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A three-year evaluation of metabolic changes in Singaporean Norplant acceptors

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Abstract

In a longitudinal study involving 100 Singaporean women, the effect of Norplant[R] on metabolic function was evaluated. With respect to liver function, the results indicate possible hepatocellular dysfunction as evidenced by a significant rise in serum bilirubin and a significant fall in total proteins and globulin during the period under review.

As regards lipid metabolism, total triglycerides and total cholesterol still remained significantly decreased at the end of the three years. The LDL, which was significantly decreased in the first year, increased during the subsequent two years to its preinsertion value at the end of three years. The HDL-cholesterol levels continued to decrease in the second and third year after a significant increase in the first year. Despite this, the HDL cholesterol/total cholesterol–HDL cholesterol remained above 0.200. As we have not incorporated a simultaneous non-pill treated control group, the observed changes in lipoprotein lipids could be attributed to extraneous factors such as diet, exercise, or other environmental changes. Nevertheless, the findings at the end of three years, though speculative, still appear to indicate Norplant use to be not directly contributory to cardiovascular risk.

The use of Norplant was not associated with any significant effects on carbohydrate metabolism after three years of use.

Introduction

The relationship between the increased risk of arterial atherosclerosis complications and changes in serum lipids is now supported by considerable evidence [1,2]. The strong relationship between low levels of high density lipoproteins (HDL- cholesterol) and low HDL-cholesterol to total cholesterol–HDL cholesterol ratios and the subsequent development of cardiovascular accidents and myocardial infarction in both men and women is well documented in epidemiological studies [3,4]. In the past, much of this increased risk of developing atherosclerosis cardiovascular disease has been attributed to the estrogen component of the combined pill. It has now been

recognized that the progestogens play an important role in lowering HDL-cholesterol and possibly predisposing to cardiovascular disease [5–8].

Given the long-acting nature of the progestogen-only Norplant implant system, this study was designed to study the effect of Norplant implant on metabolic functions in a representative Southeast Asian population as part of the long-term surveillance of this relatively new contraceptive system.

Materials and methods

One hundred women were recruited for this study. These volunteers were healthy, non-smoking, non-alcohol drinking, and non-lactating Singaporean women who had chosen the Norplant system for contraception. Clinical assessment and blood sampling for the study were done prior to insertion of the implants and after 6, 12, 24 and 36 months of use. The subjects were used as their own controls. Blood samples were obtained from fasting subjects, from the antecubital vein contralateral to the arm in which the implants were inserted, at the same time of the day (0900–1100 hours) on each occasion with the subjects having rested for at least half an hour prior to venipuncture.

Glucose was estimated using the glucose oxidase method [9] while total proteins and globulins were estimated using the Biuret method [10]. For albumin, the Bromocresol Green Dye binding method was used [11]. Total bilirubin was estimated using simple photometry [12]. The modified Bessey–Lowry Brock method was used for alkaline phosphatase [13]. HDL-cholesterol was precipitated by magnesium phosphotungstate [14], cholesterol using the CHOP-PAP method [15,16] and triglycerides using enzymatic hydrolysis determinants [17] were determined by kit methods from Boehringer Mannheim. LDL-cholesterol was calculated using the equation [18]:

$$\text{LDL-cholesterol} = \text{Total cholesterol} - \left(\text{HDL-cholesterol} + \frac{\text{Triglycerides}}{2.19}\right) \text{mmol/L.}$$

Quality control in lipid assay was monitored by running two serum control pools commercially available (normal and high levels) in every assay. For cholesterol, coefficient of variation between assay at both normal (about 3 mmol/L) and high (about 8 mmol/L) was less than 2% while for triglycerides at the normal level (about 2 mmol/L) coefficient of variation was about 3% and at the high limit (about 8 mmol/L), about 5.5%. External quality control was assessed by an International External Quality Control Assessment Scheme (IEQAS) conducted by WHO Collaborating Centre for Research and Reference Services in Clinical Chemistry, Birmingham, United Kingdom.

To assess the significance of differences from mean values, the paired '*t*' test was used. Further comparisons were also made by observing percentage changes in mean postinsertion levels compared to preinsertion levels which were designated as 100%. In the case where the results were found to be skewed, the Wilcoxon signed rank test

of statistical significance using median distribution was used to assess the statistical significance of the changes observed.

Results

(i) Liver function

The most important changes were seen in the mean bilirubin levels. Mean bilirubin levels increased significantly by about 58% in the first year. They showed a slight but non-significant fall of 4.5% in the second year of use. The level increased further in the third year and remained significantly increased as compared to the preinsertion mean (Table 1, Figure 1). When the changes in serum bilirubin levels were subjected to the Wilcoxon signed rank test, the differences retained their highly significant levels, indicating that the difference was not due to the skewed distribution of mean values.

There was a statistically significant fall in total proteins and globulins over the three years. The albumin and alkaline phosphatase in general showed no significant changes during the three years of Norplant use (Table 1, Figure 1).

However, despite the changes seen, the mean levels of bilirubin, total protein and globulin remained within the normal clinical range for the local population. Moreover, it is important to note that no individual values fell outside the normal range.

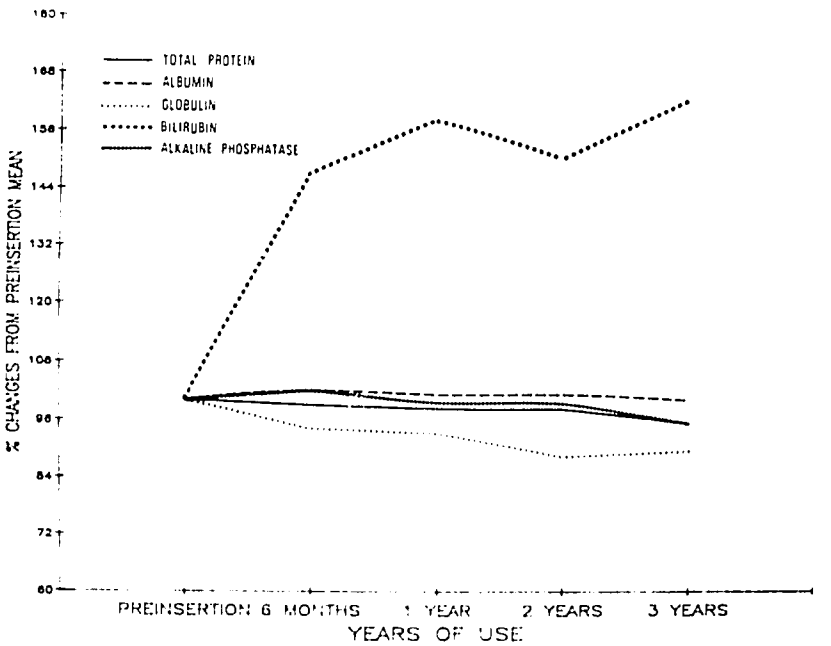

Figure 1 Changes in liver function in Norplant acceptors

Table 1 Biochemical changes in Singaporean Norplant acceptors: liver function tests

Parameters studied	*Preinsertion*	*After 6 months of use*	*After 1 year of use*	*After 2 years of use*	*After 3 years of use*
Total protein					
n	97	97	99	76	65
mean ± SD (g/dl)	7.24 ± 0.37	7.17 ± 0.44	7.08 ± 0.69	6.87 ± 0.43	6.87 ± 0.33
p value		NS	< 0.05	< 0.001	< 0.001
% difference from preinsertion mean	100	99	98	98	95
Albumin					
n	97	97	96	76	65
mean ± SD (g/dl)	4.22 ± 0.22	4.32 ± 0.27	4.27 ± 0.42	4.24 ± 0.24	4.20 ± 0.22
p value		< 0.05	< 0.05	NS	NS
% difference from preinsertion mean	100	102	101	101	100
Globulin					
n	97	97	96	76	65
mean ± SD (g/dl)	3.03 ± 0.35	2.85 ± 0.35	2.81 ± 0.45	2.63 ± 0.35	2.67 ± 0.38
p value		< 0.001	< 0.001	< 0.001	< 0.001
% difference from preinsertion mean	100	94	93	88	89
Bilirubin					
n	97	97	96	76	65
mean ± SD (mg/dl)	0.55 ± 0.19	0.81 ± 0.38	0.87 ± 0.31	0.85 ± 0.28	0.94 ± 0.31
p value		< 0.001	< 0.001	< 0.001	< 0.001
% difference from preinsertion mean	100	147	158	150	162
Alkaline phosphatase					
n	97	97	96	76	65
mean ± SD (iu/L)	61.1 ± 17.3	62.4 ± 16.8	60.3 ± 15.7	61.2 ± 14.7	57.2 ± 15.6
p value		NS	NS	NS	NS
% difference from preinsertion mean	100	102	99	99	95

(ii) Lipid metabolism

During the three years of Norplant use, there was a significant decrease in total triglycerides and total cholesterol. Both parameters remained significantly decreased as compared to preinsertion levels at the end of three years. The LDL-cholesterol was similarly significantly lower than its preinsertion value during the first two years. However, as a result of a progressive increase during the second and third year, the LDL-cholesterol was equivalent to its preinsertion mean at the end of three years. The HDL-cholesterol levels increased maximally during the first six months and remained significantly elevated after one year. During the second year, as a result of a

decrease, the HDL-cholesterol returned to its preinsertion mean. In the third year there was a further decrease and the HDL-cholesterol was significantly decreased as compared to its preinsertion mean at the end of three years (Table 2, Figure 2).

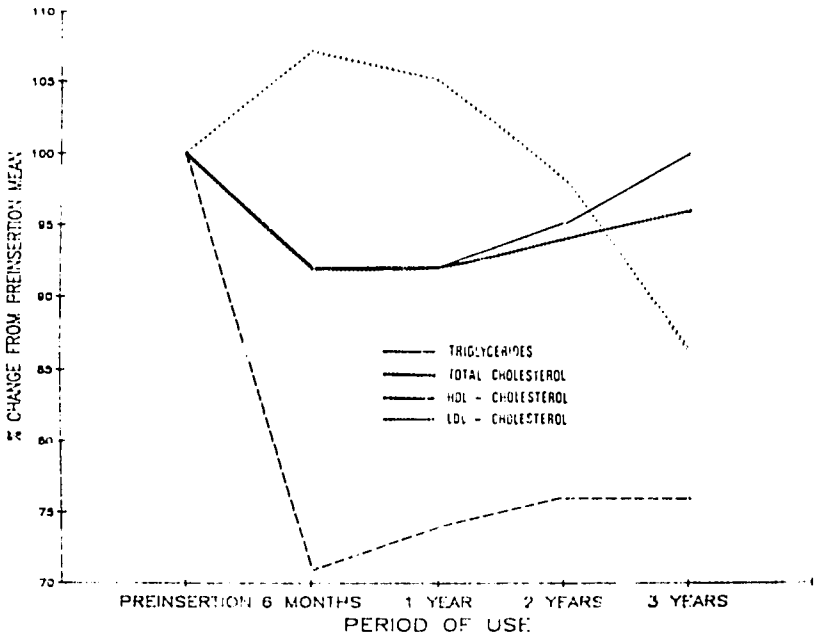

Figure 2 Changes in lipid metabolism in Norplant acceptors

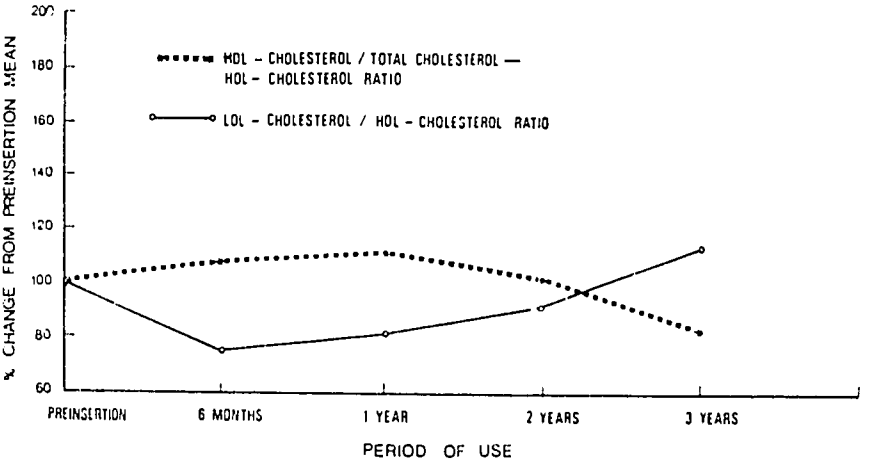

Figure 3 Changes in lipid ratios known to predict coronary heart disease risk in Norplant acceptors

Table 2 Biochemical changes in Singapore Norplant acceptors: lipid metabolism

Parameters studied	*Preinsertion*	*After 6 months of use*	*After 1 year of use*	*After 2 years of use*	*After 3 years of use*
Triglycerides					
n	97	97	96	76	65
mean ± SD (mmol/l)	1.21 ± 0.74	0.86 ± 0.46	0.89 ± 0.45	0.90 ± 0.52	0.81 ± 0.39
p value		< 0.001	< 0.001	< 0.001	< 0.001
% difference from preinsertion mean	100	71	74	76	76
Cholesterol					
n	97	97	96	76	65
mean ± SD (mmol/l)	5.05 ± 1.02	4.66 ± 0.81	4.64 ± 0.81	4.73 ± 0.83	4.73 ± 1.00
p value		< 0.001	< 0.001	< 0.001	< 0.001
% difference from preinsertion mean	100	92	92	94	96
HDL-cholesterol					
n	97	97	96	76	65
mean ± SD (mmol/l)	1.08 ± 0.34	1.16 ± 0.25	1.13 ± 0.24	1.08 ± 0.23	1.00 ± 0.22
p value		< 0.001	< 0.001	NS	< 0.01
% difference from preinsertion mean	100	107	105	98	86
LDL-cholesterol					
n	97	97	96	76	64
mean ± SD (mmol/l)	3.38 ± 0.99	3.10 ± 0.73	3.10 ± 0.72	3.25 ± 0.73	3.36 ± 0.87
p value		< 0.001	< 0.001	< 0.05	NS
% difference from preinsertion mean	100	92	92	95	100
HDL-cholesterol/total-cholesterol – HDL-cholesterol ratio					
n	97	97	96	76	64
mean ± SD	0.308 ± 0.164	0.331 ± 0.121	0.342 ± 0.111	0.311 ± 0.098	0.285 ± 0.090
p value		< 0.001	< 0.001	NS	< 0.05
% difference from preinsertion mean	100	107	111	101	83
LDL-cholesterol/HDL-cholesterol ratio					
n	97	97	96	76	64
mean ± SD	3.56 ± 1.73	2.67 ± 0.93	2.85 ± 0.90	3.17 ± 1.13	3.48 ± 1.12
p value		< 0.001	< 0.001	< 0.05	< 0.05
% difference from preinsertion mean	100	75	81	91	113

The HDL-cholesterol/total cholesterol–HDL-cholesterol ratio showed an encouraging and significant increase during the first year of use. It returned almost to its preinsertion value at the end of two years. There was a further decrease in the third

year and the ratio was thus significantly lower than its preinsertion value at the end of three years (Table 2, Figure 3). The LDL-cholesterol/HDL-cholesterol ratio, an even more pertinent ratio, showed a highly encouraging and significant decrease of 25% in the first six months. Thereafter it showed a progressive increase until it was significantly higher than the preinsertion mean at the end of the third year (Table 2, Figure 3).

(iii) Carbohydrate metabolism

Oral glucose tolerance tests using 50 gram loads were performed before insertion and subsequently annually after insertion. No clinically significant changes were observed during the three years of use (Table 3, Figure 4). When calculated on a paired basis, differences in the one hour level did reach statistical significance at the end of the first and second year. However, the absolute levels remained within the normal clinical range.

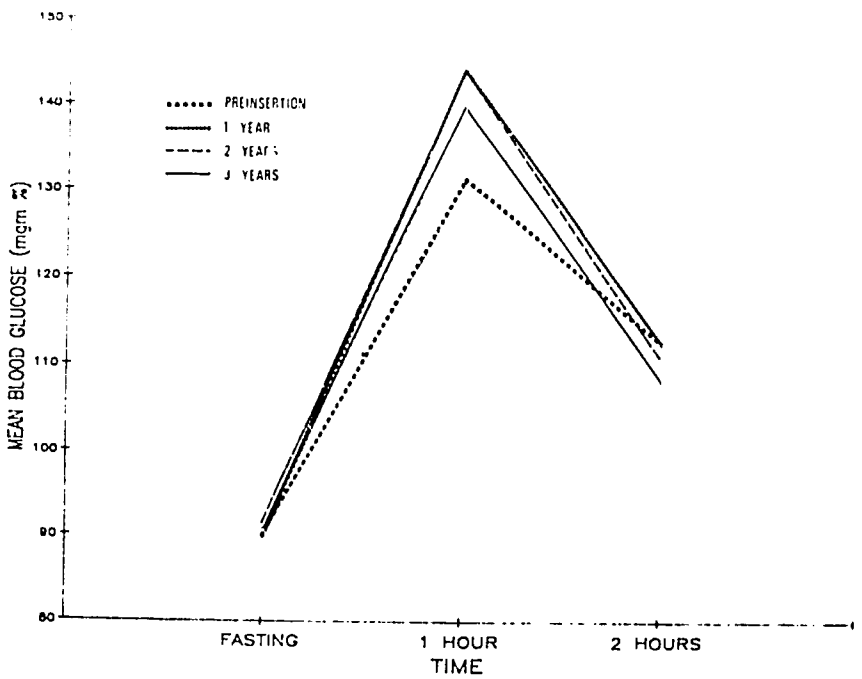

Figure 4 Changes in glucose tolerance in Norplant acceptors

Discussion

Most studies to date have shown no significant changes in liver function with Norplant use [19–21]. Shaaban *et al.* from Egypt [21] showed only a small increase in bilirubin, which reverted to normal by six months. In our study, we have seen a highly significant 58% increase in bilirubin during the first year of use [22]. After a small decrease in the second year, the mean bilirubin levels increased further and were still significantly raised as compared to preinsertion levels. Total protein and globulin were significantly decreased throughout the three years as compared to preinsertion levels. It thus seems that at the end of three years of Norplant use, there does appear to be some degree of liver dysfunction. However, despite the changes seen, it is reassuring to note that the mean levels of bilirubin, total protein and globulin remained within the normal clinical range for the population studied.

Table 3 Oral glucose tolerance test changes (mg/dl) in Singaporean Norplant acceptors

	Fasting	*1 hour*	*2 hours*
n = 97			
Glucose 0 year (preinsertion)	89.9 ± 9.9	131.3 ± 32.1	112.7 ± 27.6
n = 97			
Glucose 1 year after use	91.5 ± 9.8	144.0 ± 34.0	110.4 ± 28.2
p value	NS	< 0.001	NS
n = 76			
Glucose 2 years after use	89.1 ± 10.4	143.8 ± 35.5	112.1 ± 29.8
p value	NS	< 0.001	NS
n = 65			
Glucose 3 years after use	90.7 ± 15.9	139.7 ± 43.0	108.1 ± 32.7
p value	NS	NS	NS

The highly significant decrease in total triglycerides and total cholesterol seen in the three years is comparable with the results of other investigators [20,23–25]. Similarly, the LDL-cholesterol was seen to be significantly decreased during the first two years before reaching its preinsertion value at the end of three years. Our findings of elevated HDL-cholesterol in the first year with a return to almost preinsertion values in the second year and a significant decrease in the third year confirm the wide discrepancy in changes seen in other studies [20,23–25].

It is strongly believed that a high HDL-cholesterol/total-cholesterol–HDL-cholesterol ratio and a low LDL-cholesterol/HDL-cholesterol ratio is protective against cardiovascular complications [3,4]. In fact, a value below 0.200 for the former ratio indicates an increased risk of developing coronary heart disease or progression

of existing disease [26,27]. In this study, we have seen the HDL-cholesterol/total-cholesterol–HDL-cholesterol return to almost its preinsertion ratio at the end of two years after having a reassuring and significant increase in the first year [28]. It was further decreased significantly in the third year to 0.285. At all times the ratio was above 0.200, however. The LDL-cholesterol/HDL-cholesterol ratio had remained below its preinsertion value in the first two years. It then increased significantly and was 3.48 at the end of three years of Norplant use. It would thus appear that at least in Singaporean women, the effects of Norplant on lipid metabolism appear not to be directly contributory to cardiovascular risk for at least three years of use. Indeed, the results suggest that it may be a protective factor against cardiovascular complications in the first two years. We must concede, however, that in the absence of non-steroid treated controls in the study, the observed changes could be attributed to extraneous environmental effects.

The effects of Norplant on carbohydrate metabolism as reflected by changes in the oral glucose tolerance test at the end of three years are minimal and are unlikely to be of any clinical significance.

Conclusion

The results of the effect of Norplant implants on metabolic function in Singaporean acceptors emphasize the compelling need for long-term close surveillance of the Norplant system in different population subsets and for the entire five-year period of implant use among acceptors.

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Resumé

On a évalué dans une étude longitudinale portant sur 100 femmes singapouriennes les effets de Norplant sur la fonction métabolique. En ce qui concerne la fonction hépatique, les résultats indiquent des troubles hépatocellulaires possibles, mis en évidence par une élévation significative de la bilirubine sérique et une diminution significative des protéines totales et de la globuline pendant la période étudiée.

Quant au métabolisme des lipides, les totaux des triglycérides et du cholestérol étaient encore abaissés de façon significative au terme de la période de trois ans. Les lipoprotéines légères, qui avaient considérablement diminué pendant la première année, sont remontées pendant les deux années suivantes pour retrouver, à la fin de la troisième année, le niveau qu'elles avaient avant l'insertion. Les niveaux de cholestérol HDL (lipoprotéines lourdes) ont continué à baisser pendant les deuxième et troisième années après une élévation significative pendant le première. Malgré cela, le rapport cholestérol HDL/Cholestérol total – cholestérol HDL est resté supérieur à 0.200. N'ayant pas inclus un groupe témoin sans pillule traité simultanément, les changements observés concernant les lipides lipoprotéiniques

pourraient être attribués à des facteurs extérieurs tels que le régime alimentaire, l'activité physique ou d'autres facteurs d'environnement. Néanmoins, bien que de caractère conjectural, les constatations résultant de ces trois ans d'étude semblent encore indiquer que l'utilisation de Norplant ne contribue pas directement au risque cardiovasculaire. L'utilisation de Norplant n'a été liée à aucun effet significatif sur le métabolisme des hydrates de carbone au bout de trois ans.

Resumen

En un estudio longitudinal sobre 100 mujeres de Singapur se evaluaron los efectos de Norplant sobre la función metabólica. En lo que respecta a la función hepática, los resultados indican posibles trastornos hepatocelulares, señalados por una elevación significativa de la bilirrubina sérica y una disminución significativa de las proteínas totales y de la globulina durante el período estudiado.

En lo que respecta al metabolismo de los lípidos, los totales de triglicéridos y de colesterol continuaban significativamente disminuidos al cabo del período de tres años. Las lipoproteínas ligeras, que habían disminuido considerablement durante el primer año, aumentaron durante los dos años siguientes, alcanzando, al final del tercer año, el nivel que habían señalado antes de la inserción. Los niveles de colesterol HDL (lipoproteínas pesadas) continuaron disminuyendo en el segundo y tercer año después de un aumento significativo durante el primer año. A pesar de ello, la relación colesterol HDL/colesterol total – colesterol HDL continuó siendo superior a 0.200. Dado que no se incluyó un grupo control sin píldora tratado simultáneamente, los cambios observados respecto de los lípidos lipoproteínicos podrían atribuirse a factores exteriores, tales como el régimen alimentario, la actividad física u otros factores ambientales. No obstante, a pesar de su carácter conjetural, los resultados de este estudio de tres años parecen indicar que el uso de Norplant no contribuye directamente al riesgo cardiovascular.

El uso de Norplant no estuvo asociado con ningún efecto significativo sobre el metabolismo de los hidratos de carbono al cabo de tres años.