Menstrual Abnormalities and Associated Hormone Profile In Chronic Kidney Disease Stage 5 Patients

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Abstract:
Background: Although menstrual abnormalities and associated hormonal dysregulations are very common in the reproductive age group of Chronic Kidney Disease (CKD) patients, this remains a neglected area. This field had been poorly explored in last ten years worldwide and a few research regarding this area in Bangladesh as well.

Aim: To evaluate menstrual abnormalities occurring in CKD stage 5 (CKD5) patients undergoing twice-weekly and thrice-weekly maintenance hemodialysis (HD) also in non-dialytic CKD5 patients and to provide more detail information on hormone profile (FSH, LH, Prolactin, Estradiol) of these patients.

Materials and method: This observational study was conducted in the Department of Nephrology, DMCH, the sample population was also collected from BSMMU and NIKDU from April 2017 to March 2018. A total of 51 CKD stage 5 patients were enrolled in this study. Among them, 34 patients were dialytic (17 of them were taking twice weekly HD and 17 of them were taking thrice weekly HD) and 17 non-dialytic patients at reproductive age were evaluated. Detailed menstrual histories, thorough clinical examinations as well as investigations were done in all the patients. Serum FSH, LH, Estradiol, and Prolactin were evaluated using chemiluminescence immunoassay in the Department of Microbiology of BSMMU.

Statistical analysis of the study was done by SPSS-24. The confidence interval was considered at 95% level. P-value <0.05 was considered statistically significant.

Introduction
Chronic kidney disease (CKD) is the most important health concern worldwide, with a high prevalence and incidence [1]. CKD in women is often accompanied by menstrual and fertility disorders as a consequence of kidney-mediated endocrine disturbances [2]. The reproductive system disorders are commonly encountered in adults of both sexes with End-stage renal disease (ESRD). The majority of premenopausal women undergoing dialysis therapy experience anovulation, abnormal menstrual cycles, often associated with secondary amenorrhea, loss of libido.\textsuperscript{3,4}

Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus is pivotal to the regulation of reproductive physiology. The gonadotropes respond to GnRH pulses by releasing the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which stimulate folliculogenesis and hormone secretion from the ovaries.\textsuperscript{5}
As CKD progresses, the tonic release of GnRH regulating the basal secretion of the LH and FSH appears to remain normal, but there is loss of the normal cyclic release of GnRH by the hypothalamus resulting in impaired ovulation. So there is inhibition of high estradiol-mediated pulsatile secretion of GnRH due to CKD. Why cyclic release of GnRH is compromised in the setting of CKD is unclear, but hyperprolactinemia and high levels of GnRH and LH caused by reduced clearance have been implicated.²,⁶

Menstrual disturbances, especially secondary amenorrhea, are commonly seen among women of reproductive age group with End stage renal disease (ESRD). It is postulated that elevated serum prolactin (PRL) levels may partly contribute to menstrual disturbance. The mechanisms for hyperprolactinemia in CKD patients are not well defined, but a possible cause could be an increased autonomous production rate of PRL and a decreased metabolic clearance rate also play a role²,⁷. As a result of increased prolactin levels, normal cyclic GnRH secretion decreases, resulting in the loss of pulsatile LH and FSH release, ultimately leading to the decline and eventual absence of estradiol release and an ensuing lack of progestational changes in the endometrium.⁸,⁹

Besides, while amenorrhea was detected in women with high prolactin, regular menstruation was reported in women with the lowest level of prolactin. The most considerable cause of these menstrual abnormalities is the increment of prolactin levels and LH levels related to impaired hypothalamic-pituitary-ovarian (H-P-O) axis.⁹,¹⁰

The menstrual cycle typically remains irregular with scanty flow at the beginning of maintenance dialysis, although normal menstrual cycle is restored in some woman and ovulation might be seen with continuation of HD for longer period.⁶

Hormonal disturbances can be corrected by normalization of the serum PRL level through improving renal replacement therapy (RRT). Treatment with peritoneal or conventional HD does not restore H-P-O function; however, treatment with increased intensity of HD¹¹ and kidney transplantation,¹²,¹³ often restores menses and fertility. An important reason for this condition in these cases is the long-term HD that all patients undergo and sufficient time for improvement of blood parameters.⁵ Prolactin levels gradually decreased with longer duration of HD. In uraemic women, menses may return after a variable length of HD treatment, but their cycles may still be irregular in duration or amount of menstrual flow.⁸

Thus, the role and effects of RRT on menstrual cycle remodeling in reproductive women with ESRD is still controversial. Hence, the purpose of this study was to evaluate menstrual abnormalities occurring in CKD stage 5 patients undergoing twice-weekly and thrice-weekly maintenance HD also in non-dialytic CKD stage 5 patients and to provide more detail information on hormone profile (FSH, LH, Prolactin, Estradiol) of these patients.

Materials and Methods:
This observational study was conducted in the Department of Nephrology, Dhaka Medical College Hospital. As female CKD patients in reproductive age groups are few in numbers so patients were also collected from Bangabandhu Sheikh Mujib Medical University (BSMMU) as well as the National Institute of Kidney Diseases and Urology (NIKDU). Study period from April 2017 to March 2018. Inclusion criteria was females in the reproductive age group (15-45 years irrespective of menstrual status) CKD stage 5 non-dialytic patients and patients getting maintenance HD twice or thrice per week for at least 06 months. Patients who had any gynaecological operation eg. hysterectomy and or oophorectomy, any cranial operation, any known gynaecological disease and who use hormonal contraception were excluded from the study. Patients were divided into three groups. Group 1: ESRD patients on twice-weekly HD, n=17; Group 2: ESRD patients on thrice-weekly HD, n=17; Group 3: CKD5 patients who are not getting HD; CKDSND, n=17. Detailed menstrual history before and after the HD were obtained, various demographic characteristics: age, body mass index (BMI), gravidity, parity, abortion, curettage, whether they had amenorrhea before or after the dialysis, duration of amenorrhea were recorded. Patients who previously had periods but had the absence of menstrual periods for a time period of more than six months was labeled as secondary amenorrhea, who had period duration more than 35 days labeled as oligomenorrhoea, and who had excessive and prolonged uterine bleeding occurring at irregular and/or frequent intervals was labeled as menometrorrhagia. A thorough clinical examination was performed for all patients. Venous blood was obtained from the HD and non-HD patients, who are menstruating on the 5th to 8th day of menstruation (if they would have
dialysis on the 5th day of the menstrual cycle just before the dialysis). For the non-menstruating women, the venous blood samples were collected on the day of their enrollment to this study. Serum FSH, LH, Estradiol, and Prolactin were evaluated using chemiluminescence immunoassay in the Department of Microbiology of BSMMU. Appropriate data was collected by using a preformed data collection sheet. Statistical analysis of the study was done by computer software device as the Statistical Package for Social Science (SPSS-24). The results are presented in tables, figures, and diagrams. Categorical data are presented as frequency & percentage and numerical data as mean & standard deviation. The confidence interval was considered at a 95% level. A p-value of <0.05 is considered statistically significant.

Results:
Demographic data and comparisons of 34 patients taking hemodialysis and 17 non-dialytic CKD5 patients, a total of 51 patients are shown in Table I.

Mean and Standard Deviation was done to measure the level of significance. The mean age of the hemodialytic patients was 32.06±7.62 years and the CKD5ND patients was 31.17±6.43 years. The mean BMI of the hemodialytic patients was 24.73±3.42 kg/m2 and the CKD5ND patients were 26.35±2.43 kg/m2.

There was not any statistically significant difference (p> 0.05) between the patients in terms of age, BMI, gravidity, parity, previous abortions, and curettage.

Figure 1 shows Secondary Amenorrhea found in 43% of patients, oligomenorrhea in 21.35% patients, regular menstruation in 18% of patients, and 17.60% menometrorrhagia.

The frequency of menstrual disorders in hemodialytic and non-hemodialytic groups are compared below in figure 2.

In figure 2: Among the thrice-weekly HD group, 38% of the patients had regular menstruation, 30% of them had...
oligomenorrhea, 16% had secondary amenorrhea, and 16% had menometrorrhagia. Among the twice-weekly HD group, 20% of the patients had regular menstruation, 17% of them had oligomenorrhea, 41% had secondary amenorrhea, and 22% had menometrorrhagia. Among the CKD5ND group, 72% of patients had secondary amenorrhea, 18% had oligomenorrhoea and 10% had menometrorrhagia.

**Fig.-3:** Comparison of patients developing secondary amenorrhea at the beginning of HD. At the starting of HD, 42% HD patients developed amenorrhea in the thrice-weekly HD group and 52% in the twice-weekly HD group.

Table II shows :LH and Prolactin levels were higher in the twice-weekly HD group compared to the thrice-weekly HD group, which was statistically significant (p<0.05). In Table III:High levels of LH, Prolactin were found in the non-dialytic group compared to the HD group, and higher estradiol levels were seen in HD groups which is statistically significant (p<0.05). Despite the high level of Prolactin in the non-dialytic group, galactorrhoea was detected in only 3 patients (13%) as well as hirsutism in 1 patient (4.5%).

With subsequent HD treatment amenorrhea disappeared in 43% of patients in the thrice-weekly HD group and 22.22% patients in twice weekly HD group.

**Fig.-4:** Comparison of patients with amenorrhea disappeared and patients with amenorrhea continued. After the patients were divided into 4 groups, according to the menstrual disorder, FSH, LH, Estradiol, and Prolactin levels were compared in each group. Mean and Standard Deviation was done to measure the level of significance. The average value of Estradiol in regularly menstruating women was significantly higher compared to the other groups. In the secondary amenorrheic group, serum FSH, LH, Prolactin levels were significantly higher than the other groups (p<0.05).

Table II

<table>
<thead>
<tr>
<th></th>
<th>Twice-weekly HD (n=17)</th>
<th>Thrice-weekly HD (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/ml)</td>
<td>Mean: 9.10 ±1.31</td>
<td>Mean: 8.09 ±1.12</td>
<td>0.81</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>Mean: 17.02 ±1.79</td>
<td>Mean: 7.04 ±1.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ESTRADIOL (pg/ml)</td>
<td>Mean: 70.07 ±6.42</td>
<td>Mean: 85.04 ±7.83</td>
<td>0.09</td>
</tr>
<tr>
<td>PROLACTIN (ng/ml)</td>
<td>Mean: 80.01 ±7.03</td>
<td>Mean: 67.03 ±5.19</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Discussion:
Aim of this study was to find out patterns and incidence of menstrual abnormalities occurring in CKD5 patients undergoing twice-weekly and thrice-weekly maintenance HD also in non-dialytic CKD5 patients and to provide more detail information on hormone profile (FSH, LH, Prolactin, Estradiol) of these patients; as this field is poorly explored in recent years worldwide and very few research work regarding this area in Bangladesh as well.

In our study, 100% of non-dialytic CKD5 women had menstrual disorders and 73.52% of patients in the HD group had menstrual disorders. Near half of them had secondary amenorrhea (42.3%). One-third of them had oligomenorrhea (30.92%). And also near one-third of them had menometrorrhagia (26.78%). Authors in [6] showed that more than two-fifth of dialysis patients had menstrual disorder. Authors in [8] also showed in their study the overall prevalence of menstrual disturbances was 76.1% in patients getting HD; among them 60% patients had Amenorrhea and 17.1% had Oligomenorrhea. Authors in [13] reported that most common menstrual disorder among CKD patients on HD was secondary amenorrhoea and three quarter of dialysis patients had menstrual disorder. Authors in [14] clarified in their study that, less than two fifth of dialysis women had amenorrhoea, one third had oligomenorrhoea and one forth had regular menstruation. Authors in [15] showed 60% dialysis females had irregular menstrual pattern.

In this study, it is shown that in a total of 34 HD patients, 42% of them developed amenorrhea at the starting of dialysis in the thrice-weekly HD group and 52% of them developed amenorrhea in the twice-weekly HD group. With the subsequent HD therapy, amenorrhea disappeared in many of these patients. During the study, amenorrhea persisted only in 36% of these

**Table-III**

*Comparison of hormonal values between CKD5ND and HD patients*

<table>
<thead>
<tr>
<th></th>
<th>HD Patients</th>
<th></th>
<th>CKD5ND Patients</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=34)</td>
<td>(n=17)</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>8.59 ±1.21</td>
<td>10.09 ±1.93</td>
<td>0.546</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>9.03 ±1.41</td>
<td>18.99 ±3.76</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESTRADIOL (pg/ml)</td>
<td>73.50 ±7.12</td>
<td>32.7 ±5.39</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROLACTIN (ng/ml)</td>
<td>77.55 ±6.11</td>
<td>142.3 ±8.02</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table-IV**

*Hormone profile and their relationship with menstrual disorders in the whole studied population*

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Regular (n=9)</th>
<th>Oligomenorrhoe (n=11)</th>
<th>Secondary Amenorrhoe (n=23)</th>
<th>Menometrorrhagia (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/ml)</td>
<td>10.3 ±2.07</td>
<td>15.86* ±1.14</td>
<td>33.3*** ±4.21</td>
<td>17.6* ±1.15</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>7.49 ±1.76</td>
<td>9.08* ±2.13</td>
<td>39.98**** ±5.13</td>
<td>11.5* ±0.92</td>
</tr>
<tr>
<td>ESTRADIOL (pg/ml)</td>
<td>117.66*** ±4.71</td>
<td>85.9 ±3.05</td>
<td>44.7 ±6.18</td>
<td>5.6 ±1.07</td>
</tr>
<tr>
<td>PROLACTIN (ng/ml)</td>
<td>29.16** ±2.81</td>
<td>57.60** ±5.19</td>
<td>&gt;200**** ——</td>
<td>113*** ±4.05</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.005, ****p<0.001
patients. Authors in\textsuperscript{15} showed there are significant differences in the menstrual cycle before and after undergoing HD in women with CKD. It has been postulated that the H-P-O axis is altered following ESRD, although the normalization of hormonal status could be influenced by longer duration HD per week to correct hormonal parameters.\textsuperscript{8}

It is shown in our study that, there are higher levels of LH in non-dialytic patients compared to the HD patients (p<0.05). A similar result was found in [6,8]. Other studies have shown that LH levels were higher in premenopausal women with CKD.\textsuperscript{16} It is postulated that both the metabolic clearance of LH decreases and production increases in CKD patients.

In this present study, even though FSH levels were higher in non-hemodialytic patient compared to HD patients but there was no statistically significant difference (p>0.05). Similar result was found in studies of[8,13]. Estradiol levels in non-dialytic patients were detected lower than the HD patients and this difference was statistically significant (p<0.05). As uraemia causes loss of normal pulsatile secretion of LH and FSH which leads to decline in ovarian release of estradiol.\textsuperscript{17,18}

In our study, it is found that high levels of prolactin in 76% of patients. Besides, when the dialytic and non-dialytic CKD5 patients were compared for the prolactin levels, it is seen that prolactin levels were higher in the non-hemodialytic patients. Even though prolactin levels were high in 76% of the patients, galactorrhea was found only in 13% of them. Similarly,\textsuperscript{6} showed in their study that high levels of prolactin in the 73% of patients and galactorrhea was found only in 13% of them. Authors in\textsuperscript{19} showed incidence of hyperprolactinemia can be up to 80% in patients with HD. Prolactin levels rise due to increased production and decreased clearance, which may contribute to alterations in the H-P-O axis, causing suppression of gonadotrophins release leading to irregular menstrual cycles. Authors in\textsuperscript{8} reported, longer dialysis time per week significantly improved serum PRL removal in their patients.

In this study, when the HD and non-HD patients were divided into 4 groups as ones who had regular menstruation, amenorrhoea, oligomenorrhea and menometrorrhagia, and compared in terms of hormone profiles, FSH and LH and prolactin were statistically higher (p<0.05) in patients having secondary amenorrhoea compared to the other patient levels. While prolactin was lower in the regular group compared to the oligomenorrhoea group and lower in the oligomenorrhoea group compared to the secondary amenorrhoea group this difference was statistically significant (p<0.05). In the secondary amenorrhoea group, estradiol was lower than the other groups (p<0.05). This result is similar to [6]. They showed higher prolactin levels and lower estradiol levels in amenorrhoea group. They also stated that irregularities increase as the prolactin levels increase. It has been shown, hyperprolactinemia is an important cause of menstrual disorders in HD patients, whereas amenorrhoea was predominantly accompanied by an abnormal H-P-O axis with the highest serum prolactin, increased LH and FSH.

The main limitation of this study is the small sample size. However, The study can be further diversified by increasing the number of hospitals from different districts of the country.

Conclusion:

From the result of this study it can be said that menstrual abnormalities and associated hormonal dysregulations were significantly lower in thrice-weekly HD patients compared to twice-weekly HD patients and significantly lower in twice-weekly HD patients compared to the non-dialytic CKD5 patients. Also, it is suggested that long-duration dialysis might improve menstrual disorders in such patients as prolactin and LH levels gradually decrease with longer duration of dialysis.

References:


