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Nutrition and reproduction in women

The ESHRE Capri Workshop Group[1]

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Malnutrition is a major problem in developing countries, and obesity and eating disorders are increasingly common in developing as well as developed countries. The reproductive axis is closely linked to nutritional status, especially undernutrition in the female, and inhibitory pathways involving detectors in the hind brain suppress ovulation in subjects with weight loss. Recovery may occur after minimal reacquisition of weight because energy balance is more important than body fat mass. Anorexia nervosa and bulimia nervosa affect up to 5% of women of reproductive age causing amenorrhoea, infertility and, in those who do conceive, an increased likelihood of miscarriage. Obesity can affect reproduction through fat cell metabolism, steroids and secretion of proteins such as leptin and adiponectin and through changes induced at the level of important homeostatic factors such as pancreatic secretion of insulin, androgen synthesis by the ovary and sex hormone-binding globulin (SHBG) production by the liver. WHO estimates that 9 to 25% of women in developed countries are severely obese, and obese mothers are much more likely to have obese children, especially if they have gestational diabetes. Obesity-associated anovulation may lead to infertility and to a higher risk of miscarriage. Management of anovulation with obesity involves diet and exercise as well as standard approaches to ovulation induction. Many obese women conceive without assistance, but pregnancies in obese women have increased rates of pregnancy-associated hypertension, gestational diabetes, large babies, Cesarean section and perinatal mortality and morbidity. Among contraceptors, the fear of weight gain affects uptake and continuation of hormonal contraceptives, although existing trials indicate that any such effects are small. For all methods of hormonal contraception, weight above 70 kg is associated with increased failure rates.

Key words: contraception/miscarriage/nutrition/obesity/reproduction

Introduction

Nutrition problems are strikingly different in developing nations (deprivation and undernutrition) and developed nations (eating disorders and obesity), although obesity is on the increase even in developing countries. Malnutrition is associated with 55% of deaths among children under the age of five. Over 4 million of the 12 million annual deaths are in sub-Saharan Africa alone, where every third child is underweight and two out of five are stunted. Iron deficiency anaemia is a contributing factor in over 20% of post-birth maternal deaths in Africa and Asia. Nearly 67 million children are wasted (weigh less than they should for their height);

A meeting was organized by ESHRE (Capri, 3–4 September 2005) with an unrestricted educational grant from Institut Biochimique SA to discuss the above subjects. The speakers included D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, Simpson Centre for Reproductive Health, 51 Little France Crescent, Edinburgh EH16 4SA, UK), S. Cnattingius (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, S-171 77 Stockholm, Sweden), J. Collins (McMaster University, Faculty of Health Science, Hamilton, Ontario, Canada), J.L.H. Evers (Department of Obstetrics and Gynecology, Academic Hospital Maastricht, P. Debeyelaan 25, P.O.Box 5800, 6202 AZ Maastricht, The Netherlands), A. Glasier (Director of FP & WW Services, 18 Dean Terrace, Edinburgh, EH4 1NL, Scotland Edinburgh), B.L. Heitmann (Research Unit for Dietary Studies, Copenhagen Centre for Prospective Population Studies, Copenhagen University Hospital, Denmark), R. Norman (Research Centre for Reproductive Health and Repromed, Deptartment of Obstetrics and Gynecology, Academic Head, Repromed Pty. Ltd., Australia 5 005), K.K. Ong (Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Box 116, Hills Road, Cambridge CB2 2QQ, U.K), A. Sunde (University Hospital, Department of Obstetrics and Gynecology, N-7006 Trondheim, Norway). The discussants included: J. Cohen (8, rue de Marignan, 75008 PARIS, France), B. Cometti (Institut Biochimique SA, Pambio Noranco, Switzerland), P.G. Crosignani (Il Department of Obstetrics and Gynecology, University of Milano, Italy), P. Devroey (Centre for Reproductive Medicine, AZ-Vrije Univ. Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium), E. Diczfalusy (Rönningvägen 21, S-144 00 Rönninge, Sweden), K. Diedrich (Klinikund Frauenheilkunde und Geburtshilfe, Univ. zu Lübeck, D-2400 Lübeck, Germany), L. Fraser (Endocrinology and Reproductive Research Group, School of Biomedical Sciences, New Hunt's House, Kings College London, Guy's Campus, London Bridge, London SE1 1UL, U.K.), L. Gianaroli (S.I.S.M.E.R., Via Mazzini 12, 40138 Bologna, Italy), I. Liebaers (Academic Hospital, Vrije Univ. Brussels, Laarbeeklaan 101, B-1090 Brussels, Belgium), G. Mautone (Institut Biochimique SA, Pambio Noranco, Switzerland), G. Ragni (U.O. Ostetricia e Ginecologia III, Sterilità di Coppia e Andrologia, Milano, Italy), B. Tarlatzis (Infertility & IVF Center, Geniki Kliniki, 2 Gravias Street, Thessaloniki 546 45, Greece), A. Van Steirteghem (Academic Hospital, Vrije Univ. Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium). The report was prepared by J. Collins (Hamilton) and P.G. Crosignani (Milano).

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and about 183 million weigh less than they should for their age. Unfortunately, reducing poverty and increasing food production by themselves cannot solve the nutrition problems of the poor in developing countries (Bekele, 1998). Major public health and social expenditures are needed to address these devastating conditions that at present cannot be remedied substantially by medical practice.

In contrast, developed nations experience little deprivation, but eating disorders and obesity are increasingly common and may be amenable to medical intervention. For females, reproduction involves much greater energy expenditure than for males, and as a protective mechanism against undernutrition, the reproductive axis is closely linked to nutritional status. As one consequence, eating disorders leading to loss of weight are associated with reduced frequency or cessation of ovulation. Since energy balance more than absolute weight loss is the key factor, there may be a return of ovulation after no more than a small percentage change in body weight recovery. Obesity, however, is a less reliable risk factor of infertility except among obese women who also have polycystic ovarian disease. This review of nutrition and reproduction will address the clinical conditions that are associated with underweight and overweight in developed countries. It will outline the physiological mechanisms and clinical conditions associated with undernutrition first and then those associated with obesity.

Undernutrition

Physiological mechanisms

The reproductive system is extremely sensitive to influences from the external environment (Martin *et al*., 2004). Most animals adjust their pattern of reproduction so that the chances of their offspring surviving are maximal. A common strategy involves timing of conception by photoperiod and/or rainfall which usually ensures that birth takes place in a season when food and climatic conditions are favourable, such as spring.

Reproduction involves much greater energy expenditure in the female than in the male. The nourishing of the offspring during pregnancy and lactation and their subsequent rearing to adulthood are the biggest expenditure of energy that a female mammal will make in her lifetime. Hence, the female reproductive system is much more sensitive to disruption than the male.

Because reproduction involves energy expenditure, it is sensible that the physiological control mechanisms are linked to those involved with appetite and nutrition (Wade and Jones, 2004). Food is used as a source of energy for a variety of essential and non-essential functions. In times of deprivation it is necessary to ration available oxidizable substrate in favour of those essential functions involved in staying alive, e.g. keeping warm (Bronson, 1989). Reproduction is expendable at least in the short term and can be deferred until times are more favourable (Figure 1). During lean times animals have devised a number of strategies to reduce energy output such as huddling together in insulated nests (houses), daily torpor or hibernation. Very little energy is diverted to storage of fat. Rather, calories are mobilized from fat stores in an attempt to maintain energy balance. Thus, it is energy balance not fatness *per se* that regulates reproductive function.

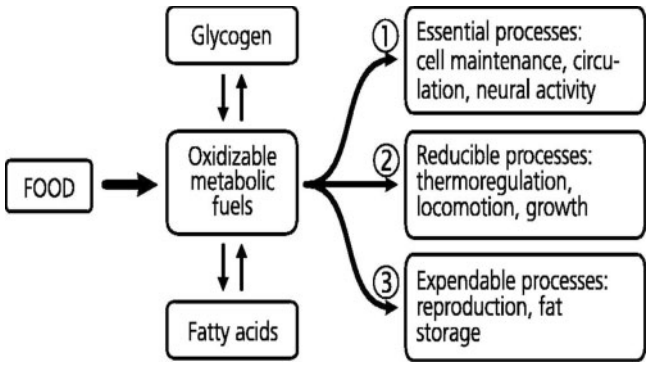

Figure 1. Partitioning of metabolic fuels by priority (Wade and Jones, 2004).

Energy balance and ovulation

Approximately 1–5% of women suffer from 'weight-related amenorrhoea' (Laughlin *et al*., 1998). Because many girls with delayed puberty are relatively thin during adolescence it has been suggested that a certain critical body weight (47 kg) or body fat content is required for onset of cyclical ovarian activity (Frisch and McArthur, 1974; Frisch, 1987). However, although ovarian activity and fat content are correlated they are not causally linked. It is relatively easy to dissociate fatness and reproductive function. Thus, for example, menstrual cycles return in some female athletes when energy expenditure is reduced such as after an injury long before there is any change in body weight or an increase in body fat (Loucks, 2003).

Reproductive function, like appetite, is responsive to short-term changes in metabolic food oxidation. For example, many breeds of sheep are capable of altering their ovulation rate and hence the number of lambs they carry depending on body condition (Martin *et al*., 2004). Feeding underweight sheep high-calorie supplement of lupins or clover hastens the onset of the breeding season ('flushing') and increases the ovulation rate. A similar effect can be produced by administration of a glucogenic 'drench' (Downing *et al*., 1995).

The mechanisms involved in this adjustment of reproductive function involve the availability of calories. When Syrian hamsters are administered 2 de-oxy-D-glucose (DG), which limits glucose oxidation, ovulatory cycles are interrupted rapidly (Schneider and Wade, 1990). It is likely that this involves both central and peripheral mechanisms. In sheep and rats infusion of DG directly into the lateral ventricles depressed LH secretion (Murahashi *et al*., 1996; Ohkura *et al*., 2000). Subsequent experimentation has helped define the pathway by which calorie deprivation leads to short-term inhibition of reproductive function. It appears that in the rat the metabolic signals are detected by chemoreceptors in an area of the hind brain area [postrema (PA)]. The signals involved in this are not entirely clear but probably include leptin and insulin/glucose (Clarke and Hendry, 1999; Foster and Nagatani, 1999) (Figure 2). Epinephrine, nor-epinephrine and neuropeptide Y (NPY) neurones connect to the forebrain to influence GnRH secretion in the hypothalamus (Sawchenko *et al*., 1985). When the animal is replete, the system is free running. The 'brake' is only applied during times of negative energy balance and involves NPY neurons (Sawchenko *et al*., 1985; Li and Ritter, 2004).

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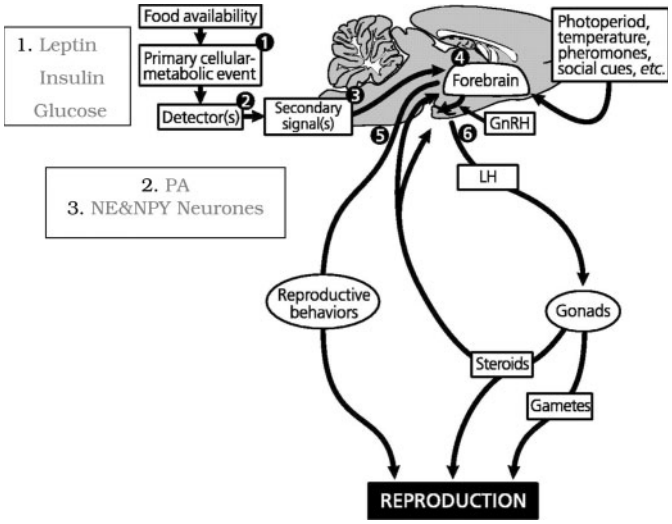

Figure 2. Nutrition and reproduction (Wade and Jones, 2004). NE, nor-epinephrine; NPY, neuropeptide Y; PA, postrema.

Recent observations in women with 'hypothalamic amenorrhoea' have suggested that these experimental studies are relevant to clinical disorders. Women with anovulation associated with strenuous exercise or who are underweight, have low levels of leptin, LH and estradiol (Welt *et al*., 2004). The frequency of gonadotropin pulses is too low to sustain development of antral follicles to the point of ovulation. When leptin was injected to restore levels to normal, there was an immediate increase in the frequency of LH pulses within 2 weeks, followed by growth of large ovarian follicles. Ovulatory cycles were restored in three out of eight women. Whether leptin acts directly on the hypothalamus or increases the availability of oxidizable metabolic substrates or both is unknown. It is likely that leptin plays a significant role in mediating this event although it should be noted that when nutritionally starved animals are refed the frequency of LH pulses increases long before there is an increase in circulating leptin (Schneider, 2004).

Energy balance and implantation

Nutrition not only influences ovulation and fertilization but also implantation and early fetal development. Paradoxically overfeeding of sheep in the first few weeks of pregnancy results in an increase in embryonic mortality associated with low levels of progesterone (Parr, 1992). The level of nutrition during pregnancy has a profound effect on fetal development and subsequent susceptibility in adulthood to disease. When ewes were underfed during mid pregnancy there was an increase in the incidence of pre-term birth (Bloomfield *et al*., 2003). The concept of fetal programming in utero which was originally derived from epidemiological studies in man has been confirmed in a number of experimental studies in animals (Barker, 2001; Gluckman and Hanson, 2004). Thus there is little doubt that nutrition plays an important role during pregnancy as well as in determining the timing and quality of reproductive activity.

Eating disorders

Undernutrition implies inadequate food intake or faulty assimilation due to low-caloric intake or limited nutritional diversity. In developed countries it is most commonly found in women with eating disorders.

Although records of undernutrition from developing countries are scarce, the experience from the Dutch famine in 1944–1945 is relevant to modern countries with a high prevalence of malnutrition. In the Western Netherlands, average daily intake fell from 1500 to less than 700 kilocalories from October 1944 to January 1945 and the birth rate fell 9 months after October 1944. Future reproductive life was affected among women who were severely affected by famine at 3 to 13 years of age: they had a 1.9 fold higher risk (95% CI = 1.3–1.8) of having fewer than the desired number of children in their lifetime (Elias *et al*., 2005).

Undernutrition due to eating disorders may affect ovulation and fertility, alter the response to conventional treatment and assisted reproduction technology for infertility and have effects on pregnancy and the newborn.

The relevant eating disorders are bulimia nervosa (excessive eating and compensatory activities such as vomiting or laxative abuse) and anorexia nervosa [low body mass index (BMI) and fear of weight gain]. Both commonly onset in adolescence and occur in 3% of young women (Becker *et al*., 1999).

Milder eating disorders (not otherwise specified) occur in a further 3–5% of women (Stewart *et al*., 1990). Anorexia nervosa (1% of young women) is defined as body weight less than 85% of expected weight or BMI less than 17.5 kg/m^2, coupled with intense fear of weight gain and an inaccurate perception of body image. Bulimia nervosa (1–5% of young women) involves recurrent binge eating, compensated by recurrent purging, excessive exercise or fasting, excessive concern about body weight or shape and the absence of anorexia nervosa (Becker *et al*., 1999). Full recovery with bulimia nervosa is more likely (74%) than with anorexia nervosa (33%), but to achieve these recovery rates required a median of 90 months of follow-up with treatment and relapses occurred in about one third of full recoveries (Herzog *et al*., 1999).

Effects on fertility

Menstrual periods often cease after a 10–15% decrease in normal body weight. In theory the mechanisms include altered regulation of gonadotropin-releasing hormone secretion and changes in the dopaminergic and opioid systems. Amenorrhoea occurs in 15–30% of women with anorexia nervosa (Watson and Andersen, 2003; Miller *et al*., 2005). Amenorrhoea is also a component of the female athletic triad, along with osteoporosis and milder versions of the eating disorders (Rome, 2003). Oligoamenorrhoea may occur with bulimia nervosa even in women with BMI in the normal range. The amenorrhoea persisted in 30% of patients who had regained their normal weight during recovery from anorexia nervosa with amenorrhoea (Falk and Halmi, 1982).

With respect to fertility, anorexia nervosa or bulimia nervosa was present in 5 (8%) of 66 consecutive infertility clinic patients; non-specified eating disorders were found in a further six (9%) (Stewart *et al*., 1990). Seven of the 11 women with eating disorders were among the 12 of 66 with oligoanovulation; thus, in this small group, eating disorders were present in about 60% of women with oligoanovulation. Although women with anovulation are unlikely to conceive, fertility may be normal in later years among women who achieve normal weight after recovery from eating disorders (Finfgeld, 2002; Rome, 2003). Women with a history of

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anorexia nervosa and community controls had similar rates of pregnancy, mean number of pregnancies per woman and age at first pregnancy (Bulik *et al*., 1999). After 11.5 years of follow-up in 173 women with bulimia nervosa, 75% had been pregnant at least once and only 2% reported that they were unable to conceive (Crow *et al*., 2002).

Effects on treatment for infertility

Undernutrition is not a reliable predictor of conception among infertile women. In 244 cycles of GnRH treatment for oligoamenorrhoea in 48 women, pregnancy rates were not affected by patients' weight or weight loss (Braat *et al*., 1991). With assisted reproduction (ART) treatment, BMI was <20 kg/m^2 in 22% of 398 French women: the delivery rates per started cycle were 21% in underweight women and 15% in those with BMI 20–25 kg/m^2 (Wittemer *et al*., 2000). Among 2860 Norwegian women having ART, BMI was <18.5 kg/m^2 in 3%; the live birth rates per started cycle were 21%, both in underweight women and in those with BMI 18.5–25 kg/m^2 (Fedorcsak *et al*., 2004).

Effects on pregnancy

Women with a history of being anorexic may have more abortions: 27% in a cohort of 66 anorexics versus 13% in a control group (Bulik *et al*., 1999). In contrast, a larger follow-up study of 246 women with either anorexia or bulimia reported that 54 women had 82 pregnancies of which 46 (56%) were live births, 25 (31%) were therapeutic abortions and only 11 (13%) were spontaneous abortions (Blais *et al*., 2000).

During pregnancy, women with eating disorders have higher rates of hyperemesis gravidarum, anaemia, impaired weight gain and compromised intrauterine fetal growth (Becker *et al*., 1999; Kouba *et al*., 2005). Premature delivery is more likely in underweight women (Figure 3). A case control study found that BMI <20 kg/m^2 was associated with a four-fold higher likelihood of pre-term labour (OR = 3.96, 95% CI = 2.61–7.09) after adjusting for other known factors (Moutquin, 2003). Rates of cesarean delivery, post-natal complications and post-partum depression are higher among mothers with anorexia nervosa (Bulik *et al*., 1999; Franko *et al*., 2001). Undernutrition is associated with low birthweight (3233 g compared with 3516 g for normal controls) (Kouba *et al*., 2005).

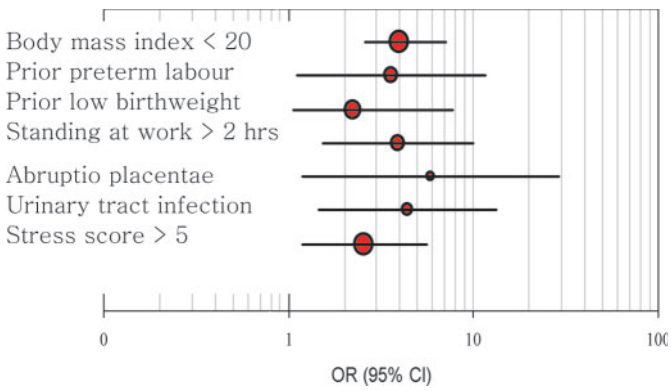

Figure 3. Factors associated with premature delivery (Moutquin, 2003). OR, odds ratio; CI, confidence interval; body mass index Kg/m^2 (standing at work >2 h/day, stress score: arbitrary scale.

Among women with eating disorders, postponement of conception until remission is recommended because of the impact of low nutrition, but all pregnant women with past or current eating disorders should be viewed as being at high risk and should be monitored closely both during and after pregnancy to ensure optimal maternal and fetal outcomes (Becker *et al*., 1999; Fedorcsak *et al*., 2004)

Overnutrition

Epidemiology of obesity

Obesity trends

The prevalence of overweight defined as BMI 25.0–29.9 and obesity defined as BMI ≥ 30 kg/m^2 is increasing around the world (Cnattingius and Lambe, 2002). WHO considers that obesity is an epidemic, as more obese people are found in developed and developing countries, among children as well as adults and elderly and among men and women (World Health Organisation, 1997). In Western countries increases in obesity prevalence range from 1–6% per year among adults and for most countries the increases are greater among men than women (Heitmann, 2000). Using the classification of BMI, 60% of the adult population in Australia are overweight and 21% are obese. This proportion in Australia and the western world is increasing and has doubled over the past 20 years. This trend of increasing obesity is likely to spread and lead to a clear association with impaired psychosocial health, type 2 diabetes, cardiovascular disease (CVD), osteoarthritis, sleep apnoea and various reproductive conditions (Pasquali *et al*., 2003). The Heart, Lung and Blood Institute concluded that the public health burden caused by obesity resembles that of smoking, which previously was the most important cause of preventable death (Anonymous, 1998).

Denmark is one country where information on obesity development has been collected from entire population groups, such as all school children or all young men at the compulsory draft board examinations. Recent data on obesity prevalences during almost six decades from Danish school health examinations show that obesity was 20-fold and 115-fold higher, among 6–8 year old girls and boys, respectively, in 2003 compared to 1947 (Pearson *et al*., 2005). Similarly, over the past 30 years the prevalence of obesity among young Danish men is consistently increased (5 per 1000 obese draftees in the mid-1970 to 73 per 1000 in 2004) (Sorensen *et al*., 1997; Forsvaret, 2004) (Figure 4). These dramatic increases among Danish children and young men are unparalleled by any other country. As Danes are among the leaner populations in the Western world, however, information from other countries on trends in obesity prevalence may be greatly underestimated (Heitmann, 2000). Underestimation of the trends may arise from bias in self-reporting. In a comparison of trends for obesity from measured and self-reported data the figures for the self-reported information are 50–100% lower (Richelsen *et al*., 2002). Also, studies have shown that those who never turn up at health examinations to have their height and weight measured are generally much more obese than those who do turn up (Sonne-Holm *et al*., 1980).

Determinants for obesity

Overweight and obesity are attributed to social changes with more sedentary lifestyle, decrease in physical activity and changes in

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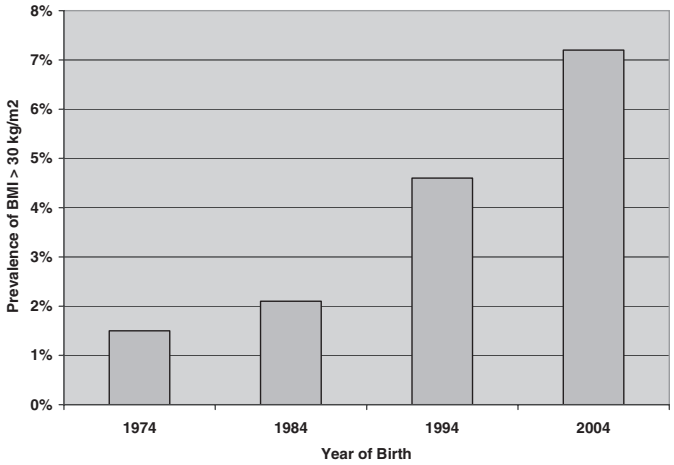

Figure 4. Prevalence of obesity among young Danish men (Sorensen *et al*., 1997; Forsvaret, 2004).

dietary energy density and composition, but the underlying cause is complex involving cultural, psychological and genetic factors that may interact with both energy intake and expenditure to affect obesity development. For instance, obesity is known to carry a clear social disadvantage, and among those from lower social economic groups, the prevalence of obesity is three to five times higher than among individuals from higher socioeconomic groups (Heitmann, 2000). Studies show that obesity not only influences social class placement, but is also a predictor of social class placement (Stunkard and Sørensen, 1993). Interestingly, adoption studies have shown a very strong negative association between social class of the adoptive parents and the BMI of the child, whereas associations between BMI in the adoptive parents and BMI in the adopted child were non-significant, suggesting that social class may modify the expression of the genes responsible for obesity development (Teasdale *et al*., 1990). Studies also show that lifestyle factors, such as dietary fat, physical activity, alcohol and smoking (Heitmann *et al*., 1997) may modify the expression of the obesity promoting genes, making the development of obesity a much more complex issue than a simple imbalance between energy intake and expenditure.

Genetic factors

The *thrifty gene hypothesis* (Neel, 1962) considers that a specific gene fosters survival in both *feast* and *famine* conditions. Eating food whenever possible and storing the energy helped early humans—hunters and gatherers—to survive conditions of famine. Thus, fatter individuals were more likely to survive. In modern life, however, feast and famine conditions do not apply in the developed part of the world, which suffers more '*feast only*' conditions. Evolutionary theory implies that species evolve over time to fit their environment best, a process that depends on variation among individuals which must be inheritable. Not all individuals in a population survive to reproduce. Some individuals can cope with selective pressures better than others. People who possess the *thrifty gene* are at an advantage in the time of famine: they can store energy; a *thrifty gene*, however, is a disadvantage in times of feast: their carriers grow too fat. If the *thrifty gene* provided an advantage to early humans, but a disadvantage to present day man, nature should take care to remove it from the gene pool since it is no longer an advantage. The question is whether survival of the fittest dictates that if obesity is no longer an evolutionary advantage, decreased fertility perhaps may be nature's remedy.

A recent review focused on converging data supporting the hypothesis that, in addition to the *thrifty gene* inheritance, individuals with metabolic syndrome—combining disturbances in glucose and insulin metabolism, excess of predominantly abdominally distributed weight, mild dyslipidemia and hypertension, with the subsequent development of obesity, type 2 diabetes mellitus and CVD—have suffered improper 'epigenetic programming' during their pre- and post-natal development due to maternal inadequate nutrition and metabolic disturbances. Moreover, as seen for obesity and type 2 diabetes, the metabolic syndrome tends to appear earlier in childhood, to be more severe from generation to generation and to affect more pregnant women (Junien *et al*., 2005). This leads to the conclusion that obesity and related metabolic disturbances are major health issues.

Prenatal predictors of obesity

Rising rates of obesity and overweight in young people and children have shifted research efforts towards the very early prevention of excess weight gain in subjects identified to have high risk of developing obesity.

Maternal obesity predicts a four-fold increased risk in offspring obesity (Reilly *et al*., 2005). Whether this is driven by genetic or behavioural factors, much of this risk is due to increased childhood weight gain. Indeed, this relationship is likely to be multifactorial because of a combination of shared lifestyles and genetic influences; in addition, maternal obesity may lead to fetal macrosomia associated with gestational diabetes (Sermer *et al*., 1995). Overall, greater birthweight is positively correlated with higher BMI in childhood and later life, although the relationship is complex. Weighing more at birth is subsequently associated with more lean mass rather than fat mass (Loos *et al*., 2001, 2002). In contrast, lower birthweight is associated with a subsequent higher fat mass to lean mass ratio and also with more central fat and insulin resistance (Valdez *et al*., 1994). This paradoxical effect of lower birthweight is at least partly explained by the observation that low birthweight infants, who have been growth restrained *in utero*, tend to gain weight more rapidly, or 'catch-up', during the early post-natal period (Ong *et al*., 2002).

Apart from the mother's current body size, factors associated with intra-uterine growth restraint include first pregnancies, smoking during pregnancy and lower birthweight of the mother, which likely reflects maternal genetic factors. The greatest risk of childhood obesity, and in particular obesity-related disease risk markers, may therefore be seen in babies born small relative to parental size, who have been more restrained *in utero*. Such infants grow more rapidly during infancy, and this appears to be associated with increased central fat deposition, insulin resistance and CVD risks in later life (Fagerberg *et al*., 2004; Ong *et al*., 2004).

Prevention of offspring obesity requires preventing maternal obesity and also needs to take into account the interactions between maternal genes that regulate the supply of fetal nutrition and post-natal genes that regulate infant appetite.

Particular risks for offspring obesity and long-term health are associated with obese mothers who have gestational diabetes and

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possibly also gestational hypertension. As these conditions are increased in obese mothers, efforts should be made to screen, monitor and intervene early in these mothers. How to safely intervene to prevent over-rapid infant weight gain is as yet unclear, and it is likely that any future advice will need to be tailored to each specific circumstance. The current WHO recommendation encourages breast-feeding and delayed introduction of solids or complementary foods until age 6 months. In addition to avoiding excess infant nutrition, this approach has advantages for infection and allergy risks (Anonymous, 2003).

Endocrine activities of fat tissue

Although under-nutrition is the dominant factor regulating reproductive activity under natural conditions, obesity is an important cause of sub-fertility in many modern societies. Adipose tissue is a complex and highly active metabolic and endocrine organ. In addition to adipocytes there are immune cells, connective tissue matrix, nerve tissue and stromovascular cells which together function as an integrated unit. White and brown types of fat tissue differ in composition, appearance and function. White adipose tissue is 60–85% lipid and 90–99% of this lipid is triglyceride. White fat tissue provides heat regulation, body cushioning and energy storage (triglycerides). Brown fatty tissue derives its colour from rich vascularization and densely packed mitochondria. The cells are polygonal in shape, have a considerable volume of cytoplasm and contain multiple lipid droplets of varying size. Their nuclei are round and almost centrally located. Brown fatty tissue may make up 5% of body weight in neonates but disappears by adulthood. It is the site of non-shivering thermogenesis or metabolic heat production without rapid contraction of muscles.

Fat tissue responds to signals from circulating hormones, but also produces its own hormones and receptors (Kershaw and Flier, 2004). Therefore the traditional view that fat tissue is a passive reservoir for lipids and has no other function is incorrect (Ahima and Flier, 2000). Many proteins with endocrine functions are synthesized by adipocytes (Table I), and adipose tissue expresses a broad range of key cytoplasmic and nuclear receptors (Table II). Among the many synthetic processes in adipose tissue, perhaps, the most important with respect to reproduction are intrafat modification of steroid hormones and secretion of adipokines (Ahima and Flier, 2000).

Enzymes involved in the metabolism of steroid hormones

Adipose tissue contains a large number of enzymes for activation, interconversion and inactivation of steroid hormones. Steroid hormones from the circulation can be converted through tissue-specific expression of steroid hormone receptors to other hormones while tissue specific pre-receptor steroid hormone metabolism also occurs. The relative contribution of adipose tissue to whole body steroid metabolism is substantial. Up to 50% of circulating testosterone in pre-menopausal women comes from fat and up to 100% of circulating estrogen in the post-menopausal women (Weisberg *et al*., 2003; Wellen and Hotamisligil, 2003).

Table I. Examples of adipocyte-derived proteins with endocrine functions

Other immune-related proteins
Proteins involved in the fibrinolytic system
Complement and complement-related proteins
Lipids and proteins for lipid metabolism or transport
Enzymes involved in steroid metabolism
Proteins of the renin angiotensin system (RAS)
Other proteins
Cytokines and cytokine-related proteins

Table II. Examples of receptors expressed in adipose tissue (Kershaw and Flier, 2004)

Receptors for traditional endocrine hormones
Insulin receptor
Glucagon receptor
Growth hormone receptor
Thyroid stimulating hormone receptor
Gastrin/cholecystokinin B gastrin receptor
Glucagon-like peptide-1 receptor
Angiotensin II receptors type I & 2
Nuclear hormone receptors
Glucocorticoid receptors
Vitamin D receptor
Thyroid hormone receptor
Androgen receptor
Estrogen receptor
Progesterone receptor
Cytokine receptors
Leptin receptor
Interleukin 6 receptor
Tumour necrosis factor α receptor
Catecholamine receptors
β1, β2, β3 receptors
α1, α2 receptors

Enzymes involved in the metabolism of glucocorticoids

Glucocorticoids can be metabolized through 11β hydroxysteroid dehydrogenase1 which is highly expressed in adipose tissue. Tissue-specific disregulation of this hormone has been implicated in a variety of common medical diseases including disturbances in reproductive mechanisms.

Adipose tissue secreted proteins

(i) Leptin: Leptin is the classic adipose secreted protein and is secreted in direct proportion to adipose tissue mass as well as nutritional status. Regulation of expression and secretion is under the control of a variety of other factors while leptin's effect on energy intake is well documented. Leptin may have an action on the endometrium and the ovary in addition to its classical action on the hypothalamic pituitary access with regard to eating.

(ii) Tumour necrosis factor (TNF α): TNF has been implicated in the pathogenesis of obesity and insulin resistance while having significant effects on other metabolic components of fat and the liver. Increases in TNFα are associated with decreased food uptake, increased energy expenditure, more lipolysis and decreased lipogenesis and decreased insulin sensitivity.

(iii) Interleukin (IL-6): This cytokine circulates in concentrations that are positively correlated with obesity, impaired glucose tolerance and insulin resistance.

(iv) Macrophage and monocyte chemoattractant protein (MCP-1): Activated macrophages secrete inflammatory factors that contribute to insulin resistance. MCP-1 recruits monocytes to inflammatory

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sites and has local as well as endocrine effects (Weisberg *et al*., 2003; Wellen and Hotamisligil, 2003).

(v) Plasminogen activator inhibitor (PAI-1): Circulating levels of PAI-1 are elevated in obesity and insulin resistance and are related to features in the metabolic syndrome and predict future risk of type 2 diabetes and cardio-vascular disease.

(vi) Adiponectin: This molecule is produced in very large quantities from fat, especially subcutaneous rather than visceral fat. It is inversely related to insulin resistance and inflammatory states. Adiponectin levels are low in obesity. Expression of adiponectin is much greater in gluteal than in fatty tissue from other subcutaneous or visceral sites.

(vii) Adipsin and acylation stimulating protein (ASP): Both these positively correlate with adiposity insulin resistance and cardio-vascular disease.

(viii) Resistin: Resistin is expressed 15-fold greater in visceral fat as opposed to subcutaneous adipose tissue in rats and links obesity with insulin resistance. Mice carrying a targeted deletion of resistin have significantly improved fasting blood glucose levels and proved glucose tolerance.

(ix) Proteins of the renin angiotensin system (RAS): These include renin, angiotensinogen, angiotensin I, angiotensin II and so on. All of these are involved with metabolic changes. There can be significant effects on blood pressure and adipose tissue development.

There are numerous contributing factors to the metabolic and endocrine activity of fat. Many of these influences are reproductive hormones, but in turn the secretions of the fat can affect the appetite and the functioning of the reproductive system (Figure 5) (Gale *et al*., 2004).

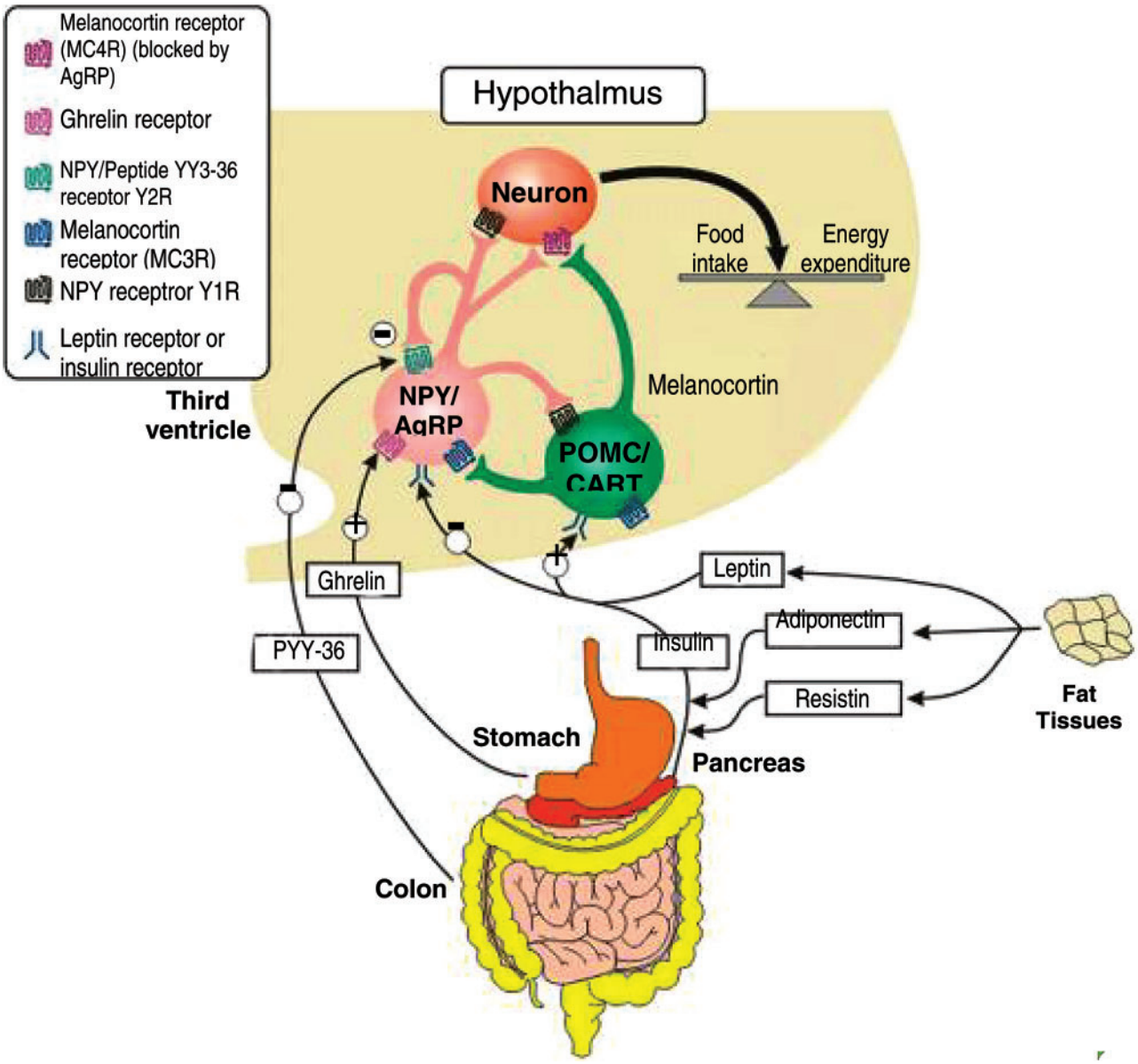

Figure 5. Appetite, fat and intestine (Gale *et al*., 2004). POMC/CART = proopiomelanocortin/cocaine- and amphetamine-regulated transcript; NPY = Neuropeptide Y; AgRP = agouti-related peptide.

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Health consequences of obesity

Obesity is a health concern because of the close relationship between obesity and major lifestyle diseases, such as diabetes and coronary heart disease (CHD). Obesity is also linked, however, to hypertension, gall bladder disease, dyslipidermia, cancer (particularly hormone dependent and gastrointestinal; such as endometrial, ovary, cervix and post-menopausal breast cancer), osteoarthritis, reproductive hormone abnormalities and psychosocial problems. Abdominal obesity is of particular concern and more clearly associated with ill health and premature death than peripheral obesity (World Health Organisation, 1997).

Several reports have documented that the costs of obesity and the related comorbidities are substantial and vary between 2 and 8% of total health care costs, depending on country. In a number of countries prevalence of diabetes type 2 is already increasing as a consequence of the obesity epidemic and this increase includes not only adults, but also children (Pinhas-Hamiel *et al*., 1996). It is feared that in less than 10–15 years the increasing diabetes prevalence will also affect morbidity and mortality from CHD and CVD if action is not taken.

Fertility in obese women

Stein and Leventhal (1934) were the first to recognize the relation between obesity and reproductive disturbances. They described what nowadays is known as syndrome 'O': overnourishment, overproduction of insulin, ovarian confusion and ovulation disruption. The impact of obesity on reproduction is shown in Table III (Pasquali *et al*., 2003).

Anovulatory infertility

Obesity and abdominal obesity are especially common in polycystic ovary syndrome (PCOS) with 10–50% of women with PCOS having a BMI outside of the acceptable range of 19–25. This enhances the features of insulin resistance and is associated with reproductive dysfunction in a high proportion of cases. Abdominal obesity particularly worsens the clinical features of menstrual irregularity and infertility and is correlated with increased serum androgens and luteinizing hormone. However, it is not clear whether it is the visceral or subcutaneous adipose tissue that is related to reproductive dysfunction. Many multiparous women are obese and indeed most obese women are able to get pregnant easily. However, the general view is that being overweight is correlated with difficulty in getting pregnant (Norman *et al*., 2004). This is particularly shown in the Nurses Health Study looking at 2527 married infertile nurses. The risk of ovulatory infertility increased from 1.3 in a group with a normal BMI to a rate of 2.7 in women with a BMI over 32 (Rich-Edwards *et al*., 1994). Treatment of anovulatory infertility of overweight women requires increased concentrations of clomiphene citrate and higher doses of gonadotrophins to induce an ovulatory follicle. Treatment of overweight women on IVF programs shows a much lower pregnancy rate (Crosignani *et al*., 1994; Wang *et al*., 2000; Fedorcsak *et al*., 2001). There is also evidence using donor eggs that the body mass of the recipient is more important than the body mass of the donor (Figure 6). This is largely due to the miscarriage rate which has been shown to increase four-fold in the obese (Bellver *et al*., 2003).

Table III. Impact of obesity on reproduction

Condition	Associated risks
Menstruation	Risk of menstrual dysfunction: amenorrhoea, oligomenorrhea and menorrhagia
Infertility	Risk of ovulatory and anovulatory infertility: anovulation, poor response to fertility drugs
Miscarriage	Risk of miscarriage, spontaneously and after infertility treatment
Glucose	Risk of impaired glucose tolerance and type 2 diabetes mellitus intolerance
Infertility treatment	Requirement for clomiphene citrate/gonadotrophin ovulation induction. Success rate for IVF/ICSI pregnancies
Pregnancy	Prevalence of pregnancy-induced hypertension, gestational diabetes, caesarean section and Down's syndrome

Weight loss management in PCOS

The primary goal of treatment in PCOS is to normalize serum androgens and to restore reproductive function. This is achieved by reducing insulin resistance through a decrease in weight and abdominal fat. Lifestyle modification has been shown overwhelmingly to be successful with interventions as little as 3–4 weeks inducing weight losses of 5–10% of initial body weight. Caloric restriction improves insulin sensitivity measured through euglycaemic hyperinsulinemic clamps, fasting glucose insulin ratios, oral glucose tolerance test (OGTT) stimulated insulin and fasting insulin. Weight loss also decreases hyperandrogenaemia and improves menstrual function, ovulation, fertility and hirsutism. The return of reproductive function occurs with modest weight loss (<10% of initial body weight) even though the end of study BMI often is over 30 kg/m^2 (Crosignani *et al*., 2003; Norman *et al*., 2004).

Weight loss is not consistent in all patients because discrepancies in appetite regulation might exist. Ghrelin is a stomach-derived hormone that increases sharply before feeding onset and decreases after a meal. In obesity, fasting levels of ghrelin are decreased and the post-prandial decrease might be impaired potentially compromising meal termination. Fasting ghrelin increases with weight loss. Weight loss is a desirable outcome in overweight women with PCOS for short- and long-term improvements in reproductive and metabolic health. Precise dietary evidence-based guidelines are needed for the treatment of this group, both in the amelioration of short-term reproductive and metabolic dysfunction

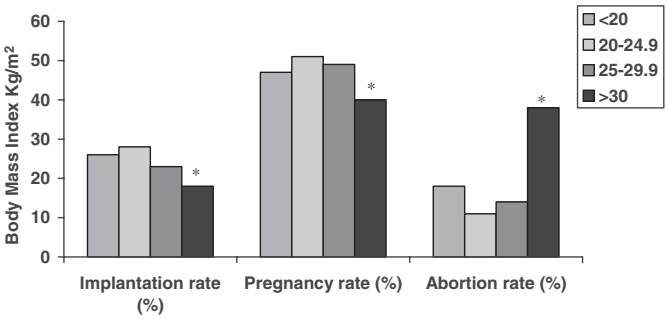

Figure 6. Body weight (BMI) of recipient is important for oocyte donation (Bellver *et al*., 2003). * = p<.05.

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Table IV. Practical approaches to weight loss

Sensible diet
Smoking cessation
Effective exercise
Avoid crash diets
Use behavioural modification for stress
Minimal role for drugs
Avoid surgery in the majority
Sympathetic physician support

Table V. Obesity increases risks of both pre-eclampsia and gestational hypertension (Ros *et al*., 1998)

Body mass index	Pre-eclampsia [OR (95% CI)]	Gestational hypertension [OR (95% CI)]
Underweight (<19.8)	1.0	1.0
Normal (19.8–26.0)	1.5 (0.8–2.9)	1.8 (0.8–3.7)
Overweight (26.1–29.0)	3.1 (1.4–6.8)	2.0 (0.8–5.3)
Obese (>29.0)	5.2 (2.4–11.5)	4.9 (2.0–11.9)

and for minimizing long-term cardiovascular and diabetic mortality and morbidity.

There are a number of dietary approaches to the overweight women with reproductive dysfunction that include high protein, high carbohydrate or low fat diets. There is a paucity of data examining the relationship between these various approaches but overall low calories are the most important component of a diet rather than its actual composition. There has been interest recently in the glycaemic index particularly by introducing a low glycaemic index diet. Practical approaches to weight loss are summarized in Table IV.

Pharmacological management

Administration of insulin sensitizing drugs is controversial although at least one study has suggested that the addition of metformin to a low calories diet and lifestyle change leads to extra benefit (Norman, 2004). The adjuvant use of such a drug with diet and exercise needs investigation. There are few studies of using appetite suppressants and lipid anti-resorption drugs in PCOS. Gastric stapling and banding may have some value in women who are very obese.

Gestation in obese patients

The prevalence of overweight in pregnancy is now 35% and one-fifth of these are obese, thus, risks of miscarriage, pregnancy complications and adverse pregnancy outcomes related to maternal overweight and obesity are important from a public health perspective (Andreasen *et al*., 2004; Cedergren, 2004).

Bodyweight and abortion

Several studies have shown that there is an increased risk of spontaneous abortion in obese women, irrespective of the coexistence of PCOS (Hamilton-Fairley *et al*., 1992; Wang *et al*., 2001; Roth *et al*., 2003). In one study involving donor oocyte pregnancies, the spontaneous miscarriage rate was increased in acceptor women with a BMI over 30 kg per m^2 (Bellver *et al*., 2003) (Figure 6). The relation between obesity and miscarriage concerns predominantly early miscarriage. Lashen *et al*. (2004) found a significant difference between early miscarriage rate in obese patients (n = 1644): 12.5% (95% CI = 11–14%) and normal weight patients (n = 3288): 10.5% (95% CI = 10–12%). There was no increase in late miscarriages. Wang *et al*. (2002) in a retrospective study of 2349 women confirmed earlier findings by Fedorcsak *et al*. (2000) in IVF patients and found a significantly increased spontaneous abortion rate after IVF in women with a BMI of 25–30 (22% abortions), 30–35 (27% abortions) and over 35 kg per m^2 (31% abortions). In the Lashen *et al*. study, the rate of recurrent early miscarriage was 0.4% in obese women (95% CI = 0.1–0.7) compared with 0.1% in women of normal weight (95% CI 0.02–0.2). Although significant, the difference was not large (Lashen *et al*., 2004).

Pregnancy complications

In animals, overfeeding of sheep in late pregnancy leads to pregnancy complications as well as dystocia at birth (Wallace *et al*., 2001). Gestational diabetes is far more common in overweight and obese women compared to women with normal weight. Swedish data show a doubling in risk of gestational diabetes among overweight women and a six-fold increase in risk among obese women (Cnattingius and Lambe, 2002). Similar results have been reported from other countries, such as the United States (Baeten *et al*., 2001). These risks are most likely related to increased insulin resistance among overweight and obese women. Since gestational diabetes increases the risk of subsequent development of type 2 diabetes, the generally increasing BMI among young women may be specially important in populations with genetic susceptibility for type 2 diabetes, i.e., many Asian populations (Table V).

Pregnancy-induced hypertensive diseases, such as gestational hypertension and pre-eclampsia, are also known to occur more often in overweight and obese women compared to women of normal weight (Ros *et al*., 1998; Nuthalampaty and Rouse, 2004). The mechanisms by which overweight increases the risk of pregnancy-induced hypertensive diseases are not clear. The increased risk of insulin resistance among overweight women gives rise to hyperinsulinemia, which may lead to hypertension by vasoconstriction. In addition, insulin resistance may also increase the risk of endothelial dysfunction (Roos *et al*., 1998).

The risk of cesarean delivery increases with BMI, partly because of weight-related risks of pregnancy complications, which increase the likelihood of induced labour. During delivery, overweight and obese women also face a substantial risk of dystocia, which can be explained by increased occurrence of fetal macrosomia, but primary and secondary inertia uteri are also more common among overweight pregnant women (Jensen *et al*., 1999). Cesarean deliveries among obese gravidas are also associated with increased risks of peri- and post-operative complications, including excessive blood loss and post-operative infections (Nuthalampaty and Rouse, 2004).

Pregnancy outcomes

The risk of stillbirth increases with BMI. Compared to women with normal BMI (20.0–24.9), the risk of stillbirth among obese (BMI ≥ 30.0) mothers is 40–100% higher (Sebire *et al*., 2001; Cnattingius and Lambe, 2002). The reasons for the weight-related increase in stillbirth remain to be determined. One possibility is that the increased risk may be due to residual social confounding.

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However, adjusting for maternal education and other social factors does not substantially influence the risks of stillbirth related to overweight and obesity (Cnattingius and Lambe, 2002). A second possibility is that the association between overweight and obesity and stillbirth risk may reflect that overweight and obesity, in fact, negatively influence fetal environment (gestational diabetes, pre-eclampsia and hyperlipidemia) which in turn increase the risk of stillbirth (Cnattingius and Lambe, 2002).

Obesity is reported to increase the risk of induced pre-term birth, an association most likely caused by obesity-related pregnancy disease, i.e., pre-eclampsia and gestational diabetes (Hendler *et al*., 2005). One study reports that obesity increased the risk of infant death (Baeten *et al*., 2001). Moreover, provided that obesity increases the risk of pre-term birth, a possible association between overweight and obesity and infant mortality may be mediated by an increased risk of pre-term birth related to high maternal BMI.

Overweight and obesity are consistently associated with increased risk of the delivery of large-for-gestational-age infants. The reduced insulin sensitivity among obese mothers increases the availability of glucose to the fetus, which thereby may increase fetal growth (Surkan *et al*., 2004). The increasing prevalence of maternal overweight and obesity seems to be the main reason for the increasing prevalence of infants born with a high birthweight in North America and Europe (Kramer *et al*., 2002; Surkan *et al*., 2004).

Finally, maternal overweight and obesity may also carry a long-term risk for the newborn infant. Rates of large-for-gestational-age infants are increasing as a consequence of increasing maternal BMI. Infants born large-for-gestational-age are at a higher risk of being overweight in adulthood (Eriksson *et al*., 2001). Thus, offspring to overweight mothers may not only face an increased risk of being large-for-gestational-age at birth, but may also carry a long-term risk of overweight and overweight-related diseases in adulthood.

Prevention of obesity

The continuing rise in the obesity epidemic calls for immediate action. Numerous treatment intervention studies have documented that *secondary prevention* is effective: significant weight loss can easily be obtained by caloric restriction. Additionally, several studies show that although weight loss *per se* may be modest after intervention with increased physical activity, the addition of activity to dietary interventions generally proves very beneficial, because the resulting increase in lean tissue at the expense of fat not only reduces fat mass, but also increases the metabolically active lean body compartments such as muscle mass (Haddock *et al*., 2002).

By contrast, there is still unconvincing evidence from the published literature that *primary* community interventions towards weight gain works. Hence, the general notion that current trends for obesity are consequences of gluttony and sloth only would seem a major simplification. Rather, a more complicated interaction between cultural, psychological, social, familial and genetic factors seems to operate. Indeed, it is likely that primary intervention trials should focus on high-risk groups, such as lean children from families where obesity is a problem, lean children from low socioeconomy families or children already modestly overweight. These focused programs may be more effective than previous prevention trials aimed at general population groups.

Contraception and weight

In most young women, contraception is the earliest reproductive consideration, and obesity influences decisions and effectiveness of hormonal contraceptives. The relationship between contraception and weight is complex. Many women attribute weight gain to the method of contraception they are using; it is a common reason for method discontinuation and fear of putting on weight deters some women from ever starting certain methods. Some hormonal methods may well cause weight gain in susceptible women and body weight appears to influence efficacy of most methods. Finally, excess body weight can be a contraindication to some methods of contraception.

The influence of weight on uptake and continuation

Most surveys of contraceptive use highlight weight gain as an important issue for women. In a survey of 967 British women of reproductive age nearly half perceived the risk of CVD (45%) or cancer (41%) as a theoretical disadvantage of oral contraception, but almost twice as many (73%) of women were worried about weight gain (Oddens *et al*., 1994). In a survey of 1466 German women, 21% of current users and 32% of past users claimed a median weight gain of 5 kg which they attributed to OC use (Oddens, 1999). Weight gain—whether caused by the contraceptive method or not—is a common reason for discontinuation. In a longitudinal survey of Swedish women followed up every 5 years, weight gain was given as the reason for one in five 19-year-old women stopping the oral contraceptive pill (Larsson *et al*., 1997). Similarly, weight gain was the commonest side effect leading to discontinuation of Depo Provera in a cohort of New Zealand women (Colli *et al*., 1999).

Fear of weight gain influences acceptability of most hormonal methods especially, perhaps, Depo Provera. In two separate studies of contraceptive use among adolescents 25% of young women preferred to use barrier methods despite their lower efficacy, because they were worried they would gain weight on the pill (Pratt and Bachrach, 1987; Dusterberg and Brill, 1990).

The influence of contraception on weight

Women—and men—gain weight during their reproductive lives. In an observational study of 1697 Brazilian women using a copper intrauterine device (IUD) the mean weight of the cohort was 58.5 kg (SD = 0.3) when the IUD was inserted. After 5 years of follow-up mean weight was 61.2 kg (SD = 0.33) and after 7 years 62.4 kg (SD = 0.55) (Hassan *et al*., 2003). It is possible that hormonal contraceptives, through a variety of mechanisms including (among others) stimulation of the RAS, altered carbohydrate metabolism or increased appetite, might cause weight gain.

In a non-systematic review of the literature on the effect of the combined pill on weight, Gupta summarized a number of comparative and non-comparative, controlled and blinded or double blind studies (Gupta, 2000). Whatever the study design, most demonstrated that roughly one third of women regardless of the method of contraception they were using gained up to 2 kg in weight over 6–12 months of follow-up. A smaller proportion of women lost weight. In a more recent Cochrane review, Gallo and colleagues reviewed 570 published reports of weight change among users of combined hormonal contraception (Gallo *et al*., 2004). The quality of reporting of the trials was ‘generally poor’

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Table VI. Hormonal contraception: weight change in placebo-controlled trials (Gallo *et al*., 2003)

Date	Estrogen (μg)	Cycles	Measurement	Likelihood
1971	100 EE	4	Gain > 2.3 kg	1.0 (0.5–2.3)
1971	100 Mestranol	4	Gain > 2.3 kg	0.6 (0.2–1.3)
1971	50 Mestranol	4	Gain > 2.3 kg	0.5 (0.2–1.2)
2001	20 EE	6	Mean difference (kg)	0.3 (–0.2–1.2)
2000	Patch (20)	9	Gain > 5%	1.0 (0.3–3.0)
2000	Patch (20)	9	Loss > 5%	0.3 (0.0–1.8)

(the description of their shortcomings takes up most of the paper). There were four placebo-controlled trials among pill users and one among women using the contraceptive patch. No statistically significant differences in weight change were identified when contraceptive users were compared with non-users (Table VI). Five of the 69 trials comparing two different formulations of combined pill did, however, demonstrate significant weight gain but the largest mean difference was 1.8 kg (95% CI = 0.7–3.4) after 1 year. The authors of the review concluded that the evidence is insufficient to rule out any effect of combined hormonal contraception on weight change but that it is unlikely that there is any large effect.

Data for the effect of progestogen-only contraceptives (POC) on weight change are less extensive. Although studies have reported variable effects of Depo Provera on weight, some have reported weight increase of 3–6 kg. In a review of the topic Westhoff (2003) points out that certain groups of women have a susceptibility to gain weight (including post-partum adolescents, African Americans, Maori and Navajo Indians) and that these groups often feature in studies of DMPA (Westhoff, 2003). A 5 year prospective study of 103 Brazilian women using DMPA reported a mean weight increase of 4.3 kg over 5 years, significantly greater than that typical of a control group of IUD users (1.8 kg) matched for age and weight at the start of the study (Bahamondes *et al*., 2001). In contrast a study of Thai women showed no difference between IUD users and DMPA users, both gaining approximately 8 kg over 10 years (Taneepanichskul *et al*., 1998). A very recent well-designed study from the United States demonstrated a mean increase of 6.1 kg in weight and 24% in body fat after 30 months of starting Depo Provera (Clark *et al*., 2005).

Most studies of contraceptive implants show an average increase in weight of 0.4–1.5 kg/year (Brache *et al*., 2002) but a controlled study comparing Norplant users with IUD users demonstrated no difference between the two groups (Sivin, 1983).

The influence of weight on contraceptive efficacy

Hormonal contraceptives, like most drugs, are administered at the same dose regardless of the weight or BMI of the user. There are data to suggest that the efficacy of some methods may be reduced when used by overweight women. Several mechanisms can be hypothesized, simple dilution of the steroids in a larger blood volume, sequestration of steroids in fat cells or different metabolism of steroids by obese women. In a retrospective cohort analysis of 755 randomly selected women in Washington State, women weighing over 70.5 kg had a significantly increased risk of oral contraceptive failure (RR1.6, 95% CI = 1.1,2.4) compared with women of lower weight. The risk of failure was inversely related to the dose of estrogen in the pill (Holt *et al*., 2002). Similar findings have been demonstrated among users of the contraceptive patch (Zieman *et al*., 2002) and of progestogen-only oral contraceptives (POP) (Vessey *et al*., 1985), and it has become common practice in the United Kingdom to prescribe a doubled dose of POP to women over 70 kg. While other variables, perhaps to do with compliance, are often cited as possible confounders, a number of trials have demonstrated increased failure rates among heavier women using Norplant when compliance is not an issue (Glasier, 2002). Since phase three clinical trials designed for the purposes of licensing drugs often specifically exclude women with a BMI over 30 or 35, data are lacking for new methods such as ImplAnonymous. It seems likely that for all hormonal contraceptives the balance between reducing the dose to improve safety and thereby jeopardizing efficacy is critical. What often gets forgotten, however, is that the absolute risk of failure is still very small and much less than that associated with less effective methods such as condoms.

The effect of weight on contraceptive effectiveness is also seen with female sterilization. In a multi-centre study of female sterilization using tubal rings, case control analysis revealed three risk factors for technical failure: obesity, previous use of an IUD and previous abdominal surgery (Chi *et al*., 1980).

The influence of weight on the side effects and safety of contraception

The vast majority of women who use contraception are well and can use any method with minimal risk of serious side effects. For some women with pre-existing medical conditions, such as hypertension for example, the risks of some contraceptives, particularly combined hormonal methods, may outweigh the benefits. Obesity is one such condition, but additionally being overweight contributes to a list of other conditions (such as smoking) which when taken together substantially increase the risks of CVD. In the WHO Medical Eligibility Criteria BMI >30 kg/m^2 is considered a category 2 condition for all combined hormonal methods indicating that the methods can generally be used but more careful follow-up may be required (World Health Organisation, 2004). The British National Formulary regards a BMI of >39 kg/m^2 as an absolute contraindication to the combined pill. Using the UK Mediplus and General Practice Research databases to identify women with venous thromboembolism while exposed to the combined oral contraceptive pill, Nightingale *et al*. (2000) identified a significant association with a BMI of over 25 kg/m^2 (Nightingale *et al*., 2000). The association rose dramatically among women with a BMI > 35 kg/m^2.

An association between weight and safety applies mainly to combined hormonal contraception; however, a study of over 9000 women undergoing sterilization identified obesity as an independent risk factor for significant complications (OR = 1.7; CI = 1.2–2.6) (Jamieson *et al*., 2000).

Conclusions

While deprivation and undernutrition are major causes of disease and death in developing countries, eating disorders and obesity are the nutrition problems most likely to interfere with reproduction in developed countries. Because preservation of female energy expenditure for reproduction is essential, appetite and the reproductive

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axis are closely linked to nutritional status. As a safeguard against untimely reproduction due to undernutrition, ovarian activity is suppressed in women with eating disorders and exercise amenorrhoea through pathways in the hindbrain. It is the balance between energy consumption and utilization that is crucial more than the body fat mass, thus recovery of ovulation may occur after a small percentage gain in weight.

The combined prevalence of bulimia nervosa and anorexia nervosa is approximately 5% among women of reproductive age, and the likelihood of cure is higher with bulimia nervosa. Both disorders suppress ovulation in severely affected women and account for up to 60% of women with anovulatory infertility. Pregnancy among underweight women increases the risk of premature labour.

Obesity and its related problems to day are major issues.

In Western countries among women the obesity rate range is from about 10–25% and is increasing through mechanisms that include genetic, biological, psychological and social factors.

The *thrifty gene hypothesis* may explain why obesity used to be an advantage in famine conditions but has turned into a disadvantage in modern society. Nature's answer may be sub-fertility and increased pregnancy complications in essence a natural selection in favour of a *profligacy gene*.

Social determinants for obesity are clearly operating and results in a much higher prevalence of obesity among the socially disadvantaged. Maternal obesity is a strong predictor of offspring obesity but the relationship is complex since the infant who have been restrained *in utero* tend to gain weight and to have more fat mass in childhood. The world-wide increase in maternal weight is of great public health concern and provides further support for the planning of prevention strategies aimed at reducing the current trend to large birthweight babies.

In countries where smoking prevalence has decreased, overweight and obesity may be the most important risk factor for poor pregnancy outcomes.

Fat tissue is metabolically active and its most important activity is intrafat modifications of steroid hormones and secretion of adipokines. Many of these factor influences are reproductive hormones, but in turn the secretions of the fat can affect the functioning of the reproductive system.

Many obese women conceive and go through pregnancy without incident, nonetheless, being overweight or obese impairs natural fertility and interferes with the response to the profertility treatments. The mechanisms are not clear, but the association between insulin resistance and anovulation may contribute. Management should involve diet and exercise programs to precede or supplement induction of ovulation. Such lifestyle programs require intensive effort but can be effective. Fortunately ovulation is often achieved after minimal weight loss, perhaps because of the alteration in energy balance.

The prevalence of overweight in pregnancy is now 35%, and one-fifth of these are obese. Among overweight and obese women who conceive, there is an increased likelihood of spontaneous pregnancy loss, mainly in the first trimester as well as pregnancy complications (pregnancy-induced hypertensive diseases and gestational diabetes) and pregnancy outcomes.

Prevention of obesity is, at the present, one of the most important program for health promotion.

Practical recommendations for preventive intervention

(i) Medical education for doctors on the art of preventing obesity and managing weight loss in women with established overweight and obesity.

(ii) Patient education regarding the role of obesity in reproduction.

(iii) Promotion of fitness and healthy living for the woman, her partner and their future family. The emphasis should be on reducing central adiposity and improving metabolic fitness rather than simply on weight and BMI reduction.

(iv) Long-term weight control. It is useless to have a short term very low-calorie diet that fails to induce results in several months time.

(v) Reduced calorie diets are more important than dietary composition.

(vi) Checks for metabolic disorders at the start and at regular intervals are essential for obese women with PCOS or any other obesity-related reproductive disorder.

(vii) Psychological advice. This is helpful for those committed to a long-term change in lifestyle and is often best provided through group therapy among women with similar problems who meet together on a regular basis.

The relationship between contraception and weight is complex and influences method choice and continuation, efficacy, side effects and safety. Since the incidence of obesity is increasing worldwide (nearly one third of all Americans are obese), this relationship is becoming increasingly relevant. There is a danger that women and their healthcare professionals loose sight of the fact that contraception is designed to prevent unwanted pregnancy. Fat women get pregnant and obesity is associated with an increased risk of complications for both the mother and the baby. It is vital that concern about the *relative* risk of contraceptive failure and of serious side effects does not overshadow the small *absolute* risks. It is important too for women to understand that weight gain is extremely common and seldom due to the method of contraception they are using.

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