New Onset Oligomenorrhea as a Consequence of Trauma among Syrian Women Refugees in Turkey /Türkiye'deki Suriyeli Kadın Mülteciler Arasında Travmanın Bir Sonucu Olarak Yeni Başlayan Oligomenore

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Abstract

Introduction: Depression is a common psychological response to trauma and stress, and research suggests that depression may play a role in the development of menstrual irregularities in women, including oligomenorrhea. Aim: The aim of this study was to investigate the gynecological symptom of oligomenorrhea as a consequence of traumatic events and its relation with depression and sexual dysfunction in Syrian refugee women in Turkey. Materials and Methods: The study was held in one of the refugee camps in Turkey (Cevdetiye, Osmaniye) in April 2013. A total of 404 Syrian refugee women were interviewed during their medical visits at the gynecology and obstetrics outpatient clinic located in the refugee camp for menstrual cycle irregularities, depression and sexual dysfunction in regard to the parameters such as the level of linguistic communication skills, ethnic origin, marital status, active involvement of husband or loss of any first degree relative in civil war. Results: A total of 404 refugee women of different ethnicities (Turkish n=310 and Arabic n=94) were interviewed. Out of 404 participants, 200 (49.5%) had secondary oligomenorrhea (study group) and 204 (50.5%) had normal menstrual cycles (control group). Oligomenorrhea was found to be significantly associated with decreased sexual function, active involvement of husband in civil war and higher depression scores. Conclusion and suggestion: Depression is one of the major component of post-traumatic events and one of the known reasons of menstrual irregularities in women. Menstrual irregularities, particularly oligomenorrhea, may be an objective and initial gynecological sign in refugee women alerting the clinicians to refer the women for further psychiatric evaluation.

Keywords: Beck Depression Inventory II, Depression, Oligomenorrhea, Posttraumatic stress, Syrian refugee women.

Öz

Giriş: Depresyon, travma ve stresin yaygın psikolojik bir tepkisi olup, araştırmalar depresyonun oligomenore dahil olmak üzere kadınlarda adet düzensizliklerinin gelişiminde bir rol oynayabileceğini göstermektedir. Amaç: Bu çalışmanın amacı, Suriyeli mülteci kadınlarda ortaya çıkan oligomenore ve bunun depresyon ve cinsel işlev bozukluğu ile ilişkisini araştırmaktı. Gereç ve Yöntemler: Çalışma, Nisan 2013'te Türkiye'deki bir mülteci kampında (Osmaniye, Cevdetiye) gerçekleştirildi. Menstrüel döngü düzensizlikleri, depresyon ve cinsel işlev bozukluğu nedeniyle jinekoloji ve obstetrik polikliniğine başvuran 404 Suriyeli mülteci kadın çalışmaya dahil edildi. Etnik köken, medeni hal, eşin savaşta aktif rol alıp almaması veya birinci derece yakınının kaybı gibi parametreler değerlendirildi.

Bulgular: Çalışmaya Türk (n=310) ve Arap (n=94) olmak üzere toplam 404 kadın dahil edildi. Katılımcıların %49.5'inde (n=200) sekonder oligomenore (çalışma grubu) saptanırken, %50.5'inin (n=204) normal menstrüel döngüleri (kontrol grubu) olduğu belirlendi. Oligomenore; cinsel işlev bozukluğu, eşin savaşta aktif rol alması ve daha yüksek depresyon skorları ile ilişkili bulundu. Sonuç ve Öneriler: Depresyon, travmatik olayların önemli bir bileşenidir ve kadınlarda menstrüel düzensizliklerin bilinen nedenlerinden biridir. Özellikle oligomenore, mülteci kadınlarda jinekolojik bir belirti olarak görülebilir ve klinisyenlerin kadınları daha ileri psikiyatrik değerlendirmeye yönlendirmeleri için bir uyarı işareti olabilir.

Anahtar Kelimeler: Beck Depresyon Envanteri II, Depresyon, Oligomenore, Travma sonrası stres, Suriyeli mülteci kadınlar.

1. Introduction

The Syrian refugee problem began in April 2011 and the political insecurity and instability forced many Syrians to flee their homes and villages. In the first refugee wave, the population was comprised of mostly elder women and children. However, within months, the flow of refugees including more young adults intensified across the borders to mostly Lebanon and Jordan and to a lesser extent to Turkey (Hampton, 2013). There are more than 3.500.000 Syrians in Turkey and consists mainly of refugees of the Syrian Civil War. Majority of the Syrian refugees in camps of Turkey was ethnically Arabic, although ethnical Turkish and Kurdish refugees were also reported. Actual number of Syrian refugees in Turkey is believed to be higher because data for unregistered or household located refugees is limited (UNICEF, 2013).

To be refugee means not only leaving his own natural habitat but also be deprived of the familiar social life. A different language, religion and social life of the receiving country also add on the problems of social adaptation and depression. Previous humanitarian crises in recent years have showed that women and girls were disproportionately affected by conflict situations (Kastrup, 2006). Several symptoms including psychosomatic disorders develop as a consequence of these diverse post-traumatic events. Possible past or ongoing exposure to sexual violence on female refugees may also enhance these symptoms (Brewin et. al. 2000; Maria et. al. 2010). Besides the basic health services such as emergency, obstetric and reproductive health services, priority should also be given to psychological assesment of the refugee women. However, culturally sensitive and appropriate psychological care is usually neither available nor enough in refugee camp settings. In order to select the high risk group and triage of women who are the candidates of post-traumatic stress and depression, we need simple methods and easily recognisable symptoms. Menstrual irregularities, particularly oligomenorrhea, are symptoms that may be easily recognized by most of the health workers without need for a professional assistance of psychiatry/psychology and may be an objective and initial sign in selection of refugee women who will need further psychiatric evaluation.

Oligomenorrhea is defined as irregular and inconsistent menstrual blood flow in a woman with menstrual cycle greater than 35 days or four to nine menstrual cycles in a year (Hennegan et. al. 2020). One of the most common causes of new onset oligomenorrhea is the functional hypothalamic amenorrhea (FHA). The proposed mechanism of FHA is the abberations in pulsatile gonadotropin-releasing hormone (GnRH) secretion impairing gonadotropins (follicle-stimulating hormone and luteinizing hormone). FHA is a state of hypogonadotropic hypogonadism leading to disturbances in hypothalamic-pituitary-ovarian axis (Berga et. al. 1989; Gordon 2010). The final outcome is a series of complex hormonal changes including anovulation and menstrual cycle changes. Three types of FHA depending on the eliciting factor are weight-loss related, stress-related and exercise-related amenorrhea (Meczekalski et. al. 2008). According to the American Society of Reproductive Medicine, new onset of oligomenorrhea occur in approximately 3-5% of adult women. FHA is responsible for 20-35% of all oligomenorrhea cases.

The association of cognitive functions, emotional and psychiatric symptoms is much more prominent in women with FHA compared with eumenorrheic controls. Women with FHA had greater difficulty in coping daily stresses and tend to endorse greater interpersonal dependence when compared to eumenorrheic women (Giles, Berga 1993). Psychosomatic disorders, particular susceptibility to daily life events and depressive traits are more common and scales for depression and anxiety are positively correlated in women with FHA (Lawson et. al. 2009; Bomba et. al. 2007). Disturbed sexual funtion, which is theoretically determined by psychological and hormonal background, is also more significant in patients with FHA (Dundon et. al. 2010).

The hypothesis underlying the present study was that new onset of menstrual irregularities may be an initial and easily recognizable gynecological sign in refugee women who would benefit for further pshychiatric evaluation. The actual aim of present study was neither to address the issue of adaptive ability nor to make a diagnosis for depression, anxiety, post-traumatic stress and adjustment disorders.

2. Materials and Methods

2.1. Type of Research

This is a prospective, case-control study.

2.2. Place and Time of Research

The study was performed in Cevdetiye Refugee Camp, Osmaniye, Turkey in April 2013. This camp was unique in population composition because of its predominancy of ethnically Turkish refugees, all of whom were native Turkish speakers (UNHCR Refugee Population Analysis, 2013).

2.3. Population, Sample and Sampling Method of Research

The total refugee population in this camp was 8,037 with women and children predominance (75%) and composed mostly of ethnically Turkish people from Lattakia region of Syria (UNHCR Turkey Syrian Refugee Daily Strep, 2013).

Among the refugee women admitting to the local health center located within the camp, the study group included women diagnosed as secondary oligomenorrhea with onset beginning from the date of displacement from their homeland and the control group included women with any gynecological complaints but with normal menstrual cycles. All cases of previous oligo/hypomenorrhea with onset before the date of displacement, postmenopausal cases, women using hormonal contaceptive methods (combined oral contraceptives, progestin-only pills and progesteron loaded intrauterine device) and those proven to be pregnant were excluded from the study. The presence of pregnancy was excluded with biochemical testing (negative blood B-hCG levels). Because most of the women did not use a modern contraceptive method, the main worry of the women with oligomenorrhea was mostly a suspected pregnancy and to a lesser extent the onset of menopause. All patients with positive B-hCG testing and requesting pregnancy termination were referred to the nearest main city hospital because of not having the appropriate set up for pregnancy termination within the health center located in the refugee camp. We added the question for the presence or absence of menopause-like vasomotor symptoms because of the worry of menopause in some women with oligomenorrhea.

Normal menstrual cycle is defined as menstruation occuring in intervals of 21 to 35 days. Oligomenorrhea is defined as menstrual periods occuring at intervals of greater than 35 days (Cohen, 2008). Because the determination of the exact onset of crisis is usually a problem especially during conflict situations, the onset of menstrual irregularity in our study group was ascribed as the time of displacement.

The ethiology of secondary oligomenorrhea is extensively studied and the proposed mechanism is thought to be through hypothalamic dysfunction. It is an easily recognized symptom and may be an initial presenting symptom experienced during post-traumatic periods (Berga, 1989; Kapci et. al. 2008). In our study, we tried to find out the association between oligomenorrhea and post-traumatic events in regard to various parameters that may affect the menstrual cycle in refugee women. Menstrual irregularities, particularly oligomenorrhea, may be an objective and easily recognised initial sign during posttraumatic periods in refugee women.

The study group included refugee women diagnosed as oligomenorrhea with onset beginning from the date of displacement from their homeland. The control group included women with gynecological complaints such as vaginal discharge, pruritus vulva, pelvic pain, urinary tract infection but having normal menstrual cycles. The data of demographic properties such as age, ethnic origin, language skills (ability to communicate with or without the assistance of a translator) and marital status were recorded for each group. The parameters related to menstrual cycle such as duration of oligomenorrhea in days, presence or absence of menopause-like vasomotor symptoms were recorded. The patients were interviewed for parameters that might contribute to depression such as first degree relative loss during the civil war and active involvement of husband at civil war. In order to scale depression levels of the patients, validated versions of Beck Depression Inventory II (BDI II) for Turkish and Arabic populations were performed and the scores were recorded for each patient.

2.4. Data Collection Tools

A preformed data sheet was used to record each patient at the time of interview. The questionnaire was developed in Turkish and simultaneously interpreted into Arabic by participant relatives when required. We used BDI II to scale depression. BDI II is one of the earliest and most commonly used self-rating system for scaling depression in both psychiatrically diagnosed patients and in normal populations. BDI II was developed in 1996 and derived from BDI. It is a 21-item self-administered survey describing symptoms of depression as specified in the DSM-IV with each item scored on a scale of 0 to 3. The cutoffs used in BDI II differ from the original scale; 0-12minimal depression, 13-18 mild depression, 19-28 moderate depression and 29-63 severe depression. Validated versions of BDI II scores were used for both Turkish and Arabic languages. The Turkish version, BDI II TR, was described by Kapci et al [20]. The Arabic version was described by Al-Musawi NM (Al-Musawi, 2001). BDI II scores were within a range of 4 to 23 in our study group, with majority of cases clustered within minimal and mild depression groups (with scores of 0-12 and 13-18). Because of insufficient number of cases within moderate depression group, mild and moderate depression groups were united.

The scaling for sexual problems was performed by both BDI II-TR and as an independent simplified question asking for any change in sexual interest. The last question of the BDI II-TR is about the sexual interest and scaled ranging from 0 to 3 points with 0 as "not noticed any recent change in interest in sex", 1 as "less interested in sex than used to be", 2 as "almost no interest in sex" and 3 as "completely lost interest in sex". We also asked a more simplified question about change in sexual interest independent from the BDI II-TR and scaled as either "no change in sexual interest" or"decreased sexual interest". All questions in both the preformed data sheet and BDI II questionnaire were asked in Turkish language by the medical secretary of our unit. All patients, even the native Turkish speaker group, were offered translation of the questions when needed.

We ascribed the onset as the time of displacement, because the exact onset of crisis was difficult to be determined. The menstrual problems of the immigrant women were asked as any changes before and after the date of displacement, in order only to include those with onset since the displacement. The ethnical heritage was primarily determined by both asking for the mother tongue and how the women described herself, either Turkish or Arabic.

2.5. Data Collection

The staff of the obstetrics and gynecology outpatient clinic which was located within the refugee camp consisted of one gynecologist, one nurse and one medical secretary. All patients were approached at the clinic by the nurse. Because we did not have a dedicated translator at the clinic and vast majority of the patients were accompanied by a friend or a relative, all of whom were females, capable of speaking both Turkish and Arabic languages, they were used as translators. Informed consents were obtained from each individual patient after it had been read by the medical secretary to both the patient and the translator.

2.6. Ethical Considerations

In accordance with the Declaration of Helsinki, our study was approved by the Local Health Governate of Osmaniye (13/03/2014-52/1713) and informed consents were obtained from all participants.

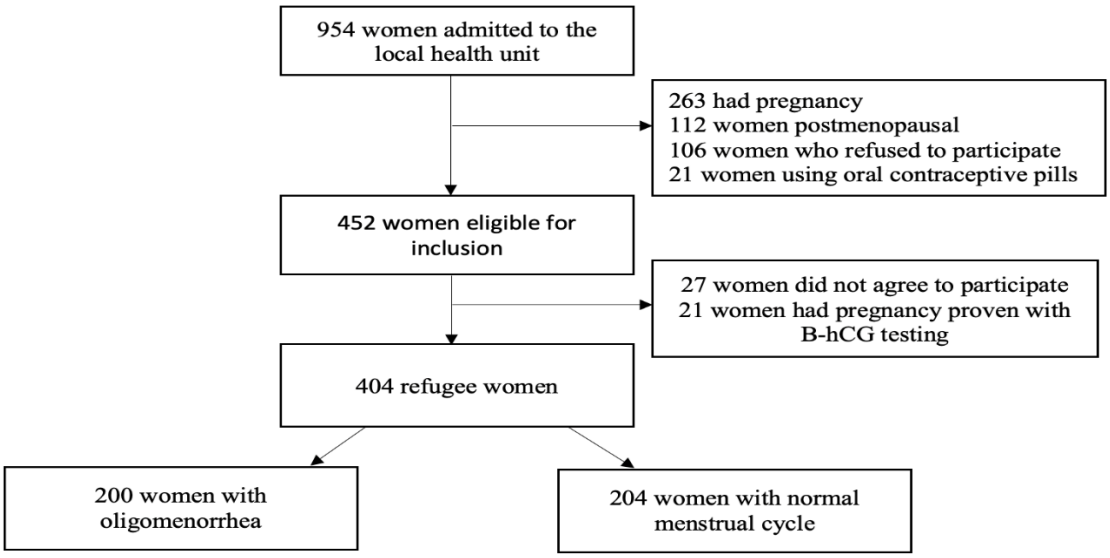
2.7. Statistical Analysis

The data were analyzed by the commercially available software, Statistic Package for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The distributions of continuous variables such as age, duration of oligomenorrhea were examined by Shapiro Wilk's test. Since all variables were non-normally distributed, they were expressed as median (min-max). Categorical variables were shown as count (%). Menstrual cycle groups were compared by Mann-Whitney U test in respect to the continuous variables. Chi-square test was used to investigate whether there is an association between the categorical variables (ethnicity, language, marital status, etc.) and menstrual cycle (normal or oligomenorrhea). The subjective change in sexual behavior was coded as either no change or decreased sexual function and desire. Univariate Logistic Regression analysis was performed to determine the effective variables for menstrual cycle. Although sexual behavior was found to be significantly different between menstrual cycle groups, the standard error of odds ratio was too high. So sexual behavior was not included in the final logistic regression model. A p value <0.05 was considered as statistically significant.

3. Results

A total of 954 women admitted to the local health unit located within the camp during the study period. Out of 954 women, 263 had pregnancy with routine follow-up at the same clinic, 112 women in postmenopausal period, 106 women who refused to participate and 21 women using oral contraceptive pills. The total number of women approached at the clinic and having the eligible criteria of inclusion was 452. However 27 women, all of whom were of ethnically Arabic origin, did not agree to participate and 21 women had pregnancy proven with B-hCG testing. 404 refugee women meeting the citeria of inclusion were included in our study (Figure 1).

Figure 1. Flow Chart of Study



The median of ages of the women recruited for the study was 31 (18-43) years. According to the ethnical origin, 310 (76.6%) were Turkish and 94 (23.3%) were Arabic. There were two groups in the study according to the menstrual cycles. Out of 404 women, 200 (49.5%) had oligomenorrhea and 204 (50.5%) had normal menstrual cycles with median of ages of 31 (18-43) years and 31 (19-43) years respectively. The number of women needing for a translator to communicate was 38 (20.1%) in oligomenorrhea group and 38 (17.7%) in women with normal menstrual cycles (Table 1).

Table 1. Patient Characteristics and Comparison of Groups

Demographic Features [n (%)]	**Oligomenorrhea (n=200)**	**Normal menstrual cycle (n=204)**	**Total(n=404)**	**p**
Age [*year*]*	31 (18-43)	31 (19-43)	31 (18-43)	0.664
Duration of oligomenorrhea [*day*]*	30 (5-90)	-	-	-
Ethnicity				0.718
Turkish	155 (77.5)	155 (76.0)	310 (76.6)	
Arabic	45 (22.5)	49 (24.0)	94 (23.3)	
Language				0.121
Turkish	150 (75.0)	166 (81.4)	316 (78.2)	
Arabic	50 (25.0)	38 (18.6)	88 (21.8)	
Translator need				0.518
Present	38 (20.1)	38 (17.7)	76 (18.8)	
Absent	151 (79.9)	177 (82.3)	328 (81.2)	
Marital status				0.757
Married	182 (96.8)	207 (95.8)	389 (96.3)	
Single or separated	6 (3.2)	9 (4.2)	15 (3.7)	

Menopause-like vasomotor symptoms					0.932
	Present	31 (15.5)	31 (15.2)	62 (15.3)	
	Absent	169 (84.5)	173 (84.8)	342 (84.7)	
1st degree relative loss in war					0.074
	Present	24 (12.0)	13 (6.4)	37 (9.2)	
	Absent	176 (88.0)	191 (93.6)	367 (90.8)	
Husband at war					**<0.001**
	Yes	76 (42.0)	6 (2.9)	82 (21.1)	
	No	105 (58.0)	202 (97.1)	307 (78.9)	
BDI-II scores*		10 (4-22)	9 (4-23)	9 (4-23)	**0.004**

BDI-II: Beck Depression Inventory II *Expressed as median (min - max)

The distribution of contraceptive methods used among refugee women were coitus interruptus (30.5%), condom (34.9%), IUD (18.3%) and BTL (1.0%). There were 62 women using no methods (15.3%).

Oligomenorrhea and normal menstrual cycle groups were compared for age, ethnicity, language, need for translator and marital status. There were no significant differences between groups in regard to these parameters. The statistical difference was also not significant between groups in regard to the presence or absence of menopause-like vasomotor symptoms and 1st degree relative loss in war. The association between oligomenorrhea and change in sexual function was significant, with a worsened sexual function in 44 women (23.3%) having oligomenorrhea, whereas it was only 4 (1.9%) in women having normal menstrual cycle ($\chi2$=40.133, p<0.001). The active involvements of the husbands in the war were 76 (42.0%) in oligomenorrhea group and 6 (2.9%) in normal menstrual cycle group and the difference was significant ($\chi2$=88.384, p<0.001) (Table 1). As a result of the logistic regression analysis, "husband at war" had significant effect on having oligomenorrhea (Wald statistics=49.010, p<0.001). The odds of oligomenorrhea is 28.470 times (%95 CI: 11.148 – 72.705) higher for those whose husbands were at war than those who had husband at home.

The associations of BDI II (TR) between the groups were analyzed both as a continuous scale of individual scores and as groups (minimal, mild, moderate depression groups). There were no significant associations when BDI groups were used in analyses; however the difference was significant when the analyses was performed for individual BDI scores (p=0.004). There was also no significant correlation between the BDI scores and duration of oligomerrhea in days (p=-0.032, p=0.582) (Table 1). Although there was no significant difference in regard to oligomenorrhea between ethnical groups, non-parametric analyses revealed lower BDI scores among ethnically Arabic group.

4. Discussion

Women are disproportionately more susceptible to developing psychosomatic disorders than men as a consequence of traumatic events (Lindsey, 2001). The increased vulnerability of women to the psychological consequences of war may be related with coping different psychological problems in different ways and having lower threshold for developing depression when compared to men (Murthy, 2006). The estimated incidence of developing adjustment disorders after trauma is 5-21%. Menstrual irregularities, particularly secondary amenorrhea/oligomenorrhea, may be a good and common initial sign of gynecological psychosomatic disorders in women. The symptom is clinically and easily recognised and relatively objective. The extent and magnitude of trauma does not always correlate with the depressive morbidity. Moreover, poor social support was found to be a stronger predictor of depressive morbidity than the extent of trauma itself (Gorst-Unsworth, 1998). Based on our findings, questioning menstrual irregularities for oligomenorrhea might be integrated to any questionnaires and

surveys used during examination of refugee women not only by the gyneacologist but by all the health workers. The finding should raise the suspicion of posttraumatic stress related disorders and may need further study for these women. However, it should be always in mind that the chance of having post-traumatic stress disorder or severe depression in women with regular menstrual cycles is still possible. However, we do not have enough data to analyze this issue. Although oligomenorrhea was found to be associated with higher depression scores according to our study results, it does not always reflect a psychosomatic disease and may be a result of natural protecting effect in women during stressfull conflict situations. Because anovulation also accompanies FHA, secondary oligomenorrhea with anovulation can be a natural adaptation protecting women to become pregnant in such unsafe conflict situations. Whatever the reason of FHA is, either pathologic or component of a physiologic adaptation, the high rates of oligomenorrhea among refugee population and significant association with depression and sexual dysfunction are important findings.

Both the decreased sexual function and involvement of women's husband at war were higher in oligomenorrhea group. However, these two parameters are closely related with each other and the question asking for any change in sexual desire and function does not always reflect the actual sexual interest but the presence or absence of the women's husband. The presence of a husband nearby (not involved at war) is not only related with sexual life but also closely related with the security of the family, especially when you are a refugee in conflict situations.

The practical implications of our findings would be using measurement of menstrual irregularities as an initial sign of depression/trauma as a result of refugee experience and preferential placement of refugees in countries where they can speak the language and share common cultural heritage. Refugees sharing the same ethnicity and language with the receiving country were supposed to have better adaptive ability and less psychosocial trauma compared with refugees of different ethnical origin and language. Therefore, the international community must step up efforts to support refugees through the hosting governments and non-governmental organizations in neighbouring countries with similar demographic properties as far as the proper regulations and security can be provided. Migration to countries geographically far away from homeland should not be promoted.

Limitations and Biases

There are several limitations and biases in planning and performing social studies; being more prominent in conflict zones and refugee settings. There was the selection bias in our study, as only women admitting to the local health center located within the camp were included. The reason for this selection bias was that we could not get the required permission from the local health directorate to interview refugees outside the borders of local health district. Another problem is about the comparability of groups and the way the endocrine system responded to the same stress; whether both female groups were exposed to the same stress for migration reasons, family situation, existing family networks, etc. Far more ethnically Turkish than Arabic women refugees were participated within our study. This apparent weakness of the study is due to heterogenous composition of populations in different camps. Future planning of a similar study in a refugee camp with Arabic predominance would cope this problem.

Before starting the study, all questionnaires and design of the study were presented to the local health governate for the permission. The questions about sexual abuse, change in sexual functions and physical violence were not allowed. After our objection, only questioning the sexual function was allowed because this question was one of the components of the BDI II and whole scaling system would be affected otherwise. The small range of depression scores, with majority of women clustered within minimal (0-12 points) and mild (13-18 points) depression groups, is another issue of limitation of the study. There were only few women in each group with moderate depression and no women with severe depression.

The need for a translator, usually a relative or a friend of the patient, during interviews with native Arabic speakers and using lay people or relatives as translators is very unfavorable. While translation may have been a necessity in these field conditions, it is a potential problem statistically (i.e., if the questions mean slightly different things to different members of the sample, this raises question marks about the validity of comparing the results within this sample), this is why translated questionnaires typically have to undergo psychometric evaluation (tests of validity and reliability) against the original questionnaires before being used to make comparisons. However, this drawback (of untested validity) was the only solution in absence of a professional translator and interpreter. In collectivist societies, as in our study group, not only everyday issues but also important questions and severe personal problems especially those related with sexual history might be considered as secret and may be hidden from the interviewer. This probability is less in native Turkish speakers on a one-to-one basis interview without any attendance of a translator. When we interpretate the results for comparison of the sexual function among the ethnically Arabic group, we had observed no worsening of sexual functions in the Arabic group. These findings may be related with the presence of a translator for the Arabic group but not for the Turkish group and be met cautiously.

The fraction of immigrants who are unrecorded and living outside the camps is another common limitation for studies of refugees. Probably the psychosocial consequences of stress and related symptoms, sexual and physical violence are more common among the immigrant population living outside of the camps illegally (Maria, 2010).

5. Conclusion and Suggestions

Depression is one of the major component of post-traumatic events and one of the known reasons of menstrual irregularities in women. Menstrual irregularities, particularly oligomenorrhea, may be an objective and initial gynecological sign in refugee women alerting the clinicians to refer the women for further psychiatric evaluation.

Declarations:

The authors declare no conflict of interest. All authors participated in the study and reviewed the final version of the manuscript. The manuscript has not been published. In accordance with the Declaration of Helsinki, our study was approved by the Local Health Governate of Osmaniye (13/03/2014-52/1713). Informed consents were obtained from each individual patient after it had been read by the medical secretary to both the patient and the translator. Authorship contribution: Ideas: IBG; Design: IBG, CK, BK, BT; Inspection: CK, BK; Resources: IBG, BK; Materials: IBG, CK, BK, BT; Data collection and/or processing: IBG, BK, CK; Analysis and/or interpretation: IBG, CK, BK; Literature research: IBG, CK, BT; Writing: IBG, CK, BK; Critical review: IBG, BT.

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