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EFFECT OF INJECTABLE COMBINATION ESTROGEN-PROGESTERONE AND PROGESTERONE-ONLY CONTRACEPTIVES ON GLUCOSE AND MALONDIALDEHID SERUM

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ABSTRACT

Injectable hormonal contraception was the most favorable contraception method in Indonesia in 2013, and its number reaches 4,128,115 acceptors (48.56%). The estrogen and progesterone contents in injectable contraception could cause stress, increased appetite, decreased leptin level, and insulin resistance, eventually leading to increased blood glucose and serum malondialdehyde levels. This study aims to observe the main effect of the use of combined estrogen-progesterone and only progesterone injectable hormonal contraceptions on glucose level in blood and malondialdehyde level in serum. This type of research is an experimental laboratory study. It uses *Randomized pre-post test group* research design for glucose level and *randomized post-test with control* for malondialdehyde level. The data are analyzed using *Anova*, followed with *post hock tukey* test. The significance value is $p<0.01$. Twenty-eight samples were divided into seven groups, and each group consists of 4 samples, namely one control group and six treatment groups consisting of P1 combined dose 0.54 mg, P2 combined dose 1.08 mg, P3 combined dose 1.62 mg, P4 DMPA dose 2.7 mg, P5 DMPA dose 5.4 mg, P6 DMPA dose 8.1 mg. Only DMPA contraception at 0.54 mg dose influences the blood glucose level increase by $p = 0.00$. Only DMPA contraception at 8.1 mg dose does not affect serum malondialdehyde level by $p = 0.1$. The conclusion is DMPA contraception has more significant, potential of causing blood glucose level increase than the combined contraception. Combined and DMPA contraceptions share the risk of increasing serum malondialdehyde levels

Keywords

Injectable hormonal contraception, blood glucose level, serum malondialdehyde level

INTRODUCTION

The use of hormonal contraception (combined and DMPA) has given a major change to humanity, birth control, and social phenomena (Norris, 2013). Hormonal contraception does not only has a therapeutic effect, but instead it also has side effects. Injectable hormonal contraception is a highly effective and long-lasting birth control method. In 2006, 12 millions/100 million of the world population used hormonal contraception (Wilopo, 2006). The use of injectable hormonal contraception in Indonesia in 2013 was placed the highest with 4,128,115 acceptors or 48.56% (Kemenkes RI, 2014). The high

concentration of sex steroids in women contributes to insulin resistance.

The high dose of estradiol can worsen the carbohydrate mechanism and reduce insulin sensitivity (Gonzales et al.,2002; Patino, Diaz-Toledo, and del Bario, 2008). Enilestradiol reduces insulin clearance (decreased insulin sensitivity), and gestagen influences the use of peripheral glucose (Baziat, 2002). Meanwhile, the effect of DMPA causes decreased glucose tolerance, which is compensated by a higher insulin level following the glucose excess (Skouby Petersen and Jespersen, 1996). Additional study also shows the bad effect of DMPA on glucose and insulin levels (Friedman et.al,1988; Dyer A.et.al,1990; Jacobs et.al,1989; Hill et.al,1999; Wagenknech et.al,1999; Haffner et.al,1994; Bild et.al, 1996). Another possible mechanism for progesterone related insulin glucose increase is associated with weight gain related to DMPA or glucocorticoid-like progestogen activity (*Crook, 1997*). Injectable hormonal contraception stimulates the center of appetite control at the hypothalamus, which can cause acceptors to eat more than they usually do.

This problem could make the glucose level in blood increase in terms of its quantity (Hartanto, 2010). Injectable hormonal contraception causes mild insulin resistance, which then worsens glucose tolerance. Progesterone hormone contains steroid hormone with low anti insulin ,i.e., it decreases the amount and affinity of insulin receptors to glucose and increases the number of free cortisol, and eventually, it increases the blood sugar level. When insulin redusing, there will be a disruption in the transport of blood sugar to the cells to be converted into energy and glycogen (glycogen is stored energy). The long-term use of DMPA will have a positive correlation with decreasing estrogen levels, which will eventually result in the reduced rate of metabolism. It causes the glucose to accumulate the blood (Irianto, 2014). Chronic hyperglycemia causes adverse effects on the body health because high glucose levels promote the formation of free radicals or reactive oxygen species through oxidation-reduction mechanism by driving more electron donor (NADH and FADH2) into electron transport chain in mitochondria (Brownlee, 2001). The largest source of free radicals occurs during the electron transport process by producing superoxide anion free radicals, and its production may increase under hyperglicemia condition (Robertson et al., 2003). Superoxide anion is transformed into hydrogen peroxide and then enters cell membranes and might cause damage to pancreatic tissue. Additionally, in an autoxidation process, glucose is also produced by hydroxyl free radicals (Robertson et al., 2004). Free radicals cause lipid peroxidation reaction by forming malondialdehyde and high malondialdehyde levels of malondialdehyde can be used as an indicator of oxidative damage (Takashi et al., 2004).

METHOD

The materials of this study were combined injectable contraception containing combined 25 mg of Depot medroxyprogesterone acetate (DMPA) +5 mg of estradiol cypionate and DMPA contraception containing DMPA 150 mg. The test animals are female Wistar rats, and their maintenance and treatment were given at LPPT IV Gadjah Mada University Yogjakarta, Indonesia. The combined contraception treatment is gave for 90 days. It is injected three times with the first one being offered on the first day. The second injection was provided on the 30th day. And the last one is provided on the 60th day. DMPA injectable contraception treatment was given only on the first day for 90 days. The blood was sampled for glucose

examination on the first day (pre) and the 90th day (post). The blood is also tested for Malondialdehyde level examination once on the 90th day compared to the control.

28 Wistar rats were used as the sample, and they were divided into seven groups and each group consists of 4 rats, namely one control group and six treatment groups consisting of P1 combined dose 0.54 mg, P2 combined dose 1.08 mg, P3 combined dose 1.62 mg, P4 DMPA dose 2.7 mg, P5 DMPA dose 5.4 mg, and P6 DMPA dose 8.1 mg.

The blood was sampled through retro-orbital plexus at 0.5 ml. The glucose is examined at the LPPT I of Gadjah Mada University, Yogjakarta, Indonesia, using the GOD-PAP method. The Malondialdehyde level was measured from the rat blood sample at 0.5 ml, and then it is centrifuged at 3000 rpm for 20 minutes at 4°C. The serum separated from the red blood cells is then used for examining Malondialdehyde level. The serum Malondialdehyde levels was tested by spectrophotometry method based on the change in purple color due to the formation of the thiobarbituric acid Malondialdehyde complex. This spectrophotometry examination was performed at 532 nm wavelength with a maximum absorbance. The Malondialdehyde level is examined at the Nutrition and Food Department of Gadjah Mada University, Yogjakarta.

RESULT

The sample used in this research is initially 35 female rats of Wistar strain, yet 2 of them die of unknown causes, i.e., one rat in the P1 group and one rat in the P6 group. In sample calculation, according to Feeder, the number of samples needed is 28 rats, thus from 33 surviving rats, it is decided to take in 4 rats for each group randomly as the research sample. The influence of injectable hormonal contraception on glucose level and Malondialdehyde level in female rats of Wistar strain was shown in the following table:

Table 1. Impact of injectable contraception on glucose level in female rats of Wistar

strain Group	Mean	SD	Minimum	Maximum	P
	Pre-post	Pre-post	Pre-post	Pre-post	
P1	38.9-69.2	1.7-1.9	21.1-51.7	52.1-77.6	0.015
P2	49.8-73.6	1.7-6.4	34.4-65.0	74.2-80.1	0.065
P3	83.3-90.4	1.5-1.2	69.7-77.1	102.7-103.4	0.052
P4	65.1-130.7	1.9-2.1	41.6-104.4	84.8-153.5	0.000
P5	77.8-111.5	1.8-4.8	61.5-107.8	99.4-118.0	0.056
P6	94.1-114.6	1.3-1.5	76.6-94.3	109.1-129.4	0.210

Table 2. Impact of injectable contraception on serum Malondialdehyde level in female rats of Wistar strain

Group	Mean	SD	Minimum	Maximum	p
Control	1.17	0.13	1.06	1.36	
P1	6.08	0.31	5.69	6.42	0.000
P2	4.22	0.42	3.82	4.77	0.000
P3	3.21	0.36	2.86	3.71	0.000
P4	5.26	0.19	5.03	5.51	0.000
P5	2.54	0.24	2.20	2.75	0.000
P6	1.78	0.17	1.58	1.98	0.100

DISCUSSION

The estrogenic components of contraception play an important role in insulin sensitivity change (Sitruk-Ware and Nate, 2013). The estrogen contained in contraception can change insulin secretion dynamics (Nadal et al., 1998). High dose estradiol causes a carbohydrate mechanism to worsen and decreases insulin sensitivity (Gonzales et al., 2002).

High progesterone makes women unstable emotionally, stimulates their appetite control center at the hipothalamus, and leads to higher and more frequent likeliness to eat, hence increasing the glucose level (Hartanto, 2010; Irianto, 2014). The high progesterone level also

results in estrogen deficiency. Thus, the leptin produced by adipose tissue decreases and the signal which regulates the energy homeostasis both centrally and peripherally is disrupted. When leptin decreases, the appetite signal increases (Limanan, 2013). Leptin influences glucose homeostasis and directly governs some metabolic pathways (Myer, 2004).

WHO acknowledges that progestin specific contraception influences carbohydrate metabolism (WHO, 2000). Hormonal contraception causes mild insulin resistance, and thus, it worsens glucose tolerance. Enilestradiol reduces insulin clearance (decreased insulin sensitivity), and gestagen influences the use of peripheral glucose (Baziat, 2002). Progesterone hormone contains low anti-insulin steroid hormone, i.e., reduce the number and affinity of insulin receptors to glucose and increasing the number of free cortisol. Decreased insulin makes fails to work optimally to transport the blood sugar into cells and it was changed into energy and glycogen. Increased fatty acid and glucose intolerance are associated with insulin resistance (Bergman, 2000; Pouliot, 1990).

Estrogen and progesterone are associated with oxidative stress in blood circulation and cell level (Thibodeau, 2002). Estrogen and progesterone in injectable contraception are xenobiotic, which could trigger accelerated use of oxygen phenomenon (*respiratory burst)* and formation of a considerable number of *reactive oxygen species* (Dawn et al., 2000; Robert, 2006) through increased glucose level. High glucose level is more likely to drive the formation of free radicals or reactive oxygen species through oxidation-reduction mechanism by driving more electron donors (NADH and FADH2) into electron transport chain in mitochondria (Brownlee, 2001). The production of free radicals might increase under hyperglycemic conditions (Robertson et.al, 2003).

CONCLUSION

DMPA contraception has more significant potential of causing blood glucose level to increase than the combined contraception. Combined and DMPA contraceptions share the risk of increasing serum malondialdehyde level

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