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Review article

Glycative stress and anti-aging: 11. Glycative stress and infertility.

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Abstract

Infertility is a state where a couple without any particular disease attempts to conceive a child through sexual intercourse without contraception, although after a certain period, are unable to succeed in becoming pregnant. "A fixed period" to judge infertility differs depending on countries and organizations. The Japan Society of Obstetrics and Gynecology generally stipulates the period as one year. The percentage of infertility in both sexes is as follows: males, 40%; females, 40%; both sexes, 15%; unclear, 5%. Three main causes of infertility are ovarian dysfunction, male infertility, and egg failure. The biggest cause of ovarian dysfunction is polycystic ovary syndrome (PCOS). As infertility treatments, there is a timed intercourse where the couple is advised to have sexual intercourse during the expected time of ovulation, and pharmacotherapy is conducted by an oral dose and an injection of hormone drugs. If patients do not become pregnant after receiving these treatments for 6-12 months, assisted reproductive technology (ART) will be considered as the next choice. In ovary cells or vascular endothelial cells of females suffering from polycystic ovary syndrome (PCOS), a high expression of AGEs (advanced glycated end products) and RAGE (receptor for AGEs) are admitted. As a rise in toxic AGE (TAGE) is assumed to be related to a reduction in the number of cells, there is a possibility that a decline in blood glucose stress level before TAGE begins to rise may suppress the reduction of the number of cells caused by the destruction of follicles. An administration of benfotiamine, metformin, and sitagliptin in the cases where patients did not succeed in becoming pregnant despite continual ART, was effective in reducing levels of N^{ε}-carboxymethyl lysine (CML) and TAGE, and for increasing the number of good embryos, which led to a rise of continued pregnancy ratio. As there is a possibility that a suppression of glycated stress may improve follicular development, embryonic development and continuation of gestation, it is considered that the improvement of a physical condition where AGEs accumulate excessively will lead to a new method of curing infertility.

***KEY WORDS*:** infertility, toxic AGE (TAGE), N^{ε}-carboxymethyl lysine (CML), pentosidine, assisted reproductive technology (ART)

1. Introduction: what is infertility?

Infertility is a state where a couple without any particular disease attempts to have a child through sexual intercourse without contraception, although after a certain period, are unable to succeed in becoming pregnant [1]. "A fixed time period" to judge infertility differs depending on countries and organizations. The Japan Society of Obstetrics and Gynecology generally stipulates the period as one year [2], while the World Health Organization (WHO) designates infertility to be "the case where infertility continues for one year" [3]. American Society for Reproductive Medicine (ASRM) stipulates that "infertility can be defined as a case where an infertility period continues for one year, however, in the case of females in their late 35's, they are advised to start examinations after six months, as six months' infertility period is long enough to show an infertile state" [4]. Generally, it often happens that young couples naturally become pregnant, even after they have passed a long period of infertility."

In the case of Japanese couples who wish to have a child, it is common for 65% of them become pregnant within six months, 80% within one year, 90% within two years, and 93% within three years, if the couples have sexual intercourse without contraception [5]. Regarding the ratio of occurrence of infertility based on gender, it is reported that males are responsible in 40%, females for 40%, both sexes for 15%, and unclear for 5% of the cases.

The causes of infertility for males are assumed to be spermatogenic dysfunction, seminal passage obstruction, vice genital disorders, and male sexual dysfunction. Many of

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these causes are attributed to problems related to sperm, such as azoospermia, oligo-astheno-teratozoospermia syndrome, immotile spermatozoa, and teratozoospermia. In the cases of females, two factors, fallopian tube patency failure and ovulation disorders, are said to cause infertility. The two factors are caused by cervical issues, endometriosis, uterine fibroid, and uterine malformations. As for females, these infertility causes work compositively, resulting in complex symptoms. About 10% of all couples are infertile due to these causes, and in many cases both genders are responsible for the situation. On the other hand, as infertility derives from dysfunctions of sperms and ovum, it is considered necessary to tackle this problem through the long-term study of infertility treatment methods in a step-by-step manner [5]. In major developed countries, about 10% of all couples suffer from infertility. Among them, those who suffer because of anatomical, immunological, genetic, and endocrinological reasons account for 5%. The main reasons include infection, environmental factors, and social factors [6].

Infertility treatments range from timing treatment where sexual intercourse is recommended based on the expected time of ovulation, and chemotherapy including oral administration/injection of hormone drugs. If a couple receives these treatments for six to twelve months and still does not become pregnant, they are recommended to undergo other methods, such as assisted reproductive technology (ART). ART refers to treatments which deal with ovum or sperm as follows: *in vitro* fertilization (IVF), IVF + intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer, and zygote intrafallopian transfer (ZIT). Globally, IVF and IVF + ICSI are the most prevalent [6]. The number of births based on ART in Japan was 215,755 in total until the year 2008. One out of 50 babies was born through ART [7].

2. Infertility and glycated stress

Three major causes of infertility are ovarian dysfunction, male infertility, and egg failure. The largest factor that causes ovarian dysfunction is polycystic ovary syndrome (PCOS). PCOS is said to occur mainly due to insulin resistance. An administration of metformin, which is an antidiabetic drug of biguanide medicine, is effective in improving the ovulation and pregnancy ratios [8,9]. In addition, as anxiety, stress, aging, obesity, being underweight, shortage of exercise, shortage of sleep, drinking, smoking, and irregular eating habits cause insulin resistance, even in the case of ovarian dysfunction except PCOS, metformin is effective in improving embryonic development and ratios of pregnancy [10]. Some of the egg tract disorders or implantation disorders are related to insulin resistance.

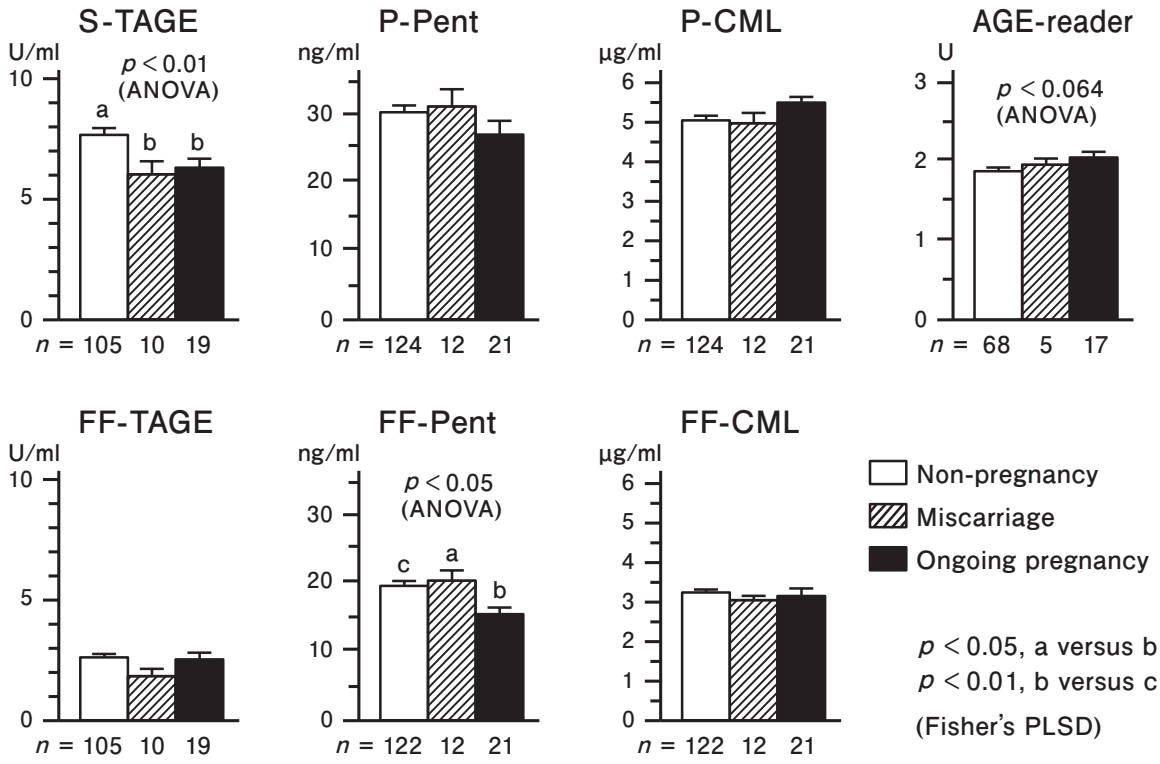

Fig. 1. **Concentrations of pentosidine and CML in plasma.**

Results are expressed as mean ± SD. Concentrations of pentosidine and CML in plasma (P-Pent and P-CML), those of TAGE in serum (S-TAGE), those of Pent, CML and TAGE in follicular fluid (FF-Pent, FF-CML and FF-TAGE), and skin AGE estimates by AGE-Reader™ were compared among women whose IVF/ICSI resulted in no pregnancy, miscarriage, and ongoing pregnancy. AGE, advanced glycation end product; CML, N^{ε}-carboxymethyl lysine; Pent, pentosidine; TAGE, toxic AGEs : IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; S, serum; P, plasma; FF, follicular fluid; ANOVA, one way analysis of variance; SD, standard deviation. The figure is adapted from Reference 17.

There are several reports concerning the relationship between infertility and AGEs (advanced glycation end products). According to these reports, in the case of ovary cells or vascular endothelial cells of females suffering from PCOS, a higher expression of AGEs and RAGE (receptor for AGEs) are observed [11], while PCOC females whose postprandial blood glucose levels are higher despite normal levels of fasting glucose levels showed a higher expression of serum AGE value and monocyte rage (RAGE), compared to healthy females (*Table 1*) [12]. Furthermore, pentosidine is shown to be observed in primordial oocytes, primary ovarian follicles, and closed follicles, which increase with aging [13]. Based on the fact that apoptosis of cells occurred when AGEs were added to human chorionic cell cultures, it is shown that there is a possibility that AGEs inflict injuries to implantation and placental function [14]. Moreover, protein that develops AGEs, or glyoxal, delays the cleavage ratio of embryos in embryonic development of the ova [15].

Causes of infertility have something in common with type II diabetes. The relative shortage of insulin in follicles, due to insulin resistance, increase glycated stress and oxidative stress, and cause postprandial hyperglycemia by the reducing the capacity of insulin secretion. In addition, due to an increase of AGE production in the tissue, a high expression of RAGE appears. Owing to this, vascular endothelial cell disorders, thrombophilia, and proinflammatory are accelerated in the follicles or the microvascular endothelial cells, which facilitates maldevelopment of the ova or follicles, as well as follicular atresia. On the other hand, infertility occurs, even in the cases where nothing but the insulin resistance in the follicles/endometrial and the reduced capacity of insulin secretion are observed. According to some reports, there are cases where infertility does not accompany general symptoms, such as hyperglycemia or abnormalities of diabetes test values [16].

3. Glycated stress and assisted reproductive technology (ART)

Concerning the relationship between the assisted reproductive technology ART and an accumulation of AGEs, one hundred fifty-seven results have been reported [17]. Toxic AGE (TAGE) , pentosidine, and N^{ε}-carboxymethyl lysine (CML) in the serum and the follicular fluid showed a significantly negative correlation with the number of growing follicles, estradiol (E2) values in serum, collected eggs, fertilized eggs, and good embryos. However, there was not a correlation between pentosidine and CML in the plasma and the amount of accumulated AGEs in the skin. Additionally, the value of pentosidine in the follicular fluid was significantly higher in the cases of non-pregnancy and abortion, compared to those of continued pregnancy (*Fig. 1*). Age, serum TAGE, and pentosidine in the follicular fluid were considered to be predictive factors of continued pregnancy. Furthermore, when we compared the females whose TAGE in the serum is over 7.24 U/mL and those with lower values, the declining trend of the number of collected eggs and the ratio of continued pregnancy were much larger than the declining, due to the aging in the case of the former, compared to the latter. On the other hand, in the case of females whose TAGE in the serum is greater than 7.24 U/mL, even though their day-3-FSH (follicle-stimulating hormone) was normal, neither the number of collected eggs nor the ratio of continued pregnancy was enough. For this reason, it is assumed that the rise of TAGE is related to a reduction in the number of follicles, showing that if glycated stress is reduced before TAGE increases, it is possible to restrict the reduction of the number of follicles due to the destruction.

The effect in improving the performance of ART was verified through the administration of benfotiamine (vitamin B1 derivatives), metformin (metformin), and sitagliptin, which was an inhibitor of DPP-4 (dipeptidyl peptidase-4). In seven cases of subjects who failed to conceive after more than three implementations of ART, we administered 75 mg of bentotiamine a day for two months, and then conducted ART once again. As a result, CML and TAGE in the follicle fluid significantly declined, which led to an increase of the ratio of good embryo per one egg [16]. Though repeated ARTs were not effective, metformin was assumed effective to thirty-three cases of subjects (37.5 ± 0.8 years old) of non-PCOS. Starting from the third day of their menstrual cycles, we administered 125 mg of metformin a day, and then increased the dose volume by 125 mg per five days. Finally, we continued administering 500-750 mg until 8-12 weeks after the beginning, and then conducted ART on the subjects. The group showed a remarkable increase in follicle diameter, serum E2 values, E2 values in the follicle fluid, the number of good embryos, as well as the ratio of continued pregnancy, compared to the group to whom metformin was not administered [9]. We administered 50 mg of sitagliptin a day for one month to forty-four elderly females (41.0 ± 0.5 years old) who had not received a good result after repetitive ART, despite the ovarian hyperstimulation,

Table 1. Levels of AGEs and RAGE expression..

Variable	Control group (n = 22)	PCOS group (n = 29)	p
Serum AGEs (U/mL)	5.11 ± 0.16	9.81 ± 0.16	< 0.0001
RAGE expression (%)	7.95 ± 2.61	30.91 ± 10.11	< 0.02

The results are expressed as means ± SEM, $p < 0.05$. AGEs, advanced glycation end products; RAGE, Receptor for AGEs; PCOS, polycystic ovary syndrome; SEM, standard error mean. The figure is adapted from Reference 11.

and then conducted ART once again. As a result, the number of growing follicles, collected eggs, embryos, and good embryos, as well as the ratio of continued pregnancy increased, compared to the cases of ART where sitagliptin was not used [16].

There is a possibility that a suppression of glycative stress in the reproductive technology will work effectively on the growth of follicles and embryos, as well as on the continuation of pregnancy. Improvement of AGE accumulation status is considered to be a new countermeasure to reduce infertility [18].

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Conflict of Interest Statement

The authors claim no conflict of interest in this study.

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