Infertility associated with Precoital Ovulation in Observant Jewish Couples; Prevalence, Treatment, Efficacy and Side Effects

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ABSTRACT: **Background:** 'Religious (halachic*) infertility' results from precoital ovulation prior to immersion in a ritual bath (*mikveh*) 7 days after menstruation, as mandated by Jewish religious law. Previous authors recommended treatment with estradiol to postpone ovulation and enhance pregnancy rates.

Objectives: To evaluate the prevalence of halachic infertility in an ultra-Orthodox Jewish community, and assess the efficacy of estradiol treatment in postponing ovulation and increasing pregnancy rates.

Methods: We reviewed 88 cycles, of which 23 were control cycles and 65 estradiol-treated cycles, and analyzed the files of 23 women who were treated with 6 mg estradiol/day from day 1 for 5 days of the cycle.

Results: The prevalence of precoital ovulation in the infertile population was 21%. Most of the patients (94%) ovulated before day 13 of the cycle. A short follicular phase due to low ovarian reserve or thyroid endocrinopathy was noted in 12% of the patients. While 64% of the women reported consultation with a Rabbinate authority, 68% of the patients sought medical therapy. Estradiol postponed ovulation for at least one day in 89% of the treatment cycles. Ovulation post-mikveh occurred in 73% of estradiol-treated cycles. The pregnancy rate was 12.5% per cycle and the cumulative pregnancy rate 35% per woman. Half the patients reported spotting during estradiol-treated cycles, and this postponed coitus.

Conclusions: Precoital ovulation is a major reason for infertility among observant couples attending fertility clinics. Estradiol treatment is effective in delaying ovulation and restoring fecundity; however, it causes some adverse effects that may decrease its effectiveness.

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According to the *Niddah* laws of separation, Orthodox Jewish women are prohibited from engaging in sexual intercourse from the start of menstruation until 7 days after the end of menses, when they immerse in a ritual bath *(mikveh)* [1,2]. Therefore, women with a prolonged menstrual flow or short follicular phase may be unable to attend the ritual bath early enough and prior to ovulation. The fertile window opens 5 days before the ovulation day, while the highest fecundity rates are achieved when coitus occurs 48 hours prior to ovulation [3]. The first sexual intercourse after ovulation results in a null chance of pregnancy. Thus, when the first coitus takes place on day 14, half the cycles are infertile. Consequently, delay of the first coitus beyond the fertile window may lead to 'religious (halachic) infertility' [4]. The duration of the menstrual prohibition is 5–7 days even if the duration of bleeding is much shorter. In case of unexpected spotting or bleeding (*zavah*), the woman should be consulted to determine the origin of the blood. In the case of uterine bleeding, intercourse is forbidden for 7 days thereafter [5].

The laws of family purity (Niddah), which regulate coitus among Orthodox Jews according to the phase of the menstrual cycle, have a potentially important impact on fertility. The length of the menstrual cycle is usually determined by the rate and quality of follicular growth and development, that is, by the length of the follicular phase of the ovarian cycle, whereas the luteal phase is fairly constant and lasts 13–15 days [6]. In 60% of women of childbearing age the menstrual cycle lasts 25–28 days. Thus, in the majority of women coital activity takes place during the fertile period. However, in about a fifth of women with short cycles of 21–25 days, ovulation can take place during the days of ritual impurity (*tum'ah* interval) before day 14 of the menstrual cycle, potentially leading to diminished fertility as a result of restricted coitus. Furthermore, women in their forties experience shorter cycle length [7]. In women with cycles of 21–25 days, if sexual intercourse is not resumed until day 15, the proportion of cycles during which coitus is restricted to the post-ovulatory phase increases from 30% to 41%, thus lowering fecundity [7,8].

Because shortening the count of the *tum'ah* days is non-negotiable, medically lengthening the pre-ovulatory phase using early follicular estrogen supplementation is a common

*Referring to *Halacha*, the body of Jewish Law practice. In the past, the estrogen-progestogen combined oral contraception pill was used to delay ovulation [9]. Recently, oral estrogen supplementation, starting on the second day of the menstrual cycle until the first 2 clean days, was shown to restore the normal (23%) fecundity rate by effectively delaying ovulation beyond the time of the ritual bath [10].

The purpose of this study was to evaluate, for the first time, the prevalence of 'religious infertility' in the infertile population attending fertility consultation in an ultra-Orthodox Jewish community, characteristics of the menstrual cycle, the impact of estradiol therapy on the ovulation date and the side effects of this treatment.

PATIENTS AND METHODS

This was a retrospective analysis of 45 infertile patients suspected of having precoital ovulation. A total of 88 cycles were reviewed, of which 23 were control cycles and 65 estradiol-treated cycles. During each cycle the length of menses and the date of attending the mikveh were reported. To assess follicular growth and ovulation date, estrogen, progesterone and luteinizing hormone levels were repeatedly measured (on average 1.58 ± 1.01 per cycle) and vaginal ultrasound performed (on average 2.02 ± 0.85 per cycle). Ovulation was defined as an increase in *P* level to > 5 ng/ml, an LH level > 180% of the baseline value, or both. Pregnancy was confirmed by a positive serum human chorionic gonadotropin result.

We analyzed the files of 23 consecutive patients who were diagnosed as having precoital ovulation during a span of 3 years and were treated with estradiol. All patients started treatment with a daily dose of 6 mg β-estradiol (Estrofem®, Novo Nordisk, Kfar Saba, Israel) (n=60) or estradiol valerate (Progynova®, Schering Pharmaceuticals, Berlin, Germany) (n=5) starting on the first day of the menstrual cycle for 5 days. The selection of the type of estrogen used was decided by the treating physician and depended largely on the availability of the preparation.

STATISTICAL ANALYSIS

The characteristics of each patient's menstrual cycle (duration of bleeding, day of ritual bath, day of ovulation, and interval between ritual bath and ovulation) with and without treatment were compared. Categorical data are presented as frequencies, and continuous data as means ± SD. Wilcoxon rank sum test and chi-square tests were performed for statistical significance where appropriate. *P* values ≤ 0.05 were considered significant.

RESULTS

The prevalence of precoital ovulation in the infertile Orthodox Jewish population applying for fertility consultation was 21% (34/161). Of the 45 infertile patients suspected of having precoital ovulation, the occurrence of precoital ovulation was confirmed in 34 (75%). Of women diagnosed with precoital ovulation, 15% (5/34) were found to have another diagnosis of infertility, such as male factor (n=3) and mechanical factor (n=2). In only 6% (2/34) did precoital ovulation occur because of prolonged menstrual bleeding for more than 10 days; the rest ovulated before day 13 of the cycle. Elevated day 3 follicle-stimulating hormone levels > 10 IU/ml, indicating low ovarian reserve as a cause for short follicular phase, were recorded in 3 patients (9%) and one patient was diagnosed as hypothyroid (3%).

Consultation with a Rabbinate authority was reported by 64% of women, but no halachic solution was provided to any of the applicants. Two-thirds of these couples were referred by the Rabbinate authority to seek medical advice and treatment. The majority of patients with precoital ovulation (23/34, 68%) chose medical treatment for halachic infertility.

The characteristics of the study population are presented in Table 1. The mean age of the study population was 26.4 ± 4.9; mean body mass index was 22.8 ± 4.4, mean gravidity 1.2 ± 1.7 (range 0–6), mean parity 0.95 ± 1.4 (range 0–5), and infertility duration 1.7 ± 1.2 years. Half the women (47.6%) had never been pregnant. The reported cycle parameters of women diagnosed as halachically infertile were mean cycle length 27.6

LH = luteinizing hormone

Table 1. Characteristics of patients with precoital ovulation (n=23)

Age (yrs, mean ± SD)	26.4 ± 4.91
BMI (kg/m2, mean ± SD)	22.8 ± 4.43
Gravidity (mean ± SD)	1.25 ± 1.67
Parity (mean ± SD)	0.95 ± 1.4
Infertility duration (yrs, mean ± SD)	1.7 ± 1.22
Primary infertility	47.6%
Cycle length (days, mean ± SD)	27.6 ± 1.93
Menses duration (days, mean ± SD)	7.1 ± 1.79
Day 3 estradiol › 200 pmol/L	61.1%
Day 3 FSH (mean ± SD)	6.2 ± 1.83
Day 3 LH (mean ± SD)	5.4 ± 1.84

FSH = follicle-stimulating hormone, LH = luteinizing hormone

Table 2. Menstrual cycle characteristics of control and estradiol-treated cycles

	Control cycles (n=23)	Treatment cycles (n=65)	*P* value
Menses length (days)	6.3 ± 1.22	5.71 ± 1.80	0.26
Ovulation day	12.52 ± 2.21	17.44 ± 3.22	‹ 0.0001
Day of first coitus mikveh day	14.33 ± 1.47	14.92 ± 3.39	0.46
Interval between first coitus and ovulation (days)	-1.80 ± 2.26	2.66 ± 4.41	‹ 0.0001

Table 3. Cycle characteristics for successful and unsuccessful cycles

	Successful cycles (n=8)	Unsuccessful cycles (n=56)	*P* value
Menses length (days)	6.3 ± 1.22	5.8 ± 1.8	0.1
Ovulation day	14.8 ± 3.3	17.8 ± 3.8	0.03
Mikveh day	12 ± 0.9	15.3 ± 3.4	0.007
Ovulation before mikveh (days)	2.8 ± 2.9	2.6 ± 4.6	0.8

± 1.9 days and menstrual duration 7.1 ± 1.8 days. Of note is the average basal (day 3) level of estradiol, which was higher than 200 pmol/L in 61% of the group, indicating early follicular recruitment and estrogen production.

Characteristics of the patients' menstrual cycle before and after estrogen therapy are shown in Table 2. In this cohort the length of menses did not decrease after estrogen therapy (6.3 ± 1.22 vs. 5.71 ± 1.80, $P = 0.26$), yet ovulation occurred later during the cycle (day 12.52 ± 2.21 vs. day 17.44 ± 3.22, $P < 0.0001$). Prior to estradiol treatment the patients ovulated on average 1.80 ± 2.26 days before the mikveh, whereas after treatment ovulation took place 2.66 ± 4.41 days after the mikveh ($P < 0.0001$). Estradiol was found to postpone ovulation for at least one day in 89% of the cycles. Ovulation post-mikveh occurred in 73% of estradiol-treated cycles, resulting in a pregnancy rate of 12.5% per cycle and a 35% cumulative pregnancy rate per woman. This reproductive outcome was achieved after an average of 2.8 cycles (range 1–11). A comparison of the women who conceived with estradiol treatment and those who did not failed to reveal specific factors that contributed to successful cycles [Table 3].

Intermenstrual spotting was the major reported side effect of this regimen of estradiol treatment, occurring in 18% (12/65) of the cycles and in 52% of treated women. This light uterine bleeding is particularly significant as it might postpone sexual intercourse by 7 days, rendering the treatment ineffective.

DISCUSSION

The distribution of the Jewish population in Israel is as follows: 42% secular, 38% traditional, 12% religious and 8% ultra-Orthodox [11]. The laws of family purity are upheld by traditional, religious and ultra-Orthodox Jews, exposing a very large portion of couples to the threat of halachic infertility.

This is the first study estimating the prevalence of precoital ovulation in a Jewish community that strictly follows the *Halacha* code of conduct. A fifth of infertile couples were diagnosed as suffering from infertility due to a religious rather than biological cause. Based on reports that a fifth of menstrual cycles are shorter than 25 days [7,8], our observation is not surprising. This significant proportion of infertile couples who suffer from sociocultural infertility mandates special attention, primarily of the Rabbinate authorities.

Of note is the relatively long average cycle length of more than 27 days, which may testify against the conception that only women with cycles shorter than 25 days suffer from infertility due to precoital ovulation. Furthermore, the reported average menstrual duration of 7 days may suggest that women may count extra days as their period.

From the medical point of view the diagnosis of precoital ovulation should not be made without exploring mechanical and male factors since 15% of couples may have a combined cause of infertility. The majority of patients who experience precoital ovulation have a short follicular phase while the minority suffers prolonged menstrual flow. We showed that some of the short follicular phases (12%) are due to endocrinopathies, such as hypo/hyperthyroidism and low ovarian reserve with early follicular recruitment. The regimen of estradiol therapy is aimed to treat women with primary short follicular phase.

A discussion of the ethics of this medical conduct, e.g., providing hormone therapy for a problem that is not caused by a medical disorder, is beyond the scope of this paper and was broadly elaborated in a previous article [2]. Since not obeying the halachic code of conduct is non-negotiable, and in view of the void of halachic solutions, most couples (68%) seek medical advice and treatment. The administration of estrogen preparations to treat religious infertility in doses commonly used for an endometrial preparation for frozen-thawed embryo transfer has already been described [10,12]. The ability of this regimen to postpone follicular recruitment is well established. The patients in the present study ovulated 12.4 days after the cessation of estrogen therapy, in agreement with the findings of de Ziegler et al. [13] that exogenous estrogen may inhibit follicular recruitment and growth for up to 2 weeks after the onset of the last menstrual period. In a later work the same group [14] showed that it is feasible and practical to program ovulation in the menstrual cycle with exogenous estrogen, starting on day 25 of the previous cycle. This regimen resulted in a pre-ovulatory LH surge 13 days after cessation of estrogen therapy [14]. Of note is that unsuccessful cycles were characterized by later ovulation and mikveh days, while the interval between them did not differ from that of successful cycles. This may suggest a lack of synchronicity between the endometrium and the ovulating follicle. A previous work [10] showed that estrogen treatment with a different regimen (4 mg/day for up to 2 days after cessation of the menstrual flow) resulted in a 23% pregnancy rate per cycle. In our series higher estradiol supplementation yielded a pregnancy rate of only 12.5% per cycle, probably due to later ovulation day and higher incidence of intermenstrual spotting due to estrogen withdrawal. Still, in our study as well, the cumulative pregnancy rate per woman achieved after an average of 2.8 cycles was high, 35%.

In summary, precoital ovulation is a common cause of infertility in observant Jewish couples. Today the medical solution is the only one available. 'Religious infertility' may be treated simply and effectively with an oral estrogen preparation to delay ovulation beyond the time of the ritual bath, when intercourse is permitted. Optimization of the treatment protocols to avoid mid-cycle spotting is still needed.

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Capsule

Crosstalk between B lymphocytes, microbiota and the intestinal epithelium governs immunity versus metabolism in the gut

Using a systems biology approach, Shulzhenko et al. discovered and dissected a three-way interaction between the immune system, the intestinal epithelium and the microbiota. The authors found that, in the absence of B cells, or of immunoglobulin A, and in the presence of the microbiota, the intestinal epithelium launches its own protective mechanisms, upregulating interferon-inducible immune response pathways and simultaneously repressing Gata4-related metabolic functions. This shift in intestinal function leads to lipid malabsorption and decreased deposition of body fat. Network analysis revealed the presence of two interconnected epithelial-cell gene networks, one governing lipid metabolism and another regulating immunity, that were inversely expressed. Gene expression patterns in gut biopsies from individuals with common variable immunodeficiency or with HIV infection and intestinal malabsorption were very similar to those of the B cell-deficient mice, providing a possible explanation for a longstanding enigmatic association between immunodeficiency and defective lipid absorption in humans.

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Capsule

Mutations causing syndromic autism define an axis of synaptic pathophysiology

Tuberous sclerosis complex and fragile X syndrome are genetic diseases characterized by intellectual disability and autism. Because both syndromes are caused by mutations in genes that regulate protein synthesis in neurons, it has been hypothesized that excessive protein synthesis is one core pathophysiological mechanism of intellectual disability and autism. Using electrophysiological and biochemical assays of neuronal protein synthesis in the hippocampus of Tsc2+/− and Fmr1−/y mice, Auerbach et al. show that synaptic dysfunction caused by these mutations actually falls at opposite ends of a physiological spectrum. Synaptic, biochemical and cognitive defects in these mutants are corrected by treatments that modulate metabotropic glutamate receptor 5 in opposite directions, and deficits in the mutants disappear when the mice are bred to carry both mutations. Thus, normal synaptic plasticity and cognition occur within an optimal range of metabotropic glutamate-receptor-mediated protein synthesis, and deviations in either direction can lead to shared behavioral impairments.

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