

## Menstrual disturbances and hormonal changes in women workers exposed to a mixture of organic solvents in a pharmaceutical company

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### Abstract

**Background:** Chemicals are among risk factors that can affect women's reproductive system. This study is aimed to investigate the association of occupational exposure to a mixture of organic solvents with menstruation disturbances and hormonal changes among female workers.

**Methods:** Female workers of a pharmaceutical company were divided into three groups of non-exposed, low-exposed and highly-exposed to a mixture of organic solvents (formaldehyde, phenol, N-hexane, and chloroform) based on workplace measurements. Menstrual disturbances (in terms of short cycles, long cycles, irregular cycles, and bleeding or spotting between periods) and mean of hormone levels (including follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, estrogen and progesterone levels) were compared between these three groups. For investigating associations, logistic regression was performed.

**Results:** Our study showed that mean length of cycles, duration of bleeding, and amount of flow and also prevalence of long cycles, irregular cycles, and bleeding or spotting between periods were higher in exposed groups ( $p \leq 0.05$ ). Odds ratio for prevalence of menstrual disturbances in the low exposure group and high exposure group were 9.69 ( $p=0.001$ ) and 3.40 ( $p=0.002$ ) respectively compared to the reference group. Estrogen and progesterone levels were not affected ( $p > 0.05$ ), but other hormones levels were significantly disturbed in the exposed groups compared with the non-exposed group ( $p=0.001$ ).

**Conclusion:** Occupational exposure to the mixture of organic solvents may be associated with the increase of menstrual disorders and hormonal changes in female workers. Based on our findings, periodic evaluation of reproductive system of female workers in pharmaceutical companies is recommended.

**Keywords:** Women, Occupational exposure, Solvents, Menstruation disturbances, Hormones.

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### Introduction

Chemicals are among risk factors that can affect women's reproductive system (1). After reports of adverse effects of certain chemicals on reproductive function, hazards to reproductive health and associated

functions have become prominent issues (1). Because of wide spread use of chemicals in industrial settings, exposure to such hazards is almost inevitable in workplaces (2). Studies suggested that exposure to chemicals such as organic solvents and pes-

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ticides could affect different aspects of women's reproductive system such as fertility, menstrual cycle and ovulation (3). In a study by Cho et al the exposure to organic solvents was associated with increased frequency of oligomenorrhea (4). Exposure to organic solvents has been related to spontaneous abortion, stillbirth, miscarriage, and small for gestational age in pregnant women (5,6). It is shown that exposure to 2-bromopropane in the workplace is associated with increased prevalence of secondary amenorrhea and elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels (7). Also exposure to benzene, toluene, and cyclohexane may lead to irregular menstrual cycles (8). It is shown that exposure to formaldehyde is associated with adverse effects on fertility of women workers in the wood-processing industry (9). Animal studies and human cell culture research have demonstrated harmful effects of phenol such as fetotoxicity and genotoxicity (10). In another study, exposure to a mixture of organic solvents including N-hexane, hexane isomers, toluene and methyl ethyl ketone in shoe manufacturing industry was associated with reduced fertility among female workers (11). Other organic solvents such as chloroform, toluene, 2-ethoxyethanol and xylene have reported to be teratogenic and cause growth retardation of the offspring in animal tests (9).

Despite of widespread use of several thousand exogenous chemicals in industrial processes, our knowledge about the effects of such hazards on reproductive system is limited.

The number of women workers is increasing worldwide and a considerable proportion of them are of reproductive age. Therefore attention to effects of occupational exposures on reproductive system is required (1).

The pharmaceutical industry employs more than 350 thousand people all over the world (12). In pharmaceutical industry solvent use is common and consistently accounts for between 80 % and 90 % of mass

utilization in a typical pharmaceutical batch chemical operation (13). Considering that usually in industrial settings workers are exposed to a variety of organic solvents in each time, we aimed to investigate the association between occupational exposure to a mixture of organic solvents and menstruation disturbances among female workers of a pharmaceutical company.

## Methods

### *Study design and population*

This cross-sectional study of menstrual disturbances was conducted among female workers in a pharmaceutical factory in Iran in 2011. All female workers of reproductive age (before menopause) that were working in laboratory or packing units and had at least one year work experience were invited to participate in the study. Demographic, medical and occupational data were collected through medical records, direct interviews, and a questionnaire. The questionnaire contained information about age, marital status, height and weight to calculate body mass index (BMI), educational level, tea consumption, smoking and exercise habits, work experience in the current position, shift working, heavy lifting, standing duration, self-perceived work satisfaction and self-perceived work stress levels, medications, age of menarche, history of pregnancy and child bearing and questions around menstrual cycle of participants.

Pregnancy or breast feeding in the past year, history of gynecological diseases or uterine disorders such as hysterectomy, ovariectomy and Asherman's syndrome, history of endocrine disease such as progesterone deficiency, polycystic ovary, thyroid disorders and diabetes mellitus, history of exposure to organic solvents in previous job or second job, any permanent non-occupational exposures to organic solvents and occupational exposure to other chemicals, considered as exclusion criteria.

There were 461 women of reproductive age working at different units of the factory. After applying the inclusion and exclu-

sion criteria, 145 female workers of new laboratory units, 73 workers of old laboratory units and 207 workers of packing unit were enrolled in the study (total=425 women). Women working in new and old laboratory units were considered as exposure groups and workers in the packing unit were considered as non-exposure group. All study participants signed informed consent and everyone was allowed to leave the study at any stage. The Ethics Committee of Tehran University of Medical Sciences approved the study.

#### *Outcome measurements*

Menstrual disorders were defined as any of four menstrual cycle characteristics: Short cycles, long cycles, irregular cycles, and bleeding or spotting between periods (inter menstrual bleeding) (14). Also duration of bleeding, amount of flow, and symptoms of dysmenorrhea were assessed.

Assessment of menstrual patterns was created based on responses to questions during the interview. Shortest cycle length, longest cycle length, range of variability in cycles' length and average of cycles' length were assessed. Length of cycle was defined as the number of days was there from the first day of one menstrual period to the first day of the next period. The beginning of a period was defined as the first day of two consecutive days of bleeding which at least one of them had to be more intense than the spotting (15). In fact, the participants were asked to report the current usual pattern of their menstrual cycles during the past one year (16).

The short cycle was defined to be a cycle less than 21 days and the long cycle to be more than 35 days (4). Irregular cycles were defined as having more than seven days of variability in the cycles' length and regular cycles were defined as having up to 7 days variability. To measure the duration of bleeding, we asked women: "on average, how many days did your flow last?". To assess the amount of flow, we asked women: "on average, how many sanitary towels did you use every day during men-

ses?".

Subjects were answered a question about their work schedule. Working at times other than normal daylight hours of approximately 7:00 AM to 6:00 PM was considered as shift work (17). Self-perceived work satisfaction and self-perceived work stress levels were classified for each worker: ("low, medium, and high" for work satisfaction and "none, low, medium, and high" for work stress levels) (18).

To evaluate the hormones levels including FSH, LH, thyroid stimulating hormone (TSH), prolactin (PRL), estrogen and progesterone levels, blood samples (one sample per volunteer) were obtained from all study subjects at the third day of their menstrual cycle and were sent to the laboratory for analysis.

#### *Exposure measurement*

In this study, measurement of all solvents present in the work environment was performed by the professional occupational hygienist team of the factory. Environmental measurement of organic solvents present in the workplace was performed at the breathing zone for each workplace. Samplers were arranged around the workplace in different points. Thirty six stations were designed for packing unit, 42 stations for new laboratory units and 29 stations were designed for old laboratory units. Air samples were collected on charcoal tubes with constant flow (100 ml/min) pumps (SKC 226-01) for laboratory units and packing unit. Air monitoring was performed continuously during all working hours. Subsequently, gas chromatography (Hewlett-Packard 5890, Avondale, PA, USA) was used to analyze the samples and the average concentration of each solvent was identified. The results of environmental monitoring showed that the solvents present in laboratory units of the factory were formaldehyde, phenol, N-hexane, and chloroform. Mean concentration of the organic solvents in new laboratory units for formaldehyde, phenol, N-hexane, and chloroform were 0.01, 0.5, 20.7, 3.2 parts per million (ppm),

respectively. Also mean concentration of the organic solvents in old laboratory units for formaldehyde, phenol, N-hexane, and chloroform were 0.03, 12, 35, 5.1 ppm, respectively. The occupational exposure to the mixture of organic solvents was evaluated according to the American Conference of Industrial Hygienists (ACGIH) equation. The following equation was used to assess the permitted limit of the mixture of organic solvents (19).

$$Em = C_1/L_1 + C_2/L_2 + \dots + C_n/L_n$$

Where  $Em$  is the equivalent exposure for the mixture of organic solvents,  $C$  is the mean concentration of organic solvents in the air of the environment, and  $L$  is the exposure limit for the organic solvents. After measuring the mean concentration of each solvent and replacing it in the equation above, values of  $Em$  larger than 1 indicate that the concentration of the mixture of organic solvents in the work environment is higher than the threshold limit values.

In the old laboratory unit, the value of  $Em$  was calculated to be 3.51 (1.32 - 4.47), indicating a higher than permitted concentration of the mixture of organic solvents in the old laboratory unit. In the new laboratory unit,  $Em$  was calculated to be 0.86 (0.54 - 0.93), indicating that the concentration of the mixture of organic solvents in the new laboratory units was in the permitted range. In addition, the organic solvents were measured in packing unit, yielding zero or negligible concentrations.

### Statistical analysis

Mean, standard deviation (SD) and range of variables were calculated. The chi-square test and ANOVA were used for comparing different variables among the groups. Also to modify the confounding factors and to evaluate the association between exposure to organic solvents and menstrual disorders more precisely, forward logistic regression analysis was used. The menstrual cycle disturbance was considered as dependent variable; and occupa-

tional exposure to organic solvents, work shift, age of menarche, regular exercise, marital status, age, BMI, duration of work, perceived job stress and job satisfaction status were considered as independent variables.  $P$  values less than 0.05 were considered statistically significant. Outcomes of the statistical analysis were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). The SPSS 11 software was used for performing mentioned calculations.

### Results

Totally 425 women workers were included in the study. Mean ( $\pm$ sd) age of all studied individuals was 31.3 ( $\pm$ 4.82) years. Mean ( $\pm$ sd) work duration of all cases was 8.8 ( $\pm$ 5.03) years. Mean ( $\pm$ sd) BMI was 23.7 ( $\pm$ 3.39)  $\text{kg/m}^2$  and 19.3% (82 women) of workers were shift workers. Table 1 demonstrates the demographic and occupational variables in the study groups. As shown in this table, there was no statistically difference between study groups in terms of studied characteristics ( $p > 0.05$ ).

There were significant differences between groups in terms of mean values of hormonal tests ( $p < 0.05$ ) (Table 2). The mean values of FSH, LH and TSH were significantly higher in the exposed groups (workers of old and new laboratory units) than the non-exposed group (workers of packing unit) ( $p = 0.001$ ). But the mean values of PRL were significantly lower in the exposed groups ( $p = 0.001$ ). There were no significant differences in the mean values of estrogen and progesterone ( $p > 0.05$ ).

The mean length of menstrual cycle of all subjects was 26.1 ( $\pm$ 3.96) days and the mean menses length was 4.9 ( $\pm$ 1.03) days. Also the average number of sanitary towels used per days of menses was 3.6 ( $\pm$ 1.40).

A total of 376 workers (88.5% of all workers) had menstrual cycle length of 21-35 days, 16 women (3.8%) had menstrual cycle length less than 21 days (short cycle) and 33 women (7.7%) reported their menstrual cycle length more than 35 days (long cycle). Fifty six workers (13.1%) had irreg-

Table 1. Demographic and occupational variables in the study groups for female workers in a pharmaceutical factory in Iran

Variable	Exposure groups			P.v
	Non-exposed (N=207)	Low-exposed (N=145)	high-exposed (N=73)	
Age (year) Mean (SD)	31.3 (4.64)	31.8 (4.31)	30.2 (5.74)	0.063
Work of duration (year) Mean (SD)	9.2 (5.02)	8.6 (5.04)	7.8 (4.78)	0.109
Body mass index (kg/m <sup>2</sup> ) Mean (SD)	24.0 (3.29)	23.5 (3.52)	23.1 (3.17)	0.067
Age of menarche (year) Mean (SD)	12.7 (1.31)	12.7 (1.46)	13.1 (1.09)	0.093
Marital status N (%)				0.481
Single	36 (17.3)	24 (16.5)	16 (21.9)	
Married	165 (79.7)	112 (77.3)	53 (72.7)	
Divorced/Separated	6 (3.0)	9 (6.2)	4 (5.4)	
Pregnancy history Yes (%)	100 (48.3)	69 (47.5)	35 (47.9)	0.775
Use of OCP <sup>c</sup> Yes (%)	33 (15.9)	23 (15.8)	11 (15.0)	0.452
Educational levels N (%)				0.235
Guidance and high school	14 (6.7)	9 (6.2)	5 (6.8)	
High school graduate	76 (36.7)	55 (37.8)	27 (36.9)	
Associate degree <sup>a</sup>	29 (14.1)	19 (13.3)	10 (13.8)	
BA <sup>b</sup>	88 (42.5)	62 (42.7)	31 (42.5)	
Tea consumption Yes (%)	132 (63.7)	91 (62.7)	45 (61.6)	0.825
Regular exercise Yes (%)	34 (16.4)	25 (17.2)	11 (15.0)	0.920
Shift work Yes (%)	46 (22.2)	26 (17.9)	10 (13.8)	0.249
Standing duration (>3 h) Yes (%)	49 (23.6)	32 (22.0)	15 (20.5)	0.270
Heavy lifting (>10 kg) Yes (%)	11 (5.3)	7 (4.8)	3 (4.1)	0.381
Perceived job satisfaction N (%)				0.943
Low	100 (48.3)	76 (52.4)	38 (52.1)	
Medium	72 (34.8)	45 (31.0)	23 (31.5)	
High	35 (16.9)	24 (16.6)	12 (16.4)	
Perceived job stress N (%)				0.983
None	14 (6.7)	11 (7.5)	4 (5.5)	
Low	64 (30.9)	48 (33.1)	25 (34.2)	
Medium	99 (47.9)	69 (47.5)	34 (46.5)	
High	30 (14.5)	17 (11.9)	10 (13.8)	

<sup>a</sup> An educational level between High school graduate and BA

<sup>b</sup> Bachelor of Science, <sup>c</sup> Oral Contraceptive Pills

ular menstrual cycles and 16 workers (3.8%) had bleeding during the menstrual cycle. In general 14.4% (61 women) of workers were suffering from menstrual disturbances. Also 49.6% (211 women) of all workers were suffering from dysmenorrhea.

Menstrual cycles' characteristics in the studied groups are shown in Table 3. As this table depicts, the mean length of menstrual cycles, length of menses, number of pads used per day and frequency of dysmenorrhea, long menstrual cycles, irregular menstrual cycles and bleeding during menstrual cycles were significantly higher in the new laboratory units workers than the

packing unit workers and these means were higher in the old laboratory units than other groups ( $p < 0.05$ ). The frequency of short menstrual cycles was not statistically significant ( $p = 0.222$ ). Generally, the frequency of menstrual disturbances in the exposed groups was significantly higher than the non-exposed group ( $p < 0.05$ ).

After adjustment for confounders, logistic regression analysis showed that there was a significant association between menstrual disturbances and occupational exposure to the mixture of organic solvents ( $p < 0.05$ ). According to the Table 4, OR for menstrual disturbances in the high exposed group was 9.69 (95% CI=4.02-23.35) and in low-

Table 2. Results of hormone tests of the study groups for female workers in a pharmaceutical factory in Iran

Measurements	Exposure group			P.v
	Non-exposed (N=207)	Low-exposed (N=145)	high-exposed (N=73)	
FSH (mIU/ml) Mean (SD)	6.6 (1.41)	8.2 (1.01)	8.5 (0.61)	0.001
LH (mIU/ml) Mean (SD)	4.7 (0.62)	5.2 (0.92)	5.8 (1.16)	0.001
TSH (uIU/ml) Mean (SD)	2.4 (0.50)	3.9 (1.20)	4.2 (1.07)	0.001
PRL (ng/ml) Mean (SD)	12.0 (3.05)	11.2 (2.99)	10.6 (2.41)	0.001

Table 3. Frequency distributions of menstrual cycles characteristics and menstrual disturbances in studied groups for female workers in a pharmaceutical factory in Iran

Variables	Exposure groups			P.v
	Non-exposed (N=207)	Low-exposed (N=145)	high-exposed (N=73)	
Length of cycle (day) (Mean± SD)	25.3±3.29	26.1±3.75	28.3±5.13	0.001
Duration of bleeding (day) (Mean± SD)	4.7±1.07	4.9±1.03	5.3±0.79	0.001
Amount of flow (sanitary towels) (Mean± SD)	3.2±1.24	3.6±1.26	4.7±1.51	0.001
Dysmenorrhea (yes) N (%)	91 (43.9)	76 (52.4)	44 (60.2)	0.040
Short menstrual cycle (21 days>) yes N (%)	5 (2.4)	6 (4.1)	5 (6.8)	0.222
Long menstrual cycle (35 days<) yes N (%)	11 (5.3)	10 (6.8)	12 (16.4)	0.008
Irregular menstrual cycle Yes N (%)	16 (7.7)	19 (13.1)	21 (28.7)	0.001
Bleeding during menstrual cycle Yes N (%)	2 (0.9)	6 (4.1)	8 (10.9)	0.001
Menstrual disturbance Yes N (%)	17 (8.2)	23 (15.8)	21 (28.7)	0.001

SD: Standard Deviation

exposed group was 3.40 (95% CI =1.56-7.38) compared to the reference group. Also, menstrual disturbances had a significant association with age, age of menarche, BMI, exercise, shift work, work experience, perceived job stress and job satisfaction ( $p < 0.05$ ), but such association was not observed between menstrual disturbances and marital status ( $p > 0.05$ ).

### Discussion

Menstrual disorders frequently affect the quality of life of adolescents and young adult women and can be indicators of serious underlying problems (20). In our study 14.4% of the workers had at least one type of menstrual disturbances described as: short cycles, long cycles, irregular cycles and inter menstrual bleeding. The results of our study showed that the prevalence of

menstrual disturbances in workers exposed to organic solvents was more than non-exposed workers. Based on the regression analysis prevalence of the menstrual disturbances in the high exposure group was 9.69 times and in the low exposure group was 3.40 times more than the non exposed group. Also in this study mean length of menstrual cycle, length of menses, number of pads used per day during the menses and prevalence of dysmenorrhea were higher in workers exposed to mixture of organic solvents.

In human studies, occupational exposure to organic solvents has been related to menstrual disorders, reduced fertility, and adverse effects on pregnancy (21,22). In a study among Iranian female workers, it has been found that occupational exposure to organic solvents could be associated with

Table 4. Association between menstrual disturbances and study variables using logistic regression analysis for female workers in a pharmaceutical factory in Iran

Variable	Status	Adjusted OR	95% CI	P.v
Solvents Exposure	Non-exposure (n=207)	1.00	-----	-----
	Low exposure (n=145)	3.40	1.56-7.38	0.002
	high exposure (n=73)	9.69	4.02-23.35	0.001
Age (year)	≤ 31 (n=195)	1.00	-----	-----
	> 31 (n=230)	3.97	1.80-8.76	0.001
Age of menarche (year)	11-16 (n=397)	1.00	-----	-----
	> 16 or <11 (n=28)	2.86	1.12-5.01	0.035
Work of duration (year)	≤ 8.5 (n=200)	1.00	-----	-----
	> 8.5 (n=225)	5.73	2.57-12.77	0.001
Body mass index (kg/m2)	≤ 23.5 (n=210)	1.00	-----	-----
	> 23.5 (n=215)	1.96	1.01-3.80	0.046
Marital status	Single(n=76)	1.00	-----	-----
	Married (n=330)	1.28	0.51-2.61	0.595
	Other status (n=19)	1.65	0.66-3.21	0.552
Regular exercise	Yes(n=70)	1.00	-----	-----
	No(n=355)	10.90	2.79-42.53	0.001
Shift work	No (n=343)	1.00	-----	-----
	Yes (n=82)	4.12	1.95-8.71	0.001
Perceived job satisfaction	High (n=71)	1.00	-----	-----
	Medium (n=140)	2.45	1.12-5.39	0.025
	Low (n=214)	2.90	1.25-6.75	0.013
Perceived job stress	None (n=29)	1.00	-----	-----
	Low (n=137)	2.55	1.16-5.65	0.035
	Medium (n=202)	2.97	1.32-6.83	0.012
	High (n=57)	3.12	1.56-7.02	0.005

adverse outcomes such as prolonged waiting time to pregnancy and increased frequency of spontaneous abortion (2). In a large study on 1408 female workers, Cho et al concluded that three or more years of exposure to a mixture of solvents including benzene, styrene, toluene and xylene were associated with a 53% increase in oligomenorrhea (4). In a cross-sectional study on 3000 women workers in a large petrochemical company, Thurston et al found a significant association between menstrual disturbances and exposure to benzene (23). Chen et al investigated the effects of occupational exposure to benzene and its analogues on luteal function of female workers in a petrochemical corporation in china. They found that occupational exposure to low concentration of benzene and its analogues could lead to shorter length of luteal phase. Also they reported a decreased level of luteal progesterone in the exposed group

(24). In a study by Pieleszek et al the prevalence of menopause among population chronically exposed to carbon disulphide (CS<sub>2</sub>) was calculated 16.59%, while in the normal population it was 8.05% (25). In a study previous exposure to ethylene glycol ethers (EGEs) could lead to prolonged menstrual cycle among female workers who worked in photolithography (26).

In our studied workplace the mixture of organic solvents was included formaldehyde, phenol, N-hexane, and chloroform. Limited studies investigated the effects of these solvents on reproductive system. In a study exposure to formaldehyde was associated with adverse effects on fertility of women workers in the wood-processing industry (9). Several animal studies revealed that low-dose exposure to bisphenol (2.4 and 50 ppb per day) can affect the timing of the onset of sexual maturation in females (27,28). In some animal and human

studies exposure to n-hexane or hexane isomers was associated with reduced fertility and reproductive impairments (11,29,30), and chloroform was showed to be teratogenic in animal studies (8).

In our study the mean values of FSH, LH and TSH were significantly higher in the exposed groups while the mean value of PRL was lower in the exposed groups compared to the non-exposed group. Levels of estrogen and progesterone remained unchanged. Luderer et al found a significant association between occupational solvent exposure and increased FSH levels, but there were no significant difference in terms of LH and testosterone levels between exposed group and reference group (31). Svensson et al assessed hormone levels among rotogravure printers exposed to toluene. They found that median plasma levels of FSH, LH and free testosterone were significantly lower than unexposed people. It was interesting that after sending eight workers to vacation, an increase in the blood levels of LH and FSH was observed and plasma levels of TSH, T3 and T4 decreased. They concluded that solvents can lead to hormonal changes and these changes may be reversible (32). Huang et al in an animal study to investigate the toxic effect of n-hexane on sex hormones levels showed that n-hexane can inhibit ovary secretion of estrogen and progesterone (29). Also Liu et al in a study to investigate the toxic effects of n-hexane on the gonad of female mice suggested that progesterone levels were affected by exposure to n-hexane (30).

The exact mechanisms of the effect of organic solvents on menstruation are not well known. According to the American College of Occupational and Environmental Medicine (ACOEM) guidance on reproductive toxicology, inhalation, skin absorption and ingestion are the most common pathways for occupational exposure to reproductive toxins (33). There are at least two little-known possible pathways that may play role in affecting menstruation in workers exposed to organic solvents. The first

pathway may be the interruption of hypothalamic-pituitary axis by solvents. Organic solvents may disturb the menstrual cycle by altering the secretion of GnRH from hypothalamus gland that controls the secretion of gonadotropins, FSH and LH from pituitary gland (23). About the second pathway, organic solvents may cause menstrual disturbances by affecting metabolism and entero-hepatic recirculation of steroids. Cytochrome P<sub>450</sub> gene families that have a great role in controlling the steroids metabolism are very susceptible to environmental exposures. It has been shown that changes in reproductive steroids metabolism may lead to adverse changes in menstrual cycle regularity (23).

In present study after performing regression analysis, there were significant association between menstrual disturbances and shift work, age, age of menarche, BMI, exercise, work experience, perceived job stress and job satisfaction.

Similar to our findings some previously published studies suggested that shift work may have a prominent role in developing menstrual disturbances (34-36). A survey among 776 women working in different jobs including teachers, office workers, nurses, factory workers and barmaids was conducted by Miyauchi et al in Japan. They observed significant increased incidence of menstrual irregularities among women working at night shifts. Also the plasma concentration of prolactin and melatonin were significantly lower in nurses working at night (34). Labyak et al introduced changes in menstrual function as a possible marker of shift work intolerance. Also they found that sleep disturbances may cause menstrual irregularities among nurses <40 years old (35). Yao et al after conducting a study on 415 female workers stated that shift work could increase the risk of premenstrual syndrome in female knitting workers (36). About associations between shift work and other studied confounding variables in our study, although results were interesting but more specifically studies are needed.

Our study had some limitations, this study was a cross-sectional study but for investigating a causative relationship cohort design is better. In other hand it was retrospective that could cause recall bias. Also it was not feasible to predict the exact level of exposure of every worker to solvents, because our samplers measured mean concentration of solvents in environment of work units. Thus, we advocate the use of personal samplers for environmental measurement of organic solvents. We also recommend conducting a prospective exploratory study in this field using daily diaries for collecting information.

The results of this study suggests that occupational exposure to the mixture of organic solvents (including formaldehyde, phenol, n-hexane, and chloroform) may be associated with menstrual disturbances and hormonal changes in female workers of the pharmaceutical factory. Also shift work, age, age of menarche, BMI, exercise, work experience, perceived job stress and job satisfaction could be considered as risk factors of menstrual disturbances. However further studies are needed to confirm these findings.

### Conclusion

Occupational exposure to the mixture of organic solvents may be associated with increased prevalence of menstrual disorders and hormonal changes in female workers. Based on our findings, periodic evaluation of reproductive system of female workers in pharmaceutical companies is logical.

We declare that we have not any competing interest.

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