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MINI REVIEW

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Preconception resveratrol intake against infertility: Friend or foe?

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Abstract

Background: Resveratrol is an antiaging, antioxidant, anti-inflammatory, and insulin-sensitizing natural polyphenolic compound. Growing evidence indicates that resveratrol has potential therapeutic effects in infertile women with diminished ovarian function, polycystic ovary syndrome (PCOS), or endometriosis. However, only one clinical trial in women undergoing in vitro fertilization (IVF) cycles using resveratrol has ever been reported. This review focuses on the potential therapeutic effects of resveratrol on pregnancy and on its advantages and disadvantages in pregnancy outcomes during infertility treatment.

Methods: We performed a literature review to describe the known impacts of resveratrol on the ovary and endometrium.

Results: Resveratrol upregulates sirtuin (SIRT)1 expression in ovaries, which is associated with protection against oxidative stress. It leads to the activation of telomerase activity and mitochondrial function, improving ovarian function. In the endometrium, resveratrol downregulates the CRABP2-RAR pathway leading to suppressing decidual and senescent changes of endometrial cells, which is essential for embryo implantation and placentation. Moreover, resveratrol may also induce deacetylation of important decidual-related genes.

Conclusions: Resveratrol has potential therapeutic effects for improving ovarian function; however, it also has anti-deciduogenic actions in uterine endometrium. In addition, its teratogenicity has not yet been ruled out; thus, resveratrol should be avoided during the luteal phase and pregnancy.

KEYWORDS

aging, assisted reproductive technology, infertility, resveratrol, sirtuin

1 | INTRODUCTION

Resveratrol (trans-3, 5, 40-trihydroxystilbene) is a natural polyphenolic compound, detected in a variety of plants, foods, and drinks, such as grapes, nuts, cranberries, and red wine.[1] Resveratrol has beneficial effects on human health, including antiaging, antioxidant, anti-inflammatory, insulin-sensitizing, cardioprotective, vasodilating, and anti-neoplastic properties[2] (Figure 1). Therefore, resveratrol intake can improve metabolic diseases, such as obesity, diabetes mellitus, and hypertension, and reduce the risk of cardiovascular diseases and malignant neoplasm.[3] Growing evidence indicates that resveratrol has potential

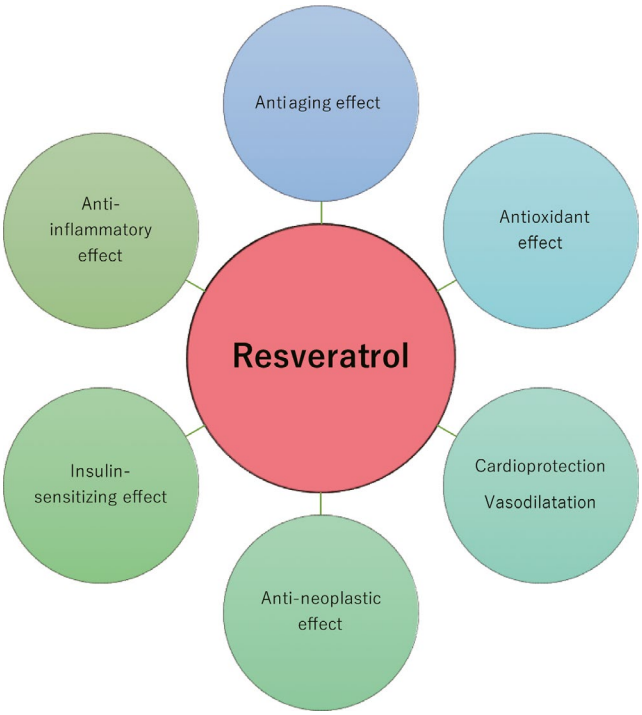

FIGURE 1 Effects of resveratrol on human health. Resveratrol has beneficial effects on human health, including antiaging, antioxidant, anti-inflammatory, insulin-sensitizing, cardioprotective, vasodilating, and anti-neoplastic properties

therapeutic effects in women with diminished ovarian function, polycystic ovary syndrome (PCOS), endometriosis, or uterine fibroids.[4-7] In addition, resveratrol may improve testicular function and sperm quality.[8,9] Therefore, resveratrol supplementation may help to treat both male and female infertility based on animal studies. However, in humans, only a single clinical trial on resveratrol for women undergoing in vitro fertilization (IVF) cycles has been carried out.[10] Our review discusses the potential therapeutic effects of resveratrol on pregnancy and its advantages and disadvantages for pregnancy outcomes during infertility treatment.

2 | IMPACT ON OVARY FOR PREGNANCY

2.1 | Aging

Aging is a major detrimental factor for achieving pregnancy[11-13] due to ovarian aging leading to mitochondrial dysfunction, telomere shortening, cohesion dysfunctions, and spindle instability. Both genetic and environmental factors contribute to aging damage, but the major mechanism underlying ovarian deterioration is chronic damage by reactive oxygen species (ROS).[11,14-16] Reactive oxygen species can damage mitochondria DNA, promoting mutations, and induce telomere shortening and cellular senescence.[17] Resveratrol is a natural activator of sirtuin, the NAD^+-dependent deacetylase. Sirtuins are emerging molecules in aging diseases.[18] In mice oocytes, sirtuin (SIRT)1 is upregulated in response to oxidative stress, whereas a SIRT1 inhibitor increases intracellular ROS.[19] SIRT1 may protect mitochondria against oxidative stress (Figure 2). However, aged oocytes have undetectable SIRT1 expression levels and low ability to regulate SIRT1.[19,20] Therefore, aged oocytes may be susceptible to the effects of oxidative stress through their decreased ability to produce SIRT1. Resveratrol may compensate for the decreased SIRT1 expression in aged oocytes, leading to the inhibition of age-associated ovarian aging changes. In rats, resveratrol intake increased the number of follicles and had ovary life-extending effects.[4] Moreover, resveratrol improved the number of follicle in aged mice ovaries.[21] Therefore, resveratrol may protect the ovarian reserve against aging *via* SIRT1 activation, resulting in prolonged ovarian life span.

2.2 | Primary ovarian insufficiency (POI)

Primary ovarian insufficiency is an ovarian dysfunction with amenorrhea and sex steroid deficiency in women younger than 40 years.[22] It can be caused by genetic abnormalities and ovarian damage due to chemotherapy, radiotherapy, or surgery. However, in most cases, the cause of premature depletion of primordial follicles is unknown.[23] During oocyte maturation and folliculogenesis, the phosphatidylinositol-4,5-bisphosphate 3 kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and nuclear factor-κ light-chain enhancer of activated B cell (NF-κB) signaling pathway play roles in the development of primordial follicles and oocytes and in the proliferation and differentiation of granulosa cells.[24,25] In a rat POI model induced by chemotherapy or radiotherapy, resveratrol inhibited oxidative stress and inflammatory events in ovaries by activating the PI3K/Akt/mTOR and NF-κB signaling pathways.[26-28] Resveratrol also improved loss of the oogonial stem cells through antiapoptotic effects in POI model mice.[29] Therefore, resveratrol may help as a therapeutic POI supplement; however, this has not yet been proven in human studies.

2.3 | PCOS and obesity-related infertility

Polycystic ovary syndrome is characterized by enlarged polycystic ovaries with a hyperplastic theca compartment and clinical and/or biochemical signs of hyperandrogenism, resulting in ovulation disorders.[30] In rat studies, resveratrol has antiproliferative effects on thecal interstitial cells *via* inhibition of the mevalonate pathway, involved in cholesterol production and steroidogenesis.[31] Moreover, resveratrol can also suppress cellular expression of the Cyp17α1 (17α-hydroxylase) that catalyzes various reactions, including androgen production.[32,33] In a rat model of PCOS, resveratrol intake improved the increased number of secondary and atretic follicles and the reduced number of Graafian follicles through antioxidant and anti-inflammatory effects, reducing aberrant elevated levels of testosterone, luteinizing hormone, and anti-Müllerian hormones.[34,35]

Advanced glycation end products (AGEs) are generated by the reaction between reducing sugars and proteins, lipids, or nucleic acids, and their accumulation in tissues has been involved in the pathogenesis of various diseases, including diabetes mellitus and PCOS.[36] Methylglyoxal is the most powerful precursor of AGEs.

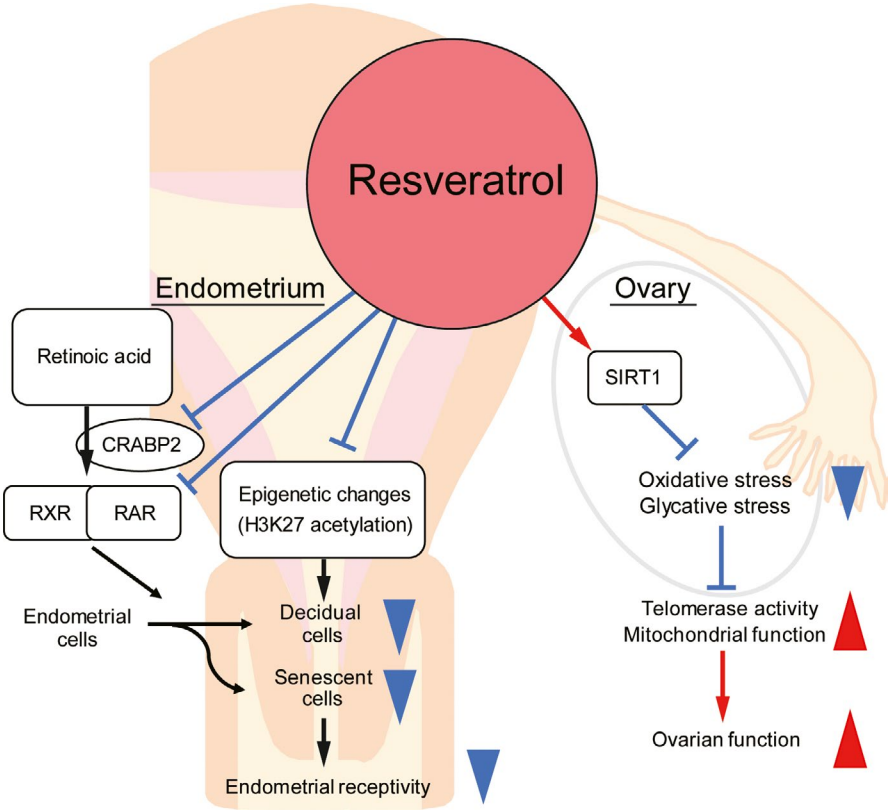

FIGURE 2 Effects of resveratrol on ovaries and endometrium. Resveratrol upregulates ovarian SIRT1 expression, which is associated with protection against oxidative stress and glycation stress. Moreover, it activates telomerase activity and mitochondrial function, improving ovarian function. In the decidualized endometrium, resveratrol accelerates downregulation of CRABP2-RAR pathway, inhibiting decidual senescence and decidualization. In addition, resveratrol may also induce deacetylation of important decidual-related genes. Up- and down-arrowheads: promotive and inhibitive actions

SIRT1 is associated with the response to methylglyoxal-dependent glycation stress, and it may have a positive effect on the ovarian function in PCOS by interfering with AGEs.[37]

In an obese mouse model study on IVF, resveratrol supplementation increased the number of oocytes collected after ovarian hyperstimulation *via* anti-inflammatory, insulin-sensitizing, and anti-hyperandrogenism effects.[38]

According to animal experiments, resveratrol is a candidate novel treatment against PCOS. In humans, a randomized double-blind clinical trial in women with PCOS showed that high-dose resveratrol administration (1.5 g per day) significantly decreased the levels of total testosterone, dehydroepiandrosterone sulfate, and fasting insulin and increased the insulin sensitivity index.[39] However, the fertility outcome following the treatment of resveratrol in women with PCOS has not been evaluated. Further clinical trials are warranted.

2.4 | In vitro maturation (IVM) and IVF

Resveratrol has a therapeutic direct effect on oocytes in in vitro culture. Treating the culture media with resveratrol improves oocyte maturation and the developmental competence of embryos to blastocysts in both animals and humans.[40-44] Moreover, during IVF treatments, minimization of the time-dependent deterioration after ovulation (postovulatory oocyte aging) is a key for successful pregnancies. Resveratrol treatment can protect against postovulatory oocyte aging in vivo in middle-aged mice.[45] This effect is attributed to the intracellular ROS level reduction and mitochondrial function improvement by resveratrol *via* SIRT1 activation. The quality and quantity of mitochondria are associated with the balance of mitochondrial biogenesis and autophagy. Resveratrol has effects on mitochondrial biogenesis as well as autophagy in the process of oocyte development, leading to remaining homeostasis in oocytes and granulosa cells through the clearance of damaged mitochondria.[44] Resveratrol also protects postovulatory human granulosa cells from apoptosis by activating the ERK pathway associated with the follicular antiapoptotic effect and by suppressing inflammatory functions of NF-κB signaling.[46]

Taken together, the addition of resveratrol to in vitro culture media may have local beneficial impacts on human oocytes, leading to improved oocyte maturation and developmental competence of embryos. However, data from human studies are still limited.

3 | IMPACT ON ENDOMETRIUM FOR PREGNANCY

3.1 | Effects on human endometrium in vitro

Successful pregnancy requires endometrial receptivity with optimal decidualization and synchronization with developmentally competent embryos.[47] Decidualization consists in cellular morphological changes of the human endometrial stromal cells (HESCs) accompanied by integrated gene expression alterations, such as those of prolactin (PRL) and insulin-like growth factor-binding protein-1 (IGFBP-1), generating an implantation window.[47,48] During decidualization, the endometrium is receptive for implantation and maintenance of pregnancy, resists oxidative stress, and promotes immune

tolerance by modulating a local inflammatory reaction to allow trophoblast invasion. By contrast, impaired decidualization causes a variety of pre- and post-pregnancy disorders, such as implantation failure, pregnancy loss, and uteroplacental dysfunction.[47,49-51]

The evidence for the effects of resveratrol on the human endometrium is still limited. Resveratrol promotes calcium-dependent, cell adhesion–related gene E-cadherin expression *via* increased expression of SIRT1 in Ishikawa cells, which means it can induce embryo attachment to the endometrium.[52] Also, resveratrol has antiapoptosis and antiproliferative effects, and it can inhibit progression of ectopic endometrium (endometriosis).[6] These reports suggest beneficial therapeutic effects of resveratrol on infertility with endometriosis.

However, implantation requires an inflammatory reaction with local secretion of proinflammatory cytokines and prostaglandins from the decidualized endometrium.[53-55] Resveratrol has anti-inflammatory actions that may suppress embryo implantation directly. The decidualization of endometrial stromal cells does not entail only cellular differentiation; the alteration requires a combination of differentiation and apoptosis/senescence.[56-58] In fact, decidual cells secrete proapoptotic factors during the decidualization of HESCs.[58] In in vitro primary cultures, the decidualization of HESCs induces senescence-associated β-galactosidase (SAβG) activity and increases expressions of major senescent markers, including p16 and p53.[56,57] Decidual cells secrete inflammatory mediators associated with endometrial receptivity, through acute cellular senescence. In addition, pro-senescent decidual cells are cleared by uterine natural killer (uNK) cells (the most abundant immune cells in the decidualized endometrium) for remodeling and rejuvenating the environment.[57] A suppressor of cellular senescence, the mTOR inhibitor rapamycin inhibits SAβG-positive cells, expression of senescent markers, and decidualization, leading to reduced expression of decidual marker genes, *PRL* and *IGFBP1*.[57] Resveratrol as an anti-senescence agent also has potential adverse effects on the decidua of humans and may impair implantation and pregnancy.

Decidual changes of HESCs depend on orchestrated reprogramming of various pathways, including that of retinoic acid (RA) signaling.[47,59] Retinoic acid regulates two opposing cell fates, differentiation and apoptosis, by binding to cellular RA-binding proteins, CRABP2 or FABP5, and getting activated by the nuclear receptors (retinoic acid receptor, RAR) to promote the activation of genes involved in apoptotic machinery and cell cycle arrest, or by peroxisome the proliferator-activated receptor (PPAR) β/δ to promote cell differentiation. Decidualization of HESCs downregulates RA signaling *via* a decrease in cytoplasmic binding proteins, CRABP2 and FABP5. Moreover, RA-binding receptors, RAR and PPARβ/δ, are induced and suppressed by decidualization, respectively. Therefore, decidualization of HESCs requires an appropriate suppression of the proapoptotic CRABP2-RAR signaling pathway.[59] SIRT1 is an important modulator of RA signaling, and it interacts with and deacetylates CRABP2[60] and also inhibits the transcriptional activity of RAR.[61] Our previous study demonstrated that resveratrol treatment accelerates downregulation of the CRABP2-RAR pathway in decidualized HESCs, leading to decreasing SAβG activity and expression of p53.[56] In addition, decidual markers were inhibited in decidual cells treated with resveratrol [56] (Figure 2). Impaired decidualization causes implantation failure and pregnancy loss.[49]

Moreover, decidualization of HESCs is associated with epigenetic changes, including H3K27 acetylation of promoter regions in decidual markers PRL and IGFBP1.[62-66] SIRT1 has histone deacetylation effects on decidual-related genes (PRL, IGFBP1, p53, and FOXO-family).[60,67-70] Thus, resveratrol supplementation may inhibit decidual senescence and induce deacetylation of important decidual-related genes, leading to decreasing endometrial receptivity, in the clinical practice (Figure 2).

3.2 | Clinical study on IVF treatment with resveratrol supplementation

Resveratrol has potential therapeutic effects in women with diminished ovarian reserve and function through its suppression of oxidative stress and its stimulation of mitochondrial biogenesis, but it also has adverse effects on implantation and endometrial decidualization. Is resveratrol "a friend or a foe" for pregnancy?

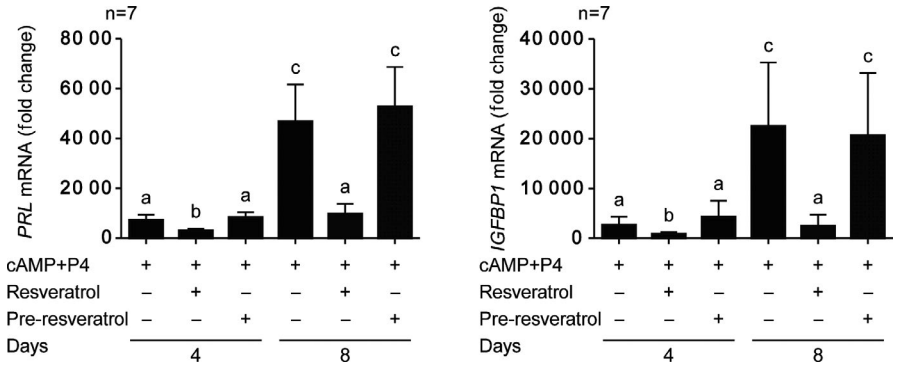

FIGURE 3 Pre-treatment with resveratrol does not inhibit decidual marker genes in the decidualized endometrium. Real-time quantitative PCR analysis of decidual markers PRL and IGFBP1 in human endometrial stromal cells (treated with 8-bromoadenosine-cAMP and progesterone (P4) with or without 100 μmol/L of resveratrol for 4 or 8 days and pre-treatment of the cells with resveratrol for 48 h followed by wash-off and decidualization without resveratrol treatment) showing fold changes (mean ± SEM) in PRL and IGFBP1 transcript levels relative to negative control (from four independent primary cultures). Different letters above the error bars suggest groups that are significantly different from each other at $P < .05$. This is a modified graph from our previous reports (Ochiai et al [56])

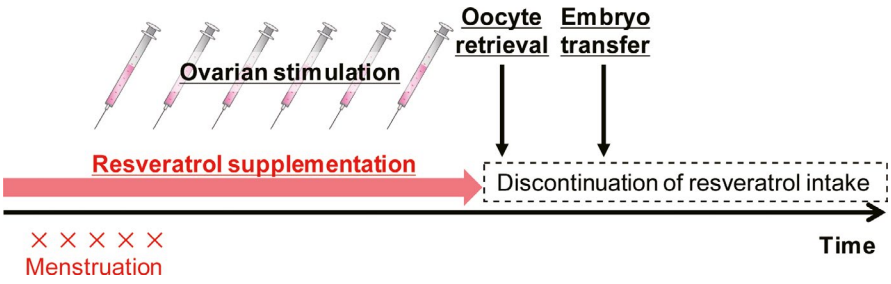

FIGURE 4 Recommendations for resveratrol supplementation in IVF treatment. We recommend discontinuation of resveratrol intake at the beginning of the luteal phase (the day of ovulation) or cryopreservation of all embryos (freeze-all policy) and vitrified and warmed ET without supplementation

We evaluated the impact of resveratrol on human pregnancy outcomes during IVF-embryo transfer (ET) cycles for the first time and found poor outcomes.[10] The retrospective cross-sectional study was carried out to compare the pregnancy outcomes after ET cycles between women with infertility using resveratrol (200 mg per day) continuously (RES group) and women in a control group not using any (non-RES group). Our multivariate logistic regression analysis demonstrated that resveratrol intake was significantly associated with low clinical pregnancy rates (post-adjusted odds ratio [OR] 0.539, 95% confidence interval [CI] 0.341-0.853) and high miscarriage rates (OR 2.602, 95% CI 1.070-6.325). In agreement with the effects of the senescence suppressor on decidualization in primary cultures, resveratrol intake may adversely impact pregnancy outcomes following ET cycles. In our clinical study, the patients in the RES group had poor pregnancy outcomes after ET even though embryos with good quality were transferred. However, in some patients with impaired ovarian reserve, resveratrol supplementation may improve oocyte quality and quantity leading to the collection of competent embryos. Our study focused on pregnancy outcomes after ET, and we had no data on ovarian function before and after resveratrol intake. Resveratrol treatment has been shown to protect against ovarian aging and to improve PCOS and endometriosis;[4-6] therefore, resveratrol intake may have benefits for some patients.

Based on these data, when using resveratrol during infertility treatments, if the tissue level of resveratrol vanishes in the endometrium before decidualization, it may not adversely affect implantation or pregnancy. In humans, the half-life of resveratrol is only 9-10 hours.[71,72] We tested this hypothesis on decidualized primary HESCs with or without treatment with 100 μmol/L of resveratrol or pre-treating cells with resveratrol for 48 hours followed by wash-off and decidualization without resveratrol treatment (Figure 3); our results showed that resveratrol treatment suppressed *PRL* and *IGFBP1* expression, but the pre-treatment had no impact on the induction of decidual markers.[56] Thus, in the clinical practice, discontinuation of resveratrol intake at the beginning of the luteal phase (the day of ovulation) or cryopreservation of all embryo (freeze-all policy) and warmed ET without supplementation (Figure 4) should help overcome these adverse effects. In all, a randomized controlled trial is needed to evaluate the use of resveratrol as an infertility treatment.

4 | POSSIBLE SIDE EFFECTS

Resveratrol does not appear to produce severe side effects at doses <1.0 g/day in various in vivo and in vitro studies with a wide range of resveratrol doses, whereas doses ≥1.0 g may produce side effects, including headache, dizziness, nausea, diarrhea, and liver dysfunction.[73-76] In a phase 2 clinical study, resveratrol intake at doses of 5.0 g in patients with refractory multiple myeloma caused severe renal failure in 5 of 24 patients before the study was stopped.[77] However, other clinical studies in patients with colorectal cancer and healthy volunteers did not show any nephrotoxicity at the same dose of resveratrol.[78,79] The renal failure may have been caused by the progression of multiple myeloma, but as a precaution, high-dose resveratrol should not be administered to infertile women. Although little is known about the maternal and fetal effects of resveratrol, its supplementation should be discontinued during pregnancy, based on the adverse decidualization effects in the human endometrium.

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

Women with advanced age face difficulties in getting pregnant due to decreased quality and quantities in their oocytes. Resveratrol has potential therapeutic effects for improving ovarian function; however, it also has anti-deciduogenic actions. Moreover, its teratogenicity has not yet been ruled out; therefore, resveratrol should be avoided during the luteal phase and pregnancy. Further clinical studies are needed to establish optimal doses and periods of resveratrol intake while preventing adverse effects on implantation, subsequent pregnancy, and the fetus.

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CONFLICT OF INTEREST

All authors declare having no conflicts of interest.

DISCLOSURES

Human/Animal rights: This article does not contain any studies with human and animal subjects performed by any of the authors.

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