

## ACCEPTED VERSION

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### **Progressing towards standard outcomes in gestational diabetes Cochrane reviews and randomised trials**

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## **MAIN TEXT**

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### **Abstract**

Outcomes in gestational diabetes Cochrane protocols and reviews before and after development of 'standard outcomes' by WOMBAT (WOMen and Babies health and wellbeing: Action through Trials) were surveyed. An increase in 'common' outcomes (those pre-specified by  $\geq 50\%$  of the protocols and reviews) over time was observed (2001-09: 27 vs. 2010-14: 46). There were discrepancies in outcomes pre-specified in reviews and reported by randomised trials. Efforts are needed to develop a core outcome set, to reduce research waste and improve health outcomes.

## **Introduction**

Gestational diabetes mellitus (GDM), traditionally defined as any degree of glucose intolerance with onset or first recognition during pregnancy,<sup>1</sup> is one of the most common medical complications of pregnancy. The estimated global prevalence of hyperglycaemia in pregnancy (including GDM, and 'total diabetes' (known/unknown pre-existing diabetes)) is 16.9%;<sup>2</sup> recent Australian GDM prevalence estimates range from 9.6% to 16.0% depending on diagnostic criteria used.<sup>3,4</sup>

In the short-term, mothers with GDM have higher risks of pre-eclampsia and preterm birth; their infants may be born large-for-gestational age, and are more likely to be born by caesarean section, or face complications, including shoulder dystocia during vaginal birth.<sup>5</sup> Predisposition to type 2 diabetes, obesity and cardiovascular disease are potential, serious, long-term consequences.<sup>5</sup> Despite controversy surrounding the diagnosis of GDM, including at what degree of hyperglycaemia interventions should be initiated, there is good evidence that risks of many adverse consequences can be reduced or eliminated with treatment.<sup>6</sup>

With the recognition of an increasing prevalence of GDM worldwide, and its serious short- and long-term consequences for the mother and child, there has been an explosion of randomised trials and systematic reviews focused on interventions for prevention, detection, management and follow up. Acknowledging that waste in research may result from important outcomes not being assessed (or reported) in trials and reviews,<sup>7,8</sup> in Australia, the WOMBAT (WOMen and Babies health and wellbeing: Action through Trials) Collaboration recognised a need to standardise outcomes.<sup>9</sup> WOMBAT was funded by a National Health and Medical Research Council (NHMRC) enabling grant (2005-2010) to support high-quality randomised trials in the perinatal area. In 2009, lists of 'standard outcomes', including for GDM, were developed through extraction (from selected trials and reviews) and group harmonisation, and published on the Collaboration's website.<sup>9</sup> Recently, the COMET (Core Outcome Measures in Effectiveness Trials) Initiative was established specifically to assist the development and application of 'core outcome sets' (COS): *"the minimum that should be measured and reported in all clinical trials of a specific condition."*<sup>10</sup> There is currently no COS for GDM research.

The aim of this study was to survey outcomes used in GDM Cochrane protocols and reviews before and after the development 'standard outcomes' by WOMBAT (2009), as one approach by which to assess progress towards core outcomes for GDM research.

## **Methods**

The Cochrane Library was searched using the term "gestational diabetes" (in Title, Abstract, and Keywords) on 19 March 2014. We included Cochrane reviews and protocols (documents

describing rationale, objectives and methods for reviews<sup>1</sup>) addressing interventions for prevention, detection, management or follow-up of GDM.

Data collected included: date published; information regarding methods (scope; number and choices of pre-specified primary and secondary outcomes); and results (number of included randomised trials (and dates published), and number of included trials reporting data for pre-specified review outcomes). Primary outcomes in Cochrane reviews are those *“that would be expected to be analysed... and conclusions... based largely on”*; <sup>11</sup> while secondary outcomes are those *“used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.”*<sup>11</sup>

Data analysis involved simple number, mean and percentage description, and results are presented narratively (and using a table and figure), comparing outcomes in Cochrane protocols and reviews before and after the development of GDM ‘standard outcomes’ by WOMBAT.

## **Results**

### ***Cochrane protocol and review characteristics***

We included four protocols and 13 reviews, with six (one protocol, five reviews) published before (2001-2009), and 11 (three protocols, eight reviews) after (2010-2014) WOMBAT’s ‘standard outcomes.’ The scope of the protocols and reviews included GDM prevention (5, 29%), detection (2, 12%), management (8, 47%) and follow up (2, 12%). The number of included randomised

trials in the 13 reviews was 49 (mean: 4 trials per review). Dates of publications of the included trials ranged from 1983 to 2012.

### ***Cochrane primary and secondary outcomes***

Protocols and reviews before and after WOMBAT's 'standard outcomes' were consistent in number of pre-specified primary outcomes (mean: 4) and choices. There were a total of 12 different pre-specified primary maternal outcomes (most commonly: GDM and caesarean birth), and nine different pre-specified primary child outcomes (most commonly perinatal mortality, large-for-gestational age and macrosomia).

An increase in the number of pre-specified secondary outcomes after WOMBAT's 'standard outcomes' was observed (mean: 26 in 2001-2009 vs. 48 in 2010-2014), particularly an increase in pre-specification of longer-term outcomes for the mother and her child (mean: 1 in 2001-2009 vs. 19 in 2010-2014). Accordingly, the total number of pre-specified outcomes increased over time (**Figure 1**).

### ***Cochrane 'common' outcomes***

An increase in the number of 'common' pre-specified outcomes (defined as outcomes pre-specified by  $\geq 50\%$  of all protocols/reviews), relating to the mother, her child, and the use of health services was observed after WOMBAT's 'standard outcomes' (27 in 2001-2009 vs. 46 in 2010-2014) (**Table 1**). The additional 'common' outcomes in 2010-2014 related predominately to longer-term health.

### ***Outcome data from included randomised trials***

For primary outcomes in Cochrane reviews, less than half of the included randomised trials reported data at all, or in a way that could be included in a meta-analysis. Considering the most common primary outcomes in reviews, the percentages of included trials reporting data were: GDM: 47% (8/17 trials; four reviews); caesarean: 40% (16/40 trials; nine reviews); perinatal mortality: 23% (6/26 trials; six reviews); large-for gestational age: 30% (9/30 trials; six reviews); macrosomia: 37% (11/30 trials; six reviews). Included randomised trials did not report outcome data for the majority of pre-specified secondary outcomes in Cochrane reviews (**Figure 1**).

### **Discussion**

'Core outcomes' for GDM randomised trials and systematic reviews have the potential to increase value and reduce research waste.<sup>10</sup> COS are designed to be the minimum that all trials or reviews in a particular area collect; thus making it easier for results to be compared and combined, such as in reviews.<sup>10</sup>

We surveyed outcomes in Cochrane protocols and reviews before and after the development of GDM 'standard outcomes' by WOMBAT (as one approach by which to assess progress towards a COS for GDM), and observed increases in the total number of pre-specified outcomes, and in the number of 'common' outcomes in Cochrane reviews over time. It is possible that some of this change may be attributed to the WOMBAT Initiative. However we acknowledge that increased recognition and understanding of the widespread consequences of GDM (particularly the longer-

term effects for the mother and child) also likely contributed to the progress towards standardised outcomes that we observed. We noted discrepancies between the outcomes pre-specified by Cochrane reviews, and reported by randomised trials, with less than half of the included trials reporting relevant data. This may reflect that the outcome data were not collected in the trials (with some measuring intermediate outcomes only, and many reporting no longer-term follow), or the selective reporting of outcome data by trials, for example, with a lack of reporting due to no observed statistical significance, or journal publication space restrictions.<sup>8</sup> However, this could reflect a 'lag' time between recognition by trialists of the importance of some outcomes (such as longer-term maternal and child outcomes), and the subsequent collection and reporting of relevant outcome data.

To date, additional published efforts focused on standardising outcomes for GDM research are limited to one other study in the United States.<sup>12</sup> In a research priority setting initiative, 'high priority' maternal and child outcomes relating to medication and birth management for women with GDM were identified, defined as those appearing in the top three lists of two or more of nine national stakeholders.<sup>12</sup> The 'priority' outcomes identified by this study were shared by the list of 'common' Cochrane protocol and review outcomes we identified, and similarly included longer-term outcomes for the mother and child.

There is now a need to move further towards an international COS for GDM research, guided by COMET and associated initiatives, including CROWN (CoRe Outcomes in WomeN's health).<sup>13</sup> Proposed methods for developing COS include a systematic literature review to identify outcomes that have been previously reported, a Delphi study using these outcomes in a number of rounds, and a final consensus meeting with all relevant stakeholders to review the outcomes.<sup>14</sup>



Encouragingly, one project, aiming to develop a COS for trials in screening, prevention and treatment of GDM has been proposed.<sup>15</sup>

There will be challenges for developing core outcomes for GDM research; a recent systematic review identified that of 198 studies involving development of COS, only 1% (2) were in the pregnancy and childbirth field,<sup>14</sup> demonstrating the lack of experience in this area to date. The pre-specified outcomes in Cochrane GDM protocols and reviews are many (compared with in other health care areas<sup>16</sup>); prioritisation of a 'core set' will need to involve and balance carefully the views of relevant stakeholders.<sup>14</sup> Harmonising definitions for outcomes in a GDM COS may be difficult. Whether one set that spans GDM prevention to follow up should be developed or separate sets, such as for prevention, detection, management and follow up, is unclear. Despite these challenges, core outcomes for GDM research, building on the work described here, have potential to reduce research waste, and ultimately contribute to preventing and reducing the consequences of GDM.

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## Figure legends

**Figure 1:** Number of pre-specified outcomes in GDM Cochrane protocols and reviews, and, where applicable, number of outcomes with no data from included trials (2001-2014, N=17)

Each bar indicates one protocol/review; patterned bars indicate protocols

## Tables

**Table 1:** Common pre-specified outcomes in Cochrane GDM protocols and reviews (2001-2014, N=17)

<b>Protocol or review outcomes</b>		
<b>Mother</b>	<b>Child</b>	<b>Health services</b>
<i>Perinatal</i>	<i>Fetal/neonatal</i>	Hospital or health professional visits for the mother
GDM*	Perinatal mortality	Length of postnatal stay (mother)
Pre-eclampsia	Large-for-gestational age	Admission to neonatal ward
Weight gain during pregnancy*	Macrosomia	Length of postnatal stay (baby)
Use of insulin or other hypoglycaemic agent	Birthweight	Costs of maternal care
Induction of labour	Small-for-gestational age*	Costs of offspring care*
Caesarean section	Ponderal index*	
Perineal trauma	Gestational age at birth	
Postpartum haemorrhage	Preterm birth	
Postpartum infection	Shoulder dystocia	
Sense of wellbeing and quality of life	Bone fracture	
View of the intervention	Nerve palsy	

<b>Longer-term</b>	Respiratory distress syndrome
BMI*	Apgar score (less than seven at five minutes)*
GDM in a subsequent pregnancy*	Hypoglycaemia requiring treatment
Type 2 diabetes*	Hyperbilirubinaemia requiring treatment
Type 1 diabetes*	<b>Childhood</b>
Impaired glucose tolerance*	BMI*
	Fat mass/fat-free mass*
	Skinfold thickness measurements*
	Blood pressure*
	Type 2 diabetes*
	Type 1 diabetes*
	Impaired glucose tolerance*
	Dyslipidaemia or metabolic syndrome*
	Neurodisability*

\*Additional 'common' outcomes in protocols and reviews after WOMBAT standard outcome development (2010-2014)

**Abbreviations:** BMI: body mass index; GDM: gestational diabetes mellitus