Journal of Developmental Origins of Health and Disease (2011), **2**(1), 25–35.

doi:10.1017/S2040174410000693

ORIGINAL ARTICLE

The ovarian dysgenesis syndrome

G. M. Buck Louis[1]*, M. A. Cooney[1] and C. M. Peterson[2]

[1]*Division of Epidemiology, Statistics & Prevention Research, National Institute of Child Health & Human Development, Rockville, MD, USA*
[2]*Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City, UT, USA*

New thinking has arisen about the origin of adult onset diseases stemming from a collective body of evidence commonly referred to as the developmental origins of health and disease. This conceptual paradigm posits that certain adult onset diseases arise during critical or sensitive windows of human development or even transgenerationally. The testicular dysgenesis hypothesis (TDS) postulates an *in utero* origin for adverse male reproductive outcomes, and is an excellent example of the early origins of the paradigm. Despite similarities in the development of the male and female reproductive tracks, noticeably absent is a collective body of evidence focusing on the plausibility of an early origin for gynecologic outcomes and later onset of adult diseases. Using the TDS paradigm, we synthesized the available literature relative to the ovarian dysgenesis syndrome (ODS), which we define as alterations in ovarian structure or function that may manifest as fecundity impairments, gynecologic disorders, gravid diseases or later onset adult diseases. We evaluated environmental exposures, particularly the role of endocrine disrupting chemicals, in relation to these outcomes, and found evidence (although fragmented) consistent with an *in utero* origin of gynecologic outcomes, which in turn is associated with later onset of adult diseases. The findings are interpreted within the ODS paradigm while delineating methodological challenges and future research opportunities designed to answer critical data gaps regarding the origin of fecundity, gravid health and chronic diseases affecting the female population.

Received 6 May 2010; Revised 11 November 2010; Accepted 2 December 2010; First published online 7 January 2011

Key words: early origins, exposome, ovarian dysgenesis

Introduction

Of late, a novel paradigm has emerged, providing a useful framework for assessing environmental chemicals and human health inclusive of fecundity and fertility. This paradigm, sometimes referred to as the Barker hypothesis, the early or fetal origins of disease, the thrifty phenotype or the developmental origin of disease and health, posits key elements that challenge past thinking about disease etiology. These include recognition that: (1) human development is more than the unfolding of the rigid genome toward one of developmental plasticity; (2) exposures during critical and sensitive windows may affect disease risk across the lifespan as a result of epigenetic-induced changes whose original intent may have been to allow the embryo/fetus to adapt by altering organogenesis for anticipated needs in later life; (3) the complexity of disease such as gene–environment interactions including the potential for low-dose additivity or synergy of chemical mixtures; and (4) the interrelatedness of health states such as fecundity, gravid health status and later onset adult disease.[1–5] In response to this evolving paradigm, innovative methodologies have emerged, such as the life course epidemiological method for assessing a multitude of exposures and diseases across the lifespan.[2] In addition, Bayesian models appropriate for the hierarchical data structure that arise from such paradigms along with joint models permitting the assessment of more than one health outcome[6,7] offer analytical techniques for researchers interested in life course epidemiological research.

Worldwide, there is speculation that human fecundity is declining and that current fertility (live birth) rates are unlikely to sustain populations.[8] Some authors speculate that environmental agents are responsible, in part, given the rather rapid onset of such declines in the absence of detectable genetic changes in human populations, whereas other authors argue that social forces are responsible. A collective body of research focusing on the early origins of male fecundity and later onset disease has been thoughtfully synthesized and articulated as the testicular dysgenesis hypothesis (TDS). Moreover, the TDS hypothesis notes the sentinel role of fecundity endpoints as an overall marker of health status and eventual disease risk.[9] Briefly, the TDS hypothesis suggests that changes in semen quality,[10,11] genitourinary (GU) malformations[12,13] and testicular cancer[14] may share a common *in utero* etiological pathway.[9] In fact, the interrelatedness of adverse male reproductive outcomes from birth through adulthood has long been reported in the literature. For example, GU malformations are associated with diminished adult fecundity as is testes cancer, even in the pre-diagnosis period.[15,16] This body of evidence is evolving in the context

*Address for correspondence: G. M. Buck Louis, Division of Epidemiology, Statistics & Prevention Research, National Institute of Child Health & Human Development, 6100 Executive Blvd., Room 7B03, Rockville, MD 20852, USA.
(Email louisg@mail.nih.gov)

of data supporting an important etiological role for periconceptional and prenatal factors in the development of many adult onset diseases such as type 2 diabetes or cancer.[17–19] Support for the TDS hypothesis is augmented by recent recognition that such exposures may permanently and irreversibly reprogram the developing organism for adult onset disease.[20] Experimental evidence supports a relationship between anti-androgenic exposures during sensitive intrauterine windows and a spectrum of adverse reproductive and developmental effects.[21]

Recent authors have summarized the available literature regarding environmental influences on female fecundity and fertility in relation to the purported ovarian dysgenesis syndrome (ODS).[3,22] First postulated by Buck Louis and Cooney,[3] the ODS hypothesis recognizes the many similarities in the embryonic development of the male and female reproductive tracts while borrowing heavily from the TDS paradigm. Although evidence supporting the TDS paradigm is well under way, empirical support for ODS is still evolving as researchers begin to assess endocrine disruptors in relation to fecundity, gravid health and later onset diseases from a life course perspective.

For purposes of this paper, we posit that genetic and environmental factors may impact the structure and function of reproductive organs and tissues manifesting in a spectrum of outcomes. As illustrated in Figure 1, alterations in ovarian development may manifest as structural or functional changes including embryogenesis, folliculogenesis and steroid signaling, respectively. A spectrum of possible effects is possible, including birth or müllerian anomalies (MA), anovulation and altered menstruation, respectively. Speculations that fecundity impairments and gynecologic disorders may increase cancer risk possibly via altered epigenetics underscore its inclusion in the figure, but with no predetermined directionality. We further conceptualize ODS as arising from exposures during the periconception or *in utero* windows and/or possibly transgenerational effects such as in the case of diethylstilbesterol (DES) exposure.

We define fecundity as the biological capacity of women for reproduction,[23] irrespective of pregnancy intentions. We define environmental exposures as all non-genetic factors, but specifically focus on environmental chemicals with a purported ability to disrupt endocrine pathways or so-called endocrine disrupting chemicals (EDCs). This paper provides an overview of the biological plausibility of the ODS conceptual paradigm followed by a review of the available human evidence in support of an early origin for female fecundity, gynecologic health and later onset diseases.

Biological plausibility of ODS

The vulnerability of the developing conceptus to a spectrum of environmental exposures is well established including exposures arising in the periconception period or the interval before, at or shortly after conception.[24] Critical windows of human development are characterized by high rates of cellular proliferation and changing metabolic capabilities.[25] Xenobiotic exposures occurring during the early embryonic period of rapid development and beyond may adversely affect the development of the gonads and female reproductive tract (i.e. uterus, cervix, fallopian tubes and vagina) with implications for female fecundity and, possibly, adult health. Kuh and Ben-Shlomo[26] have eloquently articulated the need to distinguish between critical and sensitive windows, given that exposure during the latter may still adversely affect development including adult onset diseases, though possibly with reduced magnitude. For example, an exposure during a critical embryonic window may produce structural birth defects, whereas those occurring outside the critical window may produce other nonstructural or functional deficits. This recognition challenges investigators to look beyond structural defects in considering functional changes that may manifest as a spectrum of adverse effects across the lifespan.

Delineating critical and sensitive windows is important for research focusing on the role of epigenetics in human reproduction and development in recognition that embryonic development is regulated by both genetic and epigenetic information. Genetic mechanisms are largely dependent upon the DNA code,[27] whereas epigenetic mechanisms reflect molecular alterations in gene expression or phenotype without a change in DNA sequence.[28] Considerable epigenetic reprogramming occurs during gametogenesis and early embryogenesis,[29] and exposures including assisted reproductive technologies during this window may result in disturbances in epigenetic processes with a spectrum of adverse health effects across the lifespan that may either be transitory or passed through the germline to the offspring.[30]

Epigenetic reprogramming may affect both structure and function. During critical and sensitive windows, the female gonads and reproductive tract are vulnerable to a host of xenobiotic agents during embryonic development, which commences at approximately 4 weeks post-conception. Recognition of this and other developmental windows is important for assessing and interpreting the ontogeny of MA, gonadal disorders or reproductive site cancers. Development of the female reproductive tract requires completion of a series of highly interrelated and timed processes, including müllerian duct elongation, fusion, canalization and septal resorption, which extend well into the second trimester. Exposures at any one of these stages may affect the likelihood of malformations or other adverse outcomes.[31,32] Since the reproductive and urinary tract develops during similar windows and often interdependently, interpretation of MA should be performed in conjunction with an assessment of urinary malformations.[33] Recent studies on MA suggest a strong familial aggregation and follow a polygenic and multifactorial inheritance pattern consistent with the ODS paradigm.[34]

Ovarian development begins approximately 4 weeks post-conception with the migration of embryonic germ cells from the yolk sac to the primitive gonadal folds where

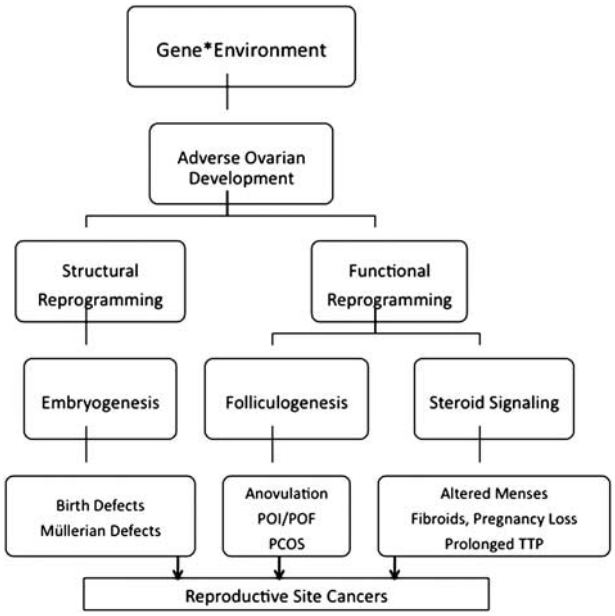

Fig. 1. Ovarian dysgenesis paradigm.

they undergo mitotic expansions and become oogonia.[32] At approximately 8–13 weeks' gestation, the oogonia enter meiosis and then remain in a protracted state of meiotic arrest surrounded by a layer of granulosa cells until just before ovulation, in response to the pre-ovulatory gonadotropin surge.[35] Primordial follicles in their arrested state represent another window of potential vulnerability to a host of toxicants, with the potential for permanent reprogramming of the organism. Similarly, reproductive tissues that are eventually responsive to ovarian steroids also represent vulnerable structures during this period in the context of ODS. Embryogenesis and gametogenesis are highly influenced by steroid hormones raising concern that endocrine disruptors may be capable of disrupting these processes with implications for both the current and future generations.

Despite the considerable interest in epigenetics that has materialized from mapping the human genome, it is noteworthy that the concept of epigenetics is not new *per se*. Rather, it was first coined by the pre-eminent developmental biologist, Conrad Waddington, in the 1940s following the blending of two concepts, that is, epigenesis + genetics = epigenetics.[36] Epigenetics refers to the chemical modification of DNA and chromatin that may affect genomic functioning possibly resulting in altered disease susceptibility across the lifespan. The prototypical chemical exposure for epigenetics is DES, though considerable evidence suggests a similar role for bisphenol A (BPA), as recently reviewed.[5] Endocrine disruptors modify chromatin packaging resulting in modification of histones and promoting DNA methylation. As such, modifications may turn on and off gene expression patterns. Exposures during the earliest stages of human development may thereby have lifetime implications for health and disease.

EDCs and ODS

EDCs include naturally occurring estrogen-like exposures such as the phytoestrogen genistein or synthetic agents such as BPA, dioxins such as polychlorinated dibenzodioxins and polychlorinated dibenzo furans, organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT) or its metabolite dichlorodiphenyldichloroethylene (DDE), phthalates and polychlorinated biphenyls (PCBs) and others.[37] Experimental and observational human data suggest a role for EDCs in broad categories of human health – fecundity, gravid health status and later onset adult diseases. For example, human uterine tissue contains several different types of cells that express steroid receptors making them potential targets for EDCs including the endometrium, which represents the end organ of the hypothalamic–pituitary–ovarian axis. The structure and function of the endometrium are delicately regulated by ovarian sex hormones (estradiol and progesterone) and are sensitive to small disturbances, such as those induced from chemical exposures. Endometrial blood vessels are critical for implantation and placentation during early pregnancy. Endothelial cells covering the luminal surface of blood vessels control vascular morphology and function via angiogenesis, vascular remodeling and functional changes. For example, PCB congeners nos 77 and 126 compromise the normal function of porcine vascular endothelial cells by increasing expression of CYP1A1 gene, oxidative stress and DNA-binding activity of nuclear factor kappa B.[38] Animal evidence shows that vascular endothelial growth factor (VEGF) secretion is decreased by 2,3,7,8-TCDD in chick embryos.[39] In rodent studies, BPA induces VEGF expression in the uterus, vagina and pituitary.[40] Human endometrial endothelial cells (HEECs) express estrogen receptor beta (ERβ) and progesterone receptor that are controlled by cyclical changes in estrogen and progesterone concentrations during menstruation and pregnancy. Expression of steroid receptors might render HEECs susceptible to EDCs. Bredhult *et al.*[41] assessed the *in vitro* effects of several EDCs (DDT, PCB 77, PCB 126, di-*n*-butyl phthalate, BPA, 2,3,7,8-TCDD) on proliferation and viability of HEECs, and noted that some EDCs affected cell viability and increased the proportion of necrotic cells. Therefore, it is possible that EDCs may have both *in vivo* and *in vitro* effects and influence processes involving endometrial angiogenesis.

Sex steroids, the aryl hydrocarbon receptor, cytochrome p450 enzymes and thyroid homeostasis are the major targets of EDCs underscoring the potential for a spectrum of reproductive and developmental impairments dependent upon a variety of factors such as the number and target ligand(s) of the EDCs, along with route of exposure, timing and dose considerations, host susceptibility and other lifestyle or behavioral factors such as stress, nutrition and lifestyle. For example, a significantly higher percentage of abnormal metaphase II-arrested eggs was observed in mice exposed to BPA, which were fed soy in comparison with animals not fed

soy, suggesting that BPA's effect on growing oocytes may be modulated by dietary phytoestrogens.[42]

EDCs may also function as agonists by mimicking the activity of endogenous hormones leading to the expression of estrogen-responsive genes by binding to the ER (e.g. DES, genistein), or as antagonists by inhibiting receptor activity such as inhibiting the binding of ER-coactivators to prevent transactivation. EDCs have transgenerational effects including transmission through the paternal line, as in the case of DES; the transgenerational effects may be more profound than those observed in the first generation.[43–47] Transgenerational effects are defined as the acquired phenotype or the disease's ability to be transmitted to subsequent generations through the germ line without direct exposure to the toxicant.[45] Thus, EDCs are of concern to both exposed individuals and subsequent generations, irrespective of their own exposures.

Human evidence for ODS

Female fecundity

Within the framework of ODS, several recent papers have reviewed the purported reproductive and developmental toxicity of EDCs and underscore the importance of assessing effects across the lifespan in keeping with the continuum of female fecundity.[48–52] A woman's reproductive years are typically defined as 15–44 years, though considerable variability exists at the population level. Recent data suggest that the reproductive lifespan has increased from 36.1 to 37.7 years for women born between 1915–1919 and 1935–1939, respectively,[53] possibly due to faster generalized growth,[54] an earlier age at menarche,[55] or a later age at natural menopause currently estimated to be 51.4 years for US women.[56] Although the implications of a longer reproductive life are speculative and include a higher risk of reproductive site cancers, considerable interest exists in identifying exposures or mechanisms that may impact either end of the reproductive lifespan.

The importance of the *in utero* environment and adult female fecundity is now recognized, especially given a growing literature supporting a relationship between fetal growth restriction and ovarian development and function. For example, girls born small-for-gestational age are reported to have poorer ovarian development, diminished follicle stimulating hormone responsiveness and increased anovulatory cycles than adequately sized girls at later ages, thus supporting a role for *in utero* programming.[57–59] We are unaware of any studies that have measured *in utero* chemical concentrations in relation to subsequent fecundity, most likely a reflection of the two plus decade follow-up that would be necessary. However, a few *in utero* exposures have been assessed in relation to time-to-pregnancy (TTP; which is a measure of female fecundity) and the secondary sex ratio (ratio of male-to-female births). *In utero* exposure to cigarette smoke was associated with a decreased fecundability odds ratio for the woman later in life denoting a longer TTP.[60] In addition, maternal preconception PCB concentration was associated with a reduction in the secondary sex ratio reflecting a female excess of live births.[61] Other authors have reported reductions in the secondary sex ratio for PCB[62] and dioxin exposures.[63,64]

A few papers have assessed EDCs and TTP . A longer TTP or diminished female fecundity has been reported for select PCB congeners in both prospective[65] and retrospective[66] cohort studies. Prolonged TTPs have been reported for other EDCs, including the retrospective capture of TTP and DDE,[66] dioxin,[67] polybrominated diphenyl ether or PBDE congeners,[68] and the prospective capture of TTP and mercury.[69] To our knowledge, no prospective cohort study has measured EDC exposures during critical and sensitive windows of human development.

In the United States, some evidence exists to support an increase in the temporal pattern of fecundity impairments or infertility among women of reproductive age. Using data from the National Survey of Family Growth, the percentage of women with both disorders increased from 9% to 13% in 1988 and 1992, respectively.[70] However, when restricted to married women, prevalence decreased largely ignoring temporal increases in cohabitation rates and births to unmarried women.[71]

Fertility patterns in the 21st century are declining throughout much of the world, possibly the result of women having fewer children or delaying births to later ages.[72] However, environmental influences on fecundity may account for some of these observed patterns assuming that fecundity impairments reduce unintended pregnancies or completed family size. In addition, the inverse relationship between age and fecundity may reflect a loss in the number of quality of germ cells.[73,74] Without querying women about their time at risk for pregnancy, it is difficult to fully interpret the declining fertility rates observed throughout the world. For example, it would be informative to know whether completed family size required 3, 5, 10 or more years of trying. This issue has prompted some investigators to articulate a need to monitor fecundity either by prospective[75] or retrospective[76] surveillance of TTP. Opponents argue that the multitude of social factors impacting fertility precludes our ability to delineate environmental causes.

GU malformations

GU malformations can impact fecundity or fertility and may arise *in utero* either through time-sensitive or transgenerational exposures. Unlike male GU malformations that are widely reported in the literature, proportionately speaking, there appears to be a smaller literature on female GU malformations from a temporal perspective. Accurate incidence or birth prevalence estimates for female GU malformations are difficult to obtain except for geographic areas served by birth defects registries. Published data often exclude minor GU malformations or rely on passive reporting mechanisms or do not stratify rates by infant sex. Despite the inclusion of MA as a part of clinical examinations among reproductive

medicine clinics, its true incidence and prevalence remain lacking at the population level. This reflects incomplete recognition and reporting, non-uniform classification systems, varying diagnostic approaches, asymptomatic nature, unclassified meosnephric anomalies and/ or differing study populations. Although plausible, assessing MA in relation to EDCs is challenging in light of these methodological limitations.

A few publications have focused on EDCs and GU malformations in girls, particularly given the evidence for DES and related structural defects (e.g. T-shaped uterus with or without a small uterine cavity and structural abnormalities of the cervix).[77,78] A recent review of the malformations literature in three different populations reported the prevalence of congenital uterine anomalies to be 6.7% in the general population, 7.3% in the infertile population and 16.7% in the recurrent miscarriage population.[79] These findings underscore the importance of choice of study population for assessing EDCs and GU malformations, and provide some evidence for a possible shared etiology for malformations and later reproductive impairments.

Uterine fibroids

Uterine fibroids (uterine leiomyomas) are benign tumors that originate from the smooth muscle layer of the myometrium and the accompanying connective tissue of the uterus.[80] Fibroids are the most common benign tumors in women and are typically diagnosed in the middle to later reproductive years. They have been a major indication for hysterectomy in the United States.[81] Although most fibroids are asymptomatic, they can result in heavy and painful menstruation, urinary frequency and urgency and pelvic or abdominal discomfort. As with most gynecologic disorders, prevalence varies by study population or sample, and is reported to affect as many as $\approx$40% of reproductive aged women.[81–83] The cumulative incidence of uterine fibroids increases with age, reaching 70–80% by age 50 years.[84] Incidence reportedly varies by race/ethnicity with a higher percentage of African-American women affected in comparison with Caucasian women.[85] Of interest is the strikingly higher aromatase mRNA levels in leiomyoma compared with adjacent myometrium in African-American compared with Caucasian women, highlighting the local role of estrogenic activity in the origin of fibroids and the potential role of estrogenic EDCs.[86] Approximately 13% of women undergoing *in vitro* fertilization have fibroids.[87] The impact of uterine fibroids on fecundity is difficult to delineate, given the varying phenotypes, non-uniform diagnostic approaches and selection bias arising from currently available studies.

Researchers have induced uterine leiomyomas in mice by administering DES to the dam on gestational days 9–16,[88] suggesting a possible *in utero* origin. Similarly, women exposed to DES are reported to have a higher odds of developing fibroids in comparison with unexposed women in a few studies,[89,90] but not all.[91] D'Aloisio *et al.*[90] noted that women who were fed soy formula during infancy compared with women fed non-soy formula or breast milk during infancy also had a higher odds of having fibroids than unexposed women.[91] These latter findings underscore the potential importance of dietary exposures in the context of EDCs during sensitive windows of human development. Although limited, there is some suggestion that EDCs may be associated with fibroids, particularly in the context of other lifestyle factors such as diet.

Polycystic ovarian syndrome (PCOS)

PCOS is a common gynecologic disorder characterized by multiple ovarian cysts and a varied phenotype. The prevalence of PCOS based upon the National Institute of Child Health and Human Development criteria is approximately 7% among women aged 18–45 years, though it is reported to be higher for black (8%) than white (5%) women.[92] Hispanic women are reported to have a prevalence of $\approx$13%.[93] Using the Rotterdam criteria for PCOS,[94] diagnosis requires the presence of two of the following signs: (1) clinical or biochemical evidence of hyper androgenism; (2) intermittent or absent menstrual cycles; and/or (3) polycystic ovary morphology as visualized by ultrasound. Prevalence is reported to be 6.3% in a representative population in Sri Lanka using these criteria, reflecting the addition of polycystic ovary morphology as visualized by ultrasound.[95]

Of all gynecologic disorders, PCOS has the most evidence supporting an *in utero* etiology. Higher birth weights and longer gestations have been reported for girls who develop PCOS in comparison with unaffected girls suggestive of an *in utero* origin. Creswell *et al.*[96] reported two forms of PCOS reflecting different *in utero* origins. Thin women with PCOS had altered hypothalamic release of luteinizing hormone possibly resulting from a prolonged gestation, whereas obese hirsute women with polycystic ovaries had higher birth weights and maternal obesity. Wickenheisser *et al.*[97] speculated that PCOS was a primary ovarian abnormality leading to androgen excess supporting early work in sheep and rhesus monkeys.[98] We are unaware of any human studies examining *in utero* chemical exposures in humans and later onset PCOS. Higher serum BPA concentrations have been reported[99] in women with PCOS, as compared with women without PCOS, and in another study, irrespective of obesity.[100] Of added note is the observation that PCOS can be induced in rhesus monkeys and sheep following *in utero* androgen exposure at environmentally relevant doses during sensitive windows of human development.[101,102] When combined, these data support additional research focusing on EDCs during critical windows and PCOS.

Endometriosis

Endometriosis is a complex disease characterized by the presence of endometrial glands and stroma outside the uterine cavity. Although incidence is difficult to estimate and is

https://doi.org/10.1017/S2040174410000693 Published online by Cambridge University Press

highly dependent upon the study population, it has been estimated to be 1.9 per 1000 person-years.[103] Prevalence varies considerably depending upon the choice of study populations and ranges from 10–15% for the general population[104,105] to 20–65% of women seeking care for pain or for infertility services.[106–110] The diagnosis of endometriosis is reported to be increasing, though reasons remain unknown. Despite a plethora of alleged etiological hypotheses, its origin remains unknown. During the past few decades, interest in an environment etiology has arisen in part following the work of Rier *et al.*[111] who observed a dose-dependent relationship between dioxin and endometriosis severity in Rhesus monkeys. Subsequently, the authors observed similar effects for select dioxin-like PCB congeners.[112] Of the 20 published human studies focusing on EDCs and endometriosis, about half reported significant associations with endometriosis, including those with exposure to dioxins,[113,114] metals,[115] phthalates[116,117] and PCBs.[118–121] It is important to note that many of the negative studies utilized a sampling framework that encompassed a low percentage of women with endometriosis relative to the size of the overall study sample, did not have laparoscopically or histologically confirmed endometriosis or utilized laboratory practices such as automatically substituting values for concentrations below the limits of detection and/or lipid-adjust concentrations. These laboratory practices have been empirically demonstrated to introduce bias.[122–124] To date, we are unaware of any studies with *in utero* measurement of EDCs and subsequent gynecologic disorders such as endometriosis.

There is evolving evidence supporting an *in utero* origin of endometriosis for other exposures. Missmer *et al.*[125] reported that women with prenatal DES exposure had an 80% higher risk of endometriosis compared with unexposed women. Furthermore, the authors found a significant inverse relationship between birth weight and risk of endometriosis. Hediger *et al.*[126] observed that endometriosis may be linked to early intrauterine life environment. Specifically, women with endometriosis were more likely to have a lower body mass index at the time of diagnosis and historically, as measured by self-reported body size at various ages through the time of diagnosis. This finding was recently confirmed in the Nurses' Health Study, where an inverse association was observed between body size in early childhood and endometriosis risk in adulthood.[127] Buck Louis *et al.*[128] reported a significant reduction in the odds of endometriosis among women whose mothers smoked during their pregnancy compared with non-smoking mothers. The authors suggested that smoking may be associated with a lower estrogenic state.

Reproductive site cancers

The temporal patterns for reproductive site cancers offer a conflicting picture with some rates increasing while others are decreasing. Over the past 25 years, breast cancer incidence rates have risen approximately 30% in westernized countries, possibly as a result of population changes in reproductive behaviors and better screening.[129] Incidence has recently decreased in the United States, possibly following reductions in the use of hormone replacement therapy in the context of mammography utilization.[130] Overall ovarian cancer rates have decreased in some countries such as the United States from 16 per 100,000 person-years in 1975 to 13 per 100,000 in 2007,[131] while they are increasing in other geographic areas. For example, rates tripled between 1974–1985 and 1992–2001 in Sassari, Sardinia (4.27/100,000 person-years *v.* 11.9/100,000, respectively),[132] suggesting considerable geographic variation in temporal patterns.

Many reproductive factors have been associated with various reproductive site cancers, particularly when assessing histological types. For instance, low parity, infertility, early age of menarche and later age reaching menopause are associated with increased risk of epithelial ovarian cancer.[133] Interestingly, women with synchronous primary cancers of the endometrium and ovary also have distinct reproductive characteristics including younger age, premenopausal status and nulliparity.[134]

For the past few decades, considerable research has focused on the role of EDCs and reproductive site cancers with equivocal results as previously reviewed.[135] Both PCB and DDT congeners have been associated with a small increased risk of endometrial cancer.[136,137] Adult exposure to EDCs and various female reproductive effects has recently been reviewed and evidence suggests that an important role may be elucidated in the years to come as we design better studies to follow women from conception through adulthood.[138] The extent to which reproductive site cancers may arise *in utero* remains speculative, but increasingly such cancers are being assessed as possible intermediates in the cancer pathway similar to the TDS paradigm. Concerted research initiatives are fueled, in part, by the carcinogenic role of DES, including transgenerationally.

A recent meta-analysis focusing on *in utero* exposures and breast cancer reported that birth weight and length were positively associated with increased risk; however, the effects of gestational age and DES on breast cancer risk remain equivocal.[139,140] Strohsnitter *et al.*[141] recently reported that *in utero* exposure to cigarette smoke may reduce the risk of breast cancer later in life by approximately half, perhaps by reducing the estrogenic intrauterine environment for the developing mammary glands.

Fecundity and later onset adult health

In weighing the available literature, a suggestive, although incomplete, body of evidence supports a possible early origin for female fecundity and its implications across the lifespan including fecundity impairments, gynecologic disorders, gravid and later onset adult diseases. Despite limited study, there is increasing speculation that gynecologic disorders may be associated with pregnancy complications, gravid and

chronic diseases, more generally. For example, fibroids may disproportionately affect nulliparous women; among parous women, they may be associated with a longer TTP, greater likelihood of pregnancy loss and/or preterm delivery.[142] As yet, a critical data gap is our inability to delineate the causal pathway between fecundity, parity, gravid health and later onset adult diseases.

The relationship between PCOS and gravid health has received considerable attention, given the growing recognition that affected women are at increased risk for pre-eclampsia, pregnancy-induced hypertension and gestational diabetes in comparison with unaffected women.[143] In addition, risks for later onset adult diseases such as cardiovascular diseases and metabolic syndrome remain for women with PCOS.[92] Conversely, women with endometriosis are reported to be at reduced risk for preeclampsia and pregnancy-induced hypertension in comparison with unaffected women,[144] but at greater risk for autoimmune and other endocrine disorders such as hypothyroidism, fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, asthma, allergies and multiple sclerosis.[145] Recent evidence suggests that women with endometriosis are at higher risk of reproductive site cancers. For example, using published survey results for the general US female population, women with endometriosis had higher rates of ovarian cancer, particularly for women with ovarian endometriomas diagnosed after 50 years of age.[146] Among Swedish women, increased risks were observed for ovarian cancer, non-Hodgkin's lymphoma, endocrine and brain tumors among women with endometriosis in comparison with unaffected women.[147] These findings may suggest a shared etiology for endometriosis and ovarian cancers, or the possible transformation of endometriosis into malignant disease.[148,149]

Conclusion and critical data gaps

Although incomplete, the ODS hypothesis provides a framework for conceptualizing an early origin for female fecundity and, subsequently, health across the woman's lifespan. The diversity of effects that may be considered in relation to EDCs or other lifestyle factors includes fecundity and fertility endpoints, gynecologic disorders, gravid health and later adult diseases arising from epigenetic changes during critical and sensitive windows of human development. Following exposure, the embryo/fetus undergoes permanent reprogramming or functional changes with possible lifelong and transgenerational implications. To this end, fecundity impairments and gynecologic disorders may be an early signal indicative of programming effects with implications for later onset adult diseases. This avenue of research requires study designs that are capable of identifying and measuring multiple exposures across the continuum of critical and sensitive windows in the context of other influences such as nutrition and lifestyle. This avenue of evolving research is the so-called 'exposome' paradigm, and is offered to complement genomic and epigenetic research emphasizing the importance of a genetic/epigenetic-environmental approach to health and disease.[150] Life course epidemiological methods coupled with newer statistical models appropriate for the hierarchical data structure and a spectrum of study endpoints offer promise for designing research sensitive to critical data gaps.

Acknowledgment

This study is supported in part with intramural funding from the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development.

Statement of Interest

None.

References

1. Barker DJ. *Mothers, Babies, and Disease Later in Life*, 1984. BMJ Publishing Group, London.
2. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002; 31, 285–293.
3. Buck Louis GM, Cooney MA. Effects of environmental contaminants on ovarian function and fertility. In *Novel Concepts in Ovarian Endocrinology* (ed. Gonzalez-Bulnes A), 2007; pp. 249–268. Transworld Research Network, Kerala.
4. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science*. 2004; 305, 1733–1736.
5. Heindel JJ. Role of exposure to environmental chemicals in the developmental basis of reproductive disease and dysfunction. *Semin Reprod Med*. 2006; 24, 168–177.
6. De Stavola BL, Nitsch D, dos SSI, *et al*. Statistical issues in life course epidemiology. *Am J Epidemiol*. 2006; 163, 84–96.
7. Carlin BP, Louis TA. *Bayesian Methods for Data Analysis*, 3rd edn, 2009. Chapman & Hall/CRC Press, Boca Raton, FL.
8. Lutz W, O'Neill BC, Scherbov S. Demographics. Europe's population at a turning point. *Science*. 2003; 299, 1991–1992.
9. Skakkebaek NE, Rajpert-De ME, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod*. 2001; 16, 972–978.
10. Andersen AG, Jensen TK, Carlsen E, *et al*. High frequency of sub-optimal semen quality in an unselected population of young men. *Hum Reprod*. 2000; 15, 366–372.
11. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *BMJ*. 1992; 305, 609–613.
12. Chilvers C, Pike MC, Forman D, Fogelman K, Wadsworth ME. Apparent doubling of frequency of undescended testis in England and Wales in 1962–81. *Lancet*. 1984; 2, 330–332.
13. Paulozzi LJ, Erickson JD, Jackson RJ. Hypospadias trends in two US surveillance systems. *Pediatrics*. 1997; 100, 831–834.
14. Moller H. Trends in sex-ratio, testicular cancer and male reproductive hazards: are they connected? *APMIS*. 1998; 106, 232–238.

15. Baker JA, Buck GM, Vena JE, Moysich KB. Fertility patterns prior to testicular cancer diagnosis. *Cancer Causes Control*. 2005; 16, 295–299.
16. Prener A, Engholm G, Jensen OM. Genital anomalies and risk for testicular cancer in Danish men. *Epidemiology*. 1996; 7, 14–19.
17. Leon DA, Lithell HO, Vagero D, *et al*. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *BMJ*. 1998; 317, 241–245.
18. Lithell HO, McKeigue PM, Berglund L, *et al*. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ*. 1996; 312, 406–410.
19. McCormack VA, dos SSI, De Stavola BL, *et al*. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. *BMJ*. 2003; 326, 248.
20. Barker DJ. *Fetal and Infant Origins of Adult Disease*, 1992. BMJ Publication, London.
21. Wilson VS, Blystone CR, Hotchkiss AK, Rider CV, Gray LE Jr. Diverse mechanisms of anti-androgen action: impact on male rat reproductive tract development. *Int J Androl*. 2008; 31, 178–187.
22. Mendola P, Buck Louis GM. Environmental contaminants, female reproductive health and fertility. In *Environmental Impacts on Reproductive Health and fertility* (eds. Woodruff TJ, Janssen SJ, Guilette LJ, Giudice LC), 2010; pp. 161–172. Cambridge University Press, Cambridge.
23. Wood J. *Dynamics of Human Reproduction: Biology, Biometry, and Demography*, 1994. Aldine de Gruyter, New York.
24. Chapin RE, Robbins WA, Schieve LA, *et al*. Off to a good start: the influence of pre- and periconceptional exposures, parental fertility, and nutrition on children's health. *Environ Health Perspect*. 2004; 112, 69–78.
25. Calabrese EJ. Sex differences in susceptibility to toxic industrial chemicals. *Br J Ind Med*. 1986; 43, 577–579.
26. Kuh D, Ben-Shlomo Y. *A Lifecourse Approach to Chronic Disease Epidemiology*, 2005. Oxford University Press, Inc., New York.
27. Lucifero D, Chaillet JR, Trasler JM. Potential significance of genomic imprinting defects for reproduction and assisted reproductive technologies. *Hum Reprod Update*. 2004; 10, 3–18.
28. Latham KE. Epigenetic modification and imprinting of the mammalian genome during development. *Curr Top Dev Biol*. 1999; 43, 1–49.
29. Obata Y, Kaneko-Ishino T, Koide T, *et al*. Disruption of primary imprinting during oocyte growth leads to the modified expression of imprinted genes during embryogenesis. *Development*. 1998; 125, 1553–1560.
30. Owen CM, Segars JH. Imprinting disorders and assisted reproductive technology. *Semin Reprod Med*. 2009; 27, 417–428.
31. Dorais J, Peterson CM. Mullerian (Paramesonephric) Anomalies and associated Wolffian (Mesonephric) Duct malformations. In *Reproductive Endocrinology and Infertility Integrating Modern Clinical and Laboratory Practice* (eds. Carrell DT, Peterson CM), 2010; pp. 265–280. Springer, Philadelphia, PA.
32. Witschi E. Migration of the germ cells of human embryos from the yolk sac to the primitive gonadal folds. *Contrib Embryol*. 1948, 67–80.
33. Acien P, Acien M, Sanchez-Ferrer M. Complex malformations of the female genital tract. New types and revision of classification. *Hum Reprod*. 2004; 19, 2377–2384.
34. Hammoud AO, Gibson M, Peterson CM, *et al*. Quantification of the familial contribution to mullerian anomalies. *Obstet Gynecol*. 2008; 111(Pt 1), 378–384.
35. Gondos B, Westergaard L, Byskov AG. Initiation of oogenesis in the human fetal ovary: ultrastructural and squash preparation study. *Am J Obstet Gynecol*. 1986; 155, 189–195.
36. Van SL. From epigenesis to epigenetics: the case of C. H. Waddington. *Ann N Y Acad Sci*. 2002; 981, 61–81.
37. Peterson CM, Carrell DT, Varner M, *et al*. The environment and reproduction: endocrine disruption, reproductive impairment, and epigenetics. In *Reproductive Endocrinology and Infertility Integrating Modern Clinical and Laboratory Practice* (eds. Carrell DT, Peterson CM), 2010; pp. 781–803. Springer, Philadelphia, PA.
38. Hennig B, Meerarani P, Slim R, *et al*. Proinflammatory properties of coplanar PCBs: in vitro and in vivo evidence. *Toxicol Appl Pharmacol*. 2002; 181, 174–183.
39. Ivnitski-Steele ID, Sanchez A, Walker MK. 2,3,7,8-tetrachlorodibenzo-p-dioxin reduces myocardial hypoxia and vascular endothelial growth factor expression during chick embryo development. *Birth Defects Res A Clin Mol Teratol*. 2004; 70, 51–58.
40. Long X, Burke KA, Bigsby RM, Nephew KP. Effects of the xenoestrogen bisphenol A on expression of vascular endothelial growth factor (VEGF) in the rat. *Exp Biol Med (Maywood)*. 2001; 226, 477–483.
41. Bredhult C, Backlin BM, Olovsson M. Effects of some endocrine disruptors on the proliferation and viability of human endometrial endothelial cells in vitro. *Reprod Toxicol*. 2007; 23, 550–559.
42. Muhlhauser A, Susiarjo M, Rubio C, *et al*. Bisphenol A effects on the growing mouse oocyte are influenced by diet. *Biol Reprod*. 2009; 80, 1066–1071.
43. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet*. 2007; 8, 253–262.
44. Newbold RR, Hanson RB, Jefferson WN, *et al*. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. *Carcinogenesis*. 1998; 19, 1655–1663.
45. Skinner MK. Endocrine disruptors and epigenetic transgenerational disease etiology. *Pediatr Res*. 2007; 61(Pt 2), 48R–50R.
46. Steinberg RM, Walker DM, Juenger TE, Woller MJ, Gore AC. Effects of perinatal polychlorinated biphenyls on adult female rat reproduction: development, reproductive physiology, and second generational effects. *Biol Reprod*. 2008; 78, 1091–1101.
47. Walker BE, Haven MI. Intensity of multigenerational carcinogenesis from diethylstilbestrol in mice. *Carcinogenesis*. 1997; 18, 791–793.
48. Buck Louis GM, Lynch CD, Cooney MA. Environmental influences on female fecundity and fertility. *Semin Reprod Med*. 2006; 24, 147–155.
49. McLachlan JA, Simpson E, Martin M. Endocrine disrupters and female reproductive health. *Best Pract Res Clin Endocrinol Metab*. 2006; 20, 63–75.

50. Mendola P, Messer LC, Rappazzo K. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. *Fertil Steril*. 2008; 89(Suppl 2), e81–e94.
51. Miller KP, Borgeest C, Greenfeld C, Tomic D, Flaws JA. In utero effects of chemicals on reproductive tissues in females. *Toxicol Appl Pharmacol*. 2004; 198, 111–131.
52. Toft G, Hagmar L, Giwercman A, Bonde JP. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. *Reprod Toxicol*. 2004; 19, 5–26.
53. Nichols HB, Trentham-Dietz A, Hampton JM, *et al*. From menarche to menopause: trends among US women born from 1912–1969. *Am J Epidemiol*. 2006; 164, 1003–1011.
54. Karpati AM, Rubin CH, Kieszak SM, Marcus M, Troiano RP. Stature and pubertal stage assessment in American boys: The 1988–1994 Third National Health and Nutrition Examination Survey. *J Adoles Health*. 2002; 30, 205–212.
55. Herman-Giddens ME, Slora EJ, Wasserman RC, *et al*. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research Office Settings network. *Pediatr*. 1997; 99, 505–512.
56. North American Menopause Society. *Menopause Core Curriculum Study Guide*, 2002. North American Menopause Society, Cleveland, OH.
57. de Bruin JP, Dorland M, Bruinse HW, *et al*. Fetal growth retardation as a cause of impaired ovarian development. *Early Hum Dev*. 1998; 51, 39–46.
58. Ibanez L, Potau N, Enriquez G, de ZF. Reduced uterine and ovarian size in adolescent girls born small for gestational age. *Pediatr Res*. 2000; 47, 575–577.
59. Ibanez L, Potau N, Ferrer A, *et al*. Reduced ovulation rate in adolescent girls born small for gestational age. *J Clin Endocrinol Metab*. 2002; 87, 3391–3393.
60. Jensen TK, Joffe M, Scheike T, *et al*. Early exposure to smoking and future fecundity among Danish twins. *Int J Androl*. 2006; 29, 603–613.
61. Taylor KC, Jackson LW, Lynch CD, Kostyniak PJ, Buck Louis GM. Preconception maternal polychlorinated biphenyl concentrations and the secondary sex ratio. *Environ Res*. 2007; 103, 99–105.
62. Weisskopf MG, Anderson HA, Hanrahan LP. Decreased sex ratio following maternal exposure to polychlorinated biphenyls from contaminated Great Lakes sport-caught fish: a retrospective cohort study. *Environ Health*. 2003; 2, 2.
63. del Rio Go mez I Marshall T, Tsai P, Shao YS, Guo YL. Number of boys born to men exposed to polychlorinated byphenyls. *Lancet*. 2002; 360, 143–144.
64. Mocarelli P, Gerthoux PM, Ferrari E, *et al*. Paternal concentrations of dioxin and sex ratio of offspring. *Lancet*. 2000; 355, 1858–1863.
65. Buck Louis GM, Dmochowski J, Lynch C, *et al*. Polychlorinated biphenyl serum concentrations, lifestyle and time-to-pregnancy. *Hum Reprod*. 2009; 24, 451–458.
66. Law DC, Klebanoff MA, Brock JW, Dunson DB, Longnecker MP. Maternal serum levels of polychlorinated biphenyls and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and time to pregnancy. *Am J Epidemiol*. 2005; 162, 523–532.
67. Eskenazi B, Warner M, Marks AR, *et al*. Serum dioxin concentrations and time to pregnancy. *Epidemiology*. 2010; 21, 224–231.
68. Harley KG, Marks AR, Chevrier J, *et al*. PBDE concentrations in women's serum and fecundability. *Environ Health Perspect*. 2010; 118, 699–704.
69. Cole DC, Wainman B, Sanin LH, *et al*. Environmental contaminant levels and fecundability among non-smoking couples. *Reprod Toxicol*. 2006; 22, 13–19.
70. Stephen EH, Chandra A. Updated projections of infertility in the United States: 1995–2025. *Fertil Steril*. 1998; 70, 30–34.
71. Stephen EH, Chandra A. Declining estimates of infertility in the United States: 1982–2002. *Fertil Steril*. 2006; 86, 516–523.
72. Daguet F. *Un Siecle de Fecondite Francaise: 1901–1999*, 2010. INSEE, Paris.
73. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. *Hum Reprod*. 2004; 19, 1548–1553.
74. Menken J, Trussell J, Larsen U. Age and infertility. *Science*. 1986; 233, 1389–1394.
75. Olsen J, Rachootin P. Invited commentary: monitoring fecundity over time – if we do it, then let's do it right. *Am J Epidemiol*. 2003; 157, 94–97.
76. Joffe M. Invited commentary: the potential for monitoring of fecundity and the remaining challenges. *Am J Epidemiol*. 2003; 157, 89–93.
77. Herbst AL, Bern HA. *Developmental Effects of Diethylstilbestrol (DES) in Pregnancy*, 1981. Thieme-Stratton, New York.
78. Kaufman RH, Adam E, Binder GL, Gerthoffer E. Upper genital tract changes and pregnancy outcome in offspring exposed in utero to diethylstilbestrol. *Am J Obstet Gynecol*. 1980; 137, 299–308.
79. Saravelos SH, Cocksedge KA, Li TC. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. *Hum Reprod Update*. 2008; 14, 415–429.
80. Dorland. *Dorland's Medical Dictionary and Illustrations*, 31st edn, 2007. W.B. Saunders, Philadelphia, PA.
81. Buttram VC Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil Steril*. 1981; 36, 433–445.
82. Stewart EA. Uterine fibroids. *Lancet*. 2001; 357, 293–298.
83. Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. *Obstet Gynecol*. 2004; 104, 393–406.
84. Viswanathan M, Hartmann K, McKoy N, *et al*. Management of uterine fibroids: an update of the evidence. *Evid Rep Technol Assess (Full Rep)*. 2007, 1–122.
85. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol*. 2003; 188, 100–107.
86. Ishikawa H, Reierstad S, Demura M, *et al*. High aromatase expression in uterine leiomyoma tissues of African-American women. *J Clin Endocrinol Metab*. 2009; 94, 1752–1756.
87. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. *Am J Obstet Gynecol*. 2008; 198, 357–366.

88. Newbold RR, Moore AB, Dixon D. Characterization of uterine leiomyomas in CD-1 mice following developmental exposure to diethylstilbestrol (DES). *Toxicol Pathol*. 2002; 30, 611–616.
89. Baird DD, Newbold R. Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. *Reprod Toxicol*. 2005; 20, 81–84.
90. D'Aloisio AA, Baird DD, Deroo LA, Sandler DP. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the sister study. *Environ Health Perspect*. 2010; 118, 375–381.
91. Wise LA, Palmer JR, Rowlings K, *et al*. Risk of benign gynecologic tumors in relation to prenatal diethylstilbestrol exposure. *Obstet Gynecol*. 2005; 105, 167–173.
92. Azziz R, Woods KS, Reyna R, *et al*. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004; 89, 2745–2749.
93. Goodarzi MO, Quinones MJ, Azziz R, *et al*. Polycystic ovary syndrome in Mexican-Americans: prevalence and association with the severity of insulin resistance. *Fertil Steril*. 2005; 84, 766–769.
94. The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Working Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004; 19, 41–47.
95. Kumarapeli V, Seneviratne RA, Wijeyaratne CN, Yapa RM, Dodampahala SH. A simple screening approach for assessing community prevalence and phenotype of polycystic ovary syndrome in a semi-urban population in Sri Lanka. *Am J Epidemiol*. 2008; 168, 321–328.
96. Cresswell JL, Barker DJ, Osmond C, *et al*. Fetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet*. 1997; 350, 1131–1135.
97. Wickenheisser JK, Nelson-DeGrave VL, McAllister JM. Human ovarian theca cells in culture. *Trends Endocrinol Metab*. 2006; 17, 65–71.
98. Abbott DH, Barnett DK, Bruns CM, Dumesic DA. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? *Hum Reprod Update*. 2005; 11, 357–374.
99. Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. *Endocr J*. 2004; 51, 165–169.
100. Tsutsumi O. Assessment of human contamination of estrogenic endocrine-disrupting chemicals and their risk for human reproduction. *J Steroid Biochem Mol Biol*. 2005; 93, 325–330.
101. Abbott DH, Dumesic DA, Franks S. Developmental origin of polycystic ovary syndrome – a hypothesis. *J Endocrinol*. 2002; 174, 1–5.
102. Eisner JR, Barnett MA, Dumesic DA, Abbott DH. Ovarian hyperandrogenism in adult female rhesus monkeys exposed to prenatal androgen excess. *Fertil Steril*. 2002; 77, 167–172.
103. Leibson CL, Good AE, Hass SL, *et al*. Incidence and characterization of diagnosed endometriosis in a geographically defined population. *Fertil Steril*. 2004; 82, 314–321.
104. Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. *Epidemiol Rev*. 1984; 6, 167–191.
105. Olive DL, Schwartz LB. Endometriosis. *N Engl J Med*. 1993; 328, 1759–1769.
106. Carter JE. Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain. *J Am Assoc Gynecol Laparosc*. 1994; 2, 43–47.
107. Mahmood TA, Templeton A. Prevalence and genesis of endometriosis. *Hum Reprod*. 1991; 6, 544–549.
108. Moen MH, Muus KM. Endometriosis in pregnant and non-pregnant women at tubal sterilization. *Hum Reprod*. 1991; 6, 699–702.
109. Strathy JH, Molgaard CA, Coulam CB, Melton III LJ. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. *Fertil Steril*. 1982; 38, 667–672.
110. Wardle PG, Hull MG. Is endometriosis a disease? *Baillieres Clin Obstet Gynaecol*. 1993; 7, 673–685.
111. Rier SE, Martin DC, Bowman RE, Dmowski WP, Becker JL. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam Appl Toxicol*. 1993; 21, 433–441.
112. Rier SE, Turner WE, Martin DC, *et al*. Serum levels of TCDD and dioxin-like chemicals in Rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicol Sci*. 2001; 59, 147–159.
113. Heilier JF, Nackers F, Verougstraete V, *et al*. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. *Fertil Steril*. 2005; 84, 305–312.
114. Mayani A, Barel S, Soback S, Almagor M. Dioxin concentrations in women with endometriosis. *Hum Reprod*. 1997; 12, 373–375.
115. Jackson LW, Zullo MD, Goldberg JM. The association between heavy metals, endometriosis and uterine myomas among premenopausal women: National Health and Nutrition Examination Survey 1999–2002. *Hum Reprod*. 2008; 23, 679–687.
116. Cobellis L, Latini G, De FC, *et al*. High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. *Hum Reprod*. 2003; 18, 1512–1515.
117. Reddy BS, Rozati R, Reddy S, *et al*. High plasma concentrations of polychlorinated biphenyls and phthalate esters in women with endometriosis: a prospective case control study. *Fertil Steril*. 2006; 85, 775–779.
118. Gerhard I, Runnebaum B. The limits of hormone substitution in pollutant exposure and fertility disorders. *Zentralbl Gynakol*. 1992; 114, 593–602.
119. Louis GM, Weiner JM, Whitcomb BW, *et al*. Environmental PCB exposure and risk of endometriosis. *Hum Reprod*. 2005; 20, 279–285.
120. Porpora MG, Ingelido AM, di DA, *et al*. Increased levels of polychlorobiphenyls in Italian women with endometriosis. *Chemosphere*. 2006; 63, 1361–1367.
121. Quaranta MG, Porpora MG, Mattioli B, *et al*. Impaired NK-cell-mediated cytotoxic activity and cytokine production in patients with endometriosis: a possible role for PCBs and DDE. *Life Sci*. 2006; 79, 491–498.
122. Richardson DB, Ciampi A. Effects of exposure measurement error when an exposure variable is constrained by a lower limit. *Am J Epidemiol*. 2003; 157, 355–363.

123. Schisterman EF, Whitcomb BW, Louis GM, Louis TA. Lipid adjustment in the analysis of environmental contaminants and human health risks. *Environ Health Perspect*. 2005; 113, 853–857.
124. Schisterman EF, Vexler A, Whitcomb BW, Liu A. The limitations due to exposure detection limits for regression models. *Am J Epidemiol*. 2006; 163, 374–383.
125. Missmer SA, Hankinson SE, Spiegelman D, *et al*. In utero exposures and the incidence of endometriosis. *Fertil Steril*. 2004; 82, 1501–1508.
126. Hediger ML, Hartnett HJ, Louis GM. Association of endometriosis with body size and figure. *Fertil Steril*. 2005; 84, 1366–1374.
127. Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. *Hum Reprod*. 2010; 25, 1325–1334.
128. Buck Louis GM, Hediger ML, Pena JB. Intrauterine exposures and risk of endometriosis. *Hum Reprod*. 2007; 22, 3232–3236.
129. Colditz GA, Sellers TA, Trapido E. Epidemiology – identifying the causes and preventability of cancer? *Nat Rev Cancer*. 2006; 6, 75–83.
130. Garcia M, Jemal A, Ward EM, *et al*. *Global Cancer Facts and Figures 2007*, 2007. American Cancer Society, Atlanta, GA.
131. Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Reserach Program, National Cancer Institute. Retrieved 20 December 2010 from http://seer.cancer.gov/faststats.
132. Cossu A, Budroni M, Capobianco G, *et al*. Epidemiological aspects of ovarian malignancies in North Sardinia in the period 1992–2001. *Eur J Gynaecol Oncol*. 2005; 26, 47–50.
133. Mok SC, Kwong J, Welch WR, *et al*. Etiology and pathogenesis of epithelial ovarian cancer. *Dis Markers*. 2007; 23, 367–376.
134. Grammatikakis I, Zervoudis S, Evangelinakis N, Tziortzioti V. Endometrium and ovarian cancer synchronous to endometriosis – a retrospective study of our experience of 7 years. *J Med Life*. 2010; 3, 76–79.
135. Ahlborg UG, Lipworth L, Titus-Ernstoff L, *et al*. Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence. *Crit Rev Toxicol*. 1995; 25, 463–531.
136. Sturgeon SR, Brock JW, Potischman N, *et al*. Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). *Cancer Causes Control*. 1998; 9, 417–424.
137. Weiderpass E, Adami HO, Baron JA, *et al*. Organochlorines and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2000; 9, 487–493.
138. Crain DA, Janssen SJ, Edwards TM, *et al*. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. *Fertil Steril*. 2008; 90, 911–940.
139. Palmer JR, Wise LA, Hatch EE, *et al*. Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2006; 15, 1509–1514.
140. Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. *Lancet Oncol*. 2007; 8, 1088–1100.
141. Strohsnitter WC, Noller KL, Titus-Ernstoff L, *et al*. Breast cancer incidence in women prenatally exposed to maternal cigarette smoke. *Epidemiology*. 2005; 16, 342–345.
142. Somigliana E, Vercellini P, Daguati R, *et al*. Fibroids and female reproduction: a critical analysis of the evidence. *Hum Reprod Update*. 2007; 13, 465–476.
143. Boomsma CM, Eijkemans MJ, Hughes EG, *et al*. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update*. 2006; 12, 673–683.
144. Brosens IA, De SP, Hamerlynck T, *et al*. Endometriosis is associated with a decreased risk of pre-eclampsia. *Hum Reprod*. 2007; 22, 1725–1729.
145. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod*. 2002; 17, 2715–2724.
146. Kobayashi H, Sumimoto K, Moniwa N, *et al*. Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan. *Int J Gynecol Cancer*. 2007; 17, 37–43.
147 Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol*. 1997; 176, 572–579.
148. Ogawa S, Kaku T, Amada S, *et al*. Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study. *Gynecol Oncol*. 2000; 77, 298–304.
149. Yoshikawa H, Jimbo H, Okada S, *et al*. Prevalence of endometriosis in ovarian cancer. *Gynecol Obstet Invest*. 2000; 50(Suppl 1), 11–17.
150. Wild CP. Complementing the genome with an 'exposome': the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev*. 2005; 14, 1847–1850.