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Effect of etonogestrel contraceptive implant (Implanon®) on portal blood flow and liver functions☆

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Abstract

Background: This study was conducted to evaluate changes in portal blood flow and liver functions among women using Implanon® for 2 years.
Study Design: Fifty healthy Implanon® users were enrolled in this longitudinal study and followed up for 24 months. Portal blood flow, assessed by color Doppler; prothrombin time and concentration; serum albumin; bilirubin; gamma-glutamyl transferase (GGT); alanine aminotransferase (ALT); and aspartate aminotransferase (AST) were measured before and 24 months after insertion.
Results: After 24 months of Implanon® insertion, there were no significant changes in portal blood flow, serum albumin, prothrombin time or concentration. However, there was a significant increase in serum levels of total and unconjugated bilirubin and GGT and a significant decrease in ALT and AST levels. All levels, however, remained within the normal range of values.
Conclusions: Implanon® use for 2 years does not seem to influence portal hemodynamics. Changes in serum levels of bilirubin, GGT, ALT and AST are unlikely to be of clinical significance.

Keywords: Implanon; Etonogestrel; Liver functions; Portal vein

1. Introduction

Implanon® is a subdermal contraceptive implant that has recently been approved by the US Food and Drug Administration to provide effective 'forgettable' contraception for 3 years. It is composed of a single nonbiodegradable rod, 40 mm long and 2 mm in diameter, containing a core of 68 mg of etonogestrel (ENG). Inhibition of ovulation occurs within 1 day of insertion [1]. It also enjoys excellent reversibility with return of fertility within 1 month after removal. Among those not using other contraceptives, 14% became pregnant within 90 days after removal [2]. Additional advantages of Implanon® include an estrogen-sparing effect, safety for breastfeeding mothers and preservation of bone mineral density [3,4]. It is a good choice for adolescents and women with systemic hypertension, diabetes mellitus, anemia and endometriosis. Bleeding problems are the most common side effects through direct and indirect effects on the endometrium [5–7].

ENG is approximately 32% bound to sex hormone-binding globulin (SHBG) and 66% bound to albumin in blood. ENG is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme and is rapidly transformed in the body to 3-keto-desogestrel, a low androgenic third-generation progestin [8]. The elimination half-life of ENG is approximately 25 h [9]. The metabolic effects of Implanon® have been studied in comparison to Norplant®. Both have a similar effect on hemostasis with no tendency for thrombosis [10–13]. Both induce mild insulin resistance without significant changes in glucose levels [13]. Implanon® was found to increase fasting levels of glycosylated hemoglobin (A_1C) after 2 years [13]. Implanon® is significantly less

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androgenic than Norplant® and increases serum levels of SHBG [14].

The effect on liver functions has also been studied. Whereas total bilirubin and serum gamma-glutamyl transferase (GGT) were reported to increase [11,15], serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were found either to decrease [11] or to remain unchanged [15]. The effect of Implanon® on hepatic perfusion has not been previously studied.

Implanon® is a viable contraceptive option for Egyptian women providing long-term contraception. The impact of Implanon® on the liver is of paramount importance in Egypt, a country where many individuals are afflicted with chronic liver disease.

The aim of the present study was to evaluate changes in portal blood flow and some selected liver functions among Egyptian women using Implanon® for 2 years.

2. Materials and methods

2.1. Subjects

Fifty healthy Egyptian women willing to use Implanon® were recruited from among the attendees of the Family Planning Clinic of the Women's Health Hospital, Assiut University, Assiut, Egypt, in this prospective study and were followed up for 24 months. Based on individual variability in portal vein blood flow measurements, this sample size was expected to detect a 20% change in portal vein blood flow. They were relatively young [mean age (±SD)=29.28±2.74, range 24–34], tested negative for hepatitis B and C, and had normal abdominal and pelvic ultrasound examinations. Institutional review board approval was attained prior to the beginning of the trial. In addition, all women gave their written consent to be included in this clinical trial after receiving adequate information about its implication.

2.2. Methods

All women were thoroughly examined clinically, were screened for hepatitis B and C, and underwent abdominal and pelvic sonography. Prior to implant insertion and 24 months after, portal blood flow was assessed by color Doppler ultrasound. Some selected liver function tests including prothrombin time and concentration, serum albumin, bilirubin, GGT, ALT and AST were also measured before and 24 months after insertion.

2.2.1. Abdominal Doppler examination

2.2.1.1. Equipment. The ultrasound equipment used for Doppler studies was the Siemens Sonoline Sienna Ultrasound Imaging System (Siemens, Germany). This system operates in several modes, a real-time 2D mode, B mode, M mode, spectral Doppler mode, color Doppler mode and power mode. The scan head is curved array (2.5–5 MHz in the Doppler mode). Doppler measurements were carried out in accordance with standard settings [16].

2.2.1.2. Examination technique. Examinations were carried out by a single examiner after an overnight fast and a resting period of 15 min in the supine position during breath-holding in mid expiration to avoid respiratory effects on venous hemodynamics. Patient characteristics, age, sex, height, weight and body surface area do not influence measurement of portal venous flow by duplex Doppler [17,18]. The flow velocity was given as the maximum flow velocity expressed in centimeters per second (corrected for Doppler angle which should be less than 60° and time averaged in veins) because this does not depend critically on the electronic equipment or geometry of the ultrasound beam; both are responsible for systematic errors (overestimation of mean flow velocity). Examination included evaluation of the portal vein and hepatic artery. The examination began by locating the portal vein. Normal blood flow in the portal system is hepatopetal and slightly pulsatile. Doppler entry angle (<60°) and wall filter (50–100 Hz) are required. The examination was made quicker by the color technique; blood flow towards the transducer is red and away from the transducer is blue. Calculation of the blood flow requires measuring the diameter of the portal vein expressed in centimeters and maximum flow velocity expressed in centimeters per second; errors of at least 20% have to be assumed [19]. Portal blood flow=$22/7\times(d)^2/4\times V_{max}/2\times 60$, expressed in milliliters per minute.

Similarly, splenic vein blood flow was measured.

2.2.2. Liver function tests

Prothrombin time and concentration were estimated using diaplastin kit [20] from Diamed (Morat, Switzerland). Serum albumin, total and direct bilirubin, ALT, AST, alkaline phosphatase (ALP) and GGT were measured using colorimetric assay on the automated clinical chemistry analyzer (BM/Hitachi 911).

Table 1
Changes in Doppler-derived parameters of portal and splenic vein hemodynamics after 2 years of Implanon® insertion

	Before Implanon® insertion	24 months after insertion	Significance
Portal vein diameter (cm)	1.05±0.14	1.16±0.13	NS
Portal vein velocity (cm/s)	26.18±2.21	23.82±2.36	NS
Portal vein blood flow (mL/min)	680.35±54.12	663±58.28	NS
Splenic vein diameter (cm)	0.69±0.60	0.66±0.59	NS
Splenic vein velocity (cm/s)	24.16±2.15	22.25±2.06	NS
Splenic vein blood flow (mL/min)	275±25.77	262±26.49	NS

Values are shown as mean±SD. NS: not significant.

2.3. Statistical analysis

Data analysis was performed with a statistical package for personal computers (SPSS, version 11, 2001; SPSS, Inc., Chicago, IL, USA) utilizing comparisons of means (Student's *t* test), Wilcoxon signed rank test and Pearson's correlation. Results are represented as mean±SD and were considered significant when p was <.05.

3. Results

After 24 months of Implanon® insertion, there were no significant changes in portal vein diameter, velocity or blood flow. Similarly, no statistically significant changes were noted in splenic vein diameter, velocity or blood flow (Table 1). Table 2 shows changes in some liver function tests after 2 years of Implanon® insertion. There were no significant changes in serum albumin, serum ALP, prothrombin time or concentration. However, there was a significant increase in serum levels of total and unconjugated bilirubin and GGT, and a significant decrease in ALT and AST levels. All levels, however, remained within the normal range of values for all parameters.

Nonparametric statistical analysis using Wilcoxon signed rank test was also used and yielded the same results. Pearson's correlation test was used to study the within-individual correlations between the ultrasound measurements made before and after 24 months of treatment and to verify the absence of significant effects on portal vein blood flow. Portal vein blood flow was noted not to correlate with any of the liver function test measures or with variables such as age, weight or BMI.

Table 2
Changes in some liver function tests after 2 years of Implanon® insertion

	Before Implanon® insertion	24 months after insertion	Significance
Total bilirubin (μmol/L)	9.25±3.37	13.35±4.14	Significant increase (p<.05)
Unconjugated bilirubin (μmol/L)	5.28±2.21	9.27±3.33	Significant increase (p<.05)
Serum albumin (g/L)	43.63±2.96	41.57±3.05	NS
AST (IU/L)	33.50±1.91	25.08±2.58	Significant decrease (p<.05)
ALT (IU/L)	28.04±2.37	19.62±3.31	Significant decrease (p<.05)
ALP (IU/L)	75.36±6.14	79.98±7.02	NS
GGT (IU/L)	17.54±5.33	27.92±5.26	Significant increase (p<.05)
Prothrombin time (s)	12.98±0.82	13.08±0.78	NS
Prothrombin concentration (%)	97.82±2.00	96.54±1.80	NS

Values are shown as mean±SD.

4. Discussion

Implanon® is a long-term implantable contraceptive containing ENG that is both safe and effective [5]. The pharmacokinetics and pharmacodynamics of Implanon® indicate that it has high contraceptive efficacy, as reflected in a zero pregnancy rate over 5629 women-years of use. Its excellent reliability, ease of use, and reversibility make Implanon® a valuable addition to current contraceptives [9]. In Egypt, the need for long-term contraception could not be overemphasized. Due to the prevalence of chronic liver disease in Egypt and the growing popularity of Implanon®, its impact on liver perfusion and liver functions is of particular importance. The splanchnic pharmacodynamic effects of drugs were poorly clarified until some years ago. The introduction of Doppler ultrasound provided a powerful tool to investigate such hemodynamic effects and brought new insights into this field [21]. Color Doppler is the only noninvasive method for the examination of the portal venous system and in the analysis of the response to drugs [22]. This is, to the best of our knowledge, the first report on the influence of Implanon® on portal and splenic hemodynamics. No significant change was seen after 2 years of insertion on portal or splenic diameter, velocity or blood flow. Earlier reports have pointed to the favorable effects of Implanon® on hemostasis with no tendency to thrombosis [10–13]. Such findings, coupled with unchanged portal and splenic vein diameter, velocity or blood flow, reflect a special advantage of Implanon® compared to combined oral contraceptives, where portal vein thrombosis is a recorded complication [23]. There is, however, no evidence in the available literature that combined oral contraceptives affect portal blood flow.

Approximately 32% of ENG is bound to SHBG and 66% is bound to albumin in blood; in vitro data show that ENG is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme [8]. The biological activity of ENG metabolites is unknown. The impact of ENG on liver functions has been studied by a number of investigators [11,15]. Whereas total bilirubin and serum GGT were reported to increase [11,15], serum levels of ALT and AST were found either to decrease [11] or to remain unchanged [15]. Unfortunately, many factors influence the level of GGT, so that increases are non–disease specific. An isolated rise in GGT may occur without liver disease, perhaps because of microsomal enzyme induction [24]. Some investigators concluded that there may be mild hepatocellular dysfunction associated with the use of Implanon®, which is possibly of no clinical significance to the healthy acceptor [15]. The overall findings of the present study conform to such a statement.

Implanon use for 2 years by Egyptian women does not seem to influence portal hemodynamics. Nonsignificant changes in serum levels of albumin, ALP, prothrombin time and concentration were noted after 2 years of insertion. Moreover, changes in serum levels of bilirubin, GGT, ALT

and AST are unlikely to be of clinical significance. It is hoped that this study could be regarded as an added piece of evidence fostering and substantiating the safety of Implanon® among women. This could pave the way for future studies focusing on its safety in women with compensated liver disease or mild hepatic dysfunction.

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