Physiol Rev 96: 873–909, 2016
Published June 1, 2016; doi:10.1152/physrev.00023.2015

PHYSIOLOGICAL ASPECTS OF FEMALE FERTILITY: ROLE OF THE ENVIRONMENT, MODERN LIFESTYLE, AND GENETICS

Roger J. Hart

School of Women's and Infants Health, University of Western Australia & Fertility Specialists of Western Australia, Subiaco, Perth Western Australia

Hart RJ. Physiological Aspects of Female Fertility: Role of the Environment, Modern Lifestyle, and Genetics. *Physiol Rev* 96: 873–909, 2016. Published June 1, 2016; doi:10.1152/physrev.00023.2015.—Across the Western World there is an increasing trend to postpone childbearing. Consequently, the negative influence of age on oocyte quality may lead to a difficulty in conceiving for many couples. Furthermore, lifestyle factors may exacerbate a couple's difficulty in conceiving due mainly to the metabolic influence of obesity; however, the negative impacts of low peripheral body fat, excessive exercise, the increasing prevalence of sexually transmitted diseases, and smoking all have significant negative effects on fertility. Other factors that impede conception are the perceived increasing prevalence of the polycystic ovary syndrome, which is further exacerbated by obesity, and the presence of uterine fibroids and endometriosis (a progressive pelvic inflammatory disorder) which are more prevalent in older women. A tendency for an earlier sexual debut and to have more sexual partners has led to an increase in sexually transmitted diseases. In addition, there are several genetic influences that may limit the number of oocytes within the ovary; consequently, by postponing attempts at childbearing, a limitation of oocyte number may become evident, whereas in previous generations with earlier conception this potentially reduced reproductive life span did not manifest in infertility. Environmental influences on reproduction are under increasing scrutiny. Although firm evidence is lacking however, dioxin exposure may be linked to endometriosis, phthalate exposure may influence ovarian reserve, and bisphenol A may interfere with oocyte development and maturation. However, chemotherapy or radiotherapy is recognized to lead to ovarian damage and predispose the woman to ovarian failure.

I.	INTRODUCTION	873
II.	PHYSIOLOGY	874
III.	PATHOLOGICAL PROCESSES,...	878
IV.	LIFESTYLE INFLUENCES...	888
V.	ENVIRONMENTAL INFLUENCES...	893
VI.	CONCLUSION	900

I. INTRODUCTION

The most powerful influence relating to a woman's chance of conceiving is her age. Female age has physiological and genetic influences on conception, relating to a reduced ovarian follicular pool, perturbations in ovulation, and an increase in meiotic errors within the oocyte. Indeed, in some instances, age could be considered a lifestyle decision; however, in most instances this is not the case, as with increasing societal and professional pressures upon women childbearing is increasingly postponed into the 30s, whereas in previous generations starting a family in the 20s was the norm. This has resulted in the increasing recourse to fertility treatment; indeed, 1 in 25 children in Australia are born as a result of in vitro fertilization (IVF) treatment, and it is believed the figure reaches 1 in 7 for women over 37 years of age (239), when the treatment is much less successful **(FIGURE 1)**.

This delay in childbearing has provided a window of opportunity for various lifestyle, pathological, and genetic perturbations to exert their influence further to reduce a couple's chance of conceiving. The lifestyle factors that have a detrimental impact on reproduction relate mainly to the metabolic influence of obesity; however, the negative impacts of low peripheral body fat, excessive exercise, the increasing prevalence of sexually transmitted diseases, and smoking all have significant negative effects on female fecundity at a population level.

Other factors that are believed to be exerting an increasing negative influence upon female conception are the greater prevalence of the polycystic ovary syndrome, which is further exacerbated by obesity. Furthermore, the incidence of uterine myomas (fibroids) and endometriosis (a progressive pelvic inflammatory disorder) are more prevalent in older women. A tendency for an earlier sexual debut and to have more sexual partners has led to

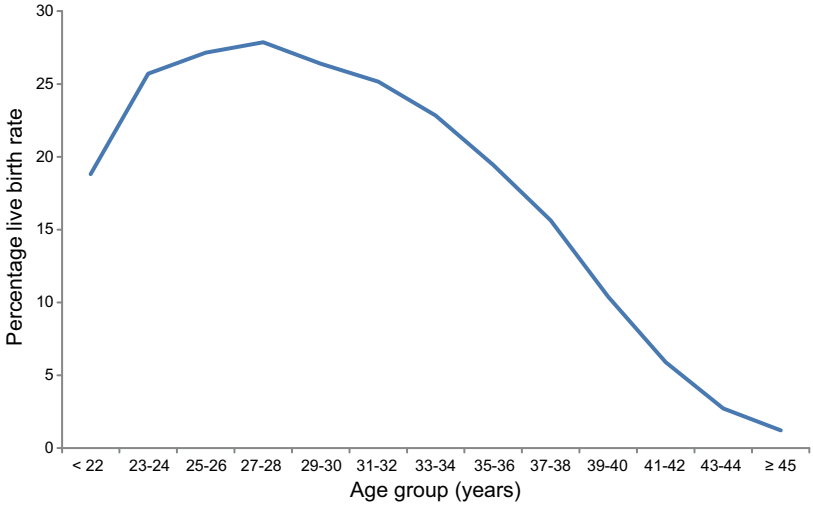

FIGURE 1. Age-specific live delivery rates per initiated autologous fresh cycle by two-year age groups, Australia and New Zealand, 2013. The highest live delivery rates were for women aged between their mid-20s to early-30s. For women aged 45 or older, only one live delivery resulted from every 80 initiated cycles compared with one live delivery from every four initiated cycles in women aged between 25 and 34. [From Macaldowie et al. (206), with permission.]

an increase in notifications of sexually transmitted diseases, a well-established cause of infertility. In addition, there are several genetic influences that may limit the "ovarian reserve," an expression of the total number of oocytes within the ovary; consequently, by postponing attempted childbearing a limitation in ovarian reserve may become evident, whereas in previous generations with earlier conception this propensity to a limited reproductive lifespan was not revealed.

Environmental influences upon reproduction are under increasing scrutiny; however, the firm evidence to date is lacking. There are suggestions that dioxin exposure may be linked to endometriosis and phthalate exposure may influence ovarian reserve, and bisphenol A may interfere with oocyte development and maturation, although very good evidence exists to relate the exposure to chemotherapy and radiotherapy to gonadal damage.

The purpose of this review is to attempt to cover the substantial field of female fertility and to try to address the influences of lifestyle and the environment on female infertility, and to provide a limited insight into genetic influences on female reproduction, from follicular development to implantation and early pregnancy.

II. PHYSIOLOGY

A. Folliculogenesis

Follicular development originates in utero during the second trimester of pregnancy by the rapid mitosis of the primordial germ cells into up to a maximum of ~6 million oogonia at 20 wk of gestation; from this point onwards the dominant activity is atresia. Indeed, there will only be 1 million germ cells surviving at birth (243). This finite reserve of primordial germ cells originates in the yolk sac endoderm and migrates to the gonadal ridge, and upon arrival enter the first meiotic division and become primary oocytes, and constitute the "ovarian reserve" [follicles that can subsequently be recruited for ovulation (20)]. These germ cells are essential for the formation and maintenance of the ovary, and in their absence the gonad degenerates into cordlike structures (215, 243). These primary oocytes are maintained at this arrested state of meiosis until the time of the surge in luteinizing hormone (LH) that presages ovulation. The oocyte is arrested in prophase I of meiosis by high levels of cAMP (323). In addition to the germ cells, the primordial follicle consists of somatic cells derived from the primitive gonad which develop into the flattened granulosa, theca, and interstitial cells. As described, this so-called follicular reserve of 6-7 million oocytes at 20 wk of gestation (20, 22) will continually deplete throughout the woman's life, the rate of which may be accelerated by factors such as genetic influences such as Turner's syndrome or Fragile X premutation carrier status (67), virological exposures such as the mumps virus (71), environmental exposure such as treatment with chemotherapy or radiotherapy (138), ovarian surgery (6), negative lifestyle factors such as smoking (308), and also in relation to autoimmune causes (367).

With the use of rodent models, factors involved in the regulation of the recruitment of these primordial follicles into a developing population of follicles for a menstrual cycle have been explored. Once puberty commences, Kit ligand and leukemia inhibitory factor (LIF) have been identified as significant promoters of the follicular transition (210, 237, 323). Kit ligand is expressed on the granulosa cells of the developing primordial follicle, with its receptor on the membrane (oolema) of the primary oocyte, and LIF is secreted from the early granulosa cells. LIF secretion is believed to regulate the local signaling involved with primordial follicle activation by promoting Kit ligand expression (323). In addition, oocyte-derived factors bone-morphogenic protein 15 (BMP-15) and growth differentiation factor-9 (GDF-9) are involved in the promotion of primordial

follicle maturation (70, 255); in addition, granulosa cell anti-Müllerian hormone (AMH) secreted by the granulosa cells of small antral follicles appears to act as a restraint (51, 184). Other paracrine signals involved in primordial follicle activation include basic fibroblast growth factor (bFGF), nobox and Foxo3, and insulin (176, 243). For a detailed description of the local factors involved in follicle and oocyte development, please refer to Sobinoff et al. (323) and Kristensen et al. (184) **(FIGURE 2)**. The flattened granulosa cells become cuboidal during the transition into a primary follicle under the influence of transcription factor Foxl2; the oocyte increases in diameter and develops a zona pellucida. This recruitment into primary follicles commences during fetal life and continues until the menopause.

B. Ovulation

The development and recruitment of these primordial follicles is regulated by paracrine and autocrine signals involving the transforming growth factor-β (TGF-β) superfamily, which includes TGF-β, inhibins, activins, follistatins, bone morphogenic proteins, growth factors, and AMH (184). Then the follicle transitions to the gonadotrophin-dependent antral follicle to the preovulatory stage; the whole process takes ~6 months (129). The gradual maturational change from the primordial follicle characterized by the cuboidal granulosa cells, through the preantral stage (up to 0.2 mm in size), involves proliferation and maturational changes and multi-layering within the granulosa and theca cells, and the development of an antrum within the follicle. With the development of the antrum, the follicle becomes responsive to gonadotrophins, which takes several months to complete (129, 243). The granulosa cell basal lamina is traversed by many gap junctions that allow communication and nutrition to surrounding granulosa cells and across the zona pellucida to the oocyte. The innermost layers of granulosa cells become differentiated as cumulus cells. In contrast, the theca cells have a greater vascular supply and are responsible for androgen synthesis, under LH stimulation. This acts as the substrate for the granulosa cell synthesis of estradiol, primarily under follicular stimulating hormone (FSH) control, the so-called "two-cell two gonadotrophin hypothesis" (21, 89). Both granulosa and theca cells secrete growth factors that modulate follicle maturation; the activators include Kit ligand, FGF-2, KGF, LIF, BMPs, and GDF-9, and the inhibitors include AMH, Foxl2, and Foxo3A (for a detailed description, see Ref. 243). The preantral follicle transition to the antral stage is modulated by AMH and stimulated by activins and GDF-9, and then as described the antral follicle becomes responsive to FSH (243).

Gonadotrophin stimulation of the ovary requires integrity of the hypothalamic-pituitary-ovary axis and appropriate peripheral signals that influence hypothalamic function. Gonadotrophin releasing hormone (GnRH) neurons arise alongside the olfactory nerves and migrate during embryological development to the hypothalamus and send neuronal projections from the arcuate nucleus to the median eminence where they release GnRH into the capillaries of the hypophysial-portal vessels (194). The GnRH then binds to the GnRH receptor on the anterior pituitary initiating the synthesis and secretion of LH and FSH (194). The control of hypothalamic secretion of GnRH is complex, relying on a complex interplay of ovarian feedback, primarily by inhibin B and estradiol and neuroendocrine signals modulated by systemic metabolic signals. Kisspeptins have the strongest influence over GnRH release via the kisspeptin receptor, coded for by *GPR54*, and are also integral to the timing and onset of puberty (232, 259; for detailed description, see Pinilla et al., Ref. 259). The kisspeptin neurons also express the

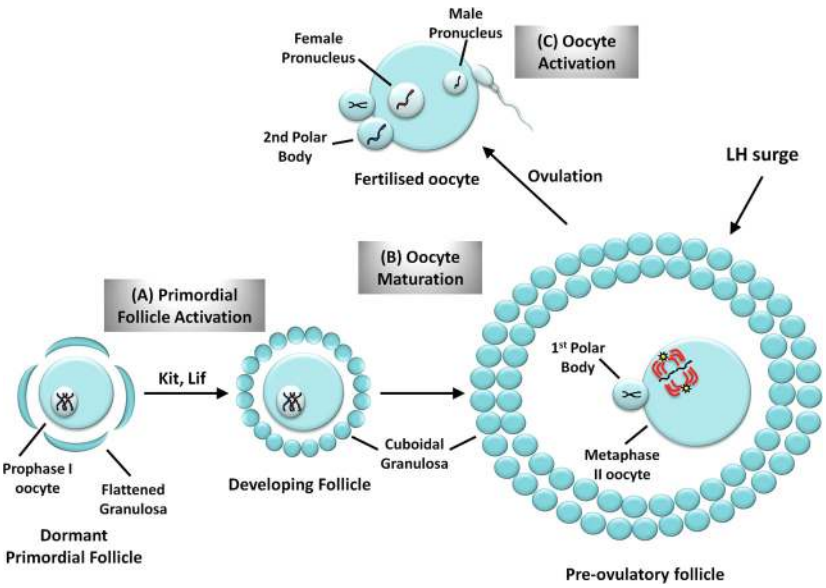

FIGURE 2. Diagrammatic representation of primordial follicle activation, oocyte maturation, and oocyte activation. *A*: the follicular activation of the dormant primordial follicle occurs in response to cytokine growth factors (e.g., Kit and LIF) and is characterized by oocyte growth and granulosa cell differentiation/proliferation. *B*: oocyte maturation occurs in response to the LH surge, resulting in meiotic resumption and arrest at metaphase II. *C*: oocyte activation occurs in ovulated oocytes after fertilization, resulting in the completion of MII, extrusion of the second polar body, and male/female pro-nuclear formation. Images are not to scale. [From Sobinoff et al. (323), with permission from Oxford University Press.]

neuropeptides neurokinin B (NKB) and dynorphin which modulate the GnRH secretion (123). Other neuropeptides integral to GnRH pulsatility are α melanocyte-stimulating hormone (αMSH), produced by proopiomelanocortin and cocaine and amphetamine-regulated transcript (POMC/CART), and the agouti-related protein (AgRP), an antagonist of αMSH, produced by the neuropeptide Y (NPY)/AgRP neurons (for review, see Navarro and Kaiser, Ref. 232). These neuropeptides are integral in the coordination of the reproductive and metabolic axes through their action in the hypothalamus (232); the neuropeptides derived from POMC/CART neurons exert a potent anorectic action, thus decreasing food intake and body weight, whereas AgRP and NPY have the opposite (orexigenic) effect, inducing food intake. In addition, these neurons express receptors for leptin (secreted by adipose tissue, anorexogenic, and a stimulus for GnRH activity), insulin, and gherlin (secreted by the gut, orexigenic, and a suppressor of GnRH activity). Furthermore, neuronal projections from the premammillary ventral nucleus which can be stimulatory (glutamatergic) or inhibitory (GABAergic) are responsive to peripheral leptin signals, leading to a complex relation of reproductive responses to metabolic signals (232).

After the antral stage of development, granulosa cell estradiol production increases by granulosa cell proliferation, increased vascularity, and an increased supply of theca cell androgens. Inhibin A secretion from larger follicles increases, promoting androgen secretion from theca cells, and there is a reduction of activin A secretion from larger follicles. Activin A acts to inhibit androgen secretion and promote oocyte developmental competence (5). As preantral follicle development progresses, there is an increase in FSH and LH receptor expression, aromatase activity, and inhibin and progesterone production (180).

The oocyte-derived BMPs and GDF-9 inhibit the premature luteinization of the follicle, which commences after the release of the oocyte at ovulation. Inhibin A secretion via pituitary feedback leads to a reduction in FSH secretion; hence, larger, or dominant follicles, will have higher concentrations of FSH and LH receptors and will continue to have higher aromatase activity and hence estradiol secretion.

Prior to ovulation, FSH induces expression of LH and progesterone receptors on the surface of the granulosa cells. The transformation to luteinization of the dominant follicle is initiated by the surge in LH and is often preceded by a slight rise in serum progesterone. The process of ovulation involves rapid expansion of the dominant follicle (1–4 mm/day), and ovulation results when tumor necrosis factor-α (TNF-α)-stimulated collagenase weakens the apical surface epithelium of the ovary and follicle rupture results (228). The corpus luteum is composed of theca and granulosa cells, endothelial, immune cells, macrophages, T and B lymphocytes, and fibroblast cells and secretes up to 40 mg of progesterone per day, in addition to estradiol and androgens (82, 83, 275). The LH surge must last more than 24 h to initiate resumption of oocyte meiosis and breakdown of the granulosa cell-oocyte gap junctions as well as to promote luteinization of the granulosa cells, ovulation, and the initiation of corpus luteum function (82, 83). It is believed that stimulation of the granulosa progesterone receptor is also a prerequisite for ovulation (66). The granulosa-lutein cells express the enzyme aromatase and produce estradiol in addition to progesterone, and the theca-lutein cells have P450C17 activity and generate the androgen precursors for granulosa cells (82), and are also believed to secrete progesterone (83). Granulosa cell steroidogenic acute regulatory protein (StAR) expression is substantially increased around the time of ovulation, induced by LH (171). StAR is essential for the movement of cholesterol carried by low-density lipoprotein into the inner membrane of the mitochondria where it becomes a substrate for P450scc to commence steroidogenesis (171). Over one-third of cells within the corpus luteum are endothelial cells representing the significant degree of vascularization the corpus luteum has undergone, induced primarily through the expression of vascular epithelial growth factor (VEGF). The immune cells are responsible for the secretion of cytokines, primarily interleukin (IL)-1β and TNF-α, which modulate steroidogenesis (82). Estradiol production by the granulosa-lutein cells is stimulated by LH and insulin-like growth factor I (IGF-I), not by FSH. In the absence of human chorionic gonadotrophin (hCG) secreted by a developing embryo or exogenously administered, there is a substantial reduction of StAR expression (84), mirrored in the serum progesterone level and reductions in P450scc and 3β hydroxysteroid dehydrogenase (HSD) (responsible for conversion of pregnenolone to progesterone) (83). Luteolysis leads to reductions in progesterone, estradiol, and inhibin A which through hypothalamic-pituitary-ovarian feedback initiates a further wave of follicular recruitment via increased GnRH pulses and the falling steroids precipitate menstruation. The process of luteolysis is not well understood, however, apoptosis is a significant feature, although the percentage of cells with apoptotic markers is low (358), and it involves breakdown of the extracellular matrix by matrix metalloproteinases (159).

At the time of embryo implantation, trophoblast production of hCG prevents the regression of the corpus luteum by increasing StAR expression within the granulosa and theca-lutein cells, increasing the vascular supply to the corpus luteal cells and a reduction in luteolysis by inhibition of the pro-apoptotic protein Bax and an increase in macrophages

that are believed to be essential for the vascular support of the corpus luteum (50, 83, 333).

C. Fertilization and Early Embryonic Development

After release of the oocyte and cumulus cell complex from the ovary to the fimbriae of the fallopian tube, the oocyte is fertilized in the ampulla of the distal end of the fallopian tube. The process of binding of the acrosomal membrane of a sperm that has undergone the acrosome reaction and capacitation to the zona pellucida (a glycoprotein matrix surrounding the oocyte) initiates release of cortical granules within the oocyte. The binding of the sperm to the zona pellucida precipitates a hardening of the zona preventing polyspermic fertilization of the oocyte (the zona reaction), intracellular calcium oscillations commence, and meiosis II is completed by extrusion of the second polar body. In addition, the sperm acrosome contains several lytic enzymes and zona pellucida binding proteins (241). The mechanism of sperm-oocyte binding to the four zona pellucida sperm binding proteins (ZP1 to 4) and the prevention of polyspermic fertilization is still subject to debate (for further discussion, see Clift and Schuh, Ref. 62), as from animal studies there are believed to be several other substances involved in the sperm-oocyte fusion, such as sperm ADAMs (consisting of a disintegrin and a metalloproteinase) and their oocyte integrin ligands, and the sperm proteins IZUMO1 and SPESP1 (98). The increase in calcium within the oocyte is a trigger for the development of the female pronucleus and the sperm DNA, which is tightly packed with protamines, undergoes decondensation, and is wrapped around nucelosomes and forms the male pronucleus (62). In addition, global DNA demethylation occurs in male pronucleus; this is active and rapid, and in the female pronucleus this is passive and slower, and epigenetic reprogramming commences. Roughly 150 genes are considered "imprinted" in that their methylation pattern (to suppress the expression of a gene) is determined by the parent of origin of the gene, and they retain their methylation pattern (260). Mitochondria that originate in the sperm are destroyed in early embryonic development, to prevent mitochondrial heteroplasmy (73).

Under the influence of the microtubules of the sperm aster (a star-shaped structure derived from the centriole of the mid-piece of the sperm), the pronuclei migrate towards the center of the oocyte (296). Syngamy is the point at which the pronuclei come together and break down completing fertilization, and subsequently the centrioles duplicate and migrate around the zygote nucleus to form opposite poles of the first mitotic spindle and commence the first cleavage (296). Early embryonic cleavage and development is regulated by mRNA transcripts and proteins within the ooplasm, and by cell division over the subsequent days with activation of the embryonic genome develops to a blastocyst of ~100 blastomeres (196).

Table 1. *Differences between fallopian tube and uterine secretion for mammalian embryos*

Component	Oviduct	Uterus
Glucose concentration, mM	0.5	3.15
Pyruvate concentration, mM	0.32	0.10
Lactate concentration, mM	10.5	5.2
Oxygen concentration, %	8	1.50
Carbon dioxide concentration, %	12	10
pH	7.5	7.1
Glycine concentration, mM	2.77	19.33
Alanine concentration, mM	0.5	1.24
Serine concentration, mM	0.32	0.8

From Lane and Gardner (191), with permission.

D. Fallopian Tube Function

The fallopian tube is derived from the Müllerian duct and averages 11 cm in length; however, it is made of four distinct regions with differing functional significance: the infundibulum and fimbria (for oocyte capture), the ampullary region (fertilization occurs at the junction with the isthmus), the isthmus, and interstitial portion of the fallopian tube (regulating the release of the embryo into the endometrial cavity), and each region has differing secretions for the nutrition of the early embryo and for capacitation and sustenance of the sperm (294). The tube is responsible for the transport and nutrition of the gametes and early embryo, by muscular contractions and ciliary action (204). As described, it is the site of fertilization and for the collection of the released oocyte, and its secretory activity, cyclical morphology, and contractility are related to the hormonal environment. In the early stages of embryo development, the fallopian tube secretion is low in glucose and has relatively high levels of pyruvate and lactate, the inverse of the uterine environment (see **TABLE 1**), a fact that is mirrored in the development of commercial embryo culture media for IVF treatment to mimic the in vivo early embryo environment by using sequential culture media as the embryo develop to the blastocyst stage (191). For a detailed review of the physiology of the fallopian tube, please refer to References 7, 16, 191.

E. Implantation

The endometrium is prepared for implantation under the influence of estrogen and progesterone; however, only approximately half of all embryos that are generated will implant and proceed to a successful on-going pregnancy (368). The window of implantation is limited to a receptive win-

dow between 7 and 10 days after ovulation when the endometrium has undergone secretory morphological changes in preparation for implantation with the development of apical epithelial protrusions-pinopodes (236, 265) and is protected against blastocyst attachment until the appropriate time by Muc-1 and facilitated by $\alpha_v\beta_3$ and $\alpha_4\beta_1$ integrin expression (134). Implantation is characterized by three phases: apposition, adhesion, and invasion into the decidualized endometrium. Decidualization describes the morphological and functional changes occurring within the endometrial stromal cells in response to progesterone in preparation for embryo implantation. Apposition of the blastocyst trophectoderm occurs with the inner cell mass directed towards the epithelium. Factors that are believed to be important in implantation and the appropriate endometrial changes are as follows: LIF, IL-1, colony stimulating factor, L-selectin, Wnt, Hoxa10/11, heparin binding epidermal growth factor, and bone morphogenic protein 2, in addition to cell adhesion molecules and glycoproteins, and it is believed that signaling from the embryo is crucial to trigger this process of endometrial decidualization (for a detailed review, see Refs. 54, 85, 134). The trophoblast cells then degrade the extracellular matrix and invade into the endometrial epithelium, basal lamina, and the stroma and placental formation commences.

III. PATHOLOGICAL PROCESSES, THEIR IMPLICATIONS, AND THERAPEUTIC OPTIONS

A. Folliculogenesis

1. Genetic

Premature ovarian insufficiency (POI) occurs in ~1% of women and is defined as the cessation of menstrual cycles under 40 years of age in the presence of an elevated serum FSH measured on two separate occasions (128). The causes may be genetic (107), environmental, infective (subsequent to mumps infection), associated with autoimmune conditions, metabolic [due to biochemical damage in the presence of galactossaemia (174)], and subsequent to cancer therapy (138) or surgery (230); however, in the majority of cases no cause is determined (128). A positive family history exists in 10–15% of cases with the suggestion that inheritance is autosomal dominant sex-linked or X-linked with incomplete penetrance (357). For a detailed review of the genetic mutations associated with premature ovarian insufficiency, please see Fortuno and Labarta (107). There are in excess of 20 genes on the X chromosome, particularly involving the critical region of the short arm of the X chromosome between Xp21.1 and Xp22.1.22 and the long arm regions Xq13.3-Xq21.1 and Xq26-Xqter (107), and well over 50 autosomal genes related to POI.

Possibly the most common genetic cause of POI is Turner syndrome (347) characterized by the loss of all, or part of an X chromosome, occurring in ~1 in 3,000 female births (336). Approximately half due to X chromosome monosomy and the majority of the remainder due to mosaicism (336). This is a condition with several phenotypic features characterized by short stature, cardiac and renal abnormalities, hypothyroidism, webbed-neck, and otological and ophthalmological abnormalities are all common in childhood (336). The ovarian insufficiency commonly found in this condition relates to disruption of the *BMP15* gene locus located at Xp11.2, within a critical region related to ovarian failure (254, 391). Spontaneous puberty occurs in approximately one quarter of girls, more commonly in mosaics; however, premature ovarian failure is universal.

Another common genetic cause of POI is related to the fragile X mental retardation protein, occurring in 3–15% of patients with POI (373). In this condition there is an expansion of the CGG triplet repeats of the *FMR1* gene at Xq27.3, and in the presence of more than 200 repeats the condition fragile X syndrome occurs. This is a severe form of mental retardation and autism; however, in the presence of the premutation of 55 and 200 triplet repeats, premature ovarian failure results (373).

The fertility options for women with premature ovarian insufficiency are essentially restricted to oocyte donation treatment only. This is a reliable and effective treatment provided the woman has been assessed as medically fit and suitable for assisted reproduction and she has adequate uterine and endometrial development, which may be lacking in some women with POI (150).

This therefore raises the specter of attempts to preserve fertility in women where it would be expected that there is a premature depletion of oocytes; such as in Turner syndrome or galactossaemia for instance. Attempts have been made by the freezing of ovarian cortical tissue for young adolescent girls or by the collection of stimulated mature oocytes as part of an IVF cycle for older girls; however, due to the restricted oocyte number, these techniques are not routine and have had to date limited success (150) but may offer promise in the future (242). Furthermore, when a woman with Turner syndrome commences fertility treatment in view of the associated increased risk of cardiovascular-related mortality in pregnancy, they should be cared for under specialized care, and indeed, Turner syndrome should be considered a relative contraindication to pregnancy (266).

B. Ovulation

1. Hypogonadotrophic hypogonadism

Insufficient ovarian stimulation with gonadotrophins LH and FSH results in the condition of hypogonadotrophic hypogonadism (HH), either due to insufficient hypotha-

lamic GnRH stimulation of the pituitary or due to insufficient secretion due to pituitary compromise. After exclusion of excessive exercise, extreme stress, or an eating disorder, and after ensuring pituitary function, other than secretion of LH and FSH, is normal, and pituitary imaging is normal the condition is considered idiopathic HH (IHH) (194). The most common cause of GnRH insufficiency is the failure of migration of the GnRH secretory neurons to the forebrain which may also result in olfactory disorder (Kallman's syndrome); in the absence of olfactory, the condition is described as normosmic IHH (354). The inheritance is either X-linked (*KAL* genes), autosomal dominant or autosomal recessive, and the condition is usually detected in adolescence with a delay or absence of pubertal development, with in excess of 20 genes implicated in this condition to date (194). Kallman's syndrome is characterized by HH and anosmia and is most commonly caused by mutations of the *KAL-1, KAL-2*, and *KAL-6* and are all implicated in interference with the neuronal migration associated with HH and anosmia, in addition to other abnormalities (354). Mutations of the *GnRH1* gene encoding GnRH are very rare; however, mutations of the *GnRHR* gene (4q13.2–3) encoding the GnRH receptor are more common and lead to variable expression of the phenotype (354). The *KISS1* gene encodes kisspeptins which stimulates GnRH release, its receptor is coded for by the *GPR54* gene, and hence mutations of either gene will lead to variable expression of IHH either in childhood or adulthood. In addition, the *TAC3* gene codes for NK3R which also stimulates GnRH neurons, mutations of which lead to perturbed GnRH secretion and hence insufficient LH and FSH secretion. In addition, mutations in the leptin gene, *Ob*, the LH and FSH β subunits, *LHB* and *FSHB*, are rare but are associated with hypogonadism. For a more detailed review of the genetics associated with IHH and Kallman's syndrome, see Valdes-Socin et al. (354) and Layman (194).

2. Hyperprolactinemia

Other central causes of HH can be caused by systemic disease, medication (such as opioids and psychotropic medication), hypothalamic or pituitary compression, or infiltration; however, the most common cause is probably hyperprolactinemia. Hyperprolactinemia may be caused by physiological states such as pregnancy, breastfeeding, stress, exercise, and some medications as well as patients with chronic hypothyroidism. Kidney disease may predispose a patient to hyperprolactinemia due to reduced clearance and altered prolactin metabolism. As prolactin secretion is suppressed by hypothalamic dopamine secretion, interruption or compression of the pituitary stalk by a non-prolactin-secreting pituitary tumor will lead to hyperprolactinemia. Furthermore, prolactin secreting adenomas, either a micro (<10 mm) or a macro adenoma (>10 mm in size), lead to prolactin inhibition of gonadotrophin secretion and anovulation (214).

3. Polycystic ovary syndrome

The polycystic ovary syndrome (PCOS) is a collection of signs and symptoms related to ovarian dysfunction, found within a phenotypically heterogeneous group of women. It is classically described by the Rotterdam criteria (285) as a syndrome consisting of two of three criteria related to infrequent or absent ovulation, a morphological description of the ovaries by ultrasound assessment, and hyperandrogenism. Other groups suggest that the excessive androgen secretion is the most significant underlying pathology as this is believed to lead to ovarian dysfunction and the longer term metabolic consequences these women experience (140), and they consequently adopt a more stringent definition of PCOS (19, 382).

The etiology of PCOS is unclear with putative causes being a genetic predisposition modulated by hyperinsulinemia or the early life environment, as there is very good evidence from animal models for a programming effect of early life exposure to androgens (1). The phenotype of PCOS is modulated by the presence of obesity, which also exacerbates the metabolic features of PCOS (226). From genome-wide association studies (GWAS), potential loci for PCOS have been identified at 9q22.32, 8p23.1, and 11p14.1 and single-nucleotide polymorphisms (SNPs) of the gonadotrophin receptors and the androgen receptor (102), and several other SNPs have been identified (18). A SNP at 11p14.1 was associated with PCOS and elevated serum LH concentration, a frequently observed feature in PCOS. Other genes believed to be associated with the development of PCOS relate to genes involved with insulin signaling and the epidermal growth factor receptor (for review, see Ref. 18). There is evidence from both human and animal studies that supraphysiological maternal androgen levels may lead to disordered folliculogenesis in female offspring with a PCOS phenotype (1, 106, 281). Animal models of PCOS have been generated with rodents (363), sheep (281), and monkeys (1) by early life exposure to supraphysiological androgens, leading to the development in the female of offspring of hyperandrogenism, hyperinsulinemia, LH hypersecretion, and ovulatory disorder. In humans, evidence from early life exposure to hyperandrogenemia in conditions such as congenital adrenal hyperplasia can lead to the development of PCOS like features (24). However, the impact of variations in maternal androgens within the normal physiological range is less well understood. One study measured maternal circulating total serum testosterone concentration at 18 wk of gestation and demonstrated a significant positive association with early follicular phase circulating AMH in female offspring in adolescence (147), but not PCOS per se (151). Serum AMH is secreted from the granulosa cells within preantral and small antral follicles and is elevated in both adolescents (142) and women with a polycystic ovarian morphology and PCOS (257). During normal pregnancy,

the fetus is protected from maternal androgens by placental aromatase. However, it is possible that placental dysfunction may expose the fetus to higher concentrations of androgens, or with the suppression of sex hormone binding globulin by hyperinsulinemia the concentration of free testosterone maybe increased. The association of bisphenol A (BPA) as a potential environmental cause of PCOS is discussed in section V.

It is believed that oocyte developmental competence and the embryos resulting from fertilization are altered in women with PCOS, compared with women without PCOS (91). There are multiple serum and follicular factors that are reportedly altered in women with PCOS that may be responsible for this poor embryonic development and reduced implantation (summarized by Qiao and Feng, see **FIGURE 3** and **TABLE 2**), although it is not clear whether this is associated with an increase in the rate of embryo aneuploidy (268). Not only is the systemic and follicular environment different in PCOS, the gene expression profile of oocytes derived from women with PCOS are distinctly different (91). These genes relate to signal transduction, transcription, RNA and DNA processing, and the regulation of the cell cycle [summarized by Dumesic and Abbott (91)]. Of particular importance in the acquisition of oocyte developmental competence is GDF-9 expression, which is reduced in the oocytes of women with PCOS (342).

The ovulatory disorder is frequently exacerbated by hyperinsulinemia, which is present in well over 50% of women with PCOS (225), and is further accentuated by central obesity, and hence lifestyle modification programs should be the first intervention strategy (88). The elevated endogenous serum insulin promotes ovarian androgen secretion, via IGF-I receptor activation of theca cell androgen secretion (317) and perturbs folliculogenesis (292). Second-line therapies consist of using the insulin sensitizer metformin, which leads to a reduction in androgen secretion, by effects on steroidogenic acute regulatory protein and 17β-hydroxylase, and inhibits FSH and induces aromatase activity in granulosa cells (277). Specifically metformin increases insulin sensitivity by decreasing gluconeogenesis and lipogenesis and enhancing glucose uptake by the liver, skeletal muscle, and adipose tissue (231). Other approaches are the use of the selective estrogen receptor modulator clomiphene citrate which leads to increased pituitary FSH secretion, exogenously administered FSH itself on an incrementally increasing regime according to response (311), and the use of aromatase inhibitors which lead to increased pituitary FSH secretion by negative feedback in response to the reduced estradiol production (155, 197, 220–222). A systematic review of the pharmacological interventions for women with PCOS was performed in 2011 and updated in 2015, and the findings are listed below (9, 341) (see **TABLE 3**). The purpose of these therapies is to induce monofollicular ovulation in the anovulatory woman, or to overcome a subtle progesterone deficiency in the luteal phase of the menstrual cycle, under strict ultrasound and serial serum estradiol assessment to ensure single follicle development and adequate endometrial thickness, and to prevent conceiving a multiple gestation (23). This approach often requires the initiation of ovulation when the dominant follicle size has reached 18 mm, by the use of exogenously administered hCG, as an LH substitute, due to the close homology of the beta chains (37). However, women with PCOS may ultimately be required to undergo IVF treatment, either as they have been unsuccessful with the treatment to date or they are required to embark on IVF

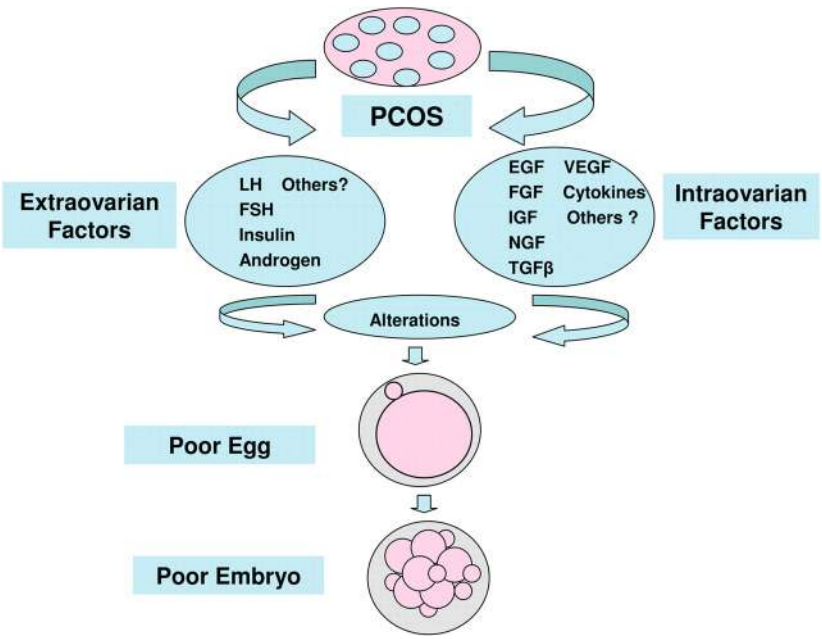

FIGURE 3. Intra- and extra-ovarian factors that are associated with the pathology PCOS that may negatively influence oocyte and subsequent embryo quality. [From Qiao and Feng (237), with permission from Oxford University Press.]

Table 2. *Factors in serum and follicular fluid of patients with PCOS with an impact on the quality of the oocytes and embryos, oocyte fertilization, and the outcome of pregnancy*

Factors	Serum Level	Follicular Fluid Level	Oocyte Quality	Fertilization Rate	Embryo Quality	Pregnancy Rate
Activin	↓	↓				
AMH	↑	↑	↑ or ↓	↑ or ~ or ↓	↑ or ~	↑ or ~
Epidermal growth factor		↑				
Fibroblast growth factor	↑ or ↓	↑ or ↓	~ or ↓	~	~	
Follistatin	↑	↑				
Brain-derived neurotrophic factor		↑				
Bone morphogenic protein-15		↑	↑	↑	↑	
Estradiol	↓	↓	↓	↓	↓	
Follicular fluid meiosis-activating sterol		↑	↑	~	~	
Growth differentiation factor-9		↑	↓			
Homocysteine	↑	↑	↓	↓	↓	
Insulin-like growth factors I & II	↓	↓	↓			
IGF binding protein	↑	↑	↓			
Interleukin-12		↓	↓	↓	↓	
Interleukin-13		↓	↓	↓	↓	
Inhibin A & B		↓ or ~	~			
Corticotrophin releasing hormone		↓	↓			
Leptin	↑	↑	↓	↓	↓	↓
Leukemia inhibitory factor		↓	↓	↓	↓	↓
Malondialdehyde	↑	↑	↓	↓	↓	
Matrix metalloproteinase 2/9		↑ or ~				
Nerve growth factor		↑ or ↓				
Renin	↓	↓	↑	↑	↑	
Resistin	~	~	~	~		~
Reactive oxygen species		↑	↓	↓	↓	↓
Soluble Fas	↓	↓	↓			
sFas ligand	↑	↑	↓			
Superoxide dismutase	↓ or ~	↓ or ~				
Total antioxidant capacity	↓	↓	↓	↓	↓	↓
Testosterone	↑	↑	↓			
Tissue metalloproteinase 1 & 2		↓ or ~				
Tumor necrosis factor	↑	↑	↓	↓	↓	↓
Vascular endothelial growth factor	↓ or ↑	↓ or ↑	↓	↓ or ~	↓	↓
Visfatin	↑	~				

↑, Increases or positive impact; ↓, decreases or negative impact; ~, similar; blank, no data. All data are as compared with controls patients without PCOS. [Modified from Qiao and Feng (237), with permission from Oxford University Press.]

treatment as either their fallopian tubes are compromised or their partner has suboptimal semen parameters. If a woman embarks on IVF treatment, she is at particular risk of developing an idiosyncratic reaction called ovarian hyperstimulation syndrome (OHSS) (267).

OHSS is triggered by the systemic release of inflammatory cytokines, particularly VEGF which leads to endothelial cell damage and increased vascular permeability and the rapid development of ascites, and potentially pleural and pericardial effusion (338). OHSS is a significant cause of morbidity and in Australia and New Zealand is reported to complicate 0.6% of IVF cycles (206). Adjuvant therapies that have been demonstrated to significantly reduce the incidence are the use of an GnRH antagonist for pituitary downregulation (378), particularly with the use of an GnRH agonist trigger (381), the VEGF receptor blocker cabergoline (338), and by combing the ovarian stimulation with metformin administration (346). Other strategies include using low doses of gonadotrophin drugs for stimulation or omitting completely (8), cancelling the IVF cycle prior to oocyte retrieval, omitting the gonadotrophin drugs for a few days–"coasting" (75) and not proceeding to an embryo trans-

Table 3. *Pharmacological options for women with PCOS who are trying to conceive*

Evidence Statement	Level of Evidence
Clomiphene citrate should be the first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility, with no other infertility factors.	A
The risk of multiple pregnancy is increased with clomiphene citrate use, and monitoring is recommended.	PP
Metformin should be combined with clomiphene citrate to improve fertility outcomes rather than persisting with further treatment with clomiphene citrate alone in women with PCOS who are clomiphene citrate resistant, anovulatory, and infertile with no other infertility factors.	A
Metformin could be used alone to improve ovulation rate and pregnancy rate in women with PCOS who are anovulatory, have a body mass index = 30 kg/m, and are infertile with no other infertility factors.	B
If one is considering using metformin alone to treat women with PCOS who are anovulatory, have a body mass index = 30 kg/m, and are infertile with no other infertility factors, clomiphene citrate should be added to improve fertility outcomes.	A
Gonadotrophins should be the second-line pharmacological therapy.	B
Laparoscopic surgery in women who are overweight or obese is associated with both intraoperative and postoperative risks.	PP
Letrozole, under caution, could be offered as a pharmacological treatment for ovulation induction indicated for infertile anovulatory women with polycystic ovary syndrome with no other infertility factors.	A

A, body of evidence can be trusted to guide practice; B, body of evidence can be trusted to guide practice in most situations; C, body of evidence provides some support for recommendation but care should be taken in its application; PP, evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations. Adapted from *Evidence Based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome*. Melbourne, Australia: Jean Hailes for Women's Health on behalf of the PCOS Australian Alliance, 2015.

fer (so-called "freeze-all" approach) (284). A further innovation is to use a different stimulation approach called in vitro maturation of oocytes (IVM) where no final trigger for oocyte maturation is administered prior to oocyte retrieval and oocyte maturation is performed in the laboratory with some centers reporting similar pregnancy rates as their standard IVF approach (362) without the risk of OHSS. The evidence for some of the therapeutic interventions employed for women with OHSS is not robust and hence for the prevention of OHSS clinicians are advised to follow guidelines provided by consensus statements after systematic review of the literature (189).

The deranged metabolic environment frequently present in women with PCOS is believed to lead to altered decidual trophoblast invasion, placental development and endovascular changes at the site of implantation (247), and increased circulating markers of oxidative stress (229). Proportionate to the degree of hyperinsulinemia and hyperandrogenemia, women with PCOS have abnormalities of homocysteine metabolism (130), correctable with adequate folate intake. Other systemic changes prevalent in women with PCOS, influencing conception and miscarriage, are an elevated serum plasminogen activator inhibitor-1 (124) and an abnormal expression of some molecular markers with the endometrium, including insulin-like growth factor binding protein-1, glycodelin, homeobox protein (HOXA 10), and a endometrial progesterone resistance (53, 249, 295, 306). The consequences of this disturbed systemic and endometrial environment is a reduced chance of conception, an increased risk of miscarriage, and in pregnancy a predisposition to growth restriction, preeclampsia, and prematurity (41, 87, 269).

C. Fallopian Tube Function

1. Disorders of ciliary action

The fallopian tube as a conduit for sperm and embryos relies on effective cilial activity to perform these tasks. The fallopian tube cilia can be affected by the environment, mainly related to infection and inflammation; however, a primary disorder of ciliary structure and function will also lead to impaired tubal transport and a predisposition to ectopic gestation implantation and subfertility. Primary ciliary dyskinesia (PCD) is associated with recurrent respiratory tract infections and potentially situs invertus. This is a very heterogeneous condition as there exist many differing structural and functional defects within the cilia, related to as yet many unidentified genetic defects; however, over 20 genetic mutations related to axonemal-dynein function have been identified (188) and in addition mutations within the retinitis pigmentosa GTPase regulator on the X chromosome have been found in men with this condition and PCD. Due to the tissue specific expression of the multiple genes responsible for PCD, not all women with the respiratory phenotype of PCD have impaired fallopian tube ciliary function, and spontaneous conceptions have been reported (99).

Table 4. *Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines for the management of fibroids, derived after systematic review of the literature*

The majority of studies relate to the impact of fibroids on fertility outcomes of women undergoing IVF treatment
1) Subserosal fibroids (the majority of the fibroid is on the exterior of the uterus) do not appear to have an effect on fertility outcomes.
2) Intramural fibroids (within the muscle wall of the uterus) may be associated with reduced fertility and an increased miscarriage rate; however, there is insufficient evidence to determine whether myomectomy will improve fertility outcomes.
3) Submucosal fibroids (a portion of the fibroid is within the endometrial cavity) are associated with reduced fertility and an increased miscarriage rate; hysteroscopic resection of submucosal fibroids is likely to improve fertility outcomes. (Quality of studies is poor, and further research is required.)
The size of the fibroid, the number, and their location within the uterus may impact on the utility of myomectomy.

Adapted from the RANZCOG guidelines, on behalf of the CREI Consensus Expert Panel on Trial evidence group.

Cystic fibrosis (CF) is a condition characterized by abnormal mucus secretion due to being homozygous, or a compound heterozygote, for one of the >1,900 mutations in the CF transmembrane regulator gene, limiting chloride and bicarbonate secretion (3). In addition to the associated symptoms of ovulatory disorder relating to poor general health and low body fat levels, CF is associated with female subfertility due to a direct effect on the epithelial cells of the reproductive tract, although not directly on cilial action. The thick cervical mucus impairs sperm penetration, although it is believed that the effect on the uterine cavity and the fallopian tube function is less significant (3), although the influence on bicarbonate metabolism may lead to problems with sperm capacitation within the fallopian tube (55).

2. Inflammatory disorders: endometriosis and infection

Inflammation within the fallopian tube due to extrinsic infection, salpingitis, or salpingitis isthimica nodosa (nodular thickening or scarring of the fallopian tubes within the isthmic fallopian tube) may lead to an activation of an inflammatory cascade via the innate immune system, within the tubal fluid and leading to fallopian tube damage from the inflammatory response, and inhibition of ciliary beat frequency (250). Salpingitis may lead to distal occlusion of the fallopian tube and permanent deciliation. The most common cause of salpingitis is pelvic inflammatory disease (PID), due to sexually transmitted infection. Hence, the risk factors for PID are multiple sexual partners, young age, smoking, and illicit drugs (223). The most common infection agent is *Chlamydia trachomatis* (CT), and it is believed that genetic polymorphisms within the Toll-like receptor genes may increase the susceptibility to upper genital tract infection, as not all women with cervical chlamydial infection will have detectable infection within the endometrium and fallopian tubes (223). CT appears to initiate a fallopian tube inflammatory response via the innate immune inflammatory response and also an adaptive T-cell response (76), and ongoing chlamydial infection is common (204), leading to continued influx of inflammatory cells, damage to host epithelium, scarring, and ultimately fibrosis and progressive tubal scarring. Furthermore, CT causes a direct cytotoxic effect on the fallopian tube mucosa (204). With increased screening of young women by cervical swabs for CT, and commencement of prompt treatment of early cervical infection in most Western countries, it is proposed that this will lead to a reduction in the incidence of PID, and consequently fallopian tube damage (244). Other fallopian tube pathogenic organisms include *Neisseria gonorrhoea*, which was traditionally the most common responsible pathogen in Western countries. In many instances the pelvic infection and the resulting fallopian tube damage may be exacerbated by the anaerobic bacterial agents often associated with bacterial vaginosis (223).

Endometriosis is another pathological pelvic inflammatory process that is known to inhibit ciliary beat frequency (203), and in severe disease leads to significant pelvic scarring and pelvic anatomy distortion, and hence is associated with doubling in the incidence of ectopic pregnancy (152), in addition to the negative impact on endometrial receptivity (discussed later). PCOS has also been associated with a doubling of the rate of ectopic pregnancies, although no mechanism has been proposed (140).

3. Other gynecological conditions

Gross anatomical distortion of the fallopian tubes, either due to extrinsic compression by large uterine fibroids and ovarian cysts, or by mechanical distortion of the fallopian tube itself by severe adhesions, fibrosis due to chronic inflammation may lead to compromise of the fallopian tube contractility and potentially cilial function. The implications of fibroids for conception and the therapeutic options for intervention have undergone systematic review (186), and a summary of the most recent review of the literature is listed in **TABLE 4**. The medical and surgical interventions for women trying to conceive with endometriosis have undergone systematic review, and the overview published in 2014 (44) is summarized in **TABLE 5**.

Table 5. *Medical and surgical interventions for women with endometriosis seeking fertility treatment*

Intervention	Influence of Intervention	Number of Studies	Grade Quality of Evidence	Assessment of Studies
Ovulation suppression versus placebo (4)	There is no evidence of benefit in the use of ovulation suppression in subfertile women with endometriosis who wish to conceive.	11 (557 patients)	Low	Lack of explanation for allocation concealment and blinding.
Long downregulation of pituitary with a GnRH agonist versus no agonist (5)	The administration of GnRH agonists for a period of 3–6 months prior to IVF in women with endometriosis increases the odds of clinical pregnancy fourfold.	3 (165 patients)	Very low	Included studies lacked blinding and explanation of allocation concealment. There was some imprecision.
Excisional versus ablative surgery for endometriomata (3)	Excisional surgery for endometriomata provides a more favorable outcome than drainage and ablation with regard to subsequent spontaneous pregnancy in women. However, in women who may subsequently undergo fertility treatment, insufficient evidence exists to determine the favored surgical approach.	2 (88 patients)	Low	Included studies lacked blinding and there was some imprecision.
Laparoscopic ablation or excision versus diagnostic laparoscopy (2)	Laparoscopic surgery for mild and moderate endometriosis was associated with a doubling live birth rate than diagnostic laparoscopy alone.	3 (528 patients)	Moderate	Two studies did not adequately describe randomization; one study was at high risk of attrition bias.

Extract adapted from Brown and Farquhar (44).

D. Embryonic Development

The human embryo is prone to chromosomal errors during development. It is believed that at the blastocyst stage (reached at the 5th or 6th day after fertilization) that three-quarters of embryos of a 30-yr-old woman will be normal; however, at 40 years of age, only 40% are normal (109). The centrosome, responsible for the subsequent spindle and microtubule development within the embryo, is derived from the sperm, hence men with significant impairment in spermatogenesis, and oligospermia, may be responsible for higher rates of aneuploidy (the gain or loss of whole chromosomes) within the subsequent embryo (209, 339). However, the most common cause of embryo aneuploidy is related to female age as the oocyte has been in a stage of arrested meiotic development in prophase since early fetal life, hence as a woman ages and is exposed to reactive oxygen species within the environment, there is a progressive loss of cohesion molecules that hold sister chromatids together, the incidence of aneuploidy increases exponentially (114), particularly the chiasmata proximal to the telomere (208). This is exacerbated by deterioration in cytoplasmic mitochondria and mRNA stores (369). This all leads to the subsequent substantial increase in the rate of miscarriage with increasing age **(FIGURE 4)**.

A significant initiator of aneuploidy which is independent of maternal age is the lack of chromosomal recombination in the fetal stages of meiosis. To prevent chromosome missegregation, it is essential that at least one crossover (recombination) is formed by recombination of each

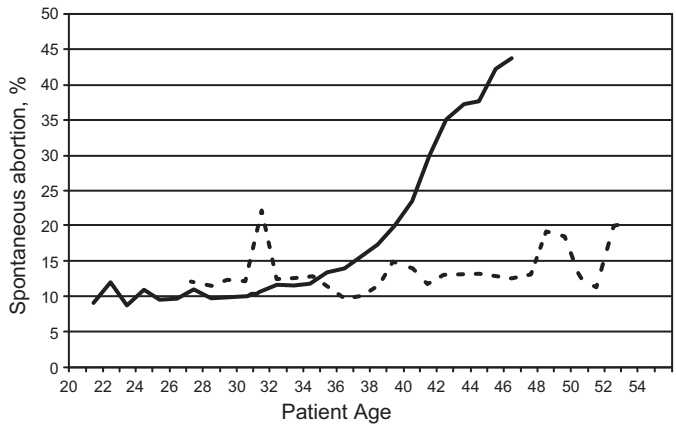

FIGURE 4. Spontaneous abortion rates for assisted reproductive technology pregnancies conceived with freshly fertilized embryos by source of oocytes used and maternal age. The solid line indicates pregnancies conceived with the patient's oocytes, and the dashed line indicates pregnancies conceived with donor oocytes. [From Schieve et al. (298), with permission from Wolters Kluwer Health, Inc.]

pair of homologous chromosomes (for review, see MacLennan et al., Ref. 208). It is estimated that ~30% of Down syndrome births are as a result of lack of recombination between homologous chromosomes 21, as the most common chromosomes prone to lack crossover within fetal oocytes are chromosomes 21 and 22 (58). Furthermore, the distance from the centromere that the single cross-over are located also determines the risk of aneuploidy, and again appears independent of maternal age. Chiasmata close to the telomere are at greatest risk of being lost as there exists less cohesion between the chromosomes predisposing to missegregation.

Embryonic mosaicism is a common finding resulting from abnormal chromosome segregation either within meiosis or mitosis due to *1*) a failure of the process whereby microtubules pull the divided chromosomes towards their respective spindles prior to cytokinesis and cell division "nondisjunction"; *2*) "anaphase lag" whereby a chromatid is not incorporated into the nucleus during mitosis, thus creating two-cell lines, one monosomic for the chromosome and the other disomic for the chromosome; and *3*) chromosomal gain by "endo-replication" (339). A further process that leads to a mosaic embryo is uniparental disomy where an embryo has two copies of either a maternally derived or paternally derived chromosome, rather than one from each (339). The earlier in development that mosaicism develops, the more significant is the implication for the developing embryo; however, it is possible that abnormal cells can be forced away from the embryo, effectively being "selected against" (330, 339).

The recent innovation of embryo morphokinetics using time-lapse imaging systems for use with IVF laboratories has enabled scientists to document abnormal embryonic development (216). However, individual laboratories will have differing culture systems, hence may have different findings, although the staging system proposed by Meseguer is one of the most widely used (216). This group demonstrated that the most predictive parameters of embryo implantation potential were the time between division to two cells and division to three cells, the time between division to three cells and subsequent division to four cells, and the time of division to five cells (114, 216). They also demonstrated that the abnormal features of uneven blastomere size at the two-cell stage and abrupt cell division to three or more cells, and multi-nucleation at the four-cell stage resulted in embryos that would not implant. Incorporation of these features into a randomized controlled trial to improve IVF outcomes demonstrated an increased on-going pregnancy rate and reduced miscarriage rate when embryos were selected using this algorithm (287).

The abnormal embryo may also display an abnormal metabolism that can be detected within the culture media within the IVF laboratory, either by proteomics of the secretome or by metabolomics to study the rate of consumption of carbohydrates, oxygen, and amino within the culture media and consequently assist with improved embryo selection during IVF treatment (114, 115).

E. Implantation

1. Systemic

It is generally believed that severe systemic illness, such as sepsis or severe renal disease, will prevent embryonic implantation, although infection is an unusual cause of early pregnancy failure (315, 318). A comprehensive list of all systemic conditions that have been demonstrated to have a significant negative influence on embryonic implantation is difficult to compile; however, conditions such as unstable diabetes (64), subclinical hypothyroidism (356), periodontal disease (144), and uncontrolled celiac disease (343) have been demonstrated to reduce rates of conception, and it is believed that low serum vitamin D (199) and active autoimmune conditions (304) are also associated with a reduced chance of conception, and strategies to control these conditions may improve conception chances. Due to their high prevalence and ease of correction of the abnormality, celiac disease and subclinical hypothyroidism are discussed further.

2. Celiac disease

In a population of women experiencing unexplained infertility or recurrent miscarriage, celiac disease is five times more prevalent than in the general population (343). A meta-analysis of patients with celiac disease found that the risk of miscarriage is 40% greater with increased risks in the pregnancy for growth restriction and premature delivery, and the effect is tempered if a gluten-free diet is observed (343).

3. Subclinical hypothyroidism

Overt thyroid disorder must be appropriately managed prior to conception; however, more subtle perturbations in thyroid function are also associated with reproductive disorder. Approximately 1 in 25 women have subclinical hypothyroidism, and thyroid antibodies are present in up to one in eight of women (153). The presence of thyroid antibodies in a woman with normal thyroid function is believed to be associated with difficulty conceiving, recurrent implantation failure of embryos, and early pregnancy loss, potentially due to an unrecognized thyroid hormone deficiency or due to a potential autoimmune cause (359). Treatment of subclinical hypothyroidism is believed to potentially improve embryo development and is recommended for women prior to conception; however, whether to treat a

woman prior to conception, who is euthyroid in the presence of thyroid antibodies, is contentious (77).

4. Thrombophilia

It has been unclear whether an inherited thrombophilia leading to microthrombi within the decidua are associated with implantation failure of the embryo as the intervillous spaces are not developed until 10 wk of gestation (164). Although it is tempting to speculate that perturbations in the clotting system may influence implantation and early embryonic development, for example, factor XII gene expression is increased in endometrial stromal cells during in vitro decidualization, this is believed to lead to an activation of the kallikrein-kininogen-kinin system during the implantation of human embryos (175). Furthermore, plasminogen activator inhibitor (PAI-1) is a significant regulator of the thrombotic/fibrinolytic process in early pregnancy and is elevated in insulin resistant women with PCOS (17). Other changes within the clotting process around the time of embryo implantation are an increase in tissue factor, an activation of the extrinsic coagulation cascade, and an increase in requirement for methylation from folic acid. Hence, inherited abnormalities of the clotting system such as the prothrombin gene mutation, factor V Leiden, methyltetrahydrofolate reductase (MTHFR), and protein S and C and anti-thrombin III would be expected to have a significant influence on implantation and the early pregnancy (164). Although the appropriate treatment is not clear, except for women with the anti-cardiolipin syndrome, where appropriate treatment must commence at conception is widely accepted (274).

Due to the effect of heparin on modulating endometrial receptivity and potentially improving implantation, in addition to its inhibition of factor Xa and thrombin, it has been proposed as a treatment for women with implantation failure undergoing IVF treatment (264). Heparin reduces the expression of E-cadherin and promotes trophoblast invasion and proliferation into the endometrial cells potentially improving implantation (95). A systematic review of women with recurrent implantation failure undergoing IVF demonstrated that use of adjunct low-molecular-weight heparin improved live birth rates, and the rate of miscarriage was substantially reduced compared with the control group (264). The authors advised caution with the interpretation of the results due to the low numbers in the studies.

5. Natural killer cells

There has been substantial interest in the assessment of blood and uterine natural killer cell populations in women with poor embryo implantation (305). Evidence would appear to suggest that women with unexplained implantation failure may have an abnormal population of natural killer (NK) cells in the blood and in the endometrium in the mid-luteal phase of the menstrual cycle (293), although strategies to improve the systemic and endometrial environment to facilitate conception have not been proven (305).

6. Endometrial and myometrial (endometriosis, leiomyomas, hydrosalpines, PCOS, obesity, endometrial polyps)

As evidenced by IVF success rates, embryonic implantation potential is decreased in the presence of endometriosis (25), leiomyomas (145), dilated fallopian tubes (hydrosalpines) (332), and PCOS (346) and have been linked to reduced endometrial expression of *HOXA10* and *HOXA11* (48). In addition, women with endometriosis have reduced expressions of endometrial integrin $\alpha_v\beta_3$ and *LIF*, hypermethylation leading to silencing of the *HOXA10* gene and endometrial progesterone resistance (48) leading to a reduction in the chance of conception which may potentially be improved by surgical intervention (90) or by use of prolonged downregulation with a GnRH analog prior to the initiation of an IVF cycle (291). Similarly to integrin $\alpha_v\beta_3$ expression normalizing with surgical intervention in the presence of endometriosis (200), the surgical removal of hydrosalpinges (salpingectomy) will restore the expression of integrin $\alpha_v\beta_3$ and *LIF* improving conception (332). Leiomyomas are common benign smooth muscle tumors of the myometrium, if they distort the endometrial cavity, a submucosal leiomyoma, implantation may be inhibited by a purely mechanical method. However, leiomyomas located in the body of the uterus (myometrium), intramural leiomyomas, may also mechanically inhibit conception implantation, but overlying endometrial atrophy and an altered endometrial environment has been demonstrated (48). Surgical intervention is believed to improve implantation potential for women with a submucosal leiomyoma; however, the case for treating small intramural leiomyomas to improve conception has yet to be proven (186). Due to the estrogenic stimulation required for the growth of leiomyomas, it has been speculated that their growth may be associated with environmental estrogenic stimulation, such as bisphenol A (BPA) (309); however, an observational study of the exposure to BPA, phthalates, and five ultraviolet filters was unable to confirm any direct association (262).

The endometrium of women with PCOS is abnormal as it is exposed to lower levels of serum progesterone in the luteal phase, the consequences of ovulatory disorder prevalent in women with PCOS. Furthermore, the endometrium is potentially exposed to elevated levels of serum IGF-I and serum androgens (140). Elevated IGF-I can lead to endometrial hyperplasia and a predisposition to endometrial malignancy; however, in contrast, the high serum androgens, often present in women with PCOS, can induce endometrial atrophy and amenorrhea. In addition, there is an increase in

estrogen receptor α, an increase in 17β hydroxysteroid dehydrogenase type 1, and a reduction in type 2 (promoting a greater local concentration of estradiol), in association with a degree of progesterone resistance promoting endometrial hyperplasia and leading to a decrease in fertility (306). In women with PCOS, there is a decreased endometrial secretory phase expression of selectins, integrin $\alpha_v\beta_3$, and *HOXA10* reducing the implantation potential of an embryo (306). A compounding factor for many women with PCOS is obesity which has a synergistic effect to reduce the chance of conception (29), leading to a greater perturbation in endometrial gene expression (29), as demonstrated by the association of an increase in BMI being associated with a reduced chance of conception using the oocyte donor model (81) [for a review, see Schulte et al. (302)]. However, lifestyle interventions with diet and exercise will lead to alterations in endometrial gene expression (348), although it is not clear whether the improved conception rates noted due to lifestyle interventions are due to an endometrial effect, an oocyte effect, or a combination of both.

Common benign overgrowths of the endometrium known as endometrial polyps may interfere with sperm transport and embryo implantation to mechanically inhibit conception, but they may promote the abnormal expression of markers of implantation; upon surgical removal of the endometrial polyps, documented increases in endometrial secretion of IGFBP-1, TNF-α, and osteopontin have been noted, assisting implantation (31).

7. Embryonic

With the advent of genetic testing of blastomeres from embryos of women undergoing IVF treatment, it has become evident that a significant cause of embryos failing to implant is due to chromosomal rearrangements developing within the embryo as described above (114). With the ability to perform a low-resolution genome-wide survey of either single blastomeres from a three-day-old embryo or by the study of several cells from the trophectoderm of a five- or six-day-old blastocyst, it has become evident that in addition to the common occurrence of aneuploidy within the embryo, usually arising during meiosis, the embryo is predisposed to segmental chromosomal imbalances (372) which arise during programmed DNA breakage and repair by homologous recombination during prophase I of meiosis (360). These rearrangements may lead to a failure to develop and implant, but also lead to phenotypic variability and hence ultimately genome evolution [for a detailed description of the origin of chromosomal rearrangement, see Voet et al. (360)]. Hence, in IVF programs the majority of apparently morphologically normal embryos fail to implant as aneuploidy is such a frequent occurrence, occurring more frequently in an older woman, and a woman with a history of failed embryonic implantation (371).

A less frequent cause of unsuccessful embryo development and implantation, or implantation then subsequent early pregnancy failure, is the prevalence of a chromosomal translocation within either one of the couple trying to conceive. The prevalence of a chromosomal translocation within a couple with a history of failed implantation undergoing IVF treatment is 1.4%, substantially less than the 4.1% prevalence within couples with a history of recurrent miscarriages (329), but significantly greater than the 0.2 and 0.3% prevalence in neonatal and general infertility patients, respectively (329). Chromosomal translocations within a phenotypically normal prospective parent can be either a balanced reciprocal translocation, whereby there is an mutual exchange of genetic material from the distal end of two different chromosomes, or a Roberstonian translocation, wherein there is a fusion of the long arm of two of the acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22) and a resulting loss of the short arms. In both instances, the gametes resulting from these chromosomes can be "balanced" containing the appropriate amount of genetic material, or "unbalanced" and contain an excess or deficit of genetic material leading to miscarriage or a risk of congenital malformations in the offspring.

F. Early Pregnancy Failure

The causes of early pregnancy failure overlap with the causes of embryo implantation failure and hence are not reiterated here. The discussion is limited to a description of possible associations of genetic variations which may influence implantation and predispose to early pregnancy loss.

1. Genetic polymorphisms

Genetic polymorphisms associated with recurrent early pregnancy loss suggest that genes regulating oxidative stress may be involved (353). Single nucleotide polymorphisms of genes associated with oxygen free radical metabolism, *ABCB1*, *COMT*, *GPX4*, and *OGG1*, have been reported to lead to a doubling of the risk of recurrent miscarriage (177). In addition, polymorphism of genes that regulate the complement cascade, such as membrane cofactor protein and C4 binding protein, have a putative role in recurrent early pregnancy loss (353). HLA-G, part of the major histocompatibility complex class I group, has been linked to the success of IVF and is believed to have an immune modulatory role, and potentially lower expression of HLA-G is associated with reduction in embryo implantation and early pregnancy failure (353).

MTHFR is responsible for the synthesis of 5-methyltetrahydrofolate required to allow the conversion of homocysteine to methionine. Patients with the 677TT genotype are reported to have up to a threefold increased risk of recurrent early pregnancy loss (233).

Due to the putative belief that an imbalance of the tolerant [T helper cell1 (Th1)] over the prorejection [T helper cell 2 (Th2)] cytokines within the adaptive immune system for women predisposed to reproductive failure these cytokines have been studied. Of note, Th1 cytokines include IL-2 and interferon-γ (INFγ), and Th2 include IL-4, IL-5, IL-6, IL-10, and IL-13. Several haplotypes leading to a reduction in serum IL-18 levels have been associated with a significant increase in recurrent early pregnancy loss (4).

IV. LIFESTYLE INFLUENCES INFLUENCING OVULATION, FALLOPIAN TUBE FUNCTION, IMPLANTATION, AND MISCARRIAGE

A. Delayed Childbearing

It is well established that oocyte quality deteriorates with advancing reproductive age, in addition to an increase in ovulatory disorder, a reduction in ovulatory frequency, an impaired luteal phase and also premature recruitment of follicles, all leading to reduced conception rates.

1. Ovulatory frequency

As a woman ages, in line with a progressive reduction in follicle number, there is a progressive reduction in ovulatory frequency. This situation is also applicable to the woman with premature ovarian insufficiency where there is a reduction in functioning granulosa cells, leading to a reduction in secretion of inhibin B, further leading to a reduction in pituitary feedback there is an increase in late follicular phase and then early follicular phase FSH secretion (45, 46). This may lead to premature initiation of follicular recruitment and early ovulation, or if there are no follicles to recruit, a low rise in inhibin B and estradiol and a prolonged anovulatory menstrual cycle. Further follicular depletion leads to an increase in the frequency of anovulatory cycles. One study demonstrated that in the last 10 cycles before the menopause, approximately only one-third of the cycles will be ovulatory (190). The consequent impact on the chances of conception are the fact that that with premature follicular recruitment the timing of intercourse may be more difficult to plan and with impaired estradiol and progesterone secretion by the corpus luteum in the luteal phase, "luteal phase insufficiency" (245), there will be a further impediment to embryo implantation, often compounded by a poorer quality oocyte.

2. Oocyte quality

The deterioration in oocyte quality is related to a predisposition to the generation of aneuploid embryos caused by chromosomal segregation errors and abnormal spindle development, epigenetic modifications (120), and a deterioration of the oocyte cytoplasm (ooplasm), related to a decrease in mitochondria, a reduction in their quality and an increase in oxidative stress within the ooplasm (2), which can lead to promote free radical formation leading to the modification of intracellular proteins, lipids, and nucleic acids macromolecules (92) and alterations in mRNA (108). Consequently, female fertility starts to rapidly decline in a woman beyond 37 years of age, as manifest by the success rates of IVF treatment (206) and also by measures of natural fertility (192). The causes of the age-related decline in embryo quality are detailed below.

A) ANEUPLOIDY. As described previously as the woman's age increases, the chiasmata more proximal to the telomere become more susceptible to missegregation as there is believed to be less cohesion between the sister chromatids, due to an age-related loss in cohesin and shugoshin cohesions proteins, as they are produced in fetal life and deteriorate with time and exposure to reactive oxygen species (ROS) (136, 208). Another reported peculiarity of the human oocyte is the slow meiotic spindle formation compared with the mouse, and consequent predisposition to spindle instability and anaphase lag whereby due to slow segregation of the chromosomes an aneuploid chromosomal constitution may arise upon cytokinesis (154). Furthermore, a reduction in supply of ATP from a progressive reduction in mitochondrial function will lead to a reduction in spindle formation, microtubular activity, and polar body extrusion, promoting aneuploidy.

B) OOCYTE MITOCHONDRIAL FUNCTION. Mitochondria are maternally inherited, and the oocyte has the largest number of mitochondria (~200,000) and copies of mitochondrial DNA (mtDNA) of any cell. They are essential ROS scavengers and for the generation of ATP for the cellular processes including cortical granule extrusion, polar body formation, spindle formation, chromosome segregation, and cytokinesis. As the selection of mitochondria and mtDNA during oocyte development is a random process, the possibility arises for the amplification of mutated mtDNA during oocyte maturation and mitochondrial expansion (32). Upon fertilization mtDNA replication ceases, leading to a progressive dilution of mtDNA within the blastomeres during embryonic development, until blastulation when replication can resume. A reduced pool of mtDNA within the oocyte has been associated with a reduced fertilization potential (276) and also a reduced ovarian reserve (213). Furthermore, ageing is associated with an adverse effect on the mitochondria [reviewed by Schatten (297)], leading to an in increase in mtDNA damage and mutations with mtDNA, structural abnormalities with the mitochondria, a reduction in ATP synthesis, and an increase in ROS production (57, 297). Putative methods to improve mitochondrial function are the oral administration of CoQ10 (32), an electron transporter involved in the transport of electrons within the respiratory chain within the mitochondria (32), to assist

mitochondrial function or even to introduce donor ooplasm to "rejuvenate" an oocyte. In the area of embryonic screening within IVF cycles, it is now feasible to combine an assessment of aneuploidy within the blastocyst with an assessment of mtDNA content within blastomeres by microarray analysis (183).

C) EMBRYO METABOLISM. Evidence from animal studies suggest that the metabolism of the developing embryo may differ according to the age of the mother, as there were measured differences in the embryo culture media of embryos generated from older mice, compared with those generated from younger mice (212). If this is translated into humans, this may lead to a reduced implantation potential for such embryos independent of aneuploidy. In this murine model, the offspring were growth restricted, which if replicated in humans may have significant implications for the child's long-term health and development (212). To date, there is limited data to suggest an adverse outcome for children born from IVF (146). However, these children may be predisposed to cardiometabolic disorder, which is also associated with a fetus not reaching its growth potential (157), which is an interesting observation in view of these animal model findings, as IVF conceived children tend to be born to a population of older mothers than naturally conceived children (146).

D) EPIGENETIC ALTERATIONS. There is some evidence of an alteration in DNA methylation patterns within oocytes derived from older female animals (120), and there is one report of an alteration of DNA methylation patterns within metaphase II oocytes derived from women over 38 years of age compared with women under 35 years of age (133), and there are reports of a reduction in histone protein deacetylation in the metaphase I and II surplus oocytes derived from older women (355), and an alteration in the expression of ubiquilin in metaphase II oocytes (131). Hence, the consensus view is that oocytes derived from older women may be at risk of epigenetic modification (120).

3. Fallopian tube function

The incidence of ectopic pregnancy increases as a woman ages, although it is unclear whether this is directly related to an age-related change in fallopian tube function (273).

B. Dietary Restriction and Over-exercise

As described earlier, an alteration of food intake can have profound effects on the complex interplay of hormones released by the gastrointestinal system and neuropeptides influencing follicular development (97). It is well established that calorie restriction and excessive exercise lead to a reduction in the frequency of ovulation, poor endometrial development, amenorrhea, and subfertility, with even recreational levels of activity potentially leading to abnormalities of gonadotrophin secretion and ovulatory disorder without inducing amenorrhea (79). This is due to a suppression of the hypothalamic-pituitary ovarian axis, due to a reduction in the systemic stimulatory signals of GnRH release. As described previously, an alteration of food intake can have profound effects on the complex interplay of hormones released by the gastrointestinal system and neuropeptides influencing follicular development (97). Interestingly, body weight in late adolescence is an important predictor of fecundity in later life, as women within the Nurses' Health Study (117) who were underweight at 18 years of age (BMI under 18.5 kg/m^2) took an average 25% longer than normal weight women at 18 years of age to conceive, suggesting adolescence is a critical time for the programming of the reproductive axis.

The negative consequences of exercise on the chance of conception are demonstrated by an observational study of women undergoing their first IVF cycle which showed that women who exercised for four or more hours per week were 40% less likely to have a live birth, twice as likely to have implantation failure, and were more likely to miscarry (227).

1. Leptin

Leptin is of particular importance in the regulation of the reproductive axis, as evidenced by restoration of gonadotrophin secretion with recombinant leptin administration to over-exercising and underweight women leading to a restoration of LH pulsatility, ovulation, and menstrual cyclicity (364). As adequate GnRH secretion is essential for normal gonadotrophin secretion, a perturbation in GnRH pulsatility may lead to impaired ovulation, inadequate maintenance of a corpus luteum, and hence may predispose a woman to infertility and early pregnancy loss (337), and appropriate weight gain may lead to restoration of ovulatory cycles (111).

2. Insulin

Circulating concentrations of insulin are related to adiposity, and concentrations are lower in amenorrheic and regularly exercising women with functional hypothalamic amenorrhea (FHA), and are associated with a reduction in leptin secretion, although insulin does not have a direct action on GnRH pulsatility as GnRH neurons do not appear to express insulin receptors.

3. Gherlin

Ghrelin secretion from the gastrointestinal tract is maximal when the stomach is empty, it has an inhibitory effect on LH secretion, and serum levels are greater in regularly exercising (78), underweight (113), women with functional hypothalamic amenorrhea with abnormal eating habits (300)

leading to disordered ovulation as a consequence of the LH suppression.

4. Protein YY

Protein YY (PYY) infusion in humans is an appetite suppressor (28), and although animal studies suggest a degree of sexual dimorphism in the response to PYY, it is believed that in humans the action of PYY is suppressive on the reproductive axis (65). Interestingly, in adolescent girls with anorexia nervosa, the fasting concentrations of PYY have been reported to be three times greater than those of girls without anorexia, suggesting that PYY may play a role in the suppression of appetite and the suppression of the reproductive axis (219).

C. Stress

Due to central neuronal corticotrophin releasing hormone (CRH) projection to GnRH cells and CRH-induced β-endorphin inhibition of GnRH secretion, stress may exert a modulating effect on subsequent pituitary LH and FSH pulsatility (33, 60), which may be overcome by modified behavior restoring ovulation (35). Higher daily reported stress levels in a cohort of normal healthy women were associated with a reduction in serum estradiol, LH, and luteal phase progesterone concentrations as well as a predisposition to anovulation (299). Furthermore, while it is known that an elevated serum cortisol concentration is related to FHA, women with FHA who resume ovulation have serum cortisol concentrations similar to eumenorrheic women, suggesting that by reducing stress levels by therapeutic interventions normal ovulation may return (34). The Nurses' Health Study demonstrated that working longer hours (over 40 h/wk) and also lifting heavy loads were associated with increased time to conceive, suggesting a relation to tiredness or stress may impact upon conception (116).

D. Obesity

Women who are overweight are less likely to ovulate (240) and spontaneously conceive (256), and upon conception, they have an increased risk of miscarriage and are predisposed to an adverse pregnancy outcome (15). Obesity appears to alter the follicular fluid environment (282), the ooplasm of the oocyte, and leads to a reduction in fertilization and impairs embryonic development (92). Evidence derived from mouse models would suggest that obesity leads to slower growth and delayed maturation of the oocyte, epigenetic modifications, increased granulosa cell apoptosis, and mitochondrial dysfunction within the oocyte (92, 327, 380). Hence, maternal obesity may exert germ-line effects by affecting oocyte quality and the methylation of imprinted genes, and in the mouse model, this has led to altered methylation patterns within metabolism-related genes in the oocytes and the liver of the offspring of obese mice (72, 118). From mouse studies it has been demonstrated that maternal obesity leads to a deterioration in blastocyst development compared with matched controls; this effect can be overcome by intervention (218). To help to determine whether there is an element of harm inflicted on the oocyte or embryo by exposure to metabolic derangement rather than the intrauterine environment, in an elegant series of experiments, embryos were transferred from diabetic mice (377) or mice that had been fed a high-fat diet (202). In this study the embryos that were transferred from the diabetic mice were more prone to develop intrauterine growth restriction and congenital malformations, and when the oocytes from the high-fat diet fed mice were analyzed, there was a greater incidence of oocyte aneuploidy and mitochondrial damage (202, 377). A retrospective human study also demonstrated phenotypic differences in oocyte morphology, embryonic metabolism, and the rate of embryonic development in embryos derived from overweight women (195).

Population data suggest that obesity is associated with adverse obstetric outcomes such as preeclampsia, gestational diabetes, premature delivery and stillbirth (303), and congenital malformations in the offspring (331). Although it is believed that an improvement in obstetric and neonatal outcomes may be achieved by weight loss (13), not all studies agree (135). The use of bariatric surgery for obesity treatment is associated with a reduced rate of gestational diabetes and large-for-gestational-age infants. However, it is associated with an increase in the incidence of small-for-gestational-age infants, a shorter pregnancy, and potentially an increased risk of stillbirth or neonatal death. Despite the potential concern for nutritional deficiencies after bariatric surgery, a recent study reported that there was no significant effect of bariatric surgery on the overall risk of congenital malformations (168); however, a delay in attempting to conceive for at least a year post surgery is a recommendation (132).

In the Nurses' Health Study (117), every 5 kg increase in body weight from the age of 18 years of age was associated with a 5% increase in the median time to conceive, but women who gained more than 20 kg since 18 years of age took on average an extra 1.4 months to conceive, compared with women who maintained their weight. Interestingly, of particular detriment to conception was being underweight at 18 years of age but overweight at the time of attempt to conceive, where this led to a doubling of the time to conception (117), similar to data derived from the Danish Birth Cohort (272).

Several studies demonstrate the benefit of weight loss as part of a structured weight loss program upon the chance of conception for overweight women, and also as part of their IVF treatment (61, 314). In a systematic review of 11 stud-

ies that met the search criteria weight loss on the outcome of subsequent IVF treatment, losing weight by either diet and lifestyle changes (7 studies), nonsurgical medical interventions (1 study), or bariatric surgery (2 studies) led to a significant increase in the natural conception rate, an increase in the number of embryos available for transfer as well as the subsequent pregnancy rate, and a decrease in the miscarriage rate (314). Due to the difficulty in completing such studies, the overall quality of the studies was reported as weak, although all interventions led to significant improvements in pregnancy or live birth rates in overweight or obese women, with several studies reporting an improvement in spontaneous pregnancy rates. Due to the heterogeneity within the studies, a quantification of the benefit was not possible; however, the greatest improvements in outcomes was reported for women embarking on a multidisciplinary structured program of dietary and lifestyle intervention (314).

Of particular importance in relation to obesity is that women with PCOS, which is characterized by hyperinsulinemia and hyperandrogenism (231), are particularly predisposed to weight gain (340), exacerbating their risk of obstetric, perinatal, and neonatal complications in addition to an increase in congenital malformations (87). In general, women with PCOS are at a greater risk of miscarriage than women without features of PCOS; in addition, they are at greater risk of gestational diabetes, preeclampsia, and premature labor in pregnancy, and the perinatal mortality rate is greater for infants born to women with PCOS (87, 139). In later life, women with PCOS were twice as likely to have a non-injury-related hospital admissions, three times more likely to develop type II diabetes, four times more likely to be obese, and were significantly more likely to have cerebrovascular and cardiovascular disease, suffer a thromboembolic event, and have a hospital admission for a mental health condition than a woman without a diagnosis of PCOS (139). Furthermore, as it is believed hyperinsulinemia is present in 75% of lean women with PCOS and 95% of overweight women with PCOS (328), the reproductive, metabolic, and psychological consequences of PCOS are further exacerbated by weight gain (231).

Overweight women take longer to conceive through natural conception (166), and overweight women who require IVF treatment to conceive are less likely to conceive and more likely to miscarry than women of normal weight (279). The ideal way to determine whether the negative influence of obesity on conception is related to a negative influence on the oocyte or to the endometrium is to use the egg donation model. Whilst one large retrospective study of young normal weight oocyte donors demonstrated a negative trend upon conception related to an increasing BMI amongst recipients (30), a recent systematic review of six data sources demonstrated that there was no negative influence of obesity upon implantation, clinical pregnancy, miscarriage rate, and live birth (169). This may suggest the primary influence may relate more to oocyte quality rather than an endometrial effect. To study this thoroughly, a study controlling for the body mass index of the donor is required. The effect of obesity on the endometrium is to alter the expression of over 150 endometrial genes, primarily related to transcription and biosynthesis, to reduce the chance of conception (29). The benefit of preconception intervention was demonstrated in an RCT of a preconception structured lifestyle modification program for women with PCOS, including a combination of calorie restriction, weight loss medication, and exercise, that led to a significant improvement in metabolic features, ovulation rates, and trend towards an increased live birth rate (198).

Obesity is associated with an increased risk of miscarriage in women undergoing IVF treatment (279), although as described above this may primarily be due to an oocyte effect, rather than an endometrial effect. However, in overweight women with PCOS, it is believed that integral to the endometrial defect is insulin resistance leading to decreased expression of $\alpha v\beta 3$ integrin, HOXA10, and IGFBP-1 and increased androgen receptor expression (302), leading to an increased risk of miscarriage [for review, see Schulte et al. (302)]. Consequently, therapies to address the insulin resistance such as weight loss (61), and use of the insulin sensitizer metformin (248), have been employed to reduce the risk of miscarriage. The practice guidelines from the systematic review of the nonpharmacological interventions for women with PCOS was performed in 2011 and updated in 2015 and the finding are listed in **TABLE 6** (9, 341).

E. Cigarette Smoking

Cigarette smoking has a profound effect on fertility for both the male and the female (80, 270); despite this, many women continue to smoke while attempting to conceive and even when undergoing IVF treatment (127). In one study, if both partners smoked, the woman's chance of conceiving was one-fifth of those couples where neither partners smoked; despite this, the authors cite data that 20% of women in the United States are believed to smoke in the 3 months prior to starting to try to conceive (263). For a cigarette smoking woman, all aspects of fertility are impaired (80), as the smoke contains heavy metals, polycylic hydrocarbons, nitrosamines, and aromatic amines (80, 86) [for review, see Dechanet et al. (80) and Camlin et al. (49)].

1. Ovarian function

In animal models cigarette smoking leads to a depletion of primordial follicles (49), further loss of follicles throughout folliculogenesis, impaired cumulus oocyte complex expansion (361) and impaired granulosa cell function, granulosa cell steroid production, impaired oocyte meiosis (49), and a predisposition to aneuploidy within the oocyte (201). It is

Table 6. *Lifestyle management for women with PCOS who are trying to conceive: recommendations after systematic review*

Evidence Statement	Level of Evidence
Lifestyle management, including diet and exercise programs, should be used throughout the life span in women PCOS to optimize health generally and to alleviate PCOS clinical severity including infertility.	C
In women with PCOS and body mass index = 30 kg/m with due consideration given to age-related infertility, intensive (frequent multidisciplinary contact) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be the first-line therapy for 3–6 months to determine if ovulation is induced.	C
Pharmacological ovulation induction should not be recommended for first-line therapy in women with PCOS who are morbidly obese (body mass index = 35 kg/m) until appropriate weight loss has occurred either through diet, exercise, bariatric surgery, or other appropriate means.	C
Pharmacological ovulation induction could be second-line therapy, after intensive lifestyle modification has been undertaken.	C
Morbid obesity increases risks during pregnancy and should be regarded as a relative contraindication to assisted fertility.	PP
Psychological factors should be considered and managed in infertile women with PCOS, to optimize engagement and adherence with lifestyle interventions.	PP

C, body of evidence provides some support for recommendation, but care should be taken in its application; PP, evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations. Adapted from *Evidence Based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome*. Melbourne, Australia: Jean Hailes for Women's Health on behalf of the PCOS Australian Alliance, 2015.

unclear how these translate for the woman that smokes cigarettes while attempting to conceive; however, it is known that smoking leads to a reduction in ovarian reserve and an advancement of the age of menopause for the woman (167, 301), potentially due to the influence of polycyclic hydrocarbons which are activated into more toxic metabolites by the liver (49, 271). Further human studies have demonstrated that oocytes derived from cigarette smoking women undergoing IVF treatment have a greater number of immature oocytes (385), an increased thickness of the zona pellucida (310), with follicles containing higher level of markers of oxidative stress within the follicular fluid (252), and within the cumulus (316).

Women embarking on an IVF cycle have a reduced ovarian response if they had been recent cigarette smokers (112). With the use of the smoking mouse model, the ovaries of cigarette smoke-exposed mice were smaller, contained fewer primordial and primary follicles, and resulted in fewer oocytes at the time of ovulation (321).

2. Fallopian tube function

Smoking is the main lifestyle and environmental agent that negatively influences fallopian tube function. Rhesus monkey and mouse studies suggest that smoking exposure reduces fallopian tube blood flow (224) and smooth muscle contraction (234), impairs fimbrial oocyte collection (181) and tubal motility, and reduces the number of ciliated cells within the fallopian tube and their beat frequency [reviewed by Shao et al. (307)]. Human studies of fallopian tube function are challenging to perform; however, it is believed that there is a close similarity between the rodent and human fallopian tube physiology assisting with our understanding of fallopian tube physiology (307). However, it is still unclear what is the cause of an ectopic embryo implantation, as it may be mechanical due to obstruction, due to a change in fallopian tube histology, or an abnormal expression of hormone receptors within the tube (307). Indeed, it is believed that smoking more than 20 cigarettes a day increases the risk of a fallopian tube ectopic gestation fourfold (43, 100). This epidemiological evidence, combined with the many animal studies, of the influence of cigarette smoking on fallopian tube function suggests that the agents, or their metabolites, within cigarette smoke are a substantial contributing cause of female infertility and ectopic gestation (80).

3. Fertilization and embryonic development

The effects of cigarette smoking exposure on the oocyte of women undergoing IVF treatment appears to consist of the development of a thicker zona pellucida compared with nonsmokers (310), a potential cause of the reported reduction in fertilization rate with IVF (185), and delayed embryo morphokinetic cleavage events in couples undergoing ICSI treatment (110), which as previously discussed may reduce embryo implantation. Furthermore, the oocyte derived from a cigarette smoking woman may have delayed maturation and be at risk of meiotic errors (385), leading to an increased risk of the development of an aneuploid embryo (384). Rodent studies also suggest slower rates of embryonic development with reduced cell numbers and implantation rates upon exposure to cigarette smoke (224).

4. Implantation

It is widely believed that cigarette smoking has a detrimental effect on implantation, as the recipient in an oocyte donation program will have less chance of conceiving if she smokes, proportionate to the amount of cigarettes smoked (319). With the use of animal models and cultures of human endometrial cells, the effect of inhalation of cigarette smoke upon the endometrium can be analyzed (80). It appears that the influence of cigarette smoke may lead to anti-estrogenic effects on the developing endometrium, altered angiogenesis within the endometrium, influence on trophoblast invasion, and altered gene expression within the endometrium (80). The actual influences are determined by the individual compounds and the dose to which the endometrium is exposed. Human placental trophoblastic cell lines exposed to compounds within cigarette smoke have been reported to lead to altered expression of epidermal growth factor (387), matrix metalloproteases (121), alterations of hCG secretion (40), L-selectin expression (383), in addition to increased apoptosis, altered cellular architecture, and reduced cytotrophoblast invasion (80, 122). Cigarette smoking women are exposed to high levels of cadmium and lead, and these metals have been found within the endometrium of cigarette smokers, correlating with the number of cigarettes smoked and the duration of smoking (289).

5. Miscarriage

Smoking is believed to increase the risk of miscarriage by ~1% per cigarette smoked (258), with the overall adjusted relative risk of miscarriage being 1.23, with a nonsignificant increased risk of miscarriage associated with passive smoking (258). The cause of the increased miscarriage risk is likely to be multifactorial. One large study that analyzed the effect of cigarette smoking on the miscarriage of chromosomally normal conceptions demonstrated a tendency towards an increased likelihood of miscarriage in this group (179), suggesting an endometrial effect in addition to the potential for an increased risk of aneuploidy described above (384).

F. Periodontal Disease

There is increasing evidence of an association of poor oral health with a number of clinically important medical conditions (370). Periodontal disease is a chronic infectious and inflammatory disease of the gums and supporting tissues and has been associated with cardiovascular disease, type 2 diabetes, respiratory disease, kidney disease, and adverse pregnancy outcomes (105, 235, 312, 313, 370). It is believed that up to 10% of the population have severe periodontal disease. Several studies suggest that successful treatment of periodontal disease may alter or modify inflammatory markers (74) and improve endothelial and vascular function after therapy (345), and it is believed to be a modifiable factor that may lead to improvements in long-term health (235, 344). An observational study of the prevalence of periodontal disease in pregnant women suggested that periodontal disease may also be a factor limiting a woman's time to conceive (143). The mechanism proposed was that it caused a low-grade inflammation reducing embryo implantation, as pregnant woman with periodontal disease took, on average, an extra 2 mo to conceive, a negative influence on conception of the same order of magnitude as obesity.

In summary, the main lifestyle factors that may have a negative impact on a woman's fertility are smoking and obesity. Fortunately, evidence suggests that smoking cessation will improve the chance of conception, and embarking on a supervised weight loss program will improve the chances of conceiving for the overweight woman. Unfortunately, the age-related decline in oocyte quality for a woman leads many women to seek fertility treatment using an oocyte donor. Potential future interventions of ovarian rejuvenation may offer some of these women in the future alternative options.

V. ENVIRONMENTAL INFLUENCES AFFECTING

It is suspected that potentially the most significant of the common environmental influences that may impact upon female fertility relate to endocrine disrupting chemicals (EDCs). EDCs are ubiquitous chemicals that interfere with hormone action, and almost all pregnant women in the United States have measurable quantities within their bodies (375). Evidence derived from environmental disasters where toxic chemical have leaked into the environment has demonstrated that permanent changes can occur to the endocrine system and confirms that environmental chemicals can act as EDCs. However, for many years there has been substantial controversy around the subject of environmental EDCs at lower levels of environmental exposure, as many stakeholders have been involved in investigating the subject, often with potential for bias, for example, the chemical industry has a vested interest in proving safety, and in contrast the media have at times generated sensational reports. The Endocrine Society published an updated systematic review in 2015 that endeavored to analyze the literature in a very balanced manner with regard to any potential conflict of interest of the investigators, any tendency towards negative or positive findings bias (depending on the source of funding for the research), and being mindful of the extrapolation of animal studies to the human situation (125).

EDCs have numerous potential mechanisms of actions in addition to traditional receptor activation and generally do not have a predictable dose-response curve, and the same chemical may have agonistic or antagonistic properties at

different concentrations and at different sites. Furthermore, they are frequently additive with other EDCs, of which there are believed to be in excess of 800 chemicals, and also they may have several active metabolites, and the effect of the EDC may depend on the timing of exposure (26, 392). Consequently, it is often difficult to determine the properties of many substances with potential endocrine disrupting actions. EDCs interfere with the action of hormones either at a hormone receptor or they may alter the number of hormone receptors within a cell, and if these influences happen at a critical stage of development, the changes may be permanent. Due to single-nucleotide polymorphisms, some individuals may be more susceptible than others. In addition, it is possible that some EDCs may cause epigenetic changes leading to a transgenerational effect by DNA methylation, histone modification, and influence on micro-RNA expression (125). A further complicating factor when analyzing the effects of EDCs is that the EDC may act on the receptors of several hormones, and depending on the levels of exposure studied, the outcome may vary as each organ may have a different threshold for disruption (125). To study the endocrine disrupting nature of a substance in the United States, the Endocrine Disruptor Screening Program employs two series of assays (Tox21 and ToxCast) to study thousands of chemicals and their signaling pathways.

Animal studies offer several advantages when studying the effects of EDCs as many biological processes are conserved across several species; furthermore, they enable the investigator to control the dosing of exposure, the timing of exposure, limit any interference from other chemicals and control for many variables, and potentially perform the study over a relatively short period of time. However, the limitations of using animals as experimental subjects are that the action in the animal may differ from their actions on humans. Many EDCs have additive effects, and this may amplify the effect of the particular chemical studied which may not be evident in an animal study. In addition, replicating the "human timing of exposure" or "window of vulnerability" in animal studies can be difficult, and in animal studies it may be required to use higher doses of an EDC for a shorter period of time, rather than prolonged low level of exposure as is often found in the human situation (374). Therefore, it is believed that observational human studies may provide useful epidemiological data; however, challenges that may be faced are that the particular EDC exposure may be difficult to identify and quantify and may be reliant on human recall, plus eliminating confounding factors may be difficult in a long-term epidemiological study (374).

The main endocrine disrupting chemicals are BPA, the phthalates and their esters, the pesticide Atrazine, and the polychlorinated biphenyls (PCBs) and DDT/DDE. They are briefly described below, and their actions are described in greater detail where they influence fertility.

1) BPA is a synthetic chemical widely used in the manufacture of plastics and resins for many years, and the main route of exposure is within the diet and through transdermal contact. In many countries its use in the manufacture of plastic bottles has been phased out. However, BPA along with phthalates are frequently measurable within urine (182), serum (141), follicular fluid (187), umbilical cord blood (162), and the amniotic fluid (162). Of particular concern was the finding that the amniotic fluid concentrations of BPA were five times greater than serum, presumably due to fetal renal clearance (162). The methods of action of BPA are that it can bind to the nuclear receptors for ERα and ERβ, with differing affinities for each which may lead to differing agonist/antagonist responses, although it is believed that the majority of its action is through other mechanisms, such as through intracellular signal transduction pathways independent of the nuclear hormone receptors, modification of cytochrome *P*-450 enzyme expression and activity, alterations in the level and activity of sex hormone binding globulin, and epigenetic modulation by the silencing of promoters by methylation [for review, see Wetherill et al. (365)]. In addition, BPA is believed to impair mitochondrial function and promote oxidative stress in high doses in rat studies (178). It is reported that more BPA is produced than any other chemical with ~15 billion pounds produced in 2013 (125). Interestingly, the United States Environmental Protection Agency safety level is set at 50 $\mu g \cdot kg^{-1} \cdot day^{-1}$, whereas the European Food Safety Authority tolerable daily intake is 4 $\mu g \cdot kg^{-1} \cdot day^{-1}$. However, it is reported in the The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals that BPA is believed to have effects at or below these levels (125).

2) Phthalates and their esters are plasticizers to provide flexibility to materials and are present widely within the home and hospital environment and are also used in personal care products, such as cosmetics. As they are noncovalently bound, they leach into the environment and they are detectable and hence they are ubiquitous within the environment (125).

3) Many pesticides have been suspected of being EDCs. Atrazine is a widely employed herbicide used in commercial crop growing in the United States, is persistent with its metabolites in ground and surface water for many years, and is detectable within drinking water (125).

4) PCBs were banned in 1979; however, they bioaccumulate within the environment and are stored in body fat, and some PCBs have thyroidogenic, estrogenic, and antiandrogenic actions (125).

5) DDT is an insecticide with a long half-life which was widely used prior to being banned in the United States in 1972 due to being linked to several cancers, and as with

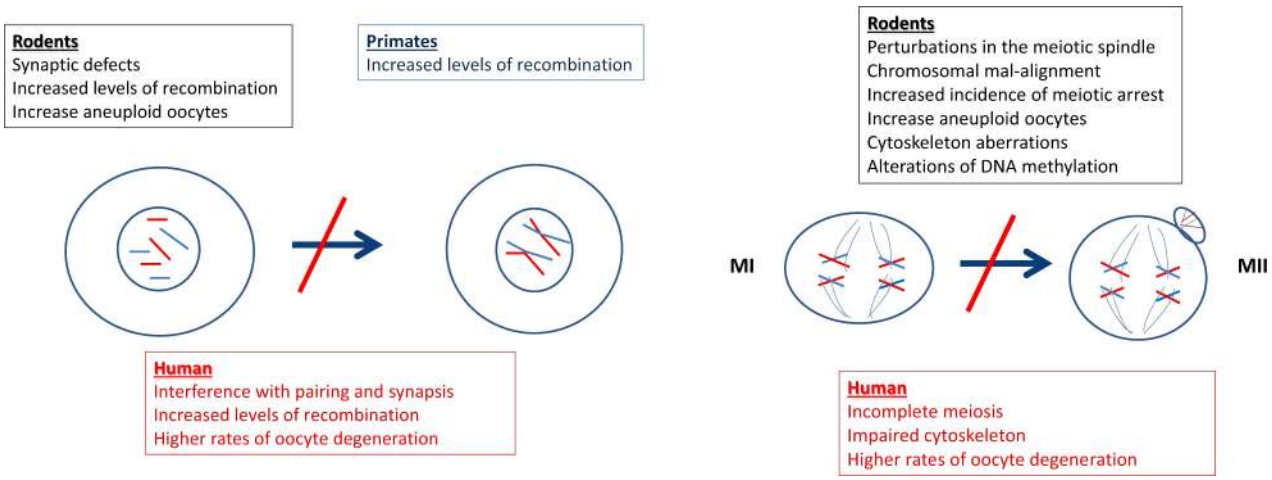

FIGURE 5. The effects of bisphenol A during early stages of oogenesis and the final stages of maturation (metaphase I and metaphase II). [From Machtinger and Orbvieto (207), with permission from Elsevier.]

PCBs, DDT is persistent within the environment due to its long half-life and bioacumulates in fat (125). The consequences of substances that are stored in fat tissue are often difficult to determine, as the measurable levels in the blood are low, however, the substances may be released rapidly within the body during periods of weight loss.

The effects of EDCs on reproduction has recently undergone an updated systematic review by the Endocrine Society and published in October 2015, and several summary statements are derived from this review (125).

A. Folliculogenesis and Ovulation

1. Premature ovarian insufficiency

Environmental causes of premature ovarian insufficiency (POI) are not well defined, other than being related to chemotherapy and radiotherapy; however, the potential for in utero or other early life exposure to gonadotoxic chemicals to lead to POI in later life is a possibility, although no common environmental chemicals or EDCs have been demonstrated to conclusively lead to POI (36, 125, 141). Although there is evidence from a series of studies performed on rats that a mixture of estrogenic EDCs (phthalates, pesticides, chemical ultraviolet filters, bisphenol A, parabens), exposed from day 7 of gestation to 22 days postnatally, may lead to a reduction in the frequency of estrous in the rats, there was no significant difference in ovarian weight or follicle count in this short study (163).

2. Influences on follicular development and ovulation

A) ENDOCRINE DISRUPTORS. *I) BPA*. With regard to folliculogenesis, animal studies suggest that maternal BPA exposure may lead to disorders of meiosis in the female offspring, increasing the risk of oocyte aneuploidy and abnormal primordial follicle development and progression through folliculogenesis (160, 386).

The multiple purported effects of BPA during early stages of oogenesis and the final stages of maturation (metaphase I and metaphase II) from human and animal studies are demonstrated in **FIGURE 5**.

Studies using culture of murine ovarian tissue demonstrate that, at exposure levels found in Chinese children, BPA may lead to a premature activation of folliculogenesis ultimately leading to a reduced follicular pool (388). Similar studies have been performed in vivo using mice, rats, sheep, and monkeys (see **TABLE 7**); however, there is limited data available on the effects of BPA on ovarian development and early folliculogenesis in humans (125). Animal studies suggest that early life exposure to BPA at higher doses appears to accelerate the follicular development leading to cystic follicles and reducing the antral follicle pool, but at lower doses decreases all follicle stages both in in vivo animal studies and in cultures of ovarian cells [summarized by Gore et al. (125)].

The negative influence of BPA upon follicular growth is believed to have several mechanisms: interference with the aryl hydrocarbon receptor, alteration of cell cycle regulators, and altered steroidogenesis (253). In animal studies BPA-induced follicular atresia is associated with increased markers of apoptosis (253). These animal studies appear to be corroborated in human studies of the antral follicle count of 209 women undergoing a fertility assessment, where there was an association of a higher urinary BPA concentration with a lower antral follicle count (326).

Both BPA and phthalates are believed to have a modulating effect on hypothalamic-pituitary action in animal studies (52), and it is hypothesized that BPA may be

Table 7. *Effects on oocytes of prenatal and postnatal BPA exposure*

Study	Sample	Dose	Route of Administration	Time of Exposure	Results
Zhang et al. (386)	Pregnant mice	0.02, 0.04, 0.08 mg·kg body wt^{-1}·day^{-1}	Oral route	12.5–18.5 day post-coital	Inhibition of meiotic progression to prophase I in 0.08 BPA-treated group; decreased mRNA expression of specific meiotic genes; inhibition of germ cell cyst breakdown
Hunt et al. (160)	Pregnant rhesus monkeys	400 μg·kg body wt^{-1}·day^{-1}	Tubing implants	GD 50–100, GD 100 to term	Disturbances in prophase events; increase in MOFs
Susiarjo et al. (335)	Pregnant mice, offspring	400 ng/day	Pellets releasing BPA	GD 11.5–17.5	Aberrant meiotic prophase; increased aneuploidy in eggs and embryos from adult females
Rivera et al. (280)	Lambs	50 μg·kg^{-1}·day^{-1}	Subcutaneous injections	PND 1–14	Decreased ovarian weight; increased primordial-to-primary follicle transition; increased incidence of MOFs; increased number of small antral atretic follicles associated with higher p27 expression
Karavan et al. (173)	Mice	10, 100 μg/day	Subcutaneous injections	PND 1–4	Increased incidence of MOFs; increased total number oocytes; increased percentage of primordial follicles
Rodriguez et al. (283)	Rats	0.05, 20 mg·kg^{-1}·day^{-1}	Subcutaneous injections	PND 1–7	In BPA 20 group stimulation of neonatal initial follicle recruitment; p27 and ERα increased expression; increased proliferation rate of granulosa cells
Chao et al. (56)	Mice	20, 40 μg/kg	Subcutaneous injections	PND 7–14, PND 5–20 (every 5 days)	Decreased methylation pattern of two maternal imprinted genes; upregulated mRNA expression of ERα; decreased primordial follicle number but increased primary, secondary, and antral follicle number; abnormal spindle assembling in meiosis

From Caserta et al. (52).

associated with a premature activation of the hypothalamic-pituitary-ovarian axis and be related to premature pubertal development (52).

Depending on the dose and the species studied, BPA is believed to have several points of action to interfere with steroidogenesis (125). Associations of higher serum BPA have been linked with a lower estradiol response in women undergoing IVF treatment, suggesting a negative impact on ovarian steroidogenesis (39, 94), and increased urinary concentrations of BPA have been associated with lower antral follicle counts in women undergoing IVF treatment (326). Although, seemingly in contrast, BPA exposure has also been associated with PCOS (1, 26, 172, 288); however, it is unclear whether this is a causal relationship as higher serum androgen concentrations are associated with delayed clearance of BPA (52), as the finding of an increased follicular count is in direct contrast to Souter et al. (326).

With regard to PCOS, BPA is probably the most studied of the environmental endocrine disrupters. BPA has been demonstrated in vitro to increase in adipocyte differentiation in human and mice cell culture (42), stimulate rat ovarian theca cells to synthesize testosterone (390), and induce insulin resistance in offspring of rats exposed in pregnancy (325). How these in vitro studies and the use of animal models relate to human programming of the disease is unclear, particularly as the "window" of exposure that may program PCOS is unknown due to the difficulties in studying transgenerational effects in humans. However, it is believed that the most likely vulnerable period of exposure is in utero and the first few years of life (26). The reasoning proposes that animal studies of

exogenous androgen exposure and human evidence of in utero growth restriction with subsequent catch-up growth, leading to the subsequent development of features of PCOS and the metabolic syndrome, suggest that a period of vulnerability exists at this time to individuals who may have a genetic predisposition to PCOS (26, 246). Indeed, with the use of both high- and low-dose exposures to BPA in early postnatal life, a rodent model of PCOS has been developed (103). From animal studies of BPA exposure at levels of exposure found in humans, animals tend to accrue body fat, leading to metabolic derangement, and develop impaired ovarian function (26), although human data are not clear (125). It is important to note that a significant vehicle of BPA exposure is transdermal; hence, larger individuals will tend to have greater exposure leading to an assumption of an association with obesity, rather than potentially being an artefact of an increased surface area. It is also important to note for substances with a high degree of transdermal absorption that since an infant has the greatest surface area-to-volume ratio, it will receive a greater exposure relative to height than an adult. No epidemiological studies of early life BPA exposure into adulthood have yet been performed, although studies suggest serum BPA concentrations are increased in the presence of PCOS in adulthood after controlling for BMI (172), as serum BPA correlates to BMI; however, this association does not demonstrate causality as, for example, the excretion of BPA may be impaired in PCOS and hence its concentration would be artificially elevated.

II) Phthalates. There is limited information on the effects of phthalates on follicular development. Animal studies suggest that DEHP, MEHP, and DBP induce follicular arrest and atresia in cultured rat and mice cells [summarized by Gore et al. (125)]. Limited human data exist, although by measuring the metabolites of phthalates in stored maternal blood, our group demonstrated a trend toward an earlier menarche in Western Australian girls, a degree of hypogonadism with a reduction in early follicular phase serum FSH associated with the phthalate metabolite MEHP (141). Of particular concern was the finding that maternal exposure to MEP, widely found in cosmetics, was associated with a reduction in their daughters' serum AMH in adolescence, a marker of antral follicles (ovarian reserve) and granulosa cell function (141). In addition, higher MEP exposure was associated with a reduced prevalence of PCOS in adolescence and reduced antral follicle count (141). A similar finding was observed in a small study of patients with PCOS where lower urine concentrations of mBP and mBzP were detected in women with PCOS (352). Several in vivo and in vitro studies have been performed on animals with phthalate exposure, and exposure, particularly to DEHP and MEHP, appears to impair estradiol, progesterone, androstenedione, and testosterone production [summarized by Gore et al. (125)].

III) Pesticides. Methoxyclor (MXC) is a pesticide and an insecticide; hence, it is present in food and water and has been used as a replacement for dichlorodiphenyltrichloroethane (DDT), and it has been reported to inhibit the response to ovarian stimulation in mice (96), and also induces apoptosis in baboon antral follicles by activation of the aryl-hydrocarbon and estrogen receptor and by the activation of apoptotic cascade and via oxidative stress [summarized by Gore et al. (125)]. In mice, it inhibits steroidogenesis at multiple points in the steroidogenic pathway, leading to a reduced antral follicle production of estradiol, testosterone, and androstenedione (27). Some of the other pesticides that have been studied in animals and are suspected to have an adverse effect upon folliculogenesis include endosulfan, malathion, cypermethrin, carbamate, imidacloprid, fenvalerate, trifluralin, bifenthrin, and diurin, and it is suggested that pesticides may alter gene expression, impair follicle growth, induce atresia, and reduce oocyte quality and impair steroidogenesis [summarized by Gore et al. (125)]. Atrazine has been associated with menstrual cycle length irregularity, as women who drunk more than 2 cups of unfiltered Illinois water (where atrazine is widely used and detectable in the drinking water) were up to six times as likely to have menstrual irregularity as women who did not drink the water (69), suggesting a disruption of the ovulatory menstrual cycle.

IV) Persistent environmental contaminants. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a dioxin and a widespread persistent environmental pollutant. It has inhibitory influences upon pubertal timing, ovarian steroidogenesis, folliculogenesis, and ovulation in several species (165, 253), although human data on the effect of TCDD upon reproduction is limited. In mice studies, TCDD and PCBs reduced ovarian weight and induced follicular atresia (261). Although, in contrast, a small observational study reported that PCOS subjects, where antral follicle counts are usually increased, had higher serum concentrations of some persistent environmental pollutants, perfluorooctanoate and perfluorooctane sulfonate (352); however, associations do not demonstrate causality.

V) Phytoestrogens. Genistein is a phytoestrogen present in soy, lentils, and chickpeas and appears to either promote or inhibit follicular development on the rat ovary, depending on the dose, strain, and age to promote, and influence sex steroid production within the follicle and activate apoptosis (253).

For a detailed description of the effect of environmental exposures in ovarian function, readers are directed to Bhattacharya and Keating (36) and Patel et al. (253). Trichloroethylene (TCE) is commonly found in adhesives and lubricants. Both TCE and its metabolites led to a reduction in fertilization of mouse oocyte (68). Exposure to 7,12-dimethylbenz[a]anthracene (DMBA), found in cigarette smoke

and car exhaust fumes, leads to a loss of mouse or rat follicles at all stages of development (161), and exposure to DMBA led to altered expression of genes regulating follicular development (322). A common by-product of pesticide, rubber, plastic, and flame retardant manufacture is 4-vinylcyclohexene (VCH). In animal studies, VCH destroys primordial and small primary follicles leading to ovarian failure (156).

B) HEAVY METALS. Heavy metals are resistant to degradation and hence may persist in the environment for many years. Potentially their concentration may be amplified by bioaccumulation within the food chain, particularly individuals with high fish intake which may be at risk of exposure to mercury. Some of these metals are essential for life in low concentrations, but highly toxic in higher concentrations, such as copper, chromium, manganese, and zinc, although cadmium, lead, mercury, and the metalloid arsenic are nonessential and are toxic (290). Women are exposed to these chemicals through inhalation, drinking contaminated water, or eating food contaminated by exposure or by bioaccumulation. With the use of mercury-based dental amalgams, dental technicians may have greater exposure than the general population as measured by urinary excretion of the metal and are potentially at risk of a dose-dependent reduction in fecundability for a woman actively trying to conceive (286), as are women who have a high fish intake in their diet (11). However, the evidence for normal environmental mercury exposure interfering with ovulation is limited (59). Despite this, it is advised that women trying to conceive should avoid processed and "fast food" and minimize exposure to mercury until completion of breast feeding by avoiding large fish such as shark, king mackerel, and tilefish (238).

Evidence exists for some heavy metals to have a potential epigenetic modification influence on various cultured cell lines (290), influencing DNA methylation leading to gene inactivation loss of acetylation and increasing histone methylation (12) as well as activating apoptosis, and arsenic is known to disrupt the cell cycle (12, 104). In women undergoing IVF treatment, higher mercury exposure has been associated with altered methylation patterns within CpG sites within whole blood, and cadmium exposure has been linked to altered methylation patterns in Andean women from Argentina, suggesting that these laboratory-observed influences on epigenetic modifications may occur at concentrations present within the environment.

A major source of exposure to heavy metals is derived from cigarette smoking, as the tobacco plant accumulates cadmium and lead from the soil and the serum concentrations of these heavy metals have been correlated to the brand and the number of cigarettes smoked (14).

B. Fallopian Tube Function and Inflammatory Disorders

1. Endocrine disrupting chemicals

Due to the estrogen responsive nature of the development of endometriosis, researchers have extensively studied the association of endometriosis and endocrine disrupting chemicals. Dioxin exposure (47, 324) and exposure to the a phthalate BzBP metabolite and its metabolites MBz, P and the DEP metabolite MEP may be associated with increased risk of endometriosis (63), although BPA exposure was not linked in an epidemiological study of women with endometriosis (350). One large cross-sectional study from the United States demonstrated an association of MBP with an increased risk of endometriosis (366), and another did not confirm the associations of phthalate exposure with endometriosis and demonstrated that MEHP had an inverse association with the presence of endometriosis (351). Serum levels of the organochlorine pesticide β-hexachlorocyclohexane have been associated with endometriosis in a cohort of women undergoing surgical exploration for the disease (349), and dioxin and dioxin-like compounds have for many years been believed to be associated with the development of endometriosis. However, the literature is conflicting (320), although a small study that performed analysis of adipose tissue at the time of laparoscopic surgery demonstrated an association between adipose concentrations of dioxin and PCBs and the presence of endometriosis at the time of surgery (211).

C. Embryonic Development

1. Teratogens

While not the focus of this fertility review, it is important to mention teratogens. Teratogens are agents that an individual may be administered or self-administered, or be exposed to in pregnancy, or around the time of conception, that may cause a structural or functional defect to the fetus (101). Hence, the most common preconception teratogen is probably being overweight or obese, as being overweight leads to an increase in the incidence of neural tube defects as well as cardiac and oro-facial abnormalities for the offspring (101). Furthermore, the use of fertility drugs themselves and IVF have been linked to an increase in congenital abnormalities in the children born (137). Consequently, it is essential that a treating physician aims to ensure a woman trying to conceive is as healthy as possible at the time of conception and she should aim to keep the use of over-the-counter and prescribed medications in pregnancy to a minimum.

In addition to medication exposure, teratogens can consist of infections, such as syphilis, rubella, and cytomegalovirus exposure. They may be caused by metabolic disturbance, such as diabetes, and may be a physical insult such as ra-

diotherapy or exposure to a chemotherapeutic agent. However, the most common teratogens are physician-prescribed medications, as up to two-thirds of women in the United States are prescribed drugs in pregnancy (251). Furthermore, as the most critical window of exposure is the first trimester, often before the woman recognizes she is pregnant, it is imperative that a doctor is vigilant to this factor in treating a woman of reproductive age and prescribes medication sparingly and also manages chronic medical conditions such as thyroid disorder and diabetes in an optimal manner to reduce the fetal exposure to teratogenic medication and also to the harm of an unstable systemic illness. The Federal Drug Administration describes drugs according to their teratogenicity by ascribing a category (A, B, C, D, and X), and this is readily available to clinicians for their reference.

2. Pollutants

Organochlorine pollutants, such as polychlorinated biphenyls and DDT, are persistent within the environment and within the body and have been speculated to be associated with an increased time to conceive for women, although this has not been verified (170). Furthermore, review of the literature did not demonstrate any association with oocyte quality, fertilization rate, embryo development, or ultimately the pregnancy rate for women embarking on IVF treatment (170). Human and animal studies demonstrated impaired steroidogenesis in granulosa cells exposed to BPA (52), and this is borne out by women with higher serum BPA concentrations undergoing IVF treatment whereby they have a lower peak estradiol concentration and reduced oocyte yield (39, 94). A recent study of hair mercury concentrations, a marker of dietary fish intake, in women undergoing IVF treatment did not find a relationship between mercury levels and ovarian responsive to stimulation, oocyte fertilization rate, embryo development, and pregnancy rates (376).

D. Implantation

1. Endocrine disrupting chemicals

An environmental exposure assessment of 501 couples trying to conceive in the United States did not determine a relationship between exposures to BPA and 14 phthalate metabolites in the urine on the length of time it took a couple to conceive, although this does not suggest that any exposures were not in some way influencing early embryonic development.

A) BPA. In animal studies, BPA exposure has led to a significant reduction in embryo implantation (379). Exposure to BPA is believed to lead to a downregulation of *HOXA10* expression (217), with IVF embryo implantation failure being more common in women with higher urinary BPA levels (93). A United States study of women with unexplained miscarriage demonstrated that those with a serum conjugated BPA concentration in the highest quartile were almost twice as likely to miscarry as those women in the lowest quartile. The authors hypothesized that the cause was due to a negative influence of BPA upon the endometrium or early placentation (193), and BPA exposure has also been associated with a predisposition to with recurrent miscarriage (334, 389).

B) PHTHALATES. There are conflicting reports on the association of urinary and follicular fluid levels of phthalates and conception, although DEHP exposure has been associated with increased time to conception and miscarriage in mice studies [summarized by Gore et al. (125)].

C) PESTICIDES. Exposures to higher levels of the pesticides DDT and DDE have been associated with subfertility and increased risk of miscarriage in observational studies from countries with a high environmental exposure [summarized by Gore et al. (125)].

2. Heavy metals

Mercury does not appear to be teratogenic within the concentrations expected due to occupational exposure (149), and in a study of women undergoing IVF treatment, total hair mercury was measured and the concentration did not correlate with any IVF treatment outcome, response to ovarian stimulation, oocyte fertilization, embryonic development, pregnancy rate, or live birth rate when controlled for confounders (376).

3. Other environmental exposures

Flight attendants and health workers using ionizing radiation may be at increased risk of exposure to radiation through their work (10, 38), which may have a detrimental impact on the developing embryo and potentially increase the risk of miscarriage; hence, employers should develop guidelines for the occupational exposure to ionizing radiation for pregnant women.

There is also the possibility that environmental exposure to excessive noise may have detrimental effects upon and implantation and increase the risk of miscarriage (278).

In summary, there is extensive evidence derived from animal studies of a negative influence of environmental chemicals on many aspects of female fertility: follicular number, ovulation, meiosis, and embryo implantation; however, the evidence of such negative associations in humans is often lacking and contradictory. Further epidemiological studies may assist in the clarification of these associations. However, the inherent difficulty with human studies lies with the varying human exposures, often over many years of poten-

tial exposure, potential intergenerational influences and the multiple confounding variables that are present when studying fertility in a population.

VI. CONCLUSION

This review aimed to provide an overview of the processes involved in conception, embryo implantation, and embryonic development. It provided an insight into the pathological conditions that may impair these processes and result in a couple having difficulty conceiving and discussed reversible lifestyle and environmental factors that may impact on conception.

ACKNOWLEDGMENTS

Address for reprint requests and other correspondence: R. J. Hart, School of Women's and Infants Health, The University of Western Australia, King Edward Memorial Hospital, 374 Bagot Rd., Subiaco, Perth Western Australia 6008 (e-mail: roger.hart@uwa.edu.au).

DISCLOSURES

The author is the Medical Director of the IVF unit Fertility Specialists of Western Australia and is a shareholder in Western IVF.

REFERENCES

1. 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* 11: 357–374, 2005.

2. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. *Reprod Biol Endocrinol* 10: 49, 2012.

3. Ahmad A, Ahmed A, Patrizio P. Cystic fibrosis and fertility. *Curr Opin Obstet Gynecol* 25: 167–172, 2013.

4. Al-Khateeb GM, Sater MS, Finan RR, Mustafa FE, Al-Busaidi AS, Al-Sulaiti MA, Almawi WY. Analysis of interleukin-18 promoter polymorphisms and changes in interleukin-18 serum levels underscores the involvement of interleukin-18 in recurrent spontaneous miscarriage. *Fertil Steril* 96: 921–926, 2011.

5. Alak BM, Coskun S, Friedman CI, Kennard EA, Kim MH, Seifer DB. Activin A stimulates meiotic maturation of human oocytes and modulates granulosa cell steroidogenesis in vitro. *Fertil Steril* 70: 1126–1130, 1998.

6. Alborzi S, Keramati P, Younesi M, Samsami A, Dadras N. The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas. *Fertil Steril* 101: 427–434, 2014.

7. Allahbadia GN, Saradogan E, Djahanbakhch O. *The Fallopian Tube*. Kent, UK: Ashnan, 2009.

8. Allersma T, Farquhar C, Cantineau AE. Natural cycle in vitro fertilisation (IVF) for subfertile couples. *Cochrane Database Syst Rev* 8: CD010550, 2013.

9. Alliance JH, Hobot PA. *Evidence Based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome*. Melbourne: Jean Hailes for Women's Health on behalf of the PCOS Australian Alliance, 2015.

10. Anderson JL, Mertens CJ, Grajewski B, Luo L, Tseng CY, Cassinelli RT 2nd. Flight attendant radiation dose from solar particle events. *Aviation Space Environ Med* 85: 828–832, 2014.

11. Arakawa C, Yoshinaga J, Mizumoto Y, Abe M. Preliminary study on measurement of human fecundity applicability of time to pregnancy with Japanese subjects. *Jpn J Public Health* 50: 414–419, 2003.

12. Arita A, Costa M. Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. *Metallomics* 1: 222–228, 2009.

13. Artal R, Catanzaro RB, Gavard JA, Mostello DJ, Friganza JC. A lifestyle intervention of weight-gain restriction: diet and exercise in obese women with gestational diabetes mellitus. *Appl Physiol Nutr Metab* 32: 596–601, 2007.

14. Ashraf MW. Levels of heavy metals in popular cigarette brands and exposure to these metals via smoking. *Scientific World J* 2012: 729430, 2012.

15. Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA* 311: 1536–1546, 2014.

16. Aviles M, Gutierrez-Adan A, Coy P. Oviductal secretions: will they be key factors for the future ARTs? *Mol Hum Reprod* 16: 896–906, 2010.

17. Aziz M, Sidelmann JJ, Faber J, Wissing MM, Naver KV, Mikkelsen AL, Nilas L, Skouby SO. Polycystic ovary syndrome: cardiovascular risk factors according to specific phenotypes. *Acta Obstet Gynecol Scand* 94: 1082–1089, 2015.

18. Azziz R. PCOS in 2015: New insights into the genetics of polycystic ovary syndrome. *Nature Rev Endocrinol* 12: 74–75, 2016.

19. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF, Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril* 91: 456–488, 2009.

20. Baerwald AR, Adams GP, Pierson RA. Ovarian antral folliculogenesis during the human menstrual cycle: a review. *Hum Reprod Update* 18: 73–91, 2012.

21. Baird DT. Evidence in vivo for the two-cell hypothesis of oestrogen synthesis by the sheep Graafian follicle. *J Reprod Fertil* 50: 183–185, 1977.

22. Baker TG. A quantitative and cytological study of germ cells in human ovaries. *Proc R Soc Lond Ser B* 158: 417–433, 1963.

23. Balen AH. Ovulation induction in the management of anovulatory polycystic ovary syndrome. *Mol Cell Endocrinol* 373: 77–82, 2013.

24. Barnes RB, Rosenfield RL, Ehrmann DA, Cara JF, Cuttler L, Levitsky LL, Rosenthal IM. Ovarian hyperandrogynism as a result of congenital adrenal virilizing disorders: evidence for perinatal masculinization of neuroendocrine function in women. *J Clin Endocrinol Metab* 79: 1328–1333, 1994.

25. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 77: 1148–1155, 2002.

26. Barrett ES, Sobolewski M. Polycystic ovary syndrome: do endocrine-disrupting chemicals play a role? *Semin Reprod Med* 32: 166–176, 2014.

27. Basavarajappa MS, Craig ZR, Hernandez-Ochoa I, Paulose T, Leslie TC, Flaws JA. Methoxychlor reduces estradiol levels by altering steroidogenesis and metabolism in mouse antral follicles in vitro. *Toxicol Appl Pharmacol* 253: 161–169, 2011.

28. Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 418: 650–654, 2002.

29. Bellver J, Martinez-Conejero JA, Labarta E, Alama P, Melo MA, Remohi J, Pellicer A, Horcajadas JA. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. *Fertil Steril* 95: 2335–2341, 2011.

30. Bellver J, Melo MA, Bosch E, Serra V, Remohi J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. *Fertil Steril* 88: 446–451, 2007.

31. Ben-Nagi J, Miell J, Yazbek J, Holland T, Jurkovic D. The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings. *Reprod Biomed Online* 19: 737–744, 2009.

32. Bentov Y, Yavorska T, Esfandiari N, Jurisicova A, Casper RF. The contribution of mitochondrial function to reproductive aging. *J Assist Reprod Genet* 28: 773–783, 2011.

33. Berga S, Naftolin F. Neuroendocrine control of ovulation. *Gynecol Endocrinol* 28 Suppl 1: 9–13, 2012.

34. Berga SL, Daniels TL, Giles DE. Women with functional hypothalamic amenorrhea but not other forms of anovulation display amplified cortisol concentrations. *Fertil Steril* 67: 1024–1030, 1997.

35. Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R, Krohn MA. Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy. *Fertil Steril* 80: 976–981, 2003.

36. Bhattacharya P, Keating AF. Impact of environmental exposures on ovarian function and role of xenobiotic metabolism during ovotoxicity. *Toxicol Appl Pharmacol* 261: 227–235, 2012.

37. Bhattacharya S, Johnson N, Tijani HA, Hart R, Pandey S, Gibreel AF. Female infertility. *BMJ Clin Evid* pii: 0819, 2010.

38. Birnie AM, Keoghane SR. Radiation exposure to a pregnant urological surgeon: what is safe? *BJU Int* 115: 683–685, 2015.

39. Bloom MS, Kim D, Vom Saal FS, Taylor JA, Cheng G, Lamb JD, Fujimoto VY. Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilization. *Fertil Steril* 96: 672–677, 2011.

40. Boadi WY, Shurtz-Swirski R, Barnea ER, Urbach J, Brandes JM, Philo E, Yannai S. Secretion of human chorionic gonadotropin in superfused young placental tissue exposed to cadmium. *Arch Toxicol* 66: 95–99, 1992.

41. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 12: 673–683, 2006.

42. Boucher JG, Boudreau A, Ahmed S, Atlas E. In vitro effects of bisphenol A beta-D-glucuronide (BPA-G) on adipogenesis in human and murine preadipocytes. *Environ Health Perspect* 123: 1287–1293, 2015.

43. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, Job-Spira N. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol* 157: 185–194, 2003.

44. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 3: CD009590, 2014.

45. Burger HG, Cahir N, Robertson DM, Groome NP, Dudley E, Green A, Dennerstein L. Serum inhibins A and B fall differentially as FSH rises in perimenopausal women. *Clin Endocrinol* 48: 809–813, 1998.

46. Burger HG, Hale GE, Dennerstein L, Robertson DM. Cycle and hormone changes during perimenopause: the key role of ovarian function. *Menopause* 15: 603–612, 2008.

47. Cai LY, Izumi S, Suzuki T, Goya K, Nakamura E, Sugiyama T, Kobayashi H. Dioxins in ascites and serum of women with endometriosis: a pilot study. *Hum Reprod* 26: 117–126, 2011.

48. Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. *Hum Reprod Update* 17: 242–253, 2011.

49. Camlin NJ, McLaughlin EA, Holt JE. Through the smoke: use of in vivo and in vitro cigarette smoking models to elucidate its effect on female fertility. *Toxicol Appl Pharmacol* 281: 266–275, 2014.

50. Care AS, Diener KR, Jasper MJ, Brown HM, Ingman WV, Robertson SA. Macrophages regulate corpus luteum development during embryo implantation in mice. *J Clin Invest* 123: 3472–3487, 2013.

51. Carlsson IB, Scott JE, Visser JA, Ritvos O, Themmen AP, Hovatta O. Anti-Mullerian hormone inhibits initiation of growth of human primordial ovarian follicles in vitro. *Hum Reprod* 21: 2223–2227, 2006.

52. Caserta D, Di Segni N, Mallozzi M, Giovanale V, Mantovani A, Marci R, Moscarini M. Bisphenol A and the female reproductive tract: an overview of recent laboratory evidence and epidemiological studies. *Reprod Biol Endocrinol* 12: 37, 2014.

53. Cermik D, Selam B, Taylor HS. Regulation of HOXA-10 expression by testosterone in vitro and in the endometrium of patients with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88: 238–243, 2003.

54. Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. *Nature Med* 18: 1754–1767, 2012.

55. Chan HC, Shi QX, Zhou CX, Wang XF, Xu WM, Chen WY, Chen AJ, Ni Y, Yuan YY. Critical role of CFTR in uterine bicarbonate secretion and the fertilizing capacity of sperm. *Mol Cell Endocrinol* 250: 106–113, 2006.

56. Chao HH, Zhang XF, Chen B, Pan B, Zhang LJ, Li L, Sun XF, Shi QH, Shen W. Bisphenol A exposure modifies methylation of imprinted genes in mouse oocytes via the estrogen receptor signaling pathway. *Histochem Cell Biol* 137: 249–259, 2012.

57. Chappel S. The role of mitochondria from mature oocyte to viable blastocyst. *Obstet Gynecol Int* 2013: 183024, 2013.

58. Cheng EY, Hunt PA, Naluai-Cecchini TA, Fligner CL, Fujimoto VY, Pasternack TL, Schwartz JM, Steinauer JE, Woodruff TJ, Cherry SM, Hansen TA, Vallente RU, Broman KW, Hassold TJ. Meiotic recombination in human oocytes. *PLoS Genet* 5: e1000661, 2009.

59. Choy CM, Lam CW, Cheung LT, Briton-Jones CM, Cheung LP, Haines CJ. Infertility, blood mercury concentrations and dietary seafood consumption: a case-control study. *BJOG* 109: 1121–1125, 2002.

60. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. *Ann Intern Med* 129: 229–240, 1998.

61. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 13: 1502–1505, 1998.

62. Clift D, Schuh M. Restarting life: fertilization and the transition from meiosis to mitosis. *Nature Rev Mol Cell Biol* 14: 549–562, 2013.

63. Cobellis L, Latini G, De Felice C, Razzi S, Paris I, Ruggieri F, Mazzeo P, Petraglia F. High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. *Hum Reprod* 18: 1512–1515, 2003.

64. Codner E, Merino PM, Tena-Sempere M. Female reproduction and type 1 diabetes: from mechanisms to clinical findings. *Hum Reprod Update* 18: 568–585, 2012.

65. Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. *Hum Reprod Update* 20: 153–174, 2014.

66. Conneely OM, Mulac-Jericevic B, DeMayo F, Lydon JP, O'Malley BW. Reproductive functions of progesterone receptors. *Recent Prog Horm Res* 57: 339–355, 2002.

67. Cordts EB, Christofolini DM, Dos Santos AA, Bianco B, Barbosa CP. Genetic aspects of premature ovarian failure: a literature review. *Arch Gynecol Obstet* 283: 635–643, 2011.

68. Cosby NC, Dukelow WR. Toxicology of maternally ingested trichloroethylene (TCE) on embryonal and fetal development in mice and of TCE metabolites on in vitro fertilization. *Fundam Appl Toxicol* 19: 268–274, 1992.

69. Cragin LA, Kesner JS, Bachand AM, Barr DB, Meadows JW, Krieg EF, Reif JS. Menstrual cycle characteristics and reproductive hormone levels in women exposed to atrazine in drinking water. *Environ Res* 111: 1293–1301, 2011.

70. Craig J, Orisaka M, Wang H, Orisaka S, Thompson W, Zhu C, Kotsuji F, Tsang BK. Gonadotropin and intra-ovarian signals regulating follicle development and atresia: the delicate balance between life and death. *Front Biosci* 12: 3628–3639, 2007.

71. Cramer DW, Welch WR, Cassells S, Scully RE. Mumps, menarche, menopause, and ovarian cancer. *Am J Obstet Gynecol* 147: 1–6, 1983.

72. Crujeiras AB, Casanueva FF. Obesity and the reproductive system disorders: epigenetics as a potential bridge. *Hum Reprod Update* 21: 249–261, 2015.

73. Cummins JM. Fertilization and elimination of the paternal mitochondrial genome. *Hum Reprod* 15 Suppl 2: 92–101, 2000.

74. D'Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready D, Tonetti MS. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res* 83: 156–160, 2004.

75. D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. *Cochrane Database Syst Rev* CD002811, 2011.

76. Darville T, Hiltke TJ. Pathogenesis of genital tract disease due to *Chlamydia trachomatis*. *J Infectious Dis* 201 Suppl 2: S114–125, 2010.

77. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 97: 2543–2565, 2012.

78. De Souza MJ, Leidy HJ, O'Donnell E, Lasley B, Williams NI. Fasting ghrelin levels in physically active women: relationship with menstrual disturbances and metabolic hormones. *J Clin Endocrinol Metab* 89: 3536–3542, 2004.

79. De Souza MJ, Miller BE, Loucks AB, Luciano AA, Pescatello LS, Campbell CG, Lasley BL. High frequency of luteal phase deficiency and anovulation in recreational women runners: blunted elevation in follicle-stimulating hormone observed during luteal-follicular transition. *J Clin Endocrinol Metab* 83: 4220–4232, 1998.

80. Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S, Hedon B, Dechaud H. Effects of cigarette smoking on reproduction. *Hum Reprod Update* 17: 76–95, 2011.

81. Dessolle L, Darai E, Cornet D, Rouzier R, Coutant C, Mandelbaum J, Antoine JM. Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers. *Hum Reprod* 24: 3082–3089, 2009.

82. Devoto L, Fuentes A, Kohen P, Cespedes P, Palomino A, Pommer R, Munoz A, Strauss JF 3rd. The human corpus luteum: life cycle and function in natural cycles. *Fertil Steril* 92: 1067–1079, 2009.

83. Devoto L, Kohen P, Munoz A, Strauss JF 3rd. Human corpus luteum physiology and the luteal-phase dysfunction associated with ovarian stimulation. *Reprod Biomed Online* 18 Suppl 2: 19–24, 2009.

84. Devoto L, Vega M, Kohen P, Castro O, Carvallo P, Palomino A. Molecular regulation of progesterone secretion by the human corpus luteum throughout the menstrual cycle. *J Reprod Immunol* 55: 11–20, 2002.

85. Dey SK, Lim H, Das SK, Reese J, Paria BC, Daikoku T, Wang H. Molecular cues to implantation. *Endocr Rev* 25: 341–373, 2004.

86. Ding YS, Trommel JS, Yan XJ, Ashley D, Watson CH. Determination of 14 polycyclic aromatic hydrocarbons in mainstream smoke from domestic cigarettes. *Environ Sci Technol* 39: 471–478, 2005.

87. Doherty DA, Newnham JP, Bower C, Hart R. Implications of polycystic ovary syndrome for pregnancy and for the health of offspring. *Obstet Gynecol* 125: 1397–1406, 2015.

88. Domecq JP, Prutsky G, Mullan RJ, Hazem A, Sundaresh V, Elamin MB, Phung OJ, Wang A, Hoeger K, Pasquali R, Erwin P, Bodde A, Montori VM, Murad MH. Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. *J Clin Endocrinol Metab* 98: 4655–4663, 2013.

89. Dorrington JH, Moon YS, Armstrong DT. Estradiol-17beta biosynthesis in cultured granulosa cells from hypophysectomized immature rats; stimulation by follicle-stimulating hormone. *Endocrinology* 97: 1328–1331, 1975.

90. Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R, Barlow DH, Jacobson TZ. Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev* 4: CD011031, 2014.

91. Dumesic DA, Abbott DH. Implications of polycystic ovary syndrome on oocyte development. *Semin Reprod Med* 26: 53–61, 2008.

92. Dumesic DA, Meldrum DR, Katz-Jaffe MG, Krisher RL, Schoolcraft WB. Oocyte environment: follicular fluid and cumulus cells are critical for oocyte health. *Fertil Steril* 103: 303–316, 2015.

93. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Berry KF, Calafat AM, Ye X, Petrozza JC, Wright D, Hauser R. Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. *Environ Health Perspect* 120: 978–983, 2012.

94. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Ye X, Calafat AM, Petrozza JC, Wright D, Hauser R. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. *Hum Reprod* 27: 3583–3592, 2012.

95. Erden O, Imir A, Guvenal T, Muslehiddinoglu A, Arici S, Cetin M, Cetin A. Investigation of the effects of heparin and low molecular weight heparin on E-cadherin and laminin expression in rat pregnancy by immunohistochemistry. *Hum Reprod* 21: 3014–3018, 2006.

96. Eroschenko VP, Swartz WJ, Ford LC. Decreased superovulation in adult mice following neonatal exposures to technical methoxychlor. *Reprod Toxicol* 11: 807–814, 1997.

97. Evans JJ, Anderson GM. Balancing ovulation and anovulation: integration of the reproductive and energy balance axes by neuropeptides. *Hum Reprod Update* 18: 313–332, 2012.

98. Evans JP. Sperm-egg interaction. *Annu Rev Physiol* 74: 477–502, 2012.

99. Ezzati M. The role of dynein and its mutations in the ciliary activity of human fallopian tubes. In: *The Fallopian Tube*, edited by Allahbadia GN, Saradogan E, and Djahanbakhch O. Kent, UK: Anshan, 2009.

100. Ezzati M, Djahanbakhch O, Arian S, Carr BR. Tubal transport of gametes and embryos: a review of physiology and pathophysiology. *J Assist Reprod Genet* 31: 1337–1347, 2014.

101. Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: established teratogens and risk factors. *Birth Defects Res A Clin Mol Teratol* 103: 652–655, 2015.

102. Ferk P, Pohar Perme M, Teran N, Gersak K. Androgen receptor gene (CAG)(n) polymorphism in patients with polycystic ovary syndrome. *Fertil Steril* 90: 860–863, 2008.

103. Fernandez M, Bourguignon N, Lux-Lantos V, Libertun C. Neonatal exposure to bisphenol a and reproductive and endocrine alterations resembling the polycystic ovarian syndrome in adult rats. *Environ Health Perspect* 118: 1217–1222, 2010.

104. Florea AM, Yamoah EN, Dopp E. Intracellular calcium disturbances induced by arsenic and its methylated derivatives in relation to genomic damage and apoptosis induction. *Environ Health Perspect* 113: 659–664, 2005.

105. Ford PJ, Raphael SL, Cullinan MP, Jenkins AJ, West MJ, Seymour GJ. Why should a doctor be interested in oral disease? *Expert Rev Cardiovasc Ther* 8: 1483–1493, 2010.

106. Forsdike RA, Hardy K, Bull L, Stark J, Webber LJ, Stubbs S, Robinson JE, Franks S. Disordered follicle development in ovaries of prenatally androgenized ewes. *J Endocrinol* 192: 421–428, 2007.

107. Fortuno C, Labarta E. Genetics of primary ovarian insufficiency: a review. *J Assist Reprod Genet* 31: 1573–1585, 2014.

108. Fragouli E, Bianchi V, Patrizio P, Obradors A, Huang Z, Borini A, Delhanty JD, Wells D. Transcriptomic profiling of human oocytes: association of meiotic aneuploidy and altered oocyte gene expression. *Mol Hum Reprod* 16: 570–582, 2010.

109. Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, Scott RT Jr. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril* 101: 656–663, 2014.

110. Freour T, Dessolle L, Lammers J, Lattes S, Barriere P. Comparison of embryo morphokinetics after in vitro fertilization-intracytoplasmic sperm injection in smoking and nonsmoking women. *Fertil Steril* 99: 1944–1950, 2013.

111. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. *Science* 185: 949–951, 1974.

112. Fuentes A, Munoz A, Barnhart K, Arguello B, Diaz M, Pommer R. Recent cigarette smoking and assisted reproductive technologies outcome. *Fertil Steril* 93: 89–95, 2010.

113. Galusca B, Prevost G, Germain N, Dubuc I, Ling Y, Anouar Y, Estour B, Chartrel N. Neuropeptide Y and alpha-MSH circadian levels in two populations with low body weight: anorexia nervosa and constitutional thinness. *PLoS One* 10: e0122040, 2015.

114. Gardner DK, Meseguer M, Rubio C, Treff NR. Diagnosis of human preimplantation embryo viability. *Hum Reprod Update* 21: 727–747, 2015.

115. Gardner DK, Wale PL, Collins R, Lane M. Glucose consumption of single post-compaction human embryos is predictive of embryo sex and live birth outcome. *Hum Reprod* 26: 1981–1986, 2011.

116. Gaskins AJ, Rich-Edwards JW, Lawson CC, Schernhammer ES, Missmer SA, Chavarro JE. Work schedule and physical factors in relation to fecundity in nurses. *Occup Environ Med* 72: 777–783, 2015.

117. Gaskins AJ, Rich-Edwards JW, Missmer SA, Rosner B, Chavarro JE. Association of fecundity with changes in adult female weight. *Obstet Gynecol* 126: 850–858, 2015.

118. Ge ZJ, Luo SM, Lin F, Liang QX, Huang L, Wei YC, Hou Y, Han ZM, Schatten H, Sun QY. DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity. *Environ Health Perspect* 122: 159–164, 2014.

120. Ge ZJ, Schatten H, Zhang CL, Sun QY. Oocyte ageing and epigenetics. *Reproduction* 149: R103–114, 2015.

121. Genbacev O, Bass KE, Joslin RJ, Fisher SJ. Maternal smoking inhibits early human cytotrophoblast differentiation. *Reprod Toxicol* 9: 245–255, 1995.

122. Genbacev O, McMaster MT, Lazic J, Nedeljkovic S, Cvetkovic M, Joslin R, Fisher SJ. Concordant in situ and in vitro data show that maternal cigarette smoking negatively regulates placental cytotrophoblast passage through the cell cycle. *Reprod Toxicol* 14: 495–506, 2000.

123. George JT, Seminara SB. Kisspeptin and the hypothalamic control of reproduction: lessons from the human. *Endocrinology* 153: 5130–5136, 2012.

124. Glueck CJ, Wang P, Fontaine RN, Sieve-Smith L, Tracy T, Moore SK. Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. *Metab Clin Exp* 48: 1589–1595, 1999.

125. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr Rev* 36: E1–E150, 2015.

126. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr Rev* 36: 593–602, 2015.

127. Gormack AA, Peek JC, Derraik JG, Gluckman PD, Young NL, Cutfield WS. Many women undergoing fertility treatment make poor lifestyle choices that may affect treatment outcome. *Hum Reprod* 30: 1617–1624, 2015.

128. Goswami D, Conway GS. Premature ovarian failure. *Hum Reprod Update* 11: 391–410, 2005.

129. Gougeon A. Dynamics of follicular growth in the human: a model from preliminary results. *Hum Reprod* 1: 81–87, 1986.

130. Grodnitskaya EE, Kurtser MA. Homocysteine metabolism in polycystic ovary syndrome. *Gynecol Endocrinol* 28: 186–189, 2012.

131. Grondahl ML, Yding Andersen C, Bogstad J, Nielsen FC, Meinertz H, Borup R. Gene expression profiles of single human mature oocytes in relation to age. *Hum Reprod* 25: 957–968, 2010.

132. Guelinckx I, Devlieger R, Vansant G. Reproductive outcome after bariatric surgery: a critical review. *Hum Reprod Update* 15: 189–201, 2009.

133. Guglielmino MR, Santonocito M, Vento M, Ragusa M, Barbagallo D, Borzi P, Casciano I, Banelli B, Barbieri O, Astigiano S, Scollo P, Romani M, Purrello M, Di Pietro C. TAp73 is downregulated in oocytes from women of advanced reproductive age. *Cell Cycle* 10: 3253–3256, 2011.

134. Halasz M, Szekeres-Bartho J. The role of progesterone in implantation and trophoblast invasion. *J Reprod Immunol* 97: 43–50, 2013.

135. Halse RE, Wallman KE, Dimmock JA, Newnham JP, Guelfi KJ. Home-based exercise improves fitness and exercise attitude and intention in women with GDM. *Med Sci Sports Exerc* 47: 1698–1704, 2015.

136. Handyside AH. Molecular origin of female meiotic aneuploidies. *Biochim Biophys Acta* 1822: 1913–1920, 2012.

137. Hansen M, Bower C, Milne E, de Klerk N, Kurinczuk JJ. Assisted reproductive technologies and the risk of birth defects–a systematic review. *Hum Reprod* 20: 328–338, 2005.

138. Hart R. Preservation of fertility in adults and children diagnosed with cancer. *BMJ* 337: a2045, 2008.

139. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. *J Clin Endocrinol Metab* 100: 911–919, 2015.

140. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. *J Clin Endocrinol Metab* jc20143886, 2014.

141. Hart R, Doherty DA, Frederiksen H, Keelan JA, Hickey M, Sloboda D, Pennell CE, Newnham JP, Skakkebaek NE, Main KM. The influence of antenatal exposure to phthalates on subsequent female reproductive development in adolescence: a pilot study. *Reproduction* 147: 379–390, 2014.

142. Hart R, Doherty DA, Norman RJ, Franks S, Dickinson JE, Hickey M, Sloboda DM. Serum antimullerian hormone (AMH) levels are elevated in adolescent girls with polycystic ovaries and the polycystic ovarian syndrome (PCOS). *Fertil Steril* 94: 1118–1121, 2010.

143. Hart R, Doherty DA, Pennell CE, Newnham IA, Newnham JP. Periodontal disease: a potential modifiable risk factor limiting conception. *Hum Reprod* 27: 1332–1342, 2012.

144. Hart R, Doherty DA, Pennell CE, Newnham IA, Newnham JP. Periodontal disease: a potential modifiable risk factor limiting conception. *Hum Reprod* 27: 1332–1342, 2012.

145. Hart R, Khalaf Y, Yeong CT, Seed P, Taylor A, Braude P. A prospective controlled study of the effect of intramural uterine fibroids on the outcome of assisted conception. *Hum Reprod* 16: 2411–2417, 2001.

146. Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment. Part I–General health outcomes. *Hum Reprod Update* 19: 232–243, 2013.

147. Hart R, Sloboda DM, Doherty DA, Norman RJ, Atkinson HC, Newnham JP, Dickinson JE, Hickey M. Circulating maternal testosterone concentrations at 18 weeks of gestation predict circulating levels of antimullerian hormone in adolescence: a prospective cohort study. *Fertil Steril* 94: 1544–1547, 2010.

148. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* CD004992, 2008.

149. Heggland I, Irgens A, Tollanes M, Romundstad P, Syversen T, Svendsen K, Melo I, Hilt B. Pregnancy outcomes among female dental personnel–a registry-based retrospective cohort study. *Scand J Work Environ Health* 37: 539–546, 2011.

150. Hewitt JK, Jayasinghe Y, Amor DJ, Gillam LH, Warne GL, Grover S, Zacharin MR. Fertility in Turner syndrome. *Clin Endocrinol* 79: 606–614, 2013.

151. Hickey M, Sloboda DM, Atkinson HC, Doherty DA, Franks S, Norman RJ, Newnham JP, Hart R. The relationship between maternal and umbilical cord androgen levels and polycystic ovary syndrome in adolescence: a prospective cohort study. *J Clin Endocrinol Metab* 94: 3714–3720, 2009.

152. Hjordt Hansen MV, Dalsgaard T, Hartwell D, Skovlund CW, Lidegaard O. Reproductive prognosis in endometriosis. A national cohort study. *Acta Obstet Gynecol Scand* 93: 483–489, 2014.

153. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 87: 489–499, 2002.

154. Holubcova Z, Blayney M, Elder K, Schuh M. Human oocytes. Error-prone chromosome-mediated spindle assembly favors chromosome segregation defects in human oocytes. *Science* 348: 1143–1147, 2015.

155. Homburg R, Hendriks ML, Konig TE, Anderson RA, Balen AH, Brincat M, Child T, Davies M, D'Hooghe T, Martinez A, Rajkhowa M, Rueda-Saenz R, Hompes P, Lambalk CB. Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study. *Hum Reprod* 27: 468–473, 2012.

156. Hooser SB, Douds DP, DeMerell DG, Hoyer PB, Sipes IG. Long-term ovarian and gonadotropin changes in mice exposed to 4-vinylcyclohexene. *Reprod Toxicol* 8: 315–323, 1994.

157. Huang RC, Mori TA, Beilin LJ. Early life programming of cardiometabolic disease in the Western Australian pregnancy cohort (Raine) study. *Clin Exp Pharmacol Physiol* 39: 973–978, 2012.

158. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation suppression for endometriosis. *Cochrane Database Syst Rev* CD000155, 2007.

159. Hulboy DL, Rudolph LA, Matrisian LM. Matrix metalloproteinases as mediators of reproductive function. *Mol Hum Reprod* 3: 27–45, 1997.

160. Hunt PA, Lawson C, Gieske M, Murdoch B, Smith H, Marre A, Hassold T, VandeVoort CA. Bisphenol A alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey. *Proc Natl Acad Sci USA* 109: 17525–17530, 2012.

161. Igawa Y, Keating AF, Rajapaksa KS, Sipes IG, Hoyer PB. Evaluation of ovotoxicity induced by 7, 12-dimethylbenz[a]anthracene and its 3,4-diol metabolite utilizing a rat in vitro ovarian culture system. *Toxicol Appl Pharmacol* 234: 361–369, 2009.

162. Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Hum Reprod* 17: 2839–2841, 2002.

163. Isling LK, Boberg J, Jacobsen PR, Mandrup KR, Axelstad M, Christiansen S, Vinggaard AM, Taxvig C, Kortenkamp A, Hass U. Late-life effects on rat reproductive system after developmental exposure to mixtures of endocrine disrupters. *Reproduction* 147: 465–476, 2014.

164. Ivanov P, Tsvyatkovska T, Konova E, Komsa-Penkova R. Inherited thrombophilia and IVF failure: the impact of coagulation disorders on implantation process. *Am J Reprod Immunol* 68: 189–198, 2012.

165. Jablonska O, Shi Z, Valdez KE, Ting AY, Petroff BK. Temporal and anatomical sensitivities to the aryl hydrocarbon receptor agonist 2,3,7,8-tetrachlorodibenzo-*p*-dioxin leading to premature acyclicity with age in rats. *Int J Androl* 33: 405–412, 2010.

166. Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P. Fecundability in relation to body mass and menstrual cycle patterns. *Epidemiology* 10: 422–428, 1999.

167. Jick H, Porter J. Relation between smoking and age of natural menopause. Report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *Lancet* 1: 1354–1355, 1977.

168. Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, Stephansson O, Neovius M. Outcomes of pregnancy after bariatric surgery. *N Engl J Med* 372: 814–824, 2015.

169. Jungheim ES, Schon SB, Schulte MB, DeUgarte DA, Fowler SA, Tuuli MG. IVF outcomes in obese donor oocyte recipients: a systematic review and meta-analysis. *Hum Reprod* 28: 2720–2727, 2013.

170. Kadhel P, Monnier P, Boucoiran I, Chaillet N, Fraser WD. Organochlorine pollutants and female fertility: a systematic review focusing on in vitro fertilization studies. *Reprod Sci* 19: 1246–1259, 2012.

171. Kallen CB, Arakane F, Christenson LK, Watari H, Devoto L, Strauss JF 3rd. Unveiling the mechanism of action and regulation of the steroidogenic acute regulatory protein. *Mol Cell Endocrinol* 145: 39–45, 1998.

172. Kandaraki E, Chatzigeorgiou A, Livadas S, Palioura E, Economou F, Koutsilieris M, Palimeri S, Panidis D, Diamanti-Kandarakis E. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. *J Clin Endocrinol Metab* 96: E480–484, 2011.

173. Karavan JR, Pepling ME. Effects of estrogenic compounds on neonatal oocyte development. *Reprod Toxicol* 34: 51–56, 2012.

174. Kaufman F, Kogut MD, Donnell GN, Koch H, Goebelsmann U. Ovarian failure in galactosaemia. *Lancet* 2: 737–738, 1979.

175. Kawato H, Tabata T, Minoura H, Murabayashi N, Ma N, Wang DF, Sagawa N. Factor XII gene expression in endometrial stromal cells during decidualisation. *Reprod Fertil Dev* 21: 840–847, 2009.

176. Kezele PR, Nilsson EE, Skinner MK. Insulin but not insulin-like growth factor-1 promotes the primordial to primary follicle transition. *Mol Cell Endocrinol* 192: 37–43, 2002.

177. Khadzhieva MB, Lutcenko NN, Volodin IV, Morozova KV, Salnikova LE. Association of oxidative stress-related genes with idiopathic recurrent miscarriage. *Free Radical Res* 48: 534–541, 2014.

178. Khan S, Beigh S, Chaudhari BP, Sharma S, Aliul Hasan Abdi S, Ahmad S, Ahmad F, Parvez S, Raisuddin S. *Mitochondrial* dysfunction induced by Bisphenol A is a factor of its hepatotoxicity in rats. *Environ Toxicol toxicology* 2015 doi: 10.1002/tox.22193.

179. Kline J, Levin B, Kinney A, Stein Z, Susser M, Warburton D. Cigarette smoking and spontaneous abortion of known karyotype. Precise data but uncertain inferences. *Am J Epidemiol* 141: 417–427, 1995.

180. Knight PG, Satchell L, Glister C. Intra-ovarian roles of activins and inhibins. *Mol Cell Endocrinol* 359: 53–65, 2012.

181. Knoll M, Talbot P. Cigarette smoke inhibits oocyte cumulus complex pick-up by the oviduct in vitro independent of ciliary beat frequency. *Reprod Toxicol* 12: 57–68, 1998.

182. Koch HM, Calafat AM. Human body burdens of chemicals used in plastic manufacture. *Philos Trans R Soc Lond B Biol Sci* 364: 2063–2078, 2009.

183. Konstantinidis M, Alfarawati S, Hurd D, Paolucci M, Shovelton J, Fragouli E, Wells D. Simultaneous assessment of aneuploidy, polymorphisms, and mitochondrial DNA content in human polar bodies and embryos with the use of a novel microarray platform. *Fertil Steril* 102: 1385–1392, 2014.

184. Kristensen SG, Andersen K, Clement CA, Franks S, Hardy K, Andersen CY. Expression of TGF-beta superfamily growth factors, their receptors, the associated SMADs and antagonists in five isolated size-matched populations of pre-antral follicles from normal human ovaries. *Mol Hum Reprod* 20: 293–308, 2014.

185. Krog M, Prior M, Carlsen E, Loft A, Forman J, Pinborg A, Andersen AN. Fertilization failure after IVF in 304 couples–a case-control study on predictors and long-term prognosis. *Eur J Obstet Gynecol Reprod Biol* 184: 32–37, 2015.

186. Kroon B, Johnson N, Chapman M, Yazdani A, Hart R, Australasian CCEPoTeg. Fibroids in infertility–consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence). *Aust N Z J Obstet Gynaecol* 51: 289–295, 2011.

187. Krotz SP, Carson SA, Tomey C, Buster JE. Phthalates and bisphenol do not accumulate in human follicular fluid. *J Assist Reprod Genet* 29: 773–777, 2012.

188. Kurkowiak M, Zietkiewicz E, Witt M. Recent advances in primary ciliary dyskinesia genetics. *J Med Genet* 52: 1–9, 2015.

189. Kwik M, Karia S, Boothroyd C. RANZCOG CREI Consensus Statement on treatment of Ovarian Hyperstimulation Syndrome. *Aust N Z J Obstet Gynaecol* 55: 413–419, 2015.

190. Landgren BM, Collins A, Csemiczky G, Burger HG, Baksheev L, Robertson DM. Menopause transition: Annual changes in serum hormonal patterns over the menstrual cycle in women during a nine-year period prior to menopause. *J Clin Endocrinol Metab* 89: 2763–2769, 2004.

191. Lane M, Gardner DK. Embryo culture medium: which is the best? *Best Pract Res Clin Obstet Gynaecol* 21: 83–100, 2007.

192. Larsen U, Vaupel JW. Hutterite fecundability by age and parity: strategies for frailty modeling of event histories. *Demography* 30: 81–102, 1993.

193. Lathi RB, Liebert CA, Brookfield KF, Taylor JA, vom Saal FS, Fujimoto VY, Baker VL. Conjugated bisphenol A in maternal serum in relation to miscarriage risk. *Fertil Steril* 102: 123–128, 2014.

194. Layman LC. The genetic basis of female reproductive disorders: etiology and clinical testing. *Mol Cell Endocrinol* 370: 138–148, 2013.

195. Leary C, Leese HJ, Sturmey RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. *Hum Reprod* 30: 122–132, 2015.

196. Lechniak D, Pers-Kamczyc E, Pawlak P. Timing of the first zygotic cleavage as a marker of developmental potential of mammalian embryos. *Reprod Biol* 8: 23–42, 2008.

197. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H, Network NRM. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 371: 119–129, 2014.

198. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, Gnatuk CL, Estes SJ, Fleming J, Allison KC, Sarwer DB, Coutifaris C, Dokras A. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 100: 4048–4058, 2015.

199. Lerchbaum E, Rabe T. Vitamin D and female fertility. *Curr Opin Obstet Gynecol* 26: 145–150, 2014.

200. Lessey BA, Young SL. Integrins and other cell adhesion molecules in endometrium and endometriosis. *Semin Reprod Endocrinol* 15: 291–299, 1997.

201. Liu Y, Li GP, Sessions BR, Rickords LF, White KL, Bunch TD. Nicotine induces multinuclear formation and causes aberrant embryonic development in bovine. *Mol Reprod Dev* 75: 801–809, 2008.

202. Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, Schedl T, Moley KH. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. *PLoS One* 7: e49217, 2012.

203. Lyons RA, Djahanbakhch O, Saridogan E, Naftalin AA, Mahmood T, Weekes A, Chenoy R. Peritoneal fluid, endometriosis, and ciliary beat frequency in the human fallopian tube. *Lancet* 360: 1221–1222, 2002.

204. Lyons RA, Saridogan E, Djahanbakhch O. The reproductive significance of human Fallopian tube cilia. *Hum Reprod Update* 12: 363–372, 2006.

205. Macaldowie A, Lee E, Chambers G. *Assisted Reproductive Technology in Australia and New Zealand 2013*. Sydney: National Perinatal Epidemiology and Statistics Unit, Univ. of New South Wales, 2015.

206. Macaldowie A, Wang Y, Chambers G, Sullivan E. *Assisted Reproductive Technology in Australia and New Zealand 2011*. Sydney: Univ. of New South Wales, 2013.

207. Machtinger R, Orvieto R. Bisphenol A, oocyte maturation, implantation, and IVF outcome: review of animal and human data. *Reprod Biomed Online* 29: 404–410, 2014.

208. MacLennan M, Crichton JH, Playfoot CJ, Adams IR. Oocyte development, meiosis and aneuploidy. *Semin Cell Dev Biol* 45: 68–76, 2015.

209. Magli MC, Gianaroli L, Ferraretti AP, Gordts S, Fredericks V, Crippa A. Paternal contribution to aneuploidy in preimplantation embryos. *Reprod Biomed Online* 18: 536–542, 2009.

210. Manova K, Huang EJ, Angeles M, De Leon V, Sanchez S, Pronovost SM, Besmer P, Bachvarova RF. The expression pattern of the c-kit ligand in gonads of mice supports a role for the c-kit receptor in oocyte growth and in proliferation of spermatogonia. *Dev Biol* 157: 85–99, 1993.

211. Martinez-Zamora MA, Mattioli L, Parera J, Abad E, Coloma JL, van Babel B, Galceran MT, Balasch J, Carmona F. Increased levels of dioxin-like substances in adipose tissue in patients with deep infiltrating endometriosis. *Hum Reprod* 30: 1059–1068, 2015.

212. Master JS, Thouas GA, Harvey AJ, Sheedy JR, Hannan NJ, Gardner DK, Wlodek ME. Low female birth weight and advanced maternal age programme alterations in next-generation blastocyst development. *Reproduction* 149: 497–510, 2015.

213. May-Panloup P, Chretien MF, Jacques C, Vasseur C, Malthiery Y, Reynier P. Low oocyte mitochondrial DNA content in ovarian insufficiency. *Hum Reprod* 20: 593–597, 2005.

214. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine S. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96: 273–288, 2011.

215. Merchant-Larios H, Centeno B. Morphogenesis of the ovary from the sterile W/Wv mouse. *Prog Clin Biol Res* 59B: 383–392, 1981.

216. Meseguer M, Herrero J, Tejera A, Hilligsoe KM, Ramsing NB, Remohi J. The use of morphokinetics as a predictor of embryo implantation. *Hum Reprod* 26: 2658–2671, 2011.

217. Milesi MM, Alarcon R, Ramos JG, Munoz-de-Toro M, Luque EH, Varayoud J. Neonatal exposure to low doses of endosulfan induces implantation failure and disrupts uterine functional differentiation at the pre-implantation period in rats. *Mol Cell Endocrinol* 401: 248–259, 2015.

218. Minge CE, Bennett BD, Norman RJ, Robker RL. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. *Endocrinology* 149: 2646–2656, 2008.

219. Misra M, Miller KK, Tsai P, Gallagher K, Lin A, Lee N, Herzog DB, Klibanski A. Elevated peptide YY levels in adolescent girls with anorexia nervosa. *J Clin Endocrinol Metab* 91: 1027–1033, 2006.

220. Misso ML, Costello MF, Garrubba M, Wong J, Hart R, Rombauts L, Melder AM, Norman RJ, Teede HJ. Metformin versus clomiphene citrate for infertility in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 19: 2–11, 2013.

221. Misso ML, Teede HJ, Hart R, Wong J, Rombauts L, Melder AM, Norman RJ, Costello MF. Status of clomiphene citrate and metformin for infertility in PCOS. *Trends Endocrinol Metab* 23: 533–543, 2012.

222. Misso ML, Wong JL, Teede HJ, Hart R, Rombauts L, Melder AM, Norman RJ, Costello MF. Aromatase inhibitors for PCOS: a systematic review and meta-analysis. *Hum Reprod Update* 18: 301–312, 2012.

223. Mitchell C, Prabhu M. Pelvic inflammatory disease: current concepts in pathogenesis, diagnosis and treatment. *Infect Dis Clinic N Am* 27: 793–809, 2013.

224. Mitchell JA, Hammer RE. Effects of nicotine on oviducal blood flow and embryo development in the rat. *J Reprod Fertil* 74: 71–76, 1985.

225. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod Update* 15: 477–488, 2009.

226. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 16: 347–363, 2010.

227. Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD. Effects of lifetime exercise on the outcome of in vitro fertilization. *Obstet Gynecol* 108: 938–945, 2006.

228. Murdoch WJ. Proteolytic and cellular death mechanisms in ovulatory ovarian rupture. *Biol Signals Receptors* 9: 102–114, 2000.

229. Murri M, Luque-Ramirez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. *Hum Reprod Update* 19: 268–288, 2013.

230. Muzii L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. *Hum Reprod* 29: 2190–2198, 2014.

231. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. *Hum Reprod Update* 21: 560–574, 2015.

232. Navarro VM, Kaiser UB. Metabolic influences on neuroendocrine regulation of reproduction. *Curr Opin Endocrinol Diabetes Obesity* 20: 335–341, 2013.

233. Nelen WL, Steegers EA, Eskes TK, Blom HJ. Genetic risk factor for unexplained recurrent early pregnancy loss. *Lancet* 350: 861, 1997.

234. Neri A, Marcus SL. Effect of nicotine on the motility of the oviducts in the rhesus monkey: a preliminary report. *J Reprod Fertil* 31: 91–97, 1972.

235. Newnham JP, Newnham IA, Ball CM, Wright M, Pennell CE, Swain J, Doherty DA. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstet Gynecol* 114: 1239–1248, 2009.

236. Nikas G, Psychoyos A. Uterine pinopodes in peri-implantation human endometrium. Clinical relevance. *Ann NY Acad Sci* 816: 129–142, 1997.

237. Nilsson EE, Kezele P, Skinner MK. Leukemia inhibitory factor (LIF) promotes the primordial to primary follicle transition in rat ovaries. *Mol Cell Endocrinol* 188: 65–73, 2002.

238. No ACO. Exposure to toxic environmental agents. *Obstet Gynecol* 122: 931–935, 2013.

239. Norman RJ. The power of one and its cost. *Med J Aust* 195: 564–565, 2011.

240. Norman RJ, Clark AM. Obesity and reproductive disorders: a review. *Reprod Fertil Dev* 10: 55–63, 1998.

241. Okabe M. The cell biology of mammalian fertilization. *Development* 140: 4471–4479, 2013.

242. Oktay K, Bedoschi G. Oocyte cryopreservation for fertility preservation in postpubertal female children at risk for premature ovarian failure due to accelerated follicle loss in turner syndrome or cancer treatments. *J Pediatr Adolescent Gynecol* 27: 342–346, 2014.

243. Oktem O, Urman B. Understanding follicle growth in vivo. *Hum Reprod* 25: 2944–2954, 2010.

244. Owusu-Edusei K Jr, Bohm MK, Chesson HW, Kent CK. Chlamydia screening and pelvic inflammatory disease: Insights from exploratory time-series analyses. *Am J Prevent Med* 38: 652–657, 2010.

245. Pal L, Zhang K, Zeitlian G, Santoro N. Characterizing the reproductive hormone milieu in infertile women with diminished ovarian reserve. *Fertil Steril* 93: 1074–1079, 2010.

246. Palioura E, Diamanti-Kandarakis E. Polycystic ovary syndrome (PCOS) and endocrine disrupting chemicals (EDCs). *Rev Endocr Metab Disorders*. In press.

247. Palomba S, Falbo A, Chiossi G, Tolino A, Tucci L, La Sala GB, Zullo F. Early trophoblast invasion and placentation in women with different PCOS phenotypes. *Reprod Biomed Online* 29: 370–381, 2014.

248. Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials. *BJOG* 120: 267–276, 2013.

249. Palomba S, Russo T, Falbo A, Di Cello A, Amendola G, Mazza R, Tolino A, Zullo F, Tucci L, La Sala GB. Decidual endovascular trophoblast invasion in women with polycystic ovary syndrome: an experimental case-control study. *J Clin Endocrinol Metab* 97: 2441–2449, 2012.

250. Papathanasiou A, Djahanbakhch O, Saridogan E, Lyons RA. The effect of interleukin-6 on ciliary beat frequency in the human fallopian tube. *Fertil Steril* 90: 391–394, 2008.

251. Parisi MA, Spong CY, Zajicek A, Guttmacher AE. We don't know what we don't study: the case for research on medication effects in pregnancy. *Am J Med Genet C Med Genet* 157C: 247–250, 2011.

252. Paszkowski T, Clarke RN, Hornstein MD. Smoking induces oxidative stress inside the Graafian follicle. *Hum Reprod* 17: 921–925, 2002.

253. Patel S, Zhou C, Rattan S, Flaws JA. The Effects of Endocrine Disrupting Chemicals on the Ovary. *Biol Reprod* 93: 20, 2015.

254. Persani L, Rossetti R, Cacciatore C, Fabre S. Genetic defects of ovarian TGF-beta-like factors and premature ovarian failure. *J Endocrinol Invest* 34: 244–251, 2011.

255. Persani L, Rossetti R, Di Pasquale E, Cacciatore C, Fabre S. The fundamental role of bone morphogenetic protein 15 in ovarian function and its involvement in female fertility disorders. *Hum Reprod Update* 20: 869–883, 2014.

256. Petersen GL, Schmidt L, Pinborg A, Kamper-Jorgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. *Fertil Steril* 99: 1654–1662, 2013.

257. Pigny P, Merlen E, Robert Y, Cortet-Rudelli C, Decanter C, Jonard S, Dewailly D. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. *J Clin Endocrinol Metab* 88: 5957–5962, 2003.

258. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. *Am J Epidemiol* 179: 807–823, 2014.

259. Pinilla L, Aguilar E, Dieguez C, Millar RP, Tena-Sempere M. Kisspeptins and reproduction: physiological roles and regulatory mechanisms. *Physiol Rev* 92: 1235–1316, 2012.

260. Plasschaert RN, Bartolomei MS. Genomic imprinting in development, growth, behavior and stem cells. *Development* 141: 1805–1813, 2014.

261. Pocar P, Fiandanese N, Secchi C, Berrini A, Fischer B, Schmidt JS, Schaedlich K, Rhind SM, Zhang Z, Borromeo V. Effects of polychlorinated biphenyls in CD-1 mice: reproductive toxicity and intergenerational transmission. *Toxicol Sci* 126: 213–226, 2012.

262. Pollack AZ, Buck Louis GM, Chen Z, Sun L, Trabert B, Guo Y, Kannan K. Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. *Environ Res* 137: 101–107, 2015.

263. Polotsky AJ, Allshouse AA, Casson PR, Coutifaris C, Diamond MP, Christman GM, Schlaff WD, Alvero R, Trussell JC, Krawetz SA, Santoro N, Eisenberg E, Zhang H, Legro RS. Impact of male and female weight, smoking, and intercourse frequency on live birth in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 100: 2405–2412, 2015.

264. Potdar N, Gelbaya TA, Konje JC, Nardo LG. Adjunct low-molecular-weight heparin to improve live birth rate after recurrent implantation failure: a systematic review and meta-analysis. *Hum Reprod Update* 19: 674–684, 2013.

265. Potts M, Psychoyos A. Evolution of the ultrastructure of the ovoendometrial connections under the influence of estrogen in the rat during experimental retardation of nidation. *Comptes Rendus hebdomadaires des seances de l'Academie des sciences Serie D: Sciences naturelles* 264: 370–373, 1967.

266. Practice Committee of American Society For Reproductive Medicine. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. *Fertil Steril* 97: 282–284, 2012.

267. Practice Committee of American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. *Fertil Steril* 90: S188–193, 2008.

268. Qiao J, Feng HL. Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. *Hum Reprod Update* 17: 17–33, 2011.

269. Qin JZ, Pang LH, Li MJ, Fan XJ, Huang RD, Chen HY. Obstetric complications in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Reprod Biol Endocrinol* 11: 56, 2013.

270. Radin RG, Hatch EE, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis AH, Wise LA. Active and passive smoking and fecundability in Danish pregnancy planners. *Fertil Steril* 102: 183–191, 2014.

271. Ramesh A, Archibong AE, Niaz MS. Ovarian susceptibility to benzo[a]pyrene: tissue burden of metabolites and DNA adducts in F-344 rats. *J Toxicol Environ Health A* 73: 1611–1625, 2010.

272. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, Bonde JP, Sorensen TI, Olsen J. Subfecundity in overweight and obese couples. *Hum Reprod* 22: 1634–1637, 2007.

273. Rana P, Kazmi I, Singh R, Afzal M, Al-Abbasi FA, Aseeri A, Singh R, Khan R, Anwar F. Ectopic pregnancy: a review. *Arch Gynecol Obstet* 288: 747–757, 2013.

274. Regan L, Rai R. Thrombophilia and pregnancy loss. *J Reprod Immunol* 55: 163–180, 2002.

275. Retamales I, Carrasco I, Troncoso JL, Las Heras J, Devoto L, Vega M. Morphofunctional study of human luteal cell subpopulations. *Hum Reprod* 9: 591–596, 1994.

276. Reynier P, May-Panloup P, Chretien MF, Morgan CJ, Jean M, Savagner F, Barriere P, Malthiery Y. Mitochondrial DNA content affects the fertilizability of human oocytes. *Mol Hum Reprod* 7: 425–429, 2001.

277. Rice S, Elia A, Jawad Z, Pellatt L, Mason HD. Metformin inhibits follicle-stimulating hormone (FSH) action in human granulosa cells: relevance to polycystic ovary syndrome. *J Clin Endocrinol Metab* 98: E1491–1500, 2013.

278. Ristovska G, Laszlo HE, Hansell AL. Reproductive outcomes associated with noise exposure: a systematic review of the literature. *Int J Environ Res Public Health* 11: 7931–7952, 2014.

279. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. *Reprod Biomed Online* 23: 421–439, 2011.

280. Rivera OE, Varayoud J, Rodriguez HA, Munoz-de-Toro M, Luque EH. Neonatal exposure to bisphenol A or diethylstilbestrol alters the ovarian follicular dynamics in the lamb. *Reprod Toxicol* 32: 304–312, 2011.

281. Robinson JE, Birch RA, Foster DL, Padmanabhan V. Prenatal exposure of the ovine fetus to androgens sexually differentiates the steroid feedback mechanisms that control gonadotropin releasing hormone secretion and disrupts ovarian cycles. *Arch Sex Behav* 31: 35–41, 2002.

282. Robker RL, Akison LK, Bennett BD, Thrupp PN, Chura LR, Russell DL, Lane M, Norman RJ. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. *J Clin Endocrinol Metab* 94: 1533–1540, 2009.

283. Rodriguez HA, Santambrosio N, Santamaria CG, Munoz-de-Toro M, Luque EH. Neonatal exposure to bisphenol A reduces the pool of primordial follicles in the rat ovary. *Reprod Toxicol* 30: 550–557, 2010.

284. Roque M. Freeze-all policy: is it time for that? *J Assisted Reprod Genet* 32: 171–176, 2015.

285. Rotterdam EASPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 81: 19–25, 2004.

286. Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. *Occup Environ Med* 51: 28–34, 1994.

287. Rubio I, Galan A, Larreategui Z, Ayerdi F, Bellver J, Herrero J, Meseguer M. Clinical validation of embryo culture and selection by morphokinetic analysis: a randomized, controlled trial of the EmbryoScope. *Fertil Steril* 102: 1287–1294, 2014.

288. Rutkowska A, Rachon D. Bisphenol A (BPA) and its potential role in the pathogenesis of the polycystic ovary syndrome (PCOS). *Gynecol Endocrinol* 30: 260–265, 2014.

289. Rzymski P, Rzymski P, Tomczyk K, Niedzielski P, Jakubowski K, Poniedzialek B, Opala T. Metal status in human endometrium: relation to cigarette smoking and histological lesions. *Environ Res* 132: 328–333, 2014.

290. Rzymski P, Tomczyk K, Rzymski P, Poniedzialek B, Opala T, Wilczak M. Impact of heavy metals on the female reproductive system. *Ann Agricultural Environmental Med* 22: 259–264, 2015.

291. Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* CD004635, 2006.

292. Sander VA, Hapon MB, Sicaro L, Lombardi EP, Jahn GA, Motta AB. Alterations of folliculogenesis in women with polycystic ovary syndrome. *J Steroid Biochem Mol Biol* 124: 58–64, 2011.

293. Santillan I, Lozano I, Illan J, Verdu V, Coca S, Bajo-Arenas JM, Martinez F. Where and when should natural killer cells be tested in women with repeated implantation failure? *J Reprod Immunol* 108: 142–148, 2015.

294. Saradogan E, Djahanbakhch O. Hormonal control of the fallopian tube. In: *The Fallopain Tube*, edited by Allahbadia GN, Saradogan E, and Djahanbakhch O. Kent: Anshan, 2009.

295. Savaris RF, Groll JM, Young SL, DeMayo FJ, Jeong JW, Hamilton AE, Giudice LC, Lessey BA. Progesterone resistance in PCOS endometrium: a microarray analysis in clomiphene citrate-treated and artificial menstrual cycles. *J Clin Endocrinol Metab* 96: 1737–1746, 2011.

296. Schatten H, Sun QY. The role of centrosomes in mammalian fertilization and its significance for ICSI. *Mol Hum Reprod* 15: 531–538, 2009.

297. Schatten H, Sun QY, Prather R. The impact of mitochondrial function/dysfunction on IVF and new treatment possibilities for infertility. *Reprod Biol Endocrinol* 12: 111, 2014.

298. Schieve LA, Tatham L, Peterson HB, Toner J, Jeng G. Spontaneous abortion among pregnancies conceived using assisted reproductive technology in the United States. *Obstet Gynecol* 101: 959–967, 2003.

299. Schliep KC, Mumford SL, Vladutiu CJ, Ahrens KA, Perkins NJ, Sjaarda LA, Kissell KA, Prasad A, Wactawski-Wende J, Schisterman EF. Perceived stress, reproductive hormones, and ovulatory function: a prospective cohort study. *Epidemiology* 26: 177–184, 2015.

300. Schneider LF, Warren MP. Functional hypothalamic amenorrhea is associated with elevated ghrelin and disordered eating. *Fertil Steril* 86: 1744–1749, 2006.

301. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *Int J Epidemiol* 43: 1542–1562, 2014.

302. Schulte MM, Tsai JH, Moley KH. Obesity and PCOS: the effect of metabolic derangements on endometrial receptivity at the time of implantation. *Reprod Sci* 22: 6–14, 2015.

303. Schummers L, Hutcheon JA, Bodnar LM, Lieberman E, Himes KP. Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. *Obstet Gynecol* 125: 133–143, 2015.

304. Sen A, Kushnir VA, Barad DH, Gleicher N. Endocrine autoimmune diseases and female infertility. *Nature Rev Endocrinol* 10: 37–50, 2014.

305. Seshadri S, Sunkara SK. Natural killer cells in female infertility and recurrent miscarriage: a systematic review and meta-analysis. *Hum Reprod Update* 20: 429–438, 2014.

306. Shang K, Jia X, Qiao J, Kang J, Guan Y. Endometrial abnormality in women with polycystic ovary syndrome. *Reprod Sci* 19: 674–683, 2012.

307. Shao R, Zou S, Wang X, Feng Y, Brannstrom M, Stener-Victorin E, Billig H. Revealing the hidden mechanisms of smoke-induced fallopian tubal implantation. *Biol Reprod* 86: 131, 2012.

308. Sharara FI, Beatse SN, Leonardi MR, Navot D, Scott RT Jr. Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test. *Fertil Steril* 62: 257–262, 1994.

309. Shen Y, Ren ML, Feng X, Cai YL, Gao YX, Xu Q. An evidence in vitro for the influence of bisphenol A on uterine leiomyoma. *Eur J Obstet Gynecol Reprod Biol* 178: 80–83, 2014.

310. Shiloh H, Lahav-Baratz S, Koifman M, Ishai D, Bidder D, Weiner-Meganzi Z, Dirnfeld M. The impact of cigarette smoking on zona pellucida thickness of oocytes and embryos prior to transfer into the uterine cavity. *Hum Reprod* 19: 157–159, 2004.

311. Shoham Z, Patel A, Jacobs HS. Polycystic ovarian syndrome: safety and effectiveness of stepwise and low-dose administration of purified follicle-stimulating hormone. *Fertil Steril* 55: 1051–1056, 1991.

312. Shub A, Wong C, Jennings B, Swain JR, Newnham JP. Maternal periodontal disease and perinatal mortality. *Aust N Z J Obstet Gynaecol* 49: 130–136, 2009.

313. Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ, Knowler WC, Nelson RG. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. *Diabetes Care* 30: 306–311, 2007.

314. Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev* 15: 839–850, 2014.

315. Simpson JL, Mills JL, Kim H, Holmes LB, Lee J, Metzger B, Knopp R, Jovanovic-Peterson L, Aarons J, Conley M. Infectious processes: an infrequent cause of first trimester spontaneous abortions. *Human Reprod* 11: 668–672, 1996.

316. Sinko I, Morocz M, Zadori J, Kokavszky K, Rasko I. Effect of cigarette smoking on DNA damage of human cumulus cells analyzed by comet assay. *Reprod Toxicol* 20: 65–71, 2005.

317. Sivalingam VN, Myers J, Nicholas S, Balen AH, Crosbie EJ. Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. *Hum Reprod Update* 20: 2853–867, 2014.

318. Smyth A, Radovic M, Garovic Women VD. Kidney disease, pregnancy. *Adv Chronic Kidney Dis disease* 20: 402–410, 2013.

319. Soares SR, Simon C, Remohi J, Pellicer A. Cigarette smoking affects uterine receptiveness. *Hum Reprod* 22: 543–547, 2007.

320. Soave I, Caserta D, Wenger JM, Dessole S, Perino A, Marci R. Environment and Endometriosis: a toxic relationship. *Eur Rev Med Pharmacol Sci* 19: 1964–1972, 2015.

321. Sobinoff AP, Beckett EL, Jarnicki AG, Sutherland JM, McCluskey A, Hansbro PM, McLaughlin EA. Scrambled and fried: cigarette smoke exposure causes antral follicle destruction and oocyte dysfunction through oxidative stress. *Toxicol Appl Pharmacol* 271: 156–167, 2013.

322. Sobinoff AP, Mahony M, Nixon B, Roman SD, McLaughlin EA. Understanding the Villain: DMBA-induced preantral ovotoxicity involves selective follicular destruction and primordial follicle activation through PI3K/Akt and mTOR signaling. *Toxicol Sci* 123: 563–575, 2011.

323. Sobinoff AP, Sutherland JM, McLaughlin EA. Intracellular signalling during female gametogenesis. *Mol Hum Reprod* 19: 265–278, 2013.

324. Sofo V, Gotte M, Lagana AS, Salmeri FM, Triolo O, Sturlese E, Retto G, Alfa M, Granese R, Abrao MS. Correlation between dioxin and endometriosis: an epigenetic route to unravel the pathogenesis of the disease. *Arch Gynecol Obstet* 292: 973–986, 2015.

325. Song S, Zhang L, Zhang H, Wei W, Jia L. Perinatal BPA exposure induces hyperglycemia, oxidative stress and decreased adiponectin production in later life of male rat offspring. *Int J Environ Res Public Health* 11: 3728–3742, 2014.

326. Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R. The association of bisphenol-A urinary concentrations with antral follicle counts and other

measures of ovarian reserve in women undergoing infertility treatments. *Reprod Toxicol* 42: 224–231, 2013.

327. Steegers-Theunissen RP, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum Reprod Update* 19: 640–655, 2013.

328. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, Teede HJ. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. *Hum Reprod* 28: 777–784, 2013.

329. Stern C, Pertile M, Norris H, Hale L, Baker HW. Chromosome translocations in couples with in-vitro fertilization implantation failure. *Hum Reprod* 14: 2097–2101, 1999.

330. Stetten G, Escallon CS, South ST, McMichael JL, Saul DO, Blakemore KJ. Reevaluating confined placental mosaicism. *Am J Med Genet A* 131: 232–239, 2004.

331. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 301: 636–650, 2009.

332. Strandell A, Lindhard A, Waldenstrom U, Thorburn J, Janson PO, Hamberger L. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. *Hum Reprod* 14: 2762–2769, 1999.

333. Sugino N, Suzuki T, Kashida S, Karube A, Takiguchi S, Kato H. Expression of Bcl-2 and Bax in the human corpus luteum during the menstrual cycle and in early pregnancy: regulation by human chorionic gonadotropin. *J Clin Endocrinol Metab* 85: 4379–4386, 2000.

334. Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. *Hum Reprod* 20: 2325–2329, 2005.

335. Susiarjo M, Hassold TJ, Freeman E, Hunt PA. Bisphenol A exposure in utero disrupts early oogenesis in the mouse. *PLoS Genet* 3: e5, 2007.

336. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 351: 1227–1238, 2004.

337. Szekeres-Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage. *Hum Reprod Update* 14: 27–35, 2008.

338. Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ. Cabergoline for preventing ovarian hyperstimulation syndrome. *Cochrane Database Syst Rev* 2: CD008605, 2012.

339. Taylor TH, Gitlin SA, Patrick JL, Crain JL, Wilson JM, Griffin DK. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. *Hum Reprod Update* 20: 571–581, 2014.

340. Teede HJ, Joham AE, Paul E, Moran LJ, Loxton D, Jolley D, Lombard C. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity* 21: 1526–1532, 2013.

341. Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BG, Wong JL, Norman RJ, Costello MF. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust* 195: S65–112, 2011.

342. Teixeira Filho FL, Baracat EC, Lee TH, Suh CS, Matsui M, Chang RJ, Shimasaki S, Erickson GF. Aberrant expression of growth differentiation factor-9 in oocytes of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 87: 1337–1344, 2002.

343. Tersigni C, Castellani R, de Waure C, Fattorossi A, De Spirito M, Gasbarrini A, Scambia G, Di Simone N. Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. *Hum Reprod Update* 20: 582–593, 2014.

344. Teughels W, Dekeyser C, Van Essche M, Quirynen M. One-stage, full-mouth disinfection: fiction or reality? *Periodontol 2000* 50: 39–51, 2009.

345. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med* 356: 911–920, 2007.

346. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 11: CD006105, 2014.

347. Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endocrinology* 23: 566–574, 1938.

348. Ujvari U, Hulchiy M, Calaby A, Nybacka A, Bystrom B, Hirschberg AL. Lifestyle intervention up-regulates gene and protein levels of molecules involved in insulin signaling in the endometrium of overweight/obese women with polycystic ovary syndrome. *Hum Reprod* 29: 1526–1535, 2014.

349. Upson K, De Roos AJ, Thompson ML, Sathyanarayana S, Scholes D, Barr DB, Holt VL. Organochlorine pesticides and risk of endometriosis: findings from a population-based case-control study. *Environ Health Perspect* 121: 1319–1324, 2013.

350. Upson K, Sathyanarayana S, De Roos AJ, Koch HM, Scholes D, Holt VL. A population-based case-control study of urinary bisphenol A concentrations and risk of endometriosis. *Hum Reprod* 29: 2457–2464, 2014.

351. Upson K, Sathyanarayana S, De Roos AJ, Thompson ML, Scholes D, Dills R, Holt VL. Phthalates and risk of endometriosis. *Environ Res* 126: 91–97, 2013.

352. Vagi SJ, Azziz-Baumgartner E, Sjodin A, Calafat AM, Dumesic D, Gonzalez L, Kato K, Silva MJ, Ye X, Azziz R. Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol A in polycystic ovary syndrome: a case-control study. *BMC Endocr Disorders* 14: 86, 2014.

353. Vaiman D. Genetic regulation of recurrent spontaneous abortion in humans. *Biomed J* 38: 11–24, 2015.

354. Valdes-Socin H, Rubio Almanza M, Tome Fernandez-Ladreda M, Debray FG, Bours V, Beckers A. Reproduction, smell, and neurodevelopmental disorders: genetic defects in different hypogonadotropic hypogonadal syndromes. *Front Endocrinol* 5: 109, 2014.

355. Van den Berg IM, Eleveld C, van der Hoeven M, Birnie E, Steegers EA, Galjaard RJ, Laven JS, van Doorninck JH. Defective deacetylation of histone 4 K12 in human oocytes is associated with advanced maternal age and chromosome misalignment. *Hum Reprod* 26: 1181–1190, 2011.

356. Van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 17: 605–619, 2011.

357. Van Kasteren YM, Hundscheid RD, Smits AP, Cremers FP, van Zonneveld P, Braat DD. Familial idiopathic premature ovarian failure: an overrated and underestimated genetic disease? *Hum Reprod* 14: 2455–2459, 1999.

358. Vega M, Urrutia L, Iniguez G, Gabler F, Devoto L, Johnson MC. Nitric oxide induces apoptosis in the human corpus luteum in vitro. *Mol Hum Reprod* 6: 681–687, 2000.

359. Vissenberg R, Manders VD, Mastenbroek S, Fliers E, Afink GB, Ris-Stalpers C, Goddijn M, Bisschop PH. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. *Hum Reprod Update* 21: 378–387, 2015.

360. Voet T, Vanneste E, Vermeesch JR. The human cleavage stage embryo is a cradle of chromosomal rearrangements. *Cytogenet Genome Res* 133: 160–168, 2011.

361. Vrsanska S, Nagyova E, Mlynarcikova A, Fickova M, Kolena J. Components of cigarette smoke inhibit expansion of oocyte-cumulus complexes from porcine follicles. *Physiol Res Acad Sci Bohem* 52: 383–387, 2003.

362. Walls ML, Hunter T, Ryan JP, Keelan JA, Nathan E, Hart RJ. In vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. *Hum Reprod* 30: 88–96, 2014.

363. Walters KA, Allan CM, Handelsman DJ. Rodent models for human polycystic ovary syndrome. *Biol Reprod* 86: 149, 141-112, 2012.

364. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, Karalis A, Mantzoros CS. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* 351: 987–997, 2004.

365. Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, Watson CS, Zoeller RT, Belcher SM. In vitro molecular mechanisms of bisphenol A action. *Reprod Toxicol* 24: 178–198, 2007.

366. Weuve J, Hauser R, Calafat AM, Missmer SA, Wise LA. Association of exposure to phthalates with endometriosis and uterine leiomyomata: findings from NHANES, 1999–2004. *Environ Health Perspect* 118: 825–832, 2010.

367. Wheatcroft NJ, Salt C, Milford-Ward A, Cooke ID, Weetman AP. Identification of ovarian antibodies by immunofluorescence, enzyme-linked immunosorbent assay or immunoblotting in premature ovarian failure. *Hum Reprod* 12: 2617–2622, 1997.

368. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med* 319: 189–194, 1988.

369. Wilding M. Can we define maternal age as a genetic disease? *Facts Views Vision in ObGyn* 6: 105–108, 2014.

370. Williams RC, Barnett AH, Claffey N, Davis M, Gadsby R, Kellett M, Lip GY, Thackray S. The potential impact of periodontal disease on general health: a consensus view. *Curr Med Res Opin* 24: 1635–1643, 2008.

371. Wilton L. Preimplantation genetic diagnosis and chromosome analysis of blastomeres using comparative genomic hybridization. *Hum Reprod Update* 11: 33–41, 2005.

372. Wilton L, Voullaire L, Sargeant P, Williamson R, McBain J. Preimplantation aneuploidy screening using comparative genomic hybridization or fluorescence in situ hybridization of embryos from patients with recurrent implantation failure. *Fertil Steril* 80: 860–868, 2003.

373. Wittenberger MD, Hagerman RJ, Sherman SL, McConkie-Rosell A, Welt CK, Rebar RW, Corrigan EC, Simpson JL, Nelson LM. The FMR1 premutation and reproduction. *Fertil Steril* 87: 456–465, 2007.

374. Woodruff TJ. Bridging epidemiology and model organisms to increase understanding of endocrine disrupting chemicals and human health effects. *J Steroid Biochem Mol Biol* 127: 108–117, 2011.

375. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ Health Perspect* 119: 878–885, 2011.

376. Wright DL, Afeiche MC, Ehrlich S, Smith K, Williams PL, Chavarro JE, Batsis M, Toth TL, Hauser R. Hair mercury concentrations and in vitro fertilization (IVF) outcomes among women from a fertility clinic. *Reprod Toxicol* 51: 125–132, 2015.

377. Wyman A, Pinto AB, Sheridan R, Moley KH. One-cell zygote transfer from diabetic to nondiabetic mouse results in congenital malformations and growth retardation in offspring. *Endocrinology* 149: 466–469, 2008.

378. Xiao JS, Su CM, Zeng XT. Comparisons of GnRH Antagonist versus GnRH Agonist Protocol in Supposed Normal Ovarian Responders Undergoing IVF: A Systematic Review and Meta-Analysis. *PloS One* 9: e106854, 2014.

379. Xiao S, Diao H, Smith MA, Song X, Ye X. Preimplantation exposure to bisphenol A (BPA) affects embryo transport, preimplantation embryo development, and uterine receptivity in mice. *Reprod Toxicol* 32: 434–441, 2011.

380. Yang X, Wu LL, Chura LR, Liang X, Lane M, Norman RJ, Robker RL. Exposure to lipid-rich follicular fluid is associated with endoplasmic reticulum stress and impaired oocyte maturation in cumulus-oocyte complexes. *Fertil Steril* 97: 1438–1443, 2012.

381. Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database Syst Rev* 10: CD008046, 2014.

382. Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome; towards a rational approach. In: *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific, 1992, p. 377–384.

383. Zdravkovic T, Genbacev O, Prakobphol A, Cvetkovic M, Schanz A, McMaster M, Fisher SJ. Nicotine downregulates the L-selectin system that mediates cytotrophoblast emigration from cell columns and attachment to the uterine wall. *Reprod Toxicol* 22: 69–76, 2006.

384. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. *Hum Reprod Update* 6: 122–131, 2000.

385. Zenzes MT, Wang P, Casper RF. Cigarette smoking may affect meiotic maturation of human oocytes. *Hum Reprod* 10: 3213–3217, 1995.

386. Zhang HQ, Zhang XF, Zhang LJ, Chao HH, Pan B, Feng YM, Li L, Sun XF, Shen W. Fetal exposure to bisphenol A affects the primordial follicle formation by inhibiting the meiotic progression of oocytes. *Mol Biol Reports* 39: 5651–5657, 2012.

387. Zhang L, Shiverick KT. Benzo(a)pyrene, but not 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, alters cell proliferation and c-myc and growth factor expression in human placental choriocarcinoma JEG-3 cells. *Biochem Biophys Res Commun* 231: 117–120, 1997.

388. Zhao Q, Ma Y, Sun NX, Ye C, Zhang Q, Sun SH, Xu C, Wang F, Li W. Exposure to bisphenol A at physiological concentrations observed in Chinese children promotes primordial follicle growth through the PI3K/Akt pathway in an ovarian culture system. *Toxicol In Vitro* 28: 1424–1429, 2014.

389. Zheng YM, Wang Y, Zhao J, Dai YH, Luo XM, Shen ZJ, Chen X, Yuan W, Shen YP. Association between serum bisphenol-A and recurrent spontaneous abortion: a 1:2 case-control study, China. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi* 33: 841–845, 2012.

390. Zhou W, Liu J, Liao L, Han S, Liu J. Effect of bisphenol A on steroid hormone production in rat ovarian theca-interstitial and granulosa cells. *Mol Cell Endocrinol* 283: 12–18, 2008.

391. Zinn AR, Tonk VS, Chen Z, Flejter WL, Gardner HA, Guerra R, Kushner H, Schwartz S, Sybert VP, Van Dyke DL, Ross JL. Evidence for a Turner syndrome locus or loci at Xp11.2-*p22*1 *Am J Hum Genet* 63: 1757–1766, 1998.

392. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ, Vom Saal FS. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology* 153: 4097–4110, 2012.