Abstract

Objective: This is a study to evaluate the effects of combined oral contraception, low estrogen type on some liver function, other physiological and biochemical characteristics of the blood.

Study design & Setting: prospective b study at Babylon medical college teaching maternity hospital, Department of Obstetrics & Gynecology, from July 2006 to June 2007.

Materials & methods: the study enrolled 330 women, attending family planning center of the hospital. They were divided into 2 groups. The study group of 250 women (they were all pills users for a variable time), the control group of 80 healthy women (were using natural methods of contraception). Liver enzymes ALT, ALP, serum bilirubin, serum cholesterol, blood sugar, blood pressure, body mass index were compared between both groups. Statistical analysis was carried out using student t test. p value was calculated, any value more than 0.005 was considered not significant.

Results:

The study revealed:

A highly significant (p<0.01) decrease in both liver enzymes ALT & ALP while there was no significant change in bilirubin (p>0.005) when compared with the control group.

There was a highly significant reduction (p<0.01) in HDL in the study group when compared with the control group.

There was a highly significant elevation (p<0.01) in total cholesterol for the study group when compared with the control group.

There was a positive correlation but it was not significant between the total cholesterol, HDL level (R=0.2, P=0.001).

There was also a highly significant elevation (p<0.01) in the glucose level in the study group, and there is a positive correlation between the mean glucose and total cholesterol in the study group.

There is a significant increase (P<0.05) of serum albumin in pills users.

The study showed a highly significant change of body weight, an increase which is positively correlated with the body glucose.

There is a highly significant increase for both systolic and diastolic blood pressure in pills users.
Introduction

The key to a successful family planning program lies in the wide range of contraceptive choices available to couples. Oral contraceptive pills are a highly effective and safe method of contraception that should be made available as a choice to couples in need of family planning. (Garza_ flores et al.,1994) (19) Oral contraception have been on the market for 40 years now and have been used by more than 200 million women around the world.

The combination of esterogen and progesterone feeds back in a negative manner on the hypothalamus and there is a relationship between dose of esterogenic component and the type and the activity of the progestin component and degree of risk for cardiovascular disorders.

Pills alters body metabolism, by evaluating liver enzymes and biochemical properties (blood tests), the liver functions is evaluated. (luxton & pallister, 1999)(29)

The monophasic pills, each tablet of 21 pills per month have the same amount of estrogen and proportion of progesterone.

Conclusion:

The study shows
1- The monophasic pills leads to changes in some liver function which on long term bases may leads to a disturbance in completely healthy women or risk group.
2- The changes in body weight, blood pressure, body mass index may lead to a complication as development of of obesity and future development of diabetes in a risky group.
3- Excess morbidity related to pills especially changes in serum cholesterol, HDL, blood glucose and proportion of esterogen and progesterone feeds back in a negative manner on the hypothalamus and progesterone.

The key to a successful family planning program lies in the wide range of contraceptive choices available as a choice to couples in need of family planning. (Garza_ flores et al.,1994) (19) Oral contraception have been on the market for 40 years now and have been used by more than 200 million women around the world.

Many side effects are experienced following use of oral pills, most excess mortality related to effects on the cardiovascular system, in 1981 study by the Royal College Of General Practitioner showed an increased risk of CV related mortality =4x current users and 4.3 in ever users. B oth esterogen and progesterone component contribute to increased risk . This is concentrated in women who are older, long-term OC users and smokers.
progestin, ethinylesteradiol, are synthetic estrogens that are metabolized to inactive compounds on first pass through the liver.

**AIM OF STUDY**

Effects of combined oral pills on some liver function

Changes associated with pills on some physiological parameters as weight, blood pressure, body mass index.

3- Exclusion of high risk group.

Materials and Methods

This is a prospective study that was carried out in the family planning center in Babylon Maternity hospital in Babylon province from July 2006 to June 2007, to study the effects of monophasic low dose estrogen oral combined pill, on some physiological and biochemical effects of pills users.

330 women attending that center was the sample of study, 80 women as a control group (pill non user) another 250 as a study group (pill user, for variable time)

Women in the control group were chosen from medical staff of the same hospital for easier follow up.

Few millimeters venous blood transferred to sterilized plain tube and was left for 10 minutes at room temperature for coagulation to occur.

Then serum was taken by centrifugations in speed of 3000rpm/min for 15 minutes and the serum was kept at -20°C for further investigation.

All blood tests was carried out in the lab of the same hospital, blood pressure measured by same hospital sphygmomanometer (each time blood pressure checked, also it was done by the same person).

The pill was monophasic low dose estrogen pill type Microgynon ED/Germany, one packet per month was taken on regular bases, the packet containing 21 tablets of contraceptive pill, each pill contain the Ethinylesteradiol (EE) of 30 Microgram, and 150 Microgram of levonogestrel, also the packet containing 7 tablets of ferrous fumarate of 75 mg.

Both groups were followed and were all had no chronic medical and genitourinary infections.

Blood sample was drawn from each women and blood pressure, body weight and body mass index (BMI) measured for both study and control group, the duration of the use was variable from one month to 10 years, and the women age was between 18-45 years.

Also they were matched in the physiological and biochemical parameters, also blood pressure, body weight, body mass index.

Statistical Analysis

Statistical analysis was done by the computer, using the mean, the standard deviation for the mean, the linear regression, the correlation coefficient depending on the statistical analysis to found the difference between the main group in the study, we use students t-test, and to find the difference between the subgroups we use the two tailed test – depending on the p value, we consider any value more than p>0.05 not significant.

**Results**

We studied the results in 2 main aspects:
Effects of low dose pill on some liver functions

Results shows the following s:-

1- There was a highly significant (p<0.01) decrease in ALT enzyme is the study group when compared to the control group.

2- There was a highly significant decrease in ALP enzyme in the study group when compared to the control group.

by studying the result of regression analysis, correlation coefficient there was a positive and significant correlations (r=0.33, p=0.01) between the enzymes ALT, ALP in their serum levels as shown in figure (1.)

3- There was non significant change (P>0.05) in the total serum bilirubin in the study group when compared with the control group.

- There was a highly significant elevation (p<0.01) is the serum cholesterol level for the study group when compared with the control group.

5- There was a highly significant reduction (p<0.01) in the high density lipoproteine HDL in the study group when compared with the control group, also the results shows that the regression analysis and correlation coefficient, there was a positive relation but it was non significant between the total cholesterol in the serum, HDL concentration for the study group.

6- The results shows that there was a highly significant elevation (p<0.01) in the glucose level in the study group.

7- The regression analysis and correlation coefficient shows there was a positive correlation between the mean glucose concentration in the serum (r=0.2, p=0.001), and the total cholesterol concentration in the study group.

8- The study shows that there was a significant increase p<0.05 in the concentration of serum albumine of the study group as compared with the control group.

B- effects of oral contraceptive pills on some physiological parameters.

1- The study shows, that body weight in woman who took the oral pills shows a highly significant changes (p<0.01).

2- The results of regression analysis and correlation coefficient showed that there was a positive correlation between the mean body weight measurement p=0.05, r=0.12 with the mean concentration of serum glucose in the study group in comparison with the control group.

3- Also the study shows a positive correlation but it was not significant relation between the body weight and concentration of serum albumine as show in table (6).

Also the study shows that there was a positive significant correlation between the mean body weight measurement r=0.7, p=0.001 with the HDL concentration in the serum of the study group.

4- The study shows that the mean systolic blood pressure increase was highly significant p<0.01 is the study group in comparison with the control group as shown in table no. (7).

5- The study shows that there was a highly significant increase in the
diastolic blood pressure p<0.001 in the study group in comparison with the control group (table no. (7)).

The regression analysis and correlation coefficient revealed that there was a positive significant correlation p=0.001, r=0.46, between the mean systolic pressure and diastolic pressure in the study group.

6- Body mass index measurement

After the measurement of body mass index studies show that there was a highly significant difference p<0.01 in the women who are pill users.

- the regression analysis and correlation coefficient shows that there was a positive significant relation between the body mass index r=0.7, p=0.001 with mean body weight (table. 8).

- there was a positive significant relation between the body mass index measurement r=0.12, p=0.05 and the mean systolic blood pressure measurement.

while in table (8) show there was no relation between the positive correlation of body mass index and the mean systolic blood pressure measurement.

The results (table 8), figure no(13) that there was a positive significant correlation between the mean BMI, r=0.34, P =0.001, and the total cholesterol level in the study group.

Discussion

A effects of low dose pill on some liver functions.

1- The liver, the largest gland in the body, has many complex functions. it had many mechanisms, enzymes, drug metabolism is one of the important liver functions.

ALT,AST changes both considered an indicator of liver injury, in this study we evaluate ALT,ALP in pill users, the results show that there was a significant decrease (p<0.05) for both enzymes in comparison with the control group. The results coincides with those of cowan (cowan et al., 1982) who referred to significant decrease in ALP for pill users, those results were confirmed by others.

(Smith & sizto, 1983; Dufour,1998;Francois et al.,1998(41)

Obataetal(1983) referred to the increase in ALP in rats treated with the pill, which occurred as a result of liver obstruction induced by ethinylesteradiol while ( Weijers ) 1983, mentioned no changes for ALT in women using the pills.(46)

pagana (pagana,2001) mentioned that during pill use there was a decrease in vitamin B6 which metabolism is increased during the use, and it affects the decrease in ALP.(33)

2- The results showed there was significant change in serum bilirubin of pill users in relation to control group.

This result, in comparison with other studies that showed to the significant decrease in the bilirubin with the pill use. (Isselbacher, 1980; knoppetal.,1995;Francois et al.,1998)(25)

Jaffer(2003) observed an increase in serum bilirubin in rabbit treated with high doses of oral pill, others did not mentioned any change (Ferraies et al.,1981)(15)
The no change can be explained by the fact that there is a delay of liver pick up of bilirubin, and a delay in its metabolism which it was temporary, especially during acute illnesses or chronic diseases, and so its level will not change, unless the liver cells was completely destroyed or in cirrhosis (Cabot, 2002).

3- Fat is considered an important energy source in the body (Guyton, 1996). The liver is considered an important place for fat metabolism, it converts the Acetyl CoA to fatty acid and cholesterol and triglycerides, and it converts cholesterol to bile acids which is secreted with the bile which affects fat metabolism (Bishop et al., 2005).

This study shows an increase in serum cholesterol concentration in pill users in comparison with the control group which was the same with other studies results (Ricalde & Ramos, 1986; Webber et al., 1991; Greenlund et al., 1998; Crook, 1997; Francois et al., 1998; Schrangel et al., 1994).

Ethinylesteradiol and levanogestrel leads to an increase in cholesterol (Schrangel et al., 2004) the estrogen component of the pill leads to increases in enzymes involved in cholesterol synthesis and the progesteron component delay its conversion to bile acids, and also the estrogen decrease in motility of the biliary passages and it leads to cholestasis. (Burtis & Ashwood, 1981).

These biomolecules differ in their size, density, and their electrical character. (Fishbach, 2000)

Liver is the place of lipoprotein synthesis, so in evaluating HDL, we are evaluating the liver function. In this study there was a decrease in HDL concentration in pill users in relation to control group.

(Godsland et al., 1990) refers to this in his study, other studies shows same results (Kuhl, 1996; Sissan & Leelamma, 1996; Greenlund et al., 1997; Schwertz, 2002; Schrangel et al., 2004).

Lanchit (1996) observed that levonogestrel of the pill had lowering effect for the HDL when it was used in monophasic preparation it has no effect when it was used in triphasic tablets, probably due to androgenic properties in fat metabolism in first type of tablets [monophasic] this was proved by (Abrams & Goldsmith, 2001).

5- The regulation of blood glucose level of the body is the main function of the human liver, the liver stores the excess glucose in form of glycogen, and it converts it again to glucose when there is a need for that. The study shows significant elevation (p<0.05) in glucose level in comparison with the control, the increase is due to carbohydrates absorption and glucose tolerance (Meyers et al., 1976), and also due to estrogen components of the pill that decrease the efficiency of insulin in lowering the blood sugar.

(Katzung, 2004) show that these changes will go back to normal when the pills is withdrawn from use.
Also the study shows positive correlation between cholesterol, glucose level in the study group, due to increase in oxidation of fat which is associated with increase in blood sugar especially with obesity (Felder et al., 1987)(14).

6- The liver is important place for protein synthesis like albumine, globulin, sex hormone binding globulin, which had great affinity to steroid hormones, the explanation for the increase in serum albumine for women on pills in relation to the control group, due to stimulant effect of steroid for albumine synthesis (Walter et al. ,1996; Bacq ,1999; Marqueau et al., 1999 )(44).

Which is more with norgestrel ( Chapdelain et al. ,1989 ) (10) than with pills containing levonogestrel type (Humpel et al. ,1990)(24).

Other studies reported different effect of the pill on protein synthesis.

Steriods affects on many receptors of the body, it increase cell input of sodium, and by stimulant effect on protein synthesis, so it maintain the oncotic pressure of the plasma.

Some literaturs mentioned different concentration, it may increase it (Smith & Szito, 1983; Loke et al., 1992)(41).

While Paterson(1988)(34) refers to decrease in albumine in women treated with oral pills, other mentioned no effects of the pill on serum albumine, (Moore et al., 1981; Shaaban et al., 1980)(31).

It is postulated that the effect due to positive correlation between glucose and albumin concentration in pill users, the cause may related to the increase in serum insulin which had an effect on increase the uptake of amino acids and convert them to protein, also insulin decreases protein breakdown and its metabolism (Guyton & Hall,1996) (22).

B- Effects of oral pills on some physiological properties.

1- Obesity or increase in body weight because of storage of excess of carbohydrates and (Guyton & Hall, 1996) (22).

The study show increase in mean body weight in pill users in relation to the control group, the longer the duration of use, the more the side effects that related to the pill use.

(Gard, 2001; Gaudet et al., 2003)(18).the effects of the pill on weight changes varies, Oelkers and his colleagues 1995 found that the progesterone with androgenic properties like levonogestrel I causes little increase in body weight, probably related to the effects of the hormones on enzymes deals with fat breakdown and metabolism, which leads to obesity, in addition to water and electrolyte retention in muscles, the steriods leads to, especially more when it occurs in the skin and blood, (Glaisier, 1998), also Taylor, Stachenfeld (2004)(20) referred to the prescenc of of increase in plasma volume, the esterogen cause, and it also affects endothelial function of the blood vessels, decrease protein transfer across these vessels, while ALawchi (2002) mentioned the increase in body weight probably is due to increase in appetite in these women because the fear of getting pregnancy is withdrawn.

2- Effects of oral pill on mean arterial systolic and diastolic blood pressures.
The study shows that there was an increase in mean systolic and diastolic blood pressure measurement in relation to the control group.

It had been mentioned in one of the British (1973) studies that there was a significant increase in systolic blood pressure and an insignificant increase in diastolic pressure as women get older and heavier and were using the pill.

Nichols and his colleagues (1993) found that there was a increase in both pressures in those using lower doses pills also the same result obtained with (Chasan_ Taber et al., 1996) (11).

The diastolic blood pressure increase between (3-6) mmHg and systolic pressure increase between 2.5 mmHg in using the pill (Kaplan & Rose, 2003) (26)

Alawchi (2002 a) mentioned that little increase in blood pressure in one women from 20 women using the pill, especially in those above the 35y of age.

The change in blood pressure varies with the type of steroid used, in preparation of ethinylestadiol and gestoden, had very little effect on blood pressure when used. While ethinylestadiol and levonogestrel especial

effect on blood pressure these changes are due to effect on Renin, Angiotentosigen system (العديد وعشر , 1989/ العلوي , 2005).

The increase in body weight could be one state of increased blood pressure other factors could be related to the increase in blood pressure such as total cholesterol, insulin resistance, vascular reactivity [Poirier et al., 2005].

With the increase in total cholesterol there will be an increase in systolic pressure, a decrease in HDL in those took the pills, probably due to deposition of lipid particles on vessel walls that lead to an increase in systolic pressure.

( Guyton &Hall,1996)

HDL had scavenger role for the lipid particles, transfer these particles by blood to the liver for metabolism (Baynes & Dominiczak, 2005) (3) that why there is an correlation between systolic pressure and HDL, not reaching to the significant levels due to decrease in HDL in serum for those using the pills.

3-Body mass index BMI

BMI is a measure for fat content of the body in relation to height and body weight (Holt 2004)(23), it measure the obesity quantitavely.

Most of studies referred to the increase in body weight in those using the pills the trend in those women is to early discontinuation of the use because of the increase in body weight. (Gallo et al., 2004;Gaudet et al., 2003) (17)

solerte and his group (1992) mention that this increase is due to significant increase in BMI (Carranza & Fontal, 2000)(9)

progesterone redistribute the lipids, which will be deposited in large amounts in the body especially in the abdomen, with high insulin resistance. (Reubinonff et al., 1995b; Jones, 1995)

the obesity will affect the sympathetic nervous system and release of fat from large fat deposits, which affects the Angiotensin II, aldsterone release.
that had a great role in vessel wall contraction (Poirier & Ecket, 2002) (36)

which is reflected in a significant positive correlation between BMI and systolic blood pressure.

CONCLUSION

The monophasic pills leads to changes in some liver function which on long term bases may precipitate a disease in a completely healthy women or risk group.

The changes induced by the pills on some physiological and biochemical blood parameters as for e.g weight, blood pressure and body mass index, leads to unwanted side effects that reflected on long term use by disease process.

Excess morbidity and mortality of OP is related to effects on cardiovascular system, especially with changes in serum cholesterol, HDL, blood glucose, which is primarily related to acceleration of atherosclerosis, increased coronary vasospasm, the risk is more in smokers, older women, family history of cardiovascular disease, longer duration of pill use.

Recommendation

1-Women can be advised that they may use combined oral pills from menarche to the menopause unless there are medical or other contraindication.

2-Women aged more than 35 years who smoke, should be advised that the risk of pill use out weigh the benefits.

3-Clinicians should take a clinical history, including details of sexual and reproductive health, medical diseases, and lifestyle, to be able to advise on eligibility for safe pills use.

4-Women with a blood pressure consistently over 140 mmHg and/or 90 mmHg diastolic should be advised against use of the pills.

5-Women should be provided with information on warning signs of any related side effects, and should have prompt medical consultation.

6-In the absence of special problems, women can begin up to 12 months, supply of pills at first visit and encouraged to return at any time if problems arise.

7-A follow up visit 3 months after the initial pills consultation allows further instruction and assessment of any problems.

8- Women should be provided with telephone numbers of appropriate local and national helplines providing advice on contraception and sexual health.

References


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45-Weigratz,I.;Jung- of oral contraceptives ethinyl estradiol and gestoden or norgestimate on lipid and lipoprotein parameters, Contraception 58:83-91.


Table (1)

<table>
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<th>No.</th>
<th>Means ± SD</th>
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<th>parameter</th>
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<td>P&lt;0.01</td>
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levels of both ALP , ALT , Total bilirubin for oral contraceptive pill users in relation to control group .
Table (2)
correlation coefficient between levels of liver enzymes and total bilirubin of the study group.

<table>
<thead>
<tr>
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<th>NO.</th>
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<th>parameters</th>
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<td>214.59 ± 8.77</td>
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<td>74.28 ± 28.06</td>
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Table (3)
changes in cholesterol concentration, lipoproteins of the study group in a relation to control group

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<td>P</td>
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Table (4)
correlation coefficient between total cholesterol, lipoproteins, of the study group

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<td>250</td>
<td>4.48 ± 1.5</td>
<td>Glucose</td>
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<tr>
<td>Users</td>
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<td>Glucose</td>
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<td>Control</td>
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<td>79.78 ± 19.24</td>
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Table (5): changes in albumin and glucose level; in the study group in relation to control group.
Table. (6)
correlation coefficient between body weight and some biophysical parameters of the study group.

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<th>Glucose</th>
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Table. (7)
changes in some physiological parameters in women taking the pill in relation to control group.

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Table. (8)
correlation coefficient between some physiological parameters in the study group.

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Table. (8)
correlation coefficient between some physiological parameters in the study group.
Figure 1 correlation coefficient between levels of liver enzymes ALT, ALP, in study group.

Figure 2 correlation coefficient and linear regression between bilirubin and ALP liver enzyme of the study group.

Figure 3 correlation coefficient and linear regression between concentration of bilirubin and ALT enzyme of the study group

Figure (4) correlation coefficient and linear regression between the total cholesterol and lipoproteins of the study group
Figure (5) the correlation coefficient and linear regression between cholesterol and glucose level of the study group.

Figure (6) correlation coefficient and linear regression between albumine concentration, glucose of pill users.

Figure (7) correlation coefficient and linear regression between glucose and body weight in pill users.
Figure. (8) correlation coefficient and linear regression between body weight and lipoprotein in pill users.

Figure. (9) correlation coefficient and linear regression between mean systolic and diastolic blood pressure in pill users.

Figure. (10) correlation coefficient and linear regression between diastolic blood pressure and total cholesterol level of pill users.

Figure. (11) correlation coefficient and linear regression between the systolic pressure and cholesterol of pill users.
Figure (12) the correlation coefficient and regression analysis between the body mass index and mean body weight in pill users.

Figure (13) correlation coefficient and regression analysis between the body mass index and systolic blood pressure in pill users.

Figure (14) correlation coefficient and linear regression between BMI and total cholesterol level in pill users.