Gestoden: An Innovative Progestogen

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Introduction

Case reports and epidemiological retrospective case control studies suggested an increased cardiovascular risk associated with the oral contraceptive pill (OC) soon after its introduction. These findings prompted the initiation of three large epidemiological prospective cohort studies: in the United Kingdom those of the Royal College of General Practitioners (RCGP) and the Oxford Family Planning Association and in the United States the Walnut Creek Contraceptive Study. All started in 1968, at a time when older high-dose preparations were those commonly used [1, 2, 3].

Only one of these studies, that of the RCGP found a statistically significant increase in cardiovascular mortality due to myocardial infarction and subarachnoid haemorrhage in two subgroups of women, those over 45 years of age and those older than 35 who smoke cigarettes. It probably was this finding on myocardial infarction that prompted the subsequent publications on the pill and HDL-cholesterol which assumed an atherosclerotic aetiology.

Were the deaths in the RCGP study due to coronary atherosclerosis? If indeed atherosclerosis was the cause of the significantly increased mortality, there should have been a time lag between the start of pill use and the increase in mortality. Furthermore, there should be a significant association between duration of pill use and mortality rate, considering the gradual development of atherosclerosis over many years. Neither is evident in the RCGP study. The remaining plausible explanation for a myocardial risk in certain subgroups of women taking the pill therefore would be that of a thromboembolic event.

This assumption is further supported by a notable absence in literature of a significantly increased incidence of angina pectoris, the clinical manifestation of coronary atherosclerosis, among OC users. Moreover, a study among 53 women taking the pill and suffering from angiographically confirmed myocardial infarction showed that 66% of them did not show any atherosclerotic changes on coronary angiography [4]. This confirms the finding of case reports and post-mortem examinations suggesting that myocardial infarction attributable to current OC use is more likely to be thrombotic than arteriosclerotic in origin [4, 5], as outlined in a previous review [6].

A more recent analysis of the Oxford Family Planning Association cohort study on pill users revealed that the association with venous thromboembolism is limited to current users, unrelated to duration of use, and lower with pills containing less oestrogen (<50 μg) [7]. The association with non-haemorrhagic
stroke was not significant, and the association with thromboembolic stroke was
significant only for pills with a higher oestrogen dose (\( \geq 50 \mu g \)) and, again, limited
to current users and unrelated to duration of use [8].

A different, more recent, large prospective study confirmed an increased as­
association with thromboembolism in pill users but no increased risk of stroke or
myocardial infarction [9, 10]. The authors speculate that this discrepancy with
older findings may be because their study population mainly used the modern,
lower dose pills which are commonly used today. Apart from these thromboem­
bolic events an increased association of pill use with hypertension was recently
confirmed again [11].

One can conclude from these recent epidemiological studies that the aetiology
of pill-associated thromboembolic events or hypertension can best be explained
by pill-induced adverse changes of the coagulation and fibrinolytic systems and
of the renin-angiotensin-aldosterone (RAA) mechanism. The synthetic ethinyles­
tradiol (EE) most commonly used in OCs has a much stronger effect on liver me­
tabolism than do natural oestrogens, thereby inducing greater metabolic and hae­
mostatic changes [12, 13]. Such oestrogen-sensitive changes are found regarding
SHBG (sex hormone binding globulin); plasma lipids and lipoproteins, e.g. in­
crease of high-density lipoprotein (HDL) cholesterol and triglycerides; and ad­
verse interference with coagulation and fibrinolytic factors and with the RAA sys­

tem. The extent of SHBG increase induced by a pill formulation can be used as
an indicator of its inherent oestrogenicity [14, 15].

EE-induced changes of lipids and lipoproteins, e.g. an increase of HDL-cho­
esterol, are probably clinically rather irrelevant as there is no evidence so far of
pill-associated arteriosclerosis or coronary sclerosis. Clinically more relevant ap-

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Table 1. Non-progestogenic effects of synthetic progestogens: the pregnan group

<table>
<thead>
<tr>
<th>Progestational agent</th>
<th>Transformation dose (mg)</th>
<th>Comparative effect/action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oestrogenic</td>
</tr>
<tr>
<td>Progesterone</td>
<td>200 IM</td>
<td>(—)</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>120</td>
<td>(—)</td>
</tr>
<tr>
<td>acetate</td>
<td></td>
<td>(+)^a</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>35</td>
<td>(—)</td>
</tr>
<tr>
<td>Chlormadinone acetate</td>
<td>30</td>
<td>(—)</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>20</td>
<td>(—)</td>
</tr>
</tbody>
</table>

ND, no data.

^a Not in the classical tests; only in the Foetus.