

## Research Article

## Depo Medroxyprogesterone Acetate Injection was Associated with a Greater Risk of Diabetes Mellitus: a Study at East Jakarta Public Health Centres

### *Hubungan Penggunaan Injeksi Depo Medroksiprogesteron Asetat dengan Kejadian Diabetes Mellitus di Puskesmas Jakarta Timur*

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#### Abstract

**Objective:** To study the relationship between the history of contraceptive injection depo medroxyprogesterone acetate (DMPA) exposure with incidence of diabetes mellitus and the associated risk factors.

**Methods:** This is a case-control study conducted in 6 Public Health Centers in East Jakarta involving 30 cases of diabetes mellitus and 61 controls. Body mass index (BMI), parity, type of contraception, duration of contraceptive use, history of gestational diabetes and breastfeeding were assessed in each group. Data were analyzed with Chi Square or Fisher's test, and logistic regression.

**Results:** The mean age of the subjects was 45.00 (35-67) years, with a median number of parity of 3.00 (0-7), and the median of BMI was 27.31 (15.24 to 40.27). The number of DMPA injections users was 31.9% and the mean duration of contraception usage was 5.36 ± 4.42 years. There was a correlation between the history of DMPA injections with incidence of diabetes mellitus, with an odds ratio of 3.36 95% CI [1.098 to 10.469]. The risk persisted after adjustment of age and BMI.

**Conclusion:** DMPA exposure was associated with a greater risk of diabetes mellitus. Risk was associated with length of use and persisted after adjustment with age and BMI.

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**Keywords:** depo medroxyprogesterone acetate (DMPA), diabetes mellitus

#### Abstrak

**Tujuan:** Mengetahui hubungan antara riwayat pajanan kontrasepsi suntikan depo medroksiprogesteron asetat (DMPA) dengan diabetes melitus dan faktor-faktor risiko yang mempengaruhinya.

**Metode:** Penelitian kasus kontrol dilakukan di 6 Puskesmas Jakarta Timur dengan mengambil 30 kasus diabetes mellitus dan 61 kontrol. Indeks massa tubuh (IMT), paritas, jenis kontrasepsi, lama penggunaan kontrasepsi, riwayat diabetes gestasional dan menyusui dinilai pada masing-masing kelompok. Data dianalisis dengan chi square atau fisher's test dan regresi logistik.

**Hasil:** Karakteristik sampel dengan usia 45,00 (35-67) tahun, riwayat paritas dengan nilai median 3,00 (0-7), dengan IMT nilai median 27,31 (15,24-40,27). Jumlah pengguna kontrasepsi suntikan DMPA sebesar 31,9% dan rerata lama penggunaan kontrasepsi 5,36±4,42 tahun. Terdapat hubungan penggunaan kontrasepsi suntikan DMPA dengan kejadian diabetes mellitus, dengan odd ratio 3,36 95% CI [1,098-10,469]. Setelah dilakukan penyesuaian pada usia dan IMT, risiko turun namun tetap bertahan.

**Kesimpulan:** DMPA dikaitkan dengan risiko lebih besar menderita diabetes melitus. Risiko berkaitan dengan lamanya penggunaan dan menetap meskipun dilakukan penyesuaian pada usia dan IMT.

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**Kata kunci:** depo medroksiprogesteron asetat (DMPA), diabetes melitus

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#### INTRODUCTION

In Indonesia, contraceptive injections ranked first as the most common contraceptive methods chosen by the community. Data from BKKBN, in 2007, showed that the number of active injection user was 3,000,483 (55.55%). The reasons that people prefer injection are because of its low compliance, inexpensive price and low failure rate.<sup>1</sup> But, a recent epidemiological studies suggested a possible increased risk of diabetes incidence in DMPA users.

DMPA is associated with weight gain, which is one of the risk factor for type 2 diabetes mellitus. This is indicated by the rising insulin level in response to contraceptive injections, causing patients with risk factors to fall into a state of glucose intolerance.<sup>2-4</sup>

One of the side effects of giving a single progestin contraceptive injection is an increase of the concentration of progesterone excessively in the

blood. Excess of progesterone in the blood affects the tolerance to glucose and sensitivity to insulin sensitivity.<sup>5-6</sup>

A similar phenomenon is found in the mechanism of Gestational Diabetes Mellitus (GDM). Intolerance to glucose in patients with GDM starts to be found at 26<sup>th</sup> week of pregnancy and increased significantly at 32<sup>nd</sup> week of pregnancy. The 32<sup>nd</sup> week of pregnancy is the culmination of blood progesterone concentration maintained until the birth process.<sup>7-9</sup>

The state of insulin resistance on the use of DMPA is similar to the state of insulin resistance in pregnancy. In normal pregnancy, there is a progressive insulin resistance that occurs in the third trimester, with a resistance level similar to that of individuals with type 2 diabetes.<sup>4</sup> Insulin sensitivity is reduced by 80%. Secretion of placental hormones such as progesterone, cortisol, placental lactogen, prolactin, growth hormone gave a major contribution in a state of insulin resistance in pregnancy. This insulin resistance aim to ensure the fetus obtaining an adequate supply of glucose and to alter maternal energy metabolism from carbohydrate to fat. Women with gestational diabetes have more severe degree of insulin resistance when compared with women with normal pregnancies. Women with gestational diabetes are susceptible to increase the compensation of insulin secretion. The decreasing insulin release showed deterioration of pancreatic beta cell function.<sup>8,9</sup>

DMPA injections users that have experienced disturbances in insulin metabolism have an increased risk to develop type 2 diabetes mellitus. This increased risk may be caused by several factors, such as initial body weight prior to the use of DMPA, the status of breast-feeding after birth, history of gestational diabetes in previous pregnancies, family history of diabetes mellitus and lipid profiles. All of these can increase the risk of DMPA users to suffer diabetes mellitus.<sup>10</sup>

## METHODS

This was a case-control study, aimed to determine the relationship between the incidence of type 2 diabetes mellitus and DMPA injections exposure history and risk factors associated.

The study was conducted in 6 health centers in East Jakarta: Kramat Jati Health Center, Cakung Health Center, Ciracas Health Center, Pulogadung

Health Center, Duren Sawit Health Center, and Makassar Health Center. The study was conducted from January 1, 2012 to March 31, 2012.

Primary data was taken from medical records regarding the diagnosis in patients with type 2 DM and a history of contraceptive use. If the data on the medical record was not complete, then we interviewed the respondents.

The estimated sample number was calculated using unpaired categorical analytic formula and we obtained the amount of sample for the case was 29, while for the control was 58.

Subjects were patients who came to the health center and gave approval to participate in the research. The data, such as age, body mass index, parity, lactation status, methods and duration of contraceptive use, were collected through medical records and interviews. Existing data was processed using SPSS 17 and presented in a narrative, tabular, and graphics.

## RESULTS

The data was collected at six health centers in East Jakarta and we obtained 30 sample cases and 61 control samples with an age range between 35-60 years.

Table 1 shows the data of body mass index, with 54 people (59.3%) were overweight. From 70 subjects who use hormonal contraceptives, most were DMPA injection users (31.9%). From all subjects, only 12 subjects (13.2%) had a history of gestational diabetes mellitus.

Table 1. Subject Characteristics

Characteristics	Freq	(%)
<b>Health center</b>		
• Ciracas	7	7.7
• Kramat jati	21	23.1
• Pulogadung	15	16.5
• Makassar	14	15.4
• Duren Sawit	16	17.6
• Cakung	18	19.8
<b>Body mass index</b>		
• Normal	37	40.7
• Overweight	54	59.3

Type of contraception		
• Hormonal		
Oral combination pill	18	19.8
Combination injection	11	12.1
DMPA injection	29	31.9
Implant	10	11.0
Mini pill	2	2.2
• Non Hormonal		
Calendar method	4	4.4
Condom	4	4.4
IUD	8	8.8
Sterilization	5	5.5
Diabetes Mellitus status		
• DM		
	30	33.0
• No DM		
	61	67.0
History of Gestational DM		
• Yes		
	12	13.2
• No		
	79	86.8

**Table 2.** Duration of DMPA injection use and the relationship with the incidence of diabetes mellitus

Duration (years)	DM	(%)	No DM	(%)	Total	(%)
> 3	10	62.5	2	15.4	12	41.4
< 3	6	37.5	11	84.6	17	58.6
p	0.022*	OR	9.167	95CI	[1.189-88.908]	

\*Fisher Exact test

Table 2 described the duration of DMPA injection use and its relationship to the incidence of diabetes mellitus. Calculated with Chi Square, the p value was 0.022 ( $p < 0.05$ ), meaning that statistically there was an association between the duration of DMPA injection use with the incidence of diabetes mellitus, with OR 9.167 95CI [1.189 to 88.908].

**Table 3.** Correlation of DMPA injections compared to non-hormonal contraceptive injections of DMPA with the incidence of diabetes mellitus

Type of hormonal	DM	(%)	No DM	(%)	Total	(%)
DMPA injection	16	59.3	13	30.2	29	58.6
Non DMPA injection	11	40.7	30	69.8	41	41.4
Total	27	100.0	43	100.0	70	100.0
p	0.017*	OR	3.36	95CI	[1.098-10.469]	

\*Chi square ( $X^2$ ) test

Table 3 described the relationship between DMPA injection and the incidence of diabetes mellitus compared with the use of non-DMPA hormonal injection. From Chi Square test, we obtained the p value of 0.017 ( $p < 0.05$ ), meaning that there is a statistically significant association between the use of DMPA injections with the incidence of diabetes mellitus, with an Odds Ratio of 3.36 95% CI [1.098 to 10.469].

**Table 4.** Odds ratio of DMPA injections compared to non-hormonal contraceptive injections with the incidence of diabetes mellitus adjusted for age, BMI, parity and history of DMG

Variable	OR	p	95% CI (lower; upper)
Age adjusted	2.590	0.035	1.600; 4.215
Age and BMI adjusted	2.111	0.048	0.533; 3.731
Age, BMI, and parity adjusted	2.087	0.434	0.550; 4.016
Age, BMI, parity and history of GDM	2.057	0.569	0.475; 3.875

In Table 4, logistic regression test was performed on the known risk variables for the occurrence of diabetes mellitus, namely age, BMI, parity, history of DMG. The cut off point of age as a risk of diabetes was assumed at 45 years old. BMI considered to have diabetes mellitus risk in overweight category  $\geq 30$ . Parity > 3 children are considered at risk for developing diabetes mellitus. And history of from DMG is considered as the risk factor of developing diabetes mellitus. And from the table, it can be concluded that the risk of diabetes mellitus decreased when adjusted for age. The risk still gradually decreased when adjusted for BMI, parity and history of DMG respectively.

## DISCUSSION

The samples were taken from six health centers in East Jakarta, with the aim of covering a population-based health center in East Jakarta. During the period January-March 2012, 30 samples of cases and 61 samples of control were collected.

Characteristics distribution of the sample showed that the median of the age was 45.00 (35-67) years, the median number of parity was 3.00 (0-7), and the median BMI was 27.31 (15.24 to 40.27). The number of subjects receiving contraceptive injections of DMPA was 31.9%, which is the highest percentage of contraceptive methods used. These data correspond to the characteristics of BKKBN

data that showed the highest injection rate of contraceptive users who reach more than 50%.

The mean duration of use of contraception was  $5:36 \pm 4:42$  years, and it was concluded that there is a relationship between the duration of DMPA injections for more than 3 years with the incidence of diabetes mellitus, where the risk of diabetes was 9.2 times higher in women using DMPA injection for more than 3 years. While to compare the contraceptive injections of DMPA with other hormonal contraceptives among contraceptive injections of DMPA gained relationship with the incidence of diabetes mellitus with  $p = 0.017$  and OR 3.36 [1.098 to 10.469]. This research result similar with research conducted by Kim C et al on the Navajo woman, they found there is an increasing number of people with diabetes mellitus in DMPA injection users. Risk increases with respect to duration of use.<sup>11</sup>

We use a conditional logistic regression analysis to eliminate confounders and effect modifiers such as age, BMI, parity and history of GDM, to get the most influential variable risk of use of DMPA injections. After adjustment of the age of the sample, the risk of diabetes mellitus decreased, and even further when adjusted for BMI. On the variables parity and a history of gestational diabetes mellitus risk continues to decline although the value was found to be statistically insignificant.

The situation above can be explained by the fact that the subjects with insulin resistance will suffer a more severe insulin resistance and finally glucose intolerance in diabetes mellitus. With increasing age and BMI, users tend to have more risk to suffer insulin resistance.<sup>12</sup> Parity is associated with insulin resistance, this was due to chronic exposure of hormones in pregnancy, in this case progesterone, which causes insulin resistance. History of gestational diabetes mellitus are also risk for falls in a state of diabetes mellitus because of defects that have occurred due to pregnancy.<sup>4,6,8,9,13</sup>

The results of this study should be interpreted with caution because it has several limitations, among others were that the status of diabetes mellitus are known only in the case, whereas in the control group there is no data for diabetes status. That is, diabetes mellitus cases could be showing more number when all of the subjects screened for diabetes mellitus. Another weakness of this research was that, we can only classify the subject according to the contraceptive used only by the longest type of contraceptive method they use, so

exposure to other contraceptives method could also have influence. Another limitation that this study did not measure lifestyle, which also plays an important role in determining the occurrence of diabetes mellitus.

Although this study showed the risk of diabetes mellitus from the use DMPA injections, but the purpose of this study should be examined carefully. DMPA injection is one method of contraception that is effective in preventing pregnancy, and restrictions on the use of DMPA injections to avoid diabetes mellitus can lead to pregnancy, which in itself increases the risk for the occurrence of diabetes mellitus.

This study aims to be a material consideration for health providers, particularly health care centers associated with government programs to support family planning. With this research, the health provider will be more selective for the selection of candidates for DMPA injection acceptors. Candidates for DMPA injection acceptors should be rated for their risk of suffering diabetes mellitus. This selection method will hopefully reduce the risk of diabetes mellitus in users of DMPA injection.

Health centers and health personnel should perform a screening for diabetes mellitus before giving DMPA injections. The examination should be performed before the injection is started if possible. Thus, the state of insulin resistance that has occurred can be detected and further defect by DMPA administration could be avoided.

## CONCLUSION

There is a relationship between the use of DMPA injections with the incidence of type 2 diabetes mellitus. Risk persists when adjusted for age and BMI. Health providers need to do a selection for DMPA users who have an increased risk to develop diabetes mellitus. And when necessary, the user's state of insulin resistance have to be checked prior to use.

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