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ORIGINAL PAPER

ASSESSMENT OF THE IMPACT OF SODIUM AND POTASSIUM METABOLISM IN WOMEN UNDERGOING HYSTEROSCOPY DUE TO PATHOLOGICAL UTERINE BLEEDING*

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ABSTRACT

Monitoring the water and electrolyte balance is an integral part of diagnostics and designing an effective therapy of many diseases. Sodium and potassium play a crucial role in the diagnosis of water and electrolyte disorders. The study was conducted to demonstrate the relationship between the occurrence of electrolyte disturbances in women undergoing hysteroscopy due to pathological uterine bleeding. Medical records of 543 patients aged 21-88 (52.8±11.8 years) hospitalized in the Gynecology and Obstetrics Department of the Provincial Specialist Hospital in Biała Podlaska, who underwent hysteroscopic diagnostics due to pathological bleeding from the uterus were collected. 212 women (39.04%) were diagnosed with pathological bleeding from the uterus, 147 women (27.07%) had endometrial hyperplasia, 104 women (19.15%) were diagnosed with an endometrial polyp, 62 women (11.42%) suffered from heavy menstruations and 18 women (3.3%) had uterine fibroids. The sodium and potassium concentrations were measured using an automated Cobas® 8000 analyzer (Roche). The average concentration of sodium in the serum was 139.84±2.13 mmol L⁻¹ ($\chi^2 = 35.079$; $P < 0.001$), and the average potassium concentration was 4.44±0.37 mmol L⁻¹ ($\chi^2 = 36.019$; $P < 0.001$). Higher values for sodium were recorded in the group of patients with adenomyosis (140.41±2.27 mmol L⁻¹) and patients with

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uterine fibroids (140.11 ± 1.94) mmol L⁻¹). Statistically significant differences were found in mean sodium concentration values depending on the causes of patients' hospitalization ($H=33.914$; $P<0.001$), and the biggest differences were between patients with ovulation disorders and patients with adenomyosis: 138.86 ± 0.21 mmol L⁻¹ vs. 140.41 ± 2.27 mmol L⁻¹ ($Z=5.169$; $P<0.001$). It seems important add measurements of sodium and potassium concentrations to the profile of tests performed in the diagnosis of gynaecological patients referred for hysteroscopy for the reasons presented in the study in order to reduce the risk of complications associated with the loss of these elements.

Keywords: gynaecology, menstruation, menstrual disorders, abnormal uterine bleeding, kalium, natrium, endometrial hyperplasia, endometrial polyp, heavy menstruation, uterine fibroids.

INTRODUCTION

Monitoring the water and electrolyte balance is an integral part of diagnostics and effective therapy of many disease entities. Renal dysfunction, heart failure, cirrhosis, massive bleeding, endocrine disorders manifest their presence with an abnormal ionogram image. Sodium and potassium play a crucial role in the diagnosis of water and electrolyte disorders (FIJOREK et al. 2014).

Hyponatraemia is the most common electrolyte disturbance in both outpatient and hospitalized patients, with a frequency of 15-20% in this group and up to 47% in the group of oncological patients (GUO et al. 2019). Literature indicates a relationship between hyponatraemia and increased susceptibility to diseases as well as a higher risk of mortality (HOORN, ZIETSE 2017). For hyponatraemia diagnostics, the plasma sodium concentration threshold is <135 mmol L⁻¹. Due to sodium concentration, we classify hyponatraemia as mild covering the range 130-134 mmol L⁻¹, moderate 125-129 mmol L⁻¹ and severe at values <125 mmol L⁻¹. Treatment of chronic hyponatraemia carries the risk of a severe complication in the form of an osmotic demyelinating syndrome, although it may prove useful in supporting cancer therapy in small cell lung cancer manifested by SIADH syndrome (FIJOREK et al. 2014, SAWICKI, KULESZA 2015, GUO et al. 2019).

The phenomenon of hypernatraemia appears when the plasma sodium concentration exceeds the value of 148 mmol L⁻¹. The excessive loss of water or reduction in its supply are the most important causes. Hypernatraemia contributes to increased susceptibility to disease and higher mortality among hospitalized patients. Untreated, it leads to excessive stiffening of blood vessels due to the conversion of G-actin endothelial cells into F-actin. In addition, it inactivates the release of endothelial nitric oxide, demonstrating hypertensinogenic activity (FIJOREK et al. 2014, SAWICKI, KULESZA 2015, WEISS et al. 2017).

Potassium imbalance disorders are a common phenomenon. Hypokalaemia is a condition of reduced plasma potassium < 3.8 mmol L⁻¹, which affects about 21% of hospitalized patients and about 2-3% of outpatients (VIERA, WOUK 2015). Loss of potassium from extracellular space results in hyperpo-

larization of cells and, depending on the amount of loss, manifests symptoms ranging from muscle weakness, paresthesia or palpitations to paralytic ileus and flaccid paralysis. Hyperkalaemia occurs if serum potassium is elevated above 5.5 mmol L⁻¹. Significance of potassium increase decide on the division of hyperkalaemia into mild (5.6-6.6 mmol L⁻¹), moderate (6.7-7.5 mmol L⁻¹) and severe (> 7.5 mmol L⁻¹).

One of the most common causes of visits to the gynaecological outpatient clinic is disruption of the monthly cycle by the appearance of episodes of abnormal uterine bleeding. Endometrial polyp, uterine leiomyoma, endometrial hyperplasia, endometrial cancer, inflammation of the lining of the uterus are the most common causes of uterine bleeding, as determined in accordance with the guidelines of The International Federation of Gynecology and Obstetrics (FIGO) as any differences in physiological menstrual bleeding and abnormal bleeding between periods. Differential diagnosis of the causes of abnormal uterine bleeding (AUB) is based on hysteroscopic examination. Safety, ease of procedure and patient comfort have made hysteroscopy a leading examination in the visualization of the uterine cavity, enabling making a preliminary diagnosis (SOGUKTAS et al. 2012, PANDEY et al. 2017). The PALM-COEIN classification developed by FIGO in 2011 presents the causes of pathological uterine bleeding, divided according to structural and non-structural aspects. A guided endometrial biopsy performed during hysteroscopy substantiates the exclusion of structural causes of abnormal uterine bleeding (DE KROON et al. 2003, MARCHETTI et al. 2005, CHODANKAR, CRITCHLEY 2019).

Under the AUB-P category, endometrial polyps formed by proliferation of the uterine epithelium with the participation of glands, endometrium and blood vessels are distinguished. The macroscopic image of polyps is varied, and most do not manifest their presence. Uterine polyps affect about 10-15% of the general population of women not affected by AUB (GOLDSTEIN et al. 2002, CLARK, STEVENSON 2017). The category of AUB-A include adenomyosis as an ectopic growth of the basal layer of the endometrium within the myometrium. The detection of adenomyosis by diagnostic hysteroscopy covers from 5 to 70% of women undergoing examination, with a histopathological analysis narrowing the range to 20-35% (ABBOTT 2017, VANNUCCINI, PETRAGLIA 2019). Uterine fibroids, also known as uterine leiomyomas, included in the AUB-L category are the most common benign tumors in the reproductive age group. Abnormal uterine bleeding is the main manifestation of fibroids, although more than half of the tumors are asymptomatic. 80% of uterine fibroids are found in women before the age of 50 (DVORSKÁ et al. 2017, LASMAR, LASMAR 2017). The category AUB-O includes ovulation disorders, which most often affect women from extremely opposite reproductive age limits. They are a manifestation of the polycystic ovary syndrome, hyperprolactinemia, hypothyroidism (risk of hyponatraemia and hypocalcemia), hormonal disorders associated with obesity or significant weight loss (ADRA et al. 2016). Disorders of local endometrial mechanisms

regulating hemostasis constitute the AUB-E category, which includes women with a normal structural image of the uterus, without disturbances of the monthly cycle and coagulopathy (MERAJ et al. 2018).

The presence of abnormal uterine bleeding and the repeatedly associated loss of large amounts of blood suggest the risk of water and electrolyte imbalance, with particular emphasis on deviations in sodium and potassium as the dominant cations in the organism. The non-specificity of the symptoms and the severe course of sodium-potassium imbalance as well as the significance of deviations in the prognostic analysis of treatment further support the need to monitor the levels of these elements in terms of standard procedures performed on women with pathological uterine bleeding. The study was conducted to demonstrate the relationship between the occurrence of electrolyte disturbances in women undergoing hysteroscopy due to pathological uterine bleeding.

MATERIALS AND METHODS

The study comprised medical records of blood samples from 543 female patients in the age range of 21-88 years (52.81 ± 11.79), hospitalized in the Gynecology and Obstetrics Department of the Provincial Specialist Hospital in Biała Podlaska, Poland. This is a retrospective study, based on data obtained over the past year. Due to the lack of a suitable group of patients who could form a control group from this hospital, no such group was created. Qualified patients underwent clinical examination during which blood samples were taken for testing. Causes of the electrolyte imbalance other than those resulting from the presence of abnormal uterine genital bleeding were ruled out on an ongoing basis in order to obtain a reliable database. Other disease cases were excluded, patients in the hospital were given the same hospital diet and did not take any medications or supplements. The patients enrolled in the study were divided according to the reason for a hysteroscopic diagnosis:

- III group – patients with pathological bleeding from the uterus - 212 females (39.04%);
- III group – patients with endometrial hyperplasia - 147 females (27.07%);
- III group – patients with endometrial polyp - 104 females (19.15%);
- IV group – patients with heavy menstruation - 62 females (11.42%);
- IV group – patients with uterine fibroids - 18 females (3.3%).

The patients were also divided according to their premenopausal or postmenopausal status:

- II. Premenopausal patients - 240 patients (44.2% of all women);
- II. Postmenopausal patients (age > 50 years) - 303 patients (55.8% of all women).

Serum sodium and potassium were tested in all patients. The laboratory test was performed in the diagnostic laboratory of the Provincial Specialist Hospital in Biala Podlaska. An automated Cobas® 8000 analyzer (Roche) was used to measure test serum ions. It is a modular analyzer containing an intermediate ion selective electrode (ISE) module for measuring sodium and potassium.

Statistical analysis

Statistical analysis was performed using the Statistica 12.0 package. Examination of the compliance of research data with normal distribution was verified by the χ^2 test. For data whose distribution differed from normal, the non-parametric Kruskal-Wallis test was used, while in order to test the significance of differences between individual means, the test of multiple comparisons of mean ranks, called the Dunn's test, was used for all tests. The p-values less than 0.050 were considered statistically significant.

RESULTS

The analyses carried out among 543 patients included in the study showed that the average concentration of sodium in blood was 139.84 ± 2.13 mmol L⁻¹ ($\chi^2 = 35.079$; $P < 0.001$), while the average potassium concentration in blood was 4.44 ± 0.37 mmol L⁻¹ ($\chi^2 = 36.019$; $P < 0.001$). The average values of the concentrations of these elements due to the reason for hospitalization are presented in Figures 1 and 2. Higher values for sodium were recorded

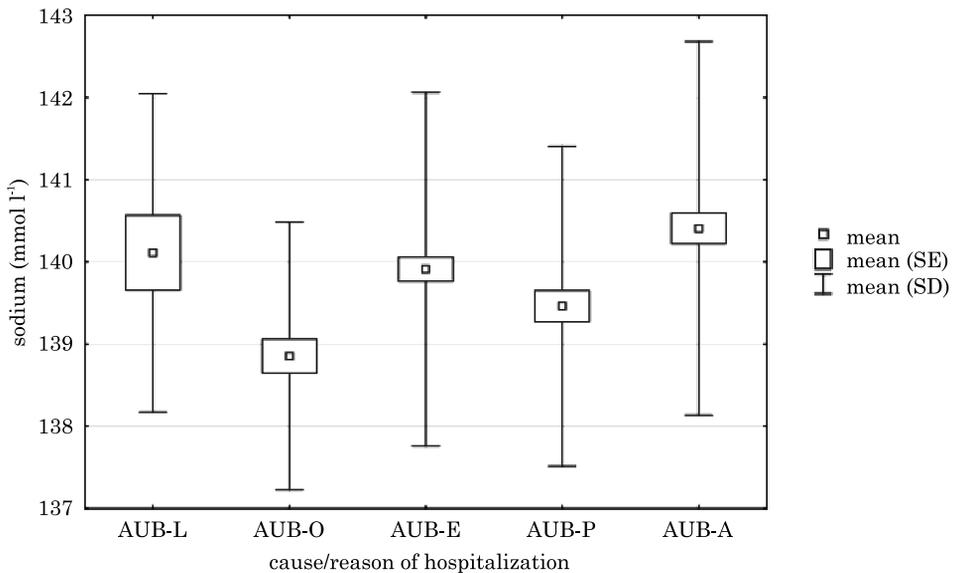


Fig. 1. Average values of the blood sodium level due to the reason of hospitalization

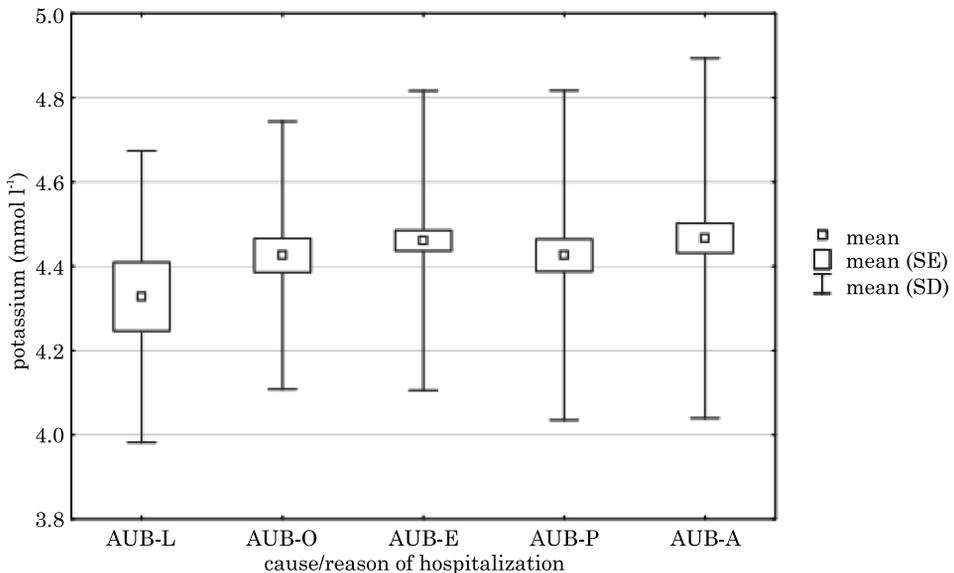


Fig. 2. Average values of the blood potassium level due to the reason of hospitalization

in the group of patients with AUB-A (140.41 ± 2.27 mmol L⁻¹ and AUB-L (140.11 ± 1.94) mmol L⁻¹). Statistically significant differences were found in mean values of the sodium concentration in relation to the causes of patients hospitalization ($H=33.914$; $P<0.001$), the biggest differences were between AUB-O and AUB-A patients - 138.86 ± 0.21 mmol L⁻¹ vs. 140.41 ± 2.27 mmol L⁻¹ ($Z = 5.169$; $P<0.001$) and AUB-P and AUB-A patients - 139.46 ± 0.19 mmol L⁻¹ vs. 140.41 ± 2.27 mmol L⁻¹ ($Z = 3.861$; $P=0.001$). As for differences in the mean values of potassium in the blood of the examined patients, no statistical significance was noted ($H=3.969$; $P=0.41$). It was observed that at low sodium levels, AUB-L patients had higher potassium levels, while for AUB-A patients low potassium levels were accompanied by lower sodium levels (Figure 3), although the statistical analysis showed no statistically significant correlation between variables $r<0.2$ ($r=0.09$; $P=0.039$).

Pathological uterine bleeding

212 women aged 27 to 85 (52.7 ± 10.1 years – Figure 4) were admitted to hospital because of abnormal uterine bleeding. 85 (40.1%) patients were in premenopausal age and 127 (59.9%) were in postmenopausal age. Two of these patients (0.95%) had mild hyponatraemia ($130-134$ mmol L⁻¹). In 7 patients (3.3%), sodium levels reached or were near the lower limit of normal ($135-136$ mmol L⁻¹). No patient had hypernatraemia (>148 mmol L⁻¹), while a result close to or equal to the upper limit ($144-145$ mmol L⁻¹) was found in 7 (3.3%) patients. The result of one patient (0.47%) was 147 mmol L⁻¹.

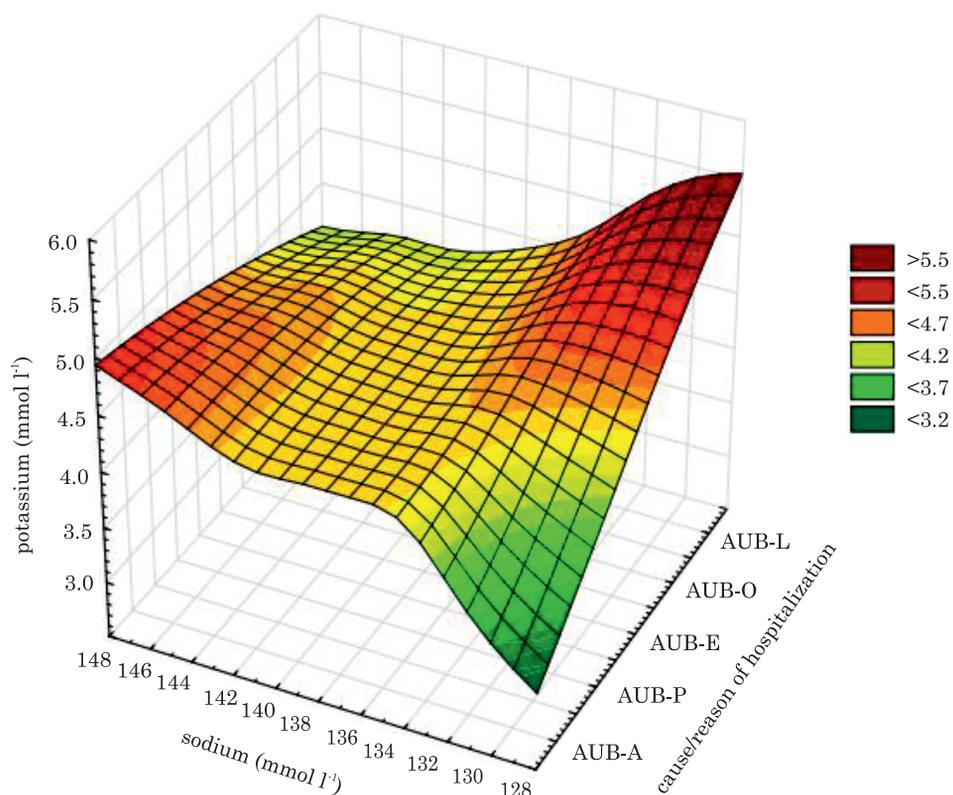


Fig. 3. Distribution of sodium and potassium values due to the reasons for hospitalization

Hypokalaemia ($<3.8 \text{ mmol L}^{-1}$) was found in 4 women (1.89%) and potassium levels near the lower normal limit ($3.8\text{-}3.9 \text{ mmol L}^{-1}$) occurred in 8 patients (3.77%). No patient developed hyperkalaemia, although the score of 2 patients (0.95%) was close to the upper limit of normal (5.4 mmol L^{-1}). Total deviation from the norm for sodium and potassium in this group of women concerned 7 women (3.3%). The average sodium concentration in the group was $139.91 \pm 2.15 \text{ mmol L}^{-1}$, and potassium $4.46 \pm 0.35 \text{ mmol L}^{-1}$.

Endometrial hyperplasia

Patients hospitalized for endometrial hyperplasia accounted for 27.07% (147 women) of all patients. The age range in this group comprised women from 34 to 88 years with an average age equal to 60.5 ± 10.9 years (Figure 4). There were 27 patients (18.4%) in premenopausal age and 120 (81.6%) in postmenopausal age. Mild hyponatraemia ($130\text{-}134 \text{ mmol L}^{-1}$) was found in 1 patient (0.68%). Sodium levels near the lower limit ($135\text{-}136 \text{ mmol L}^{-1}$) occurred in 6 patients (4.08%). The level of sodium in the remaining women was within the normal range, with 12 of them (8.16%) having values close

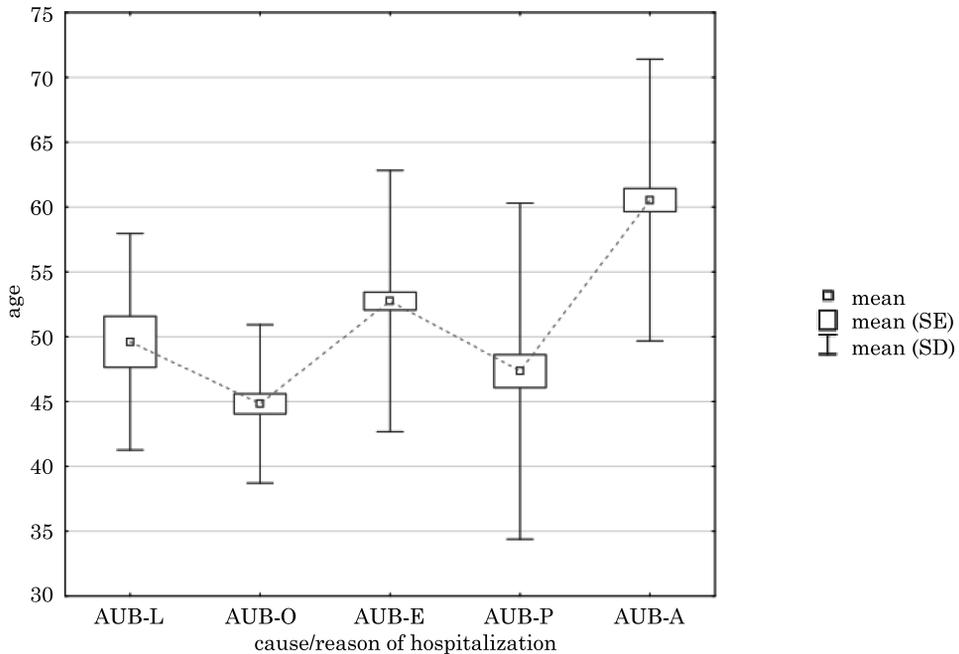


Fig. 4. Average age of patients due to the reasons for hospitalization:

AUB-A – endometrial hyperplasia, AUB-E – pathological uterine bleeding,
 AUB-L – uterine leiomyoma, AUB-O – heavy menstrual periods, AUB-P – endometrial polyp

to or equal to the upper limit of normal ($144\text{--}145\text{ mmol L}^{-1}$). Among 9 patients (6.12%) with hypokalaemia ($<3.8\text{ mmol L}^{-1}$) in 2 women (1.36%) potassium values were significantly reduced ($3.0\text{--}3.2\text{ mmol L}^{-1}$). In addition, 7 patients (4.76%) reached values close to or equal to the lower limit of normal for potassium ($3.8\text{--}3.9\text{ mmol L}^{-1}$). In 5 patients (3.4%), potassium levels were close to or equal to the upper limit of normal ($5.4\text{--}5.5\text{ mmol L}^{-1}$). No hyperkalaemia was found in this group. One patient had both hyponatraemia (130 mmol L^{-1}) and hypokalaemia (3.6 mmol L^{-1}). Deviation from the norm for sodium and potassium in this group of women concerned 10 women (6.8%). The average sodium concentration in this group was $140.41 \pm 2.27\text{ mmol L}^{-1}$, while potassium $4.47 \pm 0.43\text{ mmol L}^{-1}$.

Endometrial polyp

104 women (19.15%) in age from 21 to 78 years (47.4 ± 12.9 years) who underwent hysteroscopy have been diagnosed with an endometrial polyp. 68 (65.4%) patients were in premenopausal age and 36 (34.6%) in postmenopausal age. In 5 (4.8%) patients among this group, the sodium concentration reached the value close to or equal to the lower limit of normal ($135\text{--}136\text{ mmol L}^{-1}$). In 2 (1.92%) sodium levels were close to or equal to the upper limit ($144\text{--}145\text{ mmol L}^{-1}$) and 1 patient (0.96%) it exceeded the limit

(146 mmol L⁻¹). Hyponatraemia and hypernatraemia did not occur in any patient from this clinical group. Hypokalaemia (<3.8 mmol L⁻¹) was found in 2 women (1.92%) and a value close to or equal to the lower limit (3.8-3.9 mmol L⁻¹) in 7 patients (6.73%). Hyperkalaemia occurred in 2 women (1.92%), and a potassium value near the upper limit of normal (5.4 mmol L⁻¹) occurred in 1 patient (0.96%). Total deviation from the norm for sodium and potassium in this group of women concerned 4 women (3.85%). The average sodium concentration in this group was 139.46±1.94 mmol L⁻¹, while potassium 4.42±0.39 mmol L⁻¹.

Heavy menstrual periods

In the study group, profuse menstruation occurred in 62 women (11.42%) in the age group from 29 to 56 years (44.8±6.11 years). The premenopausal patients constituted 80.6% (50 women) and postmenopausal ones were 19.4% (12 women) of all women in this group. Mild hyponatraemia (130-134 mmol L⁻¹) was found in 1 patient (1.61%). In this group, 4 patients (6.45%) had sodium levels equal to or near the lower limit of normal (135-136 mmol L⁻¹). Sodium values in the remaining patients were within the normal range for this element. No hypernatraemia was found. Potassium levels equal to or near the lower limit of normal (3.8-3.9 mmol L⁻¹) occurred in 5 women (8.05%). No hypokalaemia or hyperkalaemia was found. Total deviation from the norm for sodium and potassium in this group of women concerned 1 woman (1.61%). The average sodium concentration in this group was 138.86±1.63 mmol L⁻¹, while potassium 4.43±0.32 mmol L⁻¹.

Uterine leiomyoma

Patients hospitalized for uterine fibroids accounted for 3.2% of all examined women (18 women). The age range was equal to the range of 37-66 years (49.6±8.4 years). Ten patients (55.5%) were in premenopausal age and 8 (44.5%) were in postmenopausal age. There was no hyponatraemia or hypernatraemia in this group. Only 1 patient (5.55%) had a sodium level of 136 mmol L⁻¹, which is close to the lower limit of normal (135 mmol L⁻¹). Hypokalaemia (<3.8 mmol L⁻¹) occurred in 1 patient (5.55%). Potassium levels near the lower limit of normal (3.8-3.9 mmol/l) also affected 1 patient (5.55%). No hyperkalaemia was found. Total deviation from the norm for sodium and potassium in this group of women concerned 1 woman (5.55%). The average sodium concentration in this group was 140.11±1.94 mmol L⁻¹, whereas potassium 4.33±0.35 mmol L⁻¹.

DISCUSSION

The results presented in this article have shown the presence of sodium-potassium disorders with a total frequency not exceeding 17% among women who underwent hysteroscopy with a diagnosis of pathological bleeding, endometrial polyps, heavy menstrual periods and uterine fibroids. The decrease in sodium and potassium levels dominating in these groups supports the importance of including a measurement of the concentrations of these elements in the profile of tests ordered during a diagnostic procedure in order to reduce the risk of complications associated with the loss of sodium and potassium. Sodium-potassium abnormalities were most often found in women with endometrial hyperplasia and primarily included hypokalaemia and elevated sodium levels. The most common disorder among the entire study group was a decrease in the serum potassium, predisposing to hypokalaemia. The second most common disorder among the women surveyed was hyponatraemia. Hyponatraemia is the most frequent electrolyte disturbance in both outpatient and hospitalized patients, with an incidence of 15-20% in this group and up to 47% in the group of oncological patients (GUO et al. 2019). Studies conducted on the impact of preoperative hyponatraemia in patients with an epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer confirm that it adversely affects the length of postoperative hospitalization, a 30-day postoperative mortality rate as well as postoperative complications (MARTIN et al. 2016, GUO et al. 2019). The third most frequently noted disturbance in the sodium-potassium balance among the examined patients was an elevated sodium level. Studies have repeatedly shown that excessive sodium accumulation stimulates the phagocytic system within the interstitial space and by the transcription factor TonBP activates the vascular endothelial growth factor VEGF-C, whose action is reduced to osmoprotective activation of lymphangiogenesis and lymphatic transport of interstitial fluid, which plays a key role in the maintenance of volemia and in the pathogenesis of hypertension (KOKOT, HYLAKLEKOT 2013).

Untreated hypernatraemia contributes to excessive stiffening of blood vessels due to the conversion of G-actin endothelial cells into F-actin. In addition, it inactivates the release of endothelial nitric oxide, demonstrating hypertensinogenic activity (KOKOT, HYLAKLEKOT 2013, FIJOREK et al. 2014, SAWICKI, KULESZA 2015, WEISS et al. 2017).

Many authors raise the issue of sodium-potassium balance disturbances but pay attention to different aspects. A combination of hypernatraemia with intracranial bleeding, including rupture of blood vessels due to excessive contraction has been demonstrated. An adverse effect of hyponatraemia in cardiac surgery patients with heart failure has been associated with the frequent presence of postoperative complications and higher mortality. Studies also demonstrate a significant correlation of hyponatraemia

with mortality prediction among outpatient patients (CRESTANELLO et al. 2013, MOHAN et al. 2013, BRAUN et al. 2015). An increased mortality risk as well as an increased stroke risk have been demonstrated also in cases of hypokalaemia (LAI et al. 2015, LASMAR, LASMAR 2017). The researchers also raise the issue of hypokalaemia as an adverse condition after subarachnoid haemorrhage (SAH) (CHEN, MITCHELL 2016, MATANO et al. 2019).

The women included in the study underwent diagnostic hysteroscopy to determine the cause of pathological uterine bleeding (AUB). In the study group, endometrial polyps were the cause of AUB in 19.15% of women. Endometrial hyperplasia was diagnosed in 27% of women who underwent hysteroscopy for AUB. In the study group, uterine fibroids affected 3.3% of women and no changes of a malignant nature were found.

In 11.42% of women, the cause of AUB was heavy menstrual periods and the reason for their occurrence requires further clinical diagnostics. Diagnostic hysteroscopy showed no macroscopically apparent cause of pathological bleeding in 39% of the examined women. It seems reasonable to broaden the scope of diagnostic procedures to include units from the COEIN categories in order to resolve ambiguous causes of AUB and determine the relationship with the sodium-potassium disorders occurring in the examined women, which affected as many as 14.15% of these patients (GOYAL et al. 2015, CHODANKAR et al. 2018).

Due to the considerable incidence of sodium and potassium metabolism disorders and their harmful effects on the body, monitoring the level of both elements seems to be important among patients hospitalized and outpatient because of pathological uterine bleeding, endometrial hyperplasia, endometrial polyps, profuse menstruation and uterine fibrosis. The study was motivated by the shortage of information in the literature concerning electrolyte disorders in women undergoing hysteroscopy due to pathological uterine bleeding and the significance of this issue in the prognostic analysis of treatment.

CONCLUSIONS

1. Disorders of the sodium-potassium management in women undergoing hysterectomy because of abnormal uterine bleeding, endometrial hyperplasia, endometrial polyps, heavy menstrual bleeding and leiomyomas of the uterus are not a common phenomenon.

2. Sodium-potassium balance disorders were most common in patients with endometrial hyperplasia and primarily included hypokalaemia and elevated sodium levels.

3. Most women with uterine leiomyomas and heavy menstrual periods had sodium and potassium levels within the normal range.

4. Sodium-potassium balance disorders were significantly more frequent in postmenopausal patients

5. A decrease in the serum potassium, which predisposes to hypokalaemia, is the most common sodium-potassium management disorder in women undergoing hysteroscopy for the reasons considered in the study.

6. In the group studied, hypokalaemia was the most common disorder of potassium-sodium metabolism among disorders not included in the range of norms for these elements.

7. Hypernatraemia and hyperkalaemia were the lowest frequency disorders.

8. It seems important to add the measurement of sodium and potassium concentrations in the profile of tests ordered during the diagnosis of gynaecological patients referred for hysteroscopy for the reasons presented in the study in order to reduce the risk of complications associated with the loss of these elements.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Contribution statement

PZ conceived the concept of the study, data collections, manuscript drafting; LS laboratory analysis and interpretation of the results, manuscript drafting; JK data collection; AS contributed to the design of the research, data collection; GW statistical analysis and interpretation of the results; PO data interpretation, literature review, manuscript preparation. All authors edited and approved the final version of the manuscript.

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