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Correlation Between Body Mass Index (BMI) to Estradiol and Progesterone Levels in Infertile Women

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ABSTRACT

Body Mass Index (BMI) was closely related to the body fat levels that can affect the menstrual cycle. Body fat contains aromatase enzyme which was needed to produce the estradiol and the excess of estradiol will inhibit the pro¬gesterone production. This may result in progesterone deficiency which further affects the mens¬trual cycle regularity and cause infertility. The aim of this study was to determine the correlation between BMI to estradiol and progesterone levels in infertility women. This study was designed as an observational-analytic with a prospective cohort study. The data of infertile women who fulfilled the study criteria were collected from January 2017 up to December 2018 at Rasi Clinic in Banda Aceh. Serum estradiol and pro¬ges¬terone levels were measured using ELISA technique. Statistical analysis was performed using SPSS version 24. Among 56 women with infertility, there were 30 patients with BMI greater than ≥ 25 (53.6%). BMI ≥ 25 in infertile women was found significantly correlated to estradiol levels (Chi-square test, p = 0.003). In 26 (86.7%) infertile women, BMI ≥ 25 had significantly increased estradiol level (Odds Ratio 1.8). BMI ≥ 25 was found significantly correlated to progesterone levels (Chi-Square test; p = 0.03). In 19 patients (63,3%) infertile women with BMI ≥ 25, the progesterone level was found significantly decreased (Odds Ratio 2.05). There was a significant correlation between BMI ≥ 25 with the increase serum estradiol and decrease progesterone levels in infertile women.

Keywords: Body Mass Index, Estradiol, Progesterone, Infertility.

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INTRODUCTION

The World Health Organization (WHO) defined infertility as the inability of a woman to become pregnant, to maintain a pregnancy and to uphold a pregnancy up to the point of a living birth. The WHO also estimates that around 50-80 million couples worldwide suffered from infertility. In developing countries, the infertility was is estimated as high as 30%, which was significantly higher compared to that in developed countries (estimated at only 5-8%). In Asia, the prevalence of infertility is 30.8% in Cambodia, 10% in Kazakhstan, 43.7% in Turkmenistan and 21.3% in Indonesia respectively.1,2

On the other hand, the increasing prevalence of obesity also has an impact on millions worldwide. Obesity sig¬nificantly affects a woman's capacity to become pregnant. Obesity is defined by Body Mass Index (BMI), in which the BMI reflects the percentage of fat in the body. Around 1 in 4 (25%) overweight women experience problems with conception. Along with other repro¬ductive health issues caused by obesity, infertility is a major problem which interferes and fails aiding reproductive techniques which help with conception.3

Women who have infertility linked with anovulation is 30% higher in those with a BMI ≥ 25 compared to women with normal body weights. Obesity causes a decrease in testosterone, FSH, inhibin B and SHBG. These caused an increase in metabolism of androgen along with an increase in estradiol levels. Inadequate level of luteinizing hormone (LH) in women with a BMI ≥ 25 also cause progesterone level to lower. An increase in estradiol com¬bined with the decrease of progesterone causes a ovulatory disturbance which subsequently increases the risk of infertility.4

The issue of infertility increases in line with the increasing problem of obesity which affects the general population. Being overweight and obese (BMI ≥ 25) is often considered a cause of infertility in women.5 This shows that BMI has an important role in resulting hormonal imbalances causing infertility. The aim of this study is to find out the association of BMI with estradiol and progesterone levels in women in Rasi Clinic, Banda Aceh, Indonesia for two years (January 2017- December 2018).

METHODS

This study was designed as an observational analytic with a prospective cohort study. Data collected from January 2017 until December 2018 has resulted 56 sam¬ples of reproductive age infertile women that can be included in this study. Those data consisted of BMI, serum estrogen and progesterone levels. The inclusion criteria included 1) married women, 2) duration of marriage > 1 year, 3) did not use any contraception within the last year, 4) normal sperm analysis results (normozoospermia). The exclusion criteria includes 1) contraception user, 2) participants unwilling to be part of the study, 3) low BMI (<18,5), 4) chronic illnesses related to infertility such as diabetes, cancer, genital infection, abnor¬mal leukorrhea, thyroid disease, tuberculosis etc.

The data was processed and analyzed descriptively (with Sta¬tistical Product and Service Solution, SPSS 24) to find out the frequency, percentage, average value and standard deviation from all the data collected including age, BMI, estradiol and progesterone levels. Statistical analysis is done to find out the correlation between BMI and estradiol and progesterone levels. Chi-square test was used to see the correlation between BMI to estrogen and progesterone.

RESULTS

Body Mass Index (BMI) is the measurement of body weight and body height (kg/m2). Asian Pa-cific Classification has classified the BMI into four categories those are underweight (BMI <18), normal (BMI 18-24.9), overweight (BMI ≥ 25) and obesity (BMI ≥ 30). In this study, the samples are grouped into two groups those are BMI ≥ 25 (overweight and obese category) and a BMI < 25 normal category). In this study we found 56 married women with infertility.

TABLE 1 UNIVARIATE ANALYSIS OF THE ANTHROPOMETRIC AND HORMONAL PARAMETERS

Anthropometric and hormonal parameters	n	%
Age < 30 years	31	55,4
Age ≥ 30 years	25	44,6
BMI ≥ 25	30	53,6
BMI < 25	26	46,4
Normal estradiol level	18	32,1
High estradiol level	38	67,9
Normal progesterone level	29	51,8
Low progesterone level	27	48,2

The mean age of women in this study is 28.4 years, ranging from 21 up to 40 years old (Table 1). This study demonstrated that 31 (55.4%) subjects are under 30 while 25 (44.6%) subjects are over 30 years old. The mean BMI is 26.9, ranging from 18.5 up to 38.4. These consisted of 53.6% (30 subjects) with high BMI (>25) 46.4% (26 subjects) with normal BMI.

TABLE 2. CORRELATION BETWEEN BMI AND ESTRADIOL LEVELS

BMI Category	Increased Estradiol (pg/mL)		Normal Estradiol (pg/mL)	
	n	%	n	%
≥ 25	26	86,7	4	9,6
< 25	12	46,2	14	53,8
Total of cases	38	67,9	28	32,1

p = 0,003

Odds Ratio value of increased estradiol level 1,87

The average value of estradiol is 121.7 pg/mL (SD 109.57) ranging from 26 pg/mL to 591 pg/mL Table 2. shows the classification of estradiol level, with 18 (32.1%) women were within normal category while 38 (67.9%) women within high category. Subjects with estradiol level ≥ 50 pg/mL are mostly found in the those with BMI ≥ 25 (86.7%), whereas the subjects with BMI < 25 consist of 12 (17.6%) women with normal estradiol level. There is a significant correlation between a increase in BMI (≥ 25) and the increase in estradiol level (Chi-square test, p = 0.003; Odds ratio = 1.87). It means that infertile women with BMI ≥ 25 are more likely to have an increase in estradiol levels compared to infertile women with BMI < 25.

TABLE 3. CORRELATION BETWEEN BMI AND PROGESTERONE LEVELS

BMI Category	Low Progesterone (ng/mL)		Normal Progesterone (ng/mL)	
	N	%	n	%
≥ 25	19	63,3	11	36,7
< 25	8	30,8	18	69,2
Total of cases	28	48,2	29	51,8

p = 0,030

Odds ratio value for low progesterone levels 2.05

The mean level of progesterone found in infertile patients in this study was 19.48 pg/n (SD 9.73) ranging from 10.7 ng/mL up to 45.0 ng/mL. These consisted of 29 subjects (51.8%) with normal and 27 subjects (48.2%) with low progesterone levels respectively (Table 3.). Low progesterone level was more often 19 subjects (63.3%) found in subjects with BMI ≥ 25. Whereas normal progesterone level was found in 36.7% (11 subjects) with a BMI < 25. Statistical analysis revealed a significant correlation between the increase in BMI and progesterone (Chi-square test, p = 0.03). Furthermore, infertile women with BMI ≥ 25 was more likely to have low progesterone level compared to infertile women with BMI < 25 (Odds ratio was 2.05).

DISCUSSION

We found a significant correlation between BMI ≥ 25 and increased estradiol level in comparison with those with BMI < 25. In this study, there were 26 subjects (86.7%) with a BMI ≥ 25 with estrogen levels > 50 pg/mL, whereas 4 subjets (13.3%) have normal estrogen levels. Based on the data collected, the risk of infertility due to ovulation disturbances may occur in women with a BMI ≥ 25. A BMI ≥ 25 may affect a woman's ability to be pregnant and also results in pregnancies with complications.5,6

Women with BMI ≥ 25 are correlated to a delay in pregnancy. Another study has found a correlation between a woman's body size and the time she needed to become pregnant. Out of1651 women participated in that study, those with BMI of 25-29 have 17% higher delay to become pregnant, those with BMI of 30-34 have 25% higher delay and those who are morbidly obese (BMI ≥ 35) have 39% higher delay in pregnancy in comparison to women with normal BMI between (20-24).7,8

Women with BMI ≥ 25 required a longer time to become pregnant compared with those with a stable and normal body weight. A study with 1950 participating women in a pregnancy program showed that changes in their body weight occured after the age of 18 affected their capability to become pregnant. For every 5 kilograms weight gained after the age of 18, 5% more time was required to become pregnant. Women needed a suitable amount of body fat in order to become pregnant. 4,9

The basis of infertility caused by high BMI stems from the ovary which is necessary to release a fertilizable mature oocyte (ovulation). Without ovulation, conception can not occur. Even when fertilization has occurred, the woman's body has to accommodate for the implantation and fetal growth in the uterus. The right amount of estradiol and progesterone is vital for this process to be carried out successfully.3,10

In addition, fat cells released an excessive amount of estrogen in overweight and obesity women. This interferes with ovulation and causes irregular menstrual cycles. Overweight woman with ovulation problems has a possibility that these two factors are linked. An excessive amount of fat tissue released estrogen which resulted in the increase of an¬drogen level. This combination caused a toxic uterine environment, which caused failure of im¬plantation or abortion after ovulation. 11

It has already been understood that body weight in women causes a change in the hormonal levels, more specifically an increase of estradiol which disturbs the ovarian potency to ovulate regularly. A rise in BMI also leads to lower progesterone levels and higher cortisol levels, both of which affects ovulation and implantation. This causes a disturbance in the reproductive system. The normal brain signals to the ovaries are also interfered, which causes a dysfunction in ovulation.12,13

Normal progesterone level had been shown by 11 (37.9%) of our study subjects whereas 19 (70.4%) of subjects with BMI ≥ 25 have low progesterone level. This study showed a significant link between women with BMI ≥ 25 and low progesterone level. An increase in BMI is related to the cessation in central production of LH, which leads to a large deficit of progesterone in the luteal phase. It has been observed that in women with a BMI ≥ 25, the progesterone secretion is significantly lower than those with normal BMI. Several studies have shown that a lower LH secretion leads to inadequate luteal stimulation and lowered luteal progesterone in women with a BMI ≥ 25. 14,15

Sherman and Korenmann16 have reported that overweight women have a longer follicular phase, have lower levels of FSH and LH, and have luteal phase with lower progesterone level. A similar study conducted by SWAN evaluating 836 menstrual cycles of reproductive women has found a link between women with BMI ≥ 25 and decreased secretion of luteal progesterone, LH and FSH.17 Our study using fewer samples than SWAN daily hormone study also has shown a significant decrease in progesterone levels ($p = 0.03$)

Obesity has a direct link with abnormal menstrual cycle. A loss of body weight may resume menstrual cycles back to normal in obese and women with anovulatory problems.18,19 Along with the rise of body weight, level of LH also decreased in women with a BMI > 25. Women with BMI ≥ 25 produced less progesterone. The hypophyseal response to endogenous GnRH is weakened due to obesity. As a whole, this data showed that a decreased level of progesterone was caused by a increase in BMI and excessive intake.20

Leptin is a product of adipose tissue which is shown to have stimulatory effects on the secretion of LH and FSH.21 An increase of leptin resistance is linked with obesity, in which obesity causes a decrease in LH stimulation which leads to a lower progesterone output. Other adipokines, such as TNF-alfa and IL-1 beta is secreted excessively when fat mass is increased, and both of which has been proven to have a negative effect on the hypophyseal production of LH when injected intra cerebroventrical in laboratory mice.22 The neutralization of anti-TNF antibodies has been found to suppress the hypothalamic hypophysis axis. Inflammatory factor adipocytokines also inhibits the corpus luteum response to produce progesterone. The production of in vitro sexual steroids has been proven to be lowered in granulosa cells of cows and mice which have been given TNF-alfa 24,25. Leptin as a whole is able to inhibit the granulosa cells of human in vitro which has been proven by the decrease of progesterone secreted by granulosa lutein cells in response to human chorionic gonadotropin and an inhibition mediated by IGF-1 of the synthesis of estradiol stimu¬lated by FSH 26,27 In addition, leptin also interfered with the normal maturity of oocytes and also functions as a sign of poor implantation.28,29

A decrease in body weight helps with the fertility of women with BMI ≥ 25. Obese women do not need to reach the ideal body weight (BMI <25). A decrease of 5-10% body weight in women with high BMI can cause a 30% reduction in visceral adipose, increased insulin sensitivity and return of normal ovulation. These factors can make a significant change in their ability to become pregnant and also increase ovulation and improve ovum quality. It will become easier for those women to become pregnant and have better quality pregnancy as a whole with few complications such as high blood pressure and diabetes during pregnancy.30

Decreasing calorie intake and increasing exercise can increase the chance of becoming pregnant. A meta analysis of 40 studies has shown that a lower calorie diet alone with exercise can increase pregnancy up to 59% in women with BMI ≥ 25 and can cause body weight to lower and ovulation to increase.31 In addition, a study32 has evaluated the effects of significant weight loss (10% of total body mass) in 52 overweight patients with infertility. Those who have reduced their body weights by 10% with diet modifi¬ca¬tions and exercises have a higher conception rate and better quality births compared with the con¬trol group. An ideal body weight is beneficial for the process of ovulation and conception. During a pregnancy program, it is also ideal to decrease body weight as well as to consume a healthy low calorie diet and to exercise regularly. Even when a woman is unable to become pregnant after weight loss, she still has a higher chance of a successful pregnancy aided by reproductive tech¬niques.31,32

The purpose of the management of women in obesity is to restore the hormonal imbalances that exist. Giving advice to patients to lower their body weight to normal can restore hormonal imbalance which causes menstrual cycles and ovulation to return to its normal state. When BMI is ideal, the estradiol production decreases, which means that FSH production by the anterior hypophysis does not occur. With normal FSH level, LH level is also affected which means that progesterone will increase and normal ovulation may occur. 33.

CONCLUSION

From the result of this study, it is concluded that there is a significant link between a BMI ≥ 25 with the increase of estradiol

level and decrease progesterone level in infertile women. A rise in BMI has a negative effect on woman's reproductive system. Obesity causes an imbalance in sexual hormones, specifically an increase in estradiol and a decrease in proges¬terone. This induces problems in menstrual cycles, ovulation and infertility. Lowering the body weight is the first option to restore women's reproductive health problems caused by obesity.

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