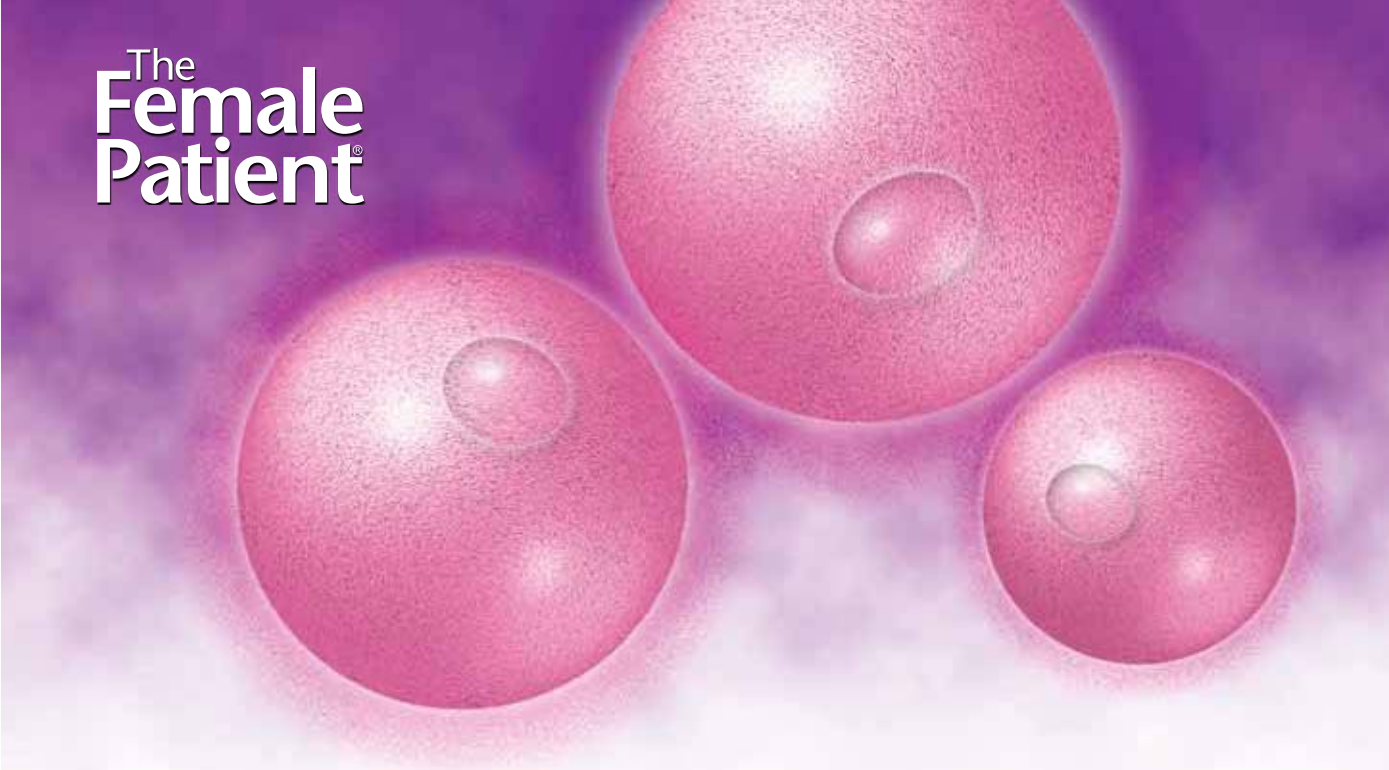
The Female Patient®



New Options for Supporting Women Having Difficulty Conceiving

James A. Simon, MD, CCD, NCMP, FACOG; Scott Roseff, MD; Howard Hait

Counseling patients and their partners who are having difficulty conceiving is a difficult and time-consuming proposition for ObGyn physicians and their collaborative practitioners (midwives, physician assistants, nurse practitioners). Clinicians may pursue a number of treatment options, but the choices remain rather limited. The proper time frame for appropriate referral to a reproductive specialist is often unclear. Recent studies investigating new approaches to managing infertility have identified additional metabolic mechanisms that may have a role. The most common causes of infertility, polycystic ovary syndrome (PCOS) and oligomenorrhea, are associated with insulin resistance. Therefore, the use of insulin-lowering or insulin-sensitizing therapy may help to improve ovarian function and menstrual cyclicity.

Myo-inositol, a dietary vitamin belonging to the B complex, has been shown in controlled studies to support and maintain menstrual cyclicity, oocyte quality, and ovulatory function through its effect on insulin receptor activity. Currently available in Europe and soon to be available in the United States, myo-inositol may contribute to improved ovulatory function and menstrual cyclicity alongside current methods for managing infertility. In anticipation of the commercial availability of this product, this review article attempts to examine and summarize the results of controlled studies of myo-inositol in the management of patients having difficulty conceiving.

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Background

For women of child-bearing potential seeking to become pregnant, the time to spontaneous pregnancy often exceeds established guidelines used to initiate a medical evaluation, which is 1 year of unprotected intercourse for women under 35 years of age or 6 months of unprotected intercourse for women over 35 years of age. Practitioners also have to deal with the psychological aspects of "patient expectations," ie, the belief that pregnancy should come almost immediately following the initiation of unprotected intercourse. For those couples exceeding the time frame for requesting a consultation and for others who are just "in a hurry," the generalist ObGyn approach is to initially consider a host of plausible factors that are typically segmented into four areas: medical issues (eg, absent or irregular menses), anatomical issues, a "male" factor, and/or a general diagnosis of unexplained infertility.

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Apart from these "usual and customary" considerations, care must be focused on patient age as well. Younger patients may include fertile women who are seeking guidance as they begin the pregnancy planning process, realizing that they have been trying for a few cycles to become pregnant but without success. Older patients (those over 35 years of age) may be professionals who have put off having children but are now trying to become pregnant, also without success. The clinical course for initiating treatment for infertility, however, does not typically commence until the patient has tried unsuccessfully to conceive for at least 12 months for the younger women and ~6 months for the older women, as noted above.

Notwithstanding the efforts of health professionals to identify the cause of infertility in a particular patient, including anatomical findings such as blocked fallopian tubes or endometriosis, concomitant with testing of the male partner, clinical evaluation may result in a diagnosis of oligomenorrhea or PCOS. Approximately 8 million women in the United States alone are estimated to be infertile, with 25% of infertile women having problems with ovulation (anovulatory infertility) and 15% of all couples of reproductive age having some type of fertility problem. If the most common diagnosis among such women and their partners is PCOS, this could then translate into a substantial attributable risk for infertility associated with that diagnosis.

PCOS is characterized by oligoovulation, anovulation, and hyperandrogenism with or without infertility and is considered the most common cause of infertility resulting from ovulation failure. Metabolic features associated with PCOS include increased production of androgens and estrogens, which is associated with long-term risks such as obesity and cardiovascular disease. PCOS is considered a product of a complicated set of functional changes that occur within the entire female reproductive system. In 1980, Burghen et al[1] reported that patients with PCOS also had associated hyperinsulinemia, stimulating further research into the role that insulin plays in gonadal function. This led to the hypothesis that treatment with insulin-sensitizing medications could act to reverse the effects of impaired glucose tolerance and restore spontaneous ovulation through an increase in ovarian activity and regularity of menstrual frequency. Since 40% of women diagnosed with PCOS have impaired glucose tolerance, this approach seemed plausible.

Treatment Options

Historically, in a general ObGyn practice, ovulation induction through the administration of pharmacological agents such as clomiphene citrate with or without metformin has been the principal tool for returning a woman to fertility and successful pregnancy. This takes place after careful clinical consideration of other conditions that may be contributory to anovulation, such as thyroid dysfunction, hyperprolactinemia, hirsutism, and obesity, as seen on examination or through a review of a patient's medical history. The potential presence of an adrenal androgen-secreting neoplasm and congenital adrenal hyperplasia must also be excluded before embarking on a course of drug therapy.

Clomiphene citrate has been the first-line treatment of choice for ovulation induction and fertility enhancement.[2] For most ObGyns, it might be considered the primary realistic tool for helping their patients achieve pregnancy with minimal concern of multiple births and ovarian hyperstimulation syndrome, although both of these consequences have been reported.[3] Clomiphene citrate is a selective estrogen receptor modula-

tor (SERM), which increases gonadotropin production and results in ovarian hyperstimulation through inhibition of estrogen receptors at both the hypothalamus and pituitary (negative feedback). By sensing less estrogenic feedback, the gonadotropin secretion increases, producing a more robust ovulatory response, thereby overcoming anovulation. Depending on the age of the patient, 3 to 6 cycles of clomiphene therapy are prescribed before moving on to other therapeutic options including those requiring referral to a reproductive specialist as appropriate. In women with PCOS, ovulation is induced in 80% of cases, with pregnancy occurring in only 20% of those treated.[3] Metformin is sometimes used as an adjunct to clomiphene in women with PCOS because of metformin's insulin-sensitizing action. In addition to the small risk of an increase in multiple pregnancies, the ovarian hyperstimulation syndrome, drying of the vaginal mucosa leading to dyspareunia, attenuation or thickening of the cervical mucus that blocks the ability of sperm to reach the uterus, and abnormal maturation of the endometrium are all adverse consequences of clomiphene treatment that lessen the chance of successfully achieving fertility rather than enhancing it.

Recently, efforts have been undertaken to explore new options for ovulation induction. A vitamin B complex-derived product, myo-inositol, has been evaluated in a number of controlled studies looking at ovulation frequency, time to ovulation, follicular maturation, and the quality of oocyte production. Myo-inositol is an insulin-sensitizing agent produced by the human body from glucose and is one of 9 distinct isomers of the "nutrient" inositol naturally produced by the human body. Myo-inositol is commercially available by its brand name, Pregnitude (Everett Laboratories, Inc; West Orange, NJ), as an oral powder formulation mixed with water that combines 2 g of myo-inositol with 200 µg of folic acid. (Total daily dosage is 4 g of myo-inositol and 400 µg of folic acid, or 2 packets taken twice daily mixed with water). Results of both observational and controlled clinical investigations have shown that myo-inositol improves ovarian function and ovulation induction in patients with oligomenorrhea or amenorrhea plus PCOS.

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Clinical Studies of Myo-Inositol in Combination With Folic Acid

The literature describing the use of myo-inositol and its analogues, inositol and D-*chiro*-inositol, is rather extensive. Two randomized, double-blind, placebo-controlled trials of the efficacy of myo-inositol have been reported.[4,5] Each considered patients with PCOS as the target population under study. Myo-inositol was used in combination with a daily dose of folic acid, whereas daily administration of folic acid alone served as a "placebo" control. Both studies used a daily myo-inositol/folic acid dose combination of 4-g myo-inositol and 400-µg folic acid, taken either as a single daily dose or as a 2-g myo-inositol/200-µg folic acid dose taken twice per day. Each study also evaluated several endpoints related to outcomes associated with ovarian function, menstrual cyclicity, and oocyte quality following standard egg retrieval procedures.

Impact on Ovarian Function

Gerli et al[4] assessed the effects of supplemental myo-inositol on ovarian function in a randomized, double-blind, placebo-controlled trial of women recruited from gynecology, endocrine, and infertility outpatient clinics in Italy. Inclusion criteria for the study were age less than 35 years and oligomenorrhea or amenorrhea with a diagnosis of PCOS (confirmed during a 4-week pretrial period). The PCOS diagnosis was obtained through a single observer-based assessment of ovarian appearance using transvaginal ultrasound, following the criteria described by Adams et al.[6] Exclusion criteria included hyperprolactinemia, abnormal thyroid function, adrenal hyperplasia, and use of medications likely to influence hormonal profiles.

Of the 92 subjects, 45 were randomized to receive 4-g myo-inositol plus 400-µg folic acid/day for 16 weeks, while the remaining 47 received 400-µg folic acid per day as a placebo. Serum samples were obtained twice weekly to assess hormonal concentrations. Circulating estradiol (E_2) concentrations increased during the first week of treatment only in the myo-inositol group, indicating that there had been a rapid effect of myo-inositol on follicular maturation. An improvement in ovulation frequency was also observed between the women receiving myo-inositol and those on placebo, with 82% of women on myo-inositol ovulating at least once

during the 14-week period and 63% of women on placebo ovulating at least once during the study period ($P = .04$) (Figure 1). The time to the first ovulation was significantly shorter in treated patients ($P < .05$); in these patients, the time to first ovulation was 24.5 days (95% confidence interval [CI]: 18, 31) while in control patients, the time to first ovulation was 40.5 days (95% CI: 27, 54).

Myo-inositol treatment also resulted in significantly increased concentrations from baseline in high density lipoprotein (HDL) cholesterol ($P = .03$); no changes were observed in the control group. Metabolic risk factor benefits of inositol treatment were not observed in a morbidly obese subgroup of patients (body mass index > 37). There were no changes in fasting glucose concentrations, fasting insulin, or insulin response to glucose challenge in either group. The authors concluded that supplemental myo-inositol improves ovarian function in women with oligomenorrhea and polycystic ovaries.

Papaleo et al[7,8] conducted studies to determine if supplemental myo-inositol could improve ovulatory function in PCOS patients. In one study, these researchers administered myo-inositol (2 g) combined with folic acid (200 µg) twice a day for up to 6 months to 25 PCOS patients of childbearing age.[7] The study subjects all had oligomenorrhea or amenorrhea (6 or fewer menstrual cycles during a period of one year), hyperandrogenism (hirsutism, acne, or alopecia) or hyperandrogenemia (elevated levels of total or free testosterone), and typical polycystic ovarian features on ultrasound scan. Patients had been regularly seen at an IVF unit for infertility for more than 14 months and were examined to rule out tubal defects as a cause of infertility. Semen from male partners was also examined to exclude poor semen quality as a cause of infertility. While receiving myo-inositol treatment, 22 out of the 25 (88%) patients had at least one spontaneous menstrual cycle during the 6-month treatment period, and 18 of these patients (72%) maintained normal ovulatory cycles during the entire 6-month study period. The study authors concluded that myo-inositol treatment is capable of restoring spontaneous ovarian activity in most patients with PCOS. During the observational period of 6 months, a total of 10 pregnancies occurred with 9 still viable at 7 weeks of gestation.

Impact on Menstrual Cyclicity

During the 14-week treatment period in the study by Gerli et al,[4] more than 70% of the women treated with myo-inositol had ovarian rhythm restored (≥ 3 ovulations during the study period) (Figure 2), compared to 13% on placebo ($P < .001$). This is especially interesting because the reduction in the number of patients who ovulated once while taking placebo (63%) was very significant, indicating a large effect in the patients taking myo-inositol. Since they had directly measured normal progesterone concentrations in a substantial

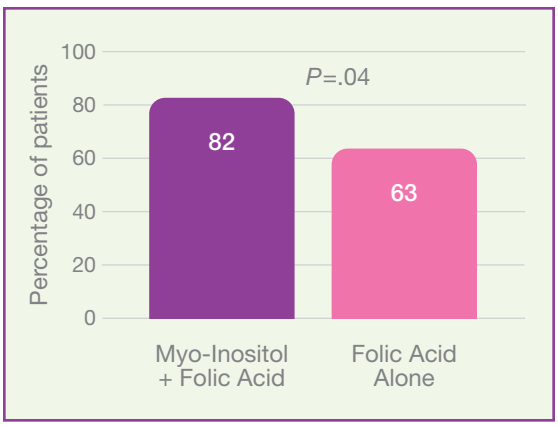

Figure 1. **Ovulatory function.** In a 14-week, randomized, double-blind controlled trial including 92 women with irregular cycles, a significantly greater percentage of patients receiving 4 g myo-inositol plus 400 µg folic acid **ovulated** compared with those who only received folic acid. Data from Gerli S et al.[4]

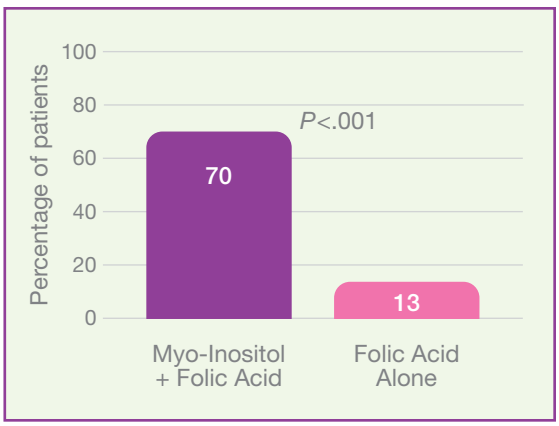

Figure 2. **Menstrual cyclicity.** In a randomized, double-blind controlled trial including 92 women with irregular cycles, a significantly greater percentage of patients receiving 4 g myo-inositol plus 400 µg folic acid **achieved normal ovarian rhythm** (≥3 ovulations) over 14 weeks compared with those who only received folic acid. Data from Gerli S et al.[4]

number of those cycles, the investigators were able to conclude that the restored cycles were potentially fertile.

Impact on Oocyte Quality

Ciotta et al[5] conducted a randomized, double-blind, controlled trial that examined the effects of myo-inositol on oocyte quality in women (< 40 years of age) with PCOS undergoing IVF. The efficacy of myo-inositol plus folic acid treatment (17 subjects) was compared to treatment with folic acid alone (17 subjects). Subjects in Group A received 2 g of myo-inositol plus 200 µg of folic acid twice a day, while Group B subjects only received 200 µg of folic acid twice a day for a period of 3 months prior to undergoing oocyte retrieval. Study outcome measures included the stimulating dose of gonadotropins (follicle stimulating hormone [FSH] units) administered, number of follicles of diameter greater than 15 mm recruited, days of stimulation, estradiol (E_2) concentration (maximum), and actual number of oocytes retrieved.

At the end of treatment, the number of follicles of diameter greater than 15 mm visible at ultrasound during stimulation and the number of oocytes recovered at the time of retrieval were found to be significantly greater in the group treated with myo-inositol (Figure 3). Additionally, the average number of embryos transferred and their macroscopic quality (embryo scores S1) (data not shown) were likewise significantly better in the myo-inositol group compared to folic acid alone ($P < .01$). Finally, a statistically significant ($P = .02$) reduction in the average number of immature oocytes (ie, those with germinal vesicles or those which had degenerated) was observed in the myo-inositol group. While no difference in the total number of positive pregnancy tests was detected between groups, the sample size may have been too small to have expected differences in this outcome. The authors concluded that myo-inositol may be useful in the treatment of PCOS patients undergoing ovulation induction, both for its insulin-sensitizing activity and its role in oocyte maturation.

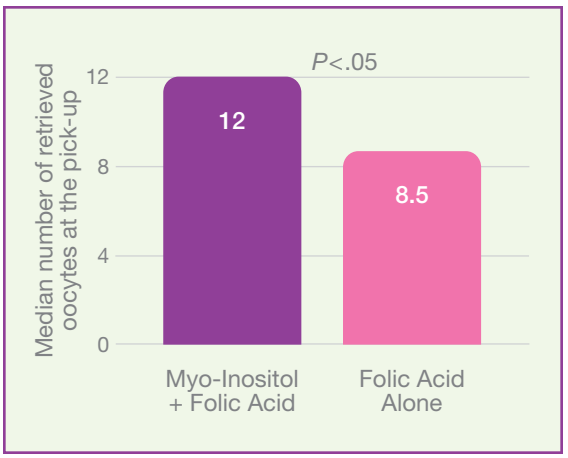

Figure 3. **Oocyte quality.** In a randomized trial including 34 women (aged <40 years) who received 4 g myo-inositol plus 200 µg folic acid or folic acid alone continuously for 3 months, **significantly more oocytes were retrieved** from patients in the myo-inositol plus folic acid treatment group. Data from Ciotta L et al.[5]

Papaleo et al[9] assessed the effects of myo-inositol on oocyte quality in PCOS patients undergoing intracytoplasmic sperm injection cycles. The subjects were patients who had been treated at an IVF clinic in Italy for at least a year. Sixty women less than 40 years of age with PCOS as indicated by oligomenorrhea (6 or fewer cycles/year), hyperandrogenism (hirsutism, acne, or alopecia), or hyperandrogenemia (elevated total or free testosterone levels) were enrolled in the study. Exclusion criteria included other conditions potentially causing ovulatory disorders (eg, hyperinsulinemia, hyperprolactinemia, hypothyroidism, adrenal hyperplasia, Cushing syndrome). Beginning on the day of gonadotropin-releasing hormone administration, 30 subjects received myo-inositol (2 g) combined with folic acid (200 µg) twice a day, and 30 subjects received folic acid alone twice a day.

There was no difference in the mean number of oocytes retrieved, but the mean number of immature oocytes (those with germinal vesicles and degenerated oocytes) was significantly reduced among patients treated with myo-inositol (1.03 ± 0.87 vs 1.63 ± 1.01, $P = .02$). However, there were no significant differences between the myo-inositol-treated and control groups in the number of pregnancies, the implantation rate, or the number of spontaneous abortions. The authors concluded that treatment with myo-inositol and folic acid, but not folic acid alone, reduces germinal vesicles and degenerated oocytes at ovum pick-up without compromising the total number of retrieved oocytes.

Discussion

Patients who are having difficulty conceiving present unique challenges for ObGyn physicians and their collaborative practitioners. Although patients often call with questions about a perceived "lack of success" after only

3 or 4 cycles of trying to conceive, the standard of care calls for active treatment of infertility to commence only after a full 12 cycles have passed without a successful pregnancy in patients under 35 years of age or for evaluation to begin following 6 months of unprotected sexual activity in women 35 years of age and older. In both of these age groups, women are often extremely anxious to have an active intervention, which may not yet be warranted because of a less-than-adequate period of attempting to conceive. In this setting, one might consider the introduction of a dietary supplement, like myo-inositol and folic acid in the dosage and formulation available as the product Pregnitude taken twice daily, as a new approach to managing women having difficulty conceiving. Doing so could improve menstrual cyclicity, particularly in women with oligoovulation or anovulation and those with PCOS. Concomitant restoration of subclinical ovulatory dysfunction with Pregnitude therapy while patients fulfill guidance-mandated timelines prior to initiation of more aggressive therapy can naturally allow conception in a timely fashion.

Overall, clinical investigations of myo-inositol in combination with folic acid support its use to improve menstrual cyclicity, oocyte quality, and ovulatory function. A variety of endpoints measuring hormonal concentrations, changes in metabolic parameters, frequency of ovulation, follicular diameter, and the number and size of retrieved oocytes all demonstrate the potential benefit of myo-inositol given with folic acid as a useful complement to current therapeutic approaches for managing patients who are having difficulty conceiving.

The major limitation of the clinical trials reviewed here is that only one study examined pregnancy rates/outcomes. Of the remaining studies, all were conducted with PCOS/IVF patients and not within the general population of women who wish to become pregnant and are unable to because of reasons other than PCOS. Therefore, while it can be suggested that myo-inositol along with folic acid may help to improve the conditions for which a successful pregnancy can take place, none of the studies were designed or conducted with a large enough sample size to directly measure the extent to which myo-inositol with folic acid can actually *increase the rate* of pregnancy either in the limited patient population studied to date or in the general population of women trying to become pregnant. Nevertheless, given that the principal aim in a general ObGyn practice of managing patients having difficulty conceiving is to restore, or at least improve, ovulatory function, Pregnitude (2-g myo-inositol and 200-µg folic acid), a dietary supplement which will soon be available in the United States without a prescription, appears to improve the conditions necessary to achieve that goal and may give ObGyns an additional tool toward achieving success in this patient population.

Dr Simon reports having served as a consultant or on advisory boards for Abbott Laboratories, Agile Therapeutics, Amgen, Ascend Therapeutics, Azur Pharma, BioSante, Boehringer Ingelheim, Depomed, Fabre-Kramer, Laboratoire HRA Pharma, Meditrina Pharmaceuticals, Merck, Merrion Pharmaceuticals, NDA Partners, Novo Nordisk, Novogyne, Pfizer, Shionogi, Slate Pharmaceuticals, Sprout Pharmaceuticals, Teva Pharmaceutical Industries, Trovis Pharmaceuticals, Warner Chilcott, and Watson Pharmaceutical; receiving grants or research support from BioSante, Boehringer Ingelheim, EndoCeutics, Novo Nordisk, Novogyne, Palatin Technologies, Teva Pharmaceutical Industries, and Warner Chilcott; and having served on speakers bureaus for Amgen, Ascend Therapeutics, Bayer, Boehringer Ingelheim, Merck, Novartis, Novo Nordisk, Novogyne, Teva Pharmaceutical Industries, and Warner Chilcott. Dr Roseff and Mr Hait report having served as consultants for Everett Laboratories.

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