EDITORIAL

Implications of the growing obesity epidemic on contraception and reproductive health

Background
There is an obesity epidemic hitting all developed countries. This is having a huge impact on health, with the direct cost of obesity to the National Health Service recently quoted as £0.5 billion. The indirect costs are even higher, being estimated at about £2 billion. Prevalence rates in developed countries have now reached record levels, with more than 25% of people in the USA and 20% in Australia being obese. In the UK 22% of men and 24% of women are obese.1

Why are we getting fatter? We are now expending less energy in daily life but are eating high calorific junk food. We are a nation of car owners – in days gone by children used to walk to school and adults to work. Worryingly, 8.5% of 6-year-olds and 15% of 15-year-olds are clinically obese. This is storing up health problems for the future with obesity being an independent risk factor for type 2 diabetes and cardiovascular disease.

Effects on fertility and pregnancy
There is some evidence to suggest that obesity may affect fertility. Most studies investigating this area have included overweight women with ovulatory dysfunction, which will bias results. A European study, however, looked at the effect of body mass index (BMI) on delayed conception (9.5 months of unprotected sexual intercourse) by using a population-based survey of pregnant women. In smokers there was a strong association between obesity (BMI≥30 kg/m²) and delayed conception [odds ratio (OR) = 11.54, 95% confidence interval (CI) 3.68–36.15]. This association was not found in non-smokers.2 Leptin is a protein hormone, secreted by adipocytes, which may have effects on the hypothalamic–pituitary axis and sex hormone levels. Circulating levels of leptin may provide the link between BMI and fecundity. In those who are overweight, increased leptin production results in appetite suppression and supposed weight loss but in the obese there appears to be ‘leptin resistance’. Smokers have lower levels of leptin, and the combination of being obese and smoking may also affect leptin levels.5

Obese pre-pregnancy weight is also associated with adverse pregnancy and perinatal outcomes through increasing hypertensive diseases (chronic hypertension and pre-eclampsia), diabetes (pre-pregnancy and gestational), rates of Caesarean section and infections. Obesity is associated with a higher rate of venous thromboembolism (VTE) and respiratory complications in pregnancy, and may be an independent risk factor for neural tube defects in infants and fetal mortality. Maternal obesity increases the risk of delivering a large-for-gestational-age neonate, which in turn increases the risk of subsequent childhood obesity.3

One study showed that compared to women weighing 100–149 lb (45–67 kg), women over 300 lb (>136 kg) had a five-fold increased risk of gestational diabetes and pre-eclampsia with almost a three-fold increased risk of Caesarean section. These women were also four times more likely to have a macrosomic infant, and infants were twice as likely to be treated in a neonatal intensive care unit even when mothers with diabetes and hypertension were excluded.4 A further study investigating more than 290 000 women in London, UK showed that maternal obesity carries significant risks for the mother and baby, with the risk increasing with the degree of obesity and persisting after accounting for other confounding demographic variables.5 Table 1 shows a summary of the results from this study.

Polycystic ovary syndrome (PCOS) is characterised by anovulation, infertility and hyperandrogenism, with clinical manifestations of irregular menstrual cycles, hirsutism and acne. The condition affects an estimated 5–10% of women of reproductive age6 in the UK, with the highest prevalence reported in the South Asian community. A recent study suggested that 52% of this population had PCOS, with 49% having associated menstrual irregularities.7 It is not surprising that the prevalence of PCOS appears to be increasing in line with the current obesity epidemic. In women with PCOS, obesity worsens both their symptomatology and endocrine profile. Weight loss in sufferers with BMI≥30 kg/m² improves these factors and the likelihood of ovulation and pregnancy.8

Obesity and contraception
Here there are three areas of importance. Is there evidence of weight gain associated with the contraceptive method? Does BMI impact on that product’s contraceptive efficacy? Will an increase in BMI affect the safety profile of the method?

Combined oral contraceptives
Many women blame their oral contraceptive when they put on weight. A recent Cochrane Review identified three placebo-controlled, randomised trials and could not find evidence supporting a causal association between combined oral contraception (COC) and weight gain.9 Initial data for combined hormonal patches also suggest no association with weight gain.10

What is the impact of prescribing a combined hormonal contraceptive to overweight women? Data suggest that obesity alone increases the risk of VTE and cardiovascular disease. Recent studies11,12 looking at COC users have shown a two- to five-fold increase in VTE risk in women with a BMI≥30 kg/m², while these and others12,13 suggest two- to six-fold increases in women with a BMI≥25 kg/m².

In a case-control study from the Netherlands adjusted for age and sex, obesity (BMI≥30 kg/m²) doubled the risk of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative risk (95% CI)</th>
<th>BMI 25–29.9</th>
<th>BMI≥30</th>
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</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td>1.68 (1.53–1.84)</td>
<td>3.60 (3.25–3.98)</td>
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<tr>
<td>Proteinuric pre-eclampsia</td>
<td>1.44 (1.28–1.62)</td>
<td>2.14 (1.85–2.47)</td>
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<tr>
<td>Induction of labour</td>
<td>2.14 (1.85–2.47)</td>
<td>1.70 (1.64–1.76)</td>
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<tr>
<td>Delivery by emergency LSCS</td>
<td>1.30 (1.25–1.34)</td>
<td>1.83 (1.74–1.93)</td>
<td></td>
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<tr>
<td>Severe postpartum haemorrhage</td>
<td>1.16 (1.12–1.21)</td>
<td>1.39 (1.32–1.46)</td>
<td></td>
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<td>Genital tract infection</td>
<td>1.24 (1.09–1.41)</td>
<td>1.30 (1.07–1.56)</td>
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<tr>
<td>Urinary tract infection</td>
<td>1.17 (1.04–1.33)</td>
<td>1.39 (1.18–1.63)</td>
<td></td>
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<tr>
<td>Wound infection</td>
<td>1.27 (1.09–1.48)</td>
<td>2.24 (1.91–2.64)</td>
<td></td>
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<td>Birth weight&gt;90th centile</td>
<td>1.57 (1.50–1.64)</td>
<td>2.36 (2.23–2.50)</td>
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<td>Intrauterine death</td>
<td>1.10 (0.94–1.28)</td>
<td>1.40 (1.14–1.71)</td>
<td></td>
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<td>Delivery before 32 weeks</td>
<td>0.73 (0.65–0.82)</td>
<td>0.81 (0.69–0.95)</td>
<td></td>
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<tr>
<td>Breast feeding at discharge</td>
<td>0.86 (0.84–0.88)</td>
<td>0.58 (0.56–0.60)</td>
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</table>

*Data from Sebire et al.5 BM, body mass index; CI, confidence interval; LSCS, lower segment Caesarean section.

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VTE. Obese individuals had higher levels of factor VIII and IX but not fibrinogen. Evaluation of the combined effect of COCs and obesity of around 15–45 years revealed that COCs further increased the effect of obesity on the risk of thrombosis, leading to a 10-fold increased risk amongst women with a BMI≥25 kg/m². Guidance from the Clinical Effectiveness Unit states that after counselling, overweight women may choose to use a COC but consideration should be given to the use of alternative contraceptive methods. The British National Formulary recommends that women with a BMI>39 kg/m² should not use COCs and this seems to be standard practice in the UK. Very recent evidence suggests a much higher risk of VTE (four-to-five-fold) in COC users when compared to data issued by the Committee on Safety of Medicines in 1995. No significant differences were observed between drospirenone-containing COCs, levonorgestrel-containing COCs and other formulations concerning cardiovascular events (i.e. VTE, myocardial infarction or stroke). These post-marketing data demonstrate the true prevalence of VTE in women taking COCs in the 21st century. With almost one in four women being obese, and in view of the recent data, safer prescribing is vital. Many ‘experts’ now suggest that in countries where there is a wide range of alternative contraceptive methods a BMI>35 kg/m² absolutely contraindicates combined hormonal methods and advise caution when prescribing to women with a BMI>30 kg/m². There are no data that suggest the combined hormonal patch behaves differently from a COC in this respect. Does weight have an effect on the efficacy of COC? Most efficacy studies recruit women of normal body weight so an effect is unlikely to be seen. A retrospective cohort study from Puget Sound in the USA has suggested that body weight may affect hormone metabolism sufficiently to compromise contraceptive efficacy in COC users. Analysis of data on 755 randomly selected women was performed with 618 women being ever-users of COCs. The authors state that during 2822 women-years of COC use the pregnancy rate was 3.8 per 100 women-years of exposure. After controlling for parity, women weighing ≥70.5 kg had a significantly increased risk of failure [relative risk (RR) 1.6, 95% CI 1.1–2.4] compared to women of a lower body weight. Those in the highest weight quartile using low dose (<50 µg ethinylestradiol) and very low dose (<35 µg ethinylestradiol) pills had between a four- and five-fold increase in risk of pregnancy. However, caution is needed in the interpretation of these results, as the heavier women may also have been less compliant pill takers. More recently studies comparing the combined hormonal patch with COCs included women who had a body weight up to 35% greater than normal. Contraceptive efficacy of the combined hormonal patch is similar to a COC. Results of pooled data from three studies comparing efficacy of the patch with different COCs showed that 5/15 on-therapy pregnancies that occurred were in a subgroup of women with baseline body weight ≥90 kg, which constituted 3% of the total study population. The Summary of Product Characteristics for the patch suggests that it may be less effective in women weighing >90 kg. Progestogen-only methods A continuing area of controversy relates to a possible increased failure of progestogen-only pills (POPs) in overweight women. This has recently been appraised and the author concluded that although there are no data showing that POPs are less effective in women weighing >70 kg, two POPs per day may be advised. A large cohort study failed to find an association between failure rates and body weight, height or BMI. However, it is possible the study was insufficiently powered to either prove or disprove this hypothesis. The recommendation is based on the fact that higher failure rates were seen in obese women using the levonorgestrel-releasing vaginal ring and in women >70 kg using the older, hard tubing formulation of Norplant. However, changing to a softer tubing made the new version of Norplant more effective in all women. There are no data to support the giving of two tablets of Cerazette® a day in women >70 kg. The main mechanism of action for this POP is inhibition of ovulation but it also has similar progestogenic effects to other POPs, producing secondary contraceptive effects in altering cervical mucus and endometrium. There are also no data to suggest that weight decreases the efficacy of Implanon (data on file, Organon Laboratories Ltd), Depo-Provera or the levonorgestrel intrauterine system (IUS). An initial study reported that serum etonogestrel levels were higher in women of lower body weight using Implanon. However, when studying the small number of reported failures with Implanon no association between body weight and efficacy has been found (data on file, Organon Laboratories Ltd) and it is therefore not necessary to replace Implanon earlier than the usual 3 years in heavier women. No studies have reported a significant association with weight change in POP users. A randomised comparative trial comparing the levonorgestrel-releasing IUS and copper-containing intrauterine device failed to show an increase in weight with the IUS. Weight change in Implanon users has also been studied, with about 60% of women gaining at least 1 kg by 24 months and 37% gaining at least 3 kg. A gradual increase in body weight over time has been shown in normal women of reproductive age so these findings may be only partly attributable to implant use and partly attributable to normal increases over time. For Depo-Provera users studies have shown that the mean weight gain after 1 year is usually about 2 kg, rising to 9 kg with 5.5 years’ use. It is thought that this is a result of increasing appetite in users, leading to deposition of fat. It is not related to fluid retention. There are no data to suggest that obese women using progestogen-only contraceptive methods face an increased risk of adverse effects compared to other overweight women. Progestogen-only methods have not been shown to increase the risks of VTE or cardiovascular disease. Other methods There are no effects of weight on the efficacy or safety of barrier methods or fertility awareness methods. However, women who gain or lose more than half a stone in weight are advised to be reassessed for the diaphragm. Female sterilisation under general anaesthesia poses increased risks for obese women. Overweight people are more likely to suffer complications of general anaesthesia and their habitus increases the chance of a failed laparoscopic procedure necessitating a mini-laparotomy. New hysteroscopic techniques such as Essure®, a minimally invasive, transcervically positioned micro-insert that occludes the Fallopian tubes, may offer advantages for such women. These micro-inserts can be inserted under hysteroscopic visualisation with intravenous sedation or paracervical block in over 85% of women. Further research is underway investigating their long-term safety and efficacy. Conclusion Much has been written in recent years about the global effects of diet, obesity and ill-health. As health
professionals working in the field of contraception, we need to sit up and take note: advise about the importance of normalising BMI pre-pregnancy, endeavour to prescribe contraception safely, and offer alternatives when obesity contraindicates the use of COCs.

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References
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