Aspirin for pregnancies at high risk for preterm pre-eclampsia

Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. (King's College Hospital, King's College London, Homerton University Hospital, North Middlesex University Hospital, and University College London Comprehensive Clinical Trials Unit, London; University of Exeter, Exeter; Medway Maritime Hospital, Gillingham, and Southend University Hospital, Westcliff-on-Sea, United Kingdom; Chinese University of Hong Kong, Hong Kong; Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Hospital Universitario San Cecilio, Granada, and Hospiten Group, Tenerife, Spain; Ospedale Maggiore Policlinico, Milan, Italy; University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium; Attikon University Hospital, Athens, Greece; Rabin Medical Center, Petach Tikva, and HyLabs Diagnostics, Rehovot, Israel; University of Iceland, Reykjavik, Iceland.) Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;**377:**613–22.

SUMMARY

This was a double-blind, placebo-controlled trial, in which aspirin at a dose of 150 mg/day was compared to a placebo that was administered from 11 to 14 weeks of gestation until 36 weeks of gestation in women with singleton pregnancies who were at high risk for preterm pre-eclampsia. The trial was conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece and Israel.

All women who had a routine prenatal visit at 11 weeks 0 days of gestation through 13 weeks 6 days of gestation in the participating hospitals were offered screening for pre-eclampsia by means of an algorithm that combined maternal factors, mean arterial pressure, uterine-artery pulsatility index and maternal serum pregnancy-associated plasma protein A and placental growth factor. Inclusion criteria for the trial were: age 18 years or more, singleton pregnancy, live foetus at the time that scanning done at 11–13 weeks of gestation and a high risk (>1 in 100) for preterm pre-eclampsia according to the screening algorithm. Exclusion criteria were: unconscious or severely ill status, learning difficulties or serious mental illness, major foetal abnormality identified at the time that scanning was done at 11–13 weeks of gestation, regular treatment with aspirin within 28 days before screening, bleeding disorder such as von Willebrand disease, peptic ulceration, hypersensitivity to aspirin, long-term use of non-steroidal anti-inflammatory medication and participation in another drug trial within 28 days before screening.

Eligible women were randomly assigned, in a 1:1 ratio, with the use of a web-based system (sealed envelope), to receive either aspirin or placebo. After randomization, the participants were prescribed the assigned trial product and received instructions to take one tablet every night throughout the trial and to stop taking tablets at 36 weeks of gestation or, in the event of early delivery, at the onset of labour. The primary outcome measure was delivery with pre-eclampsia before 37 weeks of gestation. Secondary outcomes were adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation and at or after 37 weeks of gestation; stillbirth or neonatal death; death and neonatal complications; neonatal therapy and poor foetal growth.

A total of 26 941 women with singleton pregnancies underwent screening,[1] of whom 2971 (11%) were found to be at high risk for preterm pre-eclampsia of which 1776 were eligible and underwent randomization. Of these, 878 were assigned to receive aspirin and 898 to placebo. Preterm pre-eclampsia occurred in 13 of 798 participants (1.6%) in the aspirin group, compared with 35 of 822 (4.3%) in the placebo group (adjusted odds ratio in the aspirin group, 0.38; 95% confidence interval 0.20–0.74, p=0.004). There was no significant between-group difference in the incidence of any secondary outcomes, but the trial was not powered for these outcomes.

COMMENT

Pre-eclampsia is a major cause of maternal mortality and morbidity. The foetal and neonatal outcomes are also jeopardized. The complications are more severe if the disease has an earlier onset in pregnancy resulting in pre-term delivery and consequent complications.

The prediction of pre-eclampsia and instituting an intervention for prophylaxis of pre-eclampsia has been a topic of extensive research with aspirin being the potential therapy. However, there have been much speculation on the population, dose and timing of aspirin administration to get the optimal maternal and neonatal outcome.

This trial, also called the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial, is a landmark trial that can bring considerable change in practice.

Unlike previous trials of strategies to reduce the risk of pre-eclampsia among high-risk women, which were largely based on factors in the history of the patient, the patients in this trial were identified on the basis of combined screening with maternal demographic characteristics, biophysical and biochemical markers. This model has been shown to be superior to other methods in various studies.[2–5] Efficacy of intervention based on this model reiterates the need for screening using the combined risk model.

Another important outcome of this trial is the earlier gestational age range at the onset of treatment (11–14 weeks of gestation) with aspirin. The latest meta-analysis suggested that aspirin confers greater benefit if it is started at or before 16 weeks of gestation and that prevention is confined to preterm pre-eclampsia.[6,7] This is a change from the current practice of starting aspirin even later in gestation. Currently, prophylactic aspirin is given in a low dose of 81 mg/day. However, lately, robust evidence suggests dose-dependent benefit of therapy.[8] The dose of 150 mg of aspirin per day in this trial has been proven to be effective without any untoward effects. The primary outcome measure of this trial was preterm rather than term pre-eclampsia. This is also secondary to the fact that the algorithms for the prediction of pre-eclampsia work better for the prediction of preterm pre-eclampsia.

In conclusion, in women identified by first trimester combined screening to be at high risk for preterm pre-eclampsia, the administration of aspirin at a dose of 150 mg/day from 11 to 14 weeks till 36 weeks significantly reduces the incidence of preterm pre-eclampsia. There is no significant difference in the neonatal outcome or adverse effects of aspirin.

Conflicts of interest. None declared

REFERENCES

1 Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013;**33:**8–15.

2 National Collaborating Centre for Women's and Children's Health (UK). *Hypertension in pregnancy: The management of hypertensive disorders during pregnancy*. London: RCOG Press; 2010.

3 American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122:** 1122–31.
4 O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, *et al*. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: Comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol* 2017;**49:**756–60.
5 Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, *et al*. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: A systematic review and meta-analysis. *Fetal Diagn Ther* 2012;**31:**141–6.
6 Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, *et al*. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: A meta-analysis. *Obstet Gynecol* 2010;**116:**402–14.
7 Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: A meta-analysis. *Ultrasound Obstet Gynecol* 2013;**41:**491–9.
8 Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E, *et al*. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: Systematic review and meta-analysis. *Am J Obstet Gynecol* 2017;**216:**110–20.e6.

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