

# Could Advanced Glycation End Products Explain the Poor Response to Controlled Ovarian Hyperstimulation in Obese Women?

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## Abstract

Obesity, a worldwide pandemic, adversely impacts ovarian function. The pro-inflammatory Advanced Glycation End Products (AGEs) and their cell membrane Receptors for AGEs (RAGE) are elevated in the serum and tissues of obese women, respectively. Recent data have shown that AGEs contribute to alterations in the ovarian microenvironment. This review presents and summarizes important clinical and experimental studies pertaining to the role of the AGE-RAGE system in obesity-related ovarian dysfunction. It also discusses the role of the anti-inflammatory soluble Receptor for AGEs (sRAGE) in ovarian function and its changes in obesity and following unhealthy dietary habits. Data to date demonstrated that the AGE-RAGE system affects granulosa cell function and oocyte meiosis. Follicular fluid AGEs and sRAGE have been related to *in vitro* fertilization outcome. Thus data suggest that obesity-related alterations in the AGE-RAGE system and changes in circulating sRAGE level could potentially compromise ovarian response to controlled ovarian hyperstimulation and could adversely impact oocyte competence and ultimately fertility outcome. Finally, there is a critical need to unveil the mechanistic actions of the AGE-RAGE system at the level of the oocyte and its surrounding granulosa and theca cells in order to better improve ovarian response to controlled ovarian hyperstimulation in obese women.

**Keywords:** Advanced glycation end products; RAGE; sRAGE; obesity; controlled ovarian hyperstimulation; IVF

## Introduction

Obesity is clearly becoming a worldwide pandemic and is now considered a disease that recent data have shown it affects more than one third of the adult population in the United States [1]. Obesity affects female reproduction [2-6] since compelling data showed that obese women are more predisposed to subfertility [7], have increased risk of miscarriages [8] and are more prone to having pregnancy complications such as gestational diabetes and preeclampsia [9]. As for subfertility, obese women are more predisposed to anovulation [7], have longer time to spontaneous

conception [10,11] compared to normal-weight women. As far as outcome of assisted reproductive technology, obese women undergoing Controlled Ovarian Hyperstimulation (COH) require higher doses of gonadotropins (whether or not due to fat distribution is still controversial). Thus, serum concentrations of gonadotropins have been shown to be inversely correlated to body weight because the pharmacokinetics of the medication is affected by adiposity [12]. For example, corifollitropin alfa is approved as a 100 µg dosage for patients weighing ≤60 kg and as a 150 µg dosage for patients weighing > 60 kg in women < 36 years of age [12]. Although controversial [13], we and others have shown that obese women have poorer IVF outcome as represented by the number of oocytes retrieved and number of mature oocytes [14,15], poorer fertilization and implantation rates, and lower clinical pregnancy rates and live birth rates [16]. Recently, we have demonstrated that in conventional IVF, but not in minimal stimulation IVF, the number of total oocytes retrieved and MII oocytes were significantly lower in obese compared with normal BMI women [15]. This suggests that female adiposity might impair oocyte number and maturity in conventional IVF but not in minimal stimulation IVF and that mild ovarian stimulation might yield healthier oocytes in obese women. Additionally, several studies, including ours, have shown that obese women have significantly lower ovarian reserve as represented by serum Anti-Müllerian Hormone (AMH) levels--one of the best markers of ovarian reserve--compared to normal-weight women [3,14,17]. On the other hand, an elevated serum AMH level and/or high Antral Follicle Count (AFC) by ultrasound can predict exaggerated ovarian response and ultimately ovarian achange with weight as compared to serum AMH [21].

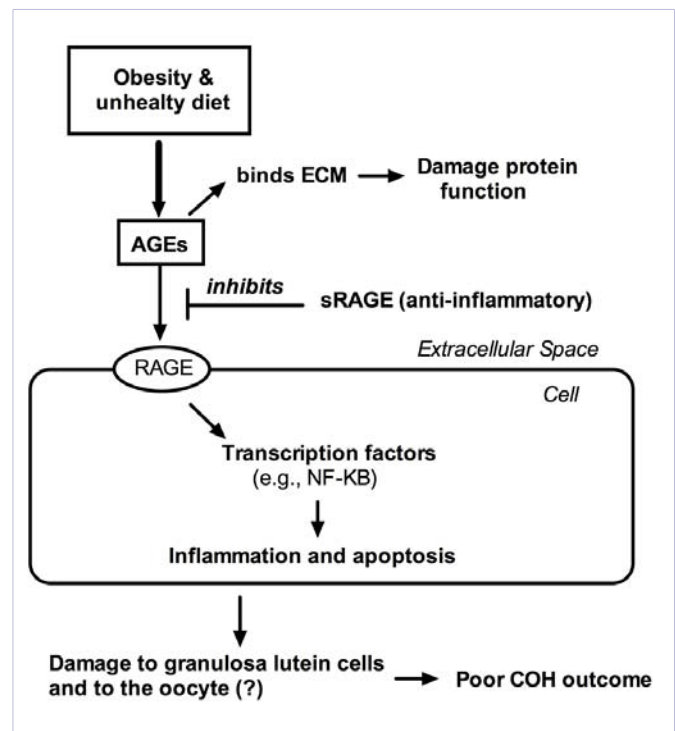
Advanced Glycation End Products (AGEs) are highly reactive pro-inflammatory molecules that have been shown to play a pathogenic role in obesity and its adverse outcomes [22-27]. AGEs are the products of a chemical reaction called Maillard reaction in which the carbonyl group of carbohydrates reacts

non-enzymatically with amino groups of proteins [28,29]. They constitute a heterogeneous group of compounds of more than 20 members, such as N-carboxymethyl-lysine (CML), pentosidine, 1,2-dicarbonyl precursor compounds glyoxal, and methylglyoxal. They play a role in the pathogenesis of type 2 diabetes mellitus, cardiovascular disease, inflammation, obesity, aging, and reproduction [22,23,25,26,30-33]. We and others have demonstrated that the AGE system is involved in ovarian dysfunction and potentially obesity-related ovarian alterations [6,22-27,34,35]. The purpose of this article is to underline and call attention to AGEs as potential molecules that could explain some of the mechanisms involved in obesity-related ovarian dysfunction. The review will provide mechanistic information regarding the pathogenesis of ovulatory dysfunction in obesity that could support the development of new therapeutic agents, such as AGE blockers, as a novel strategy to treat and/or prevent ovarian dysfunction in obese women.

### AGEs and their Two Receptors RAGE and sRAGE

AGEs are physiologically formed by a non-enzymatic modification of proteins and lipids by carbohydrates [24,36-38]. Advanced glycation results in irreversible cross-linking of proteins, and loss of protein structure and function [37,39,40]. AGEs are formed slowly under physiological conditions but they form at accelerated rate in pathologic states such as diabetes, oxidative stress, aging, and obesity [28,30,32,41-43]. Once formed, they damage cellular structures via a number of mechanisms [24,36]. Pentosidine and CML are well characterized AGEs and have been used as markers of AGE accumulation in various bodily tissues [23,34,44]. AGEs play a pivotal role in the pathogenesis of cardiovascular disease [45-47] and more recently, obesity-related ovarian dysfunction [6,27]. They can be either the trigger or the result of oxidative stress [35]. After their formation, AGEs are transported to diverse tissues via the circulation where they cause cellular damage by a number of different mechanisms. In one mechanism, AGEs can damage cellular structures via formation of cross-links between molecules in the basement membrane of the extracellular matrix e.g., collagen [23,24,36]. In another mechanism, the interaction of AGEs with their pro-inflammatory cell membrane receptor RAGE induces inflammation and apoptosis while the circulating sRAGE acts as decoy by binding the circulating AGEs and preventing AGE-RAGE interaction, thus conferring an anti-inflammatory role (Figure 1) [23,24,36].

In addition to RAGE and sRAGE, AGEs bind to a multitude of receptors such as CD36, lectin-like oxidized low-density lipoprotein receptor-1, and macrophage scavenger receptors [48-52]. Interestingly, RAGE is not solely a receptor for AGEs but is a multi-ligand member of the immunoglobulin superfamily [53-55]. RAGE is activated by many members of the proinflammatory S100/calgranulin family, amyloid fibrils, amphotericins, and High Mobility Group Box 1 (HMGB1) [56]--molecules known to induce pro-inflammatory cytokines [57]. RAGE is expressed in several tissues such as heart, lung, eye, immune cells, mammary gland, pancreas, stomach, prostate, endothelial cells, embryonic tissue, testis, and ovary [39]. This receptor is composed of



**Figure 1:** Obesity and unhealthy diet increases the levels of systemic AGEs. The interaction of AGEs with their receptor RAGE results in the generation of oxidative stress and activation of pro-inflammatory transcription factors such as Nuclear Factor kappa-B (NF-κB) leading to inflammation and apoptosis. AGEs could also bind to the Extracellular Matrix (ECM) causing tissue damage. The sRAGE receptor prevents the ligand AGEs from binding to their pro-inflammatory receptor RAGE. COH: Controlled Ovarian Hyperstimulation.

an extracellular region containing one "V"-type and two "C"-type immunoglobulin domains [39]. In healthy adults, RAGE is expressed at a low basal level in the tissues. The up-regulation of RAGE has been associated with diverse pathological events, such as diabetes, atherosclerosis and others [58]. RAGE activates several signaling cascades with significant and wide-ranging impact on inflammatory and apoptotic gene expression profiles, such as activation of the transcription factor nuclear factor-kappa B (NF-κB) (Figure 1) [59]. Furthermore, activation of RAGE induces a positive feedback loop by upregulating its own expression [59].

In addition to its full-length and membrane-bound form RAGE, a number of isoforms of RAGE have been identified [60,61]. In particular, RAGE has been shown to exist in a soluble isoform termed sRAGE that contains the same V-type and C-type regions found in RAGE but it lacks the transmembrane and cytosolic domains [60,61]. Consequently, sRAGE is found in the extracellular space and is capable of binding AGEs prior to their interaction with RAGE [27,60,61]. The sRAGE receptor is produced primarily by two mechanisms: a) from the cleaving actions of ADAM10 and MMPs on cell surface RAGE [62,63] or b) alternatively spliced pre-mRNA form of the receptor known as endogenous sRAGE [64,65]. Studies in animals have illustrated largely beneficial effects in reducing vascular and inflammatory

stress and, thereby, preventing long-term tissue damage in models of diabetes and inflammatory disorders [66,67].

### **Unhealthy Diet, as Exogenous Source of AGEs, can Affect Ovarian Function**

In addition to AGEs that form within the body, AGEs also exist in food. AGEs are naturally present in uncooked animal-derived foods, and cooking results in the formation of more AGEs within these foods [68,69]. In particular, grilling, broiling, roasting, searing, and frying accelerate the formation of new AGEs [68,69]. Dietary patterns have clearly shifted in the past decade especially in the Western countries and they now contain high levels of refined starches, sugar, saturated fats, and omega-6 fatty acids [70]. Dietary patterns high in refined starches, sugar, and saturated and trans-fatty acids, and poor in natural antioxidants and fiber from fruits, vegetables, and whole grains, and omega-3 fatty acids could cause activation of the immune system leading to excessive production of proinflammatory cytokines and reduced production of anti-inflammatory cytokines [70].

After the ingestion of an unhealthy diet, AGEs can get absorbed in the gastrointestinal tract [42,71] and then get deposited in various tissues including the ovaries. Approximately 10% of the ingested AGEs are transported into circulation: one third of which is excreted by the kidneys while two-thirds linger in the body and bind to several tissues [72]. In rats, a study demonstrated that a high-AGE diet increased serum levels of AGEs and upregulated ovarian RAGE [34]; an effect that was reversed by the ingestion of a low-AGE diet, the administration of an AGE blocker [73-75], the use of weight loss medication such as orlistat [76], and even exercise [77]. Additionally, a study by Diamanti-Kandarakis, et al. showed that long term consumption of AGEs was associated with higher levels of fasting glucose, insulin and serum AGEs, as well as increased AGEs localization and RAGE staining in rat ovarian tissue [34]. Interestingly, diet-induced weight loss has been shown to increase serum sRAGE levels [26,78], and higher baseline sRAGE was associated with better weight loss outcome following bariatric surgery [79].

### **Obesity is an Inflammatory State Characterized by Alterations in the AGE-RAGE System**

Obesity is a state of chronic inflammation characterized by elevated systemic AGEs [27,80]. Adiposity is associated with increased "pro-inflammatory" M1 macrophage accumulation in the adipose tissue [81]. Hence, in obesity, the adipose tissue is said to be "M1 polarized" [82]. The AGE-RAGE system plays an important role in modulating systemic inflammation [25,42,83]. Circulating AGEs have been shown to correlate with as C-Reactive Protein (CRP) and other oxidative stress markers [42,83,84] and induce tissue injury [83,85]. In humans, dietary AGE restriction reduced plasma levels of CRP, Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), and vascular cell adhesion molecule-1 [84,86].

AGEs are linked to adiposity [27,28]. In rats, AGEs stimulate adipogenesis by upregulating Akt signaling pathway [87], an action that was reversed by the AGE breaker alagebrium and by Akt inhibitor [87]. A recent study measured the effects of various

mouse diets containing high- or low-AGEs in the presence of high- or low-fat content on mouse weight and epididymal fat pads [88]. That study reported a significant difference in weight gain and epididymal fat pad weights in mice that received the combination diet "high-AGE and high-fat" [88]. The authors also demonstrated that leptin, TNF- $\alpha$ , interleukin-6, and myeloperoxidase levels were significantly higher in the combination "high-AGE and high-fat" group [88]. The authors concluded that a diet containing high AGEs in the presence of high fat induces weight gain in mice. High-fat diet induces peripheral inflammation and weight gain in a RAGE-dependent manner [25]. In one study [22], C57BL/6 RAGE  $-/-$  mice was provided a high-fat diet to induce obesity and they showed upregulation of RAGE. In another study [25], mice provided a high-fat diet induced expression of the RAGE ligand HMGB1 and CML epitopes in liver and adipose tissue [25]. Genetic deficiency of RAGE prevented the effects of high-fat diet on weight gain and adipose tissue inflammation [25].

We and others have shown that plasma levels of the anti-inflammatory sRAGE were inversely correlated with BMI [89]. sRAGE levels were shown to be significantly reduced in obese women compared to normal-weight women [26] and short-term weight loss program led to a significant increase in plasma sRAGE levels [26]. We recently demonstrated that sRAGE levels were negatively correlated with BMI in 31 reproductive-aged women ( $r = -0.5, p < 0.001$ ) [27]. The lower levels of sRAGE in the obese women might indicate that the intraovarian levels of AGEs exert an exaggerated effect at the level of the oocyte thus altering the molecular and energetic reserve that are needed to sustain normal meiosis in the oocyte [35]. Interestingly, caloric restriction induced weight loss increased serum sRAGE levels by approximately 150% [90] and sRAGE is expressed by inflammatory cells, such as monocytes and macrophages [91] and its production reduced systemic inflammation [92-97].

### **Controlled Ovarian Hyperstimulation in Obese Women and the AGE System**

Although infertility associated with obesity may be partly attributed to changes in the endometrial gene expression at the time of implantation [98], studies suggested that oocyte quantity and quality is also an important factor in obese women trying to conceive via assisted reproductive technology [99]. Hence, the mechanisms by which obesity causes ovarian dysfunction and poor conception rates are not completely understood. Obesity-related anovulation has been well documented to occur due to a defect in luteinizing hormone (LH) pulsatility [100]. Although infertility associated with obesity has been related to anovulation [7], data have shown that the time to spontaneous pregnancy is significantly longer in obese women even in those who have regular menstrual cycles [10-11]. Despite data pertaining to obesity and IVF success from individual centers is controversial [101-103], data from large national studies showed that, obese women undergoing COH with oocyte retrieval for IVF have significantly worse outcomes compared to normal-weight women [104-105].

Because AGEs are elevated in obese women, it is important



to assess the effect of AGEs on oocyte competency during COH for IVF. AGEs contribute to perturbations of the ovarian microenvironment leading to lower fertility status [35]. Diamanti-Kandarakis, et al. [106] demonstrated that human glycated albumin, used as a source of AGEs *in vitro*, interferes with LH action in human KGN granulosa cells by causing a sustained activation of the ERK1/2 pathway which is critical for normal folliculogenesis and ultimately ovulation. Additionally, Piperi, et al. [107] demonstrated that human glycated albumin inhibited the insulin-mediated Akt phosphorylation and significantly reduced GLUT-4 levels (glucose transporters) on KGN cell membrane [107]. In that study, human glycated albumin also significantly reduced GLUT-4 translocation to the cell membrane when added to insulin *in vitro*. Since the competency of the oocyte is highly influenced by glucose intracellular action inside the cumulus oocyte complex and the follicular fluid [108], these findings indicate that AGEs could alter folliculogenesis and ultimately ovulation. AGEs have been shown to induce meiotic delay/arrest in mouse oocyte [109], as represented by spindle aberrations, chromosomal misalignment, abnormal chromatin condensation, more chromosomal lagging, changes in mitochondrial distribution, and altered inner-mitochondrial glutathione redox potential [109]. All these functions are critical for oocyte fertilization and embryo development.

Literature from assisted reproduction technology studies partly elucidated the impact of AGEs on COH outcome. One study [110] demonstrated that higher levels of AGEs in the follicular fluid and the serum negatively correlated with follicular growth and oocyte fertilization, indication diminished fertility. Another study [111] reported a borderline positive correlation between follicular fluid sRAGE and the number of oocytes retrieved following COH for IVF. We examined the relationship between follicular fluid sRAGE and follicular fluid AMH levels which is one of the best marker of ovarian reserve in women undergoing COH [112]. Our results indicated that follicular fluid sRAGE predicted the number of oocytes retrieved (after adjusting for age, BMI, day 3 FSH and dose of gonadotropins), and positively correlated with follicular fluid AMH levels. Our study thus suggested that the anti-inflammatory sRAGE could represent a useful biological marker of the follicular environment in women undergoing COH.

We [112] and others [110,111,113] have studied the role of the AGE-RAGE system in fertility. One study [114] demonstrated that AGE-modified proteins are present on the surface of freshly isolated human granulosa lutein cells collected from women who underwent COH. This suggests that granulosa lutein cells are exposed to AGE-related damage *in vivo*. That study also observed that granulosa cells and ovarian monocytes bind AGE-modified albumin *in vitro* and that specific RAGE receptors are present on the surface of these cells [114]. These data imply that AGEs may also be involved in the decline of ovarian function and thus might lead to poorer response to COH in women with elevated AGEs, such as obese women.

Jinno, et al. [110] measured the levels of toxic AGEs in the blood and the follicular fluid of patients who underwent COH for IVF. They demonstrated that the accumulation of toxic AGEs in

follicular fluid and serum negatively correlated with follicular growth, oocyte fertilization, and embryonic development. Lower concentrations of AGEs in follicular fluid and lower concentration of AGEs in serum were the most significant predictors for achievement of ongoing pregnancy (independently from age and ovarian reserve as reflected by day 3 FSH). Again, these data indicate that there is a clinical evidence for an important role for AGEs in ovarian dysfunction and poorer COH outcome in women with elevated AGEs. Another study [113] reported a significant negative correlation between serum sRAGE levels and the number of growing follicles and retrieved oocytes following COH. Women who got pregnant following COH showed significantly higher sRAGE levels in their follicular fluid compared to those who did not get pregnant.

We examined the relationship between follicular fluid sRAGE and measures of ovarian reserve as reflected by AMH [112]. We studied 34 women who underwent COH followed by oocyte retrieval for IVF and we collected cumulus granulosa cells after which AMH and its receptor (AMHR-II) mRNA expression were quantified by RT-PCR [115]. Our results showed that the higher the follicular fluid sRAGE, the lower the dose of gonadotropins needed per COH cycle (independent of age, BMI and day 3 FSH). Follicular fluid sRAGE was also positively correlated with the number of oocytes retrieved and follicular fluid AMH protein levels.

## Conclusion

More than two thirds of the U.S. population is overweight or obese [1,116]. Presently, there is lack of targeted treatment for the costly obesity-related ovarian dysfunction that leads to poorer COH outcome for fertility treatments [117]. With respect to obese women seeking pregnancy, the use of fertility treatments including assisted reproductive technology are costly and frequently associated with poorer success in obese women compared to normal-weight women [105,117,118]. During the assisted reproductive technology process, obese women have a poorer response to gonadotropins thus requiring much higher doses of these expensive medications, produce fewer and poorer quality oocytes, generate poorer quality embryos, achieve lower pregnancy rates, and have higher miscarriage rates [119-122]. This review presents a background framework for a new hypothesis suggesting the involvement of AGEs and their receptors in COH in obese women. Since weight loss is commonly challenging and often not sustainable [123,124] with less than 20% of individuals achieving long-term weight maintenance [125,126] there is a critical need to establish therapeutic strategies for obesity-related ovarian dysfunction in order to improve ovarian response to COH. However, a major barrier to developing these therapies is a lack of understanding of the mechanisms underlying this poorer ovarian response to COH in obese women.

In the last decade, the dicarbonyl stress theory of ovarian dysfunction has gained a lot of attention. More accumulating evidence is indicating that AGEs could partly explain a mechanism for the obesity-related ovarian dysfunction. In addition to the

usual ovarian reserve markers (such as AMH, day 3 FSH and sonographic antral follicle count), it is reasonable to postulate that a plasma level of AGEs and/or sRAGE could be helpful in predicting the ovarian response to COH. Hypothetically, sRAGE could represent a potential therapeutic agent since data have shown that it is protective for ovarian follicles. Finally, the pathological significance of AGEs, these harmful pro-inflammatory molecules, in follicular health clearly requires further investigation and targeting AGEs via the development of effective and healthy AGE blockers could offer potential therapeutic options for the treatment of poor response to COH particularly in obese women.

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