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Letter to Editor

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A Critical Approach to Administration of Low-Dose Aspirin (LDA) to Improve Implantation Success

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Dear Editor,

Infertility has many causes and different pathogenesis, and there are some critical controversies against most of its therapeutic protocols. Some researchers showed that low-dose aspirin (LDA) has positive effect on ovary, fertilization and implantation for users of assisted reproductive technology (ART) such as in-vitro fertilization (IVF); but such researches are not enough and need to be investigated further. As opposed to the mentioned hypothesis, Akhtar et al (1)announced that: "Adjuvant treatment with aspirin and heparin do not improve IVF outcome." After a year, Salvatore Gizzo as a fan and defender of LDA administration announced that empirical administration without protocol can cause negative effects. He is of the conviction that LDA can increase uterine blood flow, vasodilatory and spiral artery remodeling and inhibits platelet aggregation (2). Finally we want to announce that the negative connotation of the words like inflammation, apoptosis and natural killer is not a reason that inhibiting such physiological phenomenon is always a good method. In Gizzo et al (2) research total number of follicles, size of follicles and number of mature oocytes were significantly increased after LDA administration and number of good quality embryos were decreased; but in spite of this decreasing he insisted on his hypothesis. The criticisms against the fans of LDA fall into these items. First, some of these papers used the mice dose 7.5 mg/kg 2 times a day, but they neither performed the pilot dose-assaying examination (in 4 groups: low dose, high dose, toxic dose and killing dose) nor cited the reason of using this number. Based on the Food and Drug Administration (FDA) guideline (3) their selected dose (15 mg/kg) is equivalent to human routine low dose 81 mg (of course in a 66.9 kg person) (Table 1), but it seems they employed this correct dose number only out of imitation from each other. Second, aspirin even in low dose may cause side effects.

Table 1. How to Convert Mice Dose to Human

Organism	Proportion
Mice mg/kg	37
Human mg/kg	3

Third, the reproductive system of the mice and rat is not sufficiently similar to human system. Forth, the inflammation of endometrium during luteal phase is per se a helping phenomenon for implantation, so it is not a logical idea for research proposals to use anti-inflammatory drugs.

Inoue et al (4) said that inhibition of natural-killer cells (NK) - with aspirin or prednisolone - results in better interface between embryo and maternal tissue (4) with citing the reference (5); but Clifford et al (5) believed alteration - stimulating or inhibiting - in population of NKs causes failure in early pregnancy and needs more investigation. Also, Inoue et al (4) cited the reference (6); but the mentioned reference had found no significant relation between placebo and LDA group. Haapsamo et al (6) have done the research based on the conviction that LDA can improve remodeling of spiral arteries; but it seems wrong; because decidual NKs improve remodeling of spiral arteries (7) through increasing IFN-Gamma and TNF-alpha (8). Also IFN-gamma is an apoptosis inducer (9) which seems necessary for implantation period; but the author of reference (9) counts this feature as a harmful process. It be noted that apoptosis is per se physiologic and not pathologic most of the times.

At the end of the letter we notify that designing a correct hypothesis and a valid protocol is a *sine qua non*. Regarding the review data, our thought is that LDA may have positive effects on ovary and negative effects on endometrium. Thus very short-term administration of LDA (only at the time of ovulation) should be performed in future researches.

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