This article reviews the impact of obesity on hormonal contraceptives and hormone replacement therapy (HRT) at the climacteric, with emphasis on efficacy and adverse effects in relation to arterial and venous thrombosis, myocardial infarction and stroke. The association, whether causal or otherwise, between obesity, weight gain, hormonal contraception and HRT is discussed.

Keywords efficacy / hormonal contraceptives / hormone replacement therapy / obesity / weight gain
Introduction

Obesity is a major public health concern in the western world. In England and Wales, more than two-thirds of women and half of men are overweight (over 25 kg/m²) or obese (over 30 kg/m²) according to standard definitions of body mass index (BMI).

Does higher body weight affect the efficacy of hormonal contraceptives?

It has been suggested that higher body weight could enhance the metabolism of oral contraceptives and result in insufficient serum levels with suboptimal contraceptive efficacy, but does the available evidence support this claim?

In an uncontrolled study, Sparrow found no increase in contraceptive failure in overweight women taking oral contraceptives. A cohort study by Vessey of 17,032 women taking combined oral contraceptives and progestogen-only pills did not show statistical evidence of increased risk of accidental pregnancy in obese women. This study controlled for age and parity, but may have been insufficiently powered to confirm a suggested increase in the risk of accidental pregnancy. A retrospective cohort analysis demonstrated a significantly elevated risk of failure (relative risk [RR] 1.6, 95% CI 1.1–2.4) in women with a body weight over 70.5 kg compared with women of a lower weight. In women weighing over 90 kg taking under 35 μg ethinylestradiol pills, the relative risk was 4.5 compared with a relative risk of 2.6 in users taking more than 50 μg ethinylestradiol pills. This study controlled for parity, race, religion and menstrual cycle, but was retrospective and did not take into account pill compliance, which may have contributed to pill failure. In another small study of users of 20 μg combined oral contraceptives, women with a BMI over 25 showed reduced ovarian follicle suppression (RR 1.6, 95% CI 1–2.7) with a seven-day pill-free interval compared with women of normal weight; however, the study did not investigate failure rates due to inadequate ovarian suppression. A prospective case control study showed that in consistent pill users with a BMI over 32, the risk of pregnancy was doubled i.e. an additional 2–4 pregnancies/100 woman-years of oral contraceptive use in overweight women.

For optimal contraceptive efficacy, the Clinical Effectiveness Unit (CEU) of the Faculty of Family Planning and Reproductive Health Care of the RCOG recommends two progestogen-only pills daily, usually at the same time, in women over 70 kg. In a recent questionnaire survey, 71% of experts in the UK recommended doubling the dose of progestogen-only pills in women weighing over 70 kg. More research is warranted in this field. There is no evidence to support the daily use of two progestogen-only pills in women over the age of 45 years. Due to the anovulatory effects of Cerazette® (Organon, Cambridge, Cambs), two tablets daily in women weighing more than 70 kg is unnecessary.

Evra® (Janssen-Cilag, Saunderton, Bucks), the transdermal estrogen and progestogen contraceptive patch, appears to be less effective in women over 90 kg compared with women with lower body weights in that one third of the 15 overweight women fell pregnant. The Evra summary of product characteristics advises caution in overweight women. Further research is required to clarify the relationship between body weight and efficacy of contraceptive patches. High body weight has been associated with an increasing probability of luteal activity and higher failure rate in vaginal ring users. In the World Health Organization (WHO) combined contraceptive vaginal ring study, the one-year accidental pregnancy rate was 1.8/100 in women under 49 kg and 8.2/100 in women over 70 kg. At the time of writing the new vaginal ring (NuvaRing) was not available in the UK.

As the serum concentrations with Depo-Provera (Pharmacia, Walton-on-the-Hill, Surrey) injectable contraception are above threshold levels for ovulation suppression, body weight does not impact on the efficacy. There are minor differences in the pharmacokinetics of medroxyprogesterone acetate (MPA) in normal, obese (BMI 29–38) and very obese (BMI over 38) women. Norplant® (Hoechst Marion Roussel, Guildford, Surrey) contraceptive implants were withdrawn from the UK market in 1999, but are available elsewhere. In Norplant users the pregnancy rates increased significantly with weight; the cumulative seven-year failure rate among women weighing 70 kg or more using the hard tubing formulation was up to five fold. Reports suggest that the new, softer version of Norplant is more effective in all women. After five years of use, body weight is the most important variable affecting measured levonorgestrel levels, the levels being lower in heavy women, who face a higher risk of pregnancy compared with lean women. Both the manufacturer and the British National Formulary (BNF) warn that Implanon® (Organon, Cambridge, Cambs) may not provide effective contraception during the third year of use in overweight or obese women, with a comment that earlier replacement should be considered. However, this caution is not justified, as the serum estradiol levels in the third year in overweight women are still well above threshold levels for ovulation suppression. There is a paucity of data.
on efficacy of etonogestrel implants in overweight women (Table 1).

Is there a causal relationship between hormonal contraception and weight gain?

For women choosing hormonal contraceptive methods, fear of weight gain is a real issue. Pill compliance can be dependent on the level of concern women have about perceived or actual weight gain. Rosenberg et al. showed that the relative risk of discontinuing a pill due to weight gain was 1.4. Combined oral contraceptive associated weight gain can be related to stimulation of the renin-angiotensin mechanism by estrogens and fluid retention. Estrogens can also be associated with increased subcutaneous fat, particularly in the breasts, hips and thighs. Progestogens are likely to increase appetite due to anabolic properties.

Gallo et al. found no large effect on weight from three randomised, placebo-controlled trials. However, failure to report on allocation concealment, early discontinuations, loss to follow-up, or exclusion from trials after randomisation raises the question of bias. Clinical evidence does not support a causal association between combination skin patches and weight gain, but studies are required to address this question. No clinically demonstrable increase in body weight was noted in the combined contraceptive vaginal ring (norethindrone and ethinylestradiol) users. The study failed to report on loss to follow-up, blinding, allocation concealment and randomisation. There is no indication to weigh women when prescribing combination contraceptives; however, in clinical practice, weighing women for opportunistic advice and reassurance is likely to be helpful.

Preliminary data on Yasmin® (Schering Health, Burgess Hill, West Sussex), an ethinylestradiol with drospirenone combined oral contraceptive, indicate weight loss of statistical significance compared with pills with ethinylestradiol and levonorgestrel. The progestogen drospirenone (antimineralocorticoid) in Yasmin may counteract the oedema producing effect of estrogens, initiate diuresis and diminish sodium and water retention. Body adiposity was reduced when non-obese polycystic ovarian syndrome sufferers on flutamide/metformin were switched from gestodene-containing combined oral contraceptives to Yasmin (a mean reduction in total and abdominal fat of 0.8 kg and 0.5 kg respectively).

Many women associate Depo-Provera with weight gain. This is believed to be due to the appetite stimulant effect of this progestogen and altered tryptophan metabolism. Conflicting evidence exists in that some studies refute a causal relationship between Depo-Provera use and weight gain and others demonstrate weight gain. A retrospective study of Depo-Provera and copper intrauterine device users observed statistically significant weight change in both cohorts of women at the end of five years, with a marginally higher degree of weight gain (4.3 kg) in Depo-Provera users compared with IUD users (1.8 kg). Baseline BMI is a good predictor of weight gain with Depo-Provera use; overweight adolescent girls have significant weight gain during the first year of Depo-Provera use compared with combined oral contraceptive users ($P = 0.0005$) but, due to exclusion of women who may have discontinued use before one year, bias is likely.

Perceived weight gain is a frequently reported adverse effect in implant users and a gradual mean increase in body weight over time amounting to 1.5–2% per year is observed with Norplant and Implanon contraceptive implant systems. About 60% of women gain 1 kg by two years and 37% gain 3 kg. In a retrospective study of young women using implants, an increase in BMI of 1.3 ($P = 0.03$) was noted and 42% of implants were removed due to weight gain. It has been suggested that women using a levonorgestrel intrauterine system may experience weight gain; however, clinical evidence does not support these claims. In a randomised study, weight gain among levonorgestrel intrauterine system users and copper intrauterine device users was similar (0.49 kg/year); however, users of a levonorgestrel intrauterine system are more likely to cite weight gain as their reason for discontinuation.

### Table 1

<table>
<thead>
<tr>
<th>Type of contraception</th>
<th>Contraceptive efficacy</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional POP in women &gt;70 kg</td>
<td>&gt;45 years – no impact</td>
<td>1 POP daily as per licence</td>
</tr>
<tr>
<td>Cerazette® (new POP)</td>
<td>&lt;45 years reduced efficacy</td>
<td>2 POPs daily</td>
</tr>
<tr>
<td>Euthina® in women &gt;90 kg</td>
<td>Limited data</td>
<td>1 daily</td>
</tr>
<tr>
<td>Depo-Provera®</td>
<td>Limited data, efficacy may be reduced</td>
<td>Additional contraception or alternative method</td>
</tr>
<tr>
<td>Norplant®</td>
<td>No impact</td>
<td>Stick to injections every 89 days as per licence</td>
</tr>
<tr>
<td>Implanon®</td>
<td>Efficacy after 5 years reduced with Norplant</td>
<td>Replace Norplant at 5 years in overweight women</td>
</tr>
<tr>
<td>Levonorgestrel IUS</td>
<td>No impact</td>
<td>Manufacturer advise caution with Implanon in over-weight women but caution unjustified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No change. Further data required</td>
</tr>
</tbody>
</table>

*With the combined oral contraceptive, preliminary data suggest the need for additional contraception in women weighing over 86 kg. Further work is required in this area.

BNF = British National Formulary IUS = intrauterine system POP = progestogen-only pill
**Bleeding irregularities**

Bleeding patterns in progestogen-only pill users are not known to be affected by BMI. The slow decline in blood levels of progestogen in obese Depo-Provera users has not been directly linked to bleeding problems. However, a retrospective study of Depo-Provera users showed a lower incidence of bleeding problems in overweight women with a BMI over 30 (6%), compared with women with a BMI under 25 (13%). High BMI also appears to offer protection against Depo-Provera related bone mineral density loss over two years.

**Venous thromboembolism**

Obesity is an independent risk factor for venous thromboembolism. The association between combined oral contraceptives and venous thromboembolism has been known since the 1960s, but the absolute risk attributable to combined oral contraceptive usage is small (15–25/100 000 users). The pooled relative risk of venous thromboembolism for combined oral contraceptives containing desogestrel and gestodene versus levonorgestrel in a recent meta-analysis was 1.7; a differential increase could not be explained by potential bias. Interim data from a large non-interventional comparative cohort study of different combined oral contraceptives indicates a four-fold risk of venous thromboembolism in combined oral contraceptive users compared with non users. There was no significant difference between different progestogen formulations, including Yasmin, and this may be explained by the fact that women with predisposing risk factors for venous thromboembolism were not excluded. In a case controlled study from The Netherlands, a BMI more than 30 doubled the risk of venous thromboembolism (adjusted for age and coagulation factor levels) compared with non users of normal weight. In a Danish study of combined oral contraceptive users with BMIs of 26–30 and more than 31, the adjusted odds ratio of venous thromboembolism was 1.9 (95% CI=1.5–2.5; \( P<0.01 \)) and 5.1 (95% CI=3.8–6.9; \( P<0.001 \)), respectively (Table 2). The odds ratio was adjusted against confounders of age, year of use, smoking disturbances, coagulation disturbances and family history. It is clear that the absolute risk attributable to combined oral contraceptive use increases in overweight women. There is no evidence of increase in venous thromboembolism with progestogen contraceptive hormones.

The CEU of the Faculty of Family Planning and Reproductive Health Care advise caution and informed discussion on the risk of venous thromboembolism in obese women who request a combined oral contraceptive pill. The BNF recommends that women with a BMI over 39 should not use a combined oral contraceptive. Obesity is categorised under Class 2 prescribing of combined oral contraceptives in WHO Medical Eligibility Criteria, 2004. It seems sensible and safe to avoid prescribing a combined oral contraceptive to women with a BMI over 35 when suitable safer alternative contraceptive choices like the Mirena® (Schering Health, Burgess Hill, West Sussex) intrauterine system, Implanon and progestogen-only pills are available. To date, no studies have examined whether avoiding the first pass metabolism in the liver with Evra® and NuvaRing® (Organon; NuvaRing currently unavailable in the UK) is beneficial in terms of risk of venous thromboembolism.

**Arterial disease**

Obesity is an independent risk factor for arterial disease and is associated with worsening of the cardiovascular disease risk profile. Healthy young women with no known pre-existing risk factors (i.e. diabetes, hypertension, obesity) are at little, if any, risk of myocardial infarction from combined oral contraceptives. A statistically significant benefit in terms of reduced risk of myocardial infarction is associated with the use of desogestrel and gestodene combined oral contraceptives, but this was not studied in relation to obesity. The odds ratio for myocardial infarction was 2 for the use of any combined oral contraceptive, 2.5 for levonorgestrel pill users and 1.3 for desogestrel and gestodene users; only five controls and two combined oral contraceptive users in this study had a BMI over 27.3.

The WHO multicentre studies of oral contraceptives and ischaemic stroke observed a pooled odds ratio in combined oral contraceptive users of 0.66 compared with 0.95 in those who had never used the pill. In Petitti et al. crude odds ratios for ischaemic stroke were elevated in women with a high BMI (RR 4.9; 95% CI 2.6–9.1) compared with women of normal weight. The WHO multicentre observational studies suggest a small increase in risk of subarachnoid haemorrhage attributable to combined oral contraceptive use, but obesity per se with usage of combined oral contraceptives does not increase the risk further. More studies are required to clarify the risk of stroke among combined oral contraceptive users.

<table>
<thead>
<tr>
<th>Study</th>
<th>BMI</th>
<th>Increase in risk of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdolahi et al.</td>
<td>&gt;30</td>
<td>2</td>
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<tr>
<td>Lidgaard and</td>
<td>&gt;30</td>
<td>5</td>
</tr>
<tr>
<td>Erdstrom</td>
<td>&gt;35</td>
<td>4</td>
</tr>
<tr>
<td>Farmer et al.</td>
<td>&gt;30–35</td>
<td>5</td>
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</table>

VTE = venous thromboembolism

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Body weight changes and HRT
BMI appears to increase linearly as a function of age and the menopausal transition does not have any appreciable effect on this rate of gain. Climacteric hormonal changes are associated with truncal and central android fat distribution. Physical activity and ethnicity are powerful predictors of BMI during the menopausal transition. It has been suggested that having 106 cm or more of visceral adipose tissue is associated with an elevated risk of coronary artery disease and that women with 163 cm or more have an even greater risk.

Many women decline HRT due to fear of weight gain and preoccupation with body image. Norman et al.\textsuperscript{31} studied the effect of continuous combined HRT and unopposed estrogens on body weight, BMI, waist–hip ratio, fat mass and skin fold measurement and found no statistically significant difference in mean weight gain between non users and users of unopposed estrogens (0.66 kg; 95% CI –0.62 to 1.93). Again, there was no significant difference in mean weight gain between users of estrogen–progestogen HRT and non users (−0.47 kg, 95% CI −1.63 to 0.69). Meta-analysis indicates no effect of combined estrogen and progestogen HRT on the BMI increase associated with age and estrogen–only HRT does not have an appreciable effect on rate of increase of BMI. Some studies have reported that HRT promotes a gynoid fat distribution, but there is no convincing evidence of redistribution of body fat in HRT users. Cushman et al.\textsuperscript{32} found that total body weight increased in transdermal HRT users but decreased in women on oral regimens. There was no significant weight change in the controls or in the women treated with tibolone. Angeliq\textsuperscript{®} (Schering Health, Burgess Hill, West Sussex), which contains estradiol and drospirenone, appears to be a useful addition to the HRT armamentarium and can help reduce fluid retention.

HRT and breakthrough bleeding
A non-significant trend \(P=0.14\) towards a relation between BMI and breakthrough bleeding became evident in one study\textsuperscript{33} investigating the association of breakthrough bleeding in obese postmenopausal combined HRT users.

HRT and cardiovascular disease
Obesity is a risk factor for cardiovascular disease. The view that HRT can have an overall beneficial effect on cardiovascular disease has not been substantiated by the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI) trials. A 12% statistically significant increase in cardiovascular events observed in conjugated equine estrogen users in the WHI study led to premature termination of the study in 2004.\textsuperscript{34} Mean BMI in the estrogen-only arm and in the estrogen–progestogen arm of the WHI was 30 and 28.5, respectively, indicating a higher cardiovascular risk profile and pre-existing atherosclerosis despite these women not having experienced a clinical cardiovascular event. The risk of venous thromboembolism was increased by 33% (18/10 000 more events per year) after five years of combined HRT use and there was an increase of 7/10 000 more events after seven years of estrogen-only HRT. There is little evidence to suggest HRT increases blood pressure in obese postmenopausal women. The risk of venous thromboembolism in combined HRT users in the WHI study was increased in overweight and obese women, with a hazard ratio of 3.80 (95% CI 2.08–6.94) and 5.61 (95% CI 3.12–10.11) respectively, compared with women of normal weight taking a placebo.\textsuperscript{32} The risk of venous thromboembolism increases with age. HRT results in a three-fold increase in risk. In obese women, the adjusted odds ratio for venous thromboembolism is 4.6. Cushman et al.\textsuperscript{32} found that the overall risk of venous thromboembolism was 3.5/100 woman-years in the HRT group compared with 1.7 in the placebo group. Concomitant progestin use is associated with an increased risk of venous thromboembolism compared with estrogen alone and esterified estrogens appear to be better in terms of risk compared with conjugated estrogens.\textsuperscript{12} The risk of stroke in estrogen and estrogen–progestogen users was increased by 39% (8/10 000 more strokes/year) compared with women taking a placebo.\textsuperscript{34,35}

Obesity is directly associated with an increased risk of polycystic ovarian syndrome, problems with induction of ovulation, lower birth rate after in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), endometrial cancer and postmenopausal breast cancer. Management of obesity should be recognised as an important component of gynaecological practice. Dietary modification, the help of a nutritionist and a suitable exercise programme are central to the management of obesity.

Conclusion
Future research should focus on the impact of BMI on the efficacy of contraceptive hormones and the impact of obesity on risks associated with female hormones. More understanding is required
of mechanisms of bleeding patterns in progestogen users and the association of BMI and hormonal contraceptives with bleeding patterns.

References