generations are, for obvious reasons, difficult. However the Pima Indians of Arizona have provided a unique opportunity for the study of GDM because of a very high prevalence rate of NIDDM and a tendency to develop this condition at an early age. The Pima Indians thus provide an excellent model for the study of GDM and the effect of this complication on subsequent generations.

There is a definite genetic tendency towards NIDDM. In the Pima Indians the risk is significantly higher for a child to develop NIDDM if the mother rather than the father has had NIDDM (Knowler et al, 1985). In addition, 35% of patients with GDM are offspring of diabetic mothers and diabetic mothers are five times more likely than diabetic fathers to have a daughter who develops GDM (Martin et al, 1985). The data from the Pima Indians also indicate that there is a profound intrauterine influence in addition to any genetic tendency. Impaired glucose tolerance at ages 15-19 years is present in 33% of children whose mother had diabetes during pregnancy compared to 1.4% in children whose mother developed diabetes after the pregnancy (Pettitt et al, 1988).
In the Pima Indians the probability of a child having impaired glucose tolerance or being a diabetic increased as the maternal glucose level increased following a 75g glucose challenge (Pettitt et al, 1991). This stratification of risk applies even for maternal results which by any criteria are non-diabetic. Of greatest concern, and of enormous public health importance, was the finding that those female offspring who had become pregnant had a prevalence of GDM of 18.8% if their mother’s glucose during glucose tolerance testing in pregnancy was between 5.6-6.6 mmol/L and 50% if their mother’s glucose level was ≥7.8 mmol/L but below the level considered diagnostic of diabetes.

In addition to problems associated with the development of NIDDM and GDM, the offspring of mothers with GDM also appear likely to have problems with neuropsychological development and with a lower IQ. This association was first made apparent by Churchill et al (1969) and later by Rizzo et al (1991).

Thus fetal undernutrition, most likely due to maternal protein/calorie deprivation, and fetal overnutrition, most commonly associated with maternal GDM, can lead to adult diseases and problems in subsequent generations. There appears to be no distinct and definable point of the maternal glucose level at which these complications develop and a continuum of risk can be considered to exist (Pettitt et al, 1980). Thus criteria used to define maternal GDM on the basis of the subsequent risk of the mother developing NIDDM are most likely inappropriate for the fetal risk during and after pregnancy. With respect to glucose tolerance testing in pregnancy, there may be at least two different criteria required for two different areas of risk.
Literature review - What are the effects of minor degrees of glucose intolerance on fetal and pregnancy outcomes?

The possibility that glucose levels in the mother below the threshold for the diagnosis of GDM could be a risk factor for a poor pregnancy outcome was brought into sharp focus by Tallarigo et al (1986). This paper provided the stimulus for a critical examination of the previous literature and for several prospective studies.

Tallarigo et al prospectively examined several pregnancy outcomes (macrosomia, fetal mortality, prematurity, toxaemia and Caesarean section rates) in 293 prenatal patients over a three year period. These women had had a standard 100 g GTT (O'Sullivan et al, 1964) at the beginning of the third trimester and did not have GDM. They were divided into three groups on the basis of the 2 hour plasma glucose level after the GTT. Group A had a glucose level \( \leq 5.6 \) mmol/L, group B had a glucose level between 5.7 and 6.7 mmol/L and Group C a glucose level between 6.8 and 9.1 mmol/L.

The macrosomic rate from groups A, B and C were 9.9%, 15.5% and 27.5% respectively while the rate of maternal complications (toxaemia plus Caesarean section) were 19.9%, 25.9% and 40.0%. The increasing risk with rising maternal glucose levels could not be explained by either age or body weight. The women who had macrosomic infants or who had a maternal complication had significantly higher glucose values than those who did not.

There are, however, some problems with this paper which could detract from the significance of the findings. Firstly, the type of patients who attend a prenatal clinic which sees less than 100 patients each year was not defined.
Secondly, macrosomia was defined on the basis of a birthweight ≥ 4,000 gms and was not corrected for gestational age or gender. Thirdly, the combining of toxaemia and Caesarean sections as an indication of maternal risk is not a physiological association. Fourthly the women in group C included some who would now be classified as having GDM by the WHO criteria. The "letter" criticisms which followed this publication included comments on the statistical methodology (Mimouni et al, 1987), the laboratory technique for measuring glucose (Dietrick, 1987), the inclusion of women with poor obstetric histories (Weiss, 1987), and the failure to adjust fetal birthweight data for the mother's age and weight (Jarrett, 1987).

Despite these shortcomings and criticisms this paper did provide the intellectual stimulus for others to examine pregnancy outcomes in women with glucose levels below the diagnostic criteria for GDM. These papers can be loosely divided into two groups. The first group, (Li et al, 1987; Weiner, 1988; Roberts et al, 1993) which are generally cited as evidence that there is no gradation of risk with increasing maternal glucose levels, examined major endpoints like mortality and major degrees of morbidity. The second group, (Pettitt et al, 1980; Tallarigo et al, 1986; Leiken et al, 1987; Langer et al 1989; Lindsay et al, 1989; Kaufmann et al, 1992) which have generally found an increase in adverse obstetric outcomes with increasing levels of maternal glucose, examined softer endpoints such as the rates of macrosomia, induction and Caesarean section.

In 1987 Li et al from Hong Kong compared the efficacy of the WHO GTT criteria to the NDDG criteria. As a side issue of this evaluation, some observations about perinatal outcomes were presented. On the basis of testing women with historical risk factors for GDM, 245/1546 (16%) had an
abnormal NDDG GTT and 216 subsequently had a WHO GTT. Using the WHO criteria, 111 women (51%) had normal glucose tolerance (NGTT), 98 (45%) were impaired (IGTT) and 7 (3%) had diabetes. Those women who had either a NGTT or an IGTT were divided into a control or treatment group. The authors felt that the “perinatal outcome in these two groups was comparable” and whatever differences were apparent “probably have no clinical significance”. This conclusion has been used by others to imply that as treatment produced no differences, there would appear to be little point in establishing a diagnosis which appeared not to be relevant.

However there are some difficulties with these conclusions when the substance of the paper is studied. The patients were selected on the basis of historical risk factors and ultimately there were relatively low numbers involved. The women with IGTT who were treated had a lower mean birth weight, no babies weighing more than 4000 g and only 13% of babies weighing more than the 90th centile compared to a rate of 24% in the untreated control group. No mention was made of the induction rate or the frequency of assisted deliveries.

Weiner (1988) reported on the outcomes of 312 women with normal glucose tolerance and included a “control” group of women with GDM. The rationale for this was that if increasing levels of maternal glucose posed additional risks to the pregnancy then this should be most pronounced in women with GDM.

Weiner found that if the glucose results of those women without GDM were ranked, many of the abnormalities only occurred in the highest ranked groups and thus did not suggest a gradient of risk. Overall there was a positive correlation between maternal age and the glucose result but no relationship
between birthweight and the maternal glucose result. However there was an increase in the proportion of mothers who had a baby weighing more than the 90th centile from 4.4% if the 2 hour glucose level on the GTT was < 100 mg% (5.6 mmol/L) to 18.4% if the 2 hour glucose level on the GTT was between 140-159 mg% (7.8-8.8 mmol/L). Within the same grouping the pre-eclampsia rate increased from 4.4% to 10.5%. This study was based upon relatively small numbers, relative in so far as there would need to be a much larger group to demonstrate the low probability of major complications like perinatal death or significant morbidity. The need to include a "control" group of women with GDM, who were all treated with either diet or a combination of diet and insulin, to confirm the hypothesis that the risks will continue to increase, was difficult to understand.

Witter et al (1988) investigated whether the 50 g glucose challenge test was useful for predicting macrosomia in women without GDM. They came to the conclusion that minor abnormalities of carbohydrate intolerance are a risk factor for macrosomia but the result of the glucose challenge test was a poor predictor of this. The strength of this paper was the large number of patients examined while the weakness was that macrosomia was the only outcome measured.

The final study, which is frequently cited as showing no differences in pregnancy outcomes for maternal glucose levels below the threshold for GDM is that of Roberts et al (1993) from Belfast. Over a 47 month period 953 women selected according to established risk factors for GDM (and representing only 7% of the total obstetric population) had a WHO GTT. One hundred and thirty five women had an impaired GTT and overall had no difference in the fetal outcomes selected or neonatal morbidity compared to a control group.
However despite this reassuring conclusion, the mothers with an impaired GTT had a significantly higher rate of both induced labour and Caesarean section.

The papers described above were in general able to conclude that there were no significant differences related to varying levels of maternal glucose for the endpoint selected. However if less "major" endpoints had been chosen then each of the above papers demonstrated adverse obstetric outcomes like increased risks of macrosomia, induction and Caesarean section associated with the maternal glucose level. In this respect the above papers differ little from those which will be reviewed below except that those described below have looked at a wider and more relevant range of obstetric outcomes.

Pettitt et al (1980) reported on the maternal and fetal outcomes of 811 pregnancies in 604 Pima Indian women who, over a thirteen year period, all had had a glucose tolerance test during the third trimester. The rates of perinatal mortality, macrosomia, toxaemia and Caesarean section varied directly with the glucose concentration. In addition to maternal glucose levels, maternal age and weight were predictive of both macrosomia and toxaemia. This study has particular relevance to the patients examined in this thesis because, in contrast to most American studies, the dose of glucose used was 75 g and only the 2 hour glucose level was considered. For those mothers with a glucose level at 2 hours of less than 5.6 mmol/L (100 mg%) a Caesarean section was required in 2.3%, toxaemia developed in 0.2% and there was a 23.2% rate of LGA infants. For those mothers with a 2 hour glucose level more than 11.2 mmol/L (200 mg%) the section rate was 14.3%, toxaemia developed in 62.5% and the rate of LGA infants was 80.0%. The results in between demonstrated a gradient of risk.
There are some unusual features of the Pima Indians which make these absolute rates not generally applicable. They are a population who develop NIDDM with a very high frequency and at a relatively early age. They are also much heavier than the average American. However the importance of these figures is not the absolute rates but the definite gradation and increase of risk with increasing maternal glucose levels.

Langer et al (1989) reported on the results of management in a group of women with one abnormal result on a glucose tolerance test. It had previously been demonstrated by both Langer et al (1987) and Lindsay et al (1989) that women with one abnormal value on a GTT done during pregnancy were more likely to have a fetus with macrosomia and metabolic complications than women with no abnormalities on their GTT. Leiken et al (1987) also reported similar findings and furthermore felt that the risk associated with the maternal glucose level remained after adjustment for other macrosomic risk factors. Kaufmann et al (1992) were unable to demonstrate that women with one abnormal value had a higher rate of LGA after correction of birth weight for gestational age. The suggestion was made that higher glucose levels may result in slightly longer gestational period. The observation was also made that the current NDDG criteria for GDM may be too high for predicting those women who would have a LGA infant.

The purpose of the 1989 study of Langer et al was to see if intervention in the group with one abnormal value could reduce neonatal morbidity. All women had a 50 g glucose challenge test followed in those who were positive by a 100 g glucose load GTT. Glucose values were interpreted according to the
NDDG criteria. There were 126 women with one abnormal value on their GTT (2 abnormal values being required for the diagnosis of GDM) and they were randomly divided into two groups. One group continued with their usual diet while the other group received treatment with diet and/or insulin as if they had GDM. There were 146 women in a control group who had had a normal GTT. Of the women with one abnormal value on their GTT, the treated group has a significant reduction in neonatal metabolic complications and in the number of large infants compared to the untreated group. There were no significant differences in pregnancy outcomes between the treated group and the control group.

What these studies have demonstrated is that women who do not meet the criteria for GDM but who have one abnormal value on the GTT are at increased risk of adverse pregnancy outcomes. The adverse outcomes considered have been the rate of macrosomia, toxaemia and the need for Caesarean section. The study of Langer et al (1989) demonstrated that intervention in these women can produce results similar to those women without any abnormality on glucose tolerance testing.

The studies of Pettitt et al (1980) and Tallarigo et al (1986) differ from those mentioned above. The observations about potential adverse pregnancy outcomes were extended to all levels of glucose and suggested a gradation of risk. The difficulties with these two studies are that Tallarigo et al were dealing with a relatively small number of patients and, from the information available, an unusual prenatal clinic arrangement. The study of Pettitt et al was based on the Pima Indians and information from this group has to extrapolated with care.
The present study herein reported overcomes some of the methodological problems in the papers discussed above. The number of patients included is by far the largest of any series so far reported. The maternal and fetal outcomes have been assessed across the whole range of maternal glucose values. A comparison group of women with treated GDM have also included. All of the papers reviewed above have used diagnostic criteria for GDM that use higher glucose levels than the ADIPS criteria used for the patients in this study. Consequently many of the patients with one abnormal value on a GTT would certainly have been classified as GDM by the ADIPS criteria. Thus the patients used in this study with a 2 hour glucose level < 8.0 mmol/L would be considered unequivocally normal by any other criteria and thus should help to settle the question as to whether there is a gradation of obstetric risk associated with increasing levels of maternal glucose.
This study was carried out in the Illawarra area of New South Wales. Data were collected from the prenatal clinics at Wollongong and Shellharbour hospitals and from cooperating obstetricians.

Methods: Diagnosis.

The diagnosis of GDM was based on the recommendations of the Australasian Diabetes in Pregnancy Society (ADIPS) (Martin, 1991). ADIPS specified that a definitive diagnosis of GDM was to be made after the administration of a WHO standard GTT at the beginning of the third trimester. The WHO GTT requires the administration of 75 g of anhydrous glucose in 300 mls of water in the morning after an overnight fast with venous samples taken fasting and at two hours. GDM is diagnosed if the fasting plasma glucose is ≥ 5.5mmol/L and/or the two hour plasma glucose level is ≥ 8.0 mmol/L.

Some patients in this study had a GTT and some had a modification of the GTT (MGTT). With the MGTT the standard WHO GTT was used but only the two hour sample was collected (Moses, 1992). The ADIPS criteria of a two hour plasma glucose ≥ 8.0 mmol/L was used for diagnosis.

Glucose samples were processed in air conditioned premises either by the biochemistry department of Wollongong hospital or by two private pathology companies. Laboratory standards were comparable as each performed satisfactorily on national Quality Assurance programs for all routinely measured analytes including glucose. The venous sample for plasma glucose was collected fasting and/or at two hours, immediately separated after
collection and stored at 4°C until analysed. Analysis was done by Wollongong hospital using a glucose oxidase method on a Kodak Ecktachem 700XRC (Rochester, USA). Analysis was done by the pathologists in private practice using a hexokinase method on an Olympus REPLY (Tokyo, Japan).
Methods: Data collection procedures

For the first six months of 1993 the prenatal clinic at Wollongong Hospital offered the MGTT to all women while the prenatal clinic at Shellharbour Hospital offered all patients a GTT. From July 1993, and for the remainder of the period of data collection, this situation was reversed. Only those prenatal clinic patients who were screened during 1993, and who had delivered by the end of April 1994, have been included.

Additional data were obtained from two specialist obstetricians and a general practitioner with an interest in obstetrics who offered a MGTT to all of their patients from the beginning of 1993. A third obstetrician agreed to collect data from the beginning of 1994. The patient data from these sources were all women who were tested until the end of February 1994.

Data collection at the Wollongong Hospital was done by a midwife working in the prenatal clinic. After a short evaluation period, a system of data collection suitable for the procedures and staff at Wollongong Hospital was introduced. Data collection at Shellharbour Hospital was done by a midwife working in the Labour Ward who examined the prenatal clinic records several times each week. It was not possible at Shellharbour Hospital for information about previous GDM or whether there was a positive family history of diabetes in a first degree relation to be obtained. Both midwives were on a monthly retainer.

Data collection by the private obstetricians was collated by their staff using a standardised system. Data about previous GDM and a family history of diabetes was not practicable to collect. The general practitioner collected all data herself.
Methods: Pregnancy and fetal outcome data.

Pregnancy and fetal outcome details were obtained from the NSW Midwives' Data Collection Form. It is a requirement of the NSW Department of Health that this form be completed by staff at the hospital from which the mother was eventually discharged after the completion of the pregnancy. In the Illawarra area this was Wollongong Hospital, Shellharbour Hospital or The Illawarra Hospital. The Illawarra Hospital is a private hospital where some private patients were transferred to after delivery. Parts of the Midwives’ form were completed by the Labour Ward staff after delivery and the balance by the staff of the obstetric wards.

It was not logistically possible to obtain the required data from the the Midwives’ forms at the time of discharge from hospital. The Midwives’ forms were obtained from the respective Medical Records Departments at a later date during the process of coding. The Medical Record Departments did not have the resources available to search for and present all of the Midwives’ forms to match all of the patients who had had glucose tolerance testing. During the coding process the Midwives’ forms were set aside, collected by myself on a regular basis and copied for future data entry. Dependent on the generosity of the Medical Records Departments, it was not practicable to ask for details of those patients whose forms did not become available by these means. However there was no reason to believe that the forms of any patients were held back or were dealt with in any manner which would not have made them available.

All data were stored on a Macintosh LC using Statview (Abacus Concepts, Berkeley, California).
Methods: Data collection - type and definitions.

The maternal data collected included name, the month and year at which the glucose tolerance testing was done, the hospital or obstetrician responsible for the care, the age of the patient when tested, parity, preconception weight by recall, height, the ethnic background of the mother, the number of weeks gestation at which the glucose tolerance testing was done, whether the procedure was a GTT or a MGTT and the glucose result fasting and at 2 hours. Body Mass Index (BMI) was calculated by dividing the preconception weight in Kg by the height in metres squared.

The information required for this survey from the Midwives' form included the following; whether there was Pregnancy Induced Hypertension and gestational diabetes; whether labour was spontaneous or induced; the method of delivery; whether the fetus was alive or dead; fetal gender; plurality; birthweight in grams; gestational age at delivery; Apgar score at 10 minutes; neonatal morbidity. The Apgar score is an index used to evaluate the condition of the newborn infant with a rating of 0 - 2 for each of the following five characteristics; colour, heart rate, response to stimulation of the sole of the foot, muscle tone and respiration.

Ethnic background. The mother's country of birth was recorded and grouped into geographical areas; Australasia (Australia, excluding aboriginals, and New Zealand), northern Europe, southern Europe, Asian, Indian, Aboriginal, Pacific Islanders and others. Because of small numbers the ethnic groups of Asian, Indian, Aboriginal, Pacific Islanders and “others” have been presented in the Results section as “others”. Women were classified as Southern European if they came from a country with a border on the Mediterranean Sea.
Pregnancy Induced Hypertension (PIH). The presence or absence of this complication was obtained from the Midwives' Data Form.

Induction. This information was obtained from the Midwives' Data Form. Labour was either spontaneous or induced. The different types of induction were not distinguished. Those women who had an elective Caesarean section were excluded from this section.

Method of delivery. This information was obtained from the Midwives' Data Form. The different methods of delivery were; spontaneous vaginal, forceps assisted, vacuum extraction, elective Caesarean section and emergency Caesarean section.

Neonatal morbidity. This information was obtained from the Midwives' Data Form. "Morbidity" was defined as the need for a baby to be admitted to a special care nursery. This facility was only available at Wollongong hospital and thus deliveries at Shellharbour hospital were excluded.
Methods: Exclusions.

The primary exclusions from this survey were those patients whose Midwives’ Data Form was not available using the means of collection mentioned above. Data on patients were included if they had been tested after 24 weeks of gestation, delivered after 32 weeks of gestation and had had a singleton live fetus.

With diverse people responsible for completing the Midwives’ forms there were inevitably some clerical omissions. Fetal birthweight was available on an estimated 99% of all forms. After the exclusions mentioned above, only those patients who had the fetal birthweight recorded were used for the survey. Inevitably a small amount of some of the other data were incomplete.
Methods: Statistical methods.

Unless specified otherwise, results have been expressed as a percentage or as a mean with one standard deviation in parentheses. The statistical methods used included the two-sample pooled t-test, Chi-squared analysis, multiple regression analysis and logistic regression analysis. Unless otherwise stated the result of the 2 hour glucose level after the GTT (gtt2) in the contingency tables have been presented in the following groups; \( \leq 3.9 \), 4.0 - 4.9, 5.0 - 5.9, 6.0 - 6.9, 7.0 - 7.9 and, for women with GDM, as \( \geq 8.0 \) mmol/L respectively. The fasting glucose level (gtt0) was available in 389 instances. Unless otherwise stated the gtt0 data were arranged in the contingency tables in the following groups; \( \leq 3.9 \), 4.0 - 4.1, 4.2 - 4.3, 4.4 - 4.5 and \( \geq 4.6 \) mmol/L respectively.

In order to determine at what level of gtt2 the risk of non-GDM mothers experiencing a particular characteristic (eg, non-vaginal delivery) would be equivalent to the risk experienced by the treated GDM mothers, the following calculation was used. Each risk was transformed by converting it to equivalent odds. When the risk for a particular event for GDM mothers was within the range of risks for non-GDM mothers, the odds of having this condition could be modelled by logistic regression in which the gtt2 was used as the predictor. As will be shown in the Results section, this situation only applied to large for gestational age infants (LGA) and pregnancy induced hypertension (PIH).

For example, for GDM mothers the odds of having PIH is 16/108. The log of these odds is - 1.9095. The equation which predicts the odds of PIH in terms of gtt2 for non-GDM mothers is \( \log(\text{odds}) = -3.5253 + 0.2065 \times \text{gtt2} \). If - 1.9095 is set equal to \( -3.5253 + 0.2065 \times \text{gtt2} \), then the value of gtt2 can be found which makes these equal.
All analyses were conducted on the University of Wollongong's SUN 4/470 mainframe computer, using the statistical package SAS Institute, Inc, Box 8000, Cary, NC, USA 27511-8000. Some analyses were checked using the statistical package Genstat, which is produced by the Numerical Algorithms Group Ltd, Mayfield House, 256 Banbury Road, Oxford, United Kingdom OX2 7DE.
Methods: Ethical approval.

Ethical approval for this research was provided by the Human Research Ethics Committee of the Illawarra Area Health Service and the University of Wollongong.
RESULTS

Data were available on 1441 normal pregnancies and 125 pregnancies in women with GDM who had had a singleton live fetus. The gender of the fetus was recorded in all but two instances and males comprised 51.0% of the total. A GTT was done in 388/1441 (26.9%) cases and a MGTT in 1053/1441 (73.1%) cases.

Maternal demographic, obstetric and birthing details for all of the normal women by different ethnic groups are shown in table 1.

Table 1.

Maternal demographic, obstetric and birthing details according to the ethnic origin - mean (1SD).

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Australasian</th>
<th>N. European</th>
<th>S. European</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1062</td>
<td>n=126</td>
<td>n=115</td>
<td>n=115</td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>27.2 (5.0)</td>
<td>28.1 (4.7) *</td>
<td>26.9 (4.7)</td>
<td>27.6 (5.6)</td>
</tr>
<tr>
<td>Parity</td>
<td>0.9 (1.0)</td>
<td>0.9 (1.0)</td>
<td>1.0 (1.2)</td>
<td>0.9 (1.2)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>23.9 (4.6)</td>
<td>23.9 (4.6)</td>
<td>24.7 (4.7)</td>
<td>22.8 (4.6) *</td>
</tr>
<tr>
<td>Week of test</td>
<td>28.0 (1.9)</td>
<td>28.4 (2.0) *</td>
<td>27.50 (1.9) **</td>
<td>28.2 (2.1)</td>
</tr>
<tr>
<td>gtt2 (mmol/L)</td>
<td>5.6 (1.0)</td>
<td>5.7 (1.0)</td>
<td>5.7 (1.0)</td>
<td>5.8 (1.1) *</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3448 (519)</td>
<td>3420 (519)</td>
<td>3412 (451)</td>
<td>3394 (482)</td>
</tr>
<tr>
<td>Gest. age (weeks)</td>
<td>39.5 (1.4)</td>
<td>39.5 (1.4)</td>
<td>39.6 (1.3)</td>
<td>39.3 (1.4)</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01.

The women of Northern European origin were significantly older and the women in the "others" group (mainly Asian) had a significantly lower preconception BMI. The number of women from different ethnic groups were relatively small compared to the Australasian group and therefore only the total number has been subsequently used for data analysis.
Maternal demographic, obstetric and birthing details for the normal women according to the maternal gtt2 level are shown in table 2.

### Table 2.
Maternal demographic, obstetric and birthing details for normal women according to the maternal gtt2 level - mean (1SD).

<table>
<thead>
<tr>
<th>Maternal glucose (mmol/L)</th>
<th>Age (years)</th>
<th>Parity</th>
<th>BMI (Kg/m²)</th>
<th>Birthweight (grams)</th>
<th>Gest. age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.9 mmol/L</td>
<td>28.2 (3.8)</td>
<td>1.0 (0.9)</td>
<td>22.3 (3.2)</td>
<td>3308 (487)</td>
<td>39.2 (1.6)</td>
</tr>
<tr>
<td>n = 83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0 - 4.9 mmol/L</td>
<td>27.1 (5.0)</td>
<td>0.9 (1.0)</td>
<td>23.2 (4.0)</td>
<td>3403 (504)</td>
<td>39.5 (1.5)</td>
</tr>
<tr>
<td>n = 291</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>27.0 (4.9)</td>
<td>0.9 (1.0)</td>
<td>23.7 (4.6)</td>
<td>3452 (480)</td>
<td>39.6 (1.3)</td>
</tr>
<tr>
<td>n = 561</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>27.4 (5.1)</td>
<td>0.9 (1.0)</td>
<td>24.7 (5.0)</td>
<td>3462 (522)</td>
<td>39.6 (1.4)</td>
</tr>
<tr>
<td>n = 363</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>28.3 (5.3)</td>
<td>0.7 (1.0)</td>
<td>24.5 (4.9)</td>
<td>3471 (624)</td>
<td>39.5 (1.5)</td>
</tr>
<tr>
<td>n = 142</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Maternal demographic, obstetric and birthing details for the total of all normal (non-GDM) women and the GDM mothers are shown in table 3.

Table 3.

Maternal demographic, obstetric and birthing details for the total of non-GDM mothers and for GDM mothers - mean (1SD).

<table>
<thead>
<tr>
<th></th>
<th>Total non-GDM</th>
<th>GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1441.</td>
<td>n = 125.</td>
</tr>
<tr>
<td>Age in years</td>
<td>27.3 (5.0)</td>
<td>29.1 (5.2) *</td>
</tr>
<tr>
<td>Parity</td>
<td>0.9 (1.0)</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>23.8 (4.6)</td>
<td>26.0 (5.7) *</td>
</tr>
<tr>
<td>Week of test</td>
<td>28.0 (2.0)</td>
<td>28.1 (1.9)</td>
</tr>
<tr>
<td>gtt2 (mmol/L)</td>
<td>5.6 (1.1)</td>
<td>8.9 (1.6) *</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3438 (512)</td>
<td>3402 (477)</td>
</tr>
<tr>
<td>Gest. age (weeks)</td>
<td>39.5 (1.4)</td>
<td>39.3 (1.4)</td>
</tr>
</tbody>
</table>

* p < 0.0001

The women with GDM were significantly older, had a higher preconception BMI and a higher (by definition) gtt2 level. There were no differences with respect to parity, birthweight and the gestational age of delivery.
Results: Frequency of assisted delivery.

Deliveries were classified as normal vaginal or assisted (forceps, vacuum extraction, elective Caesarean section or emergency Caesarean section).

Table 4.

Percentage of normal vaginal and assisted deliveries according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>normal vaginal %</th>
<th>assisted %</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.9 mmol/L</td>
<td>86.1</td>
<td>13.9</td>
<td>(n = 79)</td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>76.7</td>
<td>23.3</td>
<td>(n = 283)</td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>77.7</td>
<td>22.3</td>
<td>(n = 548)</td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>72.5</td>
<td>27.5</td>
<td>(n = 353)</td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>69.6</td>
<td>30.4</td>
<td>(n = 138)</td>
</tr>
<tr>
<td>≥ 8.0 mmol/L</td>
<td>66.9</td>
<td>33.1</td>
<td>(n = 121)</td>
</tr>
</tbody>
</table>

A Chi-squared analysis of contingency tables (for non-GDM mothers only) was used to examine whether the proportions of normal vaginal and assisted deliveries for non-GDM mothers were the same for each category of gtt2. There was a significant association between the level of gtt2 and the proportion of deliveries which were assisted ($X^2=10.799$, df. = 4, p = 0.029). The tendency was for the proportion of assisted deliveries to increase as the gtt2 increased.

The mean gtt2 levels were examined using a two-sample pooled t-test to see whether a significant difference existed between those mothers who had or
had not had an assisted delivery. An assisted delivery was performed in 358/1421 (25.2%) of mothers who had a mean gtt2 level of 5.8 (1.0) mmol/L. This was significantly higher than the mean gtt2 level of 5.5 (1.0) mmol/L for the 1063/1421 (74.8%) mothers who did not have an assisted delivery (t = 4.941, df. = 1419, p = 0.0001).

The logistic regression predicted equation for the odds that a birth would be an unassisted vaginal were \[ \text{logit}(p) = -3.4481 - 0.0434 \times \text{BMI} - 0.0694 \times \text{age} + 0.5302 \times \text{parity} + 0.2047 \times \text{gestational age} - 0.1646 \times \text{gtt2}. \]

Each of the variables BMI (p < 0.01), mothers age (p < 0.01), parity (p < 0.01), gestational age of delivery (p < 0.01) and gtt2 (p < 0.02) were statistically significant in the presence of the others. The odds in favour of a normal vaginal delivery are estimated to increase by 69.9% for each increase of one in the parity and by 22.7% for each advancing week of gestational age. The odds in favour of a normal vaginal delivery are estimated to decrease by 4.3% for each one unit increase in BMI, by 6.7% for each year increase in mothers age, and by 15.2% for each 1.0 mmol/L increase in gtt2.

The risk that a delivery for a GDM mother was assisted was outside the risks for non-GDM mothers. Hence it was not feasible to estimate the value of gtt2 which made the risk for non-GDM mothers equal to the risk for a GDM mother.

The various types of assisted deliveries were examined separately and are presented in table 5. It was necessary to pool the two gtt2 categories of \( \leq 3.9 \)
and 4.0-4.9 to provide sufficient numbers for analysis.

The Chi-squared test was used for non-GDM mothers only to test the null hypothesis that the relative proportions of the various types of deliveries were the same across the various levels of gtt2. The Chi-squared test suggested that the relative proportions were not constant ($X^2 = 22.658$, df. = 12, $p = 0.0308$). This came about because the number of forceps assisted deliveries and emergency Caesarean sections were larger than expected in the category 7.0-7.9 mmol/L and the number of emergency Caesarean sections were less than expected for gtt2 levels in the category 5.0-5.9 mmol/L.

### Table 5.

Percentage of normal vaginal and different assisted deliveries according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>Vaginal</th>
<th>Forceps</th>
<th>Vacuum</th>
<th>Elective Caesar</th>
<th>Emerg. Caesar</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4.9 mmol/L</td>
<td>78.7</td>
<td>1.4</td>
<td>5.3</td>
<td>7.5</td>
<td>7.2</td>
</tr>
<tr>
<td>n = 362</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>77.7</td>
<td>2.2</td>
<td>7.3</td>
<td>6.9</td>
<td>5.8</td>
</tr>
<tr>
<td>n = 548</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>72.5</td>
<td>2.0</td>
<td>6.8</td>
<td>9.6</td>
<td>9.1</td>
</tr>
<tr>
<td>n = 353</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>69.6</td>
<td>5.8</td>
<td>4.4</td>
<td>8.0</td>
<td>12.3</td>
</tr>
<tr>
<td>n = 138</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 8.0 mmol/L</td>
<td>67.7</td>
<td>3.9</td>
<td>9.5</td>
<td>11.0</td>
<td>7.9</td>
</tr>
<tr>
<td>n = 121</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean gtt2 levels were examined using a two-sample pooled t - test to see whether a significant difference existed between those mothers who had, or
had not, undergone Caesarean section (elective and emergency). A
Caesarean section was performed in 217/1441 (15.1%) of mothers who had a
mean gtt2 level of 5.8 (1.0) mmol/L. This was significantly higher than the
mean gtt2 level of 5.6 (1.0) mmol/L for the 1224/1441 (84.9%) mothers who
did not have a Caesarean section (t = 3.0078, df. = 1439, p = 0.0027).

There were 377 women who had a gtt0 level < 5.5 mmol/L. There was no
significant association between the gtt0 level and whether the delivery was
vaginal or assisted (X2 = 7.480, df. = 4, p = 0.113). There was also no
significant association between the gtt0 level and the method of assisted
delivery (X2 = 9.122, df. = 8, p = 0.332).
Results: Parity

With respect to Caesarean sections, a previous section for any reason is likely to result in a subsequent section. The following contingency table outlines the rates of elective and emergency section with parity.

Table 6.
Percentage of selected deliveries and maternal parity.

<table>
<thead>
<tr>
<th></th>
<th>parity = 0</th>
<th>parity ≥ 1</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-Caesar</td>
<td>40.0 %</td>
<td>60.0 %</td>
<td>(n = 1183)</td>
</tr>
<tr>
<td>Elect. Caesar</td>
<td>22.7 %</td>
<td>77.3 %</td>
<td>(n = 110)</td>
</tr>
<tr>
<td>Emer. Caesar</td>
<td>69.2 %</td>
<td>30.8 %</td>
<td>(n = 107)</td>
</tr>
</tbody>
</table>

This table demonstrates a significant association ($X^2 = 50.805$, df. = 2, $p < 0.001$) between parity and the type of section. Of those women who had a Caesarean section, women in their first pregnancy were far more likely to have an emergency section while women in their second and subsequent pregnancy were more likely to have an elective section.

There were 118 normal women who had a Caesarean section and who had had two or more pregnancies. Data about previous deliveries were available in 116 women of whom 79 (68.1%) had had a previous section while 37 (31.9%) had not. There were 13 women with GDM who had a Caesarean section and who had had two or more pregnancies. Of these 13 women 7 (53.8%) had had a previous section while 6 (46.2%) had not.
Results: Pregnancy induced hypertension (PIH).

The percentage of women with PIH according to their gtt2 level are shown in Table 7.

Table 7.

Percentage of women with PIH according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>no PIH</th>
<th>PIH</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.9 mmol/L</td>
<td>92.8</td>
<td>7.2</td>
<td>n = 83</td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>91.7</td>
<td>8.3</td>
<td>n = 290</td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>93.4</td>
<td>6.6</td>
<td>n = 562</td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>89.3</td>
<td>10.7</td>
<td>n = 363</td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>86.6</td>
<td>13.4</td>
<td>n = 142</td>
</tr>
</tbody>
</table>

The proportion of mothers suffering from PIH increased as the gtt2 level increased though with the Chi-squared analysis for the non-GDM mothers this trend did not quite reach significance ($X^2 = 9.304$, df. = 4, $p = 0.054$). However the mean gtt2 levels of the 125/1440 (8.7%) mothers who did have PIH at 5.8 (1.1) mmol/L was significantly higher than the mean gtt2 levels of the 1315/1440 (91.3%) mothers who did not have PIH at 5.6 (1.0) mmol/L ($t = 2.2497$, df. = 1438, $p = 0.0246$).

There was no significant association between the gtt0 level and the rate of PIH ($X^2 = 1.540$, df. = 4, $p = 0.820$).

The logistic regression predicted equation for the odds of pregnancy induced hypertension were $\text{logit}(p) = 6.1764 + 0.1074 \times \text{BMI} - 0.5654 \times \text{parity} - 0.2940$
x gestational age + 0.1343 x gtt2.

Each of the variables BMI (p < 0.01), parity (p < 0.01) and gestational age of
delivery (p < 0.01) were statistically significant in the presence of the others.
The variable gtt2 was not statistically significant.

The odds in favour of PIH are estimated to increase by 11.9% for each
increase of one unit in BMI. The odds in favour of PIH are estimated to
decrease by 25.3% for each one week increase in gestational age and by
44.1% for each increase of one in parity.

Non-GDM women with a gtt2 of ≥ 7.8 mmol/L had a risk for PIH which
exceeded the risk for treated GDM women.
Results: Rate of induction.

Labour was either classified as spontaneous or induced. Those women who had an elective Caesarean section have been excluded.

Table 8.

Percentage of women who were induced according to their maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>no induction %</th>
<th>induced %</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 3.9 \text{ mmol/L} )</td>
<td>76.3</td>
<td>23.7</td>
<td>(n = 80)</td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>70.6</td>
<td>29.4</td>
<td>(n = 265)</td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>81.2</td>
<td>18.8</td>
<td>(n = 522)</td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>76.2</td>
<td>23.8</td>
<td>(n = 327)</td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>75.4</td>
<td>24.6</td>
<td>(n = 130)</td>
</tr>
<tr>
<td>( \geq 8.0 \text{ mmol/L} )</td>
<td>62.7</td>
<td>37.3</td>
<td>(n = 110)</td>
</tr>
</tbody>
</table>

A Chi-squared analysis of the contingency table for non-GDM mothers revealed a significant association of the gtt2 level with the rate of induction (\( \chi^2 = 11.796, \text{ df} = 4, p = 0.019 \)). However as can be seen from the table, the percentage of induced births for mothers does not trend upwards with the level of gtt2. The rate of induction for mothers with gtt2 levels \( \leq 3.9 \) or \( \geq 6.0 \text{ mmol/L} \) are fairly constant and between 23 and 24%. For those mothers whose gtt2 level is 4.0-4.9 mmol/L the percentage of births induced is 29.4% while for those mothers with a gtt2 level of 5.0-5.9 mmol/L the rate falls to 18.8%. There was no significant association between the gtt0 level and whether the labour was induced (\( \chi^2 = 6.184, \text{ df} = 4, p = 0.186 \)).
The logistic regression predictive equation for the odds that a birth would be induced are
\[ \text{logit}(p) = -12.7454 + 0.0533 \times \text{BMI} + 0.0312 \times \text{age} - 0.1922 \times \text{parity} + 0.2574 \times \text{gestational age} - 0.1328 \times \text{gtt2}. \]

Each of the variables BMI (\( p < 0.01 \)), mothers age (\( p < 0.02 \)), parity (\( p < 0.02 \)), gestational age of delivery (\( p < 0.01 \)) and gtt2 (\( p < 0.05 \)) were statistically significant in the presence of the others.

The odds in favour of an induced birth are estimated to increase by 6.2% for each increase of one in the BMI, by 3.7% for each increase of one year in the mother's age and by 23.0% for each week in gestational age. The odds in favour of an induced birth are estimated to decrease by 16.9% for each one unit increase in parity and by 12.7% for each 1.0 mmol/L increase in gtt2.
Results: Birthweight of the baby.

The birthweights were considered in both absolute and relative terms.

Birthweight in absolute terms.

In absolute terms a birthweight of \( \leq 2,500 \) g was called small for gestational age (SGA) while a birthweight of \( \geq 4,000 \) g was called large for gestational age (LGA) irrespective of the gender or the gestational age of delivery.

Table 9.

Percentage of absolute SGA and LGA according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>SGA %</th>
<th>LGA %</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 3.9 ) mmol/L</td>
<td>6.0</td>
<td>6.0</td>
<td>(n = 83)</td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>4.5</td>
<td>12.4</td>
<td>(n = 291)</td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>2.1</td>
<td>12.8</td>
<td>(n = 562)</td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>3.6</td>
<td>13.5</td>
<td>(n = 363)</td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>4.9</td>
<td>15.5</td>
<td>(n = 142)</td>
</tr>
</tbody>
</table>

The Chi-squared test of the contingency table did not suggest for non-GDM mothers a significant association between gtt2 level and the percentage of babies who were either SGA or LGA (\( X^2 = 8.302, \) df. = 4, \( p = 0.0811 \)). There was also no significant association for non-GDM mothers between the gtt0 level and the percentage of babies who were either SGA or LGA (\( X^2 = 14.706, \) df. = 4, \( p = 0.065 \)). There were no significant differences in the LGA rate for treated women with GDM (13/124, 10.5%) and the non-GDM women
A baby weighing ≥4500 g was found in 29/1441 (2.0%) of the non-GDM pregnancies. The rates did not differ significantly for the maternal gt2 groups which were 2/83 (2.4%) for gt2 ≤ 3.9 mmol/l, 4/291 (1.4%) for gt2 4.0-4.9 mmol/L, 11/562 (2.0%) for gt2 5.0-5.9 mmol/L, 7/363 (1.9%) for gt2 6.0-6.9 mmol/L and 5/142 (3.5%) for gt2 7.0-7.9 mmol/L. Three of the one hundred and twenty four (2.1%) women with treated GDM had an infant weighing ≥ 4500g.

The mean gt2 level of the 184 mothers who had a LGA baby was 5.8 (1.0) mmol/L which was significantly higher than the mean gt2 level of 5.6 (1.0) mmol/L for the 1207 women who had a baby > 2,500 g and < 4,000 g (t = 2.436, df 1390, p < 0.02). The mean gt2 level of the 50 mothers who had a SGA baby was 5.6 (1.2) mmol/L which was not significantly different to the women with a baby > 2500 g and < 4000g.

In absolute terms the odds that a baby would be large for its gestational age were modelled in terms of the BMI, age of the mother, gt2 and the gestational age of delivery. The influence of maternal age and gt2 were found not to be significant (p > 0.1). When just BMI and gestational age were fitted, both were significant (p < 0.001). The odds in favour of a LGA baby are estimated to increase by 7.5% for an increase of one unit of BMI and by 61.2% for each week of gestational age.

The odds that a baby would be small for its gestational age were modelled in terms of the BMI, age of the mother, gt2 and the gestational age of delivery.
The influence of BMI, mothers age and gtt2 were not found to be significant (p > 0.1). The variable gestational age explained the odds to a significant extent (p < 0.001). The odds in favour of a SGA baby are expected to decrease by 63.7% for each increase of one week in gestational age.

The estimated value of gtt2 for which the risk of a non-GDM mother having a LGA baby in absolute terms was equal to the risk of a treated GDM mother was 4.4 mmol/L.
Birthweight in relative terms.

Sufficient data was available for deliveries between 37 and 42 weeks inclusive to calculate birthweight centiles based upon gender and the gestational age of delivery. In relative terms SGA and LGA were based on the tenth and ninetieth centiles respectively.

Table 10.

Percentage of relative SGA and LGA according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>&lt;10 th centile %</th>
<th>&gt; 90 th centile %</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.9 mmol/L</td>
<td>13.3</td>
<td>6.7</td>
<td>(n = 75)</td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>13.3</td>
<td>8.1</td>
<td>(n = 271)</td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>9.0</td>
<td>11.6</td>
<td>(n = 533)</td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>10.9</td>
<td>10.6</td>
<td>(n = 341)</td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>8.4</td>
<td>13.7</td>
<td>(n = 131)</td>
</tr>
<tr>
<td>≥ 8.0 mmol/L</td>
<td>5.9</td>
<td>11.0</td>
<td>(n = 118)</td>
</tr>
</tbody>
</table>

The Chi-squared test of the contingency table did not suggest for non-GDM mothers a significant association between gtt2 level and the percentage of babies who were either SGA or LGA in relative terms (X² = 8.528, df. = 4, p = 0.0740). There was no significant association between the gtt0 level for non-GDM mothers and the percentage of babies who were either SGA or LGA in relative terms (X² = 10.219, df. = 8, p = 0.250). There were no significant differences in the LGA rate for treated women with GDM (13/118, 11.0%) and the non-GDM women (143/1441, 9.9%) and for the SGA rate for treated women with GDM (7/118, 5.9%) and the non-GDM women (144/1441, 10.0%).
The mean gtt2 level of the 143 mothers who had a LGA baby was 5.8 (1.0) mmol/L which was significantly higher than the mean gtt2 level of 5.6 (1.0) mmol/L for the 1066 women who had a baby neither SGA nor LGA (\( t = 2.415, \) df 1253, \( p < 0.02 \)). The mean gtt2 level of the 142 mothers who had a baby SGA was 5.5 (1.1) mmol/L which was not significantly different to the women with a baby neither SGA nor LGA.

In relative terms the odds that a baby would be LGA were modelled in terms of the BMI, age of the mother and the gtt2 result. The influence of the gtt2 level was not significant (\( p > 0.1 \)). When just BMI and mothers age were fitted both were significant (\( p < 0.001 \) for BMI and \( p < 0.002 \) for mother’s age). The odds in favour of a LGA baby are estimated to increase by 9.6% for each increase of one unit in BMI and by 6.0% for each year in mother’s age.

The odds that a baby would be small for its gestational age were modelled in terms of the BMI, mothers age and the gtt2 level. The influence of age and the gtt2 level were not significant (\( p > 0.1 \)). When just BMI was fitted, it was significant (\( p < 0.001 \)). The odds in favour of a SGA baby are expected to decrease by 8.3% for each increase of one unit in BMI.

The estimated value of gtt2 for which the risk of a non-GDM mother having a LGA baby in relative terms was equal to the risk of a treated GDM mother was 5.9 mmol/L.
Results: Apgar score.

The following contingency table shows the level of gtt2 in the mother and the Apgar score for the baby. In order to obtain sufficient babies in each column of the table, those babies with scores between 0 and 6 were grouped into one category.

Table 11.

Percentage of babies with different Apgar scores according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>Apgar score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-6</td>
</tr>
<tr>
<td>≤ 3.9 mmol/L</td>
<td>0.0</td>
</tr>
<tr>
<td>n = 83</td>
<td></td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>2.0</td>
</tr>
<tr>
<td>n = 288</td>
<td></td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>1.6</td>
</tr>
<tr>
<td>n = 561</td>
<td></td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>2.2</td>
</tr>
<tr>
<td>n = 360</td>
<td></td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>2.1</td>
</tr>
<tr>
<td>n = 141</td>
<td></td>
</tr>
<tr>
<td>≥ 8.0 mmol/L</td>
<td>0.0</td>
</tr>
<tr>
<td>n = 124</td>
<td></td>
</tr>
</tbody>
</table>

A Chi-squared analysis of the contingency table for mothers without GDM suggested that there was no association between gtt2 and the Apgar score ($X^2 = 8.792$, df. = 16, $p = 0.922$). There was also no significant association with gtt0 ($X^2 = 18.025$, df. = 16, $p = 0.322$).
Results: Morbidity.

The following table displays the percentage of babies with "morbidity" according to the gtt2 level. Deliveries at Shellharbour hospital have not been included as there was no special care nursery available.

Table 12.

Percentage of babies who were admitted to the special care nursery and thus deemed to have "morbidity" according to the maternal gtt2 level.

<table>
<thead>
<tr>
<th>Maternal glucose</th>
<th>no &quot;morbidity&quot;</th>
<th>&quot;morbidity&quot;</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.9 mmol/L</td>
<td>76.0</td>
<td>24.0</td>
<td>(n = 75)</td>
</tr>
<tr>
<td>4.0-4.9 mmol/L</td>
<td>71.6</td>
<td>28.4</td>
<td>(n = 257)</td>
</tr>
<tr>
<td>5.0-5.9 mmol/L</td>
<td>71.3</td>
<td>28.7</td>
<td>(n = 506)</td>
</tr>
<tr>
<td>6.0-6.9 mmol/L</td>
<td>67.0</td>
<td>33.0</td>
<td>(n = 330)</td>
</tr>
<tr>
<td>7.0-7.9 mmol/L</td>
<td>63.2</td>
<td>36.8</td>
<td>(n = 133)</td>
</tr>
<tr>
<td>≥ 8.0 mmol/L</td>
<td>32.2</td>
<td>67.8</td>
<td>(n = 115)</td>
</tr>
</tbody>
</table>

The Chi-squared analysis of the contingency table for non-GDM mothers did not suggest any significant association of the level of gtt2 and "morbidity" ($X^2 = 6.356, \text{df.} = 4, p = 0.174$). There was also no significant association with the gtt0 level ($X^2 = 4.997, \text{df.} = 4, p = 0.288$).

The 394 (30.3%) mothers who had a baby with "morbidity" had a mean gtt2 level of 5.8 (1.1) mmol/L which was significantly higher than the mean gtt2 level of 5.5 (1.0) mmol/L for the 907 (69.7%) mothers whose baby did not have this complication ($t = 3.54, \text{df.} = 1299, p < 0.001$).
As it was conventional practice to admit to the SCN the babies of mothers who had had an assisted delivery, the results of those mothers who were “Yes” for morbidity were further analysed. With respect to unassisted deliveries, morbidity was present in 8/65 (12.3%) of mothers with a gtt2 level ≤ 3.9, in 26/210 (12.4%) of mothers with a gtt2 level 4.0 - 4.9, in 65/426 (15.3%) of mothers with a gtt2 level 5.0 - 5.9, in 38/259 (14.7%) of mothers with a gtt2 level 6.0 - 6.9 and in 21/104 (20.2%) of mothers with a gtt2 level of 7.0 - 7.9 mmol/L respectively. With respect to unassisted deliveries, the mean gtt2 level of 5.7 (1.1) mmol/L of the 161 mothers who were “Yes” for morbidity was significantly higher than the 5.5 (1.0) mmol/L of the 791 mothers who were “No” for morbidity (p < 0.02).

The logistic regression predicted equation for the odds of morbidity were

\[ \text{logit}(p) = 8.4821 + 0.0340 \times \text{BMI} - 0.2867 \times \text{gestational age} + 0.2036 \times \text{gtt2}. \]

Each of the variables BMI (p < 0.02), gestational age of delivery (p < 0.01) and gtt2 (p < 0.01) were statistically significant in the presence of the others. The odds in favour of being rated “Yes” for morbidity are estimated to increase by 3.5% for each one unit increase in BMI and by 22.6% for each unit in gtt2. The odds in favour of being rated “Yes” for morbidity are estimated to decrease by 24.9% for each one week increase in gestational age.
DISCUSSION.

Data were available on 1,441 normal pregnancies representing about half of all the deliveries in the Illawarra area during the time of the survey. There is no reason to suppose that the women included in this study were in any way different to the overall local obstetric population. When grouped according to their gtt2 result the women who had a glucose $\leq 3.9$ mmol/L and between 7.0 and 7.9 mmol/L were significantly older than the other women. There was no apparent reason for this and adjustments for this were made in the logistic regression analysis. The mean BMI rose progressively from 22.3 in women with a gtt2 result $\leq 3.9$ mmol/L to 24.5 in women with a gtt2 result of 7.0 - 7.9 mmol/L and there was also a progressive increase in mean birthweight from 3308 gm to 3471 gm. The women with a gtt2 result of $\leq 3.9$ mmol/L had a slightly lower gestational age of delivery compared to the other groups which were otherwise very similar to each other.

There were 125 women diagnosed with GDM of whom 110 were cared for by one person (RM) and treated in a standard way (Moses, 1994b). The overall incidence of GDM was 8.0% which was similar to an earlier report from the Illawarra area (Moses et al, 1994a) which used some of the patients included in this series. As could be anticipated the women with GDM were older and had a higher preconception BMI than the non-GDM mothers. There were no differences between the GDM women and the normal women with respect to parity, the number of weeks gestation at which the glucose testing was done, the mean birthweight of the babies and the gestational age of delivery. These results reinforce previous observations that parity per se is not a risk factor for GDM and well controlled women with GDM can proceed to full term.
There is considerable variation in the rate of GDM in women from different
countries (Hadden, 1985) and in women from different ethnic backgrounds in
Australia (Beischer et al, 1991; Moses et al, 1994a). In Australia, Asian women
have a one of the highest rates of GDM but generally have a lower than
average BMI. The normal women in this study did show some differences in
maternal demography when grouped according to ethnic origin. Women from
Northern Europe were slightly older while the “others” group, comprised
mainly of women from Asia, had a lower BMI and a higher gtt2 result.
Unfortunately, even in this large study, there were insufficient women in the
different ethnic groups to determine if any significant differences existed in the
maternal and fetal outcomes studied. The differences in maternal demography
outlined above could be considered of minor clinical significance, and, as
nearly three-quarters of all the women were of Australasian origin, the results
of all the women were grouped and considered as a whole.

With respect to the diagnosis of GDM, and therefore the classification of
women without GDM, the ADIPS recommendation specified either a
preliminary glucose challenge test in the non-fasting state followed by a
definitive two hour GTT in the fasting state or a two hour GTT in the fasting
state used alone.

There are potential and real problems associated with a two stage diagnostic
procedure. A hypertonic glucose solution is unpleasant to take for most
people at any time and is particularly so in pregnancy. The experience of the
first test must inevitably dissuade some from taking the second test with a
consequent reduction in the diagnostic usefulness. No published reports have
so far considered the problem of the “no show”. Other researchers in this field,
albeit from developing countries, (C Deerochanawong and P Porcera:
personal communication) have indicated that as many as 40% of patients do not present for the second glucose test. A two stage diagnostic procedure must also result in a delay in diagnosis and therefore treatment which, as pregnancy is a limited event, may have an impact on outcome.

It would therefore appear logical to “screen” and diagnose at the same time using the GTT. The problem with the GTT is that it is an inconvenient procedure requiring two venepunctures and at least a two hour presence in a laboratory collection area. In the Illawarra area, and there is no reason to suspect that this area is any different from other areas in Australia, there was some reluctance by obstetricians to test for GDM because of perceptions about the inconvenience of the procedure to their patients. These concerns were addressed in two ways. Firstly, a survey was conducted of patients with GDM (Griffiths et al, 1993) which showed that, after an explanation was provided about the importance of screening, pregnant women were not only willing to have this procedure but expected this to be conducted as an important part of routine antenatal care. Secondly, a modification of the GTT (MGTT) was introduced.

The MGTT, which was used for diagnosis in 73.1% of cases was found to be a convenient testing procedure for the following reasons (Moses, 1992). The glucose solution, instructions and explanations were provided in the prenatal clinic or the obstetrician’s office making a visit to the laboratory and the need to make an appointment for the GTT unnecessary. The glucose solution was drunk at home and the patient presented two hours later for a plasma glucose test. This test could also be combined with other routine antenatal investigations. This method of testing was found to be very convenient by the obstetricians in private practice.
The major criticism of this one test screening/diagnostic procedure was that by not taking the fasting sample those women who had an elevated fasting glucose but a normal two hour glucose would be missed. The logic is undeniable that the MGTT will therefore underdiagnose the rate of GDM. The percentage of patients who will be missed is not known for certain but is likely to be small. It was considered that increased compliance with a simplified testing procedure would compensate for the possible small number of patients who might be missed by not doing the fasting sample.

The clinical significance of a woman with a raised fasting glucose level and a normal two glucose level is doubtful. Concerns about relying on a fasting sample have recently been raised by the WHO (WHO, 1994) and the fasting sample has for many years been dispensed with entirely by Pettitt et al (1994) in their ongoing observational studies of the Pima Indians. For these very practical reasons I have suggested that it is now time to modify the GTT for the diagnosis of gestational diabetes (Moses, 1995a).

There have been several recent reports suggesting that the two hour glucose sample may be elevated at times of high ambient temperatures leading to the over diagnosis of GDM in summer and a lower rate of diagnosis in winter (Akanji et al, 1987; Akanji et al, 1991; Schmidt et al, 1994). This possibility of temperature induced changes in the gtt2 level were specifically examined in the patients used in this series and no clinically significant effect was found (Moses et al, 1995b).

Selected aspects of the maternal and fetal outcomes were examined. A higher rate of most adverse outcomes have generally been found in women with GDM and it was the purpose of this study to see whether a continuum of risk
existed across the glucose range of normal women.

The result of the fasting glucose level (gtt0) was available in nearly 400 normal women. Unlike the gtt2 level to be discussed below, the gtt0 level did not appear to be associated with any of the pregnancy outcomes considered. Specifically, the gtt0 level was not associated with whether the delivery was normal vaginal or assisted, the type of assisted delivery, the rate of PIH, the rate of induction, the Apgar score or morbidity. The gtt0 level was also not associated with the percentage of babies who were LGA or SGA in either relative or absolute terms.

Assisted deliveries are an established part of modern obstetric practice. Women with GDM have in the past had a higher rate of assisted delivery, mainly Caesarean section, due to macrosomia and associated problems. Recently the tight metabolic control of GDM has resulted in very favourable fetal outcomes with respect to macrosomia and a reduction in the Caesarean section rate, in some series, to that not significantly different from women without GDM (Langer et al, 1994; Drexel et al, 1988; Thompson et al, 1994.) Where the Caesarean section rate for women with GDM is similar to the rate in normal women, the usual indication for a Caesarean section is a previous history of a Caesarean section (Jacobson et al, 1989). In the series herein reported two-thirds of the normal multiparous women having a Caesarean section had had a previous Caesarean section. For the multiparous women with GDM who had a Caesarean section more than half had had a previous Caesarean section. Where the Caesarean section rate remains higher despite good control of GDM, it is often based on the preference of the obstetrician and not always on defined obstetric indications (Kitzmiller et al, 1992).

For the normal women the decision about the method of delivery was made by
the obstetrician responsible and there is no reason to presume that the possible knowledge of the normal glucose result would have in any way influenced this decision. The frequency of assisted deliveries increased in virtually all categories of gtt2 from 13.9% in those women with a gtt2 ≤ 3.9 mmol/L to 30.4% in those women with a gtt2 level of 7.0-7.9 mmol/L. The exception to this trend were the women with a gtt2 result of 5.0 - 5.9 mmol/L who also had the lowest mean age. Women with a gtt2 result of 7.0 - 7.9 mmol/L had the highest rate of both forceps delivery and of emergency Caesarean section. Overall those women who had an assisted delivery or a Caesarean section had a significantly higher mean glucose level than the other women. The odds in favour of a normal vaginal delivery increased very significantly with increasing parity and increasing gestational age. These findings were not unexpected as a previously successful vaginal delivery is likely to result in further successful vaginal deliveries and many interventional decisions are likely to take place before full term.

In a controlled evaluation Peipert et al (1993) confirmed previous anecdotal obstetric literature that there was an increased rate of Caesarean section with advancing age. While different variables were examined as possible explanations, the carbohydrate status of the women was not tested. In the normal women herein reported the odds in favour of an assisted delivery increased a small amount for each increase in BMI and maternal age. However the odds in favour increased by 15.2% for each increase of 1.0 mmol/L in gtt2. Thus it would seem possible that the previously observed increase in obstetric interventions with increasing maternal age could be related to an increasing, but still “normal”, maternal glucose level.

There are a large number of different reasons as to why a decision could be
made to recommend either an elective or an emergency Caesarean section. In addition to conventional obstetric indications there are also social and demographic indications like the socio-economic status of the mother (Gould et al, 1989), obstetrician preferences (Goyer et al, 1989) and increasing maternal age (Peipert et al, 1993). Vaginal delivery compared to a Caesarean section, even after a previous Caesarean section (Miller et al, 1994), has a lower complication and death rate (Petti et al, 1982, Miller et al, 1988) avoids the psychological impact of a surgical delivery (Eriksen et al, 1989) and is less expensive particularly with a decreased length of hospital stay (Clark et al, 1991).

As dietary intervention in women with GDM can reduce the number of large babies and hence one of the major indications for a Caesarean section, it is tempting to postulate that dietary intervention in women without GDM but with a high normal glucose level may also reduce the Caesarean section rate.

These results demonstrate in normal women that, after correcting for other variables, there is an increasing probability of an assisted delivery, principally an emergency Caesarean section, as the gtt2 level increases. This was a particular problem for women with a gtt2 result of 7.0 - 7.9 mmol/L.

Pregnancy induced hypertension (PIH) is a poorly understood and probably heterogeneous group of disorders which affects 6.2% of all pregnancies in NSW (NSW Midwives Data Collection 1993). Hypertension of all kinds (Jacobson et al, 1989) and specifically PIH is found with increased frequency in women with GDM (Norlander et al, 1989; Langer et al, 1989; Drexel et al, 1988). An increased rate of PIH is also found in women without GDM who have one abnormal value on their GTT (Lindsay et al, 1989). A Finnish
prospective study of the relationship between gestational glucose intolerance and PIH is relevant to the present study (Suhonen et al, 1993). In this study GDM was defined using lower glucose criteria than the ADIPS criteria and therefore included many women who would have been in the non-GDM 7.0-7.9 mmol/L group herein reported. PIH was present in 19.8% of women with GDM which was significantly higher than the rate of around 7.0% found in controls.

The percentage of women with PIH in the current study increased from 7.2% in those women with a gtt2 level ≤ 3.9 mmol/L to 13.4% in those women with a gtt2 level of 7.0 - 7.9 mmol/L. Those women with PIH had a significantly higher gtt2 level than those women without this complication. The treated women with GDM had a rate which was similar to the women with a gtt2 level of 7.0 - 7.9 mmol/L and certainly did not show the increasing trend which could have been anticipated.

For normal women the increasing trend of PIH with rising levels of gtt2 was not significant when the effect of the rising BMI was considered. The odds in favour of PIH increased by 11.9% for each one unit increase in BMI. A very substantial reduction in the odds was found for both gestational age and parity. The reduction in odds for these factors could have been anticipated as a women with PIH would be likely to have been induced early and, in addition, may not be encouraged or inclined to have further pregnancies.

Thus while the risk of PIH increased as the gtt2 level increased the most likely explanation for this was the increasing BMI rather than the glucose level per se. However either an increasing gtt2 level or an increasing BMI could be predictive of an increased risk of PIH.
A decision to induce labour can be made on a large number of factors. Surprisingly, although the Chi-squared analysis of the contingency tables did suggest a significant association with the rate of induction and the gtt2 level, this did not increase as the gtt2 level increased. Rather the association was caused by a lower than expected frequency in the women with a gtt2 level between 5.0-5.9 mmol/L who were younger than the other groups. The overall rate of induction for women in the lowest glucose group were similar the overall rate for women in the highest glucose group.

Thompson et al (1994) reported that women with GDM had an overall induction rate of 32%. Women with treated GDM in this series had the highest overall rate of induction, a rate that was nearly twice that of the rate in non-GDM women in the 5.0 - 5.9 mmol/L gtt2 group. Again, like the increased rate of assisted deliveries, this high rate is probably both traditional and precautionary and is likely to gradually change with time.

The odds in favour of an induced birth increased by 6.2% for each one unit increase in BMI and decreased by 12.7% for every 1.0 mmol/L increase in the gtt2 level.

Large for gestational age (LGA) babies have in the past been a common feature of women with GDM. Possible obstetric complications include birth trauma, shoulder dystocia, asphyxia, meconium aspiration and neonatal hypoglycaemia. A full term infant weighing more than 4500 g has a risk of mortality three to four times that of infants with an average birth weight (Spellacy et al, 1985). An increased rate of testing for GDM and an aggressive modern approach to management have reduced the rate of this complication.
to a level similar to that of the overall obstetric population (Norlander et al, 1989; Suhonen et al, 1993; Moses, 1994b). Macrosomia as a complication of GDM is now most commonly found in women who have not been tested for this problem or who are unreliable with the treatment advice (Moses, 1994b). The rate of macrosomia is still frequently used as the single most important indicator of the successful medical management of a woman with GDM though it is increasingly recognised that the birthweight is more likely to be determined by maternal variables than glycaemic control (Shelley-Jones et al, 1992; Cundy et al, 1993). The concern about macrosomia, while of arguable value for the obstetric management, is assuming greater importance as the effects of varying degrees of nutrition on the intrauterine development of fetal organs is becoming increasingly recognised and acknowledged as an associate and possible cause of many problems in adult life. Maternal hyperglycaemia of any cause results in fetal hyperinsulinism and overdevelopment of the fetal pancreatic islets.

Macrosomia can be defined in various ways including an arbitrary absolute figure such as a birthweight of $\geq 4000$ g or relatively by using the tenth centile of birthweight adjusted for gender and gestational age. The rate of macrosomia in Canada has remained unchanged over the sixties and the seventies (Boyd et al, 1983) while in Australia between the seventies and eighties there has been a gradual increase corresponding to an increase in the frequency of GDM (Shelley-Jones et al, 1992). While macrosomia is a relatively common complication of diabetes and pregnancy it is still most likely to be related to obvious factors like the gestational age of delivery, the size of both parents, maternal age, parity, fetal gender and less obvious factors like socioeconomic status (Ratten et al, 1974) and even geographical features like altitude (Sack 1969).
In the series herein reported the rate of absolute macrosomia increased from 6.0% in normal women with a gtt2 result ≤ 3.9 mmol/L to 15.5% in the normal women with a gtt2 result of 7.0 - 7.9 mmol/L. Overall those normal women who had a macrosomic infant had a gtt2 result which was significantly higher than those who did not. However when other variables were examined the maternal gtt2 level no longer remained as a significant factor. There was an anticipated increase in the rate of macrosomia with increasing gestational age and also with increasing maternal preconception BMI. With respect to absolute macrosomia the increased rate in women with increasing levels of gtt2 could be explained by an increasing level of BMI.

In the series herein reported the rate of relative macrosomia increased from 6.7% in normal women with a gtt2 result ≤ 3.9 mmol/L to 13.7% in normal women with a gtt2 result of 7.0 - 7.9 mmol/L. Overall those women who had a macrosomic infant had a gtt2 level which was significantly higher than those who did not. However when other variables were examined the maternal gtt2 level no longer remained as a significant factor. There was an increase in the rate of macrosomia with increasing maternal age and also with increasing BMI. With respect to relative macrosomia the increased rate in women with increasing levels of gtt2 could be explained mainly by an increasing level of BMI.

Small for gestational age (SGA) infants also are an undesirable outcome of any pregnancy and recent epidemiological data suggests a link between reduced fetal growth and the adult development of hypertension (Barker et al, 1990) and NIDDM (Barker et al, 1993b). Reduced fetal growth can be due to a variety of causes (King et al, 1994) and even possible over treatment of GDM (Langer et al, 1989). Langer et al (1989) felt that the fetus would grow
within limits set by the nutrient supply and fetal insulin levels are susceptible to substrate availability in either direction. The rate of SGA was significantly related in treated women with GDM to the low mean daily maternal glucose levels. In contrast, Dornhorst et al (1991) in a small series found no treated woman with GDM had an infant with a birth weight less than the 10th centile and in the series herein reported there was no significant difference in the rate of SGA for treated women with GDM compared to normal women when both relative and absolute birth weights were considered.

In the series herein reported the rate of SGA in absolute terms was dependent on the gestational age of delivery and not to the maternal gtt2 level or the BMI. The rate of SGA in relative terms was not related to the maternal gtt2 level but decreased as the BMI increased. There is thus nothing to suggest in normal women that maternal glucose levels per se will influence the rate of SGA.

There have been a limited number of reports linking maternal glucose levels with the rate of macrosomia. Leiken et al (1987) felt that minor degrees of glucose intolerance were likely to result in an increased rate of macrosomia. However the maternal glucose level was not specified and testing had been done only on women with historical risk factors for GDM. In addition, although different variables were considered as the possible cause of this association, the maternal BMI was not examined. The following year Witter et al (1988) also concluded that minor degrees of carbohydrate intolerance were associated with an increased risk of macrosomia though they felt that the 50 g glucose 1-hour screening test was a poor discriminator.

In 1994 Khan et al published a report on a large number of Pakistani women
relating maternal glucose results to the rate of macrosomia. This study has many similarities and also some notable differences to the present series. All pregnant women attending the Aga Khan University Medical Center in Karachi had a 75 g non-fasting glucose challenge test (GCT) at 16-20 weeks gestation with a single venous glucose sample taken at 2 hours. If the result was > 7.8 mmol/L a GTT was carried out. Those women with a normal GCT and those women with an abnormal GCT and a normal GTT were stratified into different groups depending upon their 2 hour glucose response to the GCT.

The rate of macrosomia, defined as a birthweight > 4000 g, increased from 1.2% in women with a glucose < 4.5 mmol/L to 9.5% in women with a glucose > 7.8 mmol/L. Similar significant trends were found when the 90th and 95th birthweight centiles were used. Macrosomia was not related to the gestational age of delivery, probably because pre and post term deliveries had been excluded.

There are both close similarities and some differences between the study of Khan et al and the present study. The population studied were Pakistani women who undoubtedly would have had a lower birthweight than the predominantly Anglo-Saxon population group herein reported. Testing was done at an earlier stage of pregnancy which would have reduced the number of abnormal results to the GCT and thus would have led some women to be included in the non-GDM group who would probably have been classified differently if the test had been done 8-10 weeks later. The GCT was also done in a non-fasting state though there is now evidence to suggest that this is unlikely to make any major difference to the result (Gough et al., 1970). The use of a 75 g glucose load and the 2 hour glucose sample were the same as
the present study. The use of a glucose result ≥ 7.9 mmol/L to define abnormality is similar to the value of ≥ 8.0 mmol/L recommended by ADIPS and used in this study. No adjustment was made for the fetal gender in determining the birthweight centiles. Whereas Khan et al have found an increase in the rate of macrosomia with increasing maternal glucose levels, no adjustment was made for maternal BMI. In the present study the maternal BMI rather than the gtt2 level was the important factor.

Jarrett (1993) in a deliberately provocative review argued that GDM was a non-diagnosis and that any association between fetal birthweight and maternal glucose is lost when adjustments are made for maternal weight and age. Leiken et al (1987) and Boyd et al (1983) found that lean women have a lower rate of macrosomia. Green et al (1991) found that maternal body habitus was the strongest predictor of fetal birthweight. In the study by Green et al there was no significant relationship between the maternal glucose level on a screening test and fetal birthweight after adjustment for the gestational age of delivery, fetal gender, parity, ethnicity and BMI. However after adjustment for the above variables there was a progressive increase in fetal birthweight for increasing levels of BMI. There are two possible difficulties with these observations. BMI was determined at the time of the screening test at the beginning of the third trimester and both overweight women and women with GDM gain relatively less weight during pregnancy (Snyder et al, 1994; Cundy et al, 1993). Cundy et al found that the fetal birthweight in women with established diabetes and GDM was correlated with the preconception BMI and not with glycaemic control or with the glucose level in control (non diabetic) pregnancies. Women who were diagnosed as having GDM appear to have been included in the overall figures with no mention of any treatment.
Not withstanding these confounding variables, the present study also agrees with the above reports that fetal birthweight and the rate of macrosomia are related to maternal glucose levels only because maternal glucose levels in normal women are largely determined by the maternal BMI. The odds in favour of a baby weighing ≥ 4000 g increased by 7.5% for each one unit increase in BMI and the odds in favour of a baby being above the 90th centile for gestational age and gender increase by 9.6% for each one unit increase in BMI.

Morbidity for the purposes of this survey was defined according to the question on the Midwives form - “Did the baby require admission to a separate facility/nursery for special care or observation”. Morbidity, in this series, is thus dependent upon the availability of a designated special care area. Within the Illawarra area a special care nursery (SCN) was only available at the Wollongong hospital and deliveries at Shellharbour hospital were therefore not included in the analysis. The decision to admit a baby to the SCN was made by the obstetrician/ paediatrician responsible for the delivery and was made independently of any possible knowledge the normal maternal glucose level.

The normal women who had their baby admitted to the SCN had a higher mean gtt2 than the normal women who did not and the odds in favour of an admission increased by 22.6% for each 1.0 mmol/L increase in the gtt2 result. With respect to some obstetric and fetal outcomes the positive association with the gtt2 level was largely explained by a higher maternal BMI. This does not appear to be the case with respect to morbidity as the odds in favour of being rated “Yes” for morbidity only increased by 3.5% for each one unit increase in BMI.
It was not possible in this survey to determine the reason for admission to the SCN as this was, in a majority of instances, not recorded in the medical record. Decisions were no doubt precautionary as well as based upon established medical indications. It is conventional practice to admit the babies of all women who have had an assisted delivery to the SCN and about half of the admissions were for this reason. However, after exclusion of those women who had an assisted delivery the mean gtt2 level of those women whose babies were admitted to SCN was still significantly higher than the gtt2 level of those women whose babies were not admitted to the SCN. These results indicate that whatever fetal indications were present leading to a decision to admit to the SCN, these were more often found in women with a higher gtt2 level.
CONCLUSIONS

GDM is a potentially serious disorder requiring vigilance and effective medical management. While most modern series of obstetric care have found no significant differences in perinatal mortality between treated women with GDM and the general obstetric population, this is partly due to a continuing improvement in obstetric care and partly because it is most unlikely that there are any diagnosed women with GDM who do not receive some form of treatment. Historical lessons can only be ignored with peril. Perinatal mortality is a finite end point but a very crude index of maternal and fetal care for developed countries in the nineties. In a sophisticated medical environment, and one that is becoming increasingly litigious, maternal and fetal outcomes will be judged on more subtle criteria. The induction rate, the frequency of assisted deliveries and the use of special care nurseries are all relevant to “best practice” obstetrics and to administrators concerned with the costs of health care. The intrauterine effects on the fetus of disorders or deviations of maternal nutrition are likely to have profound effects on the later development of adult diseases.

There can be no doubt that there are adverse fetal risks associated with maternal glucose levels sufficiently high for a diagnosis of GDM to be established. It is logical to presume that there will exist a continuum of risk for maternal glucose levels of a lesser degree. The relationship of these risks to the maternal glucose levels are more likely to be exponential rather than linear. The statistical threshold for maternal glucose levels at which these risks will become apparent will certainly vary depending on the risk being defined and with the population examined. Where the risk will be defined will depend upon the resources available for both detection and treatment.
An appropriate definition of GDM should be based on maternal and fetal outcomes, both during the pregnancy and in later years. The risks to the fetus seem to be present at a lower maternal glucose level than the glucose level that will predict the future conversion of the mother to NIDDM. For the normal women in this study the frequency of assisted deliveries and the probability of being admitted to a special care nursery were all increased, after adjustment for other variables, as the maternal glucose level increased. The rate of macrosomia was also related to rising maternal glucose levels but could be explained by a rising BMI. However in the clinical context, defining a pregnancy at risk of having a macrosomic fetus on the basis of maternal glucose levels and using maternal glucose levels to monitor the effects of interventions are more likely to produce favourable outcomes than any consideration of the BMI.

The gtt2 level in normal women is predictive of certain adverse pregnancy outcomes. Dietary treatment in women with GDM can reduce the rate of adverse outcomes associated with this condition. It is possible that dietary interventions in normal women who have a gtt2 level in the higher range may lead to an increased proportion of women with a normal pregnancy and a reduction in health care costs.
REFERENCES.


## APPENDIX

### Birthweight of males by gestational age.

<table>
<thead>
<tr>
<th>Weeks gestation</th>
<th>mean (SD)</th>
<th>10th centile</th>
<th>90th centile</th>
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<tr>
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<td>3094 (459)</td>
<td>2465</td>
<td>3805</td>
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<td>39, n = 119</td>
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<td>3153</td>
<td>4115</td>
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</table>

### Birthweight of females by gestational age.

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<tr>
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<td>2910</td>
<td>3950</td>
</tr>
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</table>

### Birthweight (total) by gestational age.

<table>
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