Title: Prophylactic Metformin after Antenatal Corticosteroids (Promac): A Double Blind Randomised Controlled Trial.

Trial Protocol

1.0 Introduction

The administration of antenatal corticosteroids is commonly used in obstetrics practice to reduce the incidence and severity of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and neonatal mortality. (Liggins et al, 1972) (Roberts et al, 2006).

A widely recognized side effect from administration of antenatal corticosteroids is maternal hyperglycemia. (Star HJ et al, 2000). In patients with gestational or pregestational diabetes, giving corticosteroids will result in deterioration of glycemic control, severe hyperglycemia and increase in insulin requirement. (Allison et al, 2012. Mathiesen et al, 2002). It is well known that corticosteroids increase hepatic glycogen synthesis, glucose production and at the same time decreases glucose uptake in peripheral tissues. (McKay et al, 2003). On the other hand, normal pregnancy is characterized by relative insulin resistance and glucose intolerance. (Butte NF, 2000). Jennifer et al. studied the pattern of glucose response to betamethasone in pregnant women with or without diabetes and demonstrated hyperglycemia in majority of the subjects regardless of diabetes status after administration of betamethasone to accelerate fetal lung maturity. Star et al. identified 85% of pregnant women without diabetes who did not receive prophylactic insulin prior to antenatal corticosteroid administration had a capillary blood glucose level of greater than 160mg/dL during a three-day study period.

The potential hyperglycemia after antenatal corticosteroids may have effect on fetal acid-base status because of the higher maternal blood glucose levels and this may coincides with the period where patient is at risk of preterm delivery. Lawrence et al administered 100g of glucose or saline to laboring women with ketonuria and found a significantly decreased fetal pH in women who had been given glucose versus those given saline (mean fetal pH 7.26 versus >7.3). Another study of maternal glucose infusion in women just prior to delivery showed that fetal cord blood sampling has fetal acidosis with moderate hyperglycemia. (Philipson et al, 1987).

Initiation of insulin therapy or increase in insulin dosage may be required for glycemic management in pregnant women after receiving corticosteroids. However, National Institute for Health and Care Excellences NICE Guideline, Fifth International Workshop-Conference in Gestational Diabetes Mellitus and American College of Obstetricians and Gynecologists (ACOG) on management of diabetes in pregnancy states that metformin may be used as an alternative or adjunct during pregnancy.

We hypothesize that prophylactic metformin following antenatal corticosteroids administration to ameliorate neonatal risk associated with prematurity will reduce the risk of subsequent short term hyperglycaemia. We sent out to test the hypothesis in a double blinded randomized controlled trial.

2.0 Research Hypothesis

To show that metformin given prophylactically after administration of antenatal corticosteroids will ameliorate the hyperglycemic effect.

3.0 Objectives

3.1 To show that metformin will ameliorate the hyperglycemic effect of antenatal corticosteroids

4.0 Primary Outcome

4.1 Hyperglycemia episodes in the 24 hours following administration of antenatal corticosteroids. Hyperglycemia is defined as pre meal blood glucose level of more than 5.3 mmol/L and 2 hours post prandial/meal blood glucose of more than 6.7 mmol/L and these are measured by point of care capillary blood glucose monitoring system at 6 points (pre and post breakfast, lunch and dinner).

5.0 Secondary Outcomes

5.1 Neonatal outcomes: These are assessed by reviewing patient's and baby's notes after delivery

5.1.1 Birth weight

5.1.2 Umbilical cord arterial pH at birth

5.1.3 Apgar score at 1^{st} and 5^{th} minute of life/birth

5.1.4 Special care nursery/ neonatal intensive care unit admission during birth admission

5.2 Maternal outcomes: These are assessed by reviewing patient's notes after delivery

5.2.1 Mode of delivery

5.2.2 Estimated blood loss during delivery

5.3 Need for additional or unplanned hypoglycaemic agent (metformin or other) use. This is indicated by capillary blood glucose level more than 11 mmol/L during the monitoring

5.4 Hyperglycaemia episodes (hyperglycaemia as defined in primary outcome measure) up to 48 hours after administration of antenatal corticosteroids (if still undelivered)

5.5 Hyperglycaemia episodes (hyperglycaemia as defined in primary outcome measure) up to 72 hours after administration of antenatal corticosteroids (if still undelivered)

5.6 Hypoglycaemia episodes (hypoglycaemia is defined as capillary blood glucose level equal or less than 3.9 mmol/L)

5.7 Diarrhoea (during study period up to Day 3 or delivery) Yes / No

5.8 Vomiting (during study period up to Day 3 or delivery) Yes / No

6.0 **Materials and Method**

6.1 Study Design

Double blind, single centre, prospective, randomized controlled trial.

6.2 Place of Study

University Malaya Medical Centre.

6.3 Sampling

All antenatal cases presented at the University Malaya Medical Centre who are about to receive or within 6 hours of first dose of antenatal corticosteroids during the study period and satisfy the inclusion and exclusion criteria are stratified to gestational diabetes mellitus and non gestational diabetes mellitus pregnancies. Then, these patients are randomized to use of metformin or placebo.

6.3.1 **Inclusion criteria**

6.3.1.1 All antenatal cases between 24-38 weeks who are about to receive or within 6 hours of first dose of antenatal corticosteroids for improvement of neonatal outcome

6.3.1.2 Age more than 18 years old

6.3.1.3 Singleton pregnancy

6.3.2 **Exclusion criteria**

6.3.2.1 Patients on hypoglycaemic agent

6.3.2.2 Pre-existing Type 1 or Type 2 diabetes mellitus

6.3.2.3 Baseline capillary blood glucose level more than 11mmol/L (at recruitment)

6.3.2.4 Patients in active labor or may deliver within the next 24 hours after administration of antenatal corticosteroids

6.3.2.5 Evidence of chorioamnionitis or other maternal or fetal infection

6.3.2.6 Patients on terbutaline or other beta-mimetic agents

6.3.3.7 Diet restrictions in anticipation of Caesarean birth

6.**4 Methodology**

The study protocol is distributed to the whole department. Patients who are about to receive or within 6 hours of first dose of antenatal corticosteroids who fulfilled the inclusion and exclusion criteria will be recruited. Written informed consent will be taken. Patients will receive intramuscular dexamethasone, 12 mg for 2 doses 12 hours apart, as per our institution protocol. Participants will be stratified to GDM and non-GDM pregnancies for separate randomization using sealed numbered envelopes which contained the study drug (a pack of six 500 mg metformin tablets or identical placebo).

Participants will be observed to take the first dose of their allocated study drug (500 mg metformin or identical placebo tablet) with the remaining five tablets to be taken twice daily which is to be taken at the start of their breakfast and dinner. If the second dose (at the next breakfast or dinner) is within 6 hours of the first dose, it should be omitted, with the second dose to be taken at the subsequent breakfast or dinner. After delivery if it occurs within the 3-day study period, the study drug is to be stopped.

Capillary blood glucose tested at recruitment and repeated 6 times per day (before and 2 hours after each breakfast, lunch and dinner for up to three consecutive days (18 readings) if undelivered. Blood glucose monitoring is to stop after delivery. Patients will be provided with blood glucose monitoring system (to be returned), test strips and taught to self-monitor their blood glucose level and record it in a provided record sheet. Participants should continue their normal diet during the study.

The participants will be instructed that if blood glucose level is more than 11 mmol/L during monitoring, they are to contact investigator immediately through the hand phone number provided (if already discharged from hospital). Open label 500 mg metformin tablets will be provided to all participants in a separate sealed pack labelled as "Rescue Metformin, Use Only as Instructed". The open label rescue metformin will be from a different manufacturer and visually distinct from study metformin/placebo tablets. In the event that glucose level is > 11 mmol/L whether pre or post prandial at any meal, 500 mg of open label metformin will be administered. Study drug should continue at breakfast and dinner as planned e.g. if the pre breakfast capillary glucose is > 11 mmol/L, the participant will take a 500 mg metformin (open label) plus the scheduled study tablet. A maximum of three open label 500 mg metformin may be taken per day. If control is insufficient, despite three open label metformin doses (plus study drug regimen), subcutaneous insulin will be used as per usual institutional practice for uncontrolled hyperglycaemia in pregnancy following rehospitalization if the patient is already discharged.

Patients will be contacted if necessary by phone or other means to retrieve the capillary blood glucose level monitoring result and glucometer if discharged undelivered prior to the 3 day study period. Also, to obtain data on side effects of nausea, vomiting, diarrhoea and satisfaction scores on glucose monitoring and drug treatment during the study period.

Demographic and laboratory data are recorded as per the Case Report Form. Capillary blood glucose was measured by using an approved commercially available glucometer. The number of hyperglycemic episodes will be recorded for each patient and hyperglycemia is defined as a fasting/premeal capillary blood glucose ≥ 5.3 mmol/l or a 2 hours post prandial glucose ≥ 6.7 mmol/l (NICE guideline 2015 and Fifth International Workshop-Conference in Gestational Diabetes Mellitus).

Symptoms of nausea, vomiting or diarrhoea will be self-charted on the participant's record form as well as the satisfaction score with the glucose monitoring and drug treatment during the study period.

The patient's notes will be retrieved to obtain the maternal outcome data such as mode of delivery and estimated blood loss during delivery. The baby's notes will be retrieved to obtain neonatal outcome data such as birth weight, umbilical cord arterial blood pH, Apgar score at 1^{st} and 5^{th} of life and any admission to the special care nursery or neonatal intensive care unit.

6.6 **Statistical Analysis**

Data will be entered into SPSS statistical software. Normally distributed continuous data will be analyzed with the Student's t test. Chi square test will be used for categorical or nominal data and Mann-Whitney U test will be used on non normally distributed or ordinal data.

6.7 **Ethical Considerations**

Good Clinical Practice ethos will be applied for this trial. Research data output will be anonymised. This trial is designed as a double blind randomised controlled trial; procedures will be in place to break the randomisation code if clinically indicated. The study has been approved by ethics committee of University Malaya Medical Centre.