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CORRESPONDENCE

Antibiotic prophylaxis before amniocentesis: a proven and effective method to preserve fetal life

APGA trial (Giorlandino *et al*., 2009) is today the biggest randomized controlled trial (RCT) ever performed in prenatal diagnosis, designed accurately to eliminate all possible confounders and to concentrate the results exclusively on a unique variable: the antibiotic. In this phase, it was imperative to eliminate any bias and to administer the study in only one centre by only one operator. The strength of the study and its general validity is based on the fact that all possible confounders were eliminated, leaving only the antibiotic prophylaxis to 'make a difference' between the two groups tested.

In this trial we demonstrated an eightfold decrease in the abortion rate from 1/348 in the control group to 1/3031 in the treatment group. Also well suggested by Alfirevic and Pilu and reported in the paper as well, a multicentric trial among centres of similar experience is needed to investigate about the external validity of the trial. However, considering the particular study design and its results, it seems improbable that such a big difference (about 80%) between the two groups in terms of abortions would not be confirmed (even if in different proportions) in other centers.

Alfirevic and Pilu reported that Tabor *et al*. (1986) and Eddleman *et al*. (2006) described a miscarriage rate of two- to threefold increase in twin pregnancies over singletons. Concerning Tabor's study, we believe that after 23 years the improvement of the skill of the operator and the routine use of continuous-ultrasound guidance during the procedure dramatically reduced the abortion rate even in the multiple procedures. The authors did a minor mistake citing the Eddleman's FASTER database (Eddleman *et al*., 2006) giving that in this study were enrolled only singleton viable pregnancies.

The APGA trial demonstrated the important role of the infections in the outcome of the amniocentesis. In fact we speculated that preterm premature rupture of membranes could be caused by reactivation of an infection that is latent in the membrane. Therefore, considering that the presence of ureplasma and mycoplasma in the uterus is the first cause responsible for the rupture of the membranes (Papantoniou *et al*., 2001; Perni *et al*., 2004), it is improbable that they could come into the membranes from the skin both to the accurate disinfection of the skin and the use of all sterile disposable material for each procedure. Finally these pathogens are rarely present on the cutis. The ultrasound probe used to carry out the amniocentesis is 8-cm tall, therefore the needle needs to be longer because it must go throughout the needle-probe. As yet reported in the paper no bedrest was suggested, patient may resume all normal activities, deferring heavy work, strenuous exercise and sexual activity for 3 days.

Alfirevic and Pilu point out the attention on a crucial point: is the antibiotic prophylaxis effective in any gestational age? In our series the stratification by gestational age adjusted with the Mantel-Haenszel test (table not shown) showed that antibiotics reduced the rate of foetal death between 16 and 18 weeks of gestational age. Before 16 weeks of gestation, antibiotics reduced the rates of preterm premature rupture of membranes but not foetal death. After 18 weeks of gestation no treatment effect was recorded either for foetal death or preterm premature rupture. However, both before 16 weeks and after 18 weeks the sample size is too small (only 4176 cases) to detect a statistically significant difference between the two groups.

We chose a follow-up period of 4 weeks because other authors reported the same follow-up period (Tabor *et al*., 1986; Johnson *et al*., 1999; Perni *et al*., 2004; Eddleman *et al*., 2006). We strongly believed that a follow-up till birth was not suggested because it would introduce a huge bias related to other prognostic factors which differed from the short-term effect of amniocentesis.

Finally Alfirevic and Pilu reported some concerns about the reassurance for a worldwide use of antibiotic in pregnancy related to the results of the ORACLE. First of all ORACLE (Kenyon *et al*., 2001) has a lot of bias. The association of neurological damage and perinatal infection is well described (Jacobsson and Hagberg, 2004); probably is the prolonged exposure to the infections of these foetuses, in women whose membrane was already broken, that cause the damaging environment. Moreover, the administration of macrolides in ORACLE is completely different from APGA in quantity (10 g in ORACLE vs 1.5 g in APGA) and duration. On the other hand, the pharmacodynamics of azithromycin is well described and during pregnancy is safe, does not have teratogenic effects, and is effective against a wide range of microbes (Sarkar *et al*., 2006).

We are aware that, giving the highest clinical evidence of the APGA trial (Ib–Recommendation A), there will be inevitable worldwide consequences in the clinical guidelines, ethical and medico-legal practice. However, this is the price to pay to reduce abortion and pPROM after the amniocentesis.

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