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Meta-analytic Tools for Research on Gestational Diabetes Mellitus

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Abstract: *The purpose of this paper is to utilize the approach of meta-analysis to survey trends in the diagnosis and management of gestational diabetes mellitus.*

Keywords: *Diabetes mellitus, Meta-analysis, Gestational diabetes, Hyperinsulinemia, Relative risks.*

Introduction

The aim of this paper is to outline the salient feature of meta-analysis in order to indicate how this approach can draw together conclusions about gestational diabetes mellitus (GDM) that are not otherwise obvious or strengthen results that might not otherwise be compelling.

It is of interest to note in passing that the official runners-up for the Nobel Prize in Physiology or Medicine in 2008 were Professor Rory Collins and Sir Richard Peto of the University of Oxford for their contributions to clinical medicine and epidemiology through the development and application of meta-analysis.

Meta-analysis as a tool

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 (Shannon [32]). Thus, Glass [12], the effective founder of meta-analysis, defines it as "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the finding".

There are a number of other ways 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 [22]. 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 significant but contradictory results. Another way of combining probabilities is Edgington's method [9] but it is restricted to small sets of studies.

That it is not more popular to attempt systematic efforts at synthesis is something of a puzzle, and Pillemer and Light [30] suggest an explanation based on prestige: "The biggest rewards in most academic disciplines have traditionally gone to researchers who begin the exciting new experiment, or design the successful new curriculum, or develop the broad new theory. In contrast, pulling together existing evidence is not considered a truly scientific activity by some because it deals with old data. We disagree. Perhaps the key idea in all of this is

'discovery'. A systematic effort to draw conclusions from many existing studies can be every bit as likely to lead to a 'discovery'…as one new study. " The question of how compelling the evidence has to be in order to be convincing is discussed by Choy and Shannon [4].

Peto [26] outlined the objectives of meta-analysis in medicine as:

- To demonstrate an effect in a direction of interest by overcoming the obscuring effect of sampling variations in a large number of small studies;
- To add quantitative effect sizes (and their uncertainty) to the qualitative results of traditional narrative literature reviews; and
- To encourage systematic collation and review of individual studies and explicit reporting of the criteria used.

Effect sizes can be calculated in a variety of ways, depending on how the original results were reported. For example,

- $\delta = \frac{(\mu_T - \mu_C)}{\sigma_C}$ if the means are given;
- $\delta = t\sqrt{\frac{1}{n_T} - \frac{1}{n_c}}$ for *t*-test designs;
- $\delta = 2\sqrt{\frac{F}{n_T + n_c}}$ for one-way ANOVA designs;
- $\delta = t_g\sqrt{2(1 - r_{xy})\left(\frac{1}{n_T} + \frac{1}{n_c}\right)}$ for raw gain scores.

It is becoming customary in meta-analyses of medical literature to qualify trends with the quality of evidence ratings as described in Choy and Shannon [3]. Table 1 indicates the levels of evidence of the papers referred to in this meta-analysis. Level I is the most scientifically stringent, though often impractical with long-term chronic illnesses.

Table 1. Quality of evidence for meta-analysis in this study

Levels	Controlled Trials	No. of Papers
I	A systematic review of all relevant randomized controlled trials	4
II	At least one properly-designed randomized controlled trial	55
IIIA	Well-designed but not randomized, controlled trials	39
IIIB	Well-designed cohort or case-control analytic studies	
IIIC	Multiple time-series with or without intervention	
IV	Opinions of experts based on clinical experience or descriptive studies	5

More specifically in diagnostic testing, Irwig *et al* [15] claimed that meta-analysis can:

- Provide an overall summary of diagnostic accuracy;
- Determine whether estimates of diagnostic accuracy depend on the study design characteristics (study validity) of the primary studies;
- Determine whether diagnostic accuracy differs in the subgroups defined by the characteristics of the patients and test; and
- Identify areas for further research.

Table 2. The issues in the papers considered in this meta-analysis

Paper Number	1	2	3	4	5	6	7	8
Pages	2	2	2	1	9	2	14	8
References	24	27	43	4	103	20	41	63
Evidence Quality	IV	IV	IV	IV	IIIB	IV	IIIA	IIIB
Macrosomia	1	0	0	1	0	1	1	0
Perinatal Mortality	0	0	1	1	0	0	0	0
Screening & Diagnosis	1	1	0	1	1	1	1	1
Follow-up Study	0	0	0	1	1	0	0	1
Insulin Sensitivity	0	0	0	0	1	0	0	0
Complications	0	0	0	0	1	0	0	0
Offspring→DM	0	0	0	0	1	0	0	0
Mother→DM	0	0	0	0	1	0	0	0
General: history/definition	0	0	0	0	1	1	0	0
Diagnostic Test Only	0	0	0	0	0	0	1	0
Treatment/Management	0	0	0	0	0	0	0	1
Control Issues	0	0	0	0	0	0	0	1
Tables/Figures	0	0	0	0	T	0	T	T
Special Paper	0	0	0	0	1	0	1	0

Gestational Diabetes Mellitus

The National Diabetes Data Group [23] defined the gestational diabetes mellitus (GDM) as carbohydrate intolerance of variable severity first diagnosed during pregnancy, and Metzger *et al* [19] noted that the definition applies whether or not insulin is used for treatment or the condition persists after pregnancy. Hod *et al* [14] carried out an extensive literature review to answer three questions (although they did not answer the third):

1. Is the condition important, namely is GDM significantly related to maternal and perinatal morbidity and mortality?
2. Is the accepted intervention (treatment modalities) effective in reducing these complications?
3. Are there effective diagnostic tests available for this condition?

We shall also address the substance of these three questions, albeit in a slightly different way. It is therefore worth noting the conclusion of Hod *et al* [17] that "GDM is not merely a clinical sign but a disease, a distinct clinical entity, with short-rang and long-range implications for both mother and offspring. "

In an earlier paper Coustan [6] had noted that international agreement was lacking about diagnostic criteria for gestational diabetes mellitus (GDM) and its treatment, and that there was debate whether gestational diabetes was a disease or merely a risk factor. The issue has been further confounded by the metabolic changes brought about by pregnancy which can have the effect of increasing the glucose response to a pure carbohydrate challenge even though fasting levels in pregnant women are lower than in non-pregnant people [6]. Nevertheless, there is general agreement that this pregnancy condition can be linked to adverse pregnancy outcomes and may be associated with subsequent diabetes in the non-pregnant state [6]. Accordingly, the criteria for this study are based on a systematic review of the literature to identify papers for the review which deal with:

a. the conversion of the mother with GDM to NIDDM;
b. the fetal and maternal outcomes;
c. results of the international symposia in 1980, 1984 and 1990;
d. the Australian diagnostic criteria;
e. multi-level selection according to:
    - population effect;
    - study type; and
    - study specific parameters.

GDM Meta-analysis

A 10 step procedure was followed in conducting the meta-analysis in this paper.

1. Development of a protocol for conducting the meta-analysis.
2. Identification of sources of information used.
3. Definition of the criteria for the selection of trials for inclusion:
    - Relevance:
        - Construct validity (the theoretical framework);
        - Eternal validity (the selection of subjects: random or convenience);
    - Acceptability:
        - Internal validity (does or can the study do what it tires to do?);
        - Statistical validity (appropriateness of statistics).
4. Reading, classification, coding, scoring, evaluating, and choosing of papers. The coding scheme used by Shannon and Hung [33] has been adapted for this study, namely:
    - Ecological features
        - Treatment variables
        - Disease variable initial state conditions
    - Methodological features
        - Assignment of patients
        - Controls
            - Experimenter effects
            - Historical effects
            - Measuring bias
            - Author bias
        - Strength of research design
    - Statistical features
        - Subject variables
            - Age
            - Sex
            - Risk factors
            - Socio-economic status
            - Ethnic/racial/geographic variables
        - Appropriateness of statistics
        - Data
    - Publication features
        - References
        - Sources of references if unpublished
        - Type of report
            - Abstract
            - Review

  - Letter
  - Conference paper
  - Editorial
- Year(s) of publication
  - Thesis
  - Internal report
  - External report
  - Journal article
  - Published by learned society
- name of publication

5. Adjudication of differences among the three readers on qualitative criteria.
6. Development of questions, procedures, and analyses to pose of trials for inclusion.
7. Reading of papers and answering of questions on the checklists.
8. Adjudication of differences which could not be reconciled among the three scorers on the quantitative measurements.
9. Combination of results an quality-assurance of the data.
10. Analysis, interpretation and reporting of results.

Thus a Medline key-words search from 1966 to 1996 came up with the numbers of references listed in Table 3.

Table 3. Medline Search of Keywords

Years	Diagnosis	GDM	Screening	Diagnosis & GDM	Screening & GDM
1992-1996	74441	133	20485	24	46
1986-1991	102640	126	22917	18	29
1980-1985	66414	30	11832	7	5
1976-1979	36038	4	5924	0	0
1966-1975	41444	0	5011	0	0

Given the relatively small number of published papers on screening and diagnosis of GDM; the likelihood of extensive quantitative combination of odds ratios or effect sizes was low. Accordingly, a sweeping search of the literature was made on the basis of Fig. 1 in order to attempt some qualitative coding and comparisons.

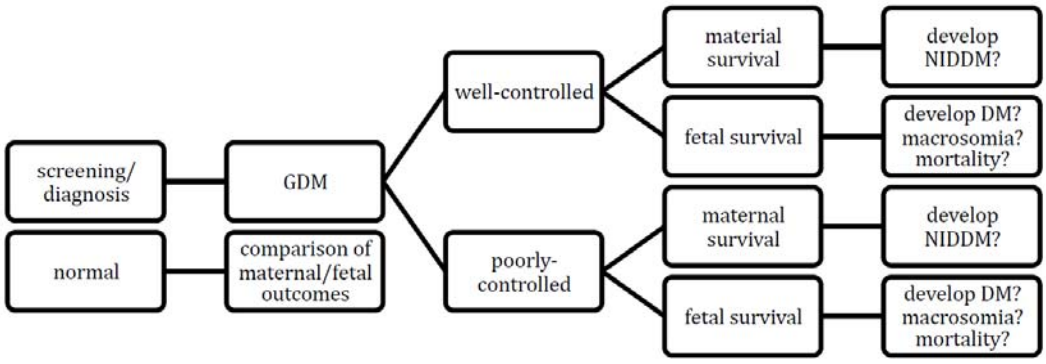

Fig. 1 Review plan

Nevertheless, much of the literature was not amenable to comination of quantitative results even when the conclusions could be compared qualitatively because they lacked adequate controls or they were a mixture of longitudinal and cross-sectional designs. Furthermore, on a few occasions we found that some references which were cited in support of a position when

examined closely either did not have anything to say on the details of the subject in question or were only marginly related to it. Such situations obviously complicated our searching and sorting processes.

An investigation of the literature relating to the existence and diagnosis of GDM helped us reach the following conclusion, which is included without discussion as an example.

Conclusion 1	Quality of Evidence
The criteria for Gestational Diabetes Mellitus should be a fasting plasma glucose level ≥ 5. 5 mmol/1 and/or a plasma glucose level ≥ mmol/1 2 hours after a 75g OGTT administered according to the WHO criteria.	II/III[1]

Management of GDM

O'Sullivan *et al* [24], in a prospective study of 187 GDMs 259 randomly selected controls, found significantly higher perinatal mortality rates among the GDMs, with age having a disproportionately adverse effect, enhanced slightly by obesity (Table 4).

Table 4. Comparisons among pregnant women

Characteristic	PDM[2]	GDM	NonDM
Delivery < 37 wk(%)	14	10	6
Macrosomia (%)	40	23	11
FPG (mmol/1) 2nd Trimester	7. 0	5. 7	4. 1
FPG (mmol/1) 3rd Trimester	5. 8	5. 1	4. 2

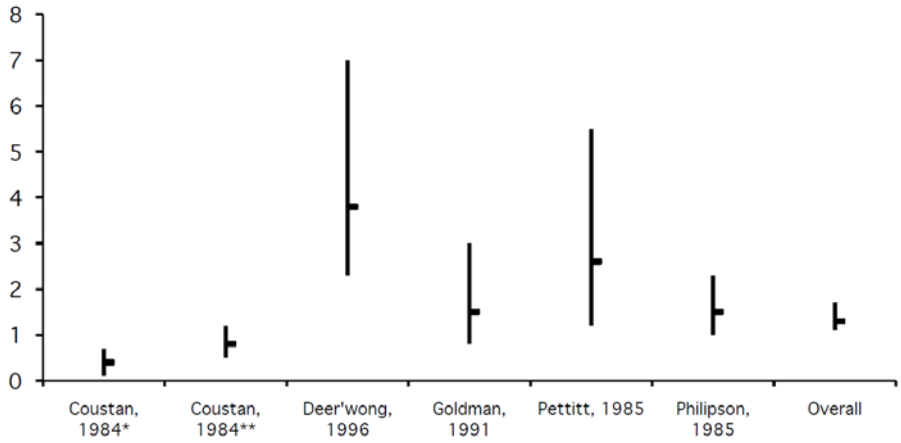

Fig. 2

The uncertainty about risk factors outlined above gives support to a healthy life style strategy as a means of multiple risk factor approach to GDM as has been suggested for NIDDM in general [17, 34]. The results of Sells *et al* [31] also indicated that mothers with IDDM "who maintain good control during pregnancy can expect to have infants who are neuro-developmentally normal".

[1] Most studies were cross-sectional observational studies, with the general consensus in favour of the WHO criteria because they pick up more cases of GDM than NDDG criteria.
[2] Pregestational Diabetes

This has been a situation of some confusion as there has been a view that pregnant women should not diet as there was a risk that cutting food intake would lead to the loss of essential nutrients to help the baby's development and growth. There seems to have been a large increase in obese women of reproductive age over the past decade. This growing group of women often need intensive antenatal care, bariatric-sized beds and are difficult to care physically during labour. Evidence is accumulating that shedding kilos may not only do no harm to mother and child but might benefit them [35]

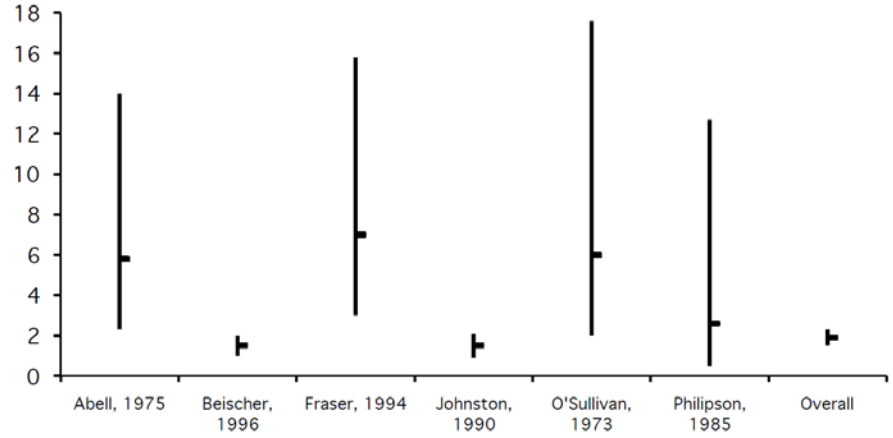

Fig. 3

Conclusion 2	Quality of Evidence
The fetal outcomes of undiagnosed or poorly managed GDM include double the risk of large for gestational age and one and a half times the risk of macrosomia (birthweight > 4000g).	III[3]

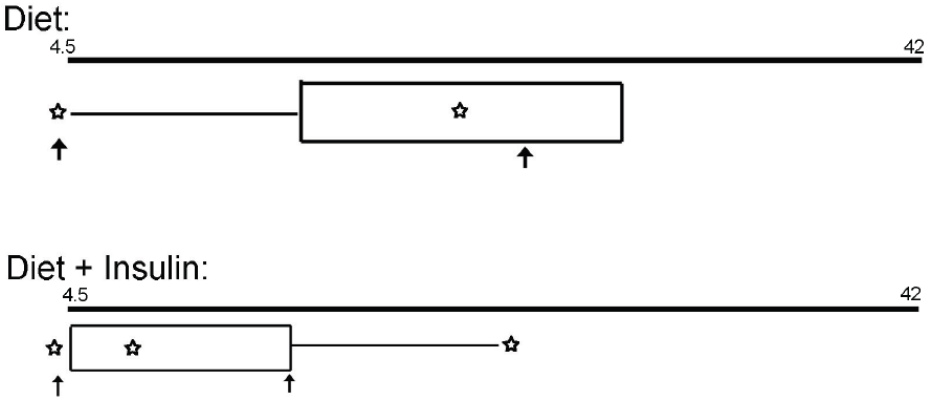

Fig. 4. Boxplot of Diet vs Diet+Insulin (%)

Tight glycaemic control is the first requirement of the management of GDM. Two ways of doing this are diet and exercise, both of which were studied by Jovanovic-Peterson and Peterson [25] who found each effective in reducing FBG over a six week period. Not surprisingly both together were found to be more effective, although the study of Maresh *et al* [18] found no statistically significant difference between the two therapies.

[3] The issue is complicated by women without hyperglycaemia who have large babies.

Fig. 4 shows that there is a definite trend, though the data are not robust enough for more sophisticated statistical analysis.

Conclusion 3	Quality of Evidence
Properly-diagnosed and well-managed GDM 'normalises' the relative risks associated with GDM, except for caesarean delivery.	II

Concluding comments

Superficially meta-analysis seems just like a very careful traditional literature review. The differences are in the structure, the coding, the qualification and the quantification of the results. In fact some medical journals (for example, journals of the American Medical Association) are sufficiently aware of the differences to the extent that they require literature reviews to be done with meta-analysis.

Although the extrapolation from animal studies to human hypotheses is problematic, animal experiments do abound to the extent that they at least suggest reasonable comparisons with human epidemiological data about any abnormal intra-uterine environment, and this is an issue which is intimately bound up with any suggestions about the management of GDM. Animal experiments are also of use because they can remove the clinical 'noise' from analysis. In fact, animal experiments are unequivocal about the adverse intra-uterine effect of undiagnosed or poorly managed GDM on the subsequent development of the offspring [27, 28]. This has important lifestyle consequences for public health planning by governments [2, 11].

Notwithstanding these recommendations, 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 Type 1 and Type 2 diabetes mellitus in childhood [36]. Moran and Teede [21] note that "there is emerging evidence that modifying diet composition has beneficial effects on weight loss and metabolic risk factors, but this approach needs to be successful and safe within a long-term sustainable lifestyle modification setting for the optimal treatment of IR (insulin resistance). " This accords well with our recommendations.

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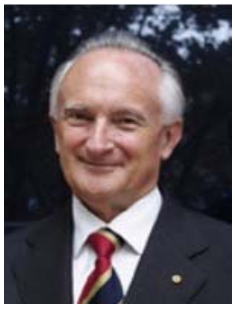

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