Project Title:	Does metformin reduce excess birthweight in offspring of obese pregnant women? A randomised controlled trial of efficacy, exploration of mechanisms and evaluation of other pregnancy complications.
Project Ref:	08-246-09
Cost:	£996,074
Lead Applicant & Institution:	Professor Jane Norman University of Edinburgh Centre for Reproductive Biology The Queens Medical Research Institute
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Plain English Summary:	The prevalence of obesity amongst pregnant women is rising rapidly. It is now over 15% in many UK hospitals including our own. Women who are obese during pregnancy have a significantly increased risk of adverse outcomes including maternal death, gestational diabetes, pre-eclampsia and caesarean section. Their babies are more likely to be stillborn and/ or larger than average when compared with lean pregnant women. In addition to these immediate problems, there is evidence that the bad effects of maternal obesity during pregnancy persist into the baby's adult life. The higher than average baby birthweight leads to increased risk of the baby having obesity in when he/she becomes an adult. If unchecked, this will lead to a further rise in the rates of obesity in the UK and other developed countries, with all the attendant medical problems (including diabetes, heart disease and premature death). We don't know how obesity in pregnant women causes these problems. We do know that obese pregnant women are more "insulin resistant" than lean pregnant women – i.e. they need to produce higher levels of the hormone insulin to keep their blood glucose levels at the same level. A modest degree of insulin resistance is normal in pregnancy so that there is a good supply of glucose and other food substrates for the baby to grow. However, excessive insulin resistance means that the food supply to the baby is potentially too great, leading to a birthweight that is too high. This link between high insulin resistance and high birthweight has already been demonstrated. Additionally, women with higher levels of blood glucose tend to have bigger babies and a greater incidence of pregnancy problems. Reducing their blood glucose seems to reduce the amount of pregnancy problems. We wish to try a drug called metformin which reduces insulin resistance. Metformin is widely used to treat Type II diabetes. It has been shown to be safe during pregnancy. The National Institute for Clinical Effectiveness in the UK now recommends metformin as an alternative to insulin in women with established diabetes in pregnancy. We will invite 400 obese pregnant women to participate in a double blind randomised study where they are

	given either metformin or placebo tablets. We will track them during pregnancy and look at the birthweight of the baby. Additionally we will collect information on other pregnancy complications for mother and baby. We will look at the effect of metformin on biochemical factors in the mother and baby's blood, and in the placenta. We believe that giving metformin to obese pregnant women will reduce their insulin resistance and therefore reduce the incidence of high birthweight. Importantly, the small studies that have been done so far suggest that metformin does not increase the risk of excessively low birthweight. We hope to confirm this in our study. We will also use metformin to explore how obesity causes pregnancy problems. We will look at women given metformin and those given placebo (likely to be those with normal and high insulin resistance) and relate this to the pregnancy outcomes they have. This should give us important information on whether reducing insulin resistance improves other pregnancy problems for obese pregnant women and their babies. By looking at changes in the blood of obese pregnant women and their babies given metformin or placebo, we will further be able to understand how obesity causes pregnancy problems. The link between maternal obesity, high birthweight of the baby and later life obesity of the baby has been shown in many studies. As more women enter pregnancy with a body mass which would define them as "obese" an intervention is urgently required to stop this health risk being passed on to the next generation. Unfortunately many drugs that might be effective are unsuitable for use in pregnancy. In contrast, metformin appears safe during pregnancy. In this study, we will (for the first time) test its efficacy in reducing high birthweight in the children of obese pregnant women.
Abstract:	Aim: The aim of this study is to determine if metformin, administered to obese women during pregnancy, reduces the future life risk of obesity and metabolic syndrome in their babies. We will use high birthweight centile as a surrogate marker for future life events as its validity has been shown in large epidemiological studies [1-3]. Secondly, we will use metformin administration as a tool to explore the mechanism by which obesity causes adverse pregnancy outcomes, with a particular focus on insulin resistance (IR). Design: Double blind placebo controlled randomised clinical trial. Setting: Antenatal clinics specialising in the care of obese pregnant women in two large maternity hospitals in the UK (Edinburgh and Liverpool). Target population: Obese pregnant women. Interventions being evaluated: Metformin, an insulin sensitising agent or matched placebo initiated between 12 and 16 weeks gestation. Primary Outcomes: (i) Efficacy outcome – z-score corresponding to the gestational age and sex adjusted birthweight centiles of the baby (ii) Mechanistic outcome - maternal insulin resistance (IR) at 36 weeks gestation which will be correlated with adverse pregnancy outcomes.

Secondary Outcomes:
(A) More detailed measurements of neonatal body composition at birth including ponderal index; skinfold thicknesses; and (Edinburgh babies only) neonatal fat mass measured using air displacement plethysmography. (B) Biological mechanisms of metformin action including (i) change in IR; hepatic and skeletal insulin sensitivity (ii) maternal and neonatal inflammatory and lipid indices including CRP, IL-6, leptin, lipids, triglycerides and PAI1/PAI2 ratio (iii) placental glucocorticoid receptor expression (iv) maternal brachial arterial endothelial dependent flow mediated dilatation (FMD) (v) in vitro measurements of maternal myometrial contractility [4] (vi) changes in maternal anthrometry. (C) Adverse pregnancy outcomes as a composite; incidence of low birthweight centile. (D) Gas chromatography mass spectrometry measurements of metformin in maternal plasma to determine compliance.

Measurement Of Outcome And Duration Of Follow Up. Birthweight will be measured by clinical staff, the result prospectively transferred from the clinical birth record to a case report form and Z score of birthweight centile calculated using www.gestation.net. Maternal IR at 36 weeks gestation will be expressed as the Matsuda index [5] (the best correlate with the gold standard the hyperinsulinaemic euglycaemic clamp in pregnant women)[6], and derived from multiple sampling during a glucose tolerance test. Change in IR will be expressed as changes in a logarithmic and reciprocal transformation of a single fasting glucose and insulin value (QUICKI), measured during a glucose tolerance test at baseline (prior to treatment), at 28 weeks and at 36 weeks gestation [6]. In a subgroup of women (n = 20 in each group) insulin resistance will be measured by the hyperinsulinaemic euglycaemic clamp, to characterise the relative effects of metformin on hepatic and peripheral skeletal muscle insulin sensitivity. Endothelial dependent FMD will be measured in a subset (n = 30 each group) at 36 weeks gestation using a non invasive, validated, and reproducible method suitable for use in pregnancy [7 8]. Initial follow up will cease once the woman and baby have been discharged postnatally, although we anticipate further funding applications to continue neonatal follow up into early childhood.

Sample size:
(1) *Birthweight Centile*. In a previous study, the mean (SD) birthweight in a cohort of obese women (mean BMI 34) was 4.0kg (0.6kg)[9]. We hypothesise that metformin will reduce mean birthweight by 200g, corresponding to a reduction in birthweight centile of 0.3 SD. We believe that this reduction in birthweight centile is clinically relevant, but is a relatively conservative estimate of likely reduction in birthweight centile induced by metformin, given that mean birthweight in the study described above in a parallel non obese cohort was 3.4kg. A sample size of 143 in each group will have 80% power to detect a difference in means birthweight centile of 0.3 SD (the difference between a placebo mean of 4.0kg and a metformin mean of 3.8kg) at the 5% significance level using a two group t-test; a sample size of 163 in each group will give the study 85% power to detect these differences. In practice we will recruit 200 women to each group to allow loss to follow up (anticipated < 5% by extrapolation from our previous studies) and suboptimal compliance.
(2) *Insulin Resistance*. In our previous study of obese women with PCOS, fasting insulin was lowered by 25% after 6 months treatment with metformin 1500mg daily [10], consistent with meta-analyses [11]. Based on published levels of fasting insulin in obese pregnant women 26.9 IU/L [12], and deriving the standard deviation as 15.7 IU/L from the published standard error of 3.5 IU/L with n=20, if a reduction in mean fasting insulin of 22% (5.4 IU/L) is achieved by metformin in pregnancy in pregnancy, a sample size of 306 will be required for the study to have 85% power to demonstrate differences between the placebo and metformin group at the 5% significance level. In practice, we will use the Matsuda index, a more accurate measure of IR so actual power of the study should be greater.

	Planned Analyses: Mean birthweight centile will be compared between the groups using essentially a two-sample t test, but with the analysis stratified for the same factors as the randomization. Correlations within the metformin and placebo groups will be used to determine association between IR and adverse pregnancy outcomes Timetable. Set up 6 months, recruit over 2 years (1-2 participants per week in each centre), follow up 1 year, analysis 6 months.
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