

# **Women with recurrent fetal loss and antiphospholipid antibodies had high rates of live births when treated with low dose aspirin or placebo**

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Neil S. Pattison, Lawrence W. Chamley, Mary Birdsall et al. **Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial.** Am J Obstet Gynecol. 2000 Oct; 183:1008-12.

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## **QUESTION**

In women with antiphospholipid antibodies (APLA) and recurrent fetal loss, does low dose aspirin result in more live births than placebo?

## **DESIGN**

Randomized controlled trial with follow-up throughout the index pregnancy.

## **SETTING**

Recurrent miscarriage clinic at a large New Zealand hospital.

## **PATIENTS**

50 women were recruited over a 39 month period. All had a history of  $\geq 3$  miscarriages and positive antiphospholipid antibodies. This was defined as anticardiolipin GPL  $\geq 5$  or anticardiolipin MPL  $\geq 5$  or a positive lupus anticoagulant (defined as a high activated partial thromboplastin time or dilute Russell viper venom test or kaolin clotting time). The few women who were not tested antepartum and tested positive intrapartum were later excluded if they did not have persistently elevated antibodies postpartum.

All had comprehensive pre-pregnancy diagnostic investigations (including anatomical, microbiological and chromosomal assessment) that were normal.

Women were excluded if they had a history of thrombosis, systemic lupus erythematosus (SLE), current or planned use of corticosteroids, nonsteroidal anti-inflammatory drugs or heparin.

The trial was conducted on an intention to treat basis.

## **INTERVENTION**

Patients were randomly allocated to aspirin 75 mg per day or placebo. Gestational age at entry ranged from 30-98 days and was similar in both groups. Length of therapy was not specified.

## **MAIN OUTCOME MEASURES**

The main outcome measured was delivery of a live infant. Other outcomes included antenatal complications and neonatal morbidity.

## **MAIN RESULTS**

10 patients (5 in each arm) were excluded after randomization because of inappropriate inclusion (high anti-nuclear antibody titres or because a subsequent test for anticardiolipin antibodies yielded a negative result). This left 40 women (20 in each arm) for analysis.

There were no statistical differences between the two groups in terms of antibody levels or type or prior obstetric history.

80% (16/20) of women in the aspirin group and 85% (17/20) of the control group had successful pregnancies. These success rates were not statistically different. All losses (in both groups) were in the first trimester. There were no differences in neonatal morbidity, birth weight, prematurity, bleeding or other antenatal complications.

## **CONCLUSION**

Not all women with recurrent fetal losses and antiphospholipid antibodies are the same. Women without thrombocytopenia, SLE or thrombosis may represent a lower risk group. Women with low antibody titres may also be at relatively low risk. This is the first placebo-controlled trial among these types of patients. The results here demonstrated a high pregnancy success rate in both the aspirin and placebo group. Therefore, in certain patients, supportive care alone may be appropriate. Future trials in this area must stratify patients according to risk by antibody level and by clinical presentation.

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## COMMENTARY

The most appropriate way to treat women with recurrent fetal loss and APLA remains unclear. This is largely due to the fact that published trials involve a very heterogeneous group of patients, are often not randomized controlled trials and involve small number of patients. Thus, making the right choice for these patients is difficult especially since the rate of live births in subsequent pregnancies may be as low as 10% (1). Nonetheless, several trials have suggested that low dose aspirin and heparin is the regimen of choice for such women (2,3). In these trials the live birth rate in the aspirin group was 42-44% and in the aspirin/heparin group was 71-80%. Once again the trials represented a spectrum of patients. One included women with very low levels of antibodies and most of the patients had a positive lupus anticoagulant. In the other, patients with lupus anticoagulant were excluded and the patients had to have significant elevations in other antibody levels.

In this study Pattison and colleagues argue that low risk women may or may not even need aspirin alone. They justify the use of a placebo arm in their trial because the women were included if they had low levels of antibodies. They defined high-risk patients as those women with previous thrombosis or SLE. These patients were excluded. Their live birth success rate was very high (85% in the control arm and 80% in the aspirin arm). Is this because their patients were at such low risk that their chance of miscarriage is the same as the general population? Maybe, but they did include some patients with high anticardiolipin antibodies and positive lupus anticoagulant.

As with other studies the number of patients was small. The authors wanted to detect a 45% relative difference in live birth rates between the two arms (55% in the control group and 80% in the aspirin group). In order to yield a power of 80% the sample size would need to be approximately 100 patients. They had a sample size of 40. In addition they excluded 20% of the patients after randomization. This is a major problem. This means the analysis was not on an intention to treat basis and the potential for bias is great.

I commend the authors for trying to address the issue of heterogeneity of patients with recurrent fetal loss and APLA. However, the answers to our questions remain as murky as ever. The authors included women with very low antibody titres and some with higher levels. A significant number of patients also had a lupus anticoagulant.

Clearly, patients with high-risk clinical presentations (history of thrombosis) should be treated with aspirin and heparin. It may be reasonable to stratify other patients according to antibody levels. We know that higher APLA levels identify patients with a greater risk of clinical events (4). Therefore it would be reasonable to treat patients with high levels of anticardiolipin antibodies with aspirin or aspirin and heparin. Women with very low levels can be treated with supportive care alone or with aspirin. I favour using aspirin since it has no significant side effects (5). Based on previous data (3) I favour the use of aspirin and heparin for women with a lupus anticoagulant.

The final answer is not in. As Pattison and colleagues point out, future trials need to be larger and include patient stratification based on clinical features and antibody level and type. A large, multicentered, randomised controlled trial is required.

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