

## Menstrual Blood Loss, Iron Nutriture, and the Effects of Alza-T IPCS 52, T-Cu 220C and Lippes Loop D in Korean Women

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**Abstract**—The upper normal limit of menstrual blood loss associated with iron deficiency, and the change in MBL and length of time necessary for development of iron depletion after IUDs insertion in healthy 193 Korean women were studied. The mean of MBL was  $33.4 \pm 23.4$ (SD) ml and the variation of MBL in different marital, age, and parity groups showed no statistical significance except for the higher values in young married women. Serum ferritin concentration was markedly decreased in women showing MBL above 40 ml and the frequency of subjects with serum ferritin below anemia criteria were increased in women showing MBL above 50 ml. Other parameters for assessing the iron nutriture showed no significant difference in different range of MBL. The mean MBL in women fitted with Alza-T IPCS 52 was significantly decreased after 3 months of insertion, but the increases in hemoglobin and serum ferritin levels were statistically significant at 12 month after insertion. The mean MBL in other IUD groups was remarkably increased at 1 month in T-Cu 220C group and during 1 to 12 month in Lippes Loop D group. Significant decrease in serum ferritin level was observed at 6 and 12 month in both groups.

**Key words:** Menstrual blood loss, Iron deficiency, Serum ferritin, IUDs

### INTRODUCTION

Iron deficiency anemia is common in women of fertile age and it is known that iron loss during menstruation is main contributing factor influencing iron balance in women (Hyttén *et al.* 1964; Hallberg *et al.* 1966a; Beaton *et al.* 1970; Cole *et al.* 1972; Bainton and Finch 1974; Cohen and Gibor 1980).

Numerous studies related with menstrual blood loss (MBL) demonstrated that incidence of iron deficiency anemia was significantly increased in women with increased MBL (Barer and Fowler 1936; Baldwin *et al.* 1961; Jacobs and Butler 1965; Hallberg *et al.* 1966a and b; Elwood *et al.* 1968; Hefnawi *et al.* 1980; Gao *et al.* 1981; Wagatsuma 1982).

But the reported figures on mean and upper nor-

mal limit of MBL were variable. Hallberg and Nilson (1964), Hallberg *et al.* (1966a), Guttorm (1971), Shaw *et al.* (1972), Hefnawi *et al.* (1974) and Israel *et al.* (1974) reported as 28 to 35.5 ml for mean value of MBL. On the other hand, Hallberg *et al.* (1966b), Gao *et al.* (1981), Cai *et al.* (1982) and Wagatsuma (1982) reported higher mean values as 43.5 to 56.3 ml using same method for MBL measurement.

Hallberg *et al.* (1966b) showed that the incidence of anemia was significantly increased in Swedish women with MBL greater than 60 ml and the blood hemoglobin and serum iron concentrations were significantly decreased in women with MBL greater than 80 ml, and defined the upper normal limit of MBL as 60 to 80 ml. Shaw *et al.* (1972), Cai *et al.* (1982), Gao *et al.* (1981) reported similar upper normal limit of MBL. A blood loss of 60 ml represents an iron loss of approximately 30 mg. Since this is approximately the same amount of iron which is absorbed each

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month by women with nutritionally adequate diet, it may be calculated that monthly blood loss exceeding 60 ml may lead to negative iron balance.

Studies quantitating MBL in women wearing intrauterine contraceptive devices (IUDs) have also been performed by many investigators (Guttorm 1971; Hefnawi *et al.* 1974; Larsson *et al.* 1975; Guillebaud *et al.* 1976; Nilsson 1977; Hefnawi *et al.* 1977; Roy *et al.* 1979; Wagatsuma 1982). They generally demonstrate that the amount of MBL and the incidence of menorrhagia (MBL greater than 60 ml) may be increased after IUDs insertion, and the bulkier, non-medicated inert IUDs usually cause more MBL than the smaller, medicated IUDs.

Thus, the female population of the developing or underdeveloped countries, where intrauterine contraception is most widely used in national family planning programs and nutritional deficiency is widespread, may be placed at very significant risk to iron deficiency by the MBL and its increment after IUDs insertion. For these reasons, the study on MBL and the effects of IUDs in Korean women is essential in attempts for assessment of iron nutrition as well as applications to gynecological and medical practices. However, the knowledge on the magnitude of MBL and its variation in Korean women is completely limited. The aims of this study are to define the range of MBL and the upper normal limit of MBL associated iron deficiency anemia in Korean women, and to determine the change of MBL and length of time necessary for development of iron depletion after insertion of currently used IUDs.

## MATERIALS AND METHODS

### 1. Subjects

Eighty-one married women aged from 22 to 48 years old were recruited from Family Health Clinic, Institute of Reproductive Medicine and Population and housewives, and 112 unmarried women, aged from 15 to 25 years old were selected randomly from medical students, hospital employees and factory workers.

All women were in good health, not on prior hormonal contraception or IUDs at least 6 months before the start of investigation. No women received either oral or peripheral iron supplementation prior to or during the study.

All women were tested for the amount of MBL of one menstrual period, blood hemoglobin(Hb), hematocrit, mean corpuscular hemoglobin concentration (MCHC), serum iron and ferritin concentra-

tions. After the baseline MBL determination, 40 subjects from married women were volunteered to take part in the IUD study and randomly selected for the three different IUDs. Fourteen women were fitted with Alza-T IPCS 52, twelve women with T-Cu 220C, and fourteen women with Lippes Loop D. Alza-T IPCS 52 group was studied for 12 months and other IUD groups were for 24 months. During the post-insertion period, sixteen women were dropped out by medical or non-medical reasons. MBL and hematological parameters for iron status after IUD insertion were determined at regular intervals.

### 2. Collection of Menstrual Pads and Peripheral Blood

Each subject was carefully instructed how to collect her menstrual blood. Special attention was paid to obtain complete collection.

The pads used for one menstrual period were collected in opaque polyethylene bag(Cryovac<sup>®</sup>, 14" × 20" × 200 g thickness, Seward Laboratories, England) and transported to laboratory within a few days of the end of each period. Venous blood was drawn within a few days of post-menstruation and serum sample was separated from an aliquot of whole blood sample.

### 3. Methods for Determination of MBL and Hematological Parameters

The amount of MBL was determined by alkaline hematin method(Shaw *et al.* 1972), and a Stomacher Laboratory Blender(Model 3500, Seward Laboratories) was used to homogenize the sanitary materials and elute the blood hemoglobin(Newton *et al.* 1977).

Blood Hb and hematocrit were determined by cyanmethemoglobin and microhematocrit methods, respectively, and the MCHC was calculated from these values. Serum iron was tested according to the method recommended by the International Committee for Standardization of Hematology (ICSH 1971), and serum ferritin concentration was measured by radioimmunoassay using Fer-Iron Ferritin RIA kit (Ramco Laboratories, Houston, U.S.A.).

## RESULTS

### 1. MBL and its Relationship with Age and Parity

The range of MBL for total 193 subjects was from 2.0 to 127.2 ml and the distribution of MBL was positively skewed; 5th, 10th, median, 90th, and 95th percentile values were 6.0, 8.9, 26.8,

**Table 1.** The mean amount(ml) of menstrual blood loss in each age group

	Unmarried		Married				Total
	Age (yr)		Age (yr)				
	15-19	20-24	25-29	30-34	35-39	40-48	
No.*	51	60	20	22	14	19	186
Mean	31.0	29.6	43.4	37.9	35.2	35.2	33.4
SD	22.5	17.2	24.2	27.9	25.6	32.1	23.4

\*Subjects showing MBL outside back-transformed mean  $\pm$  2SD of log data were excluded.

**Table 2.** Comparison of MBL(ml) by the parity

Parity	No.	Amount of MBL (Mean $\pm$ SD)	Significance Level (ANOVA test, one way)	
No. of Pregnancy	1-2	16	49.3 $\pm$ 29.2	
	3-4	24	37.5 $\pm$ 24.6	
	5-6	20	35.2 $\pm$ 35.1	N.S.
	above 7	15	31.3 $\pm$ 13.3	
No. of Parity	0	14	48.9 $\pm$ 31.0	
	1	7	42.9 $\pm$ 19.8	
	2	23	30.8 $\pm$ 20.6	N.S.
	3	21	32.6 $\pm$ 29.7	
	above 4	10	48.5 $\pm$ 31.2	
No. of Abortion	0-1	28	42.1 $\pm$ 29.7	
	2	22	48.6 $\pm$ 31.0	
	3	11	25.2 $\pm$ 11.2	0.025
	above 4	14	23.9 $\pm$ 14.4	

Figures are the results of 75 married women excluding those outside back-transformed mean  $\pm$  SD of log data of MBL for total 193 subjects.

64.7, 89.7 ml respectively, and the arithmetic and geometric means of MBL were 33.0  $\pm$  24.5 (SD) and 25.0 ( $\pm$ 1SD; 11.4 – 55.0) ml respectively. Maximum number of subjects (22.8% of total subjects) fell in a group with MBL of 10-20 ml, and 84.0% showed a MBL less than 50 ml. A noticeable difference in the distribution of MBL between the different marital state groups was that the proportion of women with MBL more than 50 ml; 9.9% for unmarried women and 24.6% for married women, but the difference between the means of two groups was not statistically significant.

The normal range of MBL calculated from log-transformed data as mean  $\pm$  2SD and transformed back to the original scale was 5.2 to 121.0 ml. Seven subjects showed MBL outside the normal

range, and the variation in the amount of MBL in different age groups was investigated after excluding these subjects (Table 1). Recalculated mean of MBL for 186 subjects was 33.4  $\pm$  23.4 (SD) ml. Mean of MBL was higher in 25-29 years married group, and low in 20-24 years unmarried group (0.02 < p < 0.025). But the observed variation between other age groups was not significant.

The relationships between the amount of MBL and the number of pregnancy, number of abortion and the parity were studied in 75 married women (Table 2). The amount of MBL was higher in 1-2 pregnancy and nulliparous groups than others having more than 3 pregnancy and multiparous groups except for the groups with parity 4 or more, but the statistical significance of these differences was not observed. On the other hand, the amount of MBL in groups with 0 to 2 abortion were significantly higher than those with the number of abortion above 3 (significance level = 0.025).

## 2. Relationship between MBL and Iron Nutriture

The relationship between MBL and the Hb, hematocrit, MCHC, and serum iron and ferritin concentrations were compared by the mean values of these parameters (Fig. 1) and the percentage of women having values below the anemia criteria (Table 3).

Beyond our expectations, lower values of parameters for iron nutriture were noticed in a group of MBL less than 10 ml. Except for this group the means of Hb and hematocrit were gradually decreased with increased MBL, but the statistical significance of these difference in six groups was not observed. The frequency of women below anemia criteria for Hb and hematocrit was slightly increased in a group with MBL more than 50 ml. There was no noticeable changes in MCHC.

The mean values of serum iron concentration were decreased in groups with MBL above 40 ml, but these difference was not significant and the

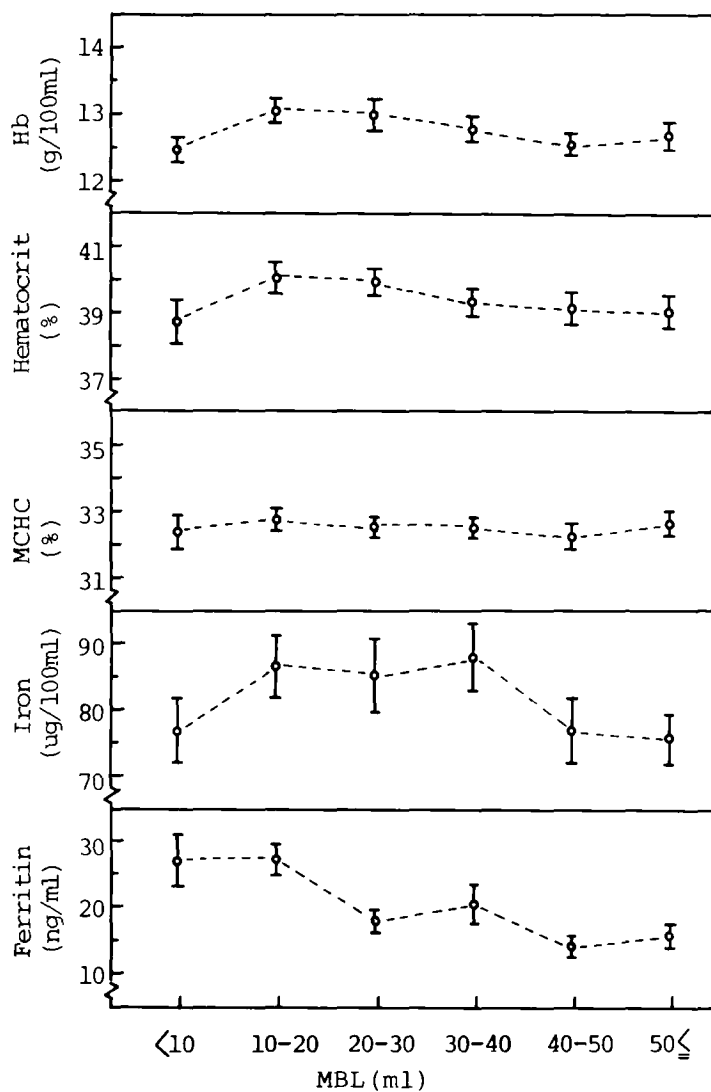


Fig. 1. Mean values of Hb, hematocrit, MCHC, and serum iron and ferritin concentrations in relation to menstrual blood loss. Points are mean values and the standard errors are represented by vertical bars.

frequency of women with iron level below 50  $\mu$  g/100 ml did not increased.

On the other hand, serum ferritin concentration was markedly decreased in women showing MBL above 40 ml (significance level = 0.005), and the frequency of women showing ferritin level below 10 ng/ml was gradually increased with the amount of MBL increases.

### 3. MBL and Iron Nutriture in IUDs Users

Table 4 shows the amount of MBL and hematological parameters during pre- and post-insertion period of Alza-T IPCS 52. The mean of pre-insertion MBL was 33.2 ml and significantly decreased to 24.6 ml (74.1% of baseline MBL) at +3 month, 16.1 ml(48.5%) at +6 month ( $p < 0.02 - p < 0.01$ ). Significant increases in Hb and serum ferritin concentration were noted at 9 and 12 month of post-insertion period ( $p < 0.05$ ).

Mean MBL during pre- and post-insertion period of T-Cu 220C group was shown in Table 5. The mean MBL at +1 month was remarkably increased (163%) in comparison with baseline MBL ( $p < 0.02$ ), but thereafter mean MBL was decreased gradually near to the baseline MBL during +12 to +24 month. Significant difference in iron parameters between pre- and post-insertion were observed in serum iron concentration at +6 month and serum ferritin concentration at +6 and +12 month ( $p < 0.05$  and  $p < 0.02$ , respectively).

Table 6 shows the mean MBL and iron parameters during pre- and post-insertion periods of Lippes Loop D group. The mean MBL was markedly increased during post-insertion periods; at 1 month after insertion, the mean MBL was 181% of baseline MBL( $p < 0.001$ ). During 3 to 12 month of post-insertion periods, the mean MBL was

Table 3. Percentage of subjects with hematological parameters below anemia criteria at different level of MBL

MBL (ml)	No. of observations	Hb (%)	Hematocrit (%)	MCHC (%)	Serum iron (%)	Serum ferritin (%)
less than 10	24	29.2	8.3	8.3	12.5	20.8
10 - 20	41	17.1	2.4	7.3	19.5	12.2
20 - 30	33	21.2	3.0	12.1	18.2	12.1
30 - 40	33	24.2	0.0	9.1	18.2	18.1
40 - 50	23	21.7	0.0	8.7	13.0	21.7
more than 50	29	31.0	6.9	10.3	13.8	34.5
Total	183	23.5	3.3	9.3	16.4	19.1

Anemia criteria: Hb, 12 g/100ml; hematocrit, 35%; MCHC, 30%; serum iron, 50  $\mu$ g/100ml; serum ferritin, 10 ng/ml.

**Table 4.** Menstrual blood loss and iron nutriture before and after Alza-T IPCS 52 insertion

	Pre-Insertion		Post-Insertion			
	-1	+1	+3	+6	+9	+12
No. of Subjects	14	14	14	11	10	10
MBL(ml)	33.2±31.5	27.6±20.0	24.6±20.4***	16.1±8.26***	13.0±7.18***	14.3±9.33**
Hb(g/100ml)	13.0±1.09	13.1±0.75	13.1±0.90	13.1±0.96	13.4±0.98*	13.4±0.92*
Hematocrit(%)	38.3±3.52	38.0±3.40	39.2±3.22	39.4±1.99	39.4±3.23	39.9±3.10
Iron(μg/100ml)	89.0±41.1	—	—	107.9±45.2	—	105.0±38.9
Ferritin(ng/ml)	16.5±13.7	—	—	23.9±13.2	—	26.3±13.0*

Figures are the mean±SD

Paired t-test: \*, p<0.05, \*\*, p<0.02, \*\*\*, p<0.01.

slightly decreased but the significance in the difference with baseline MBL was still retained. For the Hb, hematocrit, and serum iron concentration, the minimal values were observed during 6 to 12 month after insertion, but the statistical significance was not noted in any post-insertion periods. Serum ferritin concentration was significantly decreased at 6 to 12 month after insertion(p<0.05).

### DISCUSSION

The results of many studies on MBL generally demonstrate that the variation in the amount of MBL between individuals are great and the distribution of MBL shows wide skewed curve, and the range and mean values are reported as 0.1 to 500 ml and 28 to 60 ml respectively according to the characteristics of subjects, methods for MBL measurement and other variables (Barer and Fowler 1936; Hallberg and Nilson 1964; Hytten *et al.* 1964; Hallberg *et al.* 1966a and b; Cole *et al.* 1971; Guttorm 1971; Hefnawi *et al.* 1974 and 1980; Gao *et al.* 1981; Cai *et al.* 1982; Wagatsuma 1982).

In this study, the range of MBL was from 2.0 to 127.2 ml with mean value of 33.4 ml, and 84% of total subjects showed the MBL less than 50 ml. With alkaline hematin method for MBL determination, Hallberg and Nilson (1964), Hallberg *et al.* (1966a) and Shaw *et al.* (1972) reported 28 to 34 ml for mean value and 1.6 to 199.7 ml for the range of MBL. These values are very similar to the results of this study. On the other hand, some investigators reported higher mean value from 36 to 60 ml (Barer and Fowler 1936; Hallberg *et al.* 1966b; Israel *et al.* 1974; Gao *et al.* 1981; Cai *et al.* 1982; Wagatsuma 1982). Especially, Gao *et al.* (1981) and Wagatsuma (1982) reported 52 to 56 ml of mean MBL in Chinese and Japanese women, and suggested that the difference in mean between

Western and Oriental women are due to widespread use of oral contraceptives in Western countries. But in this study, women using hormonal contraception or intrauterine contraceptive devices at least 6 months before investigation were excluded. Thus observed differences of mean MBL between Korean and Japanese women seems to be affected by racial and other factors. Thorngren and Gustafson (1981) showed that a diet rich in eicosapentaenoic acid increased bleeding time and decreased platelet aggregability.

Most investigators reported that the marital state, age and parity does not effect the amount of MBL in women before pre-menopausal years. In this study, the mean of MBL in different age and marital state groups showed no significant difference. But the mean of MBL in 15 to 24 years women was lower than elder groups and the mean values in 25 to 34 years women who were mostly parous was slightly higher than other age groups. Similar with other studies, the number of pregnancy and parity does not effect the mean MBL significantly. On the other hand, the mean MBL in women with abortion below 2 was higher than in women with more abortion(significance level=0.025). Rybo (1966) reported that the parous 23 to 30 years old women showed higher MBL than nulliparous women of the same age and the parity in young women is of importance for magnitude of the MBL and the proximity to delivery is more often than old women.

A number of studies showed that the some hematological parameters were significantly decreased in women with heavier MBL (Hytten *et al.* 1964; Jacobs 1965; Hallberg *et al.* 1966a and b; Edwood 1968; Beaton 1970; Cole *et al.* 1972; Shaw *et al.* 1972; Cohen 1980; Hefnawi *et al.* 1980; Gao *et al.* 1981; Cai *et al.* 1982). Hallberg *et al.* (1966b) reported that among women having

Table 5. Menstrual blood loss and iron nutriture before and after T-Cu 220C insertion

	Pre-Insertion					Post-Insertion				
	-1	+1	+3	+6	+9	+12	+18	+24		
No. of Subject	12	12	12	12	12	10	7	7		
MBL(ml)	38.0±13.5	61.7±24.3**	49.5±16.5	49.0±32.3	44.0±17.2	38.3±14.3	37.6±14.8	39.6±23.5		
Hb(g/100ml)	12.9±0.73	12.6±0.94	12.6±1.07	12.8±0.87	12.9±0.80	12.9±0.73	12.8±0.71	12.8±0.58		
Hematocrit(%)	38.1±2.98	36.9±1.94	36.9±2.01	37.3±2.25	38.0±2.39	38.4±1.87	38.8±1.93	38.1±1.98		
Iron(µg/100ml)	90.2±22.4	—	—	64.2±16.6**	—	79.8±22.2	76.2±17.2	76.8±15.9		
Ferritin(ng/ml)	25.6±13.7	—	—	17.6±11.7*	—	15.6±12.7**	18.7±9.82	22.0±11.5		

Figures are the mean±SD

Paired t-test: \*; p<0.05, \*\*; p<0.02.

Table 6. Menstrual blood loss and iron nutriture before and after Lippes Loop D insertion

	Pre-Insertion					Post-Insertion				
	-1	+1	+3	+6	+9	+12	+18	+24		
No. of Subject	14	14	12	12	11	9	7	7		
MBL(ml)	38.2±27.6	69.2±39.6***	58.1±29.1	59.0±34.3*	66.4±34.4*	62.8±29.5*	54.9±20.8	49.3±15.4		
Hb(g/100ml)	12.9±0.67	12.9±0.79	12.9±0.94	12.8±1.00	12.7±1.03	12.7±0.90	12.8±0.63	12.9±0.58		
Hematocrit(%)	39.1±2.24	38.6±2.43	37.7±2.88	37.5±2.49	38.1±3.18	38.5±2.55	39.1±2.06	38.7±1.83		
Iron(µg/100ml)	85.3±38.8	—	—	68.8±23.4	—	77.8±26.3	79.0±26.2	71.1±24.1		
Ferritin(ng/ml)	23.3±12.2	—	—	19.1±9.49*	—	17.2±8.61*	16.4±9.13	17.2±9.60		

Figures are the mean±SD

Paired t-test: \*; p<0.05, \*\*; p<0.005, \*\*\*; p<0.001.

MBL exceeding 60 ml, Hb and serum iron were decreased and iron deficiency anemia increased two to fivefold, and the upper normal limit of MBL was regarded as 60 to 80 ml.

In this study, the Hb, hematocrit and serum iron were decreased gradually with MBL increases, but the statistical significance between different MBL groups was not observed. But in serum ferritin concentration, which is a sensitive index for body iron store and high predictive parameter for diagnosis of uncomplicated iron deficiency anemia, highly significant difference (significance level=0.005) between the different MBL groups was observed. In groups with a MBL exceeding 40 ml, the mean values of hematological parameters were lower, and the frequency of individuals with signs of iron deficiency was higher in the group with MBL more than 50 ml.

This suggests that the iron stores in body can be progressively depleted to very low levels long before significant changes occur in serum iron or blood Hb levels. This means that even though the women with MBL more than 40 ml are not in a condition of anemia, the iron storages in body is exhausted and such women are in a condition of latent or early anemic status (Heinrich, 1968), and the upper normal limit of MBL in Korean women seems to be 40 ml.

The effects of various IUDs on the amount of MBL were tested by many investigators. They reported that Lippes Loop users rank highest in volume of MBL and prevalence of menorrhagia, and the incidence of anemia is markedly increased after insertion. Lippes Loop raise MBL 50 to 100% above pre-insertion level and copper IUDs 25-50% (Hefnawi *et al.* 1974; Israel *et al.* 1974; Lasson *et al.* 1975; Liedholm *et al.* 1975; Guillebaud *et al.* 1976). On the other hand, progestogen-releasing IUDs generally diminish the MBL and reported that reduce 40-50% below pre-insertion level (WHO 1972; Zador *et al.* 1976; Wan *et al.* 1977).

In this study, the progestogen-releasing IUD, Alza-T IPCS 52, diminished the MBL 50 to 60% below the pre-insertion level. Significant decrease of MBL compared with baseline level was observed from 2-3 month after insertion, but the significant increase in serum ferritin concentration was only observed at 12 month after insertion.

In T-Cu 220C users, the mean MBL was raised 63% above pre-insertion level at 1 month after insertion, and then the mean was gradually decreased near to baseline level. The average raise in

MBL during 12 months after insertion was 28.7% above baseline level.

The highest increase in mean MBL was observed in Lippes Loop D users, and 81% raise in MBL was noted at 1 month after insertion. The mean MBL during post-insertion periods was decreased after 1 month of post-insertion, but the significant difference of mean MBL from pre-insertion level was retained until 12 month after insertion.

Significant decrease in serum iron or ferritin levels in T-Cu and Lippes Loop groups was observed during 6 to 12 month after insertion. This means that the length of time necessary for iron depletion in women with increased MBL above 50 ml by IUDs seems to be 6 to 12 months.

Although the prevalence of anemia in IUD users was not tested because of the small number of subjects and the significant difference of hematological parameters was rarely observed during long use of non-medicated IUDs, it is no wonder that the women with higher pre- or post-insertion MBL may have risk on body iron balance after the use of non-medicated IUDs.

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=국문초록=

## 한국인 월경혈손실량과 철분영양상태 및 자궁내피임장치의 영향

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한국인 월경혈손실량과 철분영양상태 및 자궁내피임장치 사용에 따른 변화를 연구하였다. 대상자 193 명의 평균 월경혈손실량은 33.4 ml로 젊은 기혼여성군을 제외하고 연령, 결혼여부 및 산과력에 따른 유의한 차이는 관찰되지 않았다.

월경혈손실량이 40 ml 이상인 군에서 평균 혈청 ferritin 농도는 매우 유의하게 감소하였고, 50 ml 이상 군에서 빈혈빈도가 증가하는 것으로 나타나 한국인 여성의 월경혈손실량 정상 상한선은 40 ml로 생각된다. 자궁내피임장치 Alza-T IPCS52 사용군에서 평균 월경혈손실량은 사용 후 2~3 개월 후부터 유의하게 낮아졌으며, 혈색농도 및 혈청 ferritin 농도는 사용 후 12 개월에서 유의하게 증가한 것으로 나타났다. 한편 T-Cu 220C 사용군에서는 사용 후 1 개월에 월경혈손실량이 크게 증가한 후 서서히 감소하여 사용 후 12 개월엔 사용 전 수준으로 돌아왔으며, Lippes Loop D 사용군에서는 1 개월부터 12 개월 사이에 유의하게 증가되었다. 양군 모두에서 혈청 ferritin 농도는 사용 후 6~12 개월에서 현저히 감소하였다.