Metformin to treat Preterm Pre-eclampsia:

A randomised, double-blind, placebo-controlled trial

Authors

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OBJECTIVE

Preterm pre-eclampsia has high rates of maternal and perinatal morbidity and mortality. Preclinical studies have identified metformin as a potential treatment. We evaluated whether metformin XR (extended release) could prolong gestation in women being expectantly managed for preterm pre-eclampsia.

DESIGN

Randomised, double-blind, placebo-controlled trial.

SETTING

Referral hospital in Cape Town, South Africa.

PARTICIPANTS

Pregnant women with preterm pre-eclampsia between 26+0 to 31+6 weeks gestation undergoing expectant management were eligible. We approached 445 women. 203 were eligible for inclusion, 23 declined and 180 women were randomised.

INTERVENTION

3 grams of oral metformin XR or placebo, in divided doses, until delivery.

MAIN OUTCOME

The primary outcome was prolongation of pregnancy.

RESULTS

We randomised 90 women to each group. After exclusions, the analysis included 87 allocated to metformin XR and 84 assigned to placebo. The median time from randomisation to delivery was 16.2 days (interquartile range (IQR) 5.2-28.8 days) in the metformin XR group and 9.5 days (IQR 3.4-22.7) days in the placebo group (difference of 6.7 days (95% Confidence Interval (CI) -0.17 to 13.64; P=0.056). In a prespecified treatment received analysis, the median prolongation was 16.2 (IQR 5.3-27.5;n=75) versus 7.4 (IQR 2.9-21.2;n=72) days, respectively (difference of 8.4 days (95%CI 1.0-15.8; P=0.026). There were no differences in composite maternal or neonatal outcomes or circulating concentrations of soluble fms-like tyrosine kinase-1, placental growth factor or soluble endoglin. There were non-significant increases in birthweight (136 gm (-12 to 285; P=0.07), and a decreased length of stay at the tertiary level neonatal nursery (6.0 days (-0.4 to 12.4); P=0.07). A posthoc analysis found a shorter period of admission in any neonatal nursery (13.0 days less (95% CI 3.5 to

22.5); P=0.007) in the metformin XR group. No serious adverse events related to trial medications were observed though gastrointestinal side effects were common among those who took metformin XR.

CONCLUSIONS

In this randomised, placebo-controlled trial, Metformin XR prolonged gestation in women with preterm pre-eclampsia. This trial provides proof of concept that treatment of preterm pre-eclampsia is possible.

TRIAL REGISTRATION

Pan African Clinical Trial Registry PACTR201608001752102 https://pactr.samrc.ac.za/

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