



Letter to the Editor

Fertility-enhancing agents



Trends in women's older age at first birth with an increased availability of diagnostic and treatment modalities are associated with needs of fertility treatment in modern society.¹ Assisted reproductive techniques (ARTs) might be one of the impressive methods to achieve parenthood in couples.^{2–4} However, many couples might have strong negative experience of ART, which result in an increased use of complementary and alternative medicine, such as herbal medicine to assist or enhance their fertility.¹ There is no doubt that women, especially in the oriental society may face the social pressure and psychologic stress, which enforces these certain subfertile women with involuntary childlessness to “try” or “do” something for getting baby.¹ Nutrition, essential trace elements and certain “nature or concentrated compounds” are reported to have an ability for improving fertility.⁵ Unfortunately, the mechanisms of these “fertility-enhancing” reagents are still uncertain. Anti-oxidant might be one of the most common proposed mechanisms. It is well known that oxidative stress has the negative impact on cellular survival and longevity. Oxidative stress also increases programmed cell death. Oxidative stress also interfere maturation of ovum and is associated with ageing process of eggs.^{6,7} Oxidative stress impairs function of trophoblasts and fibroblasts and disturbs normal neovascularization, which involves many physiological and pathological processes, including embryo implantation and wound healing.^{8–11} All might contribute to decrease the reproductive performance in women. In the October issue of the *Journal of the Chinese Medical Association*, we read Yilmaz's paper with interest.¹² The following comments are not against the value of Dr. Yilmaz's contribution, but we hope to have a further discussion.

The authors used a rat model to evaluate the effect of ginger on reproduction in female rats.¹² The study separated these female rats into three groups, including control, 100 mg ginger and 200 mg ginger.¹² Furthermore, the treatment duration was separated into either 5 day or 10 days. In the 5-day ginger treatment, the results showed that only 100 mg ginger might have improvement of female reproductive performance, including a significantly increased antral follicle count, an increased expression of vascular endothelial growth factors in both ovarian cortex and stroma. But it is relatively surprising that these positive effects of fertility-enhancement of female rats did not appear apparently in the 200 mg ginger treatment group. This observation seemed to be consistent in the 10-day

ginger treatment. The positive effect only appears in the 100 mg ginger group. The corresponding positive parameters for fertility enhancement include a dramatic increase of vascular endothelial growth factor concentration of endometrium and an increased expression of endothelial nitric oxide synthase in the ovarian stromal tissue. Similar to the 5-day treatment, these “positive” effects seemed to be not apparent in the 200 mg ginger treatment group. The current study is interesting and worthy of further discussion.

First, it is relatively challenged that the therapeutic effect of the ginger in the current animal study is not dose-dependent. It is relatively confusingly found that 100 mg ginger was effective but 200 mg ginger was ineffective. We are wondering why the authors used 100 mg and 200 mg as the tested dose? We are interested in the rationale or primitive data of authors to treat the female rats by 5 days or 10 days. Did the authors have performed the pre-test to investigate the optimal dose or optimal period of ginger on the female rats? For example, why the authors did not use 150 mg ginger as a tested dose or use 7 days or 14 days as the treatment duration? Without the titrated dose or titrated time. It might be overstated that the current study is the first in the literature to investigate the optimal dose and duration of the ginger powder on the female reproductive system.

Second, the authors used ovarian antral follicle count, the expression of vascular endothelial growth factor in ovarian cortex, stroma and uterine endometrium as a parameter to monitor the reproductive performance of female rats. We totally agree that antral follicle count is a very important parameter to predict the ovarian reserve. Low antral follicle counts, for example, less than 4 on Day 2 of the menstrual cycles in human are considered as one of important parameters to define patients with diminished ovarian reserve or poor ovarian response,¹³ since this parameter is associated with success rate of ARTs (pregnancy rate ranged from 2 to 4% per cycle). However, we concern very much for authors who used vascular endothelial growth factors as a marker. If ginger is a powerful agent for anti-oxidant, hypoxic inducible factor 1, which represents as a key molecule in the reaction of cells to hypoxia.¹³ In addition, the ratio of insulin-growth factor 1/insulin-like growth factor binding protein 3 might be a better indicator to qualify the oocyte quality and maturity.¹³

Finally, the appropriate adaption of endometrium is very important for embryo implantation.¹⁴ The authors claimed their study also supposed that ginger could enhance implantation in

rats in long term, based on a significant increase of endometrial vascular endothelial growth factor on female rats treated with 10-day 100 mg ginger therapy. It is also surprising to find that 10-day 200 mg ginger treated female rats had a lower expression of endometrial vascular endothelial growth factor than 10-day 100 mg ginger treated female rats did. It is also interesting to find that 5-day 100 mg ginger, 10-day 100 mg ginger and no ginger treated female rats had a mean of 80.86, 44.86 and 79.86, respectively. Although no statistically significant difference was noted in the 5-day evaluation groups, it is relatively confusing that a higher ginger dose is and a lower endometrial vascular endothelial growth factor is. In fact, dynamic change of cytokines and/or growth factors are very critical for the embryo implantation, since this implantation window should be evaluated in continuous and sequential.¹⁴ Only one shot done on one targeted time might increase the risk of overstatement of the finding.

At the end, our comments did not critique the value of Dr. Yilmaz's contribution; however, we are looking forward seeing the reply by authors.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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