Preconception Low-Dose Aspirin and Pregnancy Outcomes: Results from the EAGeR Randomized Trial

Abstract:

Obstetric practice is evolving; the future will see a shift in the focus of care to the pre-conceptual period and early trimester with a move towards interventions which optimise maternal and neonatal outcome. Low dose Aspirin (LDA) is one such intervention. The safety and efficacy of this medicinal product has already been proven and subsequently it is now used common in practice for at-risk pregnancies for prevention of pre-eclampsia, fetal growth restriction and complications of anti-phospholipid syndrome.

An area where the provision of LDA requires further exploration is that of pregnancy loss prevention. Pregnancy loss is a devastating event which occurs in approximately one third of all conceptions, with women that have had a previous pregnancy loss being at greater risk. Although the pathogenesis of pregnancy loss is not fully understood, it is postulated that LDA can prevent this phenomenon through the promotion of prostacyclin production in favor of vasodilation, in addition to having an anti-inflammatory effect. A question which remains unanswered is if LDA can improve live birth rates in women who have had previous pregnancy loss. The Effects of Aspirin in Gestation and Reproduction (EAGeR) trial has set out to answer this question. This multi-center double-blind randomised controlled trial of 1078 women was set in the USA from 2007 to 2011. Women that met pre-defined inclusion criteria (notably 18-40 years of age with one previous pregnancy loss with no history of infertility) were randomized to receive either folic acid 400ug and LDA 81mg versus a placebo, which also included folic acid 400ug both of which were commenced pre-conceptually until 36-completed weeks gestation. Patients were followed up until the completion of pregnancy, two peri-conception losses or failure to conceive after six menstrual cycles. The primary outcome of the study was live birth with secondary outcomes including implantation, confirmed pregnancy, pregnancy loss (>20 weeks), birth weight and serious obstetric complications (pre-eclampsia, gestational diabetes gestational hypertension or pre-term birth).

Results of the study did not demonstrate a significant difference overall between groups in terms of live birth rate (58% in LDA group vs 53% in placebo RR 1.10 (p=0.984 95% CI 0.98 to 1.22)) nor in terms of secondary outcomes as previously noted. Interestingly the study adds to the existing evidence on safety of LDA with no reported birth defects and although vaginal bleeding was more common in the LDA group (4.9% vs 1.7% placebo p=0.038), this did not increase pregnancy loss rates in this group.

Strengths of this study lie within the robust patient follow-up, clearly defined outcome measures and methodology, which add to the validity of this study. Computerized randomization, similar demographic characteristics between groups and the adoption of an intention-to-treat analysis demonstrate that the potential of selection, attrition and attrition bias was addressed and minimized. The authors cannot be accused of reporting bias as the negative and positive findings are discussed within sub-groups. Further to this the study is original in concept the first of its kind to address the proposed, highly relevant clinical question. The main weakness of this study was the fact that inclusion criteria were expanded after the study had started to include women with a previous pregnancy loss greater than 20 weeks as well as other factors that had previously been exclusion criteria. This clearly impacted upon results as there was a significant difference in outcome measures within the original stratum in terms of live birth rates (61% in LDA group vs 53% placebo RR 1.17 (95% CI 1.01 to 1.37 p=0.0466)) and notably those who became pregnant in the LDA cohort (ultrasound-confirmed pregnancy 74% LDA group vs 64% placebo RR 1.17 (95% CI 1.04 to 1.32 p=0.0113)). This difference was noted further on sensitivity analysis in this group although these results were not reported upon. Authors suggest the reason for this kind of discrepancy is that the LDA can prevent this phenomenon through the promotion of prostacyclin production in favor of vasodilation and implantation rate.

Additionally the number of patients in the study fell short of the projected power calculation of 1254 women and there was no robust scientific method to assess medicinal compliance with subjective assessment only including questionnaires and bottle weights. These factors call into question the reliability of results and as there was a significant difference in outcome measures within the original stratum in terms of live birth rates (61% in LDA group vs 53% placebo RR 1.17 (95% CI 1.01 to 1.37 p=0.0466)) and notably those who became pregnant in the LDA cohort (ultrasound-confirmed pregnancy 74% LDA group vs 64% placebo RR 1.17 (95% CI 1.04 to 1.32 p=0.0113)). This difference was noted further on sensitivity analysis in this group although these results were not reported upon. Authors suggest the reason for this kind of discrepancy is that the LDA can prevent this phenomenon through the promotion of prostacyclin production in favor of vasodilation and implantation rates.

Overall, this study concludes that preconception initiated LDA does not increase the live birth rate nor reduce rates of pregnancy loss in women with one or two previous losses. Results support what we already know about the safety of LDA, notably at doses of 81mg, which is greater than the 75mg group typically prescribed in Irish obstetric practice. The overall results are backed up by that of existing studies. However, before firm recommendations can be made for clinicians it is important to perform further RCTs which can be guided by the methodology of this study.

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References

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