Republic of Iraq
Ministry of Higher Education and
Science Research
University of Baghdad

Aphthous Stomatitis and Menstruation

A project

Submitted to the council of the collage of dentistry at the university of Baghdad, Department of oral medicine, in fulfillment of the requirement for B.D.S. Degree

Done by

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2017–2018

بسم الله الرحمن الرحيم

" وفوق كل ذي علم عليم "

صدق الله العظيم

(يوسف 76)

Dedication

To my mother **My first person in my life**

To my father **Without him I'm nothing**

To my sister **Having her as such a special part of my family**

To my fiancé **For his endless love and encouragement**

Acknowledgements

I would like to thank Dr.Rana Murtadha Hassan, for her expert advice and continuous encouragement throughout this project.

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Introduction

Recurrent aphthous stomatitis (RAS) is defined as recurrent episodes of oral aphthous ulceration where the ulcers heal spontaneously with subsequent recurrence. (Liang and Neoh, 2012) RAS is one of the most common oral mucosal disorders affecting nonkeratinized mucosa, causing much pain and interference with mastication and speech. Based on the size and the number of ulcers, RAS is classified as minor, major, or herpetiform. (Natah et al, 2004) Although the exact etiology of RAS is not clear, genetics, trauma, vitamin deficiency, microbes, and psychological stress are cited as predisposing factors. Conflicting reports exist regarding the association of hormonal changes in women and RAS. (Preeti et al, 2011) .

Aim of study

This study was to evaluate the association between recurrent aphthous stomatitis and various phases of the menstrual cycle among college of dentistry female students .

Chapter One

Review of Literature

1.1 Definition of Aphthous Stomatitis

The term “aphthous” is derived from a Greek word “aphtha” which means ulceration. Recurrent aphthous stomatitis (RAS) is one of the most common painful oral mucosal conditions seen among patients. These present as recurrent, multiple, small, round, or ovoid ulcers, with circumscribed margins, having yellow or gray floors and are surrounded by erythematous haloes, present first in childhood or adolescence.(Jurge et al, 2006)

RAS is classified according to clinical characteristics: minor ulcers, major ulcers (Sutton disease, periadenitis mucosa necrotica recurrens), and herpetiform ulcers . There are cases in which a clear distinction between minor and major ulcers is blurred, particularly in patients who experience severe discomfort from continuous episodes of ulcers. These lesions have been referred to as “severe” minor ulcers.

1.2 Clinical Features ;

RAS is characterized by recurrent bouts of solitary or multiple shallow painful ulcers, at intervals of few months to few days in patients who are otherwise well.(Scully and Porter , 2008) RAS has been described under three different clinical variants as classified by Stanley in 1972.(Stanley ,1972)

Minor aphthous stomatitis

These ulceration also called Mikulicz's aphthae or mild aphthous ulcer . patient with minor aphthous ulceration experience the fewest recurrence and the

individual lesions exhibit the shortest duration of the three variants. The ulcer arises almost exclusively on non keratinized mucosa . the lesions may be preceded by prodromal symptoms of burning. Itching or stinging, with development of an erythematous macule. The macule develops an ulceration that is covered by erythematous halo (Neville et al., 2008). The buccal and labial mucosa are the most commonly involved sites , followed by ventral surface of the tongue, mucobuccal fold , floor of the mouth and soft palate. Lesions are less common on the heavily keratinized mucosa like palate or gingiva . females are affected more frequently than males (Greenberg et al., 2008).

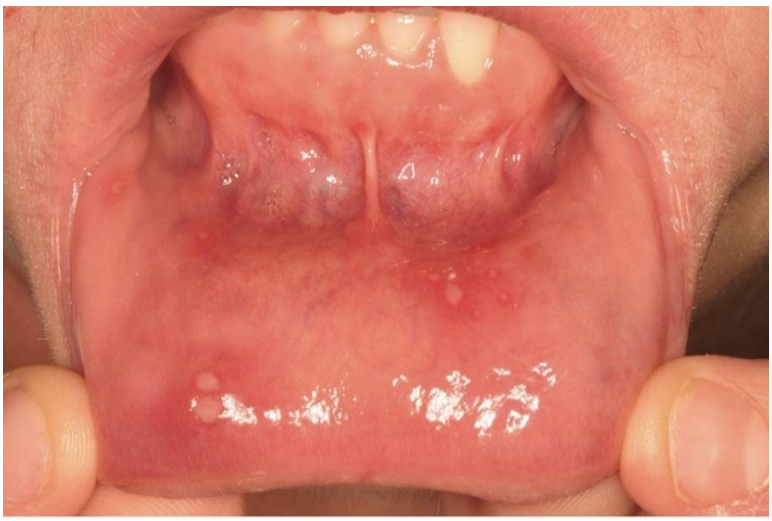

Figure (1-1): minor aphthous stomatitis (Glick, 2015)

Major aphthous stomatitis

Major aphtha (sometimes referred to as Sutton's disease) tend to involve mucosa overlying minor salivary gland (Rongers,1997). Patients with major ulcers develop deep lesions that are larger than 10 millimeter in diameter and lasts for weeks to months. In most sever cases , large portions of oral mucosa may be covered with large deep ulcer that can become confluent, which extremely painful and disabling, interfering with speech and eating and tend to appear on the lips, soft palate and throat (Greenberg et al., 2008).

The lesions may last for months and sometimes be misdiagnosed as squamous cell carcinoma, chronic granulomatous disease, or pemphigoid. The lesions heal slowly and leave scars that may result in decreased mobility of uvula and tongue (Cawson & Odell, 2008).

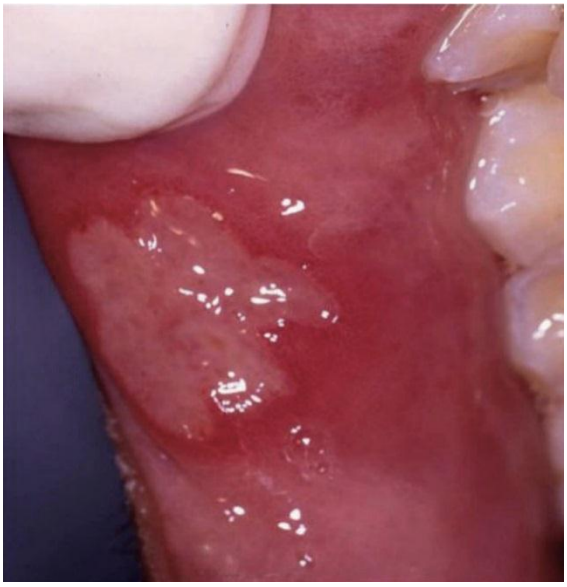

Figure (1-2): major aphthous stomatitis (Glick, 2015)

Herptiform ulceration

Constituting only 5-10 percent of all RAS cases, herptiform ulcers are rare. Multiple (5-100) 1-3 mm crops of small, rounded, painful ulcer resembling ulcers of herpes simplex are seen anywhere on the mucosa. They tend to fuse and produce much larger ulcer lasting 10 to 14 days (Rongers, 1997).

Most patients have only one to three ulcers, and some have recurrence only two to four times each year (simple aphthosis) . Other may have almost continuous disease activity with a new lesions developing as older lesions heal, or may have ulcers associated with systemic diseases (complex aphthosis) (Rongers, 1997).

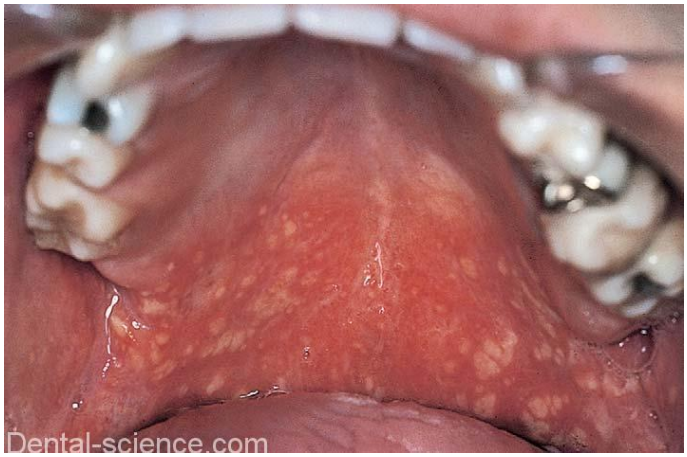

Figure (1-3): herptiform aphthous stomatitis (www.dental-science.com)

1.3 Etiology;

The major factors presently linked to RAS include genetic factors, hematologic or immunologic abnormalities, and local factors, such as trauma and smoking. there is increasing evidence linking local immune dysfunction to RAS, although the specific defect remains unknown. During the past 30 years, research has suggested a relationship between RAS and lymphocytotoxicity, antibody-dependent cell-mediated cytotoxicity, defects in lymphocyte cell sub- populations, and an alteration in the CD4 to CD8 lymphocyte ratio. (Jurge et al, 2006).

More recent research has centered on dysfunction of the mucosal cytokine network. The work of Buno and colleagues suggests that an abnormal mucosal cytokine cascade in RAS patients leads to an exaggerated cell-mediated immune response, resulting in localized ulceration of the mucosa. (Buno et al,1998).

The best documented factor is heredity. A study by Ship showed that patients with RAS-positive parents had a 90% chance of developing RAS, whereas patients with no RAS-positive parents had a 20% chance of developing the lesions.(Ship, 1972) Further evidence for the inherited nature of this disorder results from studies in which genetically specific human leukocyte antigens (HLAs) have been identified in patients with RAS, particularly in certain ethnic groups.(Eversole, 1997).

Hematologic deficiency, particularly of serum iron, folate, or vitamin B12, appears to be an etiologic factor in 5%–10% patients with aphthous-like ulcers although these sometimes occur on keratinized mucosa. (Challacombe et al, 1977).

It was initially reported in the 1960s that there is a negative correlation between RAS and a history of smoking, and many clinicians have reported that RAS is exacerbated when patients stop smoking. A study measuring a nicotine metabolite present in the blood of smokers confirmed that the incidence of RAS is significantly lower among smokers.(Chavan, 2012).

The nicotine metabolites are believed to decrease levels of proinflammatory cytokines and increase anti-inflammatory cytokines.

Other factors that have been reported associated with RAS include anxiety, periods of psychological stress, localized trauma to the mucosa, menstruation, upper respiratory infections, and food allergy.

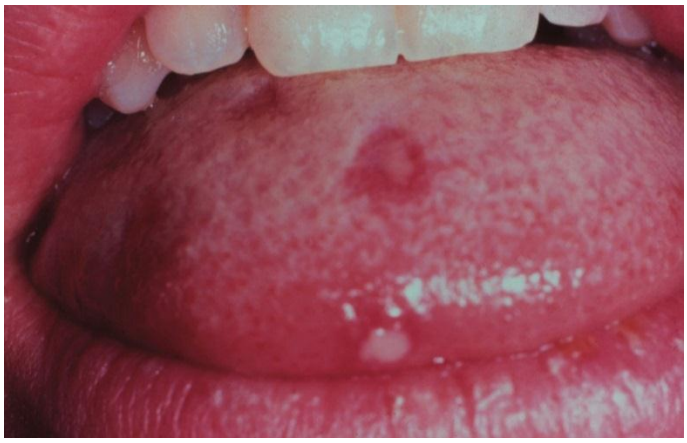

Figure (1-4): Aphthous-like ulcer associated with iron deficiency anemia; unusual location of ulcer on keratinized mucosa of the tongue dorsum; ulcers resolved when iron deficiency anemia was treated. (Glick, 2015)

1.4 Differential diagnosis

RAS is the most common cause of recurring oral ulcers and is essentially diagnosed by exclusion of other diseases. A detailed history and examination by a

knowledgeable clinician should distinguish RAS from primary acute lesions such as viral stomatitis or erythema EM, from chronic multiple lesions such as pemphigus or pemphigoid, as well as from other conditions associated with recurring ulcers, such as RIH, connective tissue disease, drug reactions, and other dermatologic disorders. e history should include obtaining symptoms of HIV, connective tissue disease such as lupus erythematosus, gastrointestinal complaints suggestive of inflammatory bowel disease, and associated skin, eye, genital, or rectal lesions. (Glick, 2015).

1.5 Management

1.5.1 DIAGNOSIS

The diagnosis of RAS is almost always based upon the history of the patient's complaint and clinical findings. Typically, patients report a history of recurrent bouts of ulceration of the mobile oral mucosal surfaces. Each bout of ulceration lasts afew weeks, healing being some- times accompanied by the development of new ulcers. Patients are typically well despite the oral ulceration.

Histopathological examination, including direct immunofluorescence of lesional tissue, is rarely of diagnostic benefit, since the histopathological features are non-specific. Hematological and serological investigations may reveal an accompanying hematinic deficiency, particularly feritin, but rarely are any other significant abnormalities likely to be detected. Detailed virological investigations of lesional tissue or serum are usually not warranted unless to exclude atypical herpetic infection.

1.5.2 THERAPY

Management is tailored to the severity of the disease. In mild cases with two or three small lesions, use of a protective emollient such as Orabase™ often

alleviates pain and facilitates healing. Pain relief of minor lesions can be effected with a topical anesthetic agent such as benzocaine or lidocaine.

In more severe cases, the use of a high-potency topical steroid preparation, such as fluocinonide, betamethasone, or clobetasol, placed directly on the lesion, shortens healing time and reduces the size of the ulcers. The effectiveness of the topical steroid is partially based on good instruction and patient compliance regarding proper use. The steroid gel should be applied directly to the lesion after meals and at bedtime two to three times a day or mixed with an adhesive such as Orabase™ prior to application. Larger lesions can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15–30 minutes to allow for longer contact of the medication. Other topical preparations that have been shown to decrease the healing time of RAS lesions include amlexanox paste and a topical tetracycline or doxycycline, which can be used either as a mouthrinse or applied as a paste directly to the lesions (Vijayabala et al, 2013) . Intralesional steroid injections can be used to treat large indolent major RAS lesions. It should be emphasized that no available topical therapy reduces the frequency of new lesions.When patients with major aphthae or severe cases of multiple minor aphthae do not improve sufficiently with topical therapy, use of systemic therapy should be considered.

Drugs that have been reported to reduce the number of ulcers in selected cases of major aphthae include colchicine, pentoxifylline, dapsone, short bursts of systemic steroids, and thalidomide(Wahba-Yahav, 1995), (Scully, 2006). Each of these drugs has the potential for side effects, and the clinician must weigh the potential benefits versus the risks.Thalidomide, a drug originally marketed as a nonaddicting hypnotic in the 1950s, was withdrawn from the market in the early 1960s due to its association with multiple, severe, deforming, and life-threatening birth defects. Further investigation demonstrated that thalidomide has significant anti-inflammatory and immunomodulatory properties and is useful in treating a number of diseases, including erythema nodosum leprosum, discoid lupus

erythematosus, graftvs-host disease, multiple myeloma, and Behçet disease.(Laiskonis, 2002)

The drug has also been shown to reduce both the incidence and severity of major RAS in both HIV-positive and HIVnegative patients. The use of thalidomide for RAS should be reserved for management of severe major RAS where other less toxic therapies, including high-potency topical steroids, colchicine, and pentoxifylline, have failed to control the disease. Thalidomide must be used with extreme caution in women during childbearing years owing to the potential for severe life-threatening and deforming birth defects. Other side effects of thalidomide include peripheral neuropathy, gastrointestinal complaints, drowsiness and deep vein thrombosis. Monitoring patients taking long-term thalidomide for the development of peripheral neuropathy with periodic nerve conduction studies is also recommended.

Currently, low level laser therapy (LLLT) has been employed for the treatment of RAS because of its biomodulation and analgesic effect by stimulation of the healing process and promoting immediate relief of pain without an overdose of medication or side effects. Hence, in the current case series, patients diagnosed with RAS were treated with LLLT using diode laser. (Anand et al,2013).

1.6 Definition of Menstrual Cycle

Menstruation refers to the shedding of the superficial layers of the endometrium in response to the interactions of hormones produced by the hypothalamus, pituitary, and ovaries, with subsequent repair in preparation for regrowth from the basalis layer. Menstruation is initiated by a fall in circulating

concentration of progesterone that follows luteal regression – failure of 'rescue' of the corpus luteum by an implanted early pregnancy. Luteal progesterone synthesis is dependent on LH from the pituitary gland. During luteolysis, progesterone secretion falls despite maintained serum concentrations of LH, since the corpus luteum becomes less sensitive to gonadotrophic support and becomes increasingly unable to maintain production of progesterone.

The 'invasion' of leucocytes and subsequent expression of inflammatory mediators has led to menstruation being likened to an inflammatory event (Kelly et al, 2001).

The menstrual cycle may be divided into two phases: (1) follicular or proliferative phase, and (2) the luteal or secretory phase.The length of a menstrual cycle is the number of days between the first day of menstrual bleeding of one cycle to the onset of menses of the next cycle. The median duration of a menstrual cycle is 28 days with most cycle lengths between 25 to 30 days (Treloar et al, 1967). Patients who experience menstrual cycles that occur at intervals less than 21 days are termed polymenorrheic, while patients who experience prolonged menstrual cycles greater than 35 days, are termed oligomenorrheic. The typical volume of blood lost during menstruation is approximately 30 mL. Any amount greater than 80 mL is considered abnormal (Hallberg et al, 1966). The menstrual cycle is typically most irregular around the extremes of reproductive life (menarche and menopause) due to anovulation and inadequate follicular development (Apter et al, 1987). The luteal phase of the cycle is relatively constant in all women, with a duration of 14 days. The variability of cycle length is usually derived from varying lengths of the follicular phase of the cycle, which can range from 10 to 16 days.

1.6.1 The follicular phase

The follicular phase begins from the first day of menses until ovulation. Lower temperatures on a basal body temperature chart, and more importantly, the development of ovarian follicles, characterize this phase. Folliculogenesis begins

during the last few days of the preceding menstrual cycle until the release of the mature follicle at ovulation.

Development of the dominant follicle has been described in three stages: (1) Recruitment, (2) Selection, and (3) Dominance. The recruitment stage takes place during days 1 through 4 of the menstrual cycle. Between cycle days 5 and 7, selection of a follicle takes place whereby only one follicle is selected from the cohort of recruited follicles to ovulate, and the remaining follicles will undergo atresia. By cycle day 8, one follicle exerts its dominance by promoting its own growth and suppressing the maturation of the other ovarian follicles thus becoming the dominant follicle.

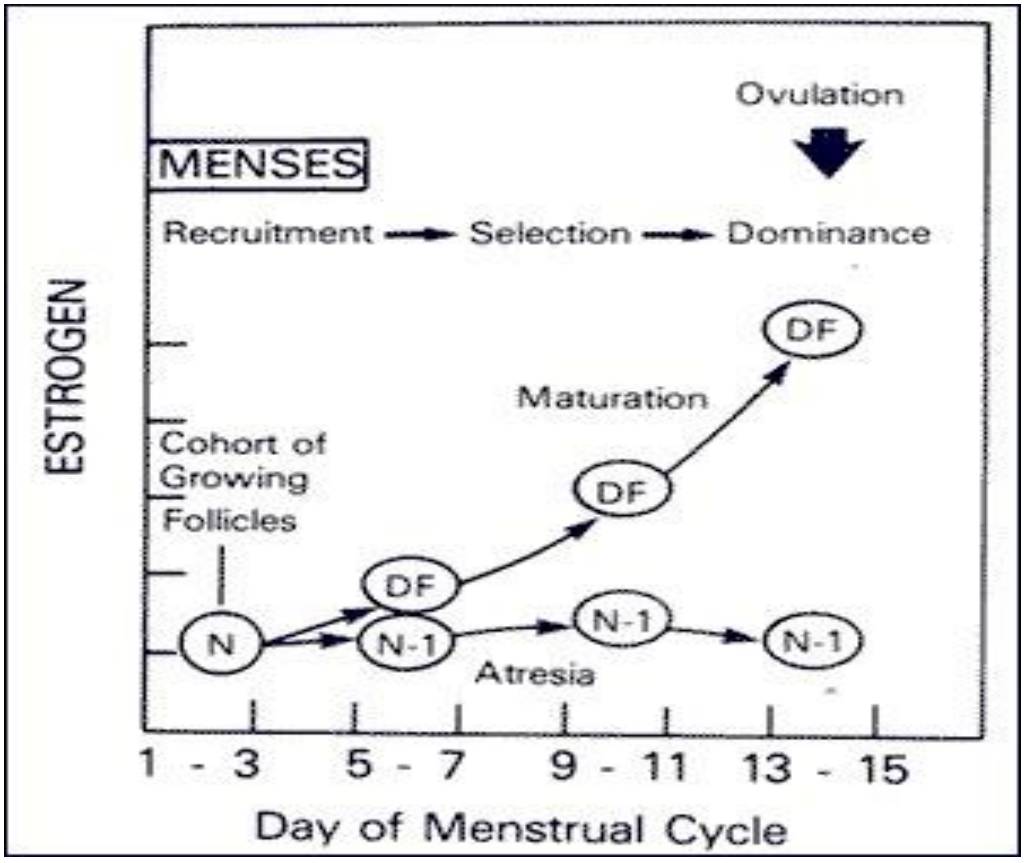

Figure (1-5) : Time course for recruitment, selection, and ovulation of the dominant ovarian follicle (DF) with onset of atresia among other follicles of the cohort (N-1). (From Hodgen GD. The dominant ovarian follicle. Fertil Steril 1982; 38:281-300).

The rise in estradiol secretion appears to increase the total number of estradiol receptors on the granulosa cells (Nimrod et al, 1976). In the presence of estradiol, FSH stimulates the formation of LH receptors on granulosa cells allowing for the secretion of small quantities of progesterone and 17-hydroxyprogesterone (17-OHP) which may exert a positive feedback on the estrogen- primed pituitary to augment luteinizing hormone (LH) release [Fink, 1988].

There are numerous substances found in follicular fluid, such as steroids, pituitary hormones, plasma proteins, proteoglycans and non-steroidal ovarian factors, which regulate the microenvironment of the ovary and regulate steroidogenesis in granulosa cells. The concentration of ovarian steroids is much higher in follicular fluid in comparison to plasma concentrations. There are 2 populations of antral follicles: (1) large follicles, which are greater than 8mm in diameter, and (2) small follicles, which are less than 8mm. In the large follicles, the concentrations of FSH, estrogen, and progesterone are high while prolactin concentration is low. In the small follicles, prolactin and androgen levels are higher compared to large antral follicles (Hillier et al, 1980).

1.6.2 Luteal Phase

This phase is usually 14 days long in most women. After ovulation, the remaining granulosa cells that are not released with the oocyte continue to enlarge, become vacuolated in appearance, and begin to accumulate a yellow pigment called lutein.

Estrogen levels rise and fall twice during the menstrual cycle. Estrogen levels rise during the mid-follicular phase and then drop precipitously after ovulation. This is followed by a secondary rise in estrogen levels during the mid-luteal phase with a decrease at the end of the menstrual cycle. The secondary rise in estradiol parallels the rise of serum progesterone and 17α-hydroxyprogesterone

levels. Ovarian vein studies confirm that the corpus luteum is the site of steroid production during the luteal phase (Niswender and Nett, 1994).

In studies looking into the mechanisms regulating the menstrual cycle, LH was established as the primary luteotropic agent in a cohort of hypophysectomized women (Wiele et al, 1970). After induction of ovulation, the amount of progesterone secreted and the length of the luteal phase is dependent on repeated LH injections. Administration of LH or HCG during the luteal phase can extend corpus luteum function for an additional two weeks.

The secretion of progesterone and estradiol during the luteal phase is episodic, and correlates closely with pulses of LH secretion (Filicori et al, 1984). The frequency and amplitude of LH secretion during the follicular phase regulates subsequent luteal phase function and is consistent with the regulatory role of LH during the luteal phase (McNeely and Soules, 1988).

1.7 Hormonal effect on Oral mucosa

Oral mucous membrane is an excellent indicator of the constitutional state of the patient.(*Monto et al, 1961*) The keratinized and non keratinized mucosae of the oral cavity are normally under trophic influence of various hormones (*Dayal et al, 2002*). Many studies have shown that oral mucosa is sensitive to the effect of sex hormones. They affect the oral cavity as their level changes during puberty, pregnancy, various phases of menstruation and menopause.(Krejei CB and Bissada, 2002)

In many women, arrival of monthly menses evokes several oral changes, like:

Gingival changes: Gingival exudate increases during menstrual cycle reaching a peak at ovulation and then declining during secretory phase (Lindhe and Altstrom, 1967, Lindhe et al 1969) (*Jonsson et al, 1988*) Increase in tooth mobility occurs due to increase in gingival exudates.(*Preckshot, 2004*) Cohen et al (1971) attributed hormonal imbalances and ovarian dysfunction to periodic gingival changes seen during menstruation.(*Prabhu, 1992*).

Machtei proposed that gingival inflammation was lower during menstruation than during ovulation and premenstruation.(*JADA, 2004*) This is attributed to serum estradiol which is a natural form of estrogen that peaks and drops during ovulation and premenstruation Other complaints seen during menstruation are as follows:

Burning sensation in the oral cavity

Prolonged hemorrhage following oral surgery

Swollen salivary glands (*Preckshot, 2004*)

Activation of herpes labialis and oral aphthous ulcers

Infections with Candida albicans: Infections with Candida albicans have been documented in some women during menstrual cycle.

Hormonal factors are capable of altering the mucosal barrier. In one study, a small group of females with aphthous stomatitis had fewer occurrences of aphthous ulcers during the luteal phase of the menstrual cycle or with use of the contraceptive pill.(Scully, 2013) , (Neville et al, 2008) This phase is associated with a fall in progestogen levels, mucosal proliferation and keratinization. This subgroup often experiences remission during pregnancy.

Chapter Two

Materials and Methods

This study was carried out during the period between February 2018 till to March 2018 by single investigator in college of dentistry of Baghdad .

The samples were collected from female students of the college of dentistry .

A total of (150) subject were incorporated in this study. The ages range from 18 to 24 years. Diagnosis of RAS was based on history and clinical examination, detailed history regarding name , age, , history of disease , menstrual phase .

Collected data were recorded on paper form in index 1 and then entered, processed and analyzed using Microsoft excel 2010.

Chapter Three

Results

3.1 : Age

A total of one hundred fifty subject have been asked and grouped into two age groups, the first group ≤ 20 contain 23 subject and about 4.3% of them were with aphthous ulcer during menstruation, the second group >20 contain 127 subject and about 3.9% of them were with aphthous ulcer during menstruation.

Table 3-1 ; prevelance of aphthous ulcer according to age

Age group	Aphthous ulcer				Total	
	presence		absence		No.	%
	N0.	%	No.	%		
≤ 20	1	4.3	22	95.7	23	15.3
>20	5	3.9	122	96.1	127	84.7
Total	6	4	144	96	150	100

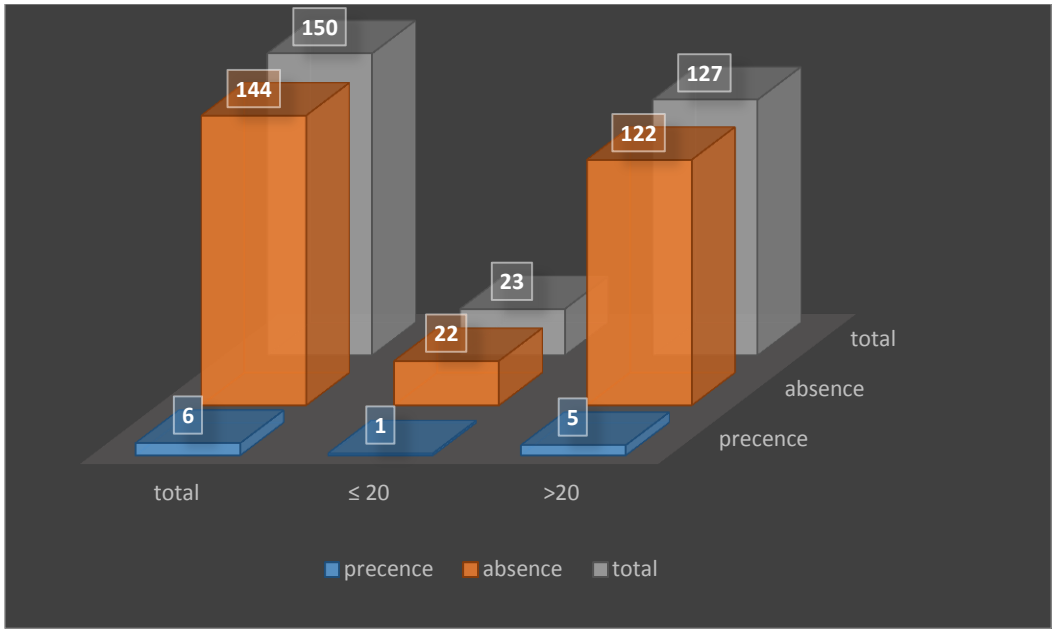

Figure 3-1 : prevelance of aphthous ulcer according to age groups

3.1 : Mentrual phases

From the total 150 subject in this study only 6 of them were affected with RAS during menstruation , 33.3% of them affected during ovulation phase and the other 66.6% affected during luteal phase.

Table 3-2 ; Distribution of aphthous ulcer during menstruation		
Menstrual phase	Aphthous ulcer presence	No. %
Ovulation phase	2	33.3%
Luteal phase	4	66.6%
Total	6	100%

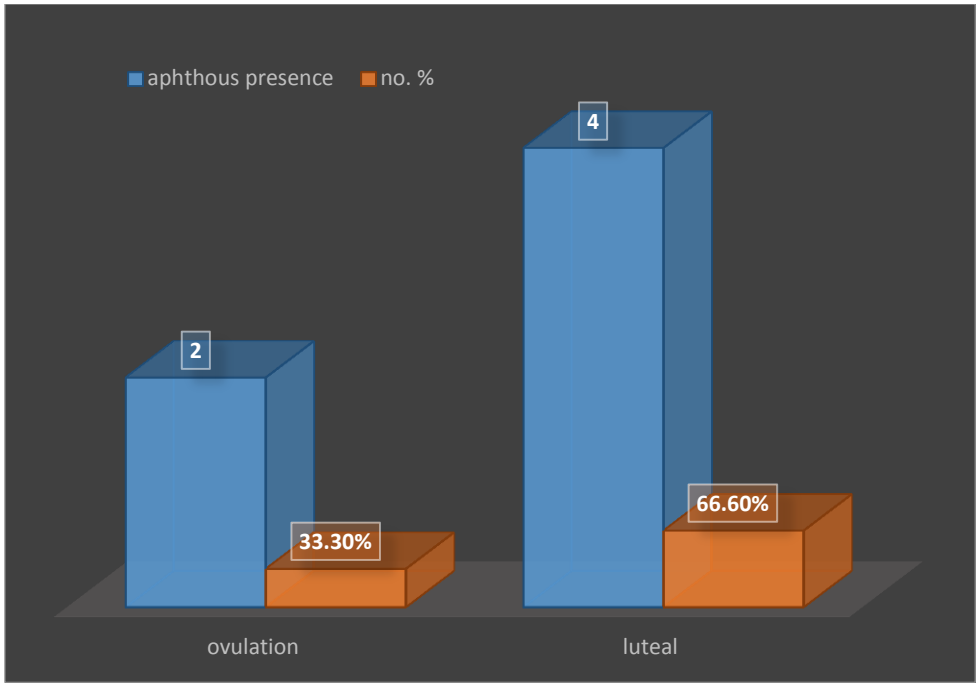

Figure 3-2 ; Distribution of aphthous ulcer during menstruation

Chapter Four

Discussion

RAS is the most common oral ulcerative condition found in clinical practice.(Liang and Neoh, 2012) RAS is reported to be more common among females, among persons in the third decade of life, and among students. (Miller and Ship, 1977),(Abdullah, 2013) The prevalence of RAS in a similar population of 150 female dental students was found to be 4% .The prevalence of RAS among the students should not be extrapolated for the prevalence of RAS in the general population because the predisposing factors, such as age, gender, stress, and nutritional status, may not be similar. In subjects with RAS, an enhanced immunologic response is assumed to occur due to some trigger factors, such as

microbial antigens, stress, hormonal changes, and mechanical injury. In this study most of the affected students were above 20 years, this results was In accordance with another study in which ((the most commonly affected age group was 20–29 years (56.9%) (Pajmane et al, 2017).

The menstrual cycle is governed by hormonal changes, and on an average the duration is about 28 days. In 1992, it has been reported that there is no association between aphthous stomatitis and premenstrual period, pregnancy, or menopause. (McCartan and Sullivan, 1992) In a minority of women, onset of cyclical ulceration was found during the luteal phase of the menstrual cycle, which happens after ovulation (14 days). (Ferguson et al, 1984). Some authors have suggested that this association is related to hormonal rates.(Ship et al, 2000) The incidence of RAS is related to the luteal phase of the menstrual cycle (Field and Allan, 2003) , (Balan et al, 2012) and also a decrease in its incidence during pregnancy, thus relating the episodes of RAS to progesterone levels. (Scully et al, 2003)

Hence, large-scale epidemiological studies are required to evaluate this association. The limitations of this study include the lack of hormonal assay, low number of study participants, and short duration.

Chapter Five

Conclusion

The onset of RAS was found to be more common in the Luteal phase of menstruation among the female dental students of our institution. Thus the role of hormones in the clinical manifestation of RAS deserves further investigation.

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