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To cite this article: S Utami et al 2018 J. Phys.: Conf. Ser. 1025 012080

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Effect of blood estrogen and progesterone on severity of minor RAS

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Abstract. Recurrent Aphthous Stomatitis (RAS) is a chronic inflammatory disease that attacks oral mucosa. Estrogen stimulates proliferation and buccal mucosa cornification and generally acts as an immunoinhibitor that can increase antibody synthesis through humoral response, while progesterone has immunosuppressive potential. This study aimed to examine the levels of blood estrogen and progesterone in females with Minor RAS of varying severity. Subjects were 42 women, 17–40 years old, with Minor RAS but without hormonal therapy or hysterectomy. They were investigated to see whether the severity of pain was related to condition of onset, recurrence and site or amount of lesions. Blood was taken on the 21st–22nd day of the menstrual cycle to test both hormone levels, using Microparticle Enzyme Immunoassay for the estrogen level, and Competitive Radioimmunoassay for the progesterone level. There was no significant relation between estrogen (p=0.530) or progesterone (p=0.717) level and the severity of Minor RAS. There is a tendency of normal estrogen level on both mild (62.5%) and severe (37.5%) Minor RAS. However, the progesterone level tends to be low both in mild (61.3%) and severe (38.7%) Minor RAS. It is assumed that the decrease of progesterone level also decreases the anti-inflammation function.

1. Introduction
Recurrent Aphthous Stomatitis (RAS) is a chronic inflammatory disease that attacks oral mucosa. It belongs to a group of chronic, inflammatory, ulcerative disease of the oral mucosa. The clinical picture of RAS is divided into three types: minor, major, and herpetiform. The subtypes differ in distribution, morphology, severity, and prognosis. The minor type of RAS or Mikulicz's aphthae is most common, covering 80 % or more of the cases. The disease occurs in the second decade of life, with 1 to 5 ulcus with a common diameter of 4 to 5 millimeters. The ulcus is circular or oval in shape, and affects the non-keratin mucosa, especially labial and buccal mucosa, and lateral and dorsal parts of the tongue, with grey or yellowish color in the bottom and red in the periphery. It takes 7 to 10 days to heal and does not leave scars. Interval of recurrence is from 1 to 4 months, though it can be very varied [1 – 6]. Up to now, the etiology of RAS is still idiopathic, but some causative agents can promote it, such as local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors. Some medications also have been associated with RAS, for example, immunosuppressive drugs [6].

One of the triggering factors that contribute to the pathogenesis of RAS is the hormonal imbalance. Several studies have been conducted on the relation between RAS and menstrual cycle, and the reported occurrence of RAS in relation to the cycle is uncommon, merely 0.6 % [7]. Ovarian
hormones related to menstrual cycles, such as estrogen and progesterone, are suspected to play roles in the occurrence of RAS. RAS is related to the decrease of progesterone level in a luteal phase of the menstrual cycle [8]. It is also reported that the low progesterone level is found in women with RAS (72.5 %), compared to the level in women without RAS (45%) (p=0.013) [6]. The highest activity of RAS occurs at seven days before and during menstruation [10]. Recurrent ulcers related to menstrual cycle (luteal phase) suffered by a few women do not occur during pregnancy or during consumption of oral contraception [1, 2, 8]. Nevertheless, no supporting data have been reported on the relationship between RAS and female sex hormones [10]. The aim of this study was to examine the relationship between blood estrogen and progesterone levels with the severity of minor RAS in females.

2. Materials and methods

2.1. Study population

The subjects were 42 women, 17–40 years old, suffering minor RAS, with no hormonal therapy nor hysterectomy. They were investigated for the severity of the pain in relation to the onset, recurrence, and site or amount of lesions.

2.2. Methods

The study was approved by the Academic Ethical and Research Commission of the Faculty of Dentistry, University of Indonesia. Blood from each sample was taken on the 21st – 22nd day of the menstrual cycle was used to test the estrogen level by using Microparticle Enzyme Immunoassay (MEIA) with kit AxSYM from Abbot Laboratories Diagnostics, and to test the progesterone levels by using Competitive Radioimmunoassay with kit Coat A Count from Diagnostic Products Corporation [11].

2.3. Statistical analysis

The data were analyzed statistically using Chi-Square testing, assuming significant differences at p < 0.05.

3. Results

The results showed that there is no significant relationship between the severity of minor RAS with estrogen level (p = 0.530, Table 1) nor with the progesterone level (p = 0.717, Table 2).

| Estrogen Level | Severity of Minor RAS | Total | p-value |
|----------------|-----------------------|-------|---------|
|                | Mild  | Severe |       |         |
| Normal         | 25    | 15     | 40    | 0.53    |
| Low            | 2     | 0      | 2    |         |
| Total          | 27    | 15     | 42    |         |

| Progesterone Level | Severity of Minor RAS | Total | p-value |
|--------------------|-----------------------|-------|---------|
|                    | Mild  | Severe |       |         |
| Normal             | 8     | 3      | 11    | 0.717   |
| Low                | 19    | 12     | 31    |         |
| Total              | 27    | 15     | 42    |         |

| Normal level of estrogen: 48-309 pg/ml |
| Low level of estrogen : < 48 pg/ml    |

| Normal level of progesterone: 10 – 30 ng/ml |
| Low level of progesterone : < 10 ng/ml     |
4. Discussion
The results showed that the estrogen level tends to be normal in both mild (92.6%, N = 27) and severe minor RAS (100%, n = 15). Estrogen stimulates proliferation and buccal mucosa cornification. Previous studies on the effect of estrogen therapy and buccal mucosa have not always given similar results. A positive correlation has been reported between the estrogen level and the maturation and keratinization of the oral mucosa. Many studies have reported that the oral mucosa is sensitive to estrogen influence and that decreased estrogen level can cause epithelial thinning and reduced keratinization of oral mucosa [3, 10, 12]. Yet other studies have found no influence of sex hormones on the oral mucosa [12]. Estrogen also increases antibody synthesis through humoral response and as a general immunoinhibitor [13, 14]. That RAS occurs before menstruation is assumed to be due to a decreased estrogen level before menstruation. Such hormonal condition causes irritation in the oral mucosal epithelium and may lead to the occurrence of RAS [3, 10, 12]. The decreased estrogen level before menstruation could also cause a decrease in antibody synthesis, especially inside the mouth, which in turn results in inflammation.

The level of progesterone tends to be low on mild (70.4%, n = 27) and severe minor RAS (80.0%, n = 15) [11]. The decrease of progesterone in this study matches that reported by Scully [8]. It is also reported that the progesterone level in a female with RAS is low, compared with no RAS [9]. Miyagi et al found that progesterone increases PMN chemotaxis, whereas estradiol will decrease it, and that in vitro there is a significant positive correlation between the concentration of female plasma progesterone and the ability of PMN chemotaxis [15]. The low progesterone level can stimulate prostaglandin that is an inflammation mediator, could also cause prostaglandin decreases, and the inflammation easily occurs. It is reported that the concentration of prostaglandin E2 (PGE2) in saliva decreases significantly during the active phase of ulcers, and increases significantly during the recovery of RAS. It is assumed that the occurrence of RAS is related to the decrease of the PGE2 level and epidermal growth factor (EGF) in saliva [16].

Progesterone is potentially immunosuppressive. Therefore it is assumed that the decreased level of progesterone will reduce the anti-inflammation function [14, 15]. Consequently, oral mucosa becomes vulnerable, and an inflammation that can lead to RAS easily occurs. Even though the estrogen level is still normal and the maturation of epithelium is expected to work well, the low progesterone level decreases the function of PMN chemotaxis [11, 15]. The hormonal imbalance affects the immune and the central nervous systems. The three systems interact with each other, mediated by cytokines, hormones, and neuropeptides that could stimulate an immune response such as minor RAS.

5. Conclusions
Low level of progesterone and normal level of estrogen represent a hormonal imbalance that can result in a decreased function of anti-inflammation and chemotaxis, triggering the onset of RAS. The mechanism also explains why RAS does not occur during pregnancy that increases the levels of estrogen and progesterone.

Acknowledgments
The authors wish to gratefully acknowledge the financial support from the Indonesian Ministry of Research, Technology and Higher Education through the University of Indonesia (EIA, Grant number 569/UN2.R3.1/HKP.05.00/2017-2018).

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