

The relationship between serum estrogen concentration and post-dural puncture headache: a retrospective study

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Abstract. – OBJECTIVE: Post-Dural puncture headache (PDPH) is a severe and undesirable complication for the patient and anesthesiologist. PDPH is more common in female patients. However, its relationship with plasma estrogen levels has not been demonstrated. This study aimed to investigate the relationship between estrogen levels and PDPH in patients who underwent spinal anesthesia for *in vitro* fertilization (IVF) with supraphysiological estrogen levels.

PATIENTS AND METHODS: In this retrospective study, the data of patients between the ages of 18-45 with the following characteristics were included in the study: those who underwent IVF procedure between January 2021 and August 2022, in the ASA I-II risk group, and who underwent spinal anesthesia using a 25 G Quincke-tipped spinal needle at the L3-L4 or L4-L5 vertebra levels. The 48 patients in the study were in two groups according to their estradiol values: 'Supra physiological estradiol levels' (Group I=24 patients) and 'Normal estradiol levels' (Group C=24 patients). The relationship between PDPH and estrogen, progesterone, spinal needle diameter, and patient demographic characteristics were evaluated.

RESULTS: The estrogen and progesterone levels of patients in Group I were higher than in Group C ($p<0.001$ and $p<0.001$, respectively). PDPH was present in 6 (25%) patients in Group I and 5 (20.8%) patients in Group C ($p=0.731$). There was no significant correlation between PDPH and estrogen and progesterone levels ($p>0.05$).

CONCLUSIONS: Since there is no relationship between the supraphysiological estrogen level and PDPH, high serum estrogen level should not be considered as an additional risk factor for PDPH in the decision of anesthesia type for IVF procedure.

Key Words:

In vitro fertilization, Post-dural puncture headache, Progesterone, Supraphysiological estrogen.

Introduction

PDPH (Post-Dural puncture headache) was first described in 1899 and is one of the most common complications of neuraxial blockade¹. This complication, which may occur following spinal anesthesia, is extremely irritating for both the patient and the physician. The incidence of PDPH varies over a wide range of 0.1-36%². The prevalence of PDPH is higher in women than in men³. Due to several factors, the incidence of PDPH is higher in women. The incidence of specific headaches, such as migraine and tension, is higher in females^{4,5}. There may be differences in the processing of nociceptive information. As a result, women may be more sensitive to experimentally induced pain and have a more temporary sum of mechanically induced pain⁶⁻⁸. Sex hormones may affect the incidence of specific headaches⁹.

During *in vitro* fertilization (IVF) treatment, ovaries are stimulated with gonadotropins in a controlled manner, and fertile egg cells in a sufficient number are obtained. If the estradiol (E2) level released from these oocytes is between 15-350 pg/ml, it is a normal E2 level; if it is above this level, it is a supraphysiological E2 level¹⁰. Estrogen modulates cerebral artery tone and dilates cerebral pial veins¹¹. Therefore, after the IVF procedure performed under spinal anesthesia, supraphysiological E2 levels may be associated with increased PDPH development. However, no study was present in the literature on this issue. This study aimed to investigate the relationship between estrogen levels and PDPH in patients who had supraphysiological estrogen levels as a result of controlled ovarian hyperstimulation for the IVF procedure and underwent spinal anesthesia for the IVF procedure.

Patients and Methods

Design and Setting

For this retrospective study, ethics approval was obtained from the University of Health Sciences, Hamidiye Scientific Research Ethics Committee (22/418) numbered and dated August 08, 2022.

Patient Enrolment

The retrospective research data is derived from the patients' files who underwent IVF procedures at Konya City Hospital, University of Health Sciences, between January and August 2022. Patients between the ages of 18-45 years, in the (American Society of Anesthesiologists) ASA I-II risk group, and successfully anesthetized with spinal anesthesia in a sitting position at once by experienced anesthesiologists using a 25 G Quinke-tipped spinal needle at the L3-L4 or L4-L5 vertebral levels were included in the study. Patients were included in 2 groups according to E2 values. The patients' exclusion criteria were: pregnant patients, patients in the perimenopausal period, patients with psychiatric disorders, patients who underwent emergency surgery, patients with multiple spinal anesthesia trials, and patients with previous spinal anesthesia experience.

Group I: Patients with E2 (350 > pg/ml) at supraphysiological levels

Group C: Patients with similar age, weight, body mass index (BMI), ASA risk group, and a normal E2 level (≤ 350 pg/ml) to Group I.

Two groups were compared in terms of PDPH.

Sample Size

The effect was 0.408 in the pilot study conducted on 20 patients using the goodness-of-fit tests: Contingency tables test with G power software. In light of these data, a power analysis was

performed using a $\alpha = 0.05$, 80% power. The sample size was 48 (24 patients in each group) patients were in the study.

Statistical Analysis

IBM-Statistical Package for Social Sciences (IBM Corp., Armonk, NY, USA) 22.0 program was used to analyze the data in the study. The normality of data was checked with the Kolmogorov-Smirnov test. Continuous variables were expressed as the mean and standard deviation or median and 25-75 percentile according to their distribution status, and categorical variables were expressed as numbers and percentages. When testing continuous variables, the Independent Samples *t*-test was used if the test's parametric assumptions were fulfilled, and the Mann-Whitney U test otherwise. The Chi-square test compared categorical variables. The Pearson correlation test was applied if its assumptions were valid; otherwise, the Spearman rho correlation test was applied. The statistical significance threshold was $p < 0.05$.

Results

Forty-eight patients were included in this study, with each group including twenty-four patients. The demographic and laboratory data of the patients are shown in Table I.

The mean age of the patients was 29.71 ± 4.74 in Group I and 31.38 ± 5.03 in Group C ($p = 0.244$). The patients' mean BMI was similar across groups (Group I = 25.40 ± 3.70 kg/m² and Group C = 26.74 ± 3.24 kg/m², $p = 0.184$). Group I had a higher median estrogen level [1444 (692-2945 pg/mL)] than Group C [34.90 (30.20-46.90 pg/mL)] ($p < 0.001$). Similarly, Group I had a higher median

Table I. Patient characteristics.

Characteristics	Group I (n=24)	Group C (n=24)	<i>p</i>
Age (year)*	29.71±4.74	31.38±5.03	0.244
Height (cm)*	160.88±5.43	163.42±4.32	0.079
Weight (kg)*	65.96±11.70	71.42±9.10	0.078
BMI (kgm ⁻²)*	25.40±3.70	26.74±3.24	0.184
ASA1/ASA2, n (%)	15 (62.5%)/9 (37.5%)	17 (70.8%)/7 (29.2%)	0.540
Estradiol concentration (pg/mL) **	1444 (692-2945)	34.90 (30.20-46.90)	<.001
Progesterone concentration (ng/mL) **	0.78 (0.36-1.45)	0.20 (0.12-0.25)	<.001

Values are presented as mean \pm SD, median (range), or n (%). BMI= Body mass index, ASA= American Society of Anesthesiologists. *Independent Samples *t*-test. **Mann-Whitney U test.

Table II. Patient PDPH ratios of groups.

Characteristics		Group I (n=24)	Group C (n=24)	<i>p</i>
PDPH	Yes	6 (25 %)	5 (20.8 %)	0.731
	No	18 (75 %)	19 (79.2 %)	

Values are presented as n (%). PDPH=Post dural puncture headache. Chi-square test was used.

level of progesterone (0.78 (0.36-1.45 ng/mL) than Group C (0.20 (0.12-0.25 ng/mL) ($p < 0.001$). PDPH was present in 6 (25%) patients in Group I and 5 (20.8%) patients in Group C ($p = 0.731$) (Table II).

The results of the correlation analysis between PDPH and demographic data are shown in Table III. No significant correlation was found between PDPH and age, height, weight, BMI, estrogen, and progesterone levels ($r = -.112$, $r = 0.087$, $r = 0.061$, $r = 0.027$, $r = 0.191$ and $r = 0.271$).

Discussion

According to the results, there was no relationship between estrogen levels and PDPH in patients with supraphysiological E2 levels after controlled ovarian hyperstimulation for IVF procedures. In addition, no relationship was present between progesterone level, age, BMI, and PDPH.

Infertility is a global health problem that affects millions of people of reproductive age around the world. According to the World Health Organization, 15% of couples of reproductive ages have infertility problems¹². Various assisted reproductive technologies are available for treating infertility. The most common of these

techniques, IVF, requires one of the anesthesia techniques, such as deep sedation, general anesthesia, spinal anesthesia, or regional anesthesia, to prevent pain and comfort of the patient^{13,14}. An ideal anesthesia technique should have a fast start and finish, be easy to apply, have no toxic effect on oocytes, and provide optimal surgical conditions¹⁴. The clinical goals of anesthesiologists in IVF should be to minimize patient movement during the procedure, to reduce pain awareness in the intraoperative period, and to accelerate discharge by minimizing the recovery time^{15,16}.

In the sedation method, spontaneous ventilation is maintained with less anesthetic exposure, and myometrium fibrils, which are not completely relaxed despite the preservation of cardiovascular functions, restrict the oocyte intake of the surgeon^{17,18}. The general anesthesia method provides better surgical comfort and complete muscle relaxation than sedation. However, the disadvantages of this technique are the long recovery time, the risk of postoperative nausea and vomiting, cardiorespiratory depression, and the use of intravenous or inhaled anesthetics may be associated with a low probability of pregnancy^{19,20}. Many studies²¹⁻²³ report that IVF results are better in the spinal anesthesia method because the blood level of anesthetic drugs is much lower. However, undesirable technique-related consequences, such as prolonged discharge, urinary retention, low back pain, and PDPH, may cause the patient and anesthesiologist to avoid the spinal anesthesia method. PDPH can seriously impair daily life in patients, as it can also cause symptoms such as nausea, vomiting, dizziness, tinnitus, hearing loss, vertigo, and paresthesia in the shoulders²⁴. In this retrospective study, PDPH developed in 6 (25%) of 24 patients who underwent the IVF procedure under spinal anesthesia.

Common patient risk factors for PDPH include needle type and diameter, female gender, pregnancy, 18 to 50 years of age compared to older or younger ages, and a history of previous headaches²⁵. There is a direct relationship between PDPH and cerebrospinal fluid (CSF) loss,

Table III. The relationship between PDPH and patient characteristics.

Characteristics	PDPH	
	<i>r</i>	<i>p</i>
Age (years)*	-.112	0.449
Height (cm)*	0.087	0.558
Weight (kg)**	0.061	0.681
BMI (kgm ⁻²)**	0.027	0.853
Estradiol concentration (pg/mL)*	0.191	0.194
Progesterone concentration (ng/mL)*	0.271	0.063

PDPH=Post dural puncture headache. BMI= Body mass index. *Pearson's correlation coefficient. ** Spearman's correlation coefficient.

and Monroe-Kelly²⁶ stated that intracranial volume loss will be compensated by blood, CSF, and brain tissue²⁷. Pen-tipped spinal needles cause less PDPH than Quincke-tipped needles, and thin needles cause less CSF loss than thick needles²⁸. The incidence of PDPH for Quincke-tipped needles is 36% in 22 G needle use, 25% in 25 G needle use, 2-12% in 26 G needle use, and 2% and less in 29 G needle use²⁹⁻³². In this study, the relationship between spinal anesthesia and PDPH, which was applied with a Quincke tip 25 G needle, was investigated in connection with clinical use. According to the results, the rate of PDPH development was similar to the literature.

Although the female sex is an independent risk factor for the development of PDPH, its specific mechanism is not clear³³. Although studies on estrogen have reported that estrogen and estrogen receptors have a critical role in pain modulation in women, they reported conflicting results⁹. Cao et al³⁴, stated that estrogen increases visceral pain, whereas Maleki et al³⁴, claimed that migraine seizures may be triggered due to increased prostaglandin levels from the hypothalamus and uterine functions by decreased estrogen levels. In this study, which we conducted with the hypothesis that there may be a relationship between estrogen levels and PDPH at the supraphysiological level, we did not find a relationship between PDPH and high estrogen levels.

Multiple mechanisms and factors may be effective in the development of PDPH. Although the mechanism of anxiety is unclear, it is a risk factor for PDPH³⁶. Khlebtovsky et al³⁷, suggested that a patient's anxiety and associated excessive muscle contraction may lead to CSF leakage and resulting PDPH. A description of the possible relationship between PDPH and anxiety may be associated with neurochemical effects at the level of neurotransmitters related to anxiety feeling. The most critical neurotransmitters in modulating anxiety responses are as follows: gamma-aminobutyric acid, serotonin, norepinephrine, opioid peptides, endocannabinoids, neuropeptide Y, oxytocin, and corticotropin-releasing hormone³⁸. Studies³⁹ have shown a positive correlation between plasma serotonin levels and CSF production. Anxiety is present more frequently in IVF patients than in the general population⁴⁰. In this study, the possible high rate of anxiety incidence in the patient population may also be a factor in PDPH development. However, the fact that this could not be evaluated since the research is retrospective is a limitation of this study. However, the fact that this could not be evaluated since the re-

search is retrospective is a limitation of this study. Also, we did not consider the impact of factors reducing PDPH incidences, such as perioperative fluid intake and postoperative bed rest. Finally, we only investigated the relationship between serum estrogen levels and PDPH following spinal anesthesia performed with a 25 G Quincke spinal needle because it is frequently used for subarachnoid anesthesia practice in our clinic.

Conclusions

In conclusion, there was no relationship between serum supraphysiological estrogen levels and PDPH in patients of reproductive age. In the decision of anesthesia type for IVF treatment, we suggest that high serum estrogen level should not be considered as an additional risk for PDPH, and that the anesthesia method should be decided by considering other factors.

Conflicts of interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The approval for this retrospective study was granted by the Ethics Committee of University of Health Sciences, Hamidiye Scientific Research Ethics Committee (decision No. 22/418, dated: August 08, 2022).

Funding

None.

Authors' Contribution

M.S. TUTAR and B. KOZANHAN both contributed to the conception and design of the study; D. GOK KORUCU and M.S. TUTAR collected and analyzed the data; C. CIFTCI and B. KOZANHAN drafted the manuscript; revised the manuscript and provided supervision; all authors approved the final version of the manuscript.

Informed Consent

Not applicable.

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