Reproduction in females: the role of the early life environment

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BACKGROUND: There is now compelling evidence that long-term health and physiological function are modified by events that occur early in life and involve interactions between the genome and the developmental environment. That reproductive function may similarly be influenced by early life events has been established in selected human populations, and investigations into underlying mechanisms are the subject of current animal studies.

METHODS: No systematic literature search was conducted. This review highlights early life influences on reproduction with a particular focus on nutritional impacts, and provides a brief overview with reference to some key studies in both the human and animal literature. We highlight the controversies, current unanswered questions and mechanisms underlying the association between the early life environment and long-term reproductive function.

RESULTS AND CONCLUSIONS: Currently, the impact of early life events on reproductive health and disease risk is poorly understood. It is clear, however, that nutrition spanning the entire developmental lifespan plays an integral role. Improved insight into the underlying mechanisms is likely to have significant implications for our current understanding of reproductive disorders, and therefore for the health and reproductive potential of future generations.
Introduction

There is now considerable epidemiological and experimental evidence indicating that early life environmental signals, including nutrition, affect subsequent development leading to patho-physiologies including obesity and insulin resistance. These signals induce highly integrated responses in endocrine-related homeostasis, resulting in persistent changes to the developmental trajectory producing an altered adult phenotype. This phenomenon has been termed developmental programming, whereby early life events trigger processes that prepare the individual for particular circumstances that are anticipated in the post-natal environment (Hanson and Gluckman, 2008). However, where the intrauterine and post-natal environments differ markedly, such modifications to the developmental trajectory may prove maladaptive in later life (Gluckman et al., 2008). Evidence that reproductive maturation and function are similarly influenced by early life events is now emerging from animal studies and selected human populations. This review will discuss evidence for the developmental programming of female reproductive maturation and function with particular attention to early life nutritional impacts and aims to provide a structured view of the current research position and will highlight gaps in current knowledge in order to inform more refined hypotheses for future research.

Methods

No systematic literature search was conducted. This review focuses on early life influences on female reproduction, providing a brief overview and summary of nutritional reproductive programming with reference to some key studies from the human and animal literature. We highlight the controversies and current unanswered questions regarding mechanisms underlying the association between the early life environment and long-term reproductive function and aim to provide future research approaches for understanding the aetiology of some reproductive pathology.

Female reproductive development: overview

For much of early developmental life the reproductive system is relatively quiescent, largely due to the inhibition of hypothalamic gonadotrophin function. After birth, the neonatal hypothalamus is released from the inhibitory feedback which predominates during late fetal life and as a result, in the neonate there is a rise both in hypothalamic GnRH secretion and in anterior pituitary secretion of both LH and FSH. These coordinated activities result in increased ovarian follicular activity and in elevated serum oestradiol concentrations in some female infants to levels similar to those observed during oвуlation in women of reproductive age. In childhood, gonadotrophin levels are nearly undetectable, believed to be due to central suppressive influences although this has not yet been fully elucidated (DiVall and Radowick, 2008).

Pubertal development is a dynamic process that is the first indicator of the emerging reproductive function. It comprises three main endocrine changes: (i) adrenarche, the rise in adrenal androgens; (ii) a reduction in the tonic inhibition of GnRH secretion; and (iii) gonadarche, an amplification of pituitary gonadotrophin and gonadal sex steroid secretion. The fundamental regulatory factors underpinning the initiation of puberty have not been clearly elucidated. However, the kis-septin family of peptides and the receptor GPR54 appear to play a key permissive role (Roa et al., 2008). Other important permissive factors including insulin, leptin, neuropeptide Y, gamma-aminobutyric acid, transforming growth factor α, ghrelin and the insulin-like growth factors (IGFs) have also been implicated either in the initiation or the maintenance of pubertal progression (Elmqquist et al., 1998; Bereket et al., 2006; Fernandez-Fernandez et al., 2006; Hughes and Kumanan, 2006; Kaplowitz, 2008; Hill et al., 2008).

Menarche marks the onset of reproductive capability in females. Age at menarche shows substantial variation between and within populations, although in most developed countries menarche occurs between the ages of 12 and 13 years (Marder et al., 1974; Rosenfield et al., 2000; Carel and Leger, 2008). This mean age is the result of a secular trend in the decline of menarcheal age. Age at menarche has declined significantly in developed countries over the last 100 years: the mean age of menarche in Europe has fallen from 17 to ~12.5 years of age during this period (Karliberg, 2002; Parent et al., 2003a, b, 2005; Gluckman and Hanson, 2006a, b), although in some developed populations this rate of decline has been shown to be slowing (Whincup et al., 2001; Papadimitriou et al., 2008). The decline has been attributed to dramatic improvements in child health since the early 19th century. Improvements in childhood nutrition and infection control have led to the suggestion that nutrition and resultant improvements in childhood weight gain and body composition may regulate the onset of reproductive maturation (Garn, 1987). This notion was supported by Frisch and Revelle’s early hypothesis that pubertal onset is linked to the achievement of a critical degree of body fat (estimated to be 22% of total weight; Frisch and Revelle, 1970, 1971; Wyshak and Frisch, 1982; Frisch, 1987), a concept now considered controversial (Ellison, 1982; Jasienska et al., 2006a). There is now much attention rather, on the prenatal nutritional and energetic capacity of the individual at birth rather than childhood body mass index (BMI) and weight gain (Gluckman and Hanson, 2006a, b; Jasienska et al., 2006a; Gluckman and Beedle, 2007; Bateson, 2008). Nevertheless, there are clear interactions between the prenatal and post-natal nutritional/energy environments (Jasienska et al., 2006a; Espeveldt Finnstad et al., 2009).

Although the mechanisms are still debated, the decline in menarcheal age (in some studies referred to as pubertal age) is real and its association with adult patho-physiology suggests that future generations of women are at risk of serious reproductive/physiological disorders. Early menarche is a risk factor for earlier sexual debut (Helm and Lidegaard, 1990), teenage depression (Kaltiala-Heino et al., 2003; Michaud et al., 2006), reduced adult height (Ibanez et al., 2000a, b) and increased risk of developing breast cancer, obesity, cardiovascular disease, insulin resistance and the metabolic syndrome in adulthood (Ibanez et al., 1998a, b, c; Clavel-Chapelon and Gerber, 2002; Frontini...
point towards a positive significant association between obesity, adiposity and pubertal maturation (He and Karlberg, 2001; Dunger et al., 2006; Kaplowitz, 2008). A prospective Swedish study demonstrated that an excessive increase in BMI between the ages of 2 and 8 years led to an advancement of puberty of 0.7 years in girls and 0.6 years in boys, and ultimately a loss in adolescent height gain (He and Karlberg, 2001). In the USA, elevated BMI at 3 years of age and a further increase in BMI between the ages of three and six were significantly associated with the advancement of pubertal changes (Lee et al., 2007). Although mechanisms underpinning these associations are unclear, data exist suggestive of disruptions in endocrine homeostasis.

In longitudinal cohort studies, low leptin concentrations in cord blood closely reflected decreased adiposity at birth and strongly predicted high rates of weight gain in infancy and catch-up growth. In adolescents, leptin concentrations rose gradually with age prior to puberty, suggestive of the presence of a leptin threshold that may trigger puberty. In girls, low leptin concentrations at the start of puberty predicted large gains in the percentage of fat mass. In life history terms, this fat mass accumulation may be in the preparation for a successful pregnancy and improved ability to care for offspring (lactation) (Ong et al., 1999a, b). More recently it has been suggested that leptin is a permissive rather than causal factor in the onset of puberty (Ahima et al., 1997; Kiess et al., 1998; Zieba et al., 2005; Cervero et al., 2006). In recent studies Ziomkiewicz et al. (2008) suggest that the relationship between female nutritional status and reproductive function is not linear. Women with very low and high body fat had significantly lower levels of E2 compared with women with low and average body fat (Ziomkiewicz et al., 2008). What remains to be determined empirically, is whether accelerated adipose accumulation early in childhood drives early pubertal onset or whether an individual who is destined for early reproductive maturation (based on environmental cues early in development) drives the deposition of childhood adipose in preparation for reproduction in the near future (Ellison, 2003; Gluckman and Hanson, 2006a, b; Jasienska et al., 2006a).

**Prenatal period**

There is no doubt that events occurring much earlier than the neonatal period influence weight gain, adiposity and metabolic function during childhood and beyond and recent reviews have begun to highlight how early life events may impact reproductive function (Gardner and Rhodes, 2009; Gardner et al., 2009; Mishra et al., 2009; Symonds et al., 2009; Wadhwa et al., 2009). David Barker using epidemiological data were one of the first to describe a significant association between events occurring before birth and later life disease risk including hypertension and type 2 diabetes (Barker and Osmond, 1986; Barker et al., 1990). Further, these events have been linked to alterations in reproductive function. One of the earliest associations between early life growth and reproductive maturation was made by Cooper et al. (1996), who highlighted for the first time that low-birthweight (LBW) predicted altered female reproductive function (Cooper et al., 1996). Since then, early life events have been associated with ovarian and breast cancer (Elias et al., 2004) as well as the timing of onset of menarche (Sloboda et al., 2007) and of menopause (Elias et al., 2003) and factors likely to negatively impact on reproductive

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**Early life events: associations with female puberty**

**Early post-natal period**

Early life events influence physiological function, with the timing and severity of these events producing different phenotypes. From a developmental perspective, childhood represents an important period during which significant growth and developmental processes occur, driven by coordinated changes in endocrine function. It is therefore to be expected that an individual will be sensitive to environmental cues during the post-natal period. Weight gain during infancy has been largely attributed to nutrition and appetite (Ounsted and Sleigh, 1975) and has been shown to be modifiable by early life events. Early post-natal weight gain patterns are associated with adiposity later in life; infants who are thin at birth and who demonstrated accelerated weight gain during infancy have elevated body mass indices at age five (Ong et al., 2000). Population studies have reported significant associations between rapid weight gain during infancy with increased body fat (Espetvedt Finstad et al., 2009; Stettler et al., 2002, 2003, 2005) and altered body fat distribution (Ong et al., 2000). Unremarkably, rapid weight gain during infancy and increased adiposity in childhood have been linked to insulin resistance (Bavdekar et al., 1999; Ong et al., 2004a, b) and these factors have been reported to influence final height attainment and reproductive maturation (He and Karlberg, 2001).

Decades ago, two hypotheses existed describing the relationship between reproductive maturity and growth; one described the relationship between bone age and puberty and the other the association between body fat and menarcheal age (Ellison, 1982). Indeed the relationship between weight gain and attainment of a critical menarcheal weight was reported by Frisch and Revelle (1970), but was disputed by some who suggested that skeletal maturity has a far greater role in determining menarcheal age than synchronization with weight (Crawford and Osler, 1975; Ellison, 1982; Scott and Johnston, 1982). Nevertheless, data exist suggesting that both too little and too much fat during critical windows leading up to puberty will directly impact on reproduction. It was hypothesized that both the absolute and relative amounts of fat are important, since lean mass and adiposity must be in a particular absolute range, as well as relative range (Johnston et al., 1971; Frisch, 1987). As a result the general hypothesis remained that poor growth (and inadequate attainment of weight) tended to delay puberty while accelerated weight gain was associated with early pubertal maturation (Frisch, 1987).

The relationship between childhood adiposity and pubertal development has been studied and reviewed extensively. Many studies et al., 2003; Lakshman et al., 2009). This is not inconsistent with recent observations that early menarche was associated with altered sex steroid levels in otherwise normal healthy women, over the course of the menstrual cycle, where early age at menarche, together with adult overweight and obesity, resulted in high levels of 17-β-estradiol throughout the menstrual cycle (Ernams et al., 2008) There is thus a strong public health incentive for understanding factors regulating menarche and those mechanisms underpinning the observed decline in age at menarche.
function (de Zeger and Ibanez, 2006, 2009; Ibanez and de Zeger, 2006; Elias et al., 2007).

Studies of selected populations have provided insight into the mechanisms that might underpin associations between LBW and reproductive function. Ibanez et al. have published a series of investigations in girls born LBW where LBW females showed a marked reduction in ovarian and uterine size both during neonatal life and in adolescence (Ibanez et al., 2000a, b). Further, LBW girls had concentrations of FSH that were persistently elevated by almost 50% at 18 years of age (Ibanez et al., 2003a, b). Growth-restricted girls demonstrate a reduction in primordial follicle number compared with gestationally matched appropriately grown infants (de Bruin et al., 1998, 2001), suggestive of a reduced ovarian follicular reserve (Broekmans et al., 2006). The impact of LBW on ovarian function is also evident at birth, with LBW female infants having an exaggerated response to GnRH and increased ovarian production the of anti-Mullerian hormone (AMH) compared with appropriately grown infants (Sir-Petermann et al., 2007). Uterine and ovarian volumes are vulnerable to changes in the intrauterine environment. We have recently demonstrated that maternal smoking was associated with an 18% decrease in uterine volume and a 10% reduction in ovarian volume even after controlling for age, time since menarche or pubertal staging (Hart et al., 2009).

Relatively little is known about the impact of reduced uterine volume on future pregnancy outcome in the normal population, although small studies in selected populations (Turner’s syndrome and pituitary insufficiency) suggest that a reduced uterine volume has a negative impact on reproductive outcomes (Abir et al., 2001).

Although there exist numerous data describing an association between reduced birthweight and later life disease, this is not linear. Large for gestational age babies are at risk of obesity and diabetes, associations that have been supported with a number of studies investigating the long-term effects of maternal hypoglycaemia (diabetes or gestational diabetes; Silverman et al., 1995; Gillman et al., 2003; Lampl and Jeanty, 2004; Fettita et al., 2006). The relationship between fetal ‘over growth’ and post-natal reproductive maturation and function is not well established. Data exist to suggest that ponderal index and concentrations of 17β estradiol during adulthood are positively associated (Jasienska et al., 2006a, b) suggestive of the hypothesis that early life programming of reproductive function results in developmentally plastic, but essentially adaptive shifts in set points of ovarian response to energetic stress (Jasienska et al., 2006b). It appears that adult concentrations of prolactin may also be determined by early life events (Su et al., 2009).

Interaction between pre- and post-natal periods

Subsequent to Barker’s papers describing associations between poor fetal growth and disease risk later in life (Barker, 1966; Barker and Osmond, 1986; Barker et al., 1989, 1990), reports emerged that an interaction exists between embryonic/fetal and post-natal (childhood) events thereby amplifying disease risk (Hales and Ozanne, 2003). Human studies have provided evidence that restricted intrauterine growth followed by accelerated (or catch-up) growth may potentially be beneficial in the short-term, but have adverse effects on subsequent metabolic function (Ong et al., 2000; Ibanez et al., 2006a, b, c), blood pressure and cardiovascular function (Hales and Ozanne, 2003; Eriksson, 2006). Similarly, opposing influences of pre-natal and post-natal growth are seen in reproductive maturation.

In largely Caucasian cohorts, lower birthweight and greater weight gain in childhood acted independently to reduce the age at menarche (Cooper et al., 1996; Adair, 2001; Sloboda et al., 2007). Similar effects are seen in central fat distribution and insulin sensitivity at age 8 years (Garnett et al., 2001; Ibanez et al., 2008a, b). We have recently shown in a normal population of adolescent girls that birthweight and post-natal BMI predicted age at menarche (Sloboda et al., 2007). The earliest age at menarche was seen in girls with lower than the median estimated birthweight and higher than the median BMI at 8 years of age (Table I). Of this group 71% of girls reached menarche by 13.0 year compared with only 42% of girls who had estimated birthweight above the median but BMI at 8 years below the median (Sloboda et al., 2007). Our data, together with those previously reported, suggest that the association between intrauterine and post-natal growth patterns and age at menarche can be extended to encompass the entire birthweight range, and not simply selected growth-restricted populations (Sloboda et al., 2007).

More recently, interactions between pre-natal and post-natal environment have been shown to have long-term effects on 17β estradiol concentrations in adult women. In normal healthy Norwegian women at reproductive age (25–35 years), birthweight and adult

<p>| Table I | Age at menarche: Stratified by expected birth weight ratio and BMI at 8 years of age. |
|------------------------------------|--------------------------------|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>EBW and BMI subgroup</th>
<th>Cohort Total N</th>
<th>Girls who reached menarche</th>
<th>Median age</th>
<th>IQ range</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBW &lt; 1 and BMI ≥ 16.3</td>
<td>231</td>
<td>120</td>
<td>52</td>
<td>12.5</td>
<td>12.1–13.2</td>
</tr>
<tr>
<td>EBW ≥ 1 and BMI ≥ 16.3</td>
<td>306</td>
<td>142</td>
<td>46</td>
<td>12.8</td>
<td>12.2–13.6</td>
</tr>
<tr>
<td>EBW &lt; 1 and BMI &lt; 16.3</td>
<td>127</td>
<td>54</td>
<td>43</td>
<td>13.0</td>
<td>12.6–14.2</td>
</tr>
<tr>
<td>EBW ≥ 1 and BMI &lt; 16.3</td>
<td>112</td>
<td>33</td>
<td>29</td>
<td>13.2</td>
<td>12.8–14.4</td>
</tr>
<tr>
<td>Total</td>
<td>776</td>
<td>349</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Sloboda et al. (2007).

N, sample size; EBW, expected birth weight ratio; BMI, body mass index.

EBW and BMI are illustrated as less than (<) or greater than/equal to (≥) the median value for the whole cohort.
BMI together predicted sex steroid levels throughout the menstrual cycle. Women with birthweights <3530 g, who later developed excess body weight (waist ≥ 84 cm), showed 33% higher 17β-estradiol concentrations over a menstrual cycle compared with women with higher birthweights (>3530 g) and adult excess body weight. The association was even more pronounced in women with birthweights <3220 g, early age at menarche (<12 years) and adult overweight (Espetvedt Finstad et al., 2009).

Increased adrenal androgen secretion has been associated with early pubertal onset (Parker, 1991) and girls small at birth who demonstrate catch-up growth with a BMI higher in childhood than at birth, are at risk of an earlier adrenarche, as manifested by increased dehydroepiandrosterone sulphate (DHEAS) secretion (Ong et al., 2004a, b). Similarly, obese children may be at risk of having higher concentrations of sex steroids, through an insulin mediated suppression of sex hormone-binding globulin (SHBG) (Dunger et al., 2006), increasing the concentration of bioactive sex steroids in the circulation (Holly et al., 1989). This relationship was more clearly demonstrated in a cohort of LBW girls with early to normal onset puberty, in whom insulin sensitization with metformin resulted in a mean delay in the timing of menarche by 1 year, associated with decreased circulating leptin and insulin-like growth factor-I (IGF-I) concentrations. In this cohort, girls who received metformin therapy had a significant postponement of menarcheal onset and breast development (Ibanez et al., 2006a, b, c). At 18 months follow-up, benefits in height, BMI and waist circumference persisted (Ong et al., 2007a, b; Ibanez et al., 2010a, b), and at 4 years of follow-up metformin-treated girls had gained 50% less fat, were less hyperandrogenic, had lower IGF-I concentrations, demonstrated a less atherogenic lipid profile, and were less likely to be post-menarcheal than untreated girls (Ibanez et al., 2008a, b; 2010a, b). It thus appears that a disruption of the adipo-insular axis may contribute significantly to the association between early growth restriction, post-natal adiposity and reproductive development. A more mechanistic understanding, however, of which specific perturbations within the adipo-insular axis underpin this association, is critical.

Alterations in reproductive function have clear impacts on future generations and investigations of the transgenerational effects of early life events on reproductive function have increased in number. In women whose early menarche was associated with increased adult weight and shorter height, their offspring were more likely to be taller and fatter (Ong et al., 2007a, b), pointing towards a feed forward cycle of obesity and early reproductive maturation. Children of overweight and obese mothers are more likely to become obese and overweight putting them at risk of early pubertal maturation. These data highlight the need to break this cycle of early maturation and obesity which likely results in subsequently programming the next generation for the same fate. Thus, a perpetuation, and possibly a compounding, of acceleration of puberty may ensue in the next generation for the same fate. Thus, a perpetuation, and possibly obesity which likely results in subsequently programming the offspring to be more obese at an earlier reproductive age.

**Early life events and age at menopause**

Several factors have been reported to affect the timing of menopause including educational level, occupation, marital status, age at menarche, parity, oral contraceptive use, physical activity and smoking (Hardy et al., 2000; Meschia et al., 2000; Evans and Racette, 2006; Parazzini, 2007; Dorigochoo et al., 2008). In fact, ovarian ageing begins early in intrauterine life; the number of follicles (5–7 million primordial oocytes) is highest during fetal life at 20 weeks of gestation, with subsequent depletion to ~1 million follicles at birth (Ginsberg, 1991; Faddy et al., 1992; Faddy and Gosden, 1996; Broekmans et al., 2007). The process of follicular atresia continues after birth, and by menarche ~300 thousand follicles are available for ovulation and reproductive fertility (Ginsberg, 1991). By menopause only a few thousand remain (Faddy and Gosden, 1996). Therefore, factors impacting on follicle production and rate of atresia are likely to impact on fertility and age at menopause (Cresswell et al., 1997a, b; Broekmans et al., 2007, 2009).

Reduced ovarian reserve is a risk factor for infertility and premature ovarian failure, and contributes to ovarian ageing (Broekmans et al., 2006). Although associations between age at menarche and age at menopause are still controversial (van Noord et al., 1997), there is evidence that early menarche may be associated with early menopause (Parazzini, 2007) and possibly reduced fertility (McKibben and Poston, 2003). This relationship is consistent with the hypothesis that early life events may influence the number of ovulatory cycles associated with the age at menopause (Kaczmarek, 2007). In this regard, women who reported onset of menstruation at age 11 or younger had an earlier age at menopause than women who started menstruating at age 12 or older (Reynolds and Obermeyer, 2003). Studies exist, however, which have reported an inverse association between menarche and menopause (early menarche, late menopause) (Frisch, 1987; Do et al., 1998). The relationship between birthweight and age at menopause in the normal population is equally unclear (Cresswell et al., 1997a, b; Hardy and Kuh, 2002; Treloar et al., 2000; Mishra et al., 2007). Evidence from twin studies comparing monozygotic and dizygotic twins did not find a relation between a lower birthweight and an earlier menopause (Treloar et al., 2000).

Age at menopause not only impacts a woman’s reproductive life cycle but may also influence her daughter’s reproductive capability. Small cross-sectional and case–control studies have shown that a woman’s age at menopause is related to her mother’s age at menopause (Torgerson et al., 1994; Cramer and Xu, 1995; Cramer et al., 1995), and a recent study reports an association between a mother’s age at menopause and her daughters’ ovarian function, with women whose mothers experienced earlier menopause having higher urinary FSH concentrations (Steiner et al., 2008). These observations may support the hypothesis that the impacts of early life events may extend to subsequent generations, although much of these studies are based upon recall of family history and involve relatively small and sometimes selected, populations. Nevertheless, events occurring during prenatal development may impact on the number and/or quality of oocytes and future reproductive outcomes of offspring and it is plausible that genetic and environmental factors (smoking, diet, exercise and socio-economic status) may modify these associations. Identification and a more thorough understanding of those events which have downstream effects on ovarian function (Meschia et al., 2000; Varea et al., 2000) as suggested by studies investigating circulating sex steroids and reproductive hormones (Espetvedt Finstad et al., 2009; Su et al., 2009), may provide the clues needed to understand the early life origins of early menopause.
Early life events and polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disturbance, affecting ~6% of the adult reproductive-aged population (Aziz, 2004; Hart et al., 2004). Definitions characterising PCOS have varied historically, and in 2004 the global definition changed from the classic National Institutes of Health (NIH) definition to include ovarian polycystic ovary morphology as a possible diagnostic criterion (Zawadzki and Dunaif, 1992; ESHRE/ASRM, 2004). Recently the Androgen Excess Society have suggested that among the criteria for PCOS diagnosis, hyperandrogenism must be present (Aziz et al., 2009). PCOS is commonly associated with insulin resistance, obesity and dyslipidaemia (Hart et al., 2004). Increased abdominal fat is a feature of obese, overweight and normal weight women with the syndrome (Kirchengast and Huber, 2001; Puder et al., 2005; Carmina et al., 2007) and the association between PCOS incidence and overweight and obesity is also seen in adolescent populations (Hickey et al., 2009). Whether women with PCOS have increased or decreased lean mass is still controversial. Some reports indicate that women with PCOS also have increased lean mass which may (Doucet et al., 2001) or may not be (Carmina et al., 2009) associated with elevated circulating androgen concentrations. Yet evidence exists to suggest that PCOS women with obesity may also have reduced lean mass (Kirchengast and Huber, 2001) which can be reversed by anti-androgen and insulin sensitising treatment in adolescence (Ibanez et al., 2003a, b).

PCOS has also been associated with increase peripheral glucocorticoid levels through the increased conversion of cortisol to cortisol. It has been shown that women with PCOS have increased peripheral expression levels of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1; the enzyme responsible for cortisol to cortisol conversion) as well as decreased peripheral insulin sensitivity and increased upper body fat distribution (Svendsen et al., 2009). PCOS may arise through a genetic predisposition interacting with the postnatal environment (Franks, 2008). The PCOS pattern of inheritance suggests an autosomal dominant trait with incomplete penetrance and shows familial clustering. The phenotype is known to vary with time in relation to the patient’s weight (Franks et al., 2001). A number of polymorphisms associated with increased androgen production as well as differential methylation of the AR gene have been proposed (Ferk et al., 2008; Shah et al., 2008), but no definitive genetic association with PCOS has been established (Simoni et al., 2008).

Both animal data and human studies from selected populations suggest that the PCOS phenotype may be modified by factors during prenatal life but these factors are not clearly defined. Girls born LBW and having accelerated childhood growth are at increased risk of precocious pubarche (Ibanez et al., 1998a, b, c), anovulation (40% compared with 4% in those of normal birthweight for gestational age), PCOS (Ibanez et al., 2002, 2007), and features of the metabolic syndrome in adolescence (Ibanez et al., 2006a, b, c). Insulin resistance has been suggested to be a central driver in these associations and metformin treatment has been shown to delay early menarche by around 1 year in girls with precocious pubarche (Ibanez et al., 2006a, b, c, 2008a, b). The relationships among intrauterine growth, birthweight and PCOS in the normal population have not been clearly defined (Cresswell et al., 1997a, b). We have recently reported that birthweight was not associated with PCOS characteristics in a prospective study of otherwise unremarkable adolescents. In this cohort, 28% of girls investigated had PCOS characteristics as defined by the Rotterdam criteria and 15% using the NIH criteria (Hickey et al., 2009) and was associated with increased adolescent androgen levels (Hickey et al., 2009). These data need to be confirmed in other normal populations of adolescents in equally large prospective studies.

Prenatal origins of PCOS: prenatal androgen hypothesis

In general, two hypotheses have been advanced to explain the prenatal origins of PCOS; (i) the prenatal androgen hypothesis and (ii) the adipose expandability hypothesis. The prenatal androgen hypothesis has been extensively reviewed (Dumesic et al., 2005, 2007; Abbott et al., 2006; Xita and Tsatsoulis, 2006; Homburg, 2009; Nisenblat and Norman, 2009) and is supported by animal data and selected human studies where fetal testosterone exposure is supra-physiological (Eisner et al., 2002; Robinson et al., 2002; Sharma et al., 2002; Abbott et al., 2005, 2006; Manikkam et al., 2006; Bruns et al., 2007; Steckler et al., 2009). Pregnant women with PCOS have elevated circulating concentrations of androgens at mid-gestation, which may increase fetal androgen exposure (Sir-Petermann et al., 2002) and female offspring of PCOS mothers have an increased risk of altered ovarian development and function which can be detected from as young as 2 years old. In a small study of pre-pubertal girls born to women with PCOS, serum AMH concentrations were significantly higher and FSH concentrations were lower compared with girls born to control mothers (Sir-Petermann et al., 2006). These data suggest that girls born to PCOS mothers have an increased follicle pool during a time when the hypothalamic–pituitary–ovarian (HPO) axis is quiescent (Sir-Petermann et al., 2006).

We have recently shown a significant positive association between maternal serum total testosterone levels at 18 weeks of pregnancy and adolescent AMH concentrations, supporting the hypothesis that maternal androgens may influence offspring ovarian function (Hart et al., 2010a, b). Furthermore, we have shown that adolescent girls with identified PCOS characteristics have elevated AMH levels (Hart et al., 2010a, b), although the mechanisms linking maternal androgens, AMH and PCOS remain unclear. Under normal circumstances the placenta provides a sufficient barrier to maternal androgens by way of the placental aromatase enzyme which converts androgens, such as androstenedione and testosterone, to estrone and estradiol respectively. Whether this placental barrier functions effectively and is sufficient to decrease fetal exposure to maternal androgens in PCOS pregnancies has yet to be investigated. However, placental dysregulation of steroid metabolism may be one source of excess androgens during prenatal life. Altered fetal HPO development and function may also contribute to prenatal androgen excess. Excessive concentrations of LH and androgens were observed in four extremely premature female infants born between 25 and 29 weeks’ gestation. In this study, the authors postulated that temporary virilization was due to an unusually high (or excessive) LH surge, in turn causing high fetal androgen concentrations (Greaves et al., 2008). One can speculate that this excessive exposure resulted in long-term changes in ovarian function and reproductive pathologies but follow-up of these selected populations is needed.
Genetic factors may also contribute to excessive prenatal androgen exposure (Goodarzi et al., 2007a, b, 2008a, b; Shah et al., 2008). There is strong support for a familial component of the regulation of androgen production in PCOS (Yildiz et al., 2006; Goodarzi et al., 2007a, b), however, direct associations between gene variants, androgen synthesis and PCOS remain contentious. Significant associations have been observed between genetic variants and metabolic indices such as hyperinsulinaemia and BMI but not directly with PCOS (Jones et al., 2009; Xu et al., 2010). Further evidence is needed to unravel the genetic modifiers of PCOS and whether the syndrome is based upon inherited changes in androgen production, although it is likely that genetic variants only contribute to the pool of factors that link prenatal androgen exposure and PCOS risk.

Regardless of the source of excess androgens, experimental animal models have clearly shown that excessive prenatal androgen exposure results in a PCOS-like phenotype. PCOS models have successfully been developed in the prenatally androgenized sheep (Unsworth et al., 2005; Forsdike et al., 2007) and monkey (Abbott et al., 2002, 2005) through maternal administration of supra-physiological doses of testosterone. These studies have shown that prenatal hyperandrogenism results in enlarged cystic ovaries, anovulation, raised LH concentrations, progressive loss of ability to develop an LH surge in response to increasing estradiol concentrations, and ovarian hyperandrogenism in female offspring (Abbott et al., 2008). Further, prenatal hyperandrogenism induces the metabolic phenotype of central obesity and insulin resistance commonly seen in PCOS (Hart and Norman, 2006; Bruns et al., 2007). In humans, patho-physiological hyperandrogenism, such as that seen in congenital adrenal hyperplasia or early virilising tumours, results in the expression of some features of PCOS such as raised basal LH concentrations and an increased responsiveness of LH and 17-hydroxyprogesterone to GnRH infusion in female offspring.

Although these experimental data appear convincing, the prenatal androgen hypothesis has only recently been tested in a prospective cohort. We have recently failed to demonstrate any association between prenatal androgen exposure during mid and late pregnancy and PCOS in a normal adolescent population (Hickey et al., 2009). In our recent study, no association between prenatal androgen exposure and PCOS was made in girls who were 15-year-old and diagnosed with PCOS by NIH or Rotterdam criteria (Hickey et al., 2009). In this explanation, de Zegher et al. (2009) have elegantly described how early growth restriction and spontaneous catch-up growth early in post-natal life may predispose offspring to a reduction in subcutaneous adipose expandability and henceforth result in long-term insulin resistance and perpetuating hyperandrogenaemia and thus PCOS (de Zegher and Ibanez, 2009) (Fig. 1A). In this opinion paper, de Zegher suggests that since the majority of adipose tissue expansion in the infant occurs subcutaneously, a reduction in adequate adipose tissue expandability at this critical window of development results in long-term risk for insulin resistance when nutrients become abundant or even excessive (Fig. 1A; de Zegher et al., 2009). This circumstance is emphasized in cases where IUGR is followed by catch-up growth (Ibanez et al., 2010a, b), but is not present in the absence of spontaneous catch-up growth, where infants have a thin layer of abdominal subcutaneous fat and a normal amount of visceral adipose (Ibanez et al., 2009a, b). This paper highlights the fact that individual set points of adipose tissue expansion depend on a broad range of genetic and lifestyle factors and points toward a hypothesis explaining how an insulin resistance phenotype with PCOS may occur without obesity. It may be that genetics plays a role where different ethnic backgrounds combined with growth restriction can confer a set-point of maximal adipose tissue expansion that is already reached at a low body weight and may lead to a state of insulin resistance and PCOS without obesity (Fig. 1B). Other ethnic backgrounds can confer a higher setpoint of adipose expandability thus resulting in obesity without characteristics of insulin resistance and PCOS (Fig. 1B; de Zegher et al., 2009).

In support of their view, prenatal growth restriction coupled with spontaneous catch-up growth during infancy results in insulin resistance and increased visceral adiposity (Verkaikiene et al., 2007; Dulloo, 2008) as well as elevated DHEAS levels and low levels of SHBG at 8 years of age (Ibanez et al., 2009a, b) clearly predisposing them to PCOS. Within their rationale, Ibanez et al. offer an explanation for the many possible triggers associated with PCOS to come under one unifying framework—that PCOS patients are unable to safely expand subcutaneous adipose tissue. Although this hypothesis needs to be tested and validated with empirical evidence, it offers an alternative explanation to the prenatal androgen hypothesis to explain early life origins of PCOS.

**Effects of nutrition on female reproductive maturation and function**

**Human studies**

Typically, studies investigating populations exposed to famine or malnutrition have highlighted the need for adequate nutritional intake for successful reproductive capability. Indeed, evidence exists to suggest...
that post-natal nutrition influences reproduction (Van der Spuy, 1985; Kirchengast and Winkler, 1996; Karlberg, 2002). Historical reports suggest that in general, poor childhood nutrition tends to delay puberty while improved childhood nutrition accelerates pubertal maturation (Garn, 1987). Studies investigating reproduction in developing countries have suggested that in women, malnutrition resulted in a shorter reproductive span, either early or late age at menarche, and early menopause (Osteria, 1983; Riley, 1994, Kirchengast and Winkler, 1996; Lindstrom and Berhanu, 1999). In some cases nutritional impact on age at menarche have also been shown to have downstream effects on age at marriage and age at first birth (Riley, 1994). Recent studies of seasonal effects on populations highlight the importance of critical windows during pregnancy, where adverse climate conditions resulting in food shortage and infection early in pregnancy strongly influenced reproductive output in Vietnamese women (Huber and Martin, 2009). Adversity of this type may be associated with changes in sex steroid regulation that have downstream effects on fertility, as women in intensive agricultural-based developing countries have been reported to have lower progesterone concentrations than those in industrialized centres (Ellison et al., 1993, Jasienska and Ellison, 1998; Ellison, 2003).

More recently, however, reports suggest that nutritional quality as well as the source of macronutrient may be associated with pubertal onset. Recent reports investigating diet quality in Dortmund Nutritional and Anthropometric Longitudinally Designed Study (DONALD Study) participants demonstrated that children with lower diet quality pre-puberty, experience pubertal growth spurt at an earlier age than children with a higher diet quality (Cheng et al.,

**Figure 1** Tissue expandability hypothesis taken from (de Zegher et al., 2009). (A) Summary of the adipose tissue expandability hypothesis on the early origins of PCOS, in particular, of the PCOS subgroup with hyperinsulinaemic androgen excess. FTO, fat mass- and obesity-associated gene. (B) The individual set point, up to which adipose tissue can be safely expanded, depends on a broad variety of genetic and epigenetic factors. Some ethnic backgrounds, particularly when combined with growth restraint in early life, confer a set point of maximal adipose tissue expansion that is already reached at a relatively low body weight (red arrow), and thus may lead to a state of insulin resistance and PCOS without frank obesity. Other ethnic backgrounds, particularly when combined with favourable growth conditions in early life, confer a set point that is located at a higher body weight, possibly even beyond the threshold for obesity (green arrow), and may thus lead to a state of obesity without frank insulin resistance or PCOS.
More thorough analyses of macronutrient intakes demonstrated that protein intake from dairy but not animal meat particularly at age 5–6 years in childhood, was associated with earlier indices of puberty (pubertal growth spurt, menarche, voice break; Gunther et al., 2010). Intriguingly, these associations were independent of BMI. These data suggest that the relationship between childhood nutrition and pubertal onset is not as simple as previously described and highlight the need for more intensive nutritional evaluation at critical periods of development. There are little data for examples describing the association between breast versus bottle feeding and reproductive development in children and adolescents.

**Undernutrition and nutritional transitions**

Early life cues influence development during critical periods that extend prior to childhood and infancy right to conception and including the early embryonic or fetal period. As such epidemiological studies have targeted historical cohorts that have undergone adversity (famine, war) during pregnancy in order to investigate the effects of early life events on post-natal physiology. Follow-up studies of survivors of the Dutch Winter Hunger have attributed altered reproductive function in the offspring of mothers who experienced famine, to contrasting prenatal and post-natal nutritional status; although no significant effect on long-term fertility was observed in this cohort (Lumey, 1998). However, menstrual irregularity (Elias et al., 2007), decreased age at natural menopause (Elias et al., 2003) and increased risk of breast cancer (Elias et al., 2004) were observed. When considering present-day social and cultural conditions, however, the globalization of agriculture and food processing has changed worldwide food availability and the last 30 years have seen a 10-fold increase in the number of people with access to high caloric diets (Seidell, 1999, 2000). Many studies of populations undergoing transition from relatively poor nutrition to a ‘Westernized’ high fat and high carbohydrate diet have demonstrated that this transition may alter key health indices in adult life and lead to lifelong adverse effects, which may include impacts on reproductive function (Victora et al., 2008). In this regard population studies of international adoption have been able to investigate a transition from relatively poor conditions early in life in developing countries, to the relatively luxurious conditions of developed countries (Domine et al., 2006).

A greater incidence of early onset puberty (Parent et al., 2005; Domine et al., 2006; Teilmann et al., 2006, 2007) and a 10–20-fold increased rate of precocious puberty (Teilmann et al., 2006) were observed in girls who at a young age migrated from a poor to a developed country, and thereby experienced a combination of prenatal early life deprivation and nutritional excess in childhood (Parent et al., 2003a, b). Pre-pubertal girls adopted when they were between 5 and 8 years old also showed signs of increased pituitary and gonadal activity, suggesting that early onset of puberty in these adopted girls was centrally driven (Teilmann et al., 2007). The manifestation of early puberty in girls adopted from India and Bangladesh to affluent developed countries has been attributed to an increase in metabolic activity (Proos et al., 1991; Parent et al., 2003a, b, 2005; Teilmann et al., 2007).

Similarly, evidence for altered ovarian function due to differences in pre- and post-natal nutritional histories comes from studies of the daughters of Bangladeshi immigrants to the UK. Nunez-de la Mora et al. (2007) investigated first- and second-generation Bangladeshi women aged 19–39 who migrated to London, UK at different points in the life-course, women still resident in Bangladesh, and women of European descent living in neighbourhoods similar to those of the migrants in London. The authors demonstrated that after controlling for anthropometric and reproductive variables, women who spend their childhood in conditions of low energy expenditure, stable energy intake, good sanitation, low immune challenges and good health care in the UK had up to 103% higher levels of salivary progesterone and an earlier maturation than women who develop in less optimal conditions in Sylhet, Bangladesh (Nunez-de la Mora et al., 2007; Fig. 2). These data raise important clues towards underlying mechanisms and support ovarian drivers in the association between nutritional transition and reproductive function. It is important to recognize however that these selected populations of girls from developing countries may not be representative of other developed populations and therefore reinforce the need for further investigation of the effects of migration and nutritional transitioning.

**Nutritional excess**

Although undernutrition remains a global crisis in many developing countries, worldwide there is an increasing focus on the role of obesity in determining health risk. Together with changes in the physical demands of work and increased mechanization, which have increased the propensity to a sedentary lifestyle (Seidell, 2000), these changes have brought about a significant increase in the global incidence of obesity. In developed countries, 15–20% of women between the ages of 25 and 55 years are obese (Seidell, 2000), and therefore have increased risks of infertility and cardiovascular and metabolic disease. Increasing numbers of women in developed countries are starting pregnancy overweight and gaining excess weight during pregnancy. In developed societies caloric and/or fat consumption are generally excessive and, maternal obesity is now a common pregnancy complication (Catalano, 2007; Jonathan et al., 2008). Importantly, these effects may be self-perpetuating, as offspring of obese mothers are themselves prone to obesity, giving rise to trans-generational effects (Armitage et al., 2008; Shankar et al., 2008).

Maternal obesity is associated with obstetric complications including fetal and neonatal death, poor lactation outcomes and is the most significant predictor of childhood obesity (Catalano et al., 2009) and metabolic syndrome in offspring (Boney et al., 2005). The underlying mechanisms are unclear, but reports suggest that adiposity and insulin resistance in children of obese mothers are already present during fetal life and high maternal weight has been associated with abnormal feto-placental function (Kristensen et al., 2005). The effects of maternal obesity on reproductive function in the offspring are unclear, although childhood obesity and insulin resistance are associated with early menarche, suggesting that reproductive and metabolic complications of offspring born to obese mothers are likely to go hand in hand (Kaplowitz et al., 2001; Kaplowitz, 2008; Armitage et al., 2005). Although the global rise in the incidence of obesity is a threat to future generations, targeted prospective investigation of maternal obesity on reproductive function in offspring is very limited and needs to be exploited.
Animal studies

Much of what we know regarding nutrition and reproductive outcomes comes from animal studies. Owing to the interest in agricultural productivity, pastoral animals have provided a wealth of knowledge (Robinson, 1996; Clarke et al., 1997). Experimentally induced fetal growth restriction in sheep did not alter pubertal onset in female lambs (Da Silva et al., 2001) but did alter fetal mRNA levels of hypothalamic and pituitary gonadal drivers (LH and FSH) and fetal ovaries contained fewer resting follicles (Rae et al., 2001). In ewes, prenatal undernutrition reduced ovulation rates in female offspring (Rae et al., 2002). Studies have demonstrated an effect of undernutrition on the concentrations of oogonia in the ovine ovary as early as Day 47 of fetal life (term is 147–150 days) and an associated postponement in the arrest of ovarian meiotic activity on Day 62 (Borwick et al., 1997).

In the rat, it is well established that post-natal fat deposition (or weight gain) is a primer for pubertal onset. In early studies it was demonstrated that body weight was significantly associated with pubertal onset independent of age (Kennedy and Mitra, 1963). In those studies optimally fed rats demonstrated vaginal canalization, first oestrus, mating and attainment of full fertility simultaneously, whereas in growth-restricted rats these events became separated in time (Kennedy and Mitra, 1963). Food intake and skeletal maturation were significantly associated with the onset of ovarian activity, independent of age. Chronic underfeeding prevented normal cycles, but not follicular growth, which eventually led to the development of follicular cysts (Kennedy and Mitra, 1963). Subsequently Frisch demonstrated that rat pups fed a diet high in fat from weaning entered puberty significantly earlier than their low-fat fed counterparts (Frisch et al., 1975). He suggested that the earlier age of estrus of the high-fat fed rats, the larger percentage of high-fat fed rats that had simultaneous vaginal opening and estrus. The longer interval between vaginal opening and estrus indicated that estrogen concentrations were prematurely elevated in the high-fat fed rats (Frisch et al., 1975). Similar observations were seen in genetically obese rats (Kirtley and Maher, 1979). Since those seminal papers, the importance of early life nutrition during both fetal and post-natal development has become increasingly apparent. As a consequence a growing number of animal studies have been performed to investigate the association between intrauterine nutrition and reproduction and provide insights into reported human associations.

Total caloric restriction during pregnancy has been shown to significantly impact reproductive development in a number of animal models. Maternal caloric restriction in sheep decreased ovarian and granulosa cell proliferation and increased apoptosis in the ovaries of offspring (Lea et al., 2006), which may be suggestive of delayed ovarian maturation mediated through nutritionally induced changes in the ovarian hormonal environment or in the hypothalamic–pituitary–gonadal axis activity. In this regard, altered follicular maturation has been demonstrated in the offspring of sheep that underwent nutritional constraint during critical windows of development (Rae et al., 2001; da Silva Faria et al., 2010) effects that may be modified by changes in androgen and estrogen receptor populations (da Silva Faria et al., 2010). Maternal protein restriction throughout pregnancy in the rat had either no effect on pubertal age in male and female offspring, but significantly reduced both long-term fertility
(Zambrano et al., 2005) and longevity in adult females (Guzman et al., 2006) or delayed pubertal onset and reduced Kiss1 mRNA levels in hypothalamus (Iwasa et al., 2010). Experimental fetal growth restriction in the rat using uterine artery ligation late in pregnancy delayed puberty in the offspring, as did late gestational and post-natal caloric restriction (Engelbregt et al., 2001; Leonhardt et al., 2003).

We have recently investigated maternal nutritional challenges at critical developmental windows to investigate effects on growth and reproductive parameters in female offspring (Howie et al., 2009; Sloboda et al., 2009). We demonstrated that in female offspring, pubertal timing and subsequent ovarian function were influenced by nutritional status in utero, with both maternal caloric restriction and maternal high-fat nutrition throughout pregnancy and lactation resulting in early pubertal onset (Sloboda et al., 2009). Importantly, depending on the offspring’s nutritional history during the prenatal and lactational periods, subsequent nutrition and body weight gain did not further influence offspring reproductive tempo and were rather dominated by prenatal nutrition (Fig. 3A and B). These results suggest that nutrition during early critical developmental windows sets the tempo of reproductive development. We also demonstrated that whereas maternal calorie restriction led to early pubertal onset, it also resulted in a reduction in progesterone concentrations in offspring later in life (Fig. 3C). In contrast, we found that maternal high-fat feeding-induced early maturation but was associated with elevated progesterone concentrations in adult offspring (Fig. 3D). We suggest that two different developmental pathways in our study led to the acceleration of pubertal timing but with different consequences for ovarian function (Sloboda et al., 2009). In earlier studies investigating the effects of prenatal nutrition on breast cancer risk, offspring of dams fed a high-fat diet during pregnancy entered puberty earlier and had their first estrus earlier compared with control offspring, and these differences were thought to be associated with elevated concentrations of estrogen (Hilakivi-Clarke et al., 1997, 1999).

**Figure 3** Data are from (Sloboda et al., 2009). (A) Percentage of offspring entering puberty over time in animals whose dams received 50% of normal nutrition. Cont, control pregnancies; UN P, dams undernourished during pregnancy only; UN L, dams undernourished during lactation only; UN PL, dams undernourished during pregnancy and lactation. (B) Percentage of offspring entering puberty over time in animals whose dams received a high-fat diet. Cont, control pregnancies; MHF, dams fed a HF diet preconceptionally and throughout pregnancy and lactation; PLHF, dams fed a chow diet preconceptionally and a HF diet through pregnancy and lactation only; +C refers to post-weaning standard control diet. (C) Circulating adult female offspring progesterone concentrations at proestrus whose mothers received 50% of normal nutrition. (D) Circulating adult female offspring progesterone concentrations at proestrus whose mothers received a high-fat diet. Data represent at least six litters per maternal dietary group. Maternal diet effect on onset of puberty; P < 0.001. Maternal diet effect on progesterone levels P < 0.05. Groups denoted by different letters are significantly different at P < 0.05.
More recently, effects of maternal nutritional challenge have been associated with very early developmental changes. Diet-induced obesity in mice has been demonstrated to result in impaired fertility, which may be due to compromised mitochondrial metabolism in maternal oocytes and developing embryos (Igosheva et al., 2010). In this regard, in vitro embryo culture systems provide models of early programming effects that are likely to be nutritional in origin. Thompson et al. (1995) found that the birthweights of lambs from embryos cultured in synthetic oviduct fluid medium supplemented with human serum were greater than those from spontaneously ovulating ewes or those derived from embryos cultured in synthetic oviduct fluid supplemented with amino acids and bovine serum albumin (Thompson et al., 1995). Therefore it is not only important to consider late gestational and childhood nutritional impacts but also the very early environment at and around the time of conception when taking into account impacts of nutrition on reproductive development.

**Early life events and reproductive maturation and function: a life history interpretation**

Life history models provide important frameworks for understanding reproduction. Life history theory argues that organisms are intrinsically and extrinsically constrained in their attempt to achieve reproductive success and this framework provides evolutionary explanations to define the relationship between these constraints. At the basis of life history theory is the existence of trade-offs between physiological components that arise since the benefits of reproduction come at a great cost; either directly through energy requirements or indirectly such as the risk of predation (Steamns, 1992, 2000; Speakman, 2008). The cost that is associated with reproductive success will drive the nature of the trade-off. For example, an immature organism will allocate energy resources to growth and energy and energetic resources will only become available for reproduction at the time of sexual maturity (Steamns, 1992). According to the classic biological theory, under conditions of low energy or resource availability organisms will delay reproductive maturation until a time when resources are adequate and reproductive activities will be successful (Tanner, 1955; Ellison, 1982; Garn, 1987; Coall and Chisholm, 2010). This is consistent with evidence suggesting that fat mass and adiposity are directly associated with pubertal onset and reproductive maturation (Johnston et al., 1971; Frisch, 1987).

There exists a wealth of theoretical and empirical evidence demonstrating that in many cases early life adversity is strongly associated with early reproductive maturation (Chisholm, 1993). In both human and animal models, poor nutrition, childhood adversity, psychosocial distress and uncertainty and poor familial relationships are associated with high mortality rates, and when life expectancy is low, life histories are fast (Chisholm, 1993; Kramer et al., 2009; Coall and Chisholm, 2010; Nettle et al., 2010). Therefore from an evolutionary perspective, one could argue that poor nutrition or adverse circumstances in early life will lead to accelerated maturation, through which the organism trades body size and longevity for earlier reproduction in a threatening environment. It has been proposed previously that fetal growth restriction as a consequence of impaired intrauterine conditions can be interpreted as part of a life history strategy in which the organism anticipates a shorter life because of a higher risk of extrinsic mortality, and therefore invests less into growth and accelerates maturation to ensure reproductive fitness (Ellison et al., 1993; Gluckman and Hanson, 2006a, b; Jasienska et al., 2006a). This life history model is supported by empirical studies demonstrating that extrinsic mortality rates are important in determining age at first birth (Kramer et al., 2009).

In rat studies, we have observed that both prenatal and lactational undernutrition accelerated puberty—although only the former was accompanied by the later development of obesity and other components of metabolic compromise (Vickers et al., 2000; Sloboda et al., 2009). The shift towards an earlier puberty after intrauterine adversity is compatible with the hypothesis that the fetus may have used maternal cues to anticipate its future environment and has adjusted its life course strategy accordingly (Gluckman and Hanson, 2006a, b). It has been suggested that early puberty may confer a fitness advantage (Ellison, 2003; Ellis, 2004) by reducing the risk of death before reproducing, or by allowing a greater number of successful reproductive episodes before death. Previous studies describing a significant relationship between early life adversity and post-natal metabolic compromise (Vickers et al., 2000; Ong et al., 2004a, b; Ozanne and Nicholas Hales, 2005), may in fact be describing a secondary outcome of a life history strategy aimed at accelerating reproductive maturation. Clearly a reproductive fitness advantage would be obtained only if there were sufficient nutrient stores to support earlier reproduction, and therefore an integrated adaptive response would require both accelerated puberty and altered metabolism.

It has also been suggested that PCOS is the result of adaptive changes made traditionally for survival during periods of infrequent nutrition or famine (Holte, 1998; Xita and Tsatsoulis, 2006; Corbett et al., 2009). Increased adiposity, insulin insensitivity and increased anabolic steroid levels would have provided an adaptive advantage during time of nutrient uncertainty but in today’s modern diet this physiology is now maladaptive and through a multitude of mechanisms has now conferred the syndrome termed PCOS (Holte, 1998). In those born to suboptimal conditions (LBW, undernutrition and inadequate nutrition) earlier maturation may be advantageous but be accompanied by a faster decline in ovarian function with aging. There are many data that suggest that at least in mice, aging may be accelerated in offspring of poorly nourished mothers. Ozanne and Nicholas Hales (2005) have reported that prenatal undernutrition, in contrast to post-natal undernutrition, leads to reduced longevity. Understanding of these theoretical frameworks that seek to integrate physiology, medicine and evolutionary processes provides a unique perspective into the underlying associations between reproductive strategies and phenotypic outcome. No doubt an integrated approach in understanding the impact of early life environment on phenotype will provide better insight into causal pathways.

**Future research directions and hypotheses to be tested**

The understanding of early life events impacting on reproductive development is gradually improving. Several animal and human studies have now addressed how the intrauterine environment may predispose to the PCOS phenotype. Although the exact mechanisms
remain unclear, it is highly likely that factors determining pubertal onset, progression and age at menarche have their origins during early life. In the context of increasing maternal and childhood obesity, determining the role of nutrition may be critical in preventing an increasing trend of earlier age at menarche. Understanding the impact of disruptors which may be commonly encountered by pregnant women may have important implications for public health education during pregnancy. Further, links between early life sex steroid production and/or exposure and later life steroid dependent cancers, such as breast cancer, could potentially lead to earlier identification of those at risk or even to improved screening programmes. Finally, it is now well established that early life adversity has effects that span more than one generation. The mechanisms underpinning this transfer of phenotype are poorly understood and represent an exciting area of research development to invest in the health and well-being of future generations.

Conclusion

There is growing evidence that reproductive health is regulated by early life events and studies investigating the relationship between early life adversity and reproductive function are now well established within the field of biomedical research. The underlying mechanisms regulating these associations are still poorly understood and it is now essential to better integrate evidence from large prospective cohort studies with targeted experimental models that will uncover specific underlying mechanisms. Disorders of reproductive health are increasing in incidence worldwide and are likely to create major economic, psychological and social burdens. Changes in the timing and tempo of puberty will have significant ramifications for later life health and will contribute to changing perceptions of adolescent health and health education. This, combined with the ever-rising rate of childhood and adolescent obesity, will significantly impact on the health of future generations. Therefore information derived from an integrated approach should strive to inform both public health and education policy.

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