Early-life nutritional effects on the female reproductive system

K A Chan[1,*], M W Tsoulis[1,*] and D M Sloboda[1,2,3]

Departments of [1]Biochemistry and Biomedical Sciences, [2]Pediatrics and [3]Obstetrics and Gynecology, McMaster University, 1280 Main Street West HSC 4H30A, Hamilton, Ontario, Canada L8S 4K1
[*](K A Chan and M W Tsoulis contributed equally to this work (co-first authors))

Correspondence should be addressed to D M Sloboda
Email
sloboda@mcmaster.ca

Abstract

There is now considerable epidemiological and experimental evidence indicating that early-life environmental conditions, including nutrition, affect subsequent development in later life. These conditions induce highly integrated responses in endocrine-related homeostasis, resulting in persistent changes in the developmental trajectory producing an altered adult phenotype. Early-life events trigger processes that prepare the individual for particular circumstances that are anticipated in the postnatal environment. However, where the intrauterine and postnatal environments differ markedly, such modifications to the developmental trajectory may prove maladaptive in later life. Reproductive maturation and function are similarly influenced by early-life events. This should not be surprising, because the primordial follicle pool is established early in life and is thus vulnerable to early-life events. Results of clinical and experimental studies have indicated that early-life adversity is associated with a decline in ovarian follicular reserve, changes in ovulation rates, and altered age at onset of puberty. However, the underlying mechanisms regulating the relationship between the early-life developmental environment and postnatal reproductive development and function are unclear. This review examines the evidence linking early-life nutrition and effects on the female reproductive system, bringing together clinical observations in humans and experimental data from targeted animal models.

Key Words
- developmental programming
- reproduction
- puberty
- ovary
- maternal nutrition
- IUGR

Journal of Endocrinology (2015) **224**, R45–R62

Introduction

Disease risk is established well before birth. Life-style associated diseases, including obesity and type 2 diabetes, are known to be influenced by fetal adaptations to *in utero* conditions and critically, these disease effects span multiple generations (Gluckman *et al*. 2007, Aiken & Ozanne 2014). Although science has made significant advances in understanding how this occurs, the exact signaling pathways still remain unclear. As germ cells (oocytes) in the growing fetal ovary are vulnerable to prenatal events, it is likely that modifications in fetal gonadal development contribute to transgenerational disease risk.

The developing organism is capable of adapting to various environments. This phenomenon has led to the hypothesis that disease risk is the result of complex gene–environment interactions (Bouchard 2008, Andreasen & Andersen 2009). This 'environment' includes the period encompassing the developmental milieu within which gametes, germ/stem, and somatic cells will not only differentiate into established organ systems but also give rise to the next generation. It is this inherent developmental plasticity of an organism that allows it to respond to cues that will ultimately determine the adult

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

phenotype. However, under some circumstances, developmental adaptations to early-life insults may lead to negative effects on long-term health (Gluckman & Hanson 2007). In this regard, epidemiological and experimental data have indicated that there is a relationship between the *in utero* environment and the risk of developing chronic disease later in life (Gluckman & Hanson 2004, 2007). A number of differential insults that induce developmental adaptations have been shown to modify disease risk (Champagne 2011, Rosenfeld 2012, Desai *et al.* 2013, Reynolds 2013, Reynolds *et al.* 2013, Sinclair & Watkins 2013, Tarantal & Berglund 2014) and to modulate reproductive function (Savabieasfahani *et al.* 2006, Sloboda *et al.* 2009, Connor *et al.* 2012, Schöpper *et al.* 2012, Lie *et al.* 2013, Barra *et al.* 2014, Zhou *et al.* 2014, Zhuo *et al.* 2014). As the gametes that will eventually give rise to grand-offspring form during fetal life, it is possible that the link between early-life adversity and postnatal disease lies in the developing ovary – involving the developing germ cells and their function. In this review, we consider the female reproductive system, how perinatal adversity modifies fetal reproductive development and the long-term effects of early-life adversity on female reproductive function. As the effects of environmental toxins and chemicals (Walker & Gore 2011, Gopinath 2013, Marques-Pinto & Carvalho 2013) on the male reproductive system have been reviewed elsewhere (Mori 2001, Hampl *et al.* 2013), this review focuses on the effects of early-life nutritional insults on the female reproductive system.

Establishment of female reproductive function: a brief overview

Central to female fertility is the ovary, which consists of oocytes surrounded by somatic cells (follicles). Two pools of follicles exist within the ovary: the resting follicle pool and the growing follicle pool. The resting follicle pool is made up of primordial follicles, which are oocytes surrounded by a single layer of flattened (squamous) granulosa cells (Hirshfield 1991). The majority of primordial follicles remain quiescent; however, a small subset is recruited to supply the growing follicle pool throughout reproductive life (McGee & Hsueh 2000). Oocytes within primordial follicles originate from primordial germ cells (PGCs) that have migrated from the hindgut to the gonadal ridge during embryonic life (Mamsen *et al.* 2012, Sánchez & Smitz 2012). Upon arrival at the gonadal anlagen, PGCs proliferate by mitosis to form oogonia; however, incomplete cytokinesis results in the formation of multi-nucleated syncitia, consisting of multiple oogonia connected by intercellular cytoplasmic bridges surrounded by somatic cells, also known as germ cell cysts (Pepling & Spradling 1998, Tingen *et al.* 2009, Haglund *et al.* 2011, Pepling 2012, Sánchez & Smitz 2012). Subsequently, oogonia enter meiosis and become arrested in the diplotene stage of meiosis I, at which point they are referred to as primary oocytes (Hunt & Hassold 2008, Pepling 2012). Concomitant with the oogonia-to-oocyte transition is breakdown of cysts and the freeing of individual oocytes to form primordial follicles (Pan *et al.* 2012). Breakdown of cysts and the establishment of the primordial follicle pool occur from postnatal (P) day 1 to P4 in rodents (Rajah *et al.* 1992, Pepling & Spradling 2001). During this time, there is a massive wave of germ cell death (atresia) via apoptosis and only 33% of oocytes survive to form primordial follicles (Pepling & Spradling 2001, Kezele *et al.* 2002). The primordial follicles begin to form near the ovarian core (medulla), and their assembly gradually shifts toward the surface (Rajah *et al.* 1992). Similarly, human primordial follicle assembly begins in medullary regions and radiates outwards into cortical regions (Sforza *et al.* 2003) with a wave of follicle atresia (Geber *et al.* 2012); however, this process begins well before birth at ~13 weeks postconception and continues until birth (Forabosco & Sforza 2007). Regardless of timing differences between species, the accumulated number of primordial follicles established early in life largely dictates the reproductive potential and lifespan of mammals, because once this pool is depleted, reproductive life ceases. Recent data have led to a challenge to this concept of a finite primordial follicle pool and on the basis of evidence which indicates that the mammalian ovary may have proliferative germ cells that could replenish the reserve (Johnson *et al.* 2004, 2005, Woods *et al.* 2012); however, this idea is still heavily debated (Tingen *et al.* 2009, Kerr *et al.* 2012, Zhang *et al.* 2012, 2013).

Follicle growth is regulated by a highly orchestrated neuroendocrine negative-feedback system characterized by hypothalamic release of gonadotropin-releasing hormone (GNRH), anterior pituitary release of gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)), and ovarian sex steroids (estradiol (E_2) and progesterone) (Walker & Gore 2011). Hypothalamic GNRH stimulates the release of LH or FSH (depending on GNRH pulsatility) from the anterior pituitary (Popat *et al.* 2008, Tsutsumi & Webster 2009). These gonadotropins bind to their cognate receptors in the ovary, stimulating the production of sex steroids that aid in follicle growth and, importantly, feedback onto the hypothalamus and

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

anterior pituitary to regulate the production of GNRH and LH/FSH (Popat *et al.* 2008). It is not until puberty that GNRH pulsatility is sufficient to induce ovulation of late-antral or fully-grown follicles (Kawagoe & Hiroi 1983, Grumbach 2002, Russell & Robker 2007). It is currently not known what exact mechanism initiates GNRH pulsatility and, consequently, the onset of puberty. However, there is evidence that metabolic status conveyed to the hypothalamic kisspeptin system by leptin (Elias & Purohit 2013), ghrelin (Tena-Sempere 2013), and adiponectin (Martos-Moreno *et al.* 2010), amongst others, is critical. Nonetheless, once puberty is reached, regular menstrual (human) and estrous (rodent) cycles, governed by GNRH, LH/FSH, and sex steroids, result in follicle recruitment, development, and ovulation of an oocyte capable of being fertilized (Popat *et al.* 2008). This occurs at every cycle until the primordial follicle pool is depleted (Skinner 2005). Thus, one can imagine that events or insults occurring during critical hypothalamic–pituitary–gonad developmental windows may disrupt reproductive function and even impair fertility.

Notably, during fetal and early neonatal folliculogenesis, massive epigenetic remodeling occurs, including remethylation of the entire genome (Walker & Ho 2012). Thus in addition to the development and differentiation of germ and somatic cells being vulnerable to early-life insults, adversity may equally (or simultaneously) result in stable changes to the epigenotype of germ cells (Pan *et al.* 2012), having long-term implications for future generations (Fig. 1). Epigenetics refers to the study of changes in gene function, without alterations in the DNA sequence that are mitotically and/or meiotically heritable (Berger *et al.* 2009, Dupont *et al.* 2009). Factors contributing to altered epigenetic states include histone post-translational modifications, noncoding RNAs, transcription factors, and DNA methylation (Sarkies & Sale 2012). The latter largely occurs on cytosines at palindromic CpG dinucleotides (Bird & Wolffe 1999), and promoter CpG methylation is generally associated with a transcriptionally silent gene (Sarkies & Sale 2012). Interestingly, the oogonium/oocyte is subjected to massive fluctuations due to CpG methylation over the course of development. Specifically, PGCs during embryonic life undergo almost complete genomic demethylation upon arrival to the gonadal ridge (Lee *et al.* 2014). Postnatally, throughout folliculogenesis, the oocyte genome is remethylated as follicle growth progresses (Reik *et al.* 2001). Post-fertilization, another wave of demethylation occurs in both paternal (Oswald *et al.* 2000) and maternal (Wang *et al.* 2014) genomes. Despite massive erasure of the methylome in PGCs, some genomic sequences become resistant (Guibert *et al.* 2012), and oocyte methylation status is known to be a strong factor in the determination of pre-implantation embryo methylation status (Smallwood *et al.* 2011).

These two lines of evidence indicate that it is possible for DNA methylation status to get transmitted across

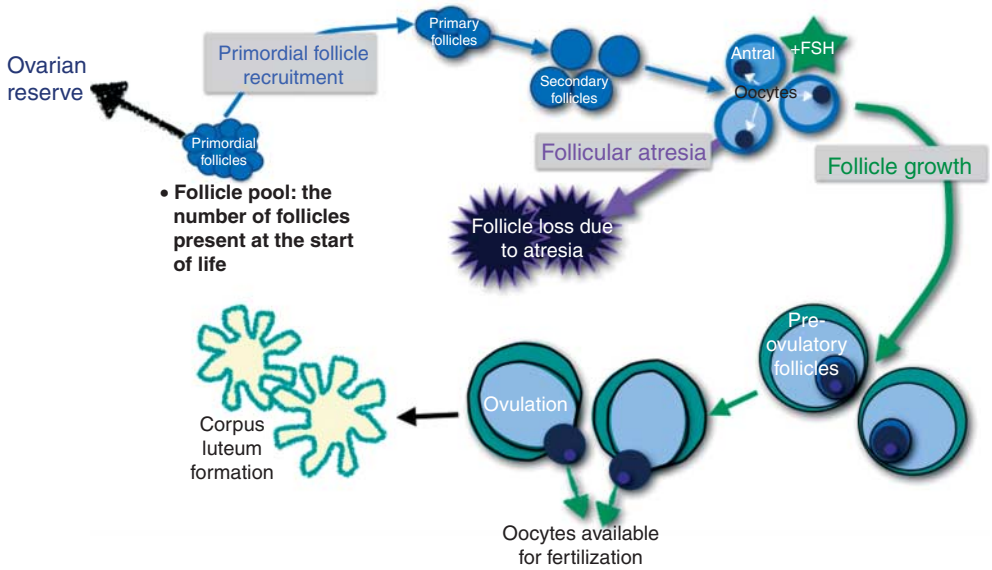

Figure 1
The lifecycle of an ovarian follicle.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

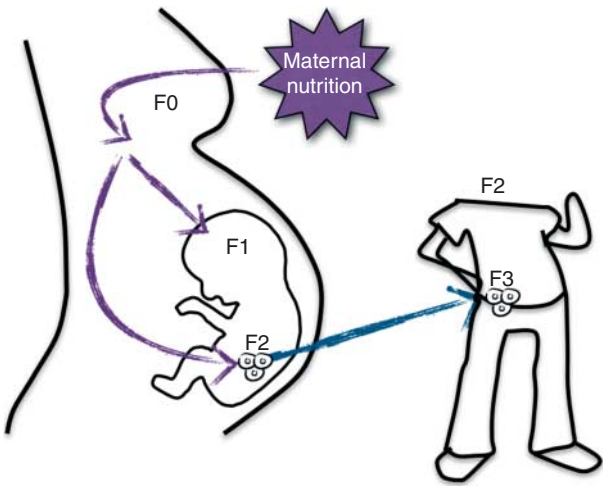

Figure 2
Effects of maternal nutrition on offspring and (great)grand-offspring reproduction.

generations. Thus exposure of a pregnant female (F0 generation) to an insult will directly expose not only her offspring (F1 generation), but also the F1 offspring's germ cells, which will later form the F2 generation (Fig. 2). Therefore, the first generation not directly exposed to an environmental insult in this scenario would be F3 generation offspring. If effects are observed in F3 generation offspring as a result of F0 exposure, it would indicate a germline-dependent transmission across generations, which has been termed transgenerational (Skinner 2008). Observation of effects only in F1 and/or F2 generation offspring would indicate germline-independent transmission across generations, which has been termed multigenerational (Skinner 2008). Moreover, epigenetic marks that are thought to reflect early-life nutritional status have been put forward as possible biomarkers of long-term disease risk (Heijmans *et al*. 2008, Godfrey *et al*. 2011, Dominguez-Salas *et al*. 2012, 2014, Khulan *et al*. 2012). Although the usefulness of these marks has not been thoroughly investigated, it is likely that technological advancement permitting the identification of specific epigenetic changes across the entire genome and linking of these marks with functional outcomes will improve our ability to understand how epigenetics modulates long-term health and disease risk.

Human studies of reproductive programming: modulatory effects of early growth

Early studies investigating the developmental origins of disease risk historically used birth weight (BW) as a proxy measure for intrauterine adversity (Barker *et al*. 1989, Barker 2006). Consequently, epidemiological investigations of populations born with low BW (LBW), due to intrauterine growth restriction (IUGR) and/or small-for-gestational age (SGA), showed significant associations between intrauterine growth, BW, and postnatal reproductive function (Cooper *et al*. 1996, van Weissenbruch & Delemarre-van de Waal 2006, Sloboda *et al*. 2007, van Weissenbruch 2007, Ibanez *et al*. 2011).

Adolescent girls and young adult women born SGA show reduced ovarian size and increased circulating gonadotropin levels, which are already detectable in infancy (Ibanez *et al*. 2000, 2002*a*). Whether disruption of ovarian development occurs as early as fetal life in humans is unclear. IUGR female fetuses show altered ovarian development characterized by reduced ovarian size and reduced proportions of primordial follicles (de Bruin *et al*. 1998), although in subsequent studies, IUGR fetuses did not show significant changes in volume or follicle number (de Bruin *et al*. 2001). A lack of change in fetal ovarian follicle numbers would indicate that the effects of IUGR on ovarian folliculogenesis may not be apparent until the post-pubertal time-point, although it is important to recall that the size of the ovary may not reflect follicle numbers and/or function.

SGA girls display exaggerated adrenarche, advanced menarche, low ovulation rates, and early-onset menopause (Cooper *et al*. 1996, Veening *et al*. 2004, Ibanez & de Zegher 2006). Furthermore, upon onset of puberty, SGA girls also display exaggerated adrenal androgen secretion, factors responsible for secondary sexual characteristics (pubic hair, deepening of voice, etc.), as well as hyperinsulinemia, which has been shown to be associated with hyperandrogenemia (Ibanez *et al*. 1999, 2004). These findings are indicative of an accelerated advancement in reproductive maturity and may be indicative of a reduced reproductive lifespan in SGA girls, compared with appropriate-for-gestational age (AGA) girls. Whether this advancement is associated with accelerated loss of ovarian follicles is unknown (although results from animal studies are indicative that this is the case, see below). Acknowledging this, it may be no surprise, therefore, that SGA girls are thought to be at an increased risk of experiencing premature infertility (Vikstrom *et al*. 2014), although these results are still contentious (Meas *et al*. 2010, Sadrzadeh-Broer *et al*. 2011). Despite the fact that results from many studies have been indicative of an association between growth restriction *in utero* and reproductive abnormalities, SGA is not always associated with early menarche (Shim *et al*. 2013) or menopause (Treloar *et al*.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

2000) and in some circumstances, associations are mild (Hernandez *et al*. 2006, de Ferran *et al*. 2011). Recent results for a non-Western cohort of children have indicated that neither BW for gestational age or SGA status was associated with age at onset of puberty and instead, that SGA children were shorter at the onset of puberty, consistent with either a trade-off between linear growth and maturation or simply with less growth potential (Hui *et al*. 2012).

Other forms of reproductive dysfunction have also been associated with early-life adversity. Polycystic ovarian syndrome (PCOS) is one of the most common female endocrine disorders, affecting between 5 and 10% of adult reproductive age women (Azziz 2004, Hart *et al*. 2004). The symptoms include anovulation, excess androgen secretion, insulin resistance, obesity, and dyslipidemia (Hart *et al*. 2004). An association exists between abdominal fat deposition in both adolescent girls and adult women with the syndrome (Kirchengast & Huber 2001, Puder *et al*. 2005, Carmina *et al*. 2007, Hickey *et al*. 2009). It has been suggested that PCOS may arise through a gene–environment interaction (Franks 2008), and although PCOS is associated with a number of polymorphisms associated with androgen synthesis (Ferk *et al*. 2008, Shah *et al*. 2008), no clear genetic association has been established (Simoni *et al*. 2008).

Although both experimental and clinical data exist indicating that events in are associated with a later life PCOS phenotype, specific predisposing factors have not been clearly defined. IUGR followed by catch up growth during childhood increases the risk of precocious pubarche (Ibanez *et al*. 1998*a*), anovulation PCOS (Ibanez *et al*. 2002*b*, 2007), and characteristics of the metabolic syndrome in adolescence (Ibanez *et al*. 2006*a*). Insulin resistance has been suggested to be a central driver in these associations and treatment with insulin sensitizers in girls with precocious pubarche has been shown to significantly delay the onset of early menarche in this population (Ibanez *et al*. 2006*b*, 2008*a*).

Although it is clear that intrauterine factors play a significant role in the development of the female reproductive system and the risk of dysfunction later in life (de Zegher & Ibanez 2006, Ibanez *et al*. 2007, Melo *et al*. 2010, Franks & Berga 2011), the causal factors are not still clearly defined (Cresswell *et al*. 1997). In a small population of girls, SGA was associated with an increased risk of developing PCOS (Ibanez *et al*. 1998*a*,*b*, 2001, 2008*b*). However, this relationship may be different in babies that had grown normally babies. In a prospective study of normal adolescents, we have recently shown that BW was not associated with PCOS characteristics. These findings, however, need to be confirmed in other populations of unremarkable adolescents in equally large prospective studies. Recently, PCOS has also been associated with being large for gestational age (Mumm *et al*. 2013) as well as having no association with BW (Sadrzadeh *et al*. 2003). Interestingly, it has been proposed that two distinct birth pathways exist to development of PCOS, where high BW was associated with hyperandrogenism (as a single symptom), while low ponderal index was associated with the presence of all three key PCOS symptoms (menstrual dysfunction, hyperandrogenism, and polycystic ovaries) (Davies *et al*. 2012).

Animal studies of reproductive programming: modulatory effects of early growth

Few animal studies have investigated specifically the modulatory effects of growth on reproductive outcome in offspring. In these studies, IUGR is induced by uterine artery ligation, thus mimicking placental insufficiency (Wigglesworth 1974). Results of several studies have indicated that IUGR female offspring display delayed pubertal onset, while others mirror the results of human studies indicating advanced pubertal onset in female offspring born with a LBW (Engelbregt *et al*. 2000, 2002). Many animal models of IUGR use nutrient restriction and thus are discussed in detail below.

Maternal nutritional effects on reproductive function of offspring

Human data

Nutritional effects on reproduction are well established (Wade *et al*. 1996, Schneider 2004, Dupont *et al*. 2014). This reciprocal relationship between nutritional cues, energy intake, and metabolic indicators is not surprising as organisms must have adequate energy stores and resources for successful reproduction. There are a number of maternal conditions and/or pregnancy complications that restrict availability of nutrients to the fetus and decrease fetal growth (Sibley *et al*. 2005, Lager & Powell 2012), but a common theme is reduced nutrient supply. An adequate supply of nutrients is required to maintain a balance between the nutrient demands of the mother and those of the fetus (Bloomfield *et al*. 2013). The most common cause of growth restriction in term newborns is decreased fetal availability of nutrients and hormones (Godfrey 1998, Rosenberg 2008, Diderholm 2009). Numerous pregnancy complications can compromise availability of nutrients, including placental insufficiency

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

and maternal nutrient restriction (Cetin & Alvino 2009, Diderholm 2009, Lausman *et al*. 2012) where impaired placental development and/or function is associated with inadequate fetal nutrient supply and LBW (Pardi *et al*. 2002, Cetin & Alvino 2009). Critically, it is now recognized that maternal obesity may also result in an environment of malnutrition as a proportion of obese mothers give birth to growth-restricted babies (Radulescu *et al*. 2013) and obesity is associated with compromised placental function (Pardi *et al*. 2002, Cetin & Alvino 2009, Diderholm 2009, Lausman *et al*. 2012, Hastie & Lappas 2014). In either case, maternal malnutrition alters maternal–fetal–placental nutrient exchange (Harding & Johnston 1995) and results in fetal adaptations that lead to increased disease risk.

How early-life nutritional cues affect PGC and reproductive development in offspring during critical prenatal windows however is unclear. Data collected from historical observations of humans have shed some lights on the effects that maternal nutrient challenges during pregnancy have on the reproductive performance and function of offspring. The Dutch Hunger Winter of 1944–1945 created a unique opportunity to study the relationship between prenatal famine exposure and adult health. Offspring born to mothers exposed to famine conditions during varying stages of pregnancy have been extensively followed up and numerous papers have been published outlining the relationship between maternal famine exposure and health outcomes of offspring (Painter *et al*. 2005, Heijmans *et al*. 2008, Roseboom *et al*. 2011) (and grand offspring) (Painter *et al*. 2008*a*, Veenendaal *et al*. 2013). Results of follow-up studies indicate that women born to mothers exposed to famine had more children earlier in life, compared with women born to control (not famine-exposed) mothers (Painter *et al*. 2008*b*), although the effect of famine on reproductive success was very small and has been disputed (Lumey & Stein 1997, 2009). Data collected on other historic cohorts indicate that women exposed to acute malnutrition during fetal life may experience negative effects on their reproductive systems, which could result in permanently impaired fecundity (Song 2013) as well as negative effects on metabolic function. There are results, however, indicating that not all offspring born under famine conditions develop postnatal metabolic complications as demonstrated in offspring of the Siege of Leningrad (Stanner *et al*. 1997, Stanner & Yudkin 2001), but effects on reproductive capacity and function in this cohort have not been thoroughly analyzed.

Data describing the relationship between *in utero* nutrient restriction and offspring age at menopause are limited. Famine during early childhood was reported to result in a decrease of 0.36 years in age at natural menopause (Elias *et al*. 2007). Consistent with this observation, malnourished women in developing countries have shorter reproductive lifespans, delayed or advanced onset of puberty, and early menopause (Osteria 1983, Riley 1994, Kirchengast & Winkler 1996, Lindstrom & Berhanu 1999). Steiner *et al*. (2010) reported a weak association between BW and age at menopause (HR 1.09; 95% CI 0.99, 1.20), but this relationship appears to be attenuated if one adjusts for gestational exposure to famine (Yarde *et al*. 2013), perhaps indicating that nutrient restriction plays a large role in the link between age at menopause and BW.

Animal data

Perinatal nutritional challenges have been shown to have long-term consequences for reproductive health (Guzman *et al*. 2006, Zambrano *et al*. 2006, Bernal *et al*. 2010, Sloboda *et al*. 2010, Aiken *et al*. 2013). Results from several animal models have indicated that pre- and/or postnatal nutrient restriction affects reproductive aging, as well as altering central regulation of reproductive hormones. The effects of maternal nutrient restriction on reproductive outcomes are sensitive to the timing of nutritional challenge during gestation as well as the type of nutrient challenge. Models involving total caloric restriction, protein restriction, or micronutrient manipulation all have shown that these challenges have reproductive effects on offspring, although the outcomes vary according to the model. This may reflect differential fetal and neonatal adaptive responses influencing reproductive developmental tempo depending on when the nutritional deficit occurred during gestation. Below we have summarized the literature on reproductive outcomes classified according to the major nutrient restriction models.

Protein restriction Protein restriction during pregnancy and/or lactation in rats produces female offspring that display irregular cycles early in life, and decreased reproductive lifespan (Zambrano *et al*. 2005, Guzman *et al*. 2006, 2014). This is probably due to diminished ovarian reserves as adult offspring born to dams fed an isocaloric, protein-restricted diet throughout pregnancy had reduced numbers of primordial follicles, elevated levels of ovarian oxidative stress, and shortened ovarian telomere length compared with controls (Aiken & Ozanne 2014). The effects also vary according to developmental windows. Female offspring exposed to protein restriction during lactation alone have shown a decrease in circulating LH and an increase in systemic FSH levels at weaning, a

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

hormone profile that is distinct from those of offspring exposed to protein restriction during either pregnancy alone or pregnancy+lactation (Guzman *et al.* 2014). Furthermore, female offspring born to dams exposed to protein restriction during pregnancy or lactation alone exhibit a reduction in numbers of preantral and antral follicular at weaning, compared with offspring of mothers restricted during pregnancy and lactation (Guzman *et al.* 2014). In addition, exposure to protein restriction during pregnancy and lactation or lactation alone results in delayed onset of puberty (Guzman *et al.* 2006). After puberty, offspring born to lactationally protein restricted dams display increased numbers of preantral and small antral follicles but reduced numbers of primordial follicles, Graafian follicles, and corpora lutea (da Silva Faria *et al.* 2008) indicative of ovulatory dysfunction. These results indicate that a mismatch between *in utero* and postnatal nutrition produces an offspring reproductive phenotype that is distinct from those observed during the perinatal period and may negatively influence future reproductive success (da Silva Faria *et al.* 2008, 2010).

Total caloric restriction It is well established that total caloric restriction during pregnancy significantly affects ovarian development and function of offspring. In sheep, maternal nutrient restriction results in a negative effect on oocyte quality which results in lower oocyte cleavage after IVF and decreased morula and blastocyst formation (Grazul-Bilska *et al.* 2012). In rats, maternal caloric restriction throughout pregnancy results in LBW offspring that experience accelerated neonatal growth and early vaginal opening (VO), a marker of sexual maturation in rodents (Sloboda *et al.* 2009, Caron *et al.* 2012, Sanchez-Garrido *et al.* 2013). Early onset of puberty, however, is not always apparent in rodent models investigating caloric restriction (Chernoff *et al.* 2009), and in some cases puberty is delayed (Gereltsetseg *et al.* 2012). Nonetheless, in adulthood, offspring of dams fed calorically restricted diets have reduced numbers of primordial and antral follicles and elevated levels of ovarian oxidative stress, which has been associated with ovarian aging (Bernal *et al.* 2010). These offspring show a decrease in mRNA levels of the granulosa cell-specific estrogen receptor β in addition to a decrease in the oocyte-specific growth factor, *GDF9* (Sloboda *et al.* 2009, Bernal *et al.* 2010), which is evidence of impaired folliculogenesis. Similarly, in cattle, maternal caloric restriction during the first trimester produces offspring with diminished ovarian reserve during adulthood, as demonstrated by reduced antral follicle count, decreased circulating anti-Müllerian hormone, and increased FSH in adulthood (Mossa *et al.* 2013). Furthermore, in sheep, offspring born to ewes fed calorie-restricted diets during the first two-thirds of pregnancy had reduced ovulation rates in adult life as determined by laparoscopic counts of corpora lutea (Rae *et al.* 2002). Together these observations are indicative of a shortened reproductive lifespan in offspring born to mothers on calorie-restricted diets. Premature ovarian aging is caused by early follicle loss or a reduction in the ovarian reserve; the finite pool of follicles that exist within the ovary. The follicular reserve is influenced by the rate of primordial follicle recruitment, follicle health, and reproductive cyclicity (Gleicher *et al.* 2011), all of which appear to be negatively affected in offspring born to calorie-restricted mothers. As outlined in the introduction, this reserve is vulnerable during the perinatal period when these nutritional insults occur, and it appears that changes in ovarian histogenesis induced by different levels of maternal nutrition contribute to the impaired reproductive phenotype of offspring (Rae *et al.* 2002, Mossa *et al.* 2013).

In sheep, maternal dietary restriction with or without micronutrient supplementation of selenium (Se) decreased cell proliferation in primordial, secondary and/or antral follicles, stromal cells, and blood vessels in fetal ovaries (Grazul-Bilska *et al.* 2009). Futhermore, maternal nutrient restriction at differing timepoints throughout pregnancy results in differential effects on ovarian development. Maternal nutrient restriction in sheep for the first 30 days of gestation reduced fetal germ-cell proliferation at day 65, but increased granulosa cell proliferation at day 110. In contrast, maternal underfeeding from 65 to 110 days or from 0 to 110 days altered the expression of genes that regulate apoptosis. Although the pathways may differ, both of these mechanisms probably contribute to the reduced number of ovarian primordial follicles that characterize this underfeeding model (Lea *et al.* 2006).

Maternal caloric restriction also modifies the development and the function of central reproductive control. In rats, maternal caloric restriction during the last week of pregnancy results in growth restriction and neonatal catch-up growth during lactation (Iwasa *et al.* 2010). The offspring were characterized by delayed VO (puberty) and decreased hypothalamic GNRH and *Kiss1* mRNA expression prepubertally (Iwasa *et al.* 2010). *Kiss1* encodes the peptide kisspeptin, which stimulates GNRH production (Matsui *et al.* 2004) and thought to be a key factor in the initiation of puberty (Seminara *et al.* 2003).

Although the female gonad develops during fetal life, with the establishment of PGCs, the breakdown of germ cell nests, and the establishment of primordial follicle

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

formation (being species-dependent), results from previous studies have indicated that nutritional challenge during the early-postnatal period influences reproductive function – even at the level of the follicles contained in the ovary. Delayed pubertal onset has been observed in rats (Castellano *et al*. 2011, Sanchez-Garrido *et al*. 2013) and mice (Caron *et al*. 2012) underfed during lactation using a model that modulates litter size and thus influences nutritional supply. In mice, this appears to be caused by a reduction in the number of axonal projections from the arcuate nucleus of the hypothalamus to the median preoptic nucleus (MPO) of the hypothalamus, which contains neurons that secrete GNRH (Caron *et al*. 2012). It was also observed that in these underfed mice that there was a reduction in the density of kisspeptin-immunoreactive fibers within the MPO, indicating that the kisspeptin input driving GNRH production is lacking (Caron *et al*. 2012). Importantly, this reduction in kisspeptin input to the MPO persisted into adulthood, potentially explaining the reduction in fertility observed in these offspring. Functionally, these alterations were associated with an inability of these offspring to produce an LH increase after ovariectomy at postnatal day 24, indicating impairment in central responsiveness to loss of negative feedback (Caron *et al*. 2012).

Micronutrient models Micronutrient deficiencies play a significant role in the modification of fetal metabolism, organ growth, and function (Allen 1994, 2005). Indeed, studies have identified significant improvement in BW outcome after maternal micronutrient supplementation, particularly in developing countries with inadequate nutrition or food insecurity (Haider & Bhutta 2006, Zagre *et al*. 2007, Haider *et al*. 2011). Most of the essential micronutrients needed for appropriate growth and development are absorbed through food consumption. Unfortunately, even in developed populations, pregnant women often do not maintain adequate nutritional intake during pregnancy. According to the Southampton Women's Survey (SWS), 13% of pregnant women do not follow national nutritional guidelines for pregnancy, and only 2.9% of pregnant women take recommended supplements (Crozier *et al*. 2009, Inskip *et al*. 2009). Pregnant adolescents have been shown to be micronutrient deficient and at a high risk of giving birth to SGA babies (Baker *et al*. 2009). Carbon-1 metabolites such as vitamin B12 and folate play a critical role in DNA and histone methylation, influencing epigenetic regulation of gene expression and modifying signaling pathways that may underlie IUGR, and the modulation of developing organ systems including gonadal and brain development (Forges *et al*. 2007, Stover 2011, Dwarkanath *et al*. 2013, Gueant *et al*. 2013). Deficiencies in folate and/or vitamin B during pregnancy increase the risk of neural tube defects, cognitive or learning disabilities, and have long-term effects on hepatic regulation of metabolic function (Blaise *et al*. 2007, Stover 2011, Safi *et al*. 2012). The effects of prenatal intake of vitamin B12 on reproductive functions of female offspring are not known. Studies investigating on reproduction functions are localized to those that investigate the postnatal intake; in sheep, B12 and methionine restricted intake enhanced the number of estrogen-active antral follicles following FSH stimulation (Kanakkaparambil *et al*. 2009). In the future, studies investigating the role of micronutrient balance are likely to be combined with alterations in macronutrient balance as well, because human dietary patterns probably have simultaneous imbalances in both macro- and micronutrients.

Several studies have also focused on the effects of antioxidants during pregnancy on ovarian functions of offspring . A commonly studied antioxidant is melatonin, which is able to cross the placenta and has been found in the milk of lactating rodents (Klein 1972, Rowe & Kennaway 2002). Melatonin protects against follicular oxidative stress and slows the process of reproductive aging in the rat (Trentini *et al*. 1992, Tamura *et al*. 2012). Maternal administration of melatonin produces offspring that display delayed VO and lowered LH levels in a rodent model (Colmenero *et al*. 1991). Similarly, postnatal administration of melatonin in adult rats also decreases LH serum levels and delays the onset of the post-reproductive constant estrous-anovulatory state as observed in reproductive aging rats (Trentini *et al*. 1992). Other antioxidants, including vitamin C and E, have been found to be detrimental to the developing fetus when administered at high doses, at least in specialized high-risk pregnancies. Results from a clinical trial by Poston *et al*. (2006) indicated that prenatal supplementation of vitamin C and E increases the risk of producing LBW babies. In rats, maternal treatment with vitamin C in a hypoxic pregnancy attenuated hypoxia-induced maternal and placental oxidative stress (Richter *et al*. 2012), but the effects of vitamin C and E supplementation during pregnancy on reproduction of offspring have not yet been investigated.

Selenium is an essential trace element. It is an antioxidant found in trace amounts in many foods including nuts, cereals, fish, and eggs and is often associated with redox reactions and signalling pathways (Kurokawa & Berry 2013), and recently has been suggested

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

to play a role in corpus luteum and/or placental function in pregnant cows (Kamada *et al*. 2014). Although essential in trace amounts, high levels of selenium result in toxicity (Gore *et al*. 2010). In zebrafish, elevated dietary selenium decreased fecundity, embryo survival, and overall reproductive success (Penglase *et al*. 2014). In sheep, maternal diet affected expression of connexin in the ovary, where selenium modulated the effects; connexin expression in the granulosa layer of antral follicles was decreased by high levels of selenium and increased in the granulosa layer of primary and theca of antral follicles (Grazul-Bilska *et al*. 2011).

Nutrient excess

Worldwide obesity has nearly doubled since 1980 with over 500 million people now considered as being obese (Frias & Grove 2012). Concomitant with the rise in obesity is an increase in the number of reproductive-aged women that are overweight or obese (Flegal *et al*. 2010, 2012). Maternal obesity is a major obstetric risk factor for adverse fetal, neonatal, and maternal outcomes (Leddy *et al*. 2008, Gaillard *et al*. 2013, Mission *et al*. 2013), in addition it has been associated with childhood obesity of offspring (Poston 2012) and an increased risk of those offspring developing the metabolic syndrome during adulthood (Rooney & Ozanne 2011, Frias & Grove 2012). Excessive gestational weight gain (Boynton-Jarrett *et al*. 2011, Deardorff *et al*. 2013) and a pre-pregnancy BMI of overweight/obese (Keim *et al*. 2009, Deardorff *et al*. 2013) are associated with early menarche in humans; however, childhood obesity, which is strongly associated with maternal obesity (Catalano *et al*. 2009), is also associated with early menarche (Kaplowitz 2008) making it difficult to ascertain independent effects. In contrast, results from rat models (Shrestha *et al*. 2011) have indicated that high-fat diet intake throughout pregnancy and lactation, inducing maternal obesity, advances the onset of puberty, and disrupts estrous cyclicity in female offspring (Connor *et al*. 2012). In particular, the offspring of obese mothers are more likely to display estrous cycles characterized by prolonged or persistent estrus, where 2 or more days spent in estrus may be indicative of premature ovarian aging (Connor *et al*. 2012). At the level of the ovary, it has recently been shown that gestating offspring born to mothers fed a high-fat/high-cholesterol diet have more atretic follicles (Leveille *et al*. 2014), which may indicate impaired fertility. Interestingly, in sheep, BWs above 5 kg are associated with a decrease in fecundity even after controlling for subcutaneous adiposity (Gardner *et al*. 2009), indicating that fetal macrosomia, which is associated with maternal obesity independently (Mission *et al*. 2013), affects future reproductive success. Similar to models of caloric restriction, these offspring phenotypes, as a result of maternal nutritional excess, are probably due in part to impaired ovarian histogenesis, as demonstrated by a decrease in primordial follicles in fetal ovaries at gestation day 103 in gestating ewes (Da Silva *et al*. 2003) allowed to feed *ad libitum*.

Exposure of pups to lactating obese dams also appears to affect reproductive development. Long Evans Tokushima (LETO) rats fostered to obese Otsuka Long Evans Tokushima fatty (OLETF) dams have more frequent cycles characterized by two or more days spent in estrus during young adulthood (Schroeder *et al*. 2013). However, onset of puberty was not different in LETO rats reared by OLETF nor did VO occur earlier in rats (Sanchez-Garrido *et al*. 2013) or mice (Caron *et al*. 2012) overfed during lactation as a result of reduction in litter size. This is in contrast to the results indicating that prenatal exposure to an obesogenic environment induced by a high-fat (Connor *et al*. 2012) or an *n*-6 polyunsaturated fatty acid-rich maternal diet (Hilakivi-Clarke *et al*. 1997) results in advanced onset of puberty.

Although early-postnatal overfeeding as a result of reduction of litter size does not advance the onset of puberty in female rats, lactationally overfed mice display significant reductions in the number of arcuate neural projections to the MPO of the hypothalamus (Caron *et al*. 2012), probably contributing to a disruption in adult estrous cyclicity and a decrease in the fertility index (Caron *et al*. 2012) demonstrating that neural alterations have functional reproductive implications. In mice, neonatal overnutrition as a result of litter manipulation (Liu *et al*. 2013*a*,*b*) or lactational maternal high-fat feeding (Vogt *et al*. 2014) results in adult-onset obesity and insulin resistance (Liu *et al*. 2013*a*), which have adverse effects on oocyte and zygote quality (Minge *et al*. 2008, Igosheva *et al*. 2010, Jungheim *et al*. 2010, Luzzo *et al*. 2012, Machtinger *et al*. 2012). Moreover, female offspring born to high-fat-fed dams produce oocytes with differentially methylated promoter regions of key metabolic genes (Ge *et al*. 2014). It is not known if these epigenetic changes result in transgenerational effects; however, it has been recently shown in mice that high-fat diet-induced maternal obesity causes metabolic effects in F2 generation offspring via maternal inheritance (King *et al*. 2013). However, It is unclear if these effects are germline-dependent or independent, which could be due to differential maternal adaptations to pregnancy in F1 offspring.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

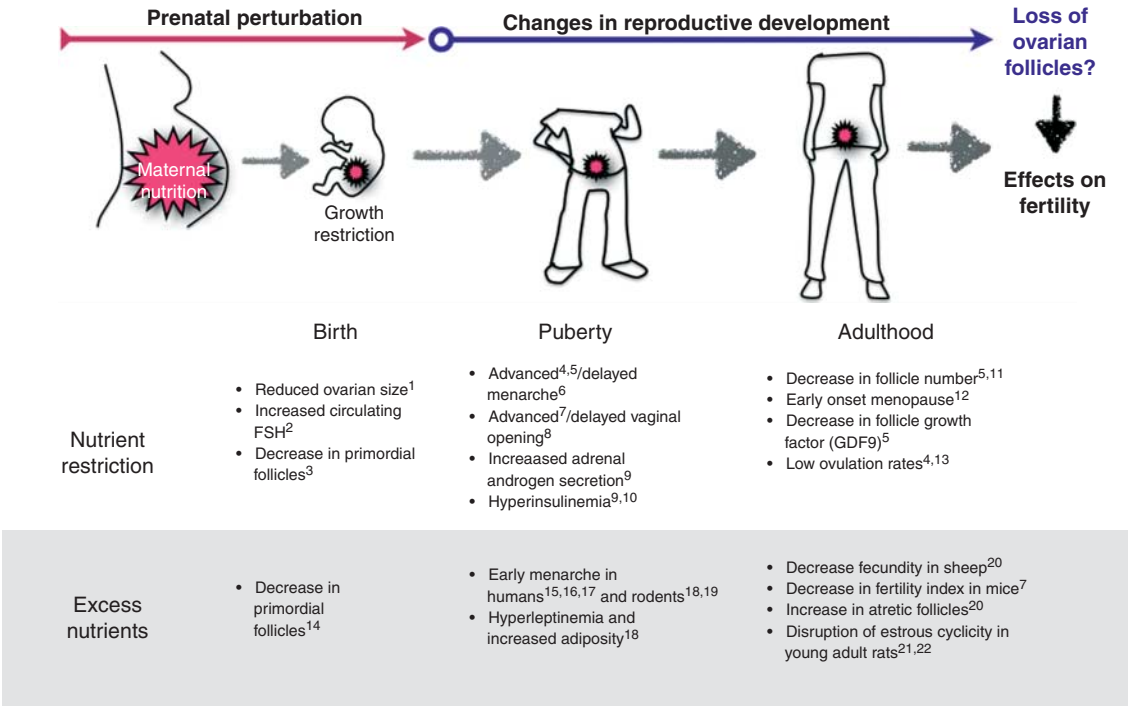

Figure 3
Summary of reproductive outcomes after early-life nutritional adversity. 1, Ibanez *et al*. 2000; 2, Ibanez *et al*. 2002*a*; 3, de Bruin *et al*. 2001; 4, Ibanez *et al*. 2011; 5, Bernal *et al*. 2010; 6, Engelbregt *et al*. 2000; 7, Caron *et al*. 2012; 8, Colmenero *et al*. 1991; 9, Ibanez *et al*. 1999; 10, Ibanez *et al*. 2004; 11, Guzman *et al*. 2014; 12, Elias *et al*. 2007; 13, Rae *et al*. 2002; 14, Da Silva *et al*. 2003; 15, Boynton-Jarrett *et al*. 2011; 16, Deardorff *et al*. 2013; 17, Keim *et al*. 2009; 18, Connor *et al*. 2012; 19, Hilakivi-Clarke *et al*. 1997; 20, Gardner *et al*. 2009; 21, Leveille *et al*. 2014; 22, Schroeder *et al*. 2013.

In addition to the increased availability and consumption of low-cost, hypercaloric food contributing to the obesity epidemic, high fructose consumption, through both beverages and food, has been identified as another important conducive factor in the progression of obesity (Sloboda *et al*. 2014). The long-term female reproductive outcomes of early-life exposure to maternal high fructose intake currently remain unclear. Interestingly, in rats, maternal fructose intake (10% in the drinking water) before and during pregnancy increases the male-to-female sex ratio of litters (Gray *et al*. 2013). This is in accordance with the Trivers–Willard hypothesis, which states that females in a better body condition produce a greater proportion of male offspring (Trivers & Willard 1973, Rosenfeld & Roberts 2004). Future studies are required to fully investigate the effects of high-carbohydrate, high-sugar, and high-fat diets, so that animal models can reflect the shifting change in our access to high-energy, low nutritional value food.

It is worth noting that offspring of obese mothers that have increased rates of obesity may suffer a double effect on their reproductive function. Adipose tissue has the capacity for aromatization – where excess adipose tissue can contribute to increases in the conversion of testosterone to E_2 (Deslypere *et al*. 1985). The pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) increases the levels of expression of the aromatase gene (Zhao *et al*. 1996), and as obesity has been classified as a pro-inflammatory environment, it is possible that TNFα contributes to increased capacity for aromatization of adipocytes. Thus, it has been suggested that in the cases of obesity, high levels of circulating E_2 due to adipocyte-induced testosterone aromatization may impair hypothalamic–pituitary–gonadal function, driving an increase in central negative feedback at the levels of the hypothalamic and the pituitary (Gosman *et al*. 2006). This results in impairments in ovulation and in oocyte development. Thus, in offspring of obese mothers, where the intrauterine environment results in ovarian modifications, there is probably a pre–postnatal interaction on ovarian dysfunction.

Conclusion

Disease risk is established well before birth. Obesity and type 2 diabetes, once thought to be lifestyle-mediated, are

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

now known to be influenced by fetal adaptations to *in utero* conditions, including poor prenatal nutrition. Critically, these disease effects span multiple generations, but how this occurs is unclear. Germ cells (oocytes) in the growing fetal ovary are similarly vulnerable to prenatal events and are likely to contribute to this transgenerational disease risk. As the gametes that will eventually give rise to grand-offspring form during fetal life, it is possible that the link between poor prenatal nutrition and postnatal disease lies in the ovary – involving the developing germ cells and their function. There is now established evidence demonstrating that poor prenatal conditions result in fetal growth restriction, LBW, postnatal reproductive dysfunction, poor pregnancy outcomes, and may even contribute to early aging and menopause (Fig. 3). A steady rise in the rate of LBW and thus increased risk of reproductive deficits and subfertility may be a reality for forthcoming generations. However, the underlying mechanisms are still poorly understood. Thus, it is now essential to integrate evidence from large prospective human studies using targeted experimental animal models that will uncover these mechanisms and begin to indicate potential interventions. This information, derived from an integrated approach, should strive to inform both public health and education policy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

D M S is funded by a Canada Research Chair in Perinatal Programming.

References

Aiken CE & Ozanne SE 2014 Transgenerational developmental programming. *Human Reproduction Update* **20** 63–75. (doi:10.1093/humupd/dmt043)

Aiken CE, Tarry-Adkins JL & Ozanne SE 2013 Suboptimal nutrition *in utero* causes DNA damage and accelerated aging of the female reproductive tract. *FASEB Journal* **27** 3959–3965. (doi:10.1096/fj.13-234484)

Allen LH 1994 Maternal micronutrient malnutrition: effects on breast milk and infant nutrition, and priorities for intervention. *SCN News* **1994** 21–24.

Allen LH 2005 Multiple micronutrients in pregnancy and lactation: an overview. *American Journal of Clinical Nutrition* **81** 1206S–1212S.

Andreasen CH & Andersen G 2009 Gene–environment interactions and obesity – further aspects of genomewide association studies. *Nutrition* **25** 998–1003. (doi:10.1016/j.nut.2009.06.001)

Azziz R 2004 PCOS: a diagnostic challenge. *Reproductive BioMedicine Online* **8** 644–648. (doi:10.1016/S1472-6483(10)61644-6)

Baker PN, Wheeler SJ, Sanders TA, Thomas JE, Hutchinson CJ, Clarke K, Berry JL, Jones RL, Seed PT & Poston L 2009 A prospective study of micronutrient status in adolescent pregnancy. *American Journal of Clinical Nutrition* **89** 1114–1124. (doi:10.3945/ajcn.2008.27097)

Barker DJ 2006 Adult consequences of fetal growth restriction. *Clinical Obstetrics and Gynecology* **49** 270–283. (doi:10.1097/00003081-200606000-00009)

Barker DJ, Osmond C, Golding J, Kuh D & Wadsworth ME 1989 Growth *in utero*, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* **298** 564–567. (doi:10.1136/bmj.298.6673.564)

Barra R, Cruz G, Mayerhofer A, Paredes A & Lara HE 2014 Maternal sympathetic stress impairs follicular development and puberty of the offspring. *Reproduction* **148** 137–145. (doi:10.1530/REP-14-0150)

Berger SL, Kouzarides T, Shiekhattar R & Shilatifard A 2009 An operational definition of epigenetics. *Genes and Development* **23** 781–783. (doi:10.1101/gad.1787609)

Bernal AB, Vickers MH, Hampton MB, Poynton RA & Sloboda DM 2010 Maternal undernutrition significantly impacts ovarian follicle number and increases ovarian oxidative stress in adult rat offspring. *PLoS ONE* **5** e15558. (doi:10.1371/journal.pone.0015558)

Bird AP & Wolffe AP 1999 Methylation-induced repression – belts, braces, and chromatin. *Cell* **99** 451–454. (doi:10.1016/S0092-8674(00)81532-9)

Blaise SA, Nedelec E, Schroeder H, Alberto JM, Bossenmeyer-Pourie C, Gueant JL & Daval JL 2007 Gestational vitamin B deficiency leads to homocysteine-associated brain apoptosis and alters neurobehavioral development in rats. *American Journal of Pathology* **170** 667–679. (doi:10.2353/ajpath.2007.060339)

Bloomfield FH, Spiroski A-M & Harding JE 2013 Fetal growth factors and fetal nutrition. *Seminars in Fetal & Neonatal Medicine* **18** 118–123. (doi:10.1016/j.siny.2013.03.003)

Bouchard C 2008 Gene–environment interactions in the etiology of obesity: defining the fundamentals. *Obesity* **16** S5–S10. (doi:10.1038/oby.2008.528)

Boynton-Jarrett R, Rich-Edwards J, Fredman L, Hibert EL, Michels KB, Forman MR & Wright RJ 2011 Gestational weight gain and daughter's age at menarche. *Journal of Women's Health* **20** 1193–1200. (doi:10.1089/jwh.2010.2517)

de Bruin JP, Dorland M, Bruinse HW, Spliet W, Nikkels PG & Te Velde ER 1998 Fetal growth retardation as a cause of impaired ovarian development. *Early Human Development* **51** 39–46. (doi:10.1016/S0378-3782(97)00073-X)

de Bruin JP, Nikkels PG, Bruinse HW, van Haaften M, Looman CW & te Velde ER 2001 Morphometry of human ovaries in normal and growth-restricted fetuses. *Early Human Development* **60** 179–192. (doi:10.1016/S0378-3782(00)00118-3)

Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, Di Fede G & Rini G 2007 Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. *Journal of Clinical Endocrinology and Metabolism* **92** 2500–2505. (doi:10.1210/jc.2006-2725)

Caron E, Ciofi P, Prevot V & Bouret SG 2012 Alteration in neonatal nutrition causes perturbations in hypothalamic neural circuits controlling reproductive function. *Journal of Neuroscience* **32** 11486–11494. (doi:10.1523/JNEUROSCI.6074-11.2012)

Castellano JM, Bentsen AH, Sanchez-Garrido MA, Ruiz-Pino F, Romero M, Garcia-Galiano D, Aguilar E, Pinilla L, Dieguez C, Mikkelsen JD *et al.* 2011 Early metabolic programming of puberty onset: impact of changes in postnatal feeding and rearing conditions on the timing of puberty and development of the hypothalamic kisspeptin system. *Endocrinology* **152** 3396–3408. (doi:10.1210/en.2010-1415)

Catalano PM, Farrell K, Thomas A, Huston-Presley L, Mencin P, de Mouzon SH & Amini SB 2009 Perinatal risk factors for childhood obesity and metabolic dysregulation. *American Journal of Clinical Nutrition* **90** 1303–1313. (doi:10.3945/ajcn.2008.27416)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

Cetin I & Alvino G 2009 Intrauterine growth restriction: implications for placental metabolism and transport. A review. *Placenta* **30**(Supplement) 77–82. (doi:10.1016/j.placenta.2008.12.006)

Champagne FA 2011 Maternal imprints and the origins of variation. *Hormones and Behavior* **60** 4–11. (doi:10.1016/j.yhbeh.2011.02.016)

Chernoff N, Gage MI, Stoker TE, Cooper RL, Gilbert ME & Rogers EH 2009 Reproductive effects of maternal and pre-weaning undernutrition in rat offspring: age at puberty, onset of female reproductive senescence and intergenerational pup growth and viability. *Reproductive Toxicology* **28** 489–494. (doi:10.1016/j.reprotox.2009.06.006)

Colmenero MD, Diaz B, Miguel JL, Gonzalez ML, Esquifino A & Marin B 1991 Melatonin administration during pregnancy retards sexual maturation of female offspring in the rat. *Journal of Pineal Research* **11** 23–27. (doi:10.1111/j.1600-079X.1991.tb00822.x)

Connor KL, Vickers MH, Beltrand J, Meaney MJ & Sloboda DM 2012 Nature, nurture or nutrition? Impact of maternal nutrition on maternal care, offspring development and reproductive function *Journal of Physiology* **590** 2167–2180. (doi:10.1113/jphysiol.2011.223305)

Cooper C, Kuh D, Egger P, Wadsworth M & Barker D 1996 Childhood growth and age at menarche. *British Journal of Obstetrics and Gynaecology* **103** 814–817. (doi:10.1111/j.1471-0528.1996.tb09879.x)

Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips DI & Fraser RB 1997 Fetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet* **350** 1131–1135. (doi:10.1016/S0140-6736(97)06062-5)

Crozier SR, Robinson SM, Borland SE, Godfrey KM, Cooper C, Inskip HM & Group SWSS 2009 Do women change their health behaviours in pregnancy? Findings from the Southampton Women's Survey *Paediatric and Perinatal Epidemiology* **23** 446–453. (doi:10.1111/j.1365-3016.2009.01036.x)

Da Silva P, Aitken RP, Rhind SM, Racey PA & Wallace JM 2003 Effect of maternal overnutrition during pregnancy on pituitary gonadotrophin gene expression and gonadal morphology in female and male foetal sheep at day 103 of gestation. *Placenta* **24** 248–257. (doi:10.1053/plac.2002.0897)

Davies MJ, March WA, Willson KJ, Giles LC & Moore VM 2012 Birthweight and thinness at birth independently predict symptoms of polycystic ovary syndrome in adulthood. *Human Reproduction* **27** 1475–1480. (doi:10.1093/humrep/des027)

Deardorff J, Berry-Millett R, Rehkopf D, Luecke E, Lahiff M & Abrams B 2013 Maternal pre-pregnancy BMI, gestational weight gain, and age at menarche in daughters. *Maternal and Child Health Journal* **17** 1391–1398. (doi:10.1007/s10995-012-1139-z)

Desai M, Beall M & Ross M 2013 Developmental origins of obesity: programmed adipogenesis. *Current Diabetes Reports* **13** 27–33. (doi:10.1007/s11892-012-0344-x)

Deslypere JP, Verdonck L & Vermeulen A 1985 Fat tissue: a steroid reservoir and site of steroid metabolism. *Journal of Clinical Endocrinology and Metabolism* **61** 564–570. (doi:10.1210/jcem-61-3-564)

Diderholm B 2009 Perinatal energy metabolism with reference to IUGR & SGA: studies in pregnant women & newborn infants. *Indian Journal of Medical Research* **130** 612–617.

Dominguez-Salas P, Cox SE, Prentice AM, Hennig BJ & Moore SE 2012 Maternal nutritional status, C_1 metabolism and offspring DNA methylation: a review of current evidence in human subjects. *Proceedings of the Nutrition Society* **71** 154–165. (doi:10.1017/S0029665111003338)

Dominguez-Salas P, Moore SE, Baker MS, Bergen AW, Cox SE, Dyer RA, Fulford AJ, Guan Y, Laritsky E, Silver MJ *et al.* 2014 Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. *Nature Communications* **5** article number 3746. (doi:10.1038/ncomms4746)

Dupont C, Armant DR & Brenner CA 2009 Epigenetics: definition, mechanisms and clinical perspective. *Seminars in Reproductive Medicine* **27** 351–357. (doi:10.1055/s-0029-1237423)

Dupont J, Reverchon M, Bertoldo MJ & Froment P 2014 Nutritional signals and reproduction. *Molecular and Cellular Endocrinology* **382** 527–537. (doi:10.1016/j.mce.2013.09.028)

Dwarkanath P, Barzilay JR, Thomas T, Thomas A, Bhat S & Kurpad AV 2013 High folate and low vitamin B-12 intakes during pregnancy are associated with small-for-gestational age infants in South Indian women: a prospective observational cohort study. *American Journal of Clinical Nutrition* **98** 1450–1458. (doi:10.3945/ajcn.112.056382)

Elias CF & Purohit D 2013 Leptin signaling and circuits in puberty and fertility. *Cellular and Molecular Life Sciences* **70** 841–862. (doi:10.1007/s00018-012-1095-1)

Elias SG, van Noord PA, Peeters PH, den Tonkelaar I, Kaaks R & Grobbee DE 2007 Menstruation during and after caloric restriction: the 1944–1945 Dutch famine. *Fertility and Sterility* **88** 1101–1107. (doi:10.1016/j.fertnstert.2006.12.043)

Engelbregt MJ, Houdijk ME, Popp-Snijders C & Delemarre-van de Waal HA 2000 The effects of intra-uterine growth retardation and postnatal undernutrition on onset of puberty in male and female rats. *Pediatric Research* **48** 803–807. (doi:10.1203/00006450-200012000-00017)

Engelbregt MJ, van Weissenbruch MM, Popp-Snijders C & Delemarre-van de Waal HA 2002 Delayed first cycle in intrauterine growth-retarded and postnatally undernourished female rats: follicular growth and ovulation after stimulation with pregnant mare serum gonadotropin at first cycle. *Journal of Endocrinology* **173** 297–304. (doi:10.1677/joe.0.1730297)

Ferk P, Pohar Perme M, Teran N & Gersak K 2008 Androgen receptor gene $(CAG)_n$ polymorphism in patients with polycystic ovary syndrome. *Fertility and Sterility* **90** 860–863. (doi:10.1016/j.fertnstert.2007.07.1291)

de Ferran K, Paiva IA, Garcia Ldos S, Gama Mde P & Guimaraes MM 2011 Isolated premature pubarche: report of anthropometric and metabolic profile of a Brazilian cohort of girls. *Hormone Research in Paediatrics* **75** 367–373. (doi:10.1159/000324107)

Flegal KM, Carroll MD, Ogden CL & Curtin LR 2010 Prevalence and trends in obesity among US adults, 1999–2008. *Journal of the American Medical Association* **303** 235–241. (doi:10.1001/jama.2009.2014)

Flegal KM, Carroll MD, Kit BK & Ogden CL 2012 Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *Journal of the American Medical Association* **307** 491–497. (doi:10.1001/jama.2012.39)

Forabosco A & Sforza C 2007 Establishment of ovarian reserve: a quantitative morphometric study of the developing human ovary. *Fertility and Sterility* **88** 675–683. (doi:10.1016/j.fertnstert.2006.11.191)

Forges T, Monnier-Barbarino P, Alberto JM, Gueant-Rodriguez RM, Daval JL & Gueant JL 2007 Impact of folate and homocysteine metabolism on human reproductive health. *Human Reproduction Update* **13** 225–238. (doi:10.1093/humupd/dml063)

Franks S 2008 Polycystic ovary syndrome in adolescents. *International Journal of Obesity* **32** 1035–1041. (doi:10.1038/ijo.2008.61)

Franks S & Berga SL 2011 Does PCOS have developmental origins? *Fertility and Sterility* **97** 2–6. (doi:10.1016/j.fertnstert.2011.11.029)

Frias AE & Grove KL 2012 Obesity: a transgenerational problem linked to nutrition during pregnancy. *Seminars in Reproductive Medicine* **30** 472–478. (doi:10.1055/s-0032-1328875)

Gaillard R, Durmus B, Hofman A, Mackenbach JP, Steegers EA & Jaddoe VW 2013 Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. *Obesity* **21** 1046–1055. (doi:10.1002/oby.20088)

Gardner DS, Ozanne SE & Sinclair KD 2009 Effect of the early-life nutritional environment on fecundity and fertility of mammals. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **364** 3419–3427. (doi:10.1098/rstb.2009.0121)

Ge ZJ, Luo SM, Lin F, Liang QX, Huang L, Wei YC, Hou Y, Han ZM, Schatten H & Sun QY 2014 DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

obesity. *Environmental Health Perspectives* **122** 159–164. (doi:10.1289/ehp.1307047)
Geber S, Megale R, Vale F, Lanna AM & Cabral AC 2012 Variation in ovarian follicle density during human fetal development. *Journal of Assisted Reproduction and Genetics* **29** 969–972. (doi:10.1007/s10815-012-9810-2)
Gereltsetseg G, Matsuzaki T, Iwasa T, Kinouchi R, Nakazawa H, Yamamoto S, Kuwahara A, Yasui T & Irahara M 2012 Delay in the onset of puberty of intrauterine growth retarded female rats cannot be rescued with hypernutrition after birth. *Endocrine Journal* **59** 963–972. (doi:10.1507/endocrj.EJ11-0392)
Gleicher N, Weghofer A & Barad DH 2011 Defining ovarian reserve to better understand ovarian aging. *Reproductive Biology and Endocrinology* **9** 23. (doi:10.1186/1477-7827-9-23)
Gluckman PD & Hanson MA 2004 Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatric Research* **56** 311–317. (doi:10.1203/01.PDR.0000135998.08025.FB)
Gluckman PD & Hanson MA 2007 Developmental plasticity and human disease: research directions. *Journal of Internal Medicine* **261** 461–471. (doi:10.1111/j.1365-2796.2007.01802.x)
Gluckman PD, Hanson MA & Beedle AS 2007 Non-genomic transgenerational inheritance of disease risk. *BioEssays* **29** 145–154. (doi:10.1002/bies.20522)
Godfrey KM 1998 Maternal regulation of fetal development and health in adult life. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **78** 141–150. (doi:10.1016/S0301-2115(98)00060-8)
Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR *et al.* 2011 Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes* **60** 1528–1534. (doi:10.2337/db10-0979)
Gopinath C 2013 Toxicology and pathology of female reproductive tract. *Cell Biology and Toxicology* **29** 131–141. (doi:10.1007/s10565-013-9244-3)
Gore F, Fawell J & Bartram J 2010 Too much or too little? A review of the conundrum of selenium *Journal of Water and Health* **8** 405–416. (doi:10.2166/wh.2009.060)
Gosman GG, Katcher HI & Legro RS 2006 Obesity and the role of gut and adipose hormones in female reproduction. *Human Reproduction Update* **12** 585–601. (doi:10.1093/humupd/dml024)
Gray C, Long S, Green C, Gardiner SM, Craigon J & Gardner DS 2013 Maternal fructose and/or salt intake and reproductive outcome in the rat: effects on growth, fertility, sex ratio, and birth order. *Biology of Reproduction* **89** 51. (doi:10.1095/biolreprod.113.109595)
Grazul-Bilska AT, Caton JS, Arndt W, Burchill K, Thorson C, Borowczyk E, Bilski JJ, Redmer DA, Reynolds LP & Vonnahme KA 2009 Cellular proliferation and vascularization in ovine fetal ovaries: effects of undernutrition and selenium in maternal diet. *Reproduction* **137** 699–707. (doi:10.1530/REP-08-0375)
Grazul-Bilska AT, Vonnahme KA, Bilski JJ, Borowczyk E, Soni D, Mikkelson B, Johnson ML, Reynolds LP, Redmer DA & Caton JS 2011 Expression of gap junctional connexin proteins in ovine fetal ovaries: effects of maternal diet. *Domestic Animal Endocrinology* **41** 185–194. (doi:10.1016/j.domaniend.2011.06.005)
Grazul-Bilska AT, Borowczyk E, Bilski JJ, Reynolds LP, Redmer DA, Caton JS & Vonnahme KA 2012 Overfeeding and underfeeding have detrimental effects on oocyte quality measured by *in vitro* fertilization and early embryonic development in sheep. *Domestic Animal Endocrinology* **43** 289–298. (doi:10.1016/j.domaniend.2012.05.001)
Grumbach MM 2002 The neuroendocrinology of human puberty revisited. *Hormone Research* **57**(Suppl 2) 2–14. (doi:10.1159/000058094)
Gueant JL, Namour F, Gueant-Rodriguez RM & Daval JL 2013 Folate and fetal programming: a play in epigenomics? *Trends in Endocrinology and Metabolism* **24** 279–289. (doi:10.1016/j.tem.2013.01.010)
Guibert S, Forne T & Weber M 2012 Global profiling of DNA methylation erasure in mouse primordial germ cells. *Genome Research* **22** 633–641. (doi:10.1101/gr.130997.111)
Guzman C, Cabrera R, Cardenas M, Larrea F, Nathanielsz PW & Zambrano E 2006 Protein restriction during fetal and neonatal development in the rat alters reproductive function and accelerates reproductive ageing in female progeny. *Journal of Physiology* **572** 97–108. (doi:10.1113/jphysiol.2005.103903)
Guzman C, Garcia-Becerra R, Aguilar-Medina MA, Mendez I, Merchant-Larios H & Zambrano E 2014 Maternal protein restriction during pregnancy and/or lactation negatively affects follicular ovarian development and steroidogenesis in the prepubertal rat offspring. *Archives of Medical Research* **45** 294–300. (doi:10.1016/j.arcmed.2014.05.005)
Haglund K, Nezis IP & Stenmark H 2011 Structure and functions of stable intercellular bridges formed by incomplete cytokinesis during development. *Communicative & Integrative Biology* **4** 1–9. (doi:10.4161/cib.13550)
Haider BA & Bhutta ZA 2006 Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* **11** CD004905. (doi:10.1002/14651858.CD004905.pub3)
Haider BA, Yakoob MY & Bhutta ZA 2011 Effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes. *BMC Public Health* **11**(Suppl 3) S19. (doi:10.1186/1471-2458-11-S3-S19)
Hampl R, Kubatova J, Heracek J, Sobotka V & Starka L 2013 Hormones and endocrine disruptors in human seminal plasma. *Endocrine Regulations* **47** 149–158. (doi:10.4149/endo_2013_03_149)
Harding J & Johnston B 1995 Nutrition and fetal growth. *Reproduction, Fertility, and Development* **7** 539–547. (doi:10.1071/RD9950539)
Hart R, Hickey M & Franks S 2004 Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. *Best Practice & Research. Clinical Obstetrics & Gynaecology* **18** 671–683. (doi:10.1016/j.bpobgyn.2004.05.001)
Hastie R & Lappas M 2014 The effect of pre-existing maternal obesity and diabetes on placental mitochondrial content and electron transport chain activity. *Placenta* **35** 673–683. (doi:10.1016/j.placenta.2014.06.368)
Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE & Lumey LH 2008 Persistent epigenetic differences associated with prenatal exposure to famine in humans. *PNAS* **105** 17046–17049. (doi:10.1073/pnas.0806560105)
Hernandez MI, Martinez A, Capurro T, Pena V, Trejo L, Avila A, Salazar T, Asenjo S, Iniguez G & Mericq V 2006 Comparison of clinical, ultrasonographic, and biochemical differences at the beginning of puberty in healthy girls born either small for gestational age or appropriate for gestational age: preliminary results. *Journal of Clinical Endocrinology and Metabolism* **91** 3377–3381. (doi:10.1210/jc.2005-2368)
Hickey M, Sloboda DM, Atkinson HC, Doherty DA, Franks S, Norman RJ, Newnham JP & Hart R 2009 The relationship between maternal and umbilical cord androgen levels and polycystic ovary syndrome in adolescence: a prospective cohort study. *Journal of Clinical Endocrinology and Metabolism* **94** 3714–3720. (doi:10.1210/jc.2009-0544)
Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E & Lippman M 1997 A maternal diet high in *n*-6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. *PNAS* **94** 9372–9377. (doi:10.1073/pnas.94.17.9372)
Hirshfield AN 1991 Development of follicles in the mammalian ovary. *International Review of Cytology* **124** 43–101. (doi:10.1016/S0074-7696(08)61524-7)
Hui LL, Leung GM, Wong M-Y, Lam TH & Schooling CM 2012 Small for gestational age and age at puberty: evidence from Hong Kong's "Children of 1997" Birth Cohort. *American Journal of Epidemiology* **176** 785–793. (doi:10.1093/aje/kws159)
Hunt PA & Hassold TJ 2008 Human female meiosis: what makes a good egg go bad? *Trends in Genetics* **24** 86–93. (doi:10.1016/j.tig.2007.11.010)
Ibanez L & de Zegher F 2006 Puberty and prenatal growth. *Molecular and Cellular Endocrinology* **254–255** 22–25. (doi:10.1016/j.mce.2006.04.010)
Ibanez L, de Zegher F & Potau N 1998*a* Premature pubarche, ovarian hyperandrogenism, hyperinsulinism and the polycystic ovary syndrome: from a complex constellation to a simple sequence of prenatal

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

onset. *Journal of Endocrinological Investigation* **21** 558–566. (doi:10.1007/BF03350781)

Ibanez L, Potau N, Francois I & de Zegher F 1998*b* Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. *Journal of Clinical Endocrinology and Metabolism* **83** 3558–3562. (doi:10.1210/jcem.83.10.5205)

Ibanez L, Potau N, Marcos MV & de Zegher F 1999 Exaggerated adrenarche and hyperinsulinism in adolescent girls born small for gestational age. *Journal of Clinical Endocrinology and Metabolism* **84** 4739–4741. (doi:10.1210/jcem.84.12.6341)

Ibanez L, Potau N, Enriquez G & de Zegher F 2000 Reduced uterine and ovarian size in adolescent girls born small for gestational age. *Pediatric Research* **47** 575–577. (doi:10.1203/00006450-200005000-00003)

Ibanez L, Valls C, Potau N, Marcos MV & de Zegher F 2001 Polycystic ovary syndrome after precocious pubarche: ontogeny of the low-birthweight effect. *Clinical Endocrinology* **55** 667–672. (doi:10.1046/j.1365-2265.2001.01399.x)

Ibanez L, Valls C, Cols M, Ferrer A, Marcos MV & de Zegher F 2002*a* Hypersecretion of FSH in infant boys and girls born small for gestational age. *Journal of Clinical Endocrinology and Metabolism* **87** 1986–1988. (doi:10.1210/jcem.87.5.8459)

Ibanez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV & de Zegher F 2002*b* Reduced ovulation rate in adolescent girls born small for gestational age. *Journal of Clinical Endocrinology and Metabolism* **87** 3391–3393. (doi:10.1210/jcem.87.7.8657)

Ibanez L, Ferrer A, Ong K, Amin R, Dunger D & de Zegher F 2004 Insulin sensitization early after menarche prevents progression from precocious pubarche to polycystic ovary syndrome. *Journal of Pediatrics* **144** 23–29. (doi:10.1016/j.jpeds.2003.08.015)

Ibanez L, Ong K, Dunger DB & de Zegher F 2006*a* Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. *Journal of Clinical Endocrinology and Metabolism* **91** 2153–2158. (doi:10.1210/jc.2005-2778)

Ibanez L, Valls C, Ong K, Dunger DB & de Zegher F 2006*b* Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in low-birth-weight girls with early-normal onset of puberty. *Journal of Clinical Endocrinology and Metabolism* **91** 2068–2073. (doi:10.1210/jc.2005-2329)

Ibanez L, Jaramillo A, Enriquez G, Miro E, Lopez-Bermejo A, Dunger D & de Zegher F 2007 Polycystic ovaries after precocious pubarche: relation to prenatal growth. *Human Reproduction* **22** 395–400. (doi:10.1093/humrep/del395)

Ibanez L, Lopez-Bermejo A, Diaz M, Marcos MV & de Zegher F 2008*a* Metformin treatment for 4 years to reduce total and visceral fat in low-birthweight girls with precocious pubarche. *Journal of Clinical Endocrinology and Metabolism* **93** 1841–1845. (doi:10.1210/jc.2008-0013)

Ibanez L, Lopez-Bermejo A, Callejo J, Torres A, Cabre S, Dunger D & de Zegher F 2008*b* Polycystic ovaries in nonobese adolescents and young women with ovarian androgen excess: relation to prenatal growth. *Journal of Clinical Endocrinology and Metabolism* **93** 196–199. (doi:10.1210/jc.2007-1800)

Ibanez L, Lopez-Bermejo A, Diaz M & Marcos MV 2011 Endocrinology and gynecology of girls and women with low birth weight. *Fetal Diagnosis and Therapy* **30** 243–249. (doi:10.1159/000330366)

Igosheva N, Abramov AY, Poston L, Eckert JJ, Fleming TP, Duchen MR & McConnell J 2010 Maternal diet-induced obesity alters mitochondrial activity and redox status in mouse oocytes and zygotes. *PLoS ONE* **5** e10074. (doi:10.1371/journal.pone.0010074)

Inskip HM, Crozier SR, Godfrey KM, Borland SE, Cooper C & Robinson SM 2009 Women's compliance with nutrition and lifestyle recommendations before pregnancy: general population cohort study. *BMJ* **338** b481. (doi:10.1136/bmj.b481)

Iwasa T, Matsuzaki T, Murakami M, Fujisawa S, Kinouchi R, Gereltsetseg G, Kuwahara A, Yasui T & Irahara M 2010 Effects of intrauterine undernutrition on hypothalamic *Kiss1* expression and the timing of puberty in female rats. *Journal of Physiology* **588** 821–829. (doi:10.1113/jphysiol.2009.183558)

Johnson J, Canning J, Kaneko T, Pru JK & Tilly JL 2004 Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature* **428** 145–150. (doi:10.1038/nature02316)

Johnson J, Bagley J, Skaznik-Wikiel M, Lee H-J, Adams GB, Niikura Y, Tschudy KS, Tilly JC, Cortes ML, Forkert R *et al.* 2005 Oocyte generation in adult mammalian ovaries by putative germ cells in bone marrow and peripheral blood. *Cell* **122** 303–315. (doi:10.1016/j.cell.2005.06.031)

Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE & Moley KH 2010 Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology* **151** 4039–4046. (doi:10.1210/en.2010-0098)

Kamada H, Nonaka I, Takenouchi N & Amari M 2014 Effects of selenium supplementation on plasma progesterone concentrations in pregnant heifers. *Animal Science Journal* **85** 241–246. (doi:10.1111/asj.12139)

Kanakkaparambil R, Singh R, Li D, Webb R & Sinclair KD 2009 B-vitamin and homocysteine status determines ovarian response to gonadotropin treatment in sheep. *Biology of Reproduction* **80** 743–752. (doi:10.1095/biolreprod.108.072074)

Kaplowitz PB 2008 Link between body fat and the timing of puberty. *Pediatrics* **121**(Suppl 3) S208–S217. (doi:10.1542/peds.2007-1813F)

Kawagoe S & Hiroi M 1983 Maturation of negative and positive estrogen feedback in the prepubertal female rat. *Endocrinologia Japonica* **30** 435–441. (doi:10.1507/endocrj1954.30.435)

Keim SA, Branum AM, Klebanoff MA & Zemel BS 2009 Maternal body mass index and daughters' age at menarche. *Epidemiology* **20** 677–681. (doi:10.1097/EDE.0b013e3181b093ce)

Kerr JB, Brogan L, Myers M, Hutt KJ, Mladenovska T, Ricardo S, Hamza K, Scott CL, Strasser A & Findlay JK 2012 The primordial follicle reserve is not renewed after chemical or γ-irradiation mediated depletion. *Reproduction* **143** 469–476. (doi:10.1530/REP-11-0430)

Kezele P, Nilsson E & Skinner MK 2002 Cell–cell interactions in primordial follicle assembly and development. *Frontiers in Bioscience* **7** d1990–d1996. (doi:10.2741/kezele)

Khulan B, Cooper WN, Skinner BM, Bauer J, Owens S, Prentice AM, Belteki G, Constancia M, Dunger D & Affara NA 2012 Periconceptional maternal micronutrient supplementation is associated with widespread gender related changes in the epigenome: a study of a unique resource in the Gambia. *Human Molecular Genetics* **21** 2086–2101. (doi:10.1093/hmg/dds026)

King V, Dakin RS, Liu L, Hadoke PW, Walker BR, Seckl JR, Norman JE & Drake AJ 2013 Maternal obesity has little effect on the immediate offspring but impacts on the next generation. *Endocrinology* **154** 2514–2524. (doi:10.1210/en.2013-1013)

Kirchengast S & Huber J 2001 Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. *Human Reproduction* **16** 1255–1260. (doi:10.1093/humrep/16.6.1255)

Kirchengast S & Winkler EM 1996 Nutritional status as indicator for reproductive success in !Kung San and Kavango females from Namibia. *Anthropologischer Anzeiger* **54** 267–276.

Klein DC 1972 Evidence for the placental transfer of 3H-acetyl-melatonin. *Nature: New Biology* **237** 117–118. (doi:10.1038/newbio237117a0)

Kurokawa S & Berry MJ 2013 Selenium. Role of the essential metalloid in health. *Metal Ions in Life Sciences* **13** 499–534. (doi:10.1007/978-94-007-7500-8_16)

Lager S & Powell TL 2012 Regulation of nutrient transport across the placenta. *Journal of Pregnancy* **2012** 179827. (doi:10.1155/2012/179827)

Lausman A, McCarthy FP, Walker M & Kingdom J 2012 Screening, diagnosis, and management of intrauterine growth restriction. *Journal of Obstetrics and Gynaecology Canada* **34** 17–28.

Lea RG, Andrade LP, Rae MT, Hannah LT, Kyle CE, Murray JF, Rhind SM & Miller DW 2006 Effects of maternal undernutrition during early pregnancy on apoptosis regulators in the ovine fetal ovary. *Reproduction* **131** 113–124. (doi:10.1530/rep.1.00844)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

Leddy MA, Power ML & Schulkin J 2008 The impact of maternal obesity on maternal and fetal health. *Reviews in Obstetrics & Gynecology* **1** 170–178.
Lee HJ, Hore TA & Reik W 2014 Reprogramming the methylome: erasing memory and creating diversity. *Cell Stem Cell* **14** 710–719. (doi:10.1016/j.stem.2014.05.008)
Leveille P, Tarrade A, Dupont C, Larcher T, Dahirel M, Poumerol E, Cordier AG, Picone O, Mandon-Pepin B, Jolivet G *et al*. 2014 Maternal high-fat diet induces follicular atresia but does not affect fertility in adult rabbit offspring. *Journal of Developmental Origins of Health and Disease* **5** 88–97. (doi:10.1017/S2040174414000014)
Lie ME, Overgaard A & Mikkelsen JD 2013 Effect of a postnatal high-fat diet exposure on puberty onset, estrous cycle regularity, and kisspeptin expression in female rats. *Reproductive Biology* **13** 298–308. (doi:10.1016/j.repbio.2013.08.001)
Lindstrom DP & Berhanu B 1999 The impact of war, famine, and economic decline on marital fertility in Ethiopia. *Demography* **36** 247–261. (doi:10.2307/2648112)
Liu HW, Srinivasan M, Mahmood S, Smiraglia DJ & Patel MS 2013*a* Adult-onset obesity induced by early life overnutrition could be reversed by moderate caloric restriction. *American Journal of Physiology. Endocrinology and Metabolism* **305** E785–E794. (doi:10.1152/ajpendo.00280.2013)
Liu Z, Lim CY, Su MY, Soh SL, Shui G, Wenk MR, Grove KL, Radda GK, Han W & Xiao X 2013*b* Neonatal overnutrition in mice exacerbates high-fat diet-induced metabolic perturbations. *Journal of Endocrinology* **219** 131–143. (doi:10.1530/JOE-13-0111)
Lumey LH & Stein AD 1997 *In utero* exposure to famine and subsequent fertility: the Dutch Famine Birth Cohort Study. *American Journal of Public Health* **87** 1962–1966. (doi:10.2105/AJPH.87.12.1962)
Lumey LH & Stein AD 2009 Increased reproductive success of women after prenatal undernutrition? *Human Reproduction* **24** 491 (author reply 491–492). (doi:10.1093/humrep/den394)
Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, Schedl T & Moley KH 2012 High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. *PLoS ONE* **7** e49217. (doi:10.1371/journal.pone.0049217)
Machtinger R, Combelles CM, Missmer SA, Correia KF, Fox JH & Racowsky C 2012 The association between severe obesity and characteristics of failed fertilized oocytes. *Human Reproduction* **27** 3198–3207. (doi:10.1093/humrep/des308)
Mamsen LS, Brochner CB, Byskov AG & Mollgard K 2012 The migration and loss of human primordial germ stem cells from the hind gut epithelium towards the gonadal ridge. *International Journal of Developmental Biology* **56** 771–778. (doi:10.1387/ijdb.120202lm)
Marques-Pinto A & Carvalho D 2013 Human infertility: are endocrine disruptors to blame? *Endocrine Connections* **2** R15–R29. (doi:10.1530/EC-13-0036)
Martos-Moreno GA, Chowen JA & Argente J 2010 Metabolic signals in human puberty: effects of over and undernutrition. *Molecular and Cellular Endocrinology* **324** 70–81. (doi:10.1016/j.mce.2009.12.017)
Matsui H, Takatsu Y, Kumano S, Matsumoto H & Ohtaki T 2004 Peripheral administration of metastin induces marked gonadotropin release and ovulation in the rat. *Biochemical and Biophysical Research Communications* **320** 383–388. (doi:10.1016/j.bbrc.2004.05.185)
McGee EA & Hsueh AJ 2000 Initial and cyclic recruitment of ovarian follicles. *Endocrine Reviews* **21** 200–214. (doi:10.1210/edrv.21.2.0394)
Meas T, Deghmoun S, Lévy-Marchal C & Bouyer J 2010 Fertility is not altered in young adults born small for gestational age. *Human Reproduction* **25** 2354–2359. (doi:10.1093/humrep/deq184)
Melo AS, Vieira CS, Barbieri MA, Rosa-E-Silva AC, Silva AA, Cardoso VC, Reis RM, Ferriani RA, Silva-de-Sá MF & Bettiol H 2010 High prevalence of polycystic ovary syndrome in women born small for gestational age. *Human Reproduction* **25** 2124–2131. (doi:10.1093/humrep/deq162)
Minge CE, Bennett BD, Norman RJ & Robker RL 2008 Peroxisome proliferator-activated receptor-γ agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. *Endocrinology* **149** 2646–2656. (doi:10.1210/en.2007-1570)
Mission JF, Marshall NE & Caughey AB 2013 Obesity in pregnancy: a big problem and getting bigger. *Obstetrical & Gynecological Survey* **68** 389–399. (doi:10.1097/OGX.0b013e31828738ce)
Mori C 2001 Possible effects of endocrine disruptors on male reproductive function. *Kaibogaku Zasshi. Journal of Anatomy* **76** 361–368.
Mossa F, Carter F, Walsh SW, Kenny DA, Smith GW, Ireland JL, Hildebrandt TB, Lonergan P, Ireland JJ & Evans AC 2013 Maternal undernutrition in cows impairs ovarian and cardiovascular systems in their offspring. *Biology of Reproduction* **88** 92. (doi:10.1095/biolreprod.112.107235)
Mumm H, Kamper-Jørgensen M, Nybo Andersen A-M, Glintborg D & Andersen M 2013 Birth weight and polycystic ovary syndrome in adult life: a register-based study on 523,757 Danish women born 1973–1991. *Fertility and Sterility* **99** 777–782. (doi:10.1016/j.fertnstert.2012.11.004)
Osteria TS 1983 Nutritional status and menarche in a rural community in the Philippines. *Philippine Journal of Nutrition* **36** 150–156.
Oswald J, Engemann S, Lane N, Mayer W, Olek A, Fundele R, Dean W, Reik W & Walter J 2000 Active demethylation of the paternal genome in the mouse zygote. *Current Biology* **10** 475–478. (doi:10.1016/S0960-9822(00)00448-6)
Painter RC, Roseboom TJ & Bleker OP 2005 Prenatal exposure to the Dutch famine and disease in later life: an overview. *Reproductive Toxicology* **20** 345–352. (doi:10.1016/j.reprotox.2005.04.005)
Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI & Roseboom TJ 2008*a* Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. *BJOG: an International Journal of Obstetrics and Gynaecology* **115** 1243–1249. (doi:10.1111/j.1471-0528.2008.01822.x)
Painter RC, Westendorp RG, de Rooij SR, Osmond C, Barker DJ & Roseboom TJ 2008*b* Increased reproductive success of women after prenatal undernutrition. *Human Reproduction* **23** 2591–2595. (doi:10.1093/humrep/den274)
Pan Z, Zhang J, Li Q, Li Y, Shi F, Xie Z & Liu H 2012 Current advances in epigenetic modification and alteration during mammalian ovarian folliculogenesis. *Journal of Genetics and Genomics* **39** 111–123. (doi:10.1016/j.jgg.2012.02.004)
Pardi G, Marconi AM & Cetin I 2002 Placental–fetal interrelationship in IUGR fetuses – a review. *Placenta* **23**(Supplement A) S136–S141. (doi:10.1053/plac.2002.0802)
Penglase S, Hamre K & Ellingsen S 2014 Selenium and mercury have a synergistic negative effect on fish reproduction. *Aquatic Toxicology* **149** 16–24. (doi:10.1016/j.aquatox.2014.01.020)
Pepling ME 2012 Follicular assembly: mechanisms of action. *Reproduction* **143** 139–149. (doi:10.1530/REP-11-0299)
Pepling ME & Spradling AC 1998 Female mouse germ cells form synchronously dividing cysts. *Development* **125** 3323–3328.
Pepling ME & Spradling AC 2001 Mouse ovarian germ cell cysts undergo programmed breakdown to form primordial follicles. *Developmental Biology* **234** 339–351. (doi:10.1006/dbio.2001.0269)
Popat VB, Prodanov T, Calis KA & Nelson LM 2008 The menstrual cycle: a biological marker of general health in adolescents. *Annals of the New York Academy of Sciences* **1135** 43–51. (doi:10.1196/annals.1429.040)
Poston L 2012 Maternal obesity, gestational weight gain and diet as determinants of offspring long term health. *Best Practice & Research. Clinical Endocrinology & Metabolism* **26** 627–639. (doi:10.1016/j.beem.2012.03.010)
Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH & Vitamins in Pre-eclampsia Trial C 2006 Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* **367** 1145–1154. (doi:10.1016/S0140-6736(06)68433-X)
Puder JJ, Varga S, Kraenzlin M, De Geyter C, Keller U & Muller B 2005 Central fat excess in polycystic ovary syndrome: relation to low-grade inflammation and insulin resistance. *Journal of Clinical Endocrinology and Metabolism* **90** 6014–6021. (doi:10.1210/jc.2005-1002)
Radulescu L, Munteanu O, Popa F & Cirstoiu M 2013 The implications and consequences of maternal obesity on fetal intrauterine growth restriction. *Journal of Medicine and Life* **6** 292–298.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

Rae MT, Kyle CE, Miller DW, Hammond AJ, Brooks AN & Rhind SM 2002 The effects of undernutrition, *in utero*, on reproductive function in adult male and female sheep. *Animal Reproduction Science* **72** 63–71. (doi:10.1016/S0378-4320(02)00068-4)

Rajah R, Glaser EM & Hirshfield AN 1992 The changing architecture of the neonatal rat ovary during histogenesis. *Developmental Dynamics* **194** 177–192. (doi:10.1002/aja.1001940303)

Reik W, Dean W & Walter J 2001 Epigenetic reprogramming in mammalian development. *Science* **293** 1089–1093. (doi:10.1126/science.1063443)

Reynolds RM 2013 Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis – 2012 Curt Richter Award Winner. *Psychoneuroendocrinology* **38** 1–11. (doi:10.1016/j.psyneuen.2012.08.012)

Reynolds RM, Labad J, Buss C, Ghaemmaghami P & Räikkönen K 2013 Transmitting biological effects of stress *in utero*: implications for mother and offspring. *Psychoneuroendocrinology* **38** 1843–1849. (doi:10.1016/j.psyneuen.2013.05.018)

Richter HG, Camm EJ, Modi BN, Naeem F, Cross CM, Cindrova-Davies T, Spasic-Boskovic O, Dunster C, Mudway IS, Kelly FJ *et al*. 2012 Ascorbate prevents placental oxidative stress and enhances birth weight in hypoxic pregnancy in rats. *Journal of Physiology* **590** 1377–1387. (doi:10.1113/jphysiol.2011.226340)

Riley AP 1994 Determinants of adolescent fertility and its consequences for maternal health, with special reference to rural Bangladesh. *Annals of the New York Academy of Sciences* **709** 86–100. (doi:10.1111/j.1749-6632.1994.tb30390.x)

Rooney K & Ozanne SE 2011 Maternal over-nutrition and offspring obesity predisposition: targets for preventative interventions. *International Journal of Obesity* **35** 883–890. (doi:10.1038/ijo.2011.96)

Roseboom TJ, Painter RC, van Abeelen AF, Veenendaal MV & de Rooij SR 2011 Hungry in the womb: what are the consequences? Lessons from the Dutch famine *Maturitas* **70** 141–145. (doi:10.1016/j.maturitas.2011.06.017)

Rosenberg A 2008 The IUGR newborn. *Seminars in Perinatology* **32** 219–224. (doi:10.1053/j.semperi.2007.11.003)

Rosenfeld CS 2012 Effects of maternal diet and exposure to bisphenol A on sexually dimorphic responses in conceptuses and offspring. *Reproduction in Domestic Animals* **47** 23–30. (doi:10.1111/j.1439-0531.2012.02051.x)

Rosenfeld CS & Roberts RM 2004 Maternal diet and other factors affecting offspring sex ratio: a review. *Biology of Reproduction* **71** 1063–1070. (doi:10.1095/biolreprod.104.030890)

Rowe SA & Kennaway DJ 2002 Melatonin in rat milk and the likelihood of its role in postnatal maternal entrainment of rhythms. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **282** R797–R804. (doi:10.1152/ajpregu.00228.2001)

Russell DL & Robker RL 2007 Molecular mechanisms of ovulation: co-ordination through the cumulus complex. *Human Reproduction Update* **13** 289–312. (doi:10.1093/humupd/dml062)

Sadrzadeh S, Klip WA, Broekmans FJ, Schats R, Willemsen WN, Burger CW, van Leeuwen FE, Lambalk CB & OMEGA Project group 2003 Birth weight and age at menarche in patients with polycystic ovary syndrome or diminished ovarian reserve, in a retrospective cohort. *Human Reproduction* **18** 2225–2230. (doi:10.1093/humrep/deg409)

Sadrzadeh-Broer S, Kuijper EA, Van Weissenbruch MM & Lambalk CB 2011 Ovarian reserve in young women with low birth weight and normal puberty: a pilot case–control study. *Gynecological Endocrinology* **27** 641–644. (doi:10.3109/09513590.2010.508544)

Safi J, Joyeux L & Chalouhi GE 2012 Periconceptional folate deficiency and implications in neural tube defects. *Journal of Pregnancy* **2012** 295083. (doi:10.1155/2012/295083)

Sánchez F & Smitz J 2012 Molecular control of oogenesis. *Molecular Genetics of Human Reproductive Failure Biochimica et Radiophysics Acta (BBA) – Molecular Basis of Disease* **1822** 1896–1912. (doi:10.1016/j.bbadis.2012.05.013)

Sanchez-Garrido MA, Castellano JM, Ruiz-Pino F, Garcia-Galiano D, Manfredi-Lozano M, Leon S, Romero-Ruiz A, Dieguez C, Pinilla L & Tena-Sempere M 2013 Metabolic programming of puberty: sexually dimorphic responses to early nutritional challenges. *Endocrinology* **154** 3387–3400. (doi:10.1210/en.2012-2157)

Sarkies P & Sale JE 2012 Cellular epigenetic stability and cancer. *Trends in Genetics* **28** 118–127. (doi:10.1016/j.tig.2011.11.005)

Savabieasfahani M, Kannan K, Astapova O, Evans NP & Padmanabhan V 2006 Developmental programming: differential effects of prenatal exposure to bisphenol-A or methoxychlor on reproductive function. *Endocrinology* **147** 5956–5966. (doi:10.1210/en.2006-0805)

Schneider JE 2004 Energy balance and reproduction. *Physiology & Behavior* **81** 289–317. (doi:10.1016/j.physbeh.2004.02.007)

Schöpper H, Klaus T, Palme R, Ruf T & Huber S 2012 Sex-specific impact of prenatal stress on growth and reproductive parameters of guinea pigs. *Journal of Comparative Physiology. B, Biochemical, Systemic, and Environmental Physiology* **182** 1117–1127. (doi:10.1007/s00360-012-0680-9)

Schroeder M, Kronfeld-Schor N & Weller A 2013 Selective leptin insensitivity and alterations in female-reproductive patterns linked to hyperleptinemia during infancy. *PLoS ONE* **8** e59937. (doi:10.1371/journal.pone.0059937)

Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr, Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG *et al*. 2003 The *GPR54* gene as a regulator of puberty. *New England Journal of Medicine* **349** 1614–1627. (doi:10.1056/NEJMoa035322)

Sforza C, Vizzotto L, Ferrario VF & Forabosco A 2003 Position of follicles in normal human ovary during definitive histogenesis. *Early Human Development* **74** 27–35. (doi:10.1016/S0378-3782(03)00081-1)

Shah NA, Antoine HJ, Pall M, Taylor KD, Azziz R & Goodarzi MO 2008 Association of androgen receptor CAG repeat polymorphism and polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* **93** 1939–1945. (doi:10.1210/jc.2008-0038)

Shim YS, Park HK, Yang S & Hwang IT 2013 Age at menarche and adult height in girls born small for gestational age. *Annals of Pediatric Endocrinology & Metabolism* **18** 76–80. (doi:10.6065/apem.2013.18.2.76)

Shrestha A, Olsen J, Ramlau-Hansen CH, Bech BH & Nohr EA 2011 Obesity and age at menarche. *Fertility and Sterility* **95** 2732–2734. (doi:10.1016/j.fertnstert.2011.02.020)

Sibley CP, Turner MA, Cetin I, Ayuk P, Boyd CA, D'Souza SW, Glazier JD, Greenwood SL, Jansson T & Powell T 2005 Placental phenotypes of intrauterine growth. *Pediatric Research* **58** 827–832. (doi:10.1203/01.PDR.0000181381.82856.23)

da Silva Faria T, de Bittencourt Brasil F, Sampaio FJ & da Fonte Ramos C 2008 Maternal malnutrition during lactation alters the folliculogenesis and gonadotropins and estrogen isoforms ovarian receptors in the offspring at puberty. *Journal of Endocrinology* **198** 625–634. (doi:10.1677/JOE-08-0121)

da Silva Faria T, de Bittencourt Brasil F, Sampaio FJ & da Fonte Ramos C 2010 Effects of maternal undernutrition during lactation on estrogen and androgen receptor expressions in rat ovary at puberty. *Nutrition* **26** 993–999. (doi:10.1016/j.nut.2009.09.027)

Simoni M, Tempfer CB, Destenaves B & Fauser BC 2008 Functional genetic polymorphisms and female reproductive disorders: part I: polycystic ovary syndrome and ovarian response. *Human Reproduction Update* **14** 459–484. (doi:10.1093/humupd/dmn024)

Sinclair KD & Watkins AJ 2013 Parental diet, pregnancy outcomes and offspring health: metabolic determinants in developing oocytes and embryos. *Reproduction, Fertility, and Development* **26** 99–114. (doi:10.1071/RD13290)

Skinner MK 2005 Regulation of primordial follicle assembly and development. *Human Reproduction Update* **11** 461–471. (doi:10.1093/humupd/dmi020)

Skinner MK 2008 What is an epigenetic transgenerational phenotype? F3 or F2 *Reproductive Toxicology* **25** 2–6. (doi:10.1016/j.reprotox.2007.09.001)

Sloboda DM, Hart R, Doherty DA, Pennell CE & Hickey M 2007 Age at menarche: influences of prenatal and postnatal growth. *Journal of*

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

Clinical Endocrinology and Metabolism **92** 46–50. (doi:10.1210/jc.2006-1378)

Sloboda DM, Howie GJ, Pleasants A, Gluckman PD & Vickers MH 2009 Pre- and postnatal nutritional histories influence reproductive maturation and ovarian function in the rat. *PLoS ONE* **4** e6744. (doi:10.1371/journal.pone.0006744)

Sloboda DM, Hickey M & Hart R 2010 Reproduction in females: the role of the early life environment. *Human Reproduction Update* **17** 210–227. (doi:10.1093/humupd/dmq048)

Sloboda DM, Li M, Patel R, Clayton ZE, Yap C & Vickers MH 2014 Early life exposure to fructose and offspring phenotype: implications for long term metabolic homeostasis. *Journal of Obesity* **2014** 203474. (doi:10.1155/2014/203474)

Smallwood SA, Tomizawa S, Krueger F, Ruf N, Carli N, Segonds-Pichon A, Sato S, Hata K, Andrews SR & Kelsey G 2011 Dynamic CpG island methylation landscape in oocytes and preimplantation embryos. *Nature Genetics* **43** 811–814. (doi:10.1038/ng.864)

Song S 2013 Assessing the impact of *in utero* exposure to famine on fecundity: evidence from the 1959–61 famine in China. *Population Studies* **67** 293–308. (doi:10.1080/00324728.2013.774045)

Stanner SA & Yudkin JS 2001 Fetal programming and the Leningrad Siege study. *Twin Research* **4** 287–292. (doi:10.1375/1369052012498)

Stanner SA, Bulmer K, Andrès C, Lantseva OE, Borodina V, Poteen VV & Yudkin JS 1997 Does malnutrition *in utero* determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study *BMJ* **315** 1342–1348. (doi:10.1136/bmj.315.7119.1342)

Steiner AZ, D'Aloisio AA, DeRoo LA, Sandler DP & Baird DD 2010 Association of intrauterine and early-life exposures with age at menopause in the sister study. *American Journal of Epidemiology* **172** 140–148. (doi:10.1093/aje/kwq092)

Stover PJ 2011 Polymorphisms in 1-carbon metabolism, epigenetics and folate-related pathologies. *Journal of Nutrigenetics and Nutrigenomics* **4** 293–305. (doi:10.1159/000334586)

Tamura H, Takasaki A, Taketani T, Tanabe M, Kizuka F, Lee L, Tamura I, Maekawa R, Aasada H, Yamagata Y *et al.* 2012 The role of melatonin as an antioxidant in the follicle. *Journal of Ovarian Research* **5** 5. (doi:10.1186/1757-2215-5-5)

Tarantal A & Berglund L 2014 Obesity and lifespan health – importance of the fetal environment. *Nutrients* **6** 1725–1736. (doi:10.3390/nu6041725)

Tena-Sempere M 2013 Ghrelin, the gonadal axis and the onset of puberty. *Endocrine Development* **25** 69–82. (doi:10.1159/000346055)

Tingen C, Kim A & Woodruff TK 2009 The primordial pool of follicles and nest breakdown in mammalian ovaries. *Molecular Human Reproduction* **15** 795–803. (doi:10.1093/molehr/gap073)

Treloar SA, Sadrzadeh S, Do KA, Martin NG & Lambalk CB 2000 Birth weight and age at menopause in Australian female twin pairs: exploration of the fetal origin hypothesis. *Human Reproduction* **15** 55–59. (doi:10.1093/humrep/15.1.55)

Trentini GP, Genazzani AR, Criscuolo M, Petraglia F, De Gaetani C, Ficarra G, Bidzinska B, Migaldi M & Genazzani AD 1992 Melatonin treatment delays reproductive aging of female rat via the opiatergic system. *Neuroendocrinology* **56** 364–370. (doi:10.1159/000126250)

Trivers RL & Willard DE 1973 Natural selection of parental ability to vary the sex ratio of offspring. *Science* **179** 90–92. (doi:10.1126/science.179.4068.90)

Tsutsumi R & Webster NJ 2009 GnRH pulsatility, the pituitary response and reproductive dysfunction. *Endocrine Journal* **56** 729–737. (doi:10.1507/endocrj.K09E-185)

Veenendaal MV, Painter RC, de Rooij SR, Bossuyt PM, van der Post JA, Gluckman PD, Hanson MA & Roseboom TJ 2013 Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine. *BJOG: an International Journal of Obstetrics and Gynaecology* **120** 548–554. (doi:10.1111/1471-0528.12136)

Veening MA, van Weissenbruch MM, Roord JJ & de Delemarre-van Waal HA 2004 Pubertal development in children born small for gestational age. *Journal of Pediatric Endocrinology & Metabolism* **17** 1497–1505. (doi:10.1515/JPEM.2004.17.11.1497)

Vikstrom J, Hammar M, Josefsson A, Bladh M & Sydsjo G 2014 Birth characteristics in a clinical sample of women seeking infertility treatment: a case–control study. *BMJ Open* **4** e004197. (doi:10.1136/bmjopen-2013-004197)

Vogt MC, Paeger L, Hess S, Steculorum SM, Awazawa M, Hampel B, Neupert S, Nicholls HT, Mauer J, Hausen AC *et al.* 2014 Neonatal insulin action impairs hypothalamic neurocircuit formation in response to maternal high-fat feeding. *Cell* **156** 495–509. (doi:10.1016/j.cell.2014.01.008)

Wade GN, Schneider JE & Li HY 1996 Control of fertility by metabolic cues. *American Journal of Physiology* **270** E1–E19.

Walker DM & Gore AC 2011 Transgenerational neuroendocrine disruption of reproduction. *Nature Reviews. Endocrinology* **7** 197–207. (doi:10.1038/nrendo.2010.215)

Walker CL & Ho SM 2012 Developmental reprogramming of cancer susceptibility. *Nature Reviews. Cancer* **12** 479–486. (doi:10.1038/nrc3220)

Wang L, Zhang J, Duan J, Gao X, Zhu W, Lu X, Yang L, Zhang J, Li G, Ci W *et al.* 2014 Programming and inheritance of parental DNA methylomes in mammals. *Cell* **157** 979–991. (doi:10.1016/j.cell.2014.04.017)

van Weissenbruch MM 2007 Premature adrenarche, polycystic ovary syndrome and intrauterine growth retardation: does a relationship exist? *Current Opinion in Endocrinology, Diabetes, and Obesity* **14** 35–40. (doi:10.1097/MED.0b013e328013da7d)

van Weissenbruch MM & Delemarre-van de Waal HA 2006 Early influences on the tempo of puberty. *Hormone Research* **65**(Suppl 3) 105–111. (doi:10.1159/000091514)

Wigglesworth JS 1974 Fetal growth retardation. Animal model: uterine vessel ligation in the pregnant rat. *American Journal of Pathology* **77** 347–350.

Woods DC, Telfer EE & Tilly JL 2012 Oocyte family trees: old branches or new stems? *PLoS Genetics* **8** e1002848. (doi:10.1371/journal.pgen.1002848)

Yarde F, Broekmans FJ, van der Pal-de Bruin KM, Schonbeck Y, te Velde ER, Stein AD & Lumey LH 2013 Prenatal famine, birthweight, reproductive performance and age at menopause: the Dutch hunger winter families study. *Human Reproduction* **28** 3328–3336. (doi:10.1093/humrep/det331)

Zagre NM, Desplats G, Adou P, Mamadoultaibou A & Aguayo VM 2007 Prenatal multiple micronutrient supplementation has greater impact on birthweight than supplementation with iron and folic acid: a cluster-randomized, double-blind, controlled programmatic study in rural Niger. *Food and Nutrition Bulletin* **28** 317–327.

Zambrano E, Rodriguez-Gonzalez GL, Guzman C, Garcia-Becerra R, Boeck L, Diaz L, Menjivar M, Larrea F & Nathanielsz PW 2005 A maternal low protein diet during pregnancy and lactation in the rat impairs male reproductive development. *Journal of Physiology* **563** 275–284. (doi:10.1113/jphysiol.2004.078543)

Zambrano E, Bautista CJ, Deas M, Martinez-Samayoa PM, Gonzalez-Zamorano M, Ledesma H, Morales J, Larrea F & Nathanielsz PW 2006 A low maternal protein diet during pregnancy and lactation has sex- and window of exposure-specific effects on offspring growth and food intake, glucose metabolism and serum leptin in the rat. *Journal of Physiology* **571** 221–230. (doi:10.1113/jphysiol.2005.100313)

de Zegher F & Ibanez L 2006 Prenatal growth restraint followed by catch-up of weight: a hyperinsulinemic pathway to polycystic ovary syndrome. *Fertility and Sterility* **86**(Suppl 1) S4–S5. (doi:10.1016/j.fertnstert.2006.03.013)

Zhang H, Zheng W, Shen Y, Adhikari D, Ueno H & Liu K 2012 Experimental evidence showing that no mitotically active female germline progenitors exist in postnatal mouse ovaries. *PNAS* **109** 12580–12585. (doi:10.1073/pnas.1206600109)

Zhang H, Adhikari D, Zheng W & Liu K 2013 Combating ovarian aging depends on the use of existing ovarian follicles, not on putative oogonial stem cells. *Reproduction* **146** R229–R233. (doi:10.1530/REP-13-0202)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.

Zhao Y, Nichols JE, Valdez R, Mendelson CR & Simpson ER 1996 Tumor necrosis factor-alpha stimulates aromatase gene expression in human adipose stromal cells through use of an activating protein-1 binding site upstream of promoter 1.4. *Molecular Endocrinology* **10** 1350–1357. (doi:10.1210/mend.10.11.8923461)

Zhou D, Zhuo Y, Che L, Lin Y, Fang Z & Wu D 2014 Nutrient restriction induces failure of reproductive function and molecular changes in hypothalamus–pituitary–gonadal axis in postpubertal gilts. *Molecular Biology Reports* **41** 4733–4742. (doi:10.1007/s11033-014-3344-x)

Zhuo Y, Zhou D, Che L, Fang Z, Lin Y & Wu D 2014 Feeding prepubescent gilts a high-fat diet induces molecular changes in the hypothalamus–pituitary–gonadal axis and predicts early timing of puberty. *Nutrition* **30** 890–896. (doi:10.1016/j.nut.2013.12.019)

Received in final form 13 October 2014
Accepted 27 October 2014
Accepted Preprint published online 27 October 2014

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0469

Published by Bioscientifica Ltd.