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# A Case-Control Study on Factors Associated With Secondary Amenorrhea Among the Medical Students of Universiti Malaysia Sabah

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## Abstract

Background and aim: This study aimed to evaluate the association between body mass index (BMI), anxiety, stress, depression, hormones, and secondary amenorrhea among female medical students at Universiti Malaysia Sabah (UMS).

Methods: In this case-control study, UMS undergraduate female medical students aged 19-25 years who did not menstruate in the last three months (with a previous history of a regular menstrual cycle) or six months (with a history of irregular menstruation) were included as cases (40 students), and students with similar criteria but no menstrual irregularities were recruited in the study as controls (40 students). The study was conducted at Polyclinic UMS from January 1, 2021, until December 31, 2022. The chi-squared test and odd ratio examined the association of the above-mentioned factors with the secondary amenorrhea. A p-value less than 0.05 was considered significant, and an odds ratio if the confidence interval did not contain one was considered significant.

Result: Both the groups had a similar frequency of different BMI grades. The cases exhibited significantly higher levels of depression, anxiety, and stress than the controls. Again, the cases demonstrated higher estradiol (E2), testosterone, and thyroid-stimulating hormone (TSH) levels and lower levels of luteinizing hormone (LH) than those with regular menstruation. The research also revealed that a one-unit decrease in follicle-stimulating hormone (FSH) levels corresponds to a threefold increase in the risk of experiencing secondary amenorrhea, while the risk escalates to fourfold for LH. Moreover, E2, testosterone, and TSH levels exhibited protective effects on secondary amenorrhea.

Conclusion: Anxiety, serum LH, and FSH were significantly associated with secondary amenorrhea. Future studies should address the diurnal variation of the hormones and consider the participants' circumstances to get a proper effect of hormonal influence and stress.

**Categories:** Obstetrics/Gynecology
**Keywords:** follicle-stimulating hormone, case-control studies, luteinizing hormone, body mass index, amenorrhea

## Introduction

Menstruation is considered an indicator of women's health, and it is a unique phenomenon that represents the beginning and end of reproductive age. Understanding menstruation patterns and factors affecting it may improve understanding of menstrual characteristics, proper management, and menstrual issues [1]. A regularly (every 21-45 days) menstruating woman is considered to have secondary amenorrhea if she has not menstruated in three months. For an irregularly menstruating woman, amenorrhea should last six months to diagnose it as secondary amenorrhea. Hypothalamic amenorrhea (HA) and polycystic ovary syndrome (PCOS) are the two most common causes of secondary amenorrhea other than pregnancy [2].

Hypothalamic amenorrhea (HA) caused by deficient secretion of hypothalamic gonadotropin-releasing hormone (GnRH) accounts for approximately 30% of cases of secondary amenorrhea in women of reproductive age. It leads to failure of pituitary gonadotropins and gonadal steroid release. Functional hypothalamic amenorrhea (FHA) is defined as hypothalamic amenorrhea (HA) occurring in the absence of a structural lesion and is predominantly caused by significant weight loss, intense exercise, or stress [3]. FHA is evidenced by low serum estradiol and gonadotropins, which lead to increased bone turnover and rapid bone loss [4].

Higher than normal levels of gonadotropins in females also lead to reproductive pathologies, most notably, polycystic ovary syndrome (PCOS), characterized by an increase specifically in luteinizing hormone (LH) and leading to elevated LH/follicle-stimulating hormone (FSH) ratio [5]. PCOS is a prevalent endocrinopathy in females, characterized by chronic oligo-anovulation, hyperandrogenism, and polycystic ovaries, all of which can worsen the quality of life for these patients [6]. The changes in female hormone levels are associated with health behaviors, obesity, and stress. Research has revealed that elevated stress levels can impact the hypothalamic-pituitary-adrenal (HPA) axis activity. Conversely, a high body mass index (BMI) has been observed to have an impact on sex hormone-binding globulin (SHBG), the free androgen index (FAI), testosterone, and insulin levels. Thus, previous studies have reported a significant association between lifestyle and menstruation [1].

Several researchers have found medical students to have higher stress, anxiety, and depressive symptoms due to the challenging and demanding nature of the medical school curriculum [7-14]. Owing to the curricular commitment, the scope of physical activities is limited [15]. Hence, medical students are prone to be exposed to obesity [16]. The prevalence of overweight and obesity among medical students at Northern Border University, Arar, Saudi Arabia, was 21.7% and 8.4%, respectively, in a study by Mehmood et al. [17]. In their reflections on the Peninsular Malaysian population, Gopalakrishnan et al. and Boo et al. found that 30.1% of the students were overweight or obese [18,19].

Again, stress has the potential to significantly contribute to or even trigger menstrual irregularities. Evidence indicates a connection between stress and menstrual irregularities [20,21]. Additionally, a notable prevalence of menstrual issues has been noticed among students pursuing studies in medicine and health sciences [22-25]. In their research, Sood et al. and Clarvit found no association between perceived stress and menstrual problems [15,26]. In contrast, other researchers reported that stress scores could predict irregular menstrual cycles [27-32]. Hence, the present study investigated the association of BMI, anxiety, stress, depression, and hormones with secondary amenorrhea among female medical students from Universiti Malaysia Sabah (UMS).

An earlier version of this article was previously posted to the Research Square preprint server on February 10, 2023.

# Materials And Methods

This case-control study was carried out during the period starting from January 1, 2021, until December 31, 2022.

## Inclusion and exclusion criteria

UMS undergraduate female medical students with an age range of 19-25 years who attended the Polyclinic UMS during the study period were included in the study as cases if they did not menstruate in the last (1) three months, with a previous history of a regular menstrual cycle or (2) six months, with a history of irregular menstruation. Female students with similar criteria but no menstrual irregularities were recruited in the study as control.

The students who received hormonal treatment in the past six months, with organic lesions of the genital tract, bleeding disorders, and pregnancy, were excluded from the study.

## Sampling

The minimum sample size required for this study was 80 (where two-sided confidence level=95%, power=90%, the ratio of controls to cases=1, percent of controls exposed: 25%, odds ratio=5, and percent of cases with exposer=62.5%) [33]. A total of 80 participants who fulfilled the inclusion criteria were included through stratified random sampling.

## Study procedure

After getting written informed consent, all respondents were asked to complete filling out self-administered questionnaires for age, level of education, and menstrual histories, such as their age at menarche, regularity of menstrual cycle, most prolonged duration without the period, usage of hormonal medication to regulate their menstruation in previous six months, any intermenstrual bleeding and its time, past medical history, current weight gained or lost, any engagement in exercise and sports, and any history of having bone density scan. Of these respondents who fulfilled the selection criteria, 40 subjects were randomly recruited as cases, and the other 40 were recruited as controls. Then, the respondents' depression, anxiety, and stress were measured by Depression, Anxiety, and Stress Scale-21 (DASS-21), and the respondent's height and weight were measured to calculate BMI, and blood samples were collected for hormonal studies. Blood samples were analyzed the same day, and the results were available within 24 hours. Hormone levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone (TT), prolactin (PRL), thyroid-stimulating hormone (TSH), and free thyroxine (T4) were measured by enzyme-linked immunosorbent assay (ELISA) method using Cobas e411 analyzer (Basel, Switzerland: Roche Holding

AG).

## Ethical permission

The research underwent a thorough review by the Medical Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, and the ethical approval code for this research is JKEtika 1/20 (12). The study complied with the ethical principles outlined in the appropriate edition of the Declaration of Helsinki, initially established in 1975 and revised in 2000.

## Data analysis

At first, the data were screened for normality and were not normally distributed. Hence, median, quartiles, and interquartile range (IQR) were used to describe the data. Mann-Whitney U tests were performed to compare the variables between the two categories, and the odds ratio determined the association between the variables. A p-value less than 0.05 was considered as the level of significance. All the statistical analysis was performed using SPSS software version 27.0 (Armonk, NY: IBM Corp.).

# Results

Within the group of participants, the median age for individuals experiencing regular menstruation was 23 years, with an interquartile range (IQR) of 2. In contrast, those with irregular menstruation had a median age of 22 years and an IQR of 2.5. Additionally, both groups exhibited a median age of menarche at 12 years, with IQRs of 1 and 1.5, respectively (Table 1).

| Factors | Menstruation | Minimum | Median | IQR | Maximum |
|---|---|---|---|---|---|
| Age (years) | Control | 21 | 23 | 2 | 25 |
| | Case | 19 | 22 | 2.5 | 27 |
| Menarche (years) | Control | 10 | 12 | 1 | 15 |
| | Case | 9 | 12 | 1.5 | 18 |

**TABLE 1: Descriptive statistics of the respondents (n=80).**

IQR: interquartile range

Among the cases, the majority (22 persons) of the participants had FHA, and the rest of the participants (18 persons) were diagnosed with PCOS (Figure 1). They were diagnosed based on their clinical evidence.

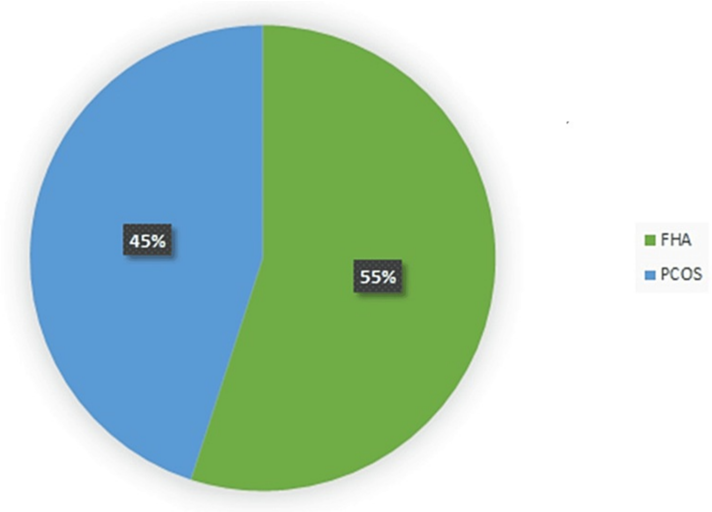


**FIGURE 1: Frequency of types of secondary amenorrhea among the respondents (n=40).**

FHA: functional hypothalamic amenorrhea; PCOS: polycystic ovary syndrome

As the subjects were selected as matched pairs, both the groups had a similar frequency of different BMI grades (Table 2 and Figure 2). As the data are not normally distributed, but the respondents were randomly selected, and the shape of the data appears to be the same, the Mann-Whitney test was performed to test the following hypothesis: $H_0$=there is no difference in BMI between the two groups and $H_1$=there is a difference in BMI between the two groups.

| Factors | | Control | | Case | |
|---|---|---|---|---|---|
| | | Frequency | Percentage | Frequency | Percentage |
| Depression | Normal | 36 | 90.0 | 31 | 77.5 |
| | Mild | 3 | 7.5 | 7 | 17.5 |
| | Moderate | 1 | 2.5 | 2 | 5.0 |
| Anxiety | Normal | 35 | 87.5 | 23 | 57.5 |
| | Mild | 4 | 10.0 | 2 | 5.0 |
| | Moderate | 1 | 2.5 | 13 | 32.5 |
| | Severe | 0 | 0 | 2 | 5.0 |
| Stress | Normal | 39 | 97.5 | 36 | 90.0 |
| | Mild | 1 | 2.5 | 3 | 7.5 |
| | Moderate | 0 | 0 | 1 | 2.5 |
| | Total | 40 | 100.0 | 40 | 100.0 |

**TABLE 2: Distribution of DASS-21 score among the respondents (n=80).**

DASS-21: Depression, Anxiety, and Stress Scale-21

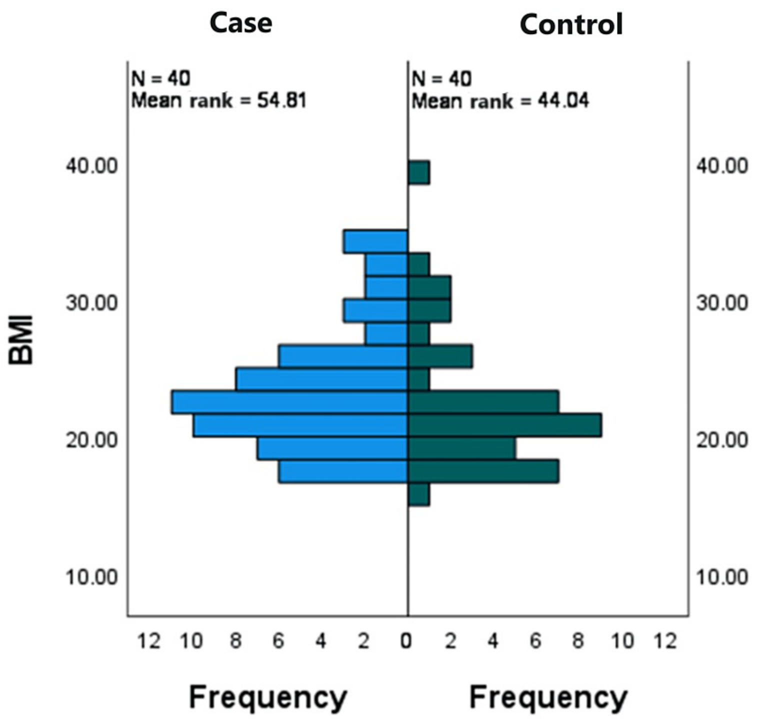


**FIGURE 2: Comparison of BMI among the case and control groups (n=80).**

The p-value was higher than the significance level, α=0.05 (Table 2). There was insufficient evidence to reject the null hypothesis. There were some apparent differences in the frequencies of depression, anxiety, and Stress (DASS-21 score) between the two groups (Table 3 and Figure 3), which was tested for the following hypothesis: $H_0$=the two groups have no difference in the DASS-21 score and $H_1$=there is a difference in DASS-21 scores between the two groups.

| Factors | | Control | | Case | |
|---|---|---|---|---|---|
| | | Frequency | Percentage | Frequency | Percentage |
| | Underweight | 8 | 20.0 | 4 | 10.0 |
| | Normal | 22 | 55.0 | 24 | 60.0 |
| BMI | Overweight | 6 | 15.0 | 7 | 17.5 |
| | Obese | 4 | 10.0 | 5 | 12.5 |
| | Total | 40 | 100.0 | 40 | 100.0 |
| Mann-Whitney U test | | | Standard error | z-Value | p-Value |
| 1458.50 | | | 142.11 | 1.819 | 0.069 ns |

**TABLE 3: Distribution of BMI score among the respondents (n=80).**

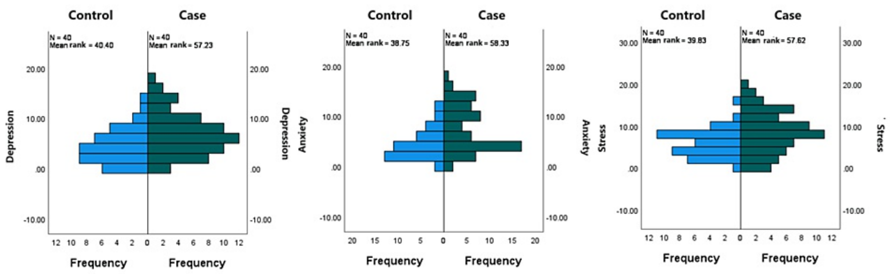


**FIGURE 3: Frequency of DASS-21 score among the case and control groups (n=80).**

DASS-21: Depression, Anxiety, and Stress Scale-21

As the samples were independent random samples and the shapes of the distributions were the same, the requirement of the Mann-Whitney test was fulfilled. The p-values for depression (0.004), anxiety (<0.001), and stress (0.003) were less than the level of significance, α=0.05 (Table 4). So, the null hypothesis was rejected. There was sufficient evidence to conclude that the DASS-21 score of the participants with irregular menstruation differed from the matched control group.

| Factors | Mann-Whitney U test | Standard error | z-Value | p-Value |
|---|---|---|---|---|
| Depression | 1604.00 | 111.53 | 2.854 | 0.004 |
| Anxiety | 1670.00 | 141.49 | 3.322 | <0.001 |
| Stress | 1627.50 | 141.65 | 3.014 | 0.003 |

**TABLE 4: Comparison of DASS-21 between case and control groups (n=80).**

DASS-21: Depression, Anxiety, and Stress Scale-21

Table 5 demonstrates that the medians of LH, estradiol, testosterone, and TSH differed from the matched control group among hormones that could influence menstrual irregularity.

| Factors | LH (mIU/mL) | | FSH (mIU/mL) | | Estradiol (pmol/L) | | Testosterone (nmol/L) | | Prolactin (ng/mL) | | Free T4 (pmol/L) | | TSH (mcIU/mL) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Case | Control | Case | Control | Case | Control | Case | Control | Case | Control | Case | Control | Case |
| Min | 3.07 | 1.56 | 2.5 | 1.18 | 28.59 | 30.42 | 0.19 | 0.36 | 6.46 | 3.07 | 13.95 | 15.41 | 0.43 | 0.47 |
| Q2 | 7.30 | 13.74 | 5.48 | 6.28 | 224.13 | 185.41 | 0.98 | 1.44 | 14.89 | 17.21 | 20.19 | 19.11 | 1.13 | 1.45 |
| IQR | 4.41 | 10.29 | 3.59 | 2.71 | 423.47 | 335.25 | 0.5 | 1.82 | 9.55 | 21.66 | 4.94 | 21.09 | 0.67 | 1.95 |
| Max | 24.6 | 83.12 | 28.34 | 19.1 | 1808.12 | 1085.20 | 2.27 | 2.91 | 34.87 | 61.72 | 29.42 | 28.2 | 4.25 | 5.72 |

**TABLE 5: Hormonal profile of the respondents (n=80).**

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone

The difference in the hormone profile was tested under the following hypothesis: $H_0$=there is no difference in hormone profile between the two groups and $H_1$=there is a difference in hormone profiles between the two groups. Besides the random distribution, Figure 4 demonstrates similar shapes for hormone profiles for the two groups. So, the assumptions for the Mann-Whitney test were achieved.

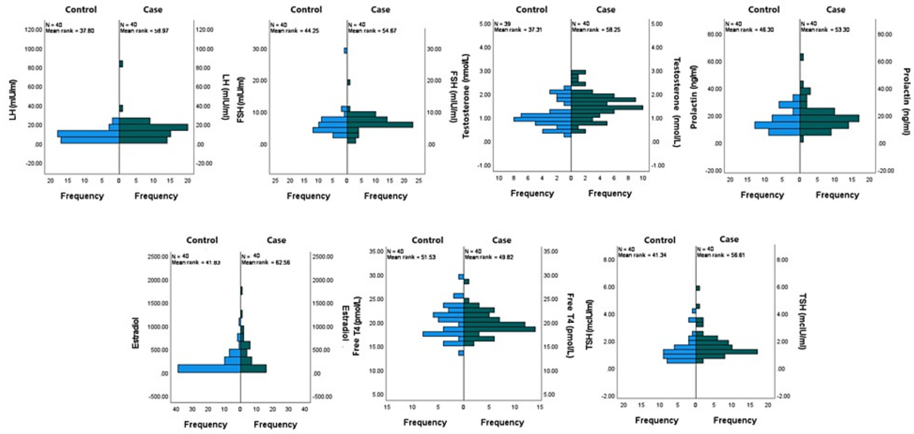

**FIGURE 4: Comparison of hormone profiles among the case and control groups (n=80).**

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone

The p-values of Table 6 for LH, testosterone, estradiol, and TSH were lower than the significant level α=0.05, but for FSH, prolactin and free T4 were higher than the significant level. There was sufficient evidence to reject the null hypothesis for LH, testosterone, estradiol, and TSH, but the evidence was insufficient to reject the null hypothesis for FSH, prolactin, and free T4. Hence, there was a significant difference in LH, testosterone, estradiol, and TSH levels.

| Factors | Mann-Whitney U test | Standard error | z-Value | p-Value |
|---|---|---|---|---|
| LH | 1708.00 | 142.13 | 3.574 | <0.001 |
| FSH | 1450.00 | 142.12 | 1.759 | 0.079 |
| Testosterone | 1665.00 | 139.63 | 3.545 | <0.001 |
| Prolactin | 1368.00 | 142.13 | 1.182 | 0.237 |
| Estradiol | 680.00 | 138.15 | -3.521 | <0.001 |
| Free T4 | 1159.00 | 142.13 | -0.288 | 0.773 |
| TSH | 1566.50 | 142.12 | 2.579 | 0.010 |

**TABLE 6: Comparison of hormone profile among the case and control groups (n=80).**

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone

The odds ratio was used to examine the relationship between depression, anxiety, stress, and hormone profiles in relation to secondary amenorrhea (Table 7).

| Secondary amenorrhea vs other factors (BMI, depression, anxiety, etc.) | | Odds ratio | 95% confidence interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| BMI | Normal/obese | 1.286 | 0.521 | 3.175 |
| Depression | Absent/present | 2.739 | 0.830 | 9.037 |
| Anxiety | Absent/present | 5.000 | 1.718 | 14.553 |
| Stress | Absent/present | 4.333 | 0.501 | 37.451 |
| FSH | Deficiency/normal | 3.000 | 1.180 | 7.627 |
| LH | Deficiency/normal | 4.500 | 1.902 | 10.647 |
| Estradiol | Low/normal | 0.364 | 0.156 | 0.850 |
| TSH | High/normal | 0.602 | 0.513 | 0.707 |
| Testosterone | High/normal | 0.583 | 0.493 | 0.691 |

**TABLE 7: Association BMI, stress, and hormones with secondary amenorrhea (n=80).**

LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone

While the odds ratio for BMI, depression, and stress occurring in secondary amenorrhea is greater than 1, the confidence interval includes 1. So, the association for these variables is insignificant. On the other hand, the odds ratio for anxiety, FSH, and LH levels is more than 1, and for estradiol, TSH, and testosterone levels is less than 1. In both cases, the interval does not include 1, which suggests that there is a significant association, although with variations.

## Discussion

In this case-control study, researchers emphasized BMI, stress, anxiety, depression, and serum levels of LH, FSH, prolactin, TSH, free T4, estradiol, and testosterone to find an association with secondary amenorrhea among the medical students of UMS.

Obesity is widely recognized as a factor that can lead to various gyneco-endocrine issues, such as hyperandrogenism, anovulation, polycystic ovary syndrome (PCOS), and fertility challenges. The resistin gene polymorphism has been linked to BMI among women with PCOS, indicating a potential connection between this genetic variation and adiposity in PCOS [34]. A randomized placebo-controlled study demonstrated that administering the insulin sensitizer rosiglitazone significantly reduced serum resistin levels among overweight women with PCOS [35]. However, in this study, researchers could not find any association between BMI and secondary amenorrhea, which corresponds to the findings of Silvestris et al. in 2018 and Aladashvili-Chikvaidze et al. in 2015 [34,36].

Functional hypothalamic amenorrhea (FHA) occurs in response to exaggerated metabolic, physical, or psychological stress such as severe dieting, heavy training, intense emotional events, or a combination of them with or without body weight loss. These stressors negatively affect GnRH release and the reproductive axis [37]. Reproductive functions and stress regulation systems are closely linked, and stress-related activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to the inhibition of the hypothalamic-pituitary-ovarian (HPO) axis at multiple levels. Hypothalamic corticotropin-releasing hormone (CRH), the principal driving factor of the HPA axis during stress, is a potent inhibitor of GnRH secretion, which delays or suppresses LH secretion. Abnormal LH secretion can cause menstrual irregularities and amenorrhea [38,39]. Cortisol, the primary effector hormone of the HPA axis, is an important biological marker of stress and is released in a pulsatile manner [40]. Physical or mental stress activates an instant increase in CRH, and Valsamakis et al. reported that an elevated resting cortisol level during intense training was involved in the hypersecretion of CRH. Therefore, increased CRH causes menstrual disturbance through cortisol activation [41]. Acute stress impairs reproduction if it occurs at a critical time during the precise time course of endocrine events that induce estrus and ovulation. However, chronic stress impairs reproduction in general. Glucocorticoids exert a wide range of effects on metabolism, which are primarily catabolic to utilize every available energy resource against the challenge enforced by stressors, and chronic stress prolongs the adaptive shift towards a generalized catabolic state. Thus, sustained HPA hyperactivity can progressively lead to decreased lean (muscle and bone) body mass, increased visceral adiposity, and insulin resistance. Body weight and fat mass are independent regulators of the HPO axis activity, and disruption of homeostatic models by chronic life stressful events must be studied regarding PCOS endocrine dysregulation [42]. Participants of this study with secondary amenorrhea (case group) exhibited significantly higher ($p>0.05$)

depression, anxiety, and stress levels than the control group. However, only the presence of anxiety increased the risk of secondary amenorrhea five times compared to the absence of it. In contrast, stress and depression could not predict the risk significantly, which corresponds to Sood et al. in 2012 and Clarvit in 1988 [15,26] but not to Harlow and Matanoski in 1991, Gordley et al. in 2000, Sherina et al. in 2004, Saipanish in 2003, Yamamoto in et al. 2009, and Tang et al. in 2020 [27-32]. In this study, most participants (90% or more) did not have stress or depression, but many participants (more than 30%) had moderate anxiety. According to the American Psychological Association, a subtle distinction exists between stress and anxiety. Both are emotional responses, but an external stimulus typically instigates stress [43]. Medical students experience stress most during examinations, and the participants only took part in this research during their off time; this factor could play a significant role in the fact that only a minority exhibited stress [44]. In contrast, anxiety is characterized by persistent and excessive concerns that persist without a specific stressor. Anxiety elicits a nearly identical array of symptoms as stress [43].

In this study, respondents with menstrual irregularity demonstrated higher E2, testosterone, and TSH levels and lower levels of LH than those with regular menstruation. The study also shows that if the FSH level decreases by 1 unit, there will be three times the risk of having secondary amenorrhea, whereas the risk is four times for LH (Table *7*). Moreover, E2, testosterone, and TSH levels exhibited protective effects on secondary amenorrhea. The common denominator of FHA is an aberration of the pulsatile secretion of GnRH from the hypothalamus, ranging from undetectable pulses to variations in amplitude or frequency. These alterations result in the deregulation of FSH and LH levels, leading to decreased ovarian estradiol production and anovulation [45]. It has been reported that there is a link between FHA and PCOS. However, it is impossible to know whether this association between PCOS and FHA depends on some specific genetic trait or the involvement of some common hypothalamic mechanism. Some patients with FHA may have subtle increases in serum androgens during gonadotropin administration and, in addition, may have ovarian morphology like women with PCOS. In most studies, serum anti-Mullerian hormone (AMH) level, which is typical in FHA, has been reported to be increased. Increased AMH levels are an important diagnostic marker for altered ovarian morphology in women with PCOS [45].

This study had some limitations to consider when interpreting the results. First, most data on the participants' menstrual history, past medical history, and current weight gained or lost were collected through self-reported questionnaires, which were not confirmed by investigations and led to statistically significant correlation coefficients relatively weak. However, these correlations do not establish causation. An experimental study design is required to establish causation. Second, we could not measure the level of corticotropin-releasing hormone (CRH) and cortisol, which are principal driving factors of the HPA axis during stress. The level of these hormones has diurnal variations, and we could not fix the time to take blood samples because students could come to the clinic only when they were free from teaching schedules.

## Conclusions

The factors associated with secondary amenorrhea (PCOS and FHA) in medical students of this research were anxiety and hormonal influences, mainly deficiency of LH and FSH. Future studies should address the diurnal variation of the hormones and consider the participants' circumstances to get a proper effect of hormonal influence and stress.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** M Tanveer Hossain Parash, Win Win Than, Nathira Binti Abdul Majeed, Khin Nyein Yin, Dg Marshitah Binti Pg Baharuddin, Ehab Helmy Abdel Malek Fahmy, Mohd Nazri Bin Mohd Daud

**Acquisition, analysis, or interpretation of data:** M Tanveer Hossain Parash

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**Supervision:** Win Win Than, Nathira Binti Abdul Majeed

### Disclosures

**Human subjects:** Consent was obtained or waived by all participants in this study. Medical Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah issued approval #JKEtika 1/20 (12). The study complied with the ethical principles outlined in the appropriate edition of the

Declaration of Helsinki, initially established in 1975 and revised in 2000. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** This work was supported by the Centre for Research and Innovation (PPI), Universiti Malaysia Sabah (UMS) (grant number: SGA-19101). **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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