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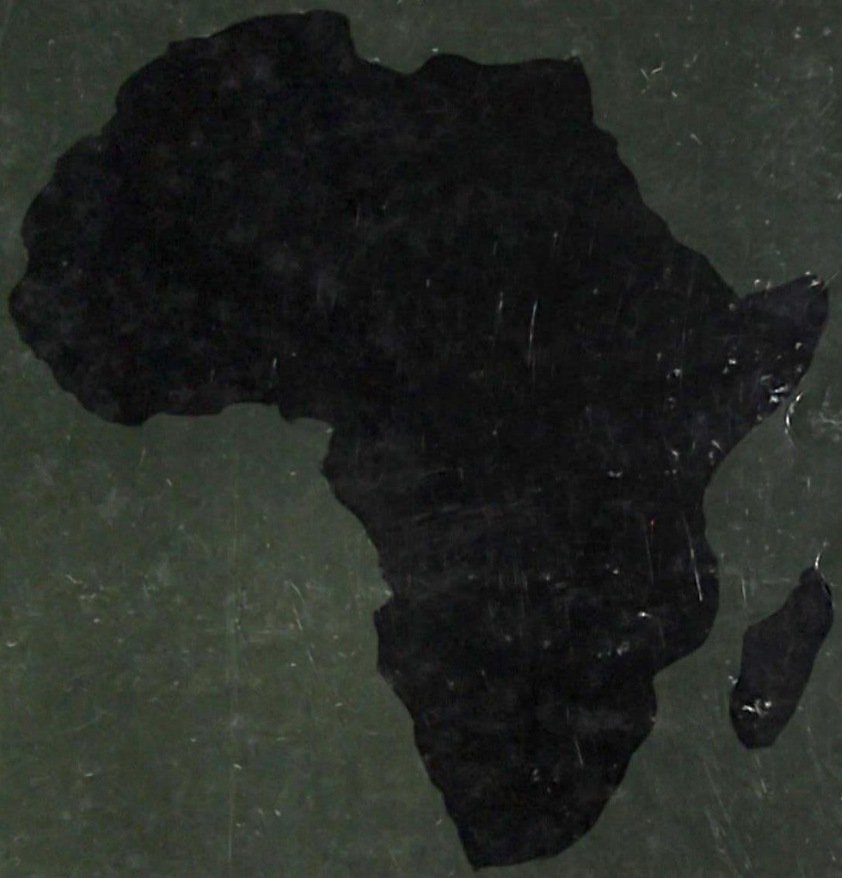

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Prolongation of electrocardiographic intervals in women on Norplant® contraceptive: what dangers?

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Summary

This study used electrocardiography to determine any inherent cardiovascular dangers with the use of Norplant®, an implant contraceptive among Nigerian females using the device. As part of a major study of metabolic, physical and cardiovascular changes consequent upon the use of Norplant® implant contraceptive, all subjects underwent serial electrocardiograms at pre-insertion, 3, 6, and 12 months of use. Given the observed prolongation of electrocardiographic intervals, the ECG of all the study subjects were secondarily analysed for QT and corrected QT (QTc) dispersions. QT intervals was measured from the ECG of each of the 21 subjects who were available at pre-insertion and 12 months post-insertion; from the onset of QRS to the end of T wave or nadir of the curve between T and U waves as the case may be. Corrected QT intervals was calculated by determining the RR interval and using the Bazett's formula. The difference of the lowest and highest QT intervals and QTc intervals over the 12 leads determined their respective dispersions. These were then analysed. The subjects whose ages ranged from 25-45 years weighed between 43 and 87.2 kg. The mean QT dispersion increased with time but did not reach statistical significance by the twelve month visit (ANOVA – QT dispersion 0 month vs12 months: F=0.98, p=0.48). However the mean QTc dispersion increased and reached statistical significance by 12 months (0 month vs 12 months: F=5.49, p=0.006). QT and QTc dispersion increases are known to predict cardiovascular death in health and disease. With the use of this device, these indices rose gradually with time reaching statistical significance by 12 months only with the QTc dispersion. The use of this device may increase the tendency to cardiovascular morbidity and mortality. Whether this translates into real risk will require a long-term study to determine. For now, application of the device on patients with cardiovascular disease or tendency thereof should still attract caution.

Keywords: *Prolongation, QTC interval, electrocardiography, norplant Nigerian women*

Résumé

Cette étude utilisée l'électrocardiographie pour déterminer les dangers cardiovasculaires associés a l'usage du Norplant®, un preservatif implanté aux femmes Nigériane. Les changements physiques et cardiovasculaires conséquence de l'usage du Norplant étaient évalués par une série d'électrogrammes a l'admission , au rendez-vous a 3,6 et 12 mois. L'age des sujects varait de 25-455 ans et un corps corporelle variable de 43-87.2 Kg. La moyenne de dispersion de l'intervalle QT augmentait avec le temps. Les intervalles étaient prolongés et le ECG était analysé. Les intervalles QT et QRS a la fin de l'onde T étaient mesurées a 21 sujects a l'admission et a 12 mois après l'insertion du NorplantR.. les intervalles QR corrigés étaient calculés pour déterminer l'intervalle RR utilisant la formule de Bazett's. la différence entre le plus haut et le plus bas intervalle QT et QTc sur les 12 conduites determinaient les dispersions respective. La moyenne de dispersion du QT augmentait avec le temps mais n'était pas statistiquement significatif au 12 mois de visite (F=0.98; *P*=0.48). Cependant la moyenne de dispersion du QTC augmentait et était statistiquement significative au 12 mois de visite(F=5.41; *P*=0.006). L'augmentation de intervalles de dispersion QT et QTc sont connu comme predicateur de la mort due a la santé cardiovasculaire. L'emploi du Norplant peut augmenter la tendence de la souffrance et la mortalite cardoivasculaire car ces indices augemntaient graduellement avec le temps seule pour la dispersion de l'intervalle QTc.. ceci se traduisant en un risque reel demande une étude prolongée sur une large population pour des précautions éventuelles.

Introduction

Use of oral contraceptives is known to be associated with a risk of hypertension [1] and other cardiovascular diseases like myocardial infarction [2]. Literature is scanty on what Norplant® (levonorgestrel sub-dermal implants) can do to cardiovascular morbidity. This may be due to its relative novelty. We had noted in a study on electrocadiographic (ECG) changes in women on Norplant® that there was a trend towards increase in ECG intervals [3]. Even though still essentially within normal limits, the increase was progressive and statistically significant. There was therefore the need to take a second look at these ECGs to see if this portends additional cardiovascular risks.

Methodology

As part of a major study which had approval of our institution's ethical committee, and focusing on metabolic, physical and cardiovascular changes occasioned by the use of Norplant® implant contraceptives, each subject had ECG done pre-insertion, and at 3 months, 6 months and 12 months post-insertion. One of us (BNO) read all the ECGs. With the finding of prolongation of intervals on ECG, the ECGs of the 27 subjects were re-evaluated with a view to determining the QT dispersion and corrected QT dispersion. These are known to predict cardiovascular morbidity and mortality [4,5,6]. Twenty-one out of the 27 subjects were available at 12 months post insertion for repeat ECG. They form the subject of this paper. This was to ensure that we compared the same subjects, so

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that they could serve as their own controls. QT intervals in the 12 leads of the ECG of these 21 subjects were measured on the surface 12 lead resting ECG (25/mm speed) using a three channel machine – Fukuda Denshi ECG/Phono System Model FD31P, made in Tokyo, Japan, by measuring from the onset of the QRS to the end of the T wave (return to T/P baseline); or to the nadir of the curve between T and U waves, where U wave is present. The RR interval was also read off on each ECG. A magnifying glass was used to improve vision and determine accurately, points of interest as stated above. The QT dispersion was taken as the difference between the lowest and highest QT intervals over the 12 leads. Corrected QT interval (QTc), was determined using the Bazett's formula $QTc = QT/RR^{1/2}$ and QTc dispersion determined as for QT dispersion. These are standard methods of determination of these values [7].

The data were entered into a computer and analysed using a statistical SPSS Software. Analysis of variance (ANOVA) and paired t-test were used to compare the data of 3, 6 and 12 months post-insertion values with that at pre-insertion. A P value of <0.05 was considered significant.

Results

Out of the 27 subjects who presented at pre-insertion, only 21 were available at 12 months for review. The 21 subjects had their ECG data subjected to ANOVA and paired t-test; and form the subject of this report. The study lasted from August 1997 to November 1998. The subjects underwent physical and baseline laboratory investigations to exclude cardiovascular diseases. Their ages ranged from 25 to 38 years with a mean of 32.4±3.98. The mean weight at pre-insertion and at the 3, 6, and 12 months follow-up visits were 63.63±10.43, 60.59±10.07, 64.08±12.15 and 62.29±12.25 kilograms respectively. The blood pressures at pre-insertion and at the 3, 6 and 12 visits were- mean systolic 111.1±9.9, 107.7±9.3, 110.8±9.5, 109.5±10.0 and mean diastolic 74.7±7.9, 73.1±11.0, 74.6±7.7, 73.5±7.4 respectively. The differences were insignificant.

Of the 21 subjects who had ECG pre- and 12 months post-insertion, 10 were available at 3 months and 11 at 6 months post-insertion. Table I shows the mean QT dispersion and corrected QT dispersion of the subjects' ECGs.

Table 1: Changes in QT and QTc dispersions among Norplant users.

Time	Nos.	QT dispersion (Sec.)	Qtc dispersion (Sec.)
Pre-insertion (0 month)	21	0.036± 0.007	0.032± 0.007
Post-insertion (3 months)	10	0.024± 0.005	0.020± 0.006
Post-insertion (6 months)	11	0.047± 0.007	0.041± 0.006
Post-insertion (12 months)	21	0.055± 0.005	0.058± 0.005

Values are mean ± S.E. of mean
QT dispersion 0 Months Vs QT 12 Months (t 1.805, p 0.086) - Not significant
QTc dispersion 0 Months Vs QT 12 Months (t-2.589,p-0.018) - Significant

There was no statistically significant difference for QT dispersion between pre-insertion and 3 months visit (F= 0.145, p=0.89), pre-insertion and 6 months visit (F=0.145, P 0.87), and pre-insertion and 12 months visit (F= 0.98P 0.43). For QTc dispersion, there was also no statistically significant difference between pre-insertion and 3 months visit (F=0.33, P 0.58), and pre-insertion and the 6 months visit (F= 1.612, P 0.27). By the 12th month however the QTc dispersion had increased to a statistically significant extent (F=5.49, P =0.006).

Using the paired t-test to ensure that comparison involved same patients, significant difference between means was recorded only for QTc dispersion comparing pre-insertion and 12 months visit values (t=2.589, P=0.018). The between group differences other pairs did not reach statistical significance.

Discussion

Prolongation of QT interval is known to predict cardiovascular death in apparently healthy individuals [8]. It is a measure of regional variation in ventricular repolarisation and its increase potentiates arrhythmias [9]. Our study has shown QT dispersion increasing gradually but not to a statistically significant level by 12 months post Norplantâ insertion (see Table 1). It is noteworthy to state that there was no increase in frequency of arrhythmias. Only 2 subjects had arrhythmias on 12 lead resting ECG, one atrial and the other ventricular ectopics. These ectopic activities were rather occasional. The subject with atrial ectopics pre-insertion also had it at 12 months, and there was no increase in frequency. The one with ventricular ectopic pre-insertion did not have it by 12 months. QT dispersion is said to probably be generated by structural left ventricular abnormalities (fibrosis, deposition) or physiological abnormalities at myocyte level (ischaemia) [10] Which of these is responsible for the prolongation in this cohort can at best be conjectural. We have not necessarily followed up another cohort of adult females not on any form of contraception to see if these values changed with time. This was because we felt that the subjects should serve as their own controls. Even though there is no agreement on the effect of heart rate on QT dispersion [10], we went on to correct QT dispersion for varying heart rates using the Bazett's formula (QTc). Significant increase was only recognised at 12 months by ANOVA (F=5.49, P=0.006).

As this study tends to suggest that use of Norplant® with time could predispose users to cardiovascular morbidity, it would be necessary to follow-up subjects for longer. This will enable a clearer picture to emerge, and tell whether users of this contraceptive actually suffer from such cardiac morbidity. As the mean systolic and diastolic blood pressures did not rise over the period [3] and none of the subjects developed left ventricular hypertrophy (evident on ECG), these changes could easily be attributed to the implant. We are now in the process of studying subjects on Norplant® for ECG changes following removal. This, we believe, will enable us know how much of these changes are to be attributed to Norplant®.

It is necessary to end this treatise with a note of caution. Discouraging the use of this device in the face of this evidence may be a rather hasty step. The risk if substantiated with time should be viewed in the background of its efficacy as a contraceptive measure. Like Stadel showed with oral pills

[11], the real number of users who actually develop cardiac disease despite the increased risk may turn out to be small. If this turns out to be so, then only young women in their active reproductive years with no cardiovascular risk factor should be given a chance on this device.

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