

## Association of HbA1c and total cholesterol levels in child bearing age using injectable contraceptives.

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### Abstract:

**Introduction:** Injectables contraceptives are convenient and highly effective methods for fertility regulation, being simple to administer and long acting, but affect lipids by increasing total cholesterol and triglycerides<sup>1</sup>, the major health risk of injectables contraceptives are cardiovascular diseases (CVS), particularly heart attacks (myocardial infarction), stroke and venous thromboembolism<sup>2</sup> Hormonal contraceptives have traditionally being thought to adversely affect carbohydrate metabolism by increasing insulin resistance and decreasing glucose tolerance<sup>3</sup>.

**Objective:** To determine and compare the values of HbA1c and total cholesterol levels in child bearing age using Depot Medroxy Progesterone Acetate (DMPA).

**Methodology:** This comparative cross-sectional study was conducted at Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi, from January 2016 to December 2016. Total 200 fertile females in their child bearing age were selected. They were divided into two groups, Group 1 (controls) and Group 2 (DMPA users). Total cholesterol levels were measured before starting therapy, in the middle and the end of the therapy by using standard procedures on semi- automatic clinical chemistry analyser (Microlab 400). HbA1c levels were measured by using semiautomatic clinical chemistry HbA1c analyser (Microlab 300). Results were analyzed by using Statistical Package for Social Sciences (SPSS) version 21.

**Results:** DMPA causes significant increase ( $p < 0.05$ ) in total cholesterol, but insignificant changes ( $p > 0.05$ ) in HbA1c levels.

**Conclusion:** It is suggested that total cholesterol and HbS1c levels should be measured before starting and during the course of injectable contraceptives to the subjects. As deranged cholesterol levels can increase the risk of cardio- vascular disease outcomes<sup>4</sup> Also injectable contraceptives may cause pre- diabetes (increased in levels of HbA1c 5.7-6.4)<sup>5</sup>.

**Key Words:** Depot medroxyprogesterone Acetate (DMPA), Glycated hemoglobin (HbA<sub>1c</sub>), Total Cholesterol, Statistical Package for Social Sciences (SPSS).

### Introduction:

Injectable contraceptives are convenient and highly effective methods for fertility regulation, being simple to administer and long acting<sup>1</sup>Injectable contraception gives protection against ectopic pregnancy, pelvicinflammatory disease and functional ovarian cysts, because ovulation is inhibited<sup>2</sup>.

Injectable contraceptive methods are safe, highly efficacious, and commonly used worldwide<sup>3</sup>.Globally6% of women using modern contraception use injectables and 1% use implants.<sup>4</sup>More than 12 millions women worldwide use injectable progestin only formulation over long intervals because of their efficacy and less side effects.<sup>5</sup>Depot medroxyprogesterone acetate is the most commonly used injectable in the United States, about 20%<sup>(3)</sup>China is the worlds most popular country with over 1.3 billion people using contraception.<sup>6</sup>In most developing countries, fertility, contraceptive use and reproductive health status in rural areas lack far behind urban populations.<sup>7</sup> In Asia, the first ever family planning program was launched by Pakistan, but it is overtly neglected and under utilized.<sup>8</sup>DMPA offer superior efficacy, great convenience, low cost, and proven safety.<sup>80</sup> countries have already approved its use<sup>9</sup>

There are two main types of hormonal contraceptive formulations, these are combined methods which

contain both estrogen and progestins,and progestogens only methods, which contain only progesterone or one of its synthetic analogues that is progestins.<sup>10</sup> Progestogens only contraceptives may be preferable in some situation, in women having absolute or relative contraindication to esterogens, side effects to estrogens, lactation and comfort and feasibility of formulation for long term use<sup>11</sup>There are many types of progestins, each differing in its potency and efficacy. The two main progestogen only injectables are depot medroxy progesterone acetate (DMPA) and norethisterone enanate. Depot medroxy progesterone acetate (DMPA) is most commonly used injectable contraceptive.<sup>12</sup>Depot medroxy progesterone acetate is an effective reversible contraception. It was developed in 1954 as a treatment for endometriosis and to prevent habitual or threatened abortion.

In 1987, the US food and drug Administration (FDA) approved DMPA as a contraception and currently been used worldwide<sup>13</sup>. Depot medroxyprogesterone acetate (DMPA) inhibit follicular development and prevent ovulation as aprimary mechanism of action .There is secondary mechanism of action of all progestogen containing contraceptives is inhibition of sperm penetration by changes in the cervical mucus. Inhibition of ovarian function during DMPA use causes the endomycinr to become thin and atrophic. These changes in the endometrium could, prevent

implantation<sup>14</sup>. It is administered subcutaneously or intramuscularly every 3 months. Its side effects mainly irregular bleeding in 80% of women while 70% women got amenorrhea after 12 months of use. Spotting and heavy bleeding can be developed<sup>15</sup>. Fertility is returned within 10 month from the last injection.<sup>16</sup> Injectable contraceptives effect lipids by increasing total cholesterol and triglycerides<sup>17</sup>. Progestogens only injectables may induce changes in lipid metabolism, reducing HDL cholesterol and increasing HDL: LDL cholesterol ratio<sup>17</sup>. Clinical data showed that estrogen, progestins and androgens influenced lipoprotein metabolism, the study of the effects of steroidal contraceptives on lipid metabolism and HbA1c had generated great interest<sup>18</sup>. Hormonal contraceptives have traditionally been thought to adversely affect carbohydrate metabolism by increasing insulin resistance and decreasing glucose tolerance. However, low dose hormonal contraceptives do not seem to cause any clinically important changes in carbohydrate metabolism. A retrospective case control study of women with type 1 DM found no difference in HbA1c levels in women who had used hormonal contraceptives for 1–7 years compared to non users<sup>19</sup>. The American College of Obstetricians and Gynaecologists has stated that among diabetic women who have vascular disease or are older than 35 years, the use of progestin only oral contraceptives, DMPA, or implants may be safer than combination.

The American Diabetes Association offers little contraceptive guidance for diabetic women, that there are no contraceptive methods that are specifically contraindicated in women with diabetes.<sup>20</sup> HbA1c becoming a more accurate and more authentic tool for diagnosing diabetes, as recommended by WHO.<sup>21</sup> However hormonal contraceptives might influence carbohydrate and lipid metabolism and increase micro and macrovascular complications. So caution in selecting a contraceptive method is required<sup>22</sup> It is very important and essential when prescribing steroidal contraception that a careful medical history is taken to exclude either a personal or family history of thromboembolic disease and risk factor for venous thromboembolism<sup>23</sup>. As low dose progestins are not associated with thrombosis, WHO recommends initiation of progestins only contraceptives during postpartum period.<sup>24</sup> The major health risk of injectables are cardiovascular diseases, particularly myocardial infarction, stroke and venous thromboembolism<sup>25</sup>. Other side effects are nausea, dizziness, breast tenderness/engorgement, acne, insomnia, leg cramps, arthralgia, scalp hair loss, depression, decrease in libido, greater risk of acquiring sexually transmitted infection, decreases bone mineral density and weight gain upto 3kg per year are observed.<sup>26</sup>

DMPA adversely affects cardiovascular health on the long run. There are marked differences between

countries in patterns of contraceptives use both in types and extent of use. These differences reflect availability and accessibility as well as social and cultural attitudes towards fertility control<sup>27</sup>. Whereas, in women with diabetes without vascular disease, the advantages of using hormonal contraceptives use in women with vascular complications of diabetes. Therefore, women with vascular complications (nephropathy, retinopathy, and neuropathy) and women with diabetes of greater than 20 years duration should avoid hormonal contraceptives use unless no other methods are available.<sup>28</sup>

#### **Rationale:**

Review of previous literature shows that injectable contraceptive use is associated with many side effects. Increase cholesterol levels is one of them, which is associated with increased risk of developing cardiovascular diseases. This study will be a significant contribution in evaluating the association between total cholesterol and HbA1c levels in DMPA users. Determination of risk factors associated with DMPA use for long term.

#### **Objectives:**

The aim of this study is to determine and compare the values of HbA1c and total cholesterol levels in DMPA users.

The objective of this study is to investigate the relation between total cholesterol and HbA1c levels in DMPA users.

To evaluate the risk factors associated with DMPA use in child bearing age.

Hypothesis.

Null hypothesis states that there is no any association between total cholesterol and HbA1c levels in DMPA users.

Alternate hypothesis states that there is an association between total cholesterol and HbA1c levels in DMPA users.

#### **Methodology:**

This was a Comparative cross-sectional Study, which was conducted at the Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi, in one-year duration from January 2016 to December 2016. Total 200 fertile females in their child bearing age were selected. They were divided into two groups, Group 1 (100 controls) and Group 2 (10 DMPA users). Subjects included in group 1 (controls) were married fertile females in reproductive age group (15-49 years) who had not used any kind of hormonal contraceptives and were non-pregnant and non-lactating. Subjects included in group 2 (DMPA Injectable contraceptive users) were married fertile females in reproductive age group (15-49 years) using DMPA injectable contraceptive at least for the last one year and were non-pregnant and non-lactating. Subjects with hypertension, cardio-vascular disease, diabetes mellitus, liver disease, abnormal nipple discharge and

undiagnosed vaginal bleeding were excluded. Women who selected DMPA (DMPA group) contraception received 150 mg intramuscular injections every 12 weeks.

Total cholesterol levels were measured using standard procedures on semi-automatic clinical chemistry analyser (microlab400). HbA1c levels were measured by using semi-automatic clinical chemistry HbA1c analyser (microlab300). Results were analyzed by using SPSS21. The p value <0.05 was taken as significant.

#### **Results:**

The mean age of the patients in group 1 (control) was 30.8±6.5 years and in group 2 (DMPA users) was 30.8±6.2. For subjects in group 1 (control) the mean ±SD concentration of serum total cholesterol was 176.2±38.5 before therapy, 177.3±38.4 mid of therapy, 177.5±38.6 end of therapy, and for group 2 (DMPA users) the mean ±SD concentration of serum total cholesterol was 176.8±38.6 before therapy, 182.6±40.5 mid of therapy, 188.9±42.5 end of therapy respectively. The mean ±SD concentration of serum total cholesterol was significantly (p <0.01) increased in group 2 (DMPA users) as compared to group 1 (control).

For subjects in group 1 (controls) the mean ±SD values of serum HbA1c was 6.1±2.3 before therapy, 6.3±2.1 mid of therapy, 6.4±2.3 end of therapy and for group 2 (DMPA users) the mean ±SD values of serum HbA1c was 6.2 ±2.2 before therapy, 6.4±2.1 mid of therapy, 6.6±2.3 end of therapy respectively. The mean ±SD of values of serum HbA1c levels was not significantly increased (p > 0.05) in group 2 (DMPA users) as compared to group 1 (control).

#### **Discussion:**

The use of hormonal contraceptives by women all over the world is increased. The major health risk of DMPA (injectables contraceptives) are cardiovascular diseases, associated with elevated concentrations of plasma total cholesterol. Hypercholesterolemia is a major indicator of risk of coronary heart diseases; for every 1% increase in the total serum cholesterol level, a 2% increase in incidence of coronary heart disease is found (Castelli et al., 1998).<sup>(29)</sup> DMPA use also associated with an increased risk of diabetes. Annual diabetes incidence rates were 19% in DMPA users<sup>30</sup>. Present study included two groups, controls and DMPA users. In this study we have seen that there is a significant increase in total cholesterol levels in DMPA users as compared to controls, but no changes have been observed in HbA1c levels in both groups.

Berenson et al in 2009, observed high total cholesterol levels in injectables contraceptives users than in non-users, as we seen in our study that there is a significant increase in total cholesterol levels in DMPA users as compare to controls, which is in favour of our study.<sup>31</sup> Abbey et al 2009, observed that

DMPA users were 2-3 times more likely to develop abnormal total cholesterol values at some point during the 12 months of study period. This also comparable with our study, as values of total cholesterol were high in DMPA users as compare to non-users. However, these adverse effects on serum lipids were temporary and levels improved over time even if DMPA was continued.<sup>32</sup> Oylola 2010, in his study on Nigerian women observed no change in TC/HDL ratio among DMPA users.<sup>33</sup> This in contrary to our findings, as we have seen that DMPA causes significant changes in total cholesterol levels. This risk may be attributable to other life style factors including lack of exercises and increased intake of cholesterol rich diets but still the hormone factor cannot be excluded in manipulating the cardiovascular disease risk.

Anny H Xiang et al 2006, observed that there was no significantly increased diabetes risk in DMPA users with triglycerides <150 mg/dl as compared to non-users. This will support our study, as there is no changes have been observed in HbA1c levels in DMPA users when compared to non-users (controls).<sup>34</sup> Kim C et al in 2007, also observed in Navajo women that Depot medroxyprogesterone acetate contraception was associated with a greater risk of diabetes. This increase risk was associated with length of use of DMPA and persist after adjustment for body mass index. This in contrast to our study as DMPA users did not show an increase levels of HbA1c when compare to non-users.<sup>35</sup> Kjos S et al in 2008, observed in Latino women with prior gestational diabetes, who elected to use DMPA had an increased risk of developing diabetes. However, the increased risk appeared to be due to a combination of factors. First family history of diabetes, second weight gain during DMPA use may have contributed in a small way to increase 7d diabetes risk, third use of DMPA with relatively high baseline triglycerides or during breast-feeding increased the risk of diabetes.<sup>36</sup> This is in oppose to our study, as there is no any significant changes have been seen in HbA1c levels in DMPA users.

Overall, we concluded that any adverse effects of DMPA we observed on the lipid profile were temporary and reversible. Consistent with our findings, an international, case control study on hormonal contraception conducted by WHO concluded that there was little or no increased risk of cardiovascular disease among users of injectables contraceptives.<sup>37</sup> However, one study observed arterial changes among women using DMPA more than one year which suggests that long term use could increase the risk of cardiovascular disease.<sup>38</sup> Previous study demonstrated that DMPA may increase the risk by increasing body fat and truncal obesity.<sup>39</sup> Additional studies with larger sample sizes are needed to clarify this issue. Our study is in agreement to these studies.

**Conclusion:**

Our study concluded that DMPA (injectables contraceptives) will increase total cholesterol levels but no significant changes in HbA1c levels. It is suggested that total cholesterol and HbA1c levels

should be measured before starting every course of injectables contraceptives to the subjects. As deranged cholesterol levels can increase the risk of cardiovascular diseases and higher HbA1c levels means increase chances of developing diabetes.

**References:**

1. Ok eke CK et al. Comparative Effects Of Injectable and Oral Hormonal Contraceptives on Lipid Profile. Eur J Cardiovascular 2012; 2(1):2042-4884.
2. Bhatena RK. The long acting progestogen only contraceptives injection: an update. Br J Obstet Gynecol. 2001; 108:3-8.
3. Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE. Oral contraceptives and renal and retinal complications in young women with insulin dependent diabetes mellitus. J Am Med Assoc. 1994; 271:1099-102
4. Faryal U, Rashid S, Hajra B. Lipid Profile in females of reproductive age group using combined oral contraceptive pills. Gomal J Med Sci 2012; 10:233-6.
5. Prediabetes.By Mayo Clinic Staff <https://www.mayoclinic.org/diseases-conditions/prediabetes/symptoms-causes/syc-20355278>

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