

**PREVALENCE AND FACTORS ASSOCIATED WITH FUNCTIONAL SECONDARY AMENORRHEA****Huda Kafeel<sup>1</sup>, Ramsha Rukh<sup>2</sup>, Asma Zubair<sup>3</sup>, Ayesha Ghazala<sup>4</sup>, Hira Muzaffar<sup>5</sup>, Hira Raees<sup>6</sup>, Kanwal Riaz<sup>7</sup>, Tania Qudsia<sup>8</sup>, Zunaira Ali<sup>9</sup>**

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**\*Corresponding author e-mail:** [huda\\_kafeel@hotmail.com](mailto:huda_kafeel@hotmail.com)**ABSTRACT**

The main objective of this study is to investigate the prevalence of functional secondary amenorrhea and also to study the different variable factors associated with it with its possible pathological outcome in our community. A retrospective study is conducted in the city of Karachi. Data regarding the occurrence of amenorrhea, specifically functional secondary amenorrhea, their related complications and symptoms were collected together with demographic variables by means of structured questionnaire. Study sample was of 1052 women (age between 13 to 48 years) out of 1258 women approached. (n= 1052 with response rate 83.62%) 12 women out of 1052 (1.14%) gave a history of primary amenorrhea with no onset of menstrual cycle even at the age of 15. Contrary there were 44.77% women having history of no onset of menstrual cycle for more than 3 months duration during the past year. (Secondary amenorrhea). 5.04% was due to established ovarian cause like PCOs and 39.73% was due to functional causes like stress, excessive dieting, exercise or use of medications (like oral contraceptives or sedative hypnotics or SSRI's) classified as Functional secondary amenorrhea. 11.12% amenorrhea was due to pregnancy. Among different variables studied weight, age, marital status, pregnancy history was found to be significant. A significant correlation between the use of oral contraceptives and secondary amenorrhea was found in about 7.03% of women. Obesity was found to be the most common effect in women having secondary amenorrhea.

**Key words:** Functional, Secondary, amenorrhea, stress, contraceptives**INTRODUCTION**

Amenorrhea is a term used for condition with no menstrual bleeding.<sup>[1]</sup> It is a normal in pre pubertal, pregnant, and postmenopausal females.<sup>[2]</sup> it can be primary or secondary. Primary amenorrhea is the absence of menstrual bleeding and secondary sexual characteristics in a girl by age 14 years or the absence of menstrual bleeding with normal development of secondary sexual characteristics in a girl by age 16 years<sup>[3]</sup> and Secondary amenorrhea is the absence of menstrual bleeding in a woman who had been menstruating but later stops menstruating for three or more months in the absence of pregnancy, lactation, cycle suppression with systemic hormonal contraceptive (birth control) pills, or menopause.<sup>[4]</sup> and if the condition of amenorrhea is due to some natural processes than it is term as natural amenorrhea, that is amenorrhea due to pregnancy,

lactation or normal menopause (at age of 50 in Asian population). According to a survey performed in Sweden in 1973, 3.3% were of 1862 gave a history of amenorrhea of more than 3 months duration during the past year and considered to have secondary amenorrhea. No case of primary amenorrhea was found. <sup>[5]</sup> functional secondary amenorrhea is an endocrine pathology appears as a result of decrease in pulsatile GnRH secretion, not involving any hypothalamus-pituitary organic lesions, to endocrine (hyperprolactinemia, hypo/hyperadrenal activity, hypo/hyperthyroidism) or systemic diseases. <sup>[6],[7]</sup> The mechanism responsible for functional secondary amenorrhea is still not clearly understood. A number of neuroendocrine dysfunctions seem to be involved in the pathogenesis, like an increase of the dopaminergic tone<sup>[8]</sup>, hyper function of hypothalamus-pituitary-adrenal axis with hyper

secretion of cortisol, CRH, ACTH<sup>[9],[10]</sup> and endogenous Opioids<sup>[11]</sup> and also a increase of the nocturnal melatonin secretion<sup>[12]</sup> This common and, reversible condition accounts for an estimated 15%–35% of cases of secondary amenorrhea.<sup>[13]</sup> need to mention that the number of life stressful events in amenorrhea patients was significantly greater than those observed in the control group (45.9 vs. 32.8%) reported by loredana fioroni<sup>[14]</sup> Exercise induced increased cortical level is another major factor of decreased estradiol and progesterone levels thus can induce amenorrhea.<sup>[14]</sup> As another major factor evaluated nutritional deprivation was reported by ME Nelson.<sup>[15]</sup>

As Karachi is a big city with highly stressed and depressed environment and because of lack of availability of data on epidemiology of functional secondary amenorrhea a large number of populations are under threat of this condition with no specific organic cause.<sup>[6],[7]</sup> as the condition of hypothalamic amenorrhea only requires effective counseling to cope with the causative factor and the condition is reversible if the responsible factors addressed and removed with in time and all the symptoms are evaluated and treated accordingly. Therefore we performed an observational study to investigate the prevalence of functional secondary amenorrhea in our population and correlate it with major contributing factors and its possible effects that might get worse if not addressed.

## METHODOLOGY

The observational study is conducted in the city of Karachi by means of a pretested and restructured questionnaire. Questionnaire is designed and reformatted on the basis of answers provided by sample group. Women approached in the gynecological OPDs of hospitals of different areas of Karachi. Women places other than hospitals in different localities, Specially Women Colleges and Universities is also been approached in a period of 3 months. (From October 2012 to December 2012). Data regarding the occurrence of secondary amenorrhea, their related causes, complications and physical symptoms were collected together with demographic variables such as age, weight, marital status, stress influence, physical exercise, early sexual growth, daily routine, pregnancy history and use of oral contraceptives etc. Study sample is of 1052 women (age between 13 to 48 years) out of 1258 women approached. An exclusion criterion was questionnaire with incomplete or inadequate data. (n= 1052 with response rate 83.62%). A second questionnaire is also been interviewed by specific groups segregated on the basis of answers provided

by them in first questionnaire on person to person contact like group designated as stressed population Hamilton Depression Rating Scale (HDRS) is used to evaluate intensity of depression in selected groups.

Since our study was not experimental and did not involve any intervention, we did not approach any ethics committee for review before conducting the study although we took informed consent from all participants and maintain strict confidentiality. The collected data were analyzed by standard statistical methods for appropriate findings.

## RESULTS

There is a total sample of 1052 women age between 13 to 48 years. The mean for the age was  $22.29 \pm 7.89$  years. Age of menarche found is 12.4 to 13.8 years. Further in a total of 117 women, amenorrhea was due to the pregnancy (11.12%) and in 46 women (4.37%) it was due to breast feed. Among them 12 women (1.14%) give a history of primary amenorrhea with no onset of menstrual cycle even at the age of 15. And only 2 women among them give a family history of primary amenorrhea (0.19%). On the other side their were 44.77% (n=471) of the women out of 1052 gives a history of no onset of menstrual cycle for more than 3 months during the past year, classified as secondary amenorrhea. 5.04% (n=53) of which have established diagnosis of polycystic ovary (PCOs). Remaining 39.73% (n=418) have demonstrated causes classified as functional secondary amenorrhea. (Figure 1) Among which 18.44% (n=194) gives a history of stressful events in their past, About 7.03% (n=74) of women having functional secondary amenorrhea in connection with oral contraceptive drugs using for about more than 6 years and they are experiencing secondary amenorrhea as post drug effects. Progressive weight loss with or without anorexia is another factor may be associated with functional secondary amenorrhea found in about 9.98% (n=105) out of 39.73% women. Further 2.75% (n=29) has an intense physical routine from past three years. Only 1.52% (n=16) amenorrheic women are found with no specific cause of amenorrhea. (Figure 2)

## DISCUSSION

There is a total sample of 1052 women age between 13 to 48 years. The mean for the age was  $22.29 \pm 7.89$  years. Age of menarche found is 12.4 to 13.8 years. Further in a total of 117 women, amenorrhea was due to the pregnancy (11.12%) and in 46 women (4.37%) it was due to breast feed. Among them 12 women (1.14%) give a history of primary amenorrhea with no onset of menstrual cycle even at

the age of 15. And only 2 women among them give a family history of primary amenorrhea (0.19%), Provides genetic basis of primary amenorrhea. A number of genetic conditions in which some or all of the normal internal female organs either fail to form normally during fetal development or fail to function properly are characterized as amenorrhea. Another cause of primary amenorrhea is diseases of the pituitary gland and hypothalamus as they play a critical role in the regulation of ovarian hormones.<sup>[15]</sup> Another genetic involving reason is turner syndrome, in which women are lacking part of one of the two X chromosomes usually present in the female. In Turner syndrome, the ovaries are replaced by scar tissue and estrogen production is minimal resulting in amenorrhea. Estrogen-induced maturation of external female genitalia and sex characteristics also fails to occur in Turner syndrome<sup>[15]</sup> Another important reported cause of primary amenorrhea in young women is Gonadal dysgenesis, a situation in which the ovaries are prematurely depleted of follicles and oocytes (egg cells) leading to premature failure of the ovaries.<sup>[16]</sup> the genetic association of premature ovarian failure is FSH receptor gene, mutations of which cause autosomal recessive hypergonadotropic hypogonadism in women who predominantly present with primary amenorrhea, with or without breast development.<sup>[17]</sup> Several 46,XX females have been described with homozygous inactivating mutations of the LH receptor These genetic females usually present with normal breast development.<sup>[18]</sup> Their endocrine profile is somewhat different than the typical patient with POF who has elevations of both gonadotropins, with FSH higher than LH. Females with LH receptor mutations may have a normal to elevated serum LH level and normal levels of FSH, or at least an elevated LH to FSH ratio.<sup>[19]</sup> On the other side their were 44.77% (n=471) of the women out of 1052 gives a history of no onset of menstrual cycle for more than 3 months during the past year, classified as secondary amenorrhea.5.04% (n=53) of which have established diagnosis of polycystic ovary (PCOs). As PCOs causes relatively high and sustained levels of hormones, rather than the fluctuating levels seen in the normal menstrual cycle<sup>[20]</sup> and involve increased testosterone and androstenedione, and elevated mean serum concentrations of leutinizing hormone<sup>[21]</sup> and finally remaining 39.73% (n=418) have demonstrated causes classified as functional secondary amenorrhea. Among which 18.44% (n=194) gives a history of stressful events in their past, here separation from partner/relationship breakup, death of loved ones, unusual/or unexpected incidents like failure in exams, or physical, mental or sexual harassments etc are counted as stressful events and thus Hamilton

Depression Rating Scale (HDRS) is also devised for selective subjects and the score obtained is >16 on average in those depressed females, and women on antidepressants and anxiolytic are also included as they not only have established diagnosis of stress and depression but at the same time the drugs like citalopram, escitalopram, fluoxetine can cause hyperprolactinemia<sup>[22]</sup> and thus contribute to amenorrhea. In another study of women ages 36 to 45, those with a history of depression exhibited 1.2 times the rate of perimenopause as nondepressed women. The findings suggest that depression might increase a woman's risk of ceasing ovarian function in her 30s or 40s.<sup>[17]</sup> Contrary in our finding the stress induced amenorrhea was equally distributed in all the age groups or independent of age, including ages between 20-48 years. That difference in findings reflects that as measurable stress is fairly common in population of Karachi even in young female of lower age groups, leading them to secondary amenorrhea or menstrual problems. However, menstruation and ovulation can return to normal after stress levels decrease as it is a purely reversible condition. About 7.03% (n=74) of women having functional secondary amenorrhea can be classified as users of oral contraceptive drugs for about more than 6 years and now even they have discontinued cycle suppressing systemic oral contraceptives for more than 10 months on average they are experiencing secondary amenorrhea as prolonged to post pill effects. All the women claimed have menstrual irregularity had normal regular cycle before the use of oral contraceptive pills with no incidence of prior menstrual irregularity. It is being evident that women on cycle suppressing ODCs some time take 3-6 months to resume their normal regular cycle<sup>[23]</sup> but in some cases chronic use of these medications can cause pathophysiological changes leads to menstrual complications. Post-pill amenorrhea is caused by under stimulation of pituitary gland which normally releases leutinizing and follicle-stimulating hormones, which controls estrogen and progesterone<sup>[24]</sup> According to study done by Petterson, the true incidence of secondary amenorrhea due to previous use of oral contraceptive agents is very low, 0.7% only.<sup>[25]</sup> but in our study the incidence of secondary amenorrhea is much higher comparatively i-e 7.03%. This is may be a indicative of a increasing trend of use of oral contraceptives with time and thus its incidence has also been increased in general population. As these cycle suppressing contraceptives contain synthetic hormones, and thus prolong exposure to these altered levels of synthetic hormones may cause menstrual complications severity depending on the length of exposure. Progressive weight loss with or without

anorexia is another factor may be associated with functional secondary amenorrhea found in about 9.98% (n=105) out of 39.73% women. Weight loss is one of the major contributors of hypothalamic dysfunction stated in one of the studies of Vigersky et al. [26] According to another study the hormonal state of patients with weight loss related amenorrhea is not the absence of the LH pulsatile release but its increased frequency with reduced pulse amplitude. [27] association of anorexia with weight loss in amenorrheic women is not significant or weight loss independent of anorexia is common factor of secondary amenorrhea. [26] starvation is closely associated with hormonal abnormalities and a common practice of self induced starvation is also common in females of all ages as a attempt to maintain their weight and that starvation effects a number of hypothalamic pituitary pathways can be a pathophysiological explanation of weight related secondary amenorrhea. Another major contributing factor is change in total body fat or mass and a simultaneous decrease in adipose secretion especially leptin secretion leads to reproductive dysfunction. the percentage of women we found in our study with rapid decrease in body fat with a period of two months with or without effort with normal regular menstrual cycle is 8.27% (n=87) that is because of increase body fat/mass in comparison of amenorrheic women. [28] Further 2.75% (n=29) has an intense physical routine from past three years. Those involve individuals with field specific job exposure, industry specific job exposure, fitness/ gym/ physical training instructor and sports teacher etc. that amenorrhea is not only due to excessive or Strenuous physical routine induced hypoestrogenemia but it has to be

accompanied by nutritional deprivation that appear as a sufficient imbalance in endocrine system. Accumulating evidence suggests that a critical metabolic or “energy” balance is intimately tied to regulation of GnRH pulsatility, and excessive physical activity results in dysfunction at the hypothalamic level specifically the gonadotropin releasing hormone (GnRH) pulse generator appears to be affected. There appears to be complete suppression of the normal pulsatile secretion of GnRH, which generally occurs every 60–90 min, as reflected in low levels of LH and to a certain extent FSH. [29]. Further Only 1.52% (n=16) amenorrheic women are found with no specific cause of amenorrhea includes individuals with normal healthy lifestyle, no measurable stress, normal physiological body weight etc that is may be due to some underline emerging pathological conditions related to endocrine system. By the personnel studies & research we had concluded that primary amenorrhea is not common among our population but secondary amenorrhea is very common in different age groups & localities having different causes. Studies also shows that loss of menstrual regularity can be a sign of ovarian insufficiency, and the associated estrogen deficiency is a well-established risk factor for osteoporosis [30], hypertension, depression and obesity. In treatment of amenorrhea first step is to treat the underlying cause. One should try to apply some lifestyle changes involving weight, physical activity or stress modification. Almost all the factors responsible for FSA are reversible and require only effective counseling for avoidance menstrual complication.

**Table 1. Prevalence of Primary and Secondary Amenorrhea**

Amenorrheic Groups	N=1052	% Prevalence
Primary Amenorrhea	12	1.14
Secondary Amenorrhea (PCOs)	53	5.04
Functional Secondary Amenorrhea	418	39.73
Pregnancy Induced Amenorrhea	117	11.12
Lactation Induced Amenorrhea	46	4.37
Women with normal menstrual cycle	406	38.60

**Table 2. Major Factors Responsible for Functional Secondary Amenorrhea**

Factors behind FSA	N=418	% of FSA Group
Stress	194	18.44
Progressive weight loss	105	9.98
Oral contraceptives	74	7.00
Intense physical routine	29	2.57
No specific cause	16	1.52
<b>FSA= Functional secondary amenorrhea</b>		

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