Pre-Pregnancy Planning for Women with Pre-Existing Diabetes (Type 1 /Type 2)

Pregnancy in women with pre-existing Type 1 (insulin dependent) and Type 2 (non insulin dependent, though may be insulin treated) diabetes continues to have a 4-11 times greater likelihood of major congenital malformations [see Appendix A] and 3-5 times greater likelihood of perinatal mortality than pregnancies in women without diabetes.

ALL WOMEN WITH PRE-GESTATIONAL DIABETES (TYPE 1 and TYPE 2) SHOULD BE REFERRED TO RPAH DIABETES CENTRE or AN ENDOCRINOLOGIST WITH DIABETES AND PREGNANCY EXPERTISE FOR PRE-PREGNANCY PLANNING and AS SOON AS POSSIBLE IF THE WOMEN FIND THEY ARE PREGNANT.

As Type 2 diabetes becomes more common in younger age groups, pregnancies in women with Type 2 diabetes:
- are now more frequently seen than pregnancies in women with Type 1 diabetes
- are tending to be associated more often with adverse outcomes than Type 1 diabetes, despite the widespread perception that Type 2 diabetes is a less serious condition
- are less often planned

Essential components of pre-pregnancy planning:
- Optimise glycaemic control: Target A1c < 7.0% - preferably lower, while minimising hypoglycaemia risk
- Complication assessment pre-pregnancy
- Folic Acid
- Review other medications (including oral diabetes agents, statins, ACE-I, A2RA)
- Revise self-management skills
- Contraception until optimal glycaemic control, stable complication status, optimum concomitant medications
- Cooperation of GP, endocrinologist, diabetes educator, dietitian, obstetrician ± renal physician ± cardiologist ± ophthalmologist with the woman with pre-existing diabetes

[A] Aims:
1. The aim of pre-pregnancy planning is to improve the outcome of pregnancies complicated by pre-existing Type 1 and Type 2 diabetes to equate with that of pregnancies without diabetes
2. The aim of this document is to provide guidelines for pre-pregnancy planning, counselling and management

[B] Pre-Pregnancy Counselling and Planning have been shown to have the following benefits:
- Reduce congenital malformation rate by up to 75%
- Reduce perinatal mortality by up to 80%
- Reduce pre-term delivery by up to 50%

[C] Avoid unplanned pregnancies.
- Advise all women with diabetes who are of child-bearing age to use contraception unless actively planning a pregnancy when glycaemic control is optimal and complication status stable.
- Inform all women with diabetes who are of child-bearing age of the potential risks of pregnancies complicated by diabetes when glycaemic control is sub-optimal and/or pregnancies unplanned.
- Metformin may improve fertility, so women being commenced on it to improve glycaemic control need to be alerted to the increased possibility of a pregnancy and the need to use contraception until glycaemic control is optimal for pregnancy.
Women with diabetes presenting for IVF/other assisted reproduction should have their diabetes status reviewed and optimised before proceeding further.

[D] General Measures:

1. Start folic acid 5mg daily 1-2 months before conception and continue it until at least 16 weeks’ gestation.
2. Encourage regular exercise.
3. Discuss weight management when appropriate.
4. Advise to cease smoking, limit alcohol (see current NHMRC safety recommendations), avoid illicit drugs.
5. Statin therapy should be ceased [see Appendix B].
6. Generally stop ACE inhibitors and A2 receptor antagonists pre-pregnancy, unless a renal physician with expertise in pregnancy specifically requests that they be continued in early pregnancy, after carefully assessing the risk:benefit ratio for that individual. However, they must be stopped by end of 1st trimester. [see Appendix C] If these agents were used for hypertension management (and not just nephroprotection), stabilise blood pressure on other anti-hypertensive agents suitable for pregnancy (examples include clonidine, methyldopa, oxprenolol, labetalol, nifedipine, prazosin. Women with diabetes and known hypertension or diabetes renal disease should be referred pre-pregnancy to a renal physician with expertise in hypertensive disorders of pregnancy.
7. Review all medications (including any complementary preparations) for safety in pregnancy.
8. Screen for infectious diseases and immune status as per the NHMRC guidelines for general pre-pregnancy management.

[E] Glycaemic control:

1. Tight glycaemic control is essential. Target A1c pre-pregnancy is < 7.0%.

   - A1c should be as close as possible to the normal range while still minimising the risk of hypoglycaemia.
   - Women with Type 1 diabetes may have some difficulty in their attempts to achieve this target. Tight glycaemic control in people with type 1 diabetes is associated with increased risk of major hypoglycaemia. It is imperative to minimise this risk when optimising control in the pre-pregnancy period, so great care must be taken.
   - Most women with Type 2 diabetes, however, should be able to reach this target A1c.
   - Women should not actively try for a pregnancy unless the target A1c has been met.
   - If a woman is unable to achieve this target despite optimum efforts to improve glycaemic control over a 6-12 month period, she should be referred to a physician experienced in management of diabetes in pregnancy to discuss the risks of proceeding to a pregnancy. A continuous sc insulin infusion pump may be an option for some women.
2. Discuss potential effects of diabetes on pregnancy outcome (increased risk of miscarriage and of congenital malformation), especially if there is suboptimal glycaemic control.
3. Review with a dietitian of overall diet including adequate calcium and iron intake. Advice on measures for dealing with morning sickness should be given.
4. Oral anti-hyperglycaemic agents: (see also Appendix D)
   4.1. Glitazones (Category B3) - cease pre-pregnancy. Lack of adequate safety data.
   4.2. Sulphonylureas (Category C) - usually cease pre-pregnancy. Neonatal hypoglycaemia has been reported. Animal studies have reported embryotoxicity and/or birth defects.
4.3. α-glucosidase inhibitors (Category B3) – cease pre-pregnancy. Lack of adequate safety data.

4.4. Miglitinides (Category C) – cease pre-pregnancy. Safety has not been established.

4.5. Metformin (Category C) – there is current debate about the safety / potential benefit of metformin in pregnancy, especially early pregnancy.

Oral agents should be ceased except in the situation that a diabetes physician may make a decision to continue an oral agent following a detailed discussion with the woman about the uncertainty regarding safety of oral anti-hyperglycaemic agents in pregnancy (including metformin). If an oral agent has been continued until pregnancy has been achieved, the oral agent should not be stopped abruptly. The changeover from metformin / sulphonylurea to insulin needs to be undertaken slowly and carefully to avoid destabilising glycaemic control at this critical time for organogenesis.

5. Insulin treatment should be commenced in women who have Type 2 diabetes if glycaemic control is not optimal and in women who have been treated with oral agents that need to be ceased.

6. A multiple insulin regimen is generally preferable to the use of pre-mixed insulin. This will allow for flexibility of insulin dose adjustment in pregnancy when there tends to be relatively higher meal-time insulin requirement and lower basal insulin requirement.

7. Minimise risk of hypoglycaemia and its potential dangers to the woman. Also, although there has not been a definite link between maternal hypoglycaemia and adverse pregnancy outcomes, hypoglycaemia in animal models has been associated with an increased rate of fetal malformations.

8. Discuss the effect of pregnancy on glycaemic control.
   i. Warn about the early pregnancy fall in insulin requirement especially overnight (anticipate with reduced insulin doses to avoid hypoglycaemia), sharper post-prandial glucose peaks, lower pre-prandial glucose.
   ii. Advise that there will be a steady increase in insulin requirement in 2nd and 3rd trimesters, and that insulin requirement may be very high if Type 2 diabetes.
   iii. Alert women with Type 1 diabetes to the possibility of ketoacidosis occurring in pregnancy with only modestly elevated BGLs.

9. Prompt review once a pregnancy is confirmed.

[F] Diabetes Self-Management Skills:
1. Revise hypoglycaemia prevention and management (including for women with Type 1 diabetes the need for in-date glucagon with appropriate education of relevant family members in its use); warn re altered hypoglycaemia symptoms; caution re driving risk.
2. Revise ketoacidosis prevention and sick day management (including need for in-date urinary ketodiastix, or ketone strips if using Optium blood glucose meter).
3. Review insulin injection technique and injection sites (lipohypertrophy alters insulin absorption).
4. Blood glucose monitoring techniques should be reviewed and accuracy of reported readings regularly checked (meter memory vs written record).
5. Discuss monitoring of diabetes during the pregnancy (self blood glucose monitoring, A1c, possibly fructosamine, possibly ketone testing).

[G] Diabetes Complication Assessment:
1. Eyes: Dilated fundal examination by a person experienced in retinal examination. If retinopathy is present, and laser photocoagulation required, treat prior to pregnancy. Retinopathy may progress during pregnancy especially if there is pre-existing retinopathy, hypertension, long duration of diabetes, rapid improvement in glycaemic control. Aim for stable glycaemic control for 6 months before conception.
2. **Kidneys**: Baseline creatinine, early morning spot urine for albumin to creatinine ratio (ACR) or timed urinary microalbumin and protein excretion and creatinine clearance. If early morning spot urinary ACR > 3.5 mg/mmol creatinine, do timed urine collection. If microalbuminuria is present there is an increased risk of preeclampsia. If serum creatinine > 200 µmol/l, there is an increased likelihood of the renal disease progressing in pregnancy. Women with nephropathy have a significant risk of pre-eclampsia, prematurity and fetal growth restriction. They must be under the care of a renal physician experienced in pregnancy-related disorders.

3. **Peripheral neuropathy**. This does not appear to be a specific concern in pregnancy.

4. **Autonomic neuropathy** - if present, significant increase risk of maternal morbidity and adverse pregnancy outcome. Gastroparesis may lead to hyperemesis, inadequate nutrition and significant difficulties with glucose control.

5. **Macrovascular disease**. If present, seek specialist assessment and advice. Specific counselling about the risks that a pregnancy will pose to the mother and infant is essential.

6. Discuss the potential effect of pregnancy on diabetes complications. Explain that ongoing complication screening will be needed in pregnancy: eye and renal status at least each trimester, review with renal physician and cardiologist on individual need. Blood pressure will need ongoing monitoring.

[H] **Associated conditions if Type 1 diabetes:**

1. Check TFT and thyroid antibodies as 10-20% women with Type 1 diabetes also have autoimmune thyroid disease. Ensure euthyroid pre-pregnancy. If require thyroxine replacement or if positive thyroid antibodies, will need ongoing TFT monitoring in pregnancy as hypothyroidism may appear in pregnancy if inadequate thyroid reserve.

2. Screen for coeliac disease (present in up to 10% women with Type 1 diabetes); often asymptomatic.

Also, consider screening for Vitamin D deficiency (25OH Vitamin D) in all pregnancies, especially if the women has little sun exposure of her skin

[I] **Relative contraindications to pregnancy**

1. Retinopathy requiring laser treatment until treatment undertaken, eye status stable and glycaemic status stable for 6 months or more.

2. Nephropathy with serum creatinine > 200µmol/l

3. Pre-existing cardiac disease, especially previous myocardial infarction

**Appendix A**

<table>
<thead>
<tr>
<th>Major Congenital Abnormalities in Offspring of Women with Pre-Existing Type 1 or Type 2 Diabetes</th>
<th>Incidence per 1000 Infants of Non-Diabetic Women</th>
<th>Relative Risk compared to infants of non-diabetic mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (Transposition, VSD, ASD, coarctation)</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Arthrogryposis</td>
<td>0.3</td>
<td>28</td>
</tr>
<tr>
<td>Ureteral Duplication</td>
<td>0.7</td>
<td>23</td>
</tr>
<tr>
<td>Cystic kidney</td>
<td>0.6</td>
<td>4</td>
</tr>
<tr>
<td>Renal agenesis</td>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td>Anorectal atresia</td>
<td>0.3</td>
<td>4</td>
</tr>
<tr>
<td>Caudal regression</td>
<td>1.3</td>
<td>212</td>
</tr>
<tr>
<td>Pseudohermaphroditism</td>
<td>0.6</td>
<td>11</td>
</tr>
</tbody>
</table>


**Overall**: Major congenital malformations occur in 5-11% infants of diabetic mothers, compared to 1-2% in infants of non-diabetic mothers.\(^1,2\)

\(^1\)Plehwe WE, Storey CN, Sharman RP, Turtle JR. Outcome of pregnancy complicated by diabetes: experience with 232 patients in a 4 year period. Diabetes Res 1984;1:67-73.  (This is RPAH data)

Appendix B

- **Statins (HMG-CoA reductase inhibitors)** are Category D drugs in pregnancy.
- Category D drugs are drugs that have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage.
- Cholesterol and its by-products are essential components of fetal development including synthesis of steroids and cell membranes.
- Possible malformations or fetal loss have been reported though the rates of these adverse events have not clearly exceeded the rates of these events in the general population.

Appendix C

- **Angiotensin converting enzyme (ACE) inhibitors and Angiotensin II receptor antagonists (A2RA)** are Category D drugs in pregnancy.
- Category D drugs are drugs that have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage.
- ACE Inhibitors and A2RA cross the placenta.
- It is not known whether exposure to ACE Inhibitors only in 1st trimester causes adverse fetal effects.
- Fetal exposure to ACE Inhibitors in 2nd and 3rd trimesters may lead to problems with the functional development of the kidneys leading to fetal hypotension, decreased renal perfusion in the fetus, renal failure, skull hypoplasia, oligohydramnios (which is presumably from decreased fetal renal function and which, in this setting, may be associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development and intraterine growth retardation), fetal death in utero.

(References for Appendices B & C: MIMS Annual 2004; Prescribing Medicines in Pregnancy, ADEC, 4th edition)

Appendix D

<table>
<thead>
<tr>
<th>Oral Hypoglycaemic Agents</th>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Diabex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diaformin</td>
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<tr>
<td></td>
<td></td>
<td>Glucophage</td>
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<tr>
<td></td>
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<td>Glucohexal</td>
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<td></td>
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<td>Glucomet</td>
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<tr>
<td>Sulphonylureas</td>
<td>Glimepiride</td>
<td>Amaryl</td>
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<tr>
<td>Longer-acting</td>
<td>Glibenclamide</td>
<td>Daonil</td>
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<tr>
<td></td>
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<td>SemiDaonil</td>
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<td></td>
<td>Glimel</td>
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<td>Shorter-acting</td>
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<td>Glyade</td>
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<td>Nidem</td>
</tr>
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<td>Glipizide</td>
<td>Minidiab</td>
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<td>Melitide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
<td>Rastinon</td>
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<tr>
<td>Combination sulphonylurea &amp; biguanide</td>
<td>Glibenclamide + Metformin</td>
<td>Glucovance</td>
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<tr>
<td>Non-Sulphonylurea Insulin Secretagogues</td>
<td>Repaglinide</td>
<td>Novonorm</td>
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<td></td>
<td>Nateglinide</td>
<td>Starlix</td>
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<td>A-Glucosidase Inhibitor</td>
<td>Acarbose</td>
<td>Glucobay</td>
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<td>Thiazolidinediones</td>
<td>Rosiglitazone</td>
<td>Avandia</td>
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<tr>
<td></td>
<td>Pioglitazone</td>
<td>Actos</td>
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