Risk Factors Associated with Gestational Diabetes Mellitus

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Abstract: *The purpose of the studies reviewed here is to consider the risk factors associated with gestational diabetes mellitus. In order to abstract general features meta-analysis is utilized as the review tool.*

Keywords: *Risk factors, Carbohydrate intolerance, Gestational diabetes mellitus, Macrosomia diabetes mellitus, Meta-analysis, Gestational diabetes, Hyperinsulinemia, Maturity onset diabetes of the young, Relative risks, Latent auto-immune diabetes in adults.*

Introduction

The purpose of this paper is to consider some risk factors for gestational diabetes mellitus (GDM) with the aid of meta-analysis. It complements a previous review [70]. The study of GDM has acquired a new urgency as there is increasing evidence that Latent Auto-immune Diabetes in Adults (LADA) is part of a spectrum between Type 1 (T1DM) and Type 2 (T2DM0, which were previously regarded as different in kind, not just degree [41].

Meta-analysis is a statistical approach which codes empirical studies of a topic to permit comparison of data, and occasionally enables one to combine the data. The latter is usually done with effect sizes (standardized mean differences), δ, or relative risks, RR, (often approximated by odds ratios).

$$\delta = \frac{(P_T - P_C)}{\sqrt{P_C(1-P_C)}}$$

$$RR = \frac{P_R}{P_C},$$

where P_T, P_C are the "proportions" associated with the treatment and control groups respectively. Some of the issues associated with evidentiary standards in meta-analysis are canvassed in Choy and Shannon [8].

More sophisticated approaches use conventional multilevel modeling and hierarchical Bayesian models to address the combination of evidence from disparate types of study. There are, in fact, quite a number of other way of combining results of independent studies. One general approach is by combining the probabilities obtained from a number of studies which are testing the same directional hypothesis. Probably the most famous of these is Fisher's method of adding the logarithms of probabilities [51]. It suffers from two drawbacks though: one is that it can yield results that are inconsistent with such overall tests as the sign test; the other is that it can support the significant but contradictory results. Another way of combining probabilities is Edington's method [18] but it is restricted to small sets of studies.

There are also ways of adding *t* scores and *Z* scores, and of testing mean *Z* and mean *p*, but in the words of Rosenthal [63]: "even if we have established a low combined *p*, we have said absolutely nothing about the typical size of the effect, the existence of which we have bee examining, We owe it to our readers to give for each combined *p* an estimate of the probable size of the effect in terms of a σ unit, a correlation coefficient, or some other estimate [9]. This estimated effect size should be accompanied, when possible, by a confidence interval."

Spitker [72] identifies three ways in which meta-analysis can pool data:

- Combining individual patients' actual raw data,
- Combining summary data of specific groups of patients from multiple trials, and
- Combining the conclusions of individual trials to create an overall average.

Nevertheless, the issue of what is compelling evidence for scientific peers, for government action, for community convincing is vexed. Level One evidence is not always possible. For example, in considering the question "how will we test the efficacy and safety of new life-prolonging technologies?", Kent [34] observes that "if senescence begins in one's 30s but the outcome (that is, death) can only be measured in one's 70s or 80s, how will researchers be able to perform timely clinical trials in humans?" Nor is Level One is always sensible, especially if the result is obvious as Smith and Pell satirise [71]. The statistical challenges in estimating small effects are taken up in Gelman and Weakliem [24].

Hayes too [29] grapples with the questions "How do you persuade yourself that a statement is true or an answer is correct? How do you persuade some else?" Thus, Fisher was troubled by Mendel's experimental data because they fitted the theory too well [21]! Table 1 indicates the levels of evidence of the papers cited in this study.

Table 1. Number of papers cited at different levels of evidence

Levels of Evidence	I	II	III	IV
Number of papers referred to in the meta-analysis	4	55	39	5

Risk factors for gestational diabetes mellitus

The National Diabetes Data Group [52] defined gestational diabetes mellitus (GDM) as carbohydrate intolerance of variable severity first diagnosed during pregnancy, and Metzger *et al.* [46] noted that the definition applies whether or not insulin is used for treatment or the condition persists after pregnancy.

Oats and Beischer [53] have identified the main controversies surrounding gestational diabetes as:

- The criteria used for diagnosis;
- The best method for screening the entire pregnant population;
- The management of identified gestational diabetes.

Usually in looking for those most likely to acquire a disease one tried to isolate risk factors. Generally agreed risk factors for GDM are:

- Maternal obesity 120% of greater;
- Family history of diabetes (first degree relatives);
- A previous pregnancy-history of macrosomia (> 4000g birth weight), unexplained stillbirth or neonatal death;
- Maternal age > 35 y;

- Glycosuria on two or more separate episode in the current pregnancy;
- Ethnicity.

Risk factors in isolation are problematic though. Obesity, for example, is neither a necessary nor a sufficient condition for NIDDM, and in some subjects obesity is not the only factor or the main risk factor [78]. However, there is a close relationship between obesity and other risk factors for NIDDM [64, 77, 80].

Furthermore, Carpenter [6] argued that historical and clinical risk factors have a low sensitivity for GDM because they are so highly prevalent among normal patients. Similarly, Marquette *et al.* [44] found a 3.3% prevalence of GDM in 178 patients with risk factors, not a statistically significant difference. They concluded that "screening on the basis of risk factors other than age is inefficient". Moses *et al.* [49] have also demonstrated that historical and clinical risk factors are not sufficiently predictive to use as the basis for testing.

In a non-current study of risk factors and perinatal outcome, Weeks *et al.* [75] found similarities between those with and without risk factors even after stratification by maternal age (≥ 30-yr) and that selective screening based on risk factors would have failed to detect more than 40% of GDMs in the study.

There is ample evidence that pregnancy is an insulin-resistant state (*cf.* [5, 7, 37]). Pendergrass *et al.* [57] also described the interaction between insulin resistance, GDM and NIDDM, and the additive effect of the associated risk factors for these metabolic diseases as in Fig. 1. Some aspects of this will be pursued further when looking at the progression from GDM to NIDDM.

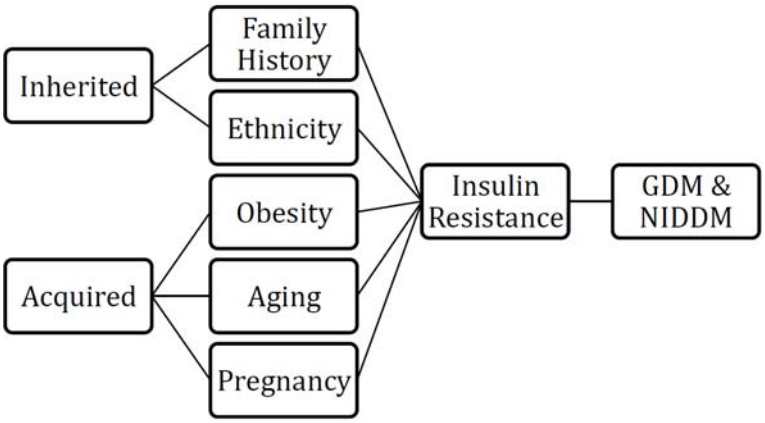

Fig. 1 Interaction of risk factors for GDM and NIDDM

Conclusion 1	Quality of Evidence
Screening for GDM on the basis of risk factors has low sensitivity.	II/III[1]

Again, without going into the detail, ethnicity as a risk factor receives separate attention.

[1] Some excellent studies with control groups: large numbers, varied ethnic populations, long term studies.

Table 2. Incident of GDM in Illawara region (after Moses *et al.*, [50])

Ethnic Grouping	N	2-h glucose	% with GDM
Australasian	1299	5.8(1.3)	7.1
North European	191	5.9(1.3)	6.3
South European	153	5.8(1.4)	9.2
Asian	59	6.1(1.5)	11.9[2]
Other[3]	101	5.7(1.3)	6.9

Ezimokhai *et al.* [19] confirmed the influence of ethnic background on the prevalence of gestational diabetes in a multiethnic and multicultural society.

Table 3. Prevalence and odds ratios for GDM among ethnic groups in Australia [76]

Ethnic Group	N	Prevalence (%)	Odds Ratio
Aboriginal	9	10.1	3.7
Anglo-Celtic	73	3.0	1.0[4]
Arab	25	7.5	2.5
Chinese	71	15.0	5.6
Indian	19	16.7	6.4
Vietnamese	37	9.6	3.6

Conclusion 2	Quality of Evidence
There has been an increasing incidence of GDM reported in Australia and there is compelling evidence that there are large ethnic variations in prevalence.	II/III

Screening and testing for GDM

The most controversial aspect of this particular study was in the place of the screening for GDM, particularly in the light of the limitations of risk factors in identifying these most likely to acquire GDM.

Those who oppose screening seem to fall into two camps: those who are opposed to any intervention and treatment unless the scientific evidence comes from randomized controlled trials, and those who are concerned about the false-negatives because intervention and treatment are crucial in a disease like GDM which has long-term implications for the health of the mother and the off-spring and for which there is a very limited window of opportunity for effective action. Whether these long-term implications are cause-and-effect will not be known for many years until some of the animal models can be demonstrated in humans.

Some results of screening GCT with diagnostic OGTT are set out in Table 4.

[2] $p \leq 0.001$
[3] 19 Pacific Islanders (2 with GDM), 12 Aboriginals (0 with GDM)
[4] Reference Group

Table 4. Screening GCT vs diagnostic OGTT

Study	*Yr*	*a*	*b*	*c*	*d*	*X*%	*Y*%	*Z*%	QE
O'Sullivan	73	15	94	4	639	79	87	14	II
Amankwah	77	71	228	–	885	100	80	24	IV
Carpenter	82	23	86	1	271	95	76	22	III
Lavin	85	30	107	–	1940	100	95	22	II
Marquette	85	10	102	2	320	83	76	9	II
Coustan	89	125	1321	–	4768	100	78	9	II
Dooley	91	123	729	7	2885	95	79	14	II
Diez	89	9	45	1	167	90	79	17	
Forsbach	88	27	80	3	583	90	88	25	III
Leiken	87	163	194	18	2030	90	90	45	
Landon	86	7	25	1	92	93	78	22	
Deerochanawong	96	9	74	1	625	90	89	11	III
Litonjua	96	217	670	12	2122	95	76	24	II
Litonjua	96	33	174	2	644	94	79	16	II
Litonjua	96	51	173	3	376	94	68	23	
Litonjua	96	74	99	3	644	96	87	43	
Litonjua	96	49	149	4	342	92	70	25	
Litonjua	96	9	63	1	131	90	68	13	
		612	3085	38	15205	94	83	17	
		433	1328	25	4259	95	76	25	
Totals		1045	4413	63	19464	94	82	19	

Legend:

- *a*: true positives; *b*: false positives; *c*: false negatives; *d*: true negatives;
- *X*: sensitivity; *Y*: specificity; *Z*: predictability.

The data were analysed chronologically but there was no significant variation over time. Nor were there significant variations for different screening tests. The individual studies were generally within the confidence intervals of these results. Indeed, if we act as conservatively as possible and combine only the largest studies (N > 2000 subjects), we obtain the contingency Table 5.

Table 5. Contingency table for studies from Table 5 with N > 2000 subjects

	Diagnosis +	Diagnosis –	Totals
Screening +	658	3921	4579
Screening –	37	13745	13782
Totals	695	17666	18361

From this we find a sensitivity of 0.95, a specificity of 0.99 and a negative predictability of 0.99 [36], but a positive predictability of only 0.14. On face value these figures would normally be high enough to recommend the two stage process of screening followed up with diagnosis where appropriate [36]. However, the positive predictability is only 0.14.

The glucose challenge screening test is highly specific so that it does not miss many women who have GDM, though it should be emphasized in the light of other findings in this review that a slight degree of under-diagnosis is likely to do harm in the case of GDM "the usefulness of a diagnostic test depends on the true prevalence of the condition in the

population being studied" [4], which is why the usefulness of the glucose challenge test is questionable. Furthermore, the window of opportunity for effective management of GDM is relatively short space of time.

The relatively low predictability of 14% is lower than expected. Sensitivity and specificity are independent of the prevalence of the condition: they are characteristics of the screening test, but they may vary when the same test is applied in different populations, whereas the predictive value of a test is dependent upon disease prevalence [23].

Given the low sensitivity of risk factors for GDM discussed in the previous two sections, one cannot reliably screen those most at risk, since the only way to increase the positive predictive value, or yield, of a screening test for a rare disease with insensitive preclinical risk factors is by increasing its specificity; that is, by changing the criterion for positivity. Thus one is forced to consider universal diagnostic glucose tolerance tests, especially as there is no significant lead time bias in favour of glucose challenge screening.

Universal testing, on the other hand, would not conflict with the approach of this report and would support the recommendation of the Australasian Diabetes in Pregnancy Society (ADIPS). The study of Moses *et al.* [49] also provided compelling evidence to support the ADIPS recommendation that there should be universal GTT testing. In fact, if you have low positive predictability, then universal screening almost implies universal testing for the outcomes to be effective.

While it may generally be considered unrealistic to overload already stressed diagnostic services, the definitive glucose tolerance test is relatively cost-effective, and we have shown in this report that the unique physiological experience of pregnancy requires precise diagnosis and appropriate management of GDM to protect the long-term health of the mother and to avoid significant fetal complications which are ultimately more expensive, not only in monetary terms but more importantly in human terms.

Conclusion 3	Quality of Evidence
Universal diagnostic testing of all non-diabetic pregnant women which an OGTT (done as in Conclusion 1) should be carried out at the beginning of the third trimester to provide sufficient time for effective management.	II/III

Neonatal outcomes

The problems of standardization of GDM criteria effect research into the subsequent development of GDM, though there is unequivocal general agreement on the predictive nature of gestational blood glucose levels for the later development of NIDDM [5, 46]. Keen [33] confirms this but wonders to what extent this simply reflects the predictive power for DM of IGT detected in the non-pregnant state. "Neonatal diabetes mellitus presents in the first 6 months of life with signs of hyperglycaemia" – particularly keto-acidosis [73].

Fig. 2 shows the resistant lines analogous to regression lines but with the use of medians and inter-quartile ranges to ignore outliers. They are thus quite conservative and they demonstrate the inevitability of NIDDM for those who have had GDM. The "half-life" or when 50% of GDM mothers might expect to have been diagnosed with NIDDM is about 10 years which is in accordance with the cumulative incidence graph of O'Sullivan [54].

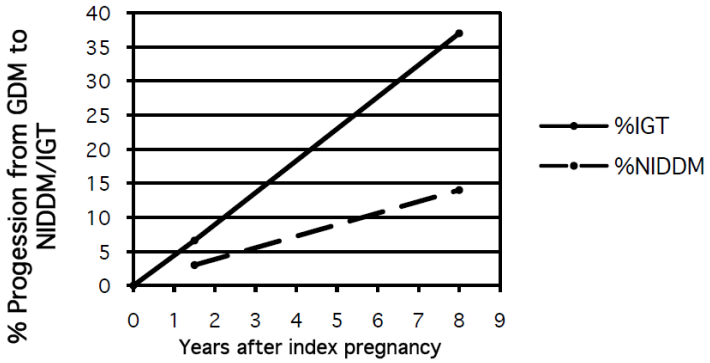

Fig. 2 Resistant Lines for NIDDM/GDM & IGT/GDM

Conclusion 4	Quality of Evidence
There is a progressive and on-going rate of conversion of the GDM mother to NIDDM.	II/III

The likelihood of the child's developing DM seem less well documented, although there are some well-designed studies. Unfortunately, disparate populations, different sampling techniques and dissimilar aims prevent any direct combination of their findings, but collectively they are pointing to similar answers to the question of what is likely to happen to the offspring of GDM mothers. In any case, there are no negative studies, In particular, Coustan (1996) argues that maternal hyperglycaemia evokes fetal hyperinsulinemia, and that the latter causes an adverse effect on the fetus. Fetal hyperinsulinism remains the driving force for excessive fetal growth; (paediatric diabetology also includes neonatal diabetes mellitus and Maturity Onset Diabetes of the Young (MODY)) [65, 14].

Conclusion 5	Quality of Evidence
There is strong and consistent circumstantial evidence of a high risk of obesity, leading to NIDDM, in the offspring of poorly-managed GDM mothers: the rate of IGT in the offspring of well controlled GDM mothers with normal carbohydrate metabolism during pregnancy.	II/III[5]

Concluding comments

By way of concluding this paper the following recommendations were made to the NSW Health Corporation which initially funded this meta-analysis.

A. Diagnosis: FPG $\geq$ 5.5 mmol·1^{-1} and/or 2PG $\geq$ 8.0 mmol·1^{-1} following 75 g OGTT.
B. Testing: All non-diabetic pregnant women with 75 g OGTT at 26 weeks gestation.
C. Management: Use of insulin when required for glycaemic control, home-monitoring of BSL, and diabetic diet.
D. Follow-up: Women with GDM should have a repeat 75 g OGTT at about six weeks *post partum* with a standard WHO criteria for the non-pregnant state.
E. Further Research:
   - Investigation of high rates of caesarean delivery with GDM.
   - Cost-effectiveness of healthcare programs associated with GDM.
   - Association between gestational ketonomia in the mother and lower IQ in the child.

[5] More long-term follow-up studies are being published.

Confirmation of diabetes at any stage during or subsequent to pregnancy should not be precluded if there are clinical features to warrant such a diagnosis, because the issues examined here are not unrelated to the world wide increase in T1DM (Type 1) and T2DM (Type 2) diabetes mellitus in childhood [45].

Finally, women who have had GDM have a tenfold greater risk of developing DM2 in the future. This risk increases if the woman:

- has a family history of diabetes,
- belongs to certain ethnic backgrounds, or
- is overweight.

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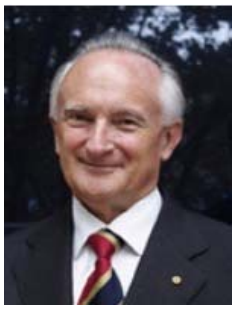

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He enjoys reading, walking, theatre, number theory, and thoroughbred racing.

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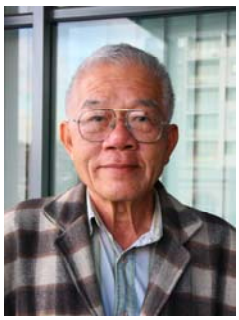

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