Updated NICE guidelines for diabetes and pregnancy: New challenges for primary care

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Citation: Platts J, Agarwal N (2015) Updated NICE guidelines for diabetes and pregnancy: New challenges for primary care. *Diabetes & Primary Care* **17**: 88–92

Article points

1. Pre-conception care is vital to improve outcomes in pregnancies complicated by diabetes.
2. The proportion of women who have type 2 diabetes in pregnancy is growing; primary care has a very important role in providing preconception care.
3. Intensive glucose control is required in pregnancy; some of the recommended medications are not licensed for use in pregnancy and a thorough understanding of the evidence is needed.
4. The diagnostic criteria for gestational diabetes are new and are based on a cost-effectiveness model.
5. Strategies to prevent type 2 diabetes are needed for women with previous gestational diabetes.

Key words

- Gestational diabetes
- NICE
- Pre-conception
- Pregnancy

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The new NICE guideline on diabetes and pregnancy is of great relevance to primary care health professionals, especially with regard to recommendations for pre-conception care, early pregnancy, gestational diabetes and post-partum care. This article explores the implications.

A pregnancy complicated by diabetes represents a significant challenge for healthcare professionals. Outcomes are significantly worse than in women without diabetes (Confidential Enquiry into Maternal and Child Health [CEMACH], 2007); however, careful pre-conception care and antenatal management may improve outcomes.

The population of women with diabetes in pregnancy is changing. In 2003, 27% of women with pre-existing diabetes complicating pregnancy had type 2 diabetes (CEMACH, 2007); by 2013 this proportion has risen to 44.9% (Health and Social Care Information Centre [HSCIC], 2014). The majority of these women will receive their diabetes management, and therefore all pre-conception care, in a primary care setting.

Most contraceptive services for women with diabetes are delivered in primary care, providing a further valuable opportunity to advise women that their pregnancies should be planned. Additionally, primary care delivers the management of early pregnancy, the majority of post-natal care, and long-term follow-up of those with previous gestational diabetes. Primary care health professionals thus have a very important role in influencing the outcomes of these pregnancies, as part of a wider multi-disciplinary team.

The new NICE guideline on diabetes and pregnancy, which was published in February 2015, therefore has particular relevance to primary care, especially with regard to recommendations for pre-conception care, early pregnancy, gestational diabetes and post-partum care (NICE, 2015). It is important to note that some of the medications recommended in the guideline are not licensed for use during pregnancy, and so the prescriber must be familiar with the rationale behind the recommendation and the safe and ethical way to prescribe in this situation.

In this article, we explore the implications for primary care of this new NICE guideline. The guideline has been eagerly awaited, not least by clinicians wishing to find out what definition of gestational diabetes (diabetes arising in pregnancy) would be adopted. Across the world, gestational diabetes has been defined, in recent years, by various diagnostic standards, with perhaps the most widely established ones being: the World Health Organization (WHO) Department of Noncommunicable Disease Surveillance (1999) criteria; and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel (2010) criteria. Clinicians in the UK were aware that the definition accepted by NICE for the UK would significantly affect, among other things, the number of women diagnosed with gestational diabetes.

Recommendations in the NICE guideline

Pre-existing diabetes

Contraception

It is well established that the risk of a major congenital malformation is correlated with HbA_{1c} at conception (Guerin et al, 2007; Bell et al, 2012). Many other outcomes in pregnancy such

as first-trimester miscarriage and risk of premature delivery are also related to glycaemic control in early pregnancy (NICE, 2015). Women should be encouraged to plan pregnancies and use contraception until the target HbA_{1c} is achieved. Advice to avoid unplanned pregnancies should start at adolescence.

New recommendations from the guideline are that the type of contraception should be based on a woman's preferences and risks, and this includes oral contraceptives, which can be used if there are no contraindications, as outlined in the *UK Medical Eligibility Criteria for Contraceptive Use*, 2009 (Faculty of Sexual and Reproductive Healthcare, 2009).

Pre-conception counselling

There is guidance on which topics should be included in pre-conception discussions, and this includes the reasons for the intensive glucose control pre-conception, the common risks of a pregnancy complicated by diabetes to the mother and baby, and the intensity of the antenatal schedule. Advice on glucose control prior to pregnancy should be given at each consultation after adolescence.

Pre-conception glucose control

An HbA_{1c} <48 mmol/mol (<6.5%) is advised pre-conception if it is possible to achieve this without problematic hypoglycaemia. This contrasts with the advice in the previous NICE guideline on diabetes and pregnancy to achieve an HbA_{1c} of 43 mmol/mol (6.1%) or less pre-conception (NICE, 2008). The National Diabetes in Pregnancy Audit of 2013 showed that only 5.1% of women with type 1 diabetes and 18.5% of women with type 2 diabetes achieved the 2008 target (HSCIC, 2014), based on first-trimester measurements. The new guidance also advises that any lowering towards this target will reduce the risk of congenital malformation.

When planning a pregnancy, all women with diabetes should be self-monitoring capillary blood glucose and should have monthly HbA_{1c} tests. Women with type 1 diabetes should have a ketone meter and know when to test for ketones and how to interpret the results.

Metformin may be continued pre-conception and during pregnancy; however, all other oral agents should be stopped and insulin substituted. Metformin does not have a specific licence for this indication; however, there is strong evidence for its safety and effectiveness (NICE, 2015). Rapid-acting analogues (see *Table 1*) are licensed in pregnancy and are preferred over human soluble insulin. Isophane insulin is suggested as the basal insulin of choice; however, if women are already well controlled on long-acting analogues such as insulin detemir or insulin glargine then these may continue (see *Table 2*). Women who are planning a pregnancy should be offered attendance at a structured education programme as soon as possible.

Teratogenic medication

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and statins should be stopped pre-conception when possible. Alternative medication for the treatment of hypertension may be necessary; methyldopa and nifedipine are commonly used and, although the data are limited, are not thought to cause fetal adverse effects.

Table 1. Availability of data on exposed pregnancies for rapid-acting insulin analogues, as reported in Section 4.6 of Summaries of Product Characteristics.

Insulin – reference	Availability of data on exposed pregnancies
Apidra® (insulin glulisine) – eMC (2013a)	"There are no or limited amount[s] of data (less than 300 pregnancy outcomes) from the use of insulin glulisine in pregnant women." "Caution should be exercised when prescribing to pregnant women."
Humalog® (insulin lispro) – eMC (2014a)	"Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn"
NovoRapid® (insulin aspart) – eMC (2015b)	"Data from two randomised controlled clinical trials (322 and 27 exposed pregnancies) do not indicate any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin"

eMC=electronic Medicines Compendium.

Table 2. Availability of data on exposed pregnancies for intermediate- and long-acting insulins, as reported in Section 4.6 of Summaries of Product Characteristics.

	Insulin – reference	Availability of data on exposed pregnancies
Intermediate-acting human isophane (NPH) insulins	Humulin® I – eMC (2012)	(no mention of data availability)
	Insulatard® – eMC (2014b)	(no mention of data availability)
	Insuman® Basal – eMC (2013b)	"… no clinical data on exposed pregnancies are available."
Long-acting insulin analogues	**Insulin – reference**	**Availability of data on exposed pregnancies**
	Lantus® (insulin glargine) – eMC (2015a)	"… no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine."
	Levemir® (insulin detemir) – eMC (2014c)	"In an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid […] The overall rates of maternal adverse events were similar for Levemir and NPH insulin treatment groups; however, a numerically higher frequency of serious adverse events in the mothers (61 (40%) vs. 49 (31%)) and in the newborn children (36 (24%) vs. 32 (20%)) was seen for Levemir compared to NPH insulin. The number of live born children of women becoming pregnant after randomisation were 50 (83%) for Levemir and 55 (89%) for NPH. The frequency of congenital malformations was 4 (5%) for Levemir and 11 (7%) for NPH with 3 (4%) major malformations for Levemir and 3 (2%) for NPH." "Post-marketing data from an additional 250 outcomes from pregnant women exposed to Levemir indicate no adverse effects of insulin detemir on pregnancy and no malformative or foetal/neonatal toxicity of insulin detemir."
	Tresiba® (insulin degludec) – eMC (2015c)	"There is no clinical experience with use of Tresiba in pregnant women."

eMC=electronic Medicines Compendium.

"If retinopathy is present, rapid optimisation of glucose levels may need to be deferred until after treatment; however, it is crucial that optimisation not be deferred if the woman is already pregnant."

Retinal and renal assessments

Retinopathy may deteriorate or arise during pregnancy. The greatest risk factors are pre-existing severe retinopathy, poor glycaemic control and hypertension. Retinal screening should be performed pre-conception. If retinopathy is present, rapid optimisation of glucose levels may need to be deferred until after treatment; however, it is crucial that optimisation not be deferred if the woman is already pregnant. Renal assessment should also be performed pre-conception. Women with a creatinine level >120 µmol/L, a microalbumin level >30 mg/mol or an estimated glomerular filtration <45 mL/min/1.73 m^2 should be referred to a nephrologist prior to pregnancy. The presence of nephropathy and microalbuminuria increase the risk of hypertension in pregnancy and of intrauterine growth restriction.

Folic acid

All women with diabetes should receive folic acid 5 mg from the pre-conception period until week 12 of pregnancy. The National Diabetes in Pregnancy Audit demonstrated that 42.6% of women with type 1 diabetes received the correct dose, compared with 24.7% of those with type 2 diabetes (HSCIC, 2014). This may reflect a greater emphasis on pre-conception care for women with type 1 diabetes. In any case, the figures indicate the magnitude of the improvement to pre-conception care that is necessary.

Glucose targets during pregnancy

Women should be advised to check capillary blood glucose levels while fasting, pre-meal, 1 hour post-meal and before bed if they are taking multiple daily insulin injections. Adequate numbers of test strips will be required to test seven or eight times a day.

The fasting glucose should be <5.3 mmol/L, while the target 1 hour postprandially is <7.8 mmol/L and the target 2 hours postprandially is <6.4 mmol/L. Achieving tight glycaemic control in the first trimester, when insulin requirements are lowest, puts a woman at increased risk of hypoglycaemia.

She should be warned of this and be given a fast-acting form of glucose. She should also be provided with glucagon and family members instructed on its use. Although not covered in the guideline, it should be borne in mind that if hypoglycaemia is severe or there is unawareness, the women may need to be advised to stop driving and to notify the Driver and Vehicle Licensing Agency, in accordance with the agency's guidance.

Gestational diabetes

As is mentioned in the introduction, there are various definitions of gestational diabetes in use across the world, including: the WHO definition of 1999; and the IADPSG definition of 2010, which requires a fasting glucose ≥5.1 mmol/L, a 1-hour glucose ≥10.0 mmol/L or a 2-hour glucose ≥8.5 mmol/L. The latter definition has been adopted by organisations such as the American Diabetes Association (ADA, 2015) and, more recently, WHO itself (WHO, 2013). The new NICE guideline adopts neither of these and instead opts for a modified definition.

Gestational diabetes is diagnosed if the fasting glucose is ≥5.6 mmol/L or the 2-hour glucose is ≥7.8 mmol/L on a 2-hour 75-g oral glucose tolerance test. These figures are based on cost-effectiveness analysis. The definition will increase the number of women diagnosed with gestational diabetes in the UK.

The IADPSG recommends screening all pregnant women for gestational diabetes at 24–28 weeks gestation (IADPSG Consensus Panel, 2010). The new NICE guideline suggests screening women with risk factors for gestational diabetes, which are identified at booking (unchanged from the 2008 version):

- BMI >30 kg/m^2.
- Previous macrosomic baby weighing ≥4.5 kg.
- Previous gestational diabetes.
- Family history of diabetes (first-degree relative with diabetes).
- Minority ethnic family origin with a high prevalence of diabetes.

Women with risk factors should generally be screened at 24–28 weeks for gestational diabetes. The exception is women with previous gestational diabetes, who should either self-monitor blood glucose or have a 75-g oral glucose tolerance test soon after booking, with a repeat test at 24 weeks if this is normal. Glycosuria is also considered to be a reason to screen for gestational diabetes (using either 2+ on one occasion or 1+ on two occasions), and this is new for the 2015 NICE guideline.

If gestational diabetes is identified, women should be seen in combined diabetes ante-natal clinic within a week and the primary care team should be informed. Blood glucose targets for gestational diabetes should be the same as for pre-existing diabetes. Women should be given advice on dietary changes from a state-registered dietitian and advice on exercise. In addition, it is recommended that women with gestational diabetes take a fasting blood glucose level each day and also test 1 hour after every meal, if they are on diet and exercise therapy or are taking oral therapy or single-dose intermediate-acting or long-acting insulin.

If targets are not met, metformin should be commenced, and if capillary glucose levels remain outside targets, insulin should be added. However, if the fasting glucose is >7.0 mmol/L at diagnosis, immediate insulin should be offered. This should also be offered if the fasting glucose is between 6 and 6.9 mmol/L and a complication such as macrosomia is present.

New for 2015 is the recommendation to consider glibenclamide for women who are not well controlled on metformin but who do not wish to use insulin or who cannot tolerate metformin. Glibenclamide is not licensed for this indication, and it is advised that the prescriber takes full responsibility for this decision and obtains informed written consent.

Post-partum care

Women with gestational diabetes will have their medication stopped at delivery and blood glucose levels should be checked post-partum in hospital to ensure they are normal. Those women whose glucose levels return to normal post-partum will need a fasting plasma glucose measurement taken between 6 and 13 weeks post-partum.

- Where the fasting glucose is less than 6.0 mmol/L, individuals should be informed that they are at moderate risk of diabetes in the future, and if it is between 6.1 and 6.9 mmol/L they should be informed that they are at a high risk of diabetes in the future. These women should be offered a 75-g oral glucose tolerance test.

"Achieving tight glycaemic control in the first trimester, when insulin requirements are lowest, puts a woman at increased risk of hypoglycaemia. She should be warned of this and be given a fast-acting form of glucose. She should also be provided with glucagon and family members instructed on its use."

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- If the glucose is above 7.0 mmol/L, they should have tests to confirm the diagnosis of diabetes.

For those without persistent diabetes, preventative measures should be started, including advice on weight control, diet and exercise. Annual screening for diabetes should be commenced with the use of HbA_{1c} or fasting glucose levels.

Finally, all women developing gestational diabetes should be informed that they are at high risk of the condition in future pregnancies, and, while not explicitly stated in the guideline, it would seem prudent to test these women pre-conception where possible.

Detecting undiagnosed type 2 diabetes in pregnancy

The guideline suggests that HbA_{1c} should be tested at the time of diagnosis of gestational diabetes to detect those with undiagnosed type 2 diabetes; however, it is stated elsewhere in the guidance that HbA_{1c} is a poor marker of glycaemic control in the second and third trimesters, which is when most gestational diabetes will be diagnosed. The ADA (2015) recommends a test to detect diabetes when a woman initially presents with a pregnancy; this approach has the advantage of detecting type 2 diabetes early in pregnancy to allow early intervention. This may represent a missed opportunity to improve outcomes for a proportion of high-risk women and their babies.

Conclusion

One of the key recommendations from the National Diabetes in Pregnancy Audit of 2013 was to improve pre-conception care for women with diabetes. The new NICE guideline contains recommendations of how this should be achieved. Primary care practitioners have a very important role in delivering pre-conception care and are likely to be champions for implementing these recommendations.

The proportion of women with gestational diabetes will increase as these recommendations are adopted With this there will be an increase in the prescriptions of glucose testing strips, insulin and medications outside their licensed indications. There will also be an increase in interventions to prevent type 2 diabetes following gestational diabetes and in post-partum surveillance for the development of type 2 diabetes. Primary care will be central to the delivery of these new recommendations. ■

Further reading

Some useful information on pre-conception care is available on the Diabetes UK website and can be accessed via:

http://bit.ly/1zxuVcf

American Diabetes Association (2015) Classification and Diagnosis of Diabetes. *Diabetes Care* **38**: S8–S16

Bell R, Glinianaia SV, Tennant PW et al (2012) Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: A population-based cohort study. *Diabetologia* **55**: 936–47

Confidential Enquiry into Maternal and Child Health (2007) *Diabetes in pregnancy: are we providing the best care?* CEMACH, Bristol

electronic Medicines Compendium (2012) *Humulin Vials, Cartridges and KwikPens*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/3425 (accessed 08.04.15)

electronic Medicines Compendium (2013a) *Apidra 100 Units/ml, solution for injection in a cartridge*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/26476 (accessed 08.04.15)

electronic Medicines Compendium (2013b) *Insuman Basal 100 IU/ml suspension for injection in a cartridge*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/26468 (accessed 08.04.15)

electronic Medicines Compendium (2014a) *Humalog 100U/ml, solution for injection in vial, Humalog 100U/ml, solution for injection in Cartridge, Humalog KwikPen 100U/ml, solution for injection*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/9314 (accessed 08.04.15)

electronic Medicines Compendium (2014b) *Insulatard 100 international units/ml, Insulatard Penfill 100 international units/ml, Insulatard InnoLet 100 international units/ml*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/3512 (accessed 08.04.15)

electronic Medicines Compendium (2014c) *Levemir Cartridge 100 units/ml – Penfill, Levemir Pre-filled Pen 100 units/ml – FlexPen and InnoLet*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/14584 (accessed 08.04.15)

electronic Medicines Compendium (2015a) *Lantus cartridge*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/25507 (accessed 08.04.15)

electronic Medicines Compendium (2015b) *NovoRapid 100 units/ml in a vial, NovoRapid Penfill 100 units/ml, NovoRapid FlexPen 100 units/ml, NovoRapid FlexTouch 100 units/ml*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/25033 (accessed 08.04.15)

electronic Medicines Compendium (2015c) *Tresiba 100 units/mL Cartridge (Penfill)*. eMC, Leatherhead. Available at: http://www.medicines.org.uk/emc/medicine/27360 (accessed 08.04.15)

Faculty of Sexual and Reproductive Healthcare (2009) *UK Medical Eligibility Criteria for Contraceptive Use*. FSRH, London. Available at: http://www.fsrh.org/pdfs/UKMEC2009.pdf (accessed 08.04.15)

Guerin A, Nisenbaum R, Ray J (2007) Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. *Diabetes Care* **30**: 1920–5

Health and Social Care Information Centre (2014) *National Pregnancy in Diabetes Audit, 2013*. HSCIC, Leeds. Available at: http://bit.ly/1Et0pzl (accessed 08.04.15)

International Association of Diabetes and Pregnancy Study Groups Consensus Panel (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* **33**: 676–82

NICE (2008) *Diabetes in pregnancy: Management of diabetes and its complications from pre-conception to the postnatal period* (CG63). NICE, London. Available at: http://www.nice.org.uk/guidance/cg63 (accessed 08.04.15)

NICE (2015) *Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period* (NG3). NICE, London. Available at: http://www.nice.org.uk/guidance/ng3 (accessed 08.04.15)

World Health Organization (2013) *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. WHO, Geneva, Switzerland

World Health Organization Department of Noncommunicable Disease Surveillance (1999) *Definition, diagnosis and classification of diabetes mellitus and its complications*. WHO, Geneva, Switzerland