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Does Aspirin Still Have a Role during Pregnancy?

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Several recent studies have called into question the interest of aspirin in preventing some complications of pregnancy, preeclampsia in particular.

One of these studies concerned a population at high risk [1], and the other two low-risk populations [2, 3]. Among the explanations evoked by the authors of these studies to explain the absence of any difference between the placebo and aspirin groups, a statistical bias has been suggested.

In particular, the authors suggest that the trials that have demonstrated an effect from aspirin were those with only a few subjects, and that larger trials have found no difference. The authors add that, generally, small trials without any significant results might not be published, which would explain the apparent distortion.

We think that these arguments are simplistic, reductive, and (involuntarily) ignore other differences between the trials that found aspirin ineffective and those observing a positive effect.

What are these differences? What reflections might they nourish?

Our group's first publications [4, 5] involved patients at high risk of preeclampsia and especially of intrauterine growth retardation (IUGR), with vascular aspects. Two points must be mentioned.

(1) The risk level is important: when the EPREDA trial analyses stratified patients with an obstetric history, that is, severe IUGR (3rd percentile), death in utero or abruptio placentae associated with high blood pressure, by the number of such previous incidents (one, or two or more), the efficacy of aspirin was more marked for the patients

with two incidents (risk of recurrence: 25–30%) than for those with only one (risk of recurrence: 10–15%).

(2) The population was relatively homogeneous, and it is possible that a high risk level in a heterogeneous population would not lead to the same results. One example involves the degree of growth retardation (or even fetal weight), which was the principal end-point in our trial (which included more than 300 patients). It appears difficult to induce changes in this end-point in a population with inclusion criteria as diverse as insulin-dependent

diabetes before pregnancy or multiple pregnancy or chronic hypertension (which, as we know, is difficult to define). Two other points must be stressed: most important, both dose and beginning of treatment seem to be decisive factors in the efficacy of aspirin.

In our two trials, all patients before 20 weeks of gestation (14–20 weeks) were included, compared to 0–50% in all the larger trials. In some articles, inclusion occurred as late as 32 weeks, which is too late to have any chance to work, if aspirin is intended to affect the initial or at least the early stage of placental implantation. Our trials used doses of 150 mg aspirin, and we recommend initial doses of a minimum of 100 mg per day. Most of the trials without conclusive results used daily doses of 50, 60 or 70 mg.

Two arguments confirm the importance of the dose. First, a meta-analysis by Leitich et al. [6] has recently shown the influence of dose and time of treatment initiation on the efficacy of aspirin. The second argument is based on a recent study by Dumont et al. [7], on a series of 185 patients who received prophylactic doses of 100–150 mg of aspirin daily. A multiparameter study of these patients found two criteria strongly associated with treatment failure and recurrence of the previous disorder: these were lateness of treatment initiation and absence of a significant variation in bleeding time (with Ivy's method) under treatment. The latter result, which again points to the clinical efficacy of aspirin, highlights the importance of patients' individual sensitivity to aspirin, including doses that are sometimes inadequate.

Overall, several conclusions can be drawn from the studies to date: (1) aspirin has been partially (because it can only reduce the risk of recurrence) effective among

multiparas at high risk of preeclampsia or IUGR because of an obstetric history of one or two pathologic episodes; (2) the systematic prescription of aspirin does not seem useful for primiparas, the largest category of patients tested; (3) nor does the systematic prescription of aspirin seem useful for patients with a history of diabetes, chronic hypertension, or multiple pregnancies; (4) on the other hand, initially encouraging results [8, 9] suggest that one primiparous population may benefit from aspirin: women identified by a pathologic uterine artery Doppler. Two very large French trials (Erasmus in the Nord and the Seine Saint Denis trial) are testing the double hypothesis of (a) identification of at-risk primiparas by uterine Doppler, and (b) randomized use of aspirin or placebo among the patients so identified. The results of these two trials should be available by early 1999. In conclusion, we recall that there are important arguments in favor of using aspirin among patients with autoimmune disorders, especially among those with an antiphospholipid syndrome.

Moreover, the combination of aspirin with other products deserves more study: use with Calciparine, ketanserin, corticoids, even to nitric oxide donors.

Finally, another modality merits careful study – the prescription of aspirin before conception. We are currently doing this intuitively among patients who have not had successful pregnancy outcomes, despite early aspirin treatment.

In conclusion, aspirin remains appropriate for certain indications, and new modalities, either preconception or in combination with other products, ought to be explored.

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