THE ROLE OF METFORMIN IN 2016

Dr Myra Yeo
Endocrinologist
Epworth Freemasons Hospital
• What is metformin?
• Use in type 2 diabetes
• Use in PCOS/ MRS
• Use in pregnancy
  • Use in ovulation induction
  • Use in gestational diabetes
  • Use in obese, non-diabetic pregnant women
• Metformin as an anti-cancer drug
What is metformin?

- A biguanide class anti-diabetic medication with multiple action
- Taken orally, it is absorbed across the intestinal epithelium and then conveyed via the portal vein to the liver, where it accumulates
- The liver is its primary site of action
- Metformin is not metabolized and is excreted unchanged in the urine and bile
• Decrease intestinal absorption of glucose
• Impairs hepatic gluconeogenesis
• Stimulates glucose uptake by muscle cells via glucose transport (GLUT) system to improve peripheral sensitivity of insulin
Metformin in type 2 diabetes

- Metformin is the preferred and the most cost-effective first-line oral therapy for the treatment of type 2 DM.
- The US Diabetes Prevention programme found metformin reduces the risk of frank diabetes in patients with impaired glucose tolerance by as much as 31% when compared to placebo, although lifestyle interventions that achieve weight loss and regular exercise are even more effective (58% reduction in risk) (Knowler et al 2002, Ramachandran et al 2006).
• Metformin
  • Reasonably well-tolerated
  • Not complicated by hypoglycaemia
  • Promotes weight loss
  • Main side effects – gastrointestinal symptoms
  • Most serious side effects – lactic acidosis – rarely seen in patients with normal renal and hepatic function – 3/100,000 patient-years of use
Metformin in PCOS

- PCOS = Metabolic Reproductive Syndrome (MRS)
- Metformin is prescribed off-label in PCOS
- In women with PCOS, metformin (independent of weight loss)
  - Reduces insulin resistance
  - Improves hyperandrogenemia
  - Normalises menstrual abnormalities
Cochrane review (Costello et al 2010) – insulin-sensitising drugs (ISDs - metformin) vs. OCP for hirsutism, acne and risk of cardiovascular disease, and endometrial cancer in PCOS

- To assess the effectiveness and safety of ISDs vs. OCP
- Authors’ conclusion
  - Up to 12 months treatment with the OCP was associated with an improvement in menstrual pattern and serum androgen levels compared with metformin
  - BUT metformin resulted in a reduction in fasting insulin and lower triglyceride levels compared to OCP
  - Side effect profiles differ between the 2 drugs
  - Limited data on clinical outcomes such as development of diabetes, cardiovascular disease or endometrial cancer
Metformin in Pregnancy – ovulation induction

- Metformin is used as an ovulation induction agent, either alone or with clomiphene to improve ovulation rate

- In PCOS, metformin can
  - Reduce hyperinsulinemia
  - Suppress the excessive ovarian production of androgens
Mixed results

Cochrane review (Tang et al 2012) – 38 trials with a total of 3495 patients; median daily dose of 1500 mg of metformin over 4-48 weeks

- Metformin is effective in achieving ovulation in women with PCOS when comparing metformin vs placebo (odd ratio 1.81)
- Metformin is also effective when comparing metformin and clomiphene vs. clomiphene alone (OR 1.74)
- Although using metformin for ovulation induction improved pregnancy rates,
  - It did not reduce miscarriage rates
  - It did not results in higher live birth rates
• Metformin in IVF or ICSI in women with PCOS
  • Cochrane meta-analysis (Tso et al, 2014) concluded that the benefit in the context of IVF therapy for women with PCOS is
    • Increased clinical pregnancy rates
    • Decreased risk of ovarian hyperstimulation syndrome (OHSS)
  • No conclusive evidence that metformin increases live birth rates in women with PCOS
• Cochrane review (Sinawar et al 2012) – long vs short course treatment with metformin and clomiphene citrate for ovulation induction in women with PCOS
  • No RCT identified from literature review
  • Authors’ conclusion: insufficient data whether a short-course metformin pre-treatment is as effective as the conventional long-course metformin pre-treatment before initiation of clomiphene citrate for ovulation induction in infertile women with PCOS
• Metformin therapy during pregnancy in PCOS
  • Some early studies, with inferior design, suggested that metformin may reduce the miscarriage rate in women with PCOS
  • Subsequent studies (Palomba et al 2009, Morin-Papunen et al 2012) have shown this is not the case

• A Norwegian multicentre RCT (Vanky et al 2010) found
  • No improvement in complication rate (GDM, pregnancy-induced hypertension, pre-eclampsia) with continued use of metformin from late first trimester to delivery
  • ?appeared to have a reduction in late miscarriage and preterm delivery rates
Metformin in Pregnancy – gestational diabetes

• Use of metformin in pre-existing type 2 DM and newly diagnosed diabetes in pregnancy (GDM)
  • At least 3 retrospective studies, 2 non-randomized prospective studies and 5 RCTs published regarding pregnancy outcomes
  • No reports of an increase in congenital abnormalities or deleterious effects on foetal growth or short-term neonatal health
• Observations from these metformin studies
  • Reduction in maternal weight gain during pregnancy
  • Maternal hypoglycaemia is less prevalent in women treated with metformin alone
  • 10-46% of women with GDM treated with metformin have required supplemental insulin therapy in order to optimal glycaemic control
  • The total dose of insulin in metformin-treated women is lower than in women treated with insulin alone
The majority of the studies did not identify a significant difference in the short-term neonatal outcomes in women treated with metformin compared with insulin, although the individual trials were not powered to demonstrate differences in severe perinatal morbidity or perinatal mortality.

- Neonatal birthweight, frequency of large for gestational age, small for gestational age, preterm deliveries and neonatal unit admissions were not different between the groups for the majority of the studies (Rowan et al 2008, Terri et al 2008, Goh et al 2011, Ijas et al 2011, Niromanesh et al 2012, Spaulonci 2013).
- Neonatal hypoglycaemia was reduced in the metformin group in GDM (MiG trial (Rowan et al 2008).
- A reduction in neonatal anthropometric measurements (head, arm and chest circumference) was demonstrated in the study by Niromanesh et al (2012), but this was not shown in the larger MiG trial (Rowan et al 2008).
• Long-term child health outcomes?
• MiG trial (Rowan et al 2011) were followed up to 2 years of age
  • Anthropometric assessments performed on the children did not identify differences between the groups in central fat measures, total fat mass, percentage of body fat, or central-to-peripheral fat
  • Children exposed to metformin in utero had larger upper arm circumference, and bigger biceps and subscapular skinfolds – authors concluded that the exposure to metformin in utero leads to a shift in fat deposition from visceral fat stores to subcutaneous sites
Metformin in Pregnancy – obese, non-diabetic pregnant women

- Metformin in obese non-diabetic pregnant women randomised trial – NEJM 2016; 374: 434
  - Metformin use in the 2nd and 3rd trimesters
  - Reduced gestational weight gain compared to placebo (4.6 kg vs 6.3 kg)
  - Reduced rate of preeclampsia (3% vs 11.3%)
  - DID NOT reduce the frequency of large for gestational age neonates
  - DID NOT reduce adverse neonatal outcome
- Authors in UpToDate believe the use of metformin in pregnancy should be limited to management of hyperglycaemia – EMPOWaR study – Lancet Diab Endocrinol 2015: 3: 778
Metformin as an anti-cancer drug

- Epidemiological studies have linked metformin exposure to decreased risk of cancer
  - Metformin may be effective as an anti-cancer agent in tumours driven by insulin resistance and obesity
  - Metformin has a growth-static effect on several cancers, including endometrial, breast, pancreatic, ovarian and prostate cancers
- Prospective observational studies suggested that patients with type 2 DM taking metformin were not only at lower risk of developing cancers (Libby et al 2009), but were also less likely to die from it (Evans et al 2005)
Most of the published studies have focused on breast cancer

- Proliferation is a hallmark of cancer and Ki-67 is only expressed in proliferating cells; Ki-67 has been extensively validated as a prognostic and predictive biomarker of clinical response in breast cancer (Dowsett et al 2007)
- 2 small uncontrolled pilot studies found a significant reduction in Ki-67 expression by breast tumours following short-term pre-surgical administration of metformin (range 13-21 days)
• A larger placebo-controlled trial (n=200) went on to show that metformin reduced tumour Ki-67 expression (by ~10%) in overweight and insulin-resistant breast cancer patients, but not in the whole metformin-treated population (Bonanni et al 2012)

• Early phase clinical study on prostate cancer treated pre-surgically with metformin also yielded promising results
  • 24 patients who received neoadjuvant metformin for a mean duration of 41 days prior to radical prostatectomy – metformin reduced the Ki-67 proliferation index by 29% compared with the pre-treatment biopsy
• **Endometrial cancer**
  
  • The cancer that is most strongly associated with obesity
  • Excess body fat increased endometrial cancer risk in a dose-dependent manner – every 5 kg/m² increase in BMI confer a 1.6-fold increased risk
  • Metformin may inhibit tumour growth by reducing its nutrient supply (glucose) and by thwarting its growth-stimulatory environment (reduced insulin and IGF levels)
  • No published study on testing metformin for endometrial cancer in the adjuvant setting
• Could metformin be used as a long-term chemopreventative agent in women at high risk of endometrial cancer
• Several case reports and one small randomized open label study have demonstrated resolution of endometrial hyperplasia following treatment with metformin
• No definitive chemopreventative trial of metformin in high risk women available yet
• The epidemiological data linking metformin use in type 2 DM patients to reduced cancer risk are inconsistent.
  • One meta-analysis of 11 retrospective studies – metformin reduced cancer risk by one-third (DeCensi et al 2010)
  • Another meta-analysis of 14 RCTs reported no association between metformin and cancer risk – heterogeneity of the trials, short follow-up period (average 4.1 years), etc.
Metformin - conclusions

- Used in treatment of gestational diabetes
- Effect on fertility in PCOS is uncertain
- Epidemiological evidence as well as pre-clinical and early phase clinical trials have indicated a role of metformin in the prevention and treatment of cancer – role unproven but promising