



# The management of gestational diabetes mellitus after pregnancy

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## Introduction

Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, was officially recognised as a clinical entity in 1979. At this time the National Diabetes Data Group issued an updated classification of diabetes types, including one that was present only during pregnancy.<sup>1</sup> The known risks associated with GDM are those of higher incidence of congenital abnormalities, fetal macrosomia, neonatal hypoglycaemia and shoulder dystocia, caesarean delivery, and spontaneous preterm delivery among others.<sup>2,3</sup> The focus of this article, however, is the management after pregnancy for a woman who has had GDM. The two most pertinent questions that arise following a diagnosis of GDM are: 'Does the woman still have diabetes after delivery?' and 'If she does not, how can future type 2 diabetes mellitus (T2DM) be prevented?'

## Screening following a GDM pregnancy: when and how?

The American Diabetes Association (ADA) recommends: 'Women with GDM should be screened for diabetes six weeks postpartum and should be followed up for the development of diabetes or pre-diabetes (impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]).'<sup>4</sup> The ADA has not updated this position statement since 2004. However, in its most up-to-date document 'Standards of medical care in diabetes' published in 2010 it states that women should be screened for diabetes six to 12 weeks postpartum using non-pregnant oral glucose

## ABSTRACT

Gestational diabetes mellitus (GDM) is common, with an average prevalence in England and Wales of approximately 3.5%. It is associated with a 70% lifetime risk of developing type 2 diabetes mellitus (T2DM) for the women in the long term. It is therefore important to continue lifelong monitoring for abnormalities of glucose metabolism.

There is a lack of international consensus on the best postpartum screening test, its timing, and the frequency and duration of long-term follow up after GDM. In general, screening rates are suboptimal across the globe with perhaps an optimistic trend in recent years with just over half of the women completing postpartum screening. Postpartum diabetes screening may detect T2DM and enable early treatment of hyperglycaemia, reducing the risk of adverse fetal outcomes in subsequent pregnancies and maternal microvascular complications. Screening can also identify women who might benefit from diabetes prevention interventions. Metformin has been shown to reduce the rate of diabetes development following delivery by 50% and should be considered in all cases of GDM if tolerated. Copyright © 2010 John Wiley & Sons.

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## KEY WORDS

gestational diabetes; postpartum screening; diabetes prevention

tolerance test (OGTT) criteria with three-yearly screening thereafter using either fasting plasma glucose (FPG), HbA<sub>1c</sub> or OGTT.<sup>5</sup> The UK National Institute for Health and Clinical Excellence (NICE) updated its recommendations in 2008.<sup>6</sup> NICE recommends measuring blood glucose prior to discharge to the community for the woman who had GDM in order to exclude persistent hyperglycaemia, and reminding the woman of the symptoms of hyperglycaemia. Its advice includes a single FPG measurement at the sixth week postnatal check and annually thereafter. This is a move away from its previous preference for the OGTT prior to 2008.

There are concerns that a single FPG may not detect all the cases of T2DM and particularly of pre-diabetes as illustrated below. The two-hour glucose value is particularly important in high-risk populations, especially those of mixed ethnic

composition, to identify T2DM or pre-diabetes.<sup>7,8</sup> According to one study of a high-risk ethnic population with GDM, with FPG alone, more than half (54%) of IGT and 10% of T2DM could be missed.<sup>8</sup>

The optimal time for testing glucose tolerance following pregnancy has not been established. The traditionally adopted time-point of six weeks after delivery appears to be arbitrary.<sup>9</sup> It would be the most practical moment as certainly in the UK standard postpartum care for all new mothers involves a midwife visit around that time. It is believed that hormonal changes associated with pregnancy resolve shortly after delivery.<sup>10,11</sup> However, the sequence of physiological events has not been clearly defined and it is conceivable that the non-pregnant state takes longer to re-establish.

The earliest time to diagnose persistent T2DM or pre-diabetes is also not clear. There are studies where

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women with GDM have been tested as early as four weeks postpartum but these results have not been reported separately.<sup>12</sup> On the other hand, does it matter how late women are tested after delivery? A delay of a few weeks is unlikely to be clinically significant, unless it results in the test never being done at all. What is clear is that GDM, although a condition diagnosed during pregnancy, carries risks that outlast it for many years.

### How often are women actually screened postpartum, and what are the findings?

According to NICE (2008), the prevalence of GDM in England and Wales is approximately 3.5%.<sup>6</sup> In the United States of America, a study of the temporal trends from 1989–2004 showed a striking increase in prevalence of GDM from 1.9% to 4.2%.<sup>13</sup>

Women from ethnic groups other than white were identified to have a higher frequency of GDM than white women some years ago<sup>14</sup> and this discrepancy still exists.<sup>15</sup>

With some adjustments, these data may be applicable to most countries. In general, the prevalence rates of GDM are high and, more worryingly, appear set to rise in the future. This will have significant implications on the health of a nation as well as its health economics.

The targets for postpartum testing as set out in various guidelines are in reality difficult to achieve. Most studies that have examined the follow-up rates after delivery have reported an improvement on previous years but in general the results are suboptimal. The TRIAD study group found a striking increase in the proportion of women receiving postpartum screening from 20.7% in 1995 to 53.8% in 2006.<sup>16</sup> However, the majority of this rise was attributable to a dedicated nurse-led service for screening. Similarly, a case-manager nurse appointed to deal with the poor postpartum screening rate in Texas, resulted in an increase in rates from 18% to 57%.<sup>17</sup> This region of Texas had a predominant (>90%) Hispanic population. The significant improvement in the follow-up rate is commendable. However, women who were unable to attend the scheduled postpartum

testing were visited individually by the case-manager nurse to provide in-home OGTT and this might have been expected to improve the screening rate beyond what was actually achieved. Worryingly, women who did not attend or who could not be traced for testing were deemed at higher risk for developing T2DM by the study group as they had more severe GDM, were more likely to have previously had GDM, and were more likely to require pharmacotherapy to treat their GDM which was poorly controlled during pregnancy.

The TRIAD study group reported on a survey of a practice catering to over three million members in Northern California over a 12-year period from 1995–2006.<sup>16</sup> Overall, the age- and ethnicity-adjusted prevalence of pre-diabetes in their study was 31% whereas that of T2DM was 2–3%. Thirty-eight percent of women diagnosed to have T2DM or pre-diabetes had normal fasting glucose and would have been missed without OGTT.

### What are the obstacles to complete follow up?

As the medical fraternity struggles to come to an international consensus on the best postpartum screening test, its timing<sup>18</sup> and to some extent the diagnostic thresholds, what remains unchanged is poor user involvement across the world. There appear to be several barriers in achieving adequate postpartum screening for women diagnosed with GDM.

The finding by Hunt *et al.*<sup>17</sup> that women who returned for screening had fewer children compared to those who did not perhaps highlights the practical inconvenience for the new mothers. In a retrospective study, women who were screened were more often married, were more likely to have used insulin during the pregnancy, were more likely to have had any visit with a diabetes specialist during pregnancy, had had a greater number of prenatal visits, and were more likely to have seen a diabetes specialist or obstetrician after delivery.<sup>19</sup> The study authors speculate on women's limited knowledge of the significance of their diagnosis and perhaps a lack of health care provider knowledge of the association between

diseases of pregnancy and maternal health after delivery in playing a role. Fragmentation of medical care from the prenatal to postpartum periods is thought also to contribute towards low testing rates.<sup>19</sup> Poor communication between teams can result in missed postpartum tests.<sup>20</sup> This may well hold true for the two-pronged care system in the UK involving the diabetes physicians (in most cases) during the antenatal phase with primary care physicians taking over care after delivery.

The lack of international consensus in the method of postpartum testing may not help the cause. A survey of obstetricians in the USA found lack of universal support for glucose testing after delivery a barrier to testing.<sup>19</sup> Use of the OGTT has higher cost implications and it is more labour-intensive compared to a single FPG measurement. Although NICE in the UK does not endorse OGTT for postpartum testing,<sup>6</sup> bodies like the International Workforce Conference on Gestational Diabetes and the Canadian Diabetes Association do.<sup>16</sup>

Improved adherence rates have been observed with the use of electronic medical records and computerised reminder systems.<sup>21</sup> However, efficient use of electronic records is dependent upon their accurate completion. Incomplete records can lead to inadequate management.<sup>20</sup>

### What is the rate of progression to T2DM?

Bellamy and colleagues<sup>22</sup> meta-analysis of 20 retrospective and prospective cohort studies found that women with a previous history of GDM have a 7.4-fold greater chance of developing T2DM in the future than do those women who remain normoglycaemic during pregnancy.

In the Diabetes Prevention Program (DPP), the estimated cumulative incidence of T2DM three years after the diagnosis of GDM was 38.4% compared with 25.7% for women without a history of GDM.<sup>23</sup> It is important to note that all women (with and without a history of GDM) in the DPP had IGT therefore implying that the risk of progression of IGT to T2DM is higher for women with previous GDM than for those with IGT alone.



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A question that arises from the above discussion is whether all women with GDM would eventually develop T2DM. In some ways, 'risk of T2DM' as a term may be misleading as it perhaps depends on the length of the observation period. In 1964, O'Sullivan and Mahan estimated a lifetime increased risk of over 70% for the future development of T2DM in women with GDM. A systematic literature review of 28 articles published between January 1965 and August 2001, in which subjects underwent testing for T2DM after delivery, attempted to address the above question.<sup>24</sup> The conversion rates to T2DM in this review ranged from 2.6–70% over a period from six weeks to 28 years postpartum. Cumulative incidence increased markedly in the first five years, and then appeared to increase more slowly after 10 years. The authors' analysis revealed less marked differences between ethnic groups which was unexpected and was attributed to differences in cohort definitions. In general, it is widely recognised that women of certain ethnic origin, particularly those of Hispanic, south Asian or African origin, are at higher risk for developing T2DM after GDM than Caucasian women.<sup>18,25</sup>

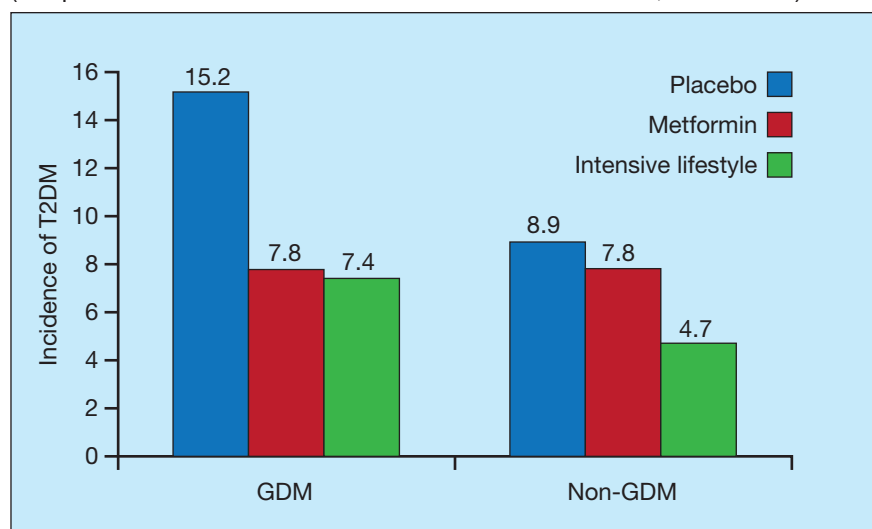
Schaefer-Graf *et al.* carried out a retrospective analysis of 1861 pregnancies complicated by GDM to evaluate the relative importance of multiple clinical risk factors related to the mother, pregnancy and neonate for prediction of T2DM postpartum.<sup>26</sup> Highest FPG of >6.5mmol/L during pregnancy conferred 36.7% risk whereas previous history of GDM conferred 29.1% risk of developing T2DM within the ensuing year. Lawrence and associates<sup>27</sup> in their study showed that the risk of IFG/IGT was higher for women who needed pharmacotherapy for GDM. There was a 40% risk of pre-diabetes with metformin use and 56% with that of insulin use during pregnancy.

Table 1 summarises the reported incidence of T2DM after GDM. There is overwhelming evidence to support a high likelihood of developing T2DM in women with GDM taking into account the heterogeneity of the data mentioned above.

**Table 1.** Reported incidence of type 2 diabetes after gestational diabetes mellitus

Estimated lifetime risk of type 2 diabetes (T2DM)	70% <sup>22</sup>
Estimated cumulative incidence 3 years later (if also known to have pre-diabetes)	38.4% <sup>23</sup>
Prevalence of pre-diabetes 4–12 weeks postpartum	31% <sup>16</sup>
Prevalence of T2DM 4–12 weeks postpartum	2–3% <sup>16</sup>
Risk of T2DM with highest fasting plasma glucose >6.5mmol/L during pregnancy	36.7% <sup>26</sup>

**Figure 1.** Effect of treatment on the incidence of type 2 diabetes. Incidence expressed as number of cases per 100 person-years, adjusted for age. (Adapted from Ratner *et al.* *J Clin Endocrinol Metab* 2008; **93**: 4774–9)<sup>23</sup>



### Can the progression to T2DM be prevented?

Postpartum diabetes screening may detect T2DM and enable early treatment of hyperglycaemia, reducing the risk of adverse fetal outcomes in subsequent pregnancies and maternal microvascular complications.<sup>23</sup> Screening can also identify women who might benefit from diabetes prevention interventions.<sup>23</sup>

The Diabetes Prevention Program (DPP) included women with IGT who self-reported previous history of GDM as part of a questionnaire before randomisation to placebo, metformin or intensive lifestyle (ILS).<sup>23</sup> Among women with a history of GDM, metformin afforded this group 50% risk reduction similar to that achieved by ILS of 53%. ILS was equally beneficial for women without a history of GDM achieving 49% risk reduction. Interestingly, however, metformin

therapy did not offer significant benefit to women without a history of GDM. The DPP findings are summarised in Figure 1.

There are difficulties in implementing exercise and diet in women with small children.<sup>24</sup> In the DPP, women with GDM were less able to sustain the prescribed level of physical activity and demonstrated lower peak weight loss as well as a more rapid weight gain, resulting in significantly lower weight loss (1.6kg) over time than women in the ILS group without a history of GDM (4kg).<sup>23</sup> More recently, an Australian study of women with previous history of GDM assessed the prevalence of self-reported health enhancing physical activity (time spent walking, and in moderate and vigorous physical activity) by a questionnaire. Women who were about six months postpartum had significantly lower (37.2%) levels



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of physical activity compared to those of women of similar age in the general population (53.8%).<sup>28</sup>

Other oral hypoglycaemic agents apart from metformin have been studied in this subgroup. Troglitazone achieved a 55% risk reduction of future DM in the high-risk group of Hispanic women with a prior history of GDM albeit with a resultant 6kg weight gain over six years.<sup>29</sup> Troglitazone is no longer in clinical use. Another thiazolidinedione, pioglitazone was tested by the troglitazone study group in the PIPOD study, where the incidence of T2DM was 4.6% per year during the three years of treatment compared with the rate of 12.1% per year observed during placebo treatment.<sup>30</sup> The interpretation of these figures is made difficult by the fact that there was no parallel control group in the PIPOD study itself, and also that the average annual drop-out rate was 9.6%. Prescribing attitudes since Nissen's meta-analysis<sup>31</sup> involving rosiglitazone appear to have changed in the field of diabetes. There may be general reluctance towards wider prescribing of thiazolidinediones but there is a trend favourable to pioglitazone.<sup>32</sup>

### Recommendations

To summarise the above discussion, women who have GDM are the highest risk group for developing T2DM, with a risk higher than that of the hitherto considered highest risk group – i.e. those with IGT. Those women whose FPG is higher than 6.5mmol/L during pregnancy are most likely to have T2DM post-delivery.<sup>26</sup> At postpartum testing about one-third of the cohort will have pre-diabetes, and 2–3% will have T2DM.<sup>16</sup>

Follow-up screening in the early postpartum period for all women with GDM must be achieved. In the twenty-first century it should be possible to implement sophisticated databases with computerised reminder systems as well as programs capable of flagging records as 'high risk for T2DM' to their regular care-providers during routine or unrelated visits. It is important we devise strategies to improve follow up as the cohort at stake consists of women of young age-group and those who are

likely to undergo future pregnancies and, in doing so, not only will it help the individual woman but perhaps may also impact on the ever-rising incidence of T2DM. Another strategy would be to allocate a dedicated individual (e.g. dedicated midwife or case finder) caring throughout pregnancy into the postpartum period, and to improve communication between primary and secondary care.

When testing glucose status, a risk-stratified approach as suggested by McClean *et al.*<sup>8</sup> would call for use of the OGTT for postpartum testing in women with high-risk ethnic background whereas in women of European origin FPG measurement may be adequate. It is important to acknowledge the generally poor follow-up rates and that OGTT is cumbersome. FPG is relatively straightforward and therefore efforts must be directed towards implementing this as the screening test presently. Educating women about their likely risk of T2DM and prevention measures such as intensive lifestyle modification could be the key.

The most impressive evidence on prevention to date is a 50% reduction in progression to T2DM in women with IGT and a history of GDM by the use of metformin. Metformin is considered safe<sup>33,34</sup> and is used extensively during pregnancy. We therefore recommend that metformin use should be considered in all women with GDM, especially in those with pre-diabetes.

Finally, it is of paramount importance to emphasise that GDM is a condition not just limited to pregnancy but one that carries a significant risk of developing T2DM in the future. Therefore, annual assessment of glucose status is to be recommended for the individual's lifetime.

### Areas for future research

From the evidence available so far a significantly high risk of progression to T2DM has been established although the figure varies with the study under consideration and is somewhat dated. This raises the question as to whether pregnancy itself accelerates progression to T2DM, and the answer to this is not known.

Secondly, the optimal time for postpartum testing lacks evidence as

### Key points

- Women with GDM are the highest risk group for developing T2DM
- Lifetime risk of T2DM following GDM approaches 70%
- All women with GDM must have glucose testing in the early postpartum period followed by lifelong assessment
- Progression to T2DM of women with pre-diabetes and a history of GDM can be reduced by intensive lifestyle therapy by 53%
- Metformin reduces the risk of progression to T2DM by 50% at par with intensive lifestyle therapy. Therefore, metformin should be considered routinely in women with impaired glucose tolerance and a history of GDM

we do not yet know when, if at all, dysglycaemia could be diagnosed at the earliest following delivery. Overall timing of the test would matter if the concept were to capture women during what could be called the nadir phase, a phase when abnormalities of carbohydrate metabolism arising from pregnancy subside and those related to T2DM begin. This is a concept that needs affirmation or otherwise with physiological studies.

Thirdly, further health care services research is required looking into optimal methods of postpartum testing in this context including healthy economic assessment to identify the barriers in achieving near total follow-up rates. In addition, the most discriminatory test to assess glucose status postpartum that is acceptable to the user and achieves high follow-up rate needs more evidence.

Finally, we need randomised controlled trials in order to establish whether any of the other oral hypoglycaemic agents would be suitable for long-term use like metformin, could be safely prescribed in the postpartum period, and would be effective in preventing progression to T2DM in women with GDM.

### Conflict of interest statement

There are no conflicts of interest.

### References

References are available at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).



## REVIEW



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