normal circumstances, unlikely to be reversed and can be regarded as "built-in" risks for reproductive cancers for women born in affluent environmental conditions. Therefore, it is of crucial importance that specific behaviors (e.g., exercise programs) and/or hormonal interventions, such as those suggested by Short (1976) and others (Eaton et al., 1994), are undertaken to reduce breast cancer risk in the populations that as a result of their developmental characteristics (rapid growth and maturation) are already at comparatively high risk.

In conclusion, in this chapter we have proposed a model for human ovarian function in which chronic energetic conditions *during the postnatal period* establish an overall program of energy allocation into growth, maintenance, and reproduction via the regulation of metabolic hormones such as insulin and/or IGFs (Lipson, 2001; Poretsky et al., 1999). One of the consequences of this program is the establishment of set points for ovarian function around which short-term adjustments are made according to acute fluctuations in energy availability during adult life. From an evolutionary perspective, such fine-tuned regulation should lead to the optimization of reproductive effort and, ultimately, fitness (Ellison, 1996; Lipson, 2001).

The downside of this phenotypic flexibility for modern human females living in affluent conditions is the increased health risk for reproductive cancers in later life that accompanies exposure to higher steroid hormone levels. The value, however, of an evolutionary perspective on reproductive function is that specific behavioral recommendations could be made to reduce the risks of acquiring high ovarian steroid levels. Obviously, we do not want to compromise the nutritional well-being of developing children or their immune status either by restricting food intake or increasing their exposure to pathogens. Nor do we know the potential risks of administering exogenous hormones that might delay menarche but have other long-term side effects. However, schools (and parents) in industrialized countries could promote high levels of exercise for children (at least up until the age of 8 years old and ideally through adolescence) as a healthy, low-risk, and cost-effective means of lowering steroid levels and reducing cancer risks in the next generation of adult women. Framing such health promotion within the context of how far removed we are now (in affluent, industrialized countries) from the kinds of environments in which our human ancestors lived (and expended their energies) for many thousands of years (as has been done by many earlier scholars, e.g., Eaton et al., 1994) is perhaps a fundamental part now of the evolutionary medicine paradigm. But the next step surely, if evolutionary medicine is to move beyond theory, is to try and implement these recommendations in specific settings.

CHAPTER 8

Impaired Reproductive Function in Women in Western and "Westernizing" Populations

An Evolutionary Approach

Tessa M. Pollard and Nigel Unwin

What happens when women live in evolutionarily novel Western environments that promote conditions of obesity, insulin resistance, and hyperinsulinemia? In this chapter Pollard and Unwin describe the significance of high levels of insulin, induced both by high-calorie Western diets and reduced energy output, for women's reproductive function. Hyperinsulinemia promotes high levels of free androgens, mainly by reducing levels of sex hormone-binding globulin. In turn, high levels of free androgens negatively affect reproductive function. Women in "Westernizing" populations undergoing socioeconomic transition often experience particularly high levels of insulin, and there is some evidence to suggest that, as a consequence, they are also likely to face particularly severe impairment of reproductive function. Pollard and Unwin explore this issue in relation to British Pakistani women. They emphasize the importance of studying sex hormone-binding globulin levels in studies of reproductive function. This chapter explores issues that are important for our understanding of reproductive function and are new to evolutionary medicine.

INTRODUCTION

Compared with those living in less affluent countries, women living in Western societies generally experience higher levels of the ovarian hormones progesterone and estradiol (Bentley, Harrigan, & Ellison, 1998; Ellison et al., 1993; Key, Chen, Wang, Pike, & Boreham, 1990; Vitzthum, Spielvogel, & Thornburg, 2004; see also Chapter 7), and ovarian hormone levels in Western women are considered to represent the extreme of the global distribution of ovarian function (Ellison et al., 1993). Within evolutionary medicine and biological anthropology groundbreaking work has highlighted links between these

high estrogen and progesterone levels and high rates of breast cancer in the West (Ellison 1999; Jasienska, Thune, & Ellison, 2000). Ellison (2001, p. 213) suggests that such population variation in ovarian function is related to chronic energy availability. Thus high levels of estradiol and progesterone in Western women are the result of environments in which calorifically dense foods are readily available in combination with minimal required energetic expenditure.

For the same reasons, women living in the affluent West are at high risk of pathological changes in the metabolic system, and we show here that these changes are likely to have adverse consequences for reproductive function. In particular, in women of reproductive age there are important interactions between insulin levels and ovarian function. In this chapter we describe the significance of high levels of insulin and consider how, why, and to what degree chronically high levels of insulin can lead to significant problems with reproductive function. We further explore and highlight escalations of these problems among women from populations in socioeconomic transition.

INSULIN RESISTANCE AND INSULIN LEVELS IN AFFLUENT WESTERN POPULATIONS

Insulin resistance is the main underlying pathology of type 2 diabetes and an important risk factor for cardiovascular disease (Reaven, 1988). The main role of insulin is to regulate levels of glucose in the body. Insulin is secreted by the pancreas when blood glucose levels rise as a result of the consumption of carbohydrates. It prompts the uptake, storage, and use of glucose by almost all tissues of the body and suppresses the production of glucose by the liver. It is also an important regulator of lipid metabolism. In people with insulin resistance, skeletal muscle and liver do not respond in the normal way to insulin. As a result the body secretes more insulin, leading to higher insulin levels or hyperinsulinemia, and this may regulate glucose levels successfully for a time. Elevated blood glucose and finally type 2 diabetes result when the pancreas is no longer able to produce sufficient insulin to overcome insulin resistance and maintain normal glucose levels (Greenspan & Gardner, 2004)

Insulin resistance and hyperinsulinemia are strongly associated with excess body weight and physical inactivity (Ryan, 2003), and particularly with abdominal obesity, which is caused by excessive visceral fat (Despres, 2006). In addition, certain types of diet increase the risk of insulin resistance, particularly diets low in fiber and with a high glycemic index (foods that cause a particularly large increase in blood glucose levels) (McKeown et al., 2004). Most refined starchy foods, including bread and starchy root vegetables, have a high glycemic index, whereas nonstarchy vegetables, fruit, and legumes tend to have a low glycemic index (Ludwig, 2002). Levels of obesity are high and levels of physical activity are low in Western societies (Catanese, Koetting O'Byrne & Poston, 2001; Flegal, Carroll, Kuczmarski & Johnson, 1998; Katzmarzyk, 2002), while refined grain products with a high glycemic load now supply 20% of the energy in the typical U.S. diet and high glycemic load sugars supply 16% of energy (Cordain, Eades, & Eades, 2003). For all these reasons, levels of insulin resistance in Western populations are high.

Diet and physical activity levels during most of human evolutionary history were very different, as deduced from studies of modern-day hunter-gatherers, who have very low

levels of obesity and high levels of physical activity and usually eat a high proportion of nonstarchy fruit, vegetables, and legumes (Eaton, Eaton, & Konner, 1999; Jenike, 2001). Unfortunately, we have little direct information on insulin resistance or hyperinsulinemia in people living as hunter-gatherers. However, suggestive data were collected by O'Dea (1984), who accompanied a group of overweight diabetic Australian Aborigines while they reverted to a traditional hunter-gatherer lifestyle for 7 weeks. She found that during this period the participants experienced significant weight loss, a striking improvement in levels of insulin resistance, and a reduction in fasting insulin levels.

Thus, persistently high insulin levels are an evolutionarily new phenomenon, and they are an important cause of ill health in affluent Western societies. In addition to type 2 diabetes and cardiovascular disease, increasing numbers of other diseases have been linked to hyperinsulinemia via a number of physiological pathways, including breast, colon, and prostate cancer, myopia, and acne (Cordain et al., 2003).

INTERACTIONS BETWEEN INSULIN LEVELS AND OVARIAN FUNCTION IN AFFLUENT WESTERN POPULATIONS

Lipson (2001) has suggested that metabolic hormones, principally insulin, and the closely related insulin-like growth factor (IGF)-1, as well as leptin, signal energetic conditions to the reproductive system. The ovaries are influenced by an insulin-related regulatory system (Poretsky, Cataldo, Rosenwaks, & Giudice, 1999), and metabolic hormones may also have effects at the hypothalamic level. Several studies have shown that levels of metabolic hormones indicating an energy deficit were associated with disrupted or reduced ovarian function (Lipson, 2001). Lipson (2001) also suggests that, conversely, high levels of insulin and IGF-1 probably stimulate high levels of ovarian steroid concentrations, although this has not been consistently demonstrated in vivo (Poretsky et al., 1999). Early menarche, as seen in Western populations, may be associated with increased insulin concentrations in overweight girls (Lipson, 2001). Thus metabolic hormones appear to provide a mechanism that links energetic availability and ovarian function (Ellison, 2001, see also Chapter 7).

So what happens when women live in evolutionarily novel Western environments that promote conditions of obesity, insulin resistance, and hyperinsulinemia? Obesity is known to be positively associated with risks of oligomenorrhea (infrequent menstruation), amenorrhea (absence of menstruation), and chronic anovulation, and it is thought that hyperinsulinemia is the main cause of these effects (Pasquali, Pelusi, Genghini, Cacciari, & Gambineri, 2003). The main effects of abnormally high levels of insulin do not appear to be on ovarian secretion of progesterone and estrogens (although level of these hormones may be high). Rather, the most important effects are on the ovarian secretion of androgens and the production by the liver of sex hormone-binding globulin (SHBG) (Livingston & Collison, 2002). SHBG is the main binding protein for testosterone and estradiol, and the level of SHBG is an important determinant of levels of free and biologically active testosterone and estradiol in both men and women. Because testosterone has a relatively high affinity to SHBG, any reduction in SHBG increases the bioavailability of circulating testosterone, in particular, and also increases the ratio of free testosterone to free estradiol. Thus hyperinsulinemia promotes high levels of

androgens, referred to as hyperandrogenism, in women (Figure 8-1) (Livingston & Collison, 2002; Poretsky et al., 1999). Hyperandrogenism in turn contributes to insulin resistance, leading to a damaging cycle of interaction whereby androgen and insulin levels cycle upwards (Livingston & Collison, 2002). This is illustrated by a recent meta-analysis, which showed that testosterone levels are higher in women with type 2 diabetes than in nondiabetic women. Additionally, in prospective studies, women with lower SHBG levels had a higher risk of developing type 2 diabetes (Ding, Song, Malik, & Liu, 2006).

Androgens have adverse effects on the growth of follicles in the ovary during the early stages of the menstrual cycle (Balen, 1999). It is not surprising then that low SHBG and high free androgens are associated with reduced fecundity in women (van der Spuy & Dyer, 2004). For example, van Hooff et al. (2004) showed that testosterone level at age 15 was positively associated with persistence of oligomenorrhoea at age 18 in girls. Apter and Vihko (1990) showed that women with relatively high serum androgen concentrations conceived at a lower rate than other women.

Low SHBG and high free androgens are also associated with polycystic ovary syndrome (PCOS), one of the "hyperinsulinemic diseases of civilization" identified by Cordain et al. (2003). PCOS is a syndrome of ovarian dysfunction characterized by biochemical and clinical signs of hyperandrogenism, menstrual irregularity, and polycystic ovary morphology (enlarged ovaries with multiple cysts). In PCOS multiple dysfunctional small cysts develop in the ovary, instead of one dominant follicle as in a normal menstrual cycle, and ovulation does not generally occur. PCOS is strongly associated with insulin resistance. It is the most common endocrine cause of infertility in women in the West (Balen, 1999) and is reported to occur in 5–10% of women of reproductive age in affluent populations (Dunaif, 1997). More women (perhaps 20% of Western women (Dunaif, 1997)) have polycystic ovaries but not the full symptomology of PCOS. Dunaif also notes that up to 75% of women with secondary amenorrhoea meet the diagnostic criteria for PCOS. Women with PCOS who become pregnant have an increased risk of miscarriage, preeclampsia, and gestational diabetes (Patel & Nestler, 2006).

Perhaps because PCOS is clearly a pathological aberration of ovarian function, it has been studied mainly by clinicians working in the field of infertility and has largely

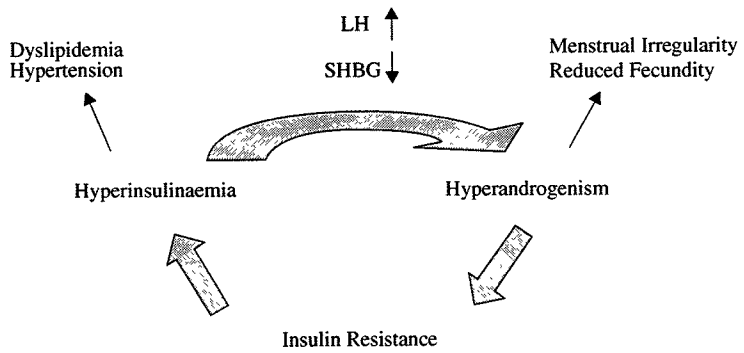

FIGURE 8-1 A simplified representation of the damaging cycle linking insulin and androgen levels in premenopausal women.

escaped the attention of human biologists with an interest in evolutionary theory. Meanwhile, despite the known links with insulin resistance, clinicians have not considered that rates of PCOS may be unusually high in Western populations. It seems clear, however, that we should think of PCOS as one of a number of pathological conditions associated with the novel human experience of living in affluent Western environments. We should also consider it, like type 2 diabetes, as the tip of an iceberg. In this case the invisible part of the iceberg consists of large numbers of women with tendencies towards high androgen levels, irregular menstrual cycles, and low levels of fecundity.

INTERACTIONS BETWEEN INSULIN LEVELS AND WOMEN'S REPRODUCTIVE FUNCTION IN POPULATIONS IN TRANSITION

Insulin Levels in Populations in Transition

We use the term populations in transition to refer to populations that are experiencing changes that are moving them towards the Western lifestyle. The term "nutrition transition" is often used to describe this process in relation to diet (Popkin, 2001). Other terms are also applied to these populations, such as "Westernizing" or "modernizing." We apply the term "populations in transition" particularly to populations living in urban areas of developing countries, but it is also relevant to migrants from developing to Western countries and to indigenous people living in countries colonized by Europeans. Millions of people worldwide fall into these categories.

Very high levels of type 2 diabetes are seen in some populations in transition. The best known examples are groups of indigenous people living in the United States, Canada, and Australia, who have rates of type 2 diabetes that are higher than even the high levels seen in the general populations in those countries (O'Dea, Hopper, Patel, Traianedes, & Kubisch, 1993; Száthmary, 1994; Weiss, Ferrell, & Hanis, 1984). This difference is reflected in high levels of fasting insulin and in the large insulin response to glucose in Australian Aborigines and Native Americans (Guest, O'Dea, Hopper, & Larkins, 1993; O'Dea et al., 1993; Ritenbaugh et al., 2003). In general, these groups of indigenous people followed their traditional subsistence ways of life before the arrival of Europeans, which often had an enormous impact on their social and economic systems, although there was considerable variation in these processes across populations and continents (Kunitz, 1994). In most cases diets are now very poor (high in fats and sugar and lacking in fruit and vegetables) and levels of physical activity are low in these populations (Szathmáry, 1994, Young, Reading, Elias, & O'Neil, 2000). Several groups of Pacific Islanders, most notably the people of Nauru, have also recently adopted Western lifestyles and developed high rates of obesity and type 2 diabetes (Zimmet, Taft, Guinea, Guthrie, & Thoma, 1977). Finally, migrants from some of the poorest parts of the world to the affluent West have been shown to have very high levels of insulin resistance and type 2 diabetes. The best known example is probably that of South Asian populations living in the West, particularly those living in the United Kingdom (e.g., Misra & Vikram, 2004). However, there are other examples, such as the high rates of diabetes suggested by a high relative risk of death from diabetes in Turkish, Moroccan, Surinamese, and Antillean/Aruban migrant groups in the Netherlands (Stirbu, Kunst, Bos, & Jackenback,

2006). Evidence from poor countries, such as India and Tanzania, suggests that the prevalence of type 2 diabetes and associated cardiovascular disease risk factors tends to be much higher in urban compared to rural areas (Aspray et al., 2000; Singh et al., 1997; Vorster, Venter, Wissin & Margetts, 2005).

Competing hypotheses have been posited for the high rates of insulin resistance, hyperinsulinemia, and type 2 diabetes in these populations. Some researchers have focused on putative genetic differences (the "thrifty genotype" hypothesis) (Diamond, 2003; Zimmet et al., 1977), while others have focused on the possibility that slow growth in early life, especially in utero, may increase predisposition to insulin resistance if risk factors for diabetes, such as lack of physical activity, are encountered in later life (the "thrifty phenotype" hypothesis) (Bateson et al., 2004; Drake & Walker, 2004; see also Chapter 18). The thrifty phenotype hypothesis may seem to imply that future generations born into a Western environment will have dramatically improved insulin sensitivity, but intergenerational effects (see Chapter 18) may mean that this will not be the case and that it will take several generations before these populations show levels of insulin sensitivity similar to those in established Western populations.

Whether the increased risk of insulin resistance and elevated insulin levels in Westernizing populations is caused by a genetic predisposition, by a mismatch between early and later environment, or by a combination of both, they have implications for reproductive function in Westernizing populations. These implications are outlined below.

Reproductive Function in Populations in Transition

We should expect high rates of insulin resistance in populations in transition to have adverse consequences for aspects of ovarian and wider reproductive function, as outlined above for Western women. If rates of insulin resistance are very high, then we expect the consequences for ovarian function will be correspondingly greater.

Unfortunately, information on reproductive function in populations in transition is far more sparse than information on insulin resistance, hyperinsulinemia, and rates of type 2 diabetes. However, some relevant work has been done with Pima (Native American) women. In a study of 695 nonpregnant Pima women aged 18–44 years, Roumain et al. (1998) found a history of menstrual irregularity (defined as an interval of 3 months or more between menstrual periods after the age of 18) in 21% of women. This compares with a rate of menstrual irregularity, defined in the same way, of 4% in a Swedish population-based study (Petterson, Fries, & Nillius, 1973; Solomon, 1999). Weiss et al. (1994) set out to test whether Pima women with higher insulin levels had elevated androgens and menstrual irregularities compared to women with lower insulin levels. They found that a high proportion (50%) of women in their "high-insulin" group reported menstrual irregularities. Total testosterone levels did not differ between high- and low-insulin groups of women, however. Given that high insulin levels are known to suppress production of SHBG, the authors speculated that those in the high-insulin group were likely to have low SHBG and therefore higher free testosterone levels. Thus, while no difference in total testosterone was observed between the low- and high-insulin groups, it is still possible that the high-insulin group had more free, biologically active, androgens.

We conducted a study of insulin levels and androgen levels in a group of British Pakistani women, an example of a population in transition. Half of the British Pakistani women were immigrants from Pakistan, while the other half were daughters of immigrant

women; our primary aim was to compare these two groups (Pollard, Unwin, Fischbacher, & Chamley, 2006). We present these data here as a relevant case study, comparing the British Pakistani women as a whole with a group of European women.

Insulin Levels, SHBG, and Testosterone Levels in British Pakistani Women: A Case Study

Compared to levels in the general population, there is a high level of coronary heart disease and type 2 diabetes in people of South Asian origin living in the United Kingdom, including British Pakistanis (McKeigue, Shah, & Marmot, 1991). We examined reproductive function and cardiovascular and type 2 diabetes risk factors in premenopausal British Pakistani women, with a main focus on intergenerational change. We were also interested in interactions between risk factors for cardiovascular disease and type 2 diabetes and reproductive function.

The participants were 85 women aged between 20 and 40, of whom 60 were British Pakistani (30 women born in Pakistan, 30 born in the United Kingdom) and 25 were women of European origin born in the United Kingdom (Table 8-1). The women were recruited mostly using snowballing techniques, whereby participants guide the researcher to others who may be eligible to participate in the study (Robson, 1993). Women who reported absent or irregular menses or diabetes were excluded because we wanted to sample estradiol on a specific day of the menstrual cycle (data not reported here). Thus the sample is not representative of the general population of premenopausal British Pakistani women and can only provide information on variation in androgen levels in regularly menstruating women. Of the women born in Pakistan, 4 migrated as young children (<8 years) and 26 migrated aged 15 or over. The majority of migrants had been

TABLE 8-1 Characteristics of Study Group[a]

	British Pakistani	European	*p*-value[b]
n	60	25	
Age (years)	30.1 ± 5.5	34.6 ± 4.2	<0.001
Height (m)	1.58 ± 0.06	1.63 ± 0.05	0.001
BMI	25.3 ± 4.8	27.3 ± 6.2	0.11
Birthplace			
Pakistan	30	0	
UK	30	25	
Highest educational level			0.45
None	1	0	
Primary	2	0	
Secondary	20	9	
Higher	30	14	
Occupation			0.002
Looking after home	22	4	
Employed	19	18	
Other	11	1	

[a] *Means and standard deviation are given for continuous variables. Sample sizes are given where there are missing data.*

[b] *p-values were calculated using ANOVA for age and chi-squared test for education and occupation.*

born and had grown up in northwest Pakistan, either in the Mirpur district of Azad Kashmir or in the Punjab. These are mainly poor rural areas, although many families who send migrants have benefited from remittances from other family members already in the United Kingdom (Shaw, 2000).

The methods for the study, other than for the assessment of cardiovascular risk factors, are described in Pollard et al. (2006). Briefly, women were visited in their own homes during the morning and following an overnight fast on day 9, 10, or 11 of the menstrual cycle. We assessed body composition using anthropometry, including skinfold measurements, and also levels of serum SHBG and testosterone, allowing us to calculate the free androgen index (as 100 x testosterone (nmol/l) / SHBG (nmol/l)). Fasting levels of glucose and insulin were assessed from serum. Insulin resistance was estimated from fasting glucose and insulin using the homeostasis modeling assessment (HOMA) method (Haffner, Miettinen, & Stern, 1997).

After adjusting for age and BMI using analysis of covariance, the British Pakistani women had significantly higher levels of insulin resistance, as assessed by HOMA-IR, than the European women ($p = 0.03$), although the difference in insulin levels was not

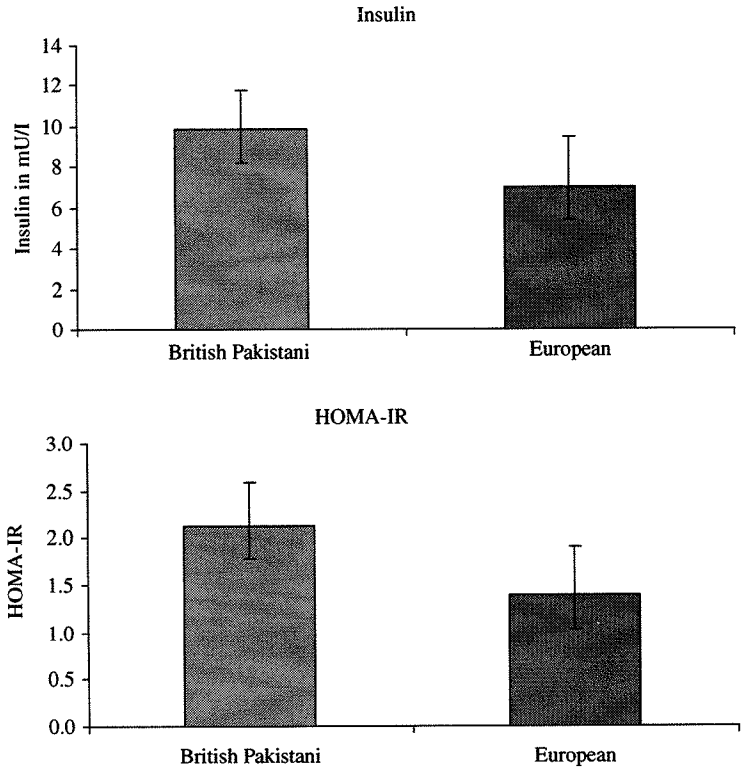

FIGURE 8-2 Geometric means for insulin level and insulin resistance (as assessed by HOMA-IR) adjusted for age and body mass index in British Pakistani women ($N = 57$) and white European women ($N = 24$). Error bars show 95% confidence intervals.

significant ($p = 0.07$) (Figure 8-2). After adjusting for age and BMI, there were also significant differences for SHBG ($p = 0.03$) (British Pakistani women had lower levels than white European women) and for free androgen index ($p = 0.02$) (British Pakistani women had higher levels), but not for total testosterone ($p = 0.39$) (Figure 8-3). There

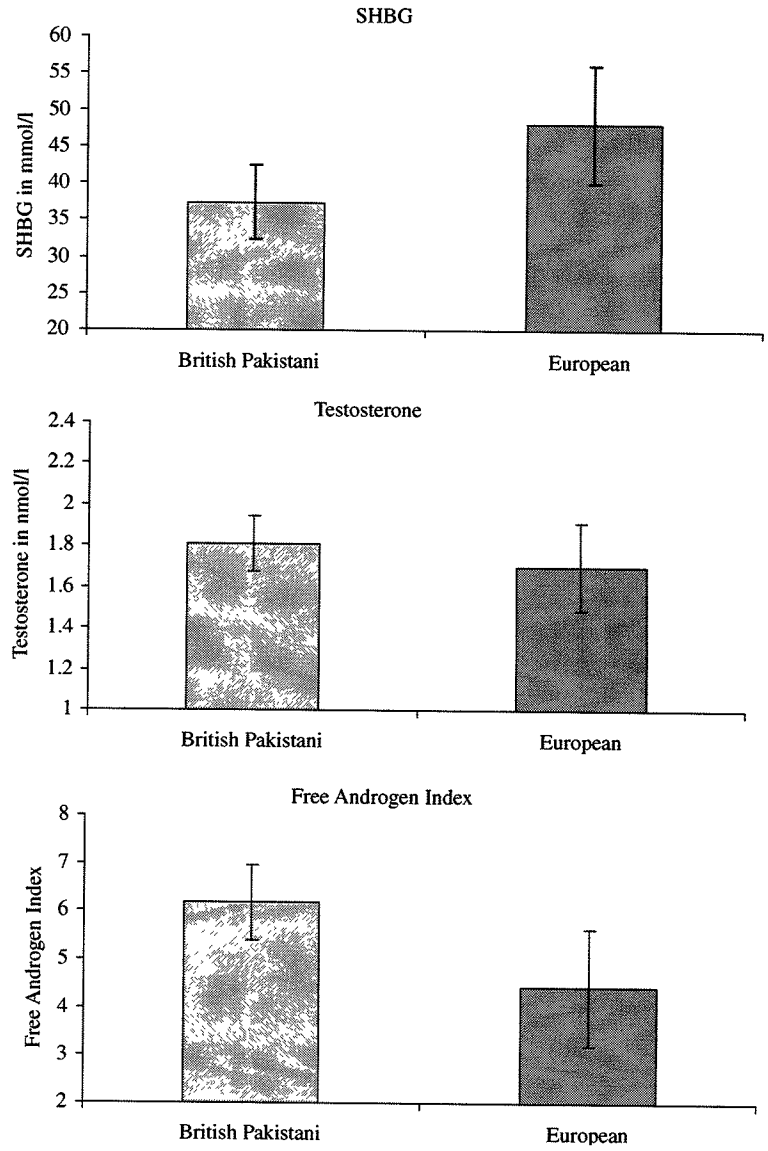

FIGURE 8-3 Means for SHBG, testosterone, and free androgen index adjusted for age and body mass index in British Pakistani ($N = 60$) and white European ($N = 25$) women. Error bars show 95% confidence intervals.

TABLE 8-2 Pearson Correlation Coefficients for Correlations Between Insulin and Insulin Resistance Levels and SHBG, Testosterone, and Free Androgen Index in 85 Premenopausal Women

	SHBG	Testosterone	Free androgen index
Insulin	−0.49***	−0.06	0.41***
HOMA-IR	−0.51***	−0.03	0.45***

***$p < 0.001$

were significant correlations between the insulin and insulin-resistance measures and the androgen-related measures in the expected directions (Table 8-2).

Thus there is evidence in this small group that regularly menstruating British Pakistani women had higher levels of insulin resistance, lower levels of SHBG, and higher levels of free androgens than regularly menstruating British women of European origin for a given age and level of BMI. Higher levels of insulin and insulin resistance were also associated with lower SHBG and a higher free androgen index. These are not surprising results given what we know about high levels of insulin resistance in the South Asian origin population in the United Kingdom and the known relationships between insulin resistance, insulin levels, and levels of SHBG and free androgens outlined above. Two previous studies of people of South Asian origin in the United Kingdom reported lower SHBG levels in South Asian than in European women (Reddy & Sanders, 1992; Reed et al., 1993), and Reed et al. also found higher free testosterone levels in South Asian women. Thus there has been some previous indication of greater androgenicity in women of South Asian origin living in the United Kingdom. There is also some evidence to suggest that PCOS may be more common in South Asian women in the United Kingdom than among European women. Rodin, Bano, Bland, Taylor, & Nussey (1998) described a prevalence of polycystic ovaries on ultrasound, which is more common than PCOS, of 52% in South Asian women in London, which can be compared to rates of around 20% in European populations (Polson, Adams, Wadsworth, & Franks, 1988). Together all these results suggest that there may be a high level of fertility problems in British South Asian women. However, there has been no study of PCOS prevalence rates in the British South Asian population, and we are not aware of any research on levels of infertility in British South Asian women. Such studies are clearly warranted, particularly as fertility is very important to many women of South Asian origin (Pollard et al., 2006).

METHODOLOGICAL IMPLICATIONS FOR STUDIES OF REPRODUCTIVE FUNCTION IN WOMEN

An understanding of the likely existence of high levels of androgenicity and associated problems in affluent Western populations and in populations in transition has important methodological implications for studies of ovarian function in these populations. First, such studies typically rely on the assessment of women experiencing regular menstrual

cycles, excluding women with irregular or absent cycles (as we did in our study of British Pakistani women). This is usually done because of the need to assess estradiol and progesterone over a menstrual cycle or at particular points in the menstrual cycle. Such exclusions impose biases on our assessment of ovarian function and reproductive health.

Another methodological message to emerge is the importance of SHBG as a determinant of free hormone levels. In Western and Westernizing women SHBG levels are likely to be low on average because of high levels of obesity and insulin resistance. Low levels of SHBG increase free testosterone and estradiol levels (with the greatest effect on free androgens). Studies of salivary estradiol measure only free estradiol levels and cannot determine the relative influences of ovarian secretion of total estradiol and SHBG levels on free estradiol levels. The importance of SHBG levels is illustrated in work on the effects of the high levels of consumption of phytoestrogens in women in Asia, which appears to provide protection against breast cancer. Although phytoestrogens do not appear to affect ovarian production of estrogen to any great extent, it is thought that they stimulate hepatic production of SHBG, leading to a reduction in free estradiol levels (Adlercreutz, 2002). SHBG levels rise during the luteal phase of the menstrual cycle, but a single serum sample timed in relation to the menstrual cycle has been shown to provide a good characterization of interindividual differences in premenopausal SHBG levels (Ahmad, Pollard, & Unwin, 2002; Plymate et al., 1985).

SHBG levels are also important determinants of levels of salivary testosterone in men. Campbell, Leslie, and Campbell (2006) assessed total testosterone, SHBG, and free testosterone and concluded that population variation in the rates of age-related decline in free testosterone reflect the impact of energetic status on SHBG levels as much as differential decline in testosterone production with age.

In the future, researchers should aim so far as possible (it may not be possible in difficult field situations) to assess salivary free estradiol and testosterone levels in combination with serum levels of total estradiol and testosterone and SHBG. This will provide a much more complete picture of reproductive function, including information on how much observed variation in free estradiol or testosterone levels is due to variation in the gonadal secretion of these hormones and how much is due to variation in SHBG levels.

CONCLUSION

High and increasing levels of obesity, insulin resistance, and insulin in Western and Westernizing populations have potentially harmful effects on ovarian and reproductive function in women. In particular, hyperinsulinemia is associated with hyperandrogenism, irregular menstrual cycles, reduced fecundity, and PCOS. Thus it is appropriate to consider hyperandrogenism, irregular menstrual cycles, PCOS, and associated low levels of fecundity in women as problems created by the evolutionarily novel Western environment, and as conditions that are likely to be experienced at particularly high levels in populations in transition. These are conditions that can profoundly affect quality of life for women. It is also worth noting that hyperinsulinemia may increase reproductive cancer risk (Solomon, 1999). We suggest that the influence of insulin resistance and high insulin

levels on reproductive function and reproductive health in Western populations and populations in transition has not yet received the recognition it deserves within evolutionary medicine.

ACKNOWLEDGMENTS

We would like to thank Colin Fischbacher and Jazz Chamley for their collaboration in our work with British Pakistani women. We would also like to thank Gillian Bentley for her helpful comments on a draft of the chapter.

CHAPTER 9

Should Women Menstruate?

An Evolutionary Perspective on Menstrual-Suppressing Oral Contraceptives

Lynnette Leidy Sievert

Approximately 80% of women in the United States choose to take oral contraceptives at some point in their lives. Many do so in order to eliminate the inconveniences associated with menstrual cycling, as well as for contraception. And while it may appear that such high usage reflects a general ease with hormone alteration, as Sievert indicates, many questions about potential side effects remain unresolved. Indeed, any discussion of whether or not ovulation and menstruation should be artificially or chemically suppressed, including questions pertaining to when and for how long, necessarily cuts across cultural and religious domains, as well as scientific ones. In fact, Sievert points out that menstrual-suppressing oral contraceptives (MSOCs) are often prescribed and/or advertised (even advocated) through various internet websites. Her intent in this chapter, especially for women already using contraceptives, is to provide an array of evolutionary hypotheses about why menstruation may have evolved in the first place, using them as a basis for exploring both empirical and theoretical ideas that might help all women to become more fully informed about reproductive cycling. An important part of this chapter is determining if menstrual-suppressing contraceptive pills actually mimic what has already been described in this volume as the potentially safer hormonal milieu experienced by ancestral hominin women who had a low frequency of menstrual cycles due to repeated pregnancies and periods of lactation (see Chapters 2, 3, 7, and 8). Sievert concludes that in no way are the effects of MSOCs analogous to that experienced in the evolutionary or historic past and that they cannot be used to mimic the beneficial effects of "Stone Age life histories." Her chapter should help initiate and refocus the direction of any discussion of this topic in new ways.