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COMMENT

How low-dose aspirin works in preeclampsia—the monumental challenge to delay and prevent the onset of the disease

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A recent article by Han et al. [1] showed that low-dose aspirin (LDA) had a significant effect on recurrent preeclampsia (PE), with a mean interval of 5.45 years. This is consistent with previous findings regarding the background of patients who have had PE recurrences, such as a higher complication rate of diabetes mellitus at the time of recurrence, a higher rate of severe first-time PE, and an earlier week of onset at the time of recurrence. A new finding revealed that the onset of PE was significantly delayed in those who received LDA, whereas those who did not receive LDA had a significantly earlier onset week of PE recurrence. One bias to note is that the aspirin-treated cases showed an earlier onset week of the first incidence of PE (mean initial onset week for aspirin-treated cases: 32.11 weeks; for non-treated cases: 37.11 weeks) and were not randomly assigned for LDA treatment. However, the "delayed onset" effect of PE by a prophylactic LDA dose is similar to the results to the first well-known study Fig. 1.

Although many obstetricians have long realized the potential of LDA in reducing the incidence of PE, the scientific evidence is insufficient. In 2017, Rolnik et al. [2] reported a study in which pregnant women at high risk of developing PE were randomly assigned to receive LDA until term, between 11 and 14 weeks of gestation. They were selected using a unique algorithm combining medical history, patient background, serum markers (pregnancy-associated plasma protein A and placental growth factor), and ultrasound screening of uterine artery Doppler flow. The study showed a clear reduction in the incidence of PE from 4.3% in the placebo group to 1.6% in the LDA group, representing a one-third reduction. One of the main issues is that risk calculations in this study cannot be made for all countries worldwide with the current content of serum marker tests and ultrasound techniques; however, this report has been praised by obstetricians worldwide for paving the way for the prophylactic treatment of PE, an agonizing disease that is not yet fully understood, leading to death or developmental handicap of the newborn, as well as maternal death or lifelong disease in some cases.

However, it is well-known that LDA only relieves the inflammation in tissues by inflammatory factors originating from the placenta [3] and is not expected to cure the fundamental underlying cause. Although there is no single cause for the development of PE, the most prevalent cause is the failure of placentation/implantation in early pregnancy (poor uterine spiral artery remodeling), followed by hypoxia and inflammation of the placenta in the second and third trimesters of pregnancy, with the systemic effects of the extracellular vesicles released from the placenta. The use of LDA increased bleeding during delivery [4]. Therefore, we can predict that the use of LDA reduces microthrombosis in the placenta by suppressing coagulation and may also reduce the development of the disease; however, there have not been many studies demonstrating this mechanism. As a result, LDA is thought to delay the onset of the disease only and does not provide a fundamental solution for this intractable disease.

Additionally, one lead author of the large randomized controlled trial mentioned above stated that all pregnancies will develop PE due to placental aging if the pregnancy is prolonged for too long (Professor Liona Poon, personal communication). Therefore, delaying disease onset may be the best currently conceivable treatment strategy. Nevertheless, obstetricians worldwide are keen to explore treatments that can reliably "cancel" the onset of PE. Recent attempts have been made to use pravastatin, a drug familiar

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Graphical Opinion

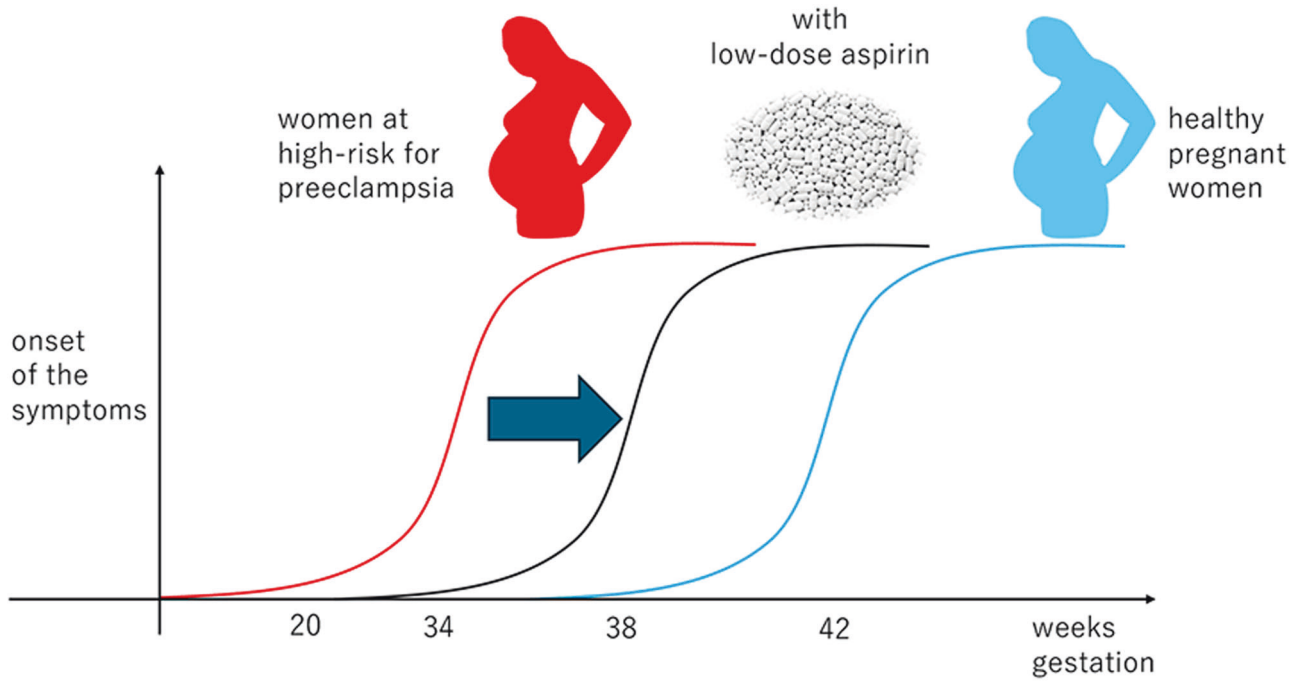

Fig. 1 Low-dose aspirin "delays" the onset of preeclampsia in high-risk pregnant subjects. All pregnancies including healthy subjects will also develop PE if the pregnancy is prolonged for too long

with
low-dose aspirin
women at
high-risk for
preeclampsia
healthy
pregnant
women
onset
of the
symptoms
20
34
38
42
weeks
gestation

to physicians, for the treatment of PE. Unfortunately, no significant benefit appears to have been demonstrated yet [5]; however, if PE can be treated with a drug that has been proven safe for both mother and fetus, it may be possible to further reduce this dreadful disease that robs many mothers and babies of their lives and a healthy future. In the interim, we will continue to use LDA to delay the onset of PE based on useful studies, such as those presented here.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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