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REVIEW

Bisphenol A, oocyte maturation, implantation, and IVF outcome: review of animal and human data

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Abstract Recent data have raised concerns about the detrimental effect of chronic exposure to environmental chemicals. Some chemicals affect the endocrine system (endocrine disruptors) and have been linked to several diseases, including infertility. One such endocrine disruptor is bisphenol A (BPA), a monomer widely used in the plastic industry, with nearly ubiquitous exposure. In this review, data on the effects of BPA on female fertility are summarized. Specifically, its effect is considered on folliculogenesis, oocyte maturation, embryo quality, and implantation, both in animal and human models. Animal studies have shown that BPA might impair prophase I, follicular growth, and implantation, and may be associated with spindle abnormalities. In humans, while in-vitro studies have suggested an association between BPA exposure and impaired oocyte meiosis, clinical evidence indicate possible adverse effects of BPA exposure on IVF outcomes. As human clinical data are still scarce, larger studies are required to further elucidate the effects of BPA exposure on female fertility.

KEYWORDS: bisphenol A, endocrine disruptors, folliculogenesis, IVF, meiosis

Introduction

Growing evidence indicates that exposure to environmental contaminants negatively affects animal and human health. Because some of these substances can mimic and alter the endocrine system, they are referred to as endocrine disruptors (EDC). These are widespread and include industrial compounds with affinity to oestrogen, thyroid, or androgen receptors, and may also mimic or antagonize the activity of steroidogenic enzymes (Caserta et al., 2008; Schug et al.,

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2011). These chemicals are found in a variety of products used daily (Calafat et al., 2005; Calafat et al., 2008; Vandenberg et al., 2007a, 2007b; Rochester, 2013). Studies in animal models suggest that lifestyle and exposure to EDC may play a role in the pathogenesis of infertility (Mendola et al., 2008), and several studies have also investigated the association between exposure to EDC and human infertility.

According to Schug et al. (2011), BPA is among the highest-volume industrial chemicals produced worldwide for the manufacture of polymers. Potential sources of the monomer BPA include a variety of consumer products, including linings of cans used for food and beverages, polycarbonate bottles, thermal receipts and dental sealants.(Vandenberg et al., 2007a; Caserta et al., 2008). It was first thought that BPA had weak oestrogenic activity, 1000–100,000-fold less than oestradiol (17 beta-oestradiol), depending on the method of determining biological activity, the tissue evaluated and target receptors (Cummings and Laws, 2000; Knez, 2013; Vandenberg et al., 2009; Welshons et al., 2003); it was therefore defined as an endocrine disruptor. The endocrine effects of BPA have been investigated in animal and in human models. Studies have shown that BPA also has the ability to act as an antiandrogen (Bonefeld-Jorgensen et al., 2007; Wetherill et al., 2007), stimulate prolactin release (Steinmetz et al., 1997), impair aromatase expression (Castro et al., 2013) and alter thyroid hormone action (Wetherill et al., 2007; Zoeller et al., 2007). Human exposure to BPA is nearly ubiquitous and takes place through inhalation, ingestion, and dermal absorption. In the National Health and Nutrition Examination Survey, USA, BPA was detected in the urine of more than 90% of participants (Calafat et al., 2008;) and also in other human fluids, such as blood, amniotic fluid and even follicular fluid (Ikezuki et al., 2002).

According to mainstream dogma, females have a reproductive lifespan that is determined at the time of birth (Pepling, 2012). Females are born with a limited number of oocytes, which through progressive apoptosis significantly decrease in number from the second trimester of the fetal period until menopause (Baker, 1963). Animal studies and in-vitro human studies suggest that exposure of females to EDC during the prenatal, adolescent, and reproductive periods may alter normal oocyte meiosis (Hunt and Hassold, 2008; Governini et al., 2011). Evidence is also accumulating of possible adverse effects of BPA on IVF outcome (Bloom et al., 2011a; Ehrlich et al., 2012a, 2012b; Fujimoto et al., 2011; Mok-Lin et al., 2010). Laboratory studies in male rodents have shown that BPA exposure was associated with developmental genitourinary anomalies, decreased epididymal weight, increased prostate weight reduced sperm count and quality, DNA damage induced in spermatozoa and epigenetic modifications in offspring (Dobrzyńska and Radzikowska, 2013; Knez, 2013; Manikkam et al., 2013; Nagel et al., 1997; Richter et al., 2007; Salian et al., 2009; vom Saal et al., 1998; Williams et al., 2001; Wright et al., 2014). In humans, the association between BPA levels, sperm quality and embryo development is controversial (Bloom et al., 2011b; Knez et al., 2014; Meeker et al., 2010). To date, however, most of these clinical studies are of low power, of small size, or both.

In this review, the effects of BPA on female fertility are summarized: meiosis, embryo development and implantation (in-vivo and in-vitro animal models, and in-vitro human models), as well as examining the association between BPA levels and IVF clinical outcomes.

Oocyte development

Oocytes arise from the primordial germ cells during development of the fetus. After DNA replication, oocytes enter the prophase of the first meiotic division (prophase I), when the chromosomes condense and undergo recombination. Later the chromosomes become dispersed and the oocytes become surrounded by a single layer of granulosa cells (primordial follicles) (Rodrigues et al., 2008). Oocytes remain arrested at prophase I, at the germinal vesicle stage, until puberty. During the female reproductive years, oocytes and follicles enter the growth phase and gradually resume meiosis in response to LH surge (Neal et al., 1975; Rodrigues et al., 2008). The first sign of the resumption of meiosis is germinal vesicle breakdown, followed by metaphase I, anaphase I, telophase I, and metaphase II. Several stages of oocyte development might be specifically vulnerable to EDC, including meiotic initiation in the fetal ovary, follicle formation in the perinatal period, and oocyte growth and resumption of meiosis in the adult (Hunt and Hassold, 2008).

BPA exposure and the early stages of meiosis

The early stages of follicular formation, until prophase I of the first meiosis take place in the fetal ovary. During the first prophase, pairing, synapsis, and recombination between homologous chromosomes occurs. The effect of BPA on these first steps of meiosis has been evaluated in animal models, including both rodents and Rhesus monkeys. Treatment of pregnant mice during mid-gestation with daily low doses of BPA (400 ng) resulted in abnormalities in prophase I (e.g. synaptic defects and increased rates of recombination) in oocytes from the exposed fetuses, similar to that which occurs in mice homozygous for a targeted disruption of the oestrogen receptor beta. This raised the possibility that BPA exposure during the early stages of oogenesis might impair oogenesis by impairing the action of oestrogen receptor beta (Susiarjo et al., 2007). In mice, BPA delays germ cell cyst breakdown and formation of primordial follicles by inhibiting the expression of *Stra8*, which plays a key role in the initiation of meiosis in mice (Zhang et al., 2012). Mature female mice exposed to BPA *in utero* had more aneuploid oocytes and embryos than unexposed females (Susiarjo et al., 2007). Similar results were obtained in pregnant Rhesus monkeys exposed to BPA during the stages of germ-cell differentiation, meiotic entry and follicle formation (Hunt et al., 2012). Similar to the findings in rodents, fetal ovaries of primates showed sensitivity to BPA and exhibited alterations in the meiotic prophase, significant increases in recombination, and impaired follicular formation (Hunt et al., 2012).

In-vitro study of human fetal oocytes has shown that exposure to BPA at early stages of meiosis results in an increased incidence of crossing over (i.e. interference with pairing synapsis and recombination) and higher rates of oocyte degeneration (Brieno-Enriquez et al., 2011). A further study from the same group showed that exposure of human fetal

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oocytes to BPA was associated with up-regulation of genes involved in double-strand break generation, signalling, and repair (Brieno-Enriquez et al., 2012). The effects of BPA during the early stages of oogenesis are shown in **Figure 1**.

BPA exposure and the final stages of meiosis

Hodges et al. (2002) were the first to report an increase in meiotic abnormalities and even aneuploidy among oocytes exposed to BPA during the final stages of meiosis (Hunt et al., 2003). In another study, the same group of investigators collected germinal vesicle-stage oocytes from mice that were treated with daily injections of BPA (0, 20, 40 and 100 ng/g per body weight) for 6–8 days. The authors reported that exposure to BPA during the final stages of meiosis was associated with perturbations in the meiotic spindle, chromosomal mal-alignment, increased incidence of meiotic arrest, and even aneuploidy among mouse oocytes (Hunt et al., 2003). To the best of our knowledge, however, a correlation between BPA exposure and aneuploidy has not been documented by others.

Another in-vivo study examined the effects of BPA exposure on meiotic maturation of mouse oocytes. Mice were divided into three exposure groups: acute–once at a concentration of 0.2 mg/kg; sub-chronic for 7 days at a concentration of 0.04 mg/kg; and chronically, for 7 weeks in drinking water (0.5 mg/l). Chronic exposure was associated with a significant increase in the incidence of aberrant metaphase II (MII) oocytes with prematurely segregated chromatids (Pacchierotti et al., 2008).

Using both an in-vitro and an in-vivo approach, investigators exposed mice to low oral doses of BPA for a week and cultured denuded germinal vesicle oocytes *in vitro* (Eichenlaub-Ritter et al., 2008). Exposure to BPA was associated with perturbed spindle morphology and lower rates of MII oocytes but no increase in aneuploidy.

The effects of chronic exposure to BPA on follicle growth, oocyte maturation, and spindle and chromosome alignment were examined. Follicles were incubated for 12 days in medium with various concentrations of BPA (3 nM to 30 μM) (Lenie et al., 2008). Exposure to the highest concentrations of BPA led to a decrease in granulosa cell proliferation and oestrogen production, although the follicles still developed and formed antral-like cavities. Follicles exposed to 30 μM BPA showed significantly more cytoskeletal abnormalities such as MI-arrested oocytes with both spindle aberrations and unaligned chromosomes as well as abnormal TI-arrested oocytes. Prolonged in-vitro exposure to low concentrations of BPA (3 nM–3 μM) produced a non-linear dose-dependent effect on the meiotic spindle with perturbation in chromosome alignment in MII oocytes.

In-vitro exposure of mouse follicle-free cumulus-oocyte complexes to BPA (10 and 30 μM) during the first meiotic division resulted in a significant reversible and dose-dependent meiotic delay as well as spindle abnormalities (Can et al., 2005). The investigators demonstrated elongation and loosening of meiotic spindles and compaction and dispersion of pericentriolar material, depending on the BPA dose.

In another study, mouse oocytes were cultured *in vitro* with BPA at various concentrations (50 ng/ml to 10 μg/ml) (0.2 μM–44 μM) (Eichenlaub-Ritter et al., 2008). Only oocytes cultured in medium containing 10 μg/ml BPA showed a significantly higher incidence of cytoskeleton aberrations compared with controls.

On the basis of findings in mice studies, the effect of BPA on the final stages of human oocyte maturation *in vitro* was recently assessed (Machtinger et al., 2013). Signed informed consent was obtained from patients undergoing IVF, germinal vesicle-stage oocytes (that would otherwise have been discarded) were cultured with and without BPA in concentrations from 20 ng/ml (0.09 μM) to 20,000 ng/ml (88 μM). A dose-response effect was reported between BPA exposure and oocyte maturation. As BPA increased, oocytes became significantly less likely to complete meiosis and become MII and significantly more likely to degenerate or undergo activation when a polar body was present. Exposure to BPA was correlated with impaired cytoskeleton among MII oocytes. As BPA dose increased, a significantly decreased incidence of bipolar spindles and aligned chromosomes (Machtinger et al., 2013). The effects of BPA during the final stages of oocyte maturation are presented in **Figure 2**.

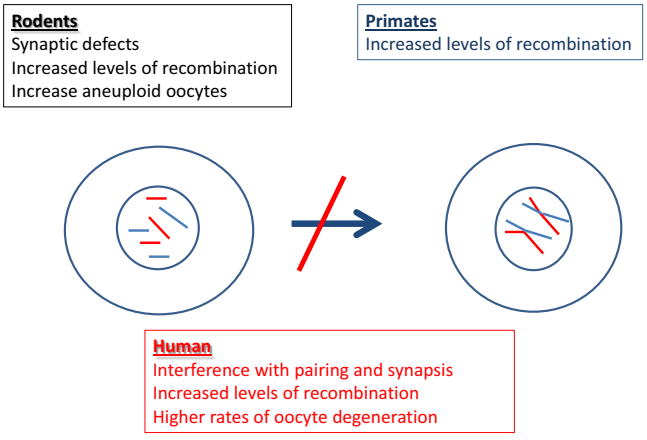

Figure 1 The effects of bisphenol A during the early stages of oogenesis.

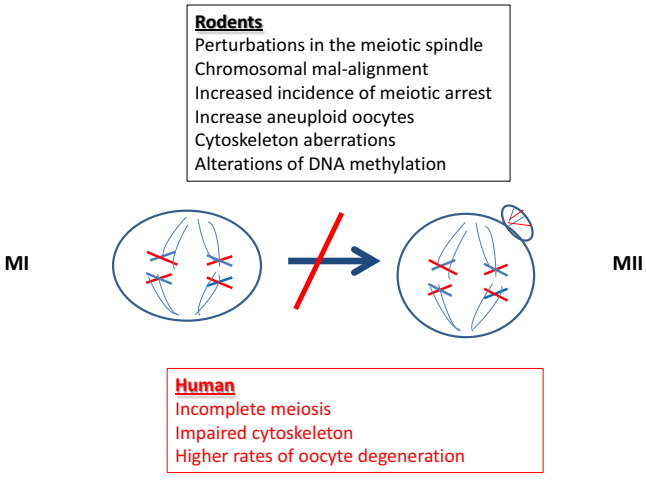

Figure 2 The effects of bisphenol A during the final stages of oocyte maturation. MI, metaphase I; MII, metaphase II.

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BPA exposure and epigenetic changes in oocytes and embryos

Accumulating evidence indicates that EDC might cause epigenetic changes, which might in turn lead to developmental abnormalities (Baccarelli and Bollati, 2009). Exposure to EDC during the vulnerable final stages of oocyte maturation, fertilization and early embryo development might be associated with alterations of DNA methylation (Susiarjo et al., 2013; Weaver et al., 2009).

Exposure of pregnant mice to physiologically relevant doses of BPA during the late stages of meiosis and early stages of embryo development resulted in significant alterations in imprinted gene expression, which impaired fetal, placental, and postnatal development (Susiarjo et al., 2013). In contrast, BPA treatment of pregnant females later in pregnancy (beyond the vulnerable epigenetic window), did not affect genomic imprinting. BPA exposure specifically impaired several genes (*Snrpn*, *Ube3a*, *Igf2*, *Kcnq1ot1*, *Cdkn1c*, and *Ascl2*) that were reported to be associated with imprinting disorders in humans. Most of the affected genes were abnormally expressed in the placenta (Susiarjo et al., 2013).

In-vitro exposure of mice follicles to 3 nM BPA was associated with both changes in DNA methylation and histone modification, providing evidence that low BPA exposure might induce epigenetic changes that lead to chromosome congression failure and meiotic errors (Trapphoff et al., 2013).

BPA exposure and follicular development

Normal folliculogenesis is a key feature in the development of a competent oocyte. Any impairment in follicular growth might cause abnormalities in steroidogenesis that further lead to follicular atresia (Eppig et al., 1996; Peretz et al., 2011, 2012). An in-vitro study in rodents investigated the effect of BPA exposure on antral follicle growth and follicular atresia (Peretz et al., 2011). The researchers measured follicular growth after culture of antral follicles in medium containing BPA (1–100 μg/ml) (4.4–440 μM) or vehicle control (dimethylsulfoxide) and assessed follicular growth every 24 h for 96–120 h. Exposure to a concentration of 100 μg/ml (440 μM) BPA significantly decreased follicular growth and increased atresia rates compared with controls. The investigators suggested that BPA impaired cell cycle independently of the genomic oestrogenic pathway (Peretz et al., 2012).

The effect of BPA exposure on follicular growth has also been evaluated in primates (Hunt et al., 2012). The investigators found significantly more secondary and antral follicles containing two to three oocytes, four to five oocytes, or over five oocytes among female Rhesus monkeys treated with a single daily dose of BPA (400 μg/kg body weight) compared with controls ($P < 0.001$). The proportion of follicles with more than five oocytes was significantly increased among monkeys exposed to a continuous implanted BPA regimen, producing serum levels ranging from 2.2–3.3 ng/ml (i.e. 10–15 nM) compared with controls. Chronic exposure to BPA also produced follicles containing oocytes of different sizes, and the medullary region of ovaries from animals exposed to BPA showed many small unenclosed oocytes in secondary and antral follicles. Similar to the findings of rodent studies, primate fetuses with intrauterine exposure to BPA at the final stages of pregnancy presented with more multi-oocyte follicles compared with controls.

BPA exposure, blastocyst formation, and implantation: animal studies

In a series of studies, the effect of BPA on blastocyst implantation and pregnancy loss among mice was assessed (Berger et al., 2007, 2008, 2010). Doses of 6.75 mg/day and 10.125 mg/day BPA interfered with normal implantation in mice. Subcutaneous treatment with BPA at a concentration of 10.125 mg/day was associated with a decrease in the number of implantation sites (Berger et al., 2007). The same group later showed that an injection of a single dose of 10.125 mg BPA on the day of insemination, or a single dose of 6.75 mg/10.125 mg of BPA on the day after insemination resulted in a decrease in the number of implantation sites (Berger et al., 2008). Exposure to BPA (subcutaneously) at a dose of 3.375 mg/day during the first 4 days of gestation significantly reduced litter size and exposure to 10.125 mg/day was associated with a significant reduction in the number of pregnancies.

In another in-vivo study, pregnant mice were treated subcutaneously with 0, 0.025, 0.5, 10, 40, or 100 mg/kg/day of BPA (Xiao et al., 2011). Exposure to 100 mg/kg/day of BPA delayed embryo development and produced complete absence of implantation sites. Absence of implantation sites when untreated healthy embryos were transferred to pseudo-pregnant females treated with 100 mg/kg/day BPA was also reported. Exposure of pregnant mice to 40 mg/kg/day BPA in this study resulted in delayed implantation and increased perinatal mortality of the offspring. Lower BPA exposure did not result in impaired implantation. Those researchers suggested that exposure to BPA might disrupt implantation either by mismatch between the timing of blastocyst formation and the uterine receptivity window or by direct perturbation of uterine receptivity to blastocyst implantation owing to the oestrogenic properties of BPA (Berger et al., 2007, 2008; Varayoud et al., 2011).

BPA exposure and fertility outcome: data from human IVF studies

Association between BPA levels and ovarian reserve parameters

The correlation between specific gravity-adjusted urinary BPA concentrations and markers of ovarian reserve (antral follicular count [AFC], day-3 serum FSH, and ovarian volume) was delineated in a cohort of 209 women undergoing IVF (Souter et al., 2013). Most urine samples contained BPA at geometric mean levels around 1.6 μg/L. The authors demonstrated an average decrease in AFC of 12%, 22%, and 17%, in the second, third and fourth specific gravity-adjusted urinary BPA quartiles, respectively, compared with the first quartile. No correlations between urinary BPA levels, FSH, or ovarian volume were noted. Bloom et al. (2011a) also investigated the effect of BPA on ovarian reserve parameters,

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specifically serum BPA levels, among a cohort of 44 women undergoing IVF. No associations were detected between fasting serum BPA levels and ovarian reserve variables (i.e. day 3 serum FSH levels), nor between BPA and baseline AFC. The disparate results between the two studies might be attributable to the different strategies for assessing BPA. Because it is not clear how urine and serum levels correlate as biomarkers of exposure, it is difficult to compare these two studies.

The association between urinary and blood BPA levels, peak oestradiol levels and number of retrieved oocytes

Several groups have investigated the association between urinary and blood BPA and IVF outcomes. Mok-Lin et al. (2010) collected urine samples from 84 women undergoing IVF. Each participant provided two urine samples per cycle, reducing within-cycle variability. One sample was collected at the beginning of the gonadotrophin stimulation, and the second sample was collected on the day of oocyte retrieval. The 84 women contributed 112 IVF cycles, and 23 (27%) contributed more than one IVF cycle during the study period. A total of 85% of the urine samples contained BPA, with a range between less than 0.4 and 25.5 μg/L (geometric mean 2.52 ± SD 3.2). Levels of BPA were inversely correlated with the number of oocytes retrieved and peak oestradiol levels (on the day of HCG triggering). For each log unit increase in specific gravity-adjusted urinary BPA, an average decrease of 12% was reported in the number of oocytes retrieved and an average decrease of 213 pg/ml in oestradiol levels. A similarly significant decrease in peak oestradiol levels with increased quartiles of urinary BPA concentrations was also shown when the sample size was increased (mean decreases of 40, 253, and 471 pg/ml for urinary BPA quartiles 2, 3, and 4, respectively, when compared with the lowest quartile (Ehrlich et al., 2012a).

In a different cohort study, the effect of serum BPA levels on oocyte maturation was investigated. Among the entire cohort of 57 women, no association was found between BPA levels and oocyte maturation. In a sub-analysis, however, a 9% decrease was found in the probability of mature oocytes among nine Asian women undergoing ICSI (Fujimoto et al., 2011). On the basis of fasting unconjugated serum BPA levels among 44 women undergoing IVF from the same cohort (Bloom et al., 2011a), BPA was detected in the serum of 86.4% of the participants, with a median concentration of 2.5 ng/ml (range 0.0 to 67.4 ng/ml). Similar to Mok-Lin et al. (2010), Fujimoto et al. (2011) reported an inverse correlation between BPA and peak oestradiol levels. For each log unit increase in serum unconjugated BPA, they reported a decrease of 106 pg/ml in peak oestradiol. In contrast with Mok-Lin et al. (2010), Fujimoto et al. (2011) did not find a correlation between BPA levels and the number of oocytes retrieved. They suggest that the difference between the studies in the association between BPA levels and number of oocytes retrieved might be attributed to different assessment strategies (Bloom et al., 2011a). In fact, for that very reason, comparing the results of these two studies might be associated with potential bias. BPA measured in the urine consists of both conjugated (with glucuronic acid) and unconjugated (free) fractions and is dominated by the biologically inactive conjugated form (Volkel et al., 2002), whereas BPA measured in the serum consists mainly of the biologically active fraction (unconjugated BPA) (Matthews et al., 2001).

BPA oocyte quality, embryo quality and implantation rate

Ehrlich et al. (2012a) investigated the relationship between total urinary BPA levels (the sum of unconjugated [free] and conjugated BPA) and embryo quality among 174 women undergoing 237 IVF cycles. Urinary BPA was detected in 88% of the participants. The geometric mean (SD) for urinary BPA concentrations among their cohort was 1.50 (2.22) μg/l. The authors reported a significant linear dose-response association between increased BPA and decreased number of oocytes during retrieval and a decrease in mature oocytes (metaphase II oocyte). The average number of oocytes retrieved per cycle for women in the lowest BPA quartile and the highest quartile of urinary BPA concentrations were 12 and nine oocytes per woman, respectively. The inverse correlation between the number of mature oocytes and BPA levels is in line with the findings of the in-vitro study of human oocytes by Machtinger et al. (2013). Ehrlich et al. (2012a) also reported an inverse correlation between BPA levels and the rate of normally fertilized oocytes, with a decrease of 24 and 27%, respectively, for the highest versus the lowest quartile of urinary BPA. No dose-response association was observed between urinary BPA concentrations and day 3 embryo quality.

The same group also examined the relationship between urinary BPA levels and implantation failure (Ehrlich et al., 2012b). Urine samples from 137 IVF patients enrolled as part of a larger prospective study were analysed, and the correlation between urinary BPA levels and embryo implantation was assessed. Odds of implantation failure increased linearly with increasing quartile of urinary BPA concentrations for quartiles 2, 3, and 4, respectively, compared with the lowest quartile. Results did not differ after adjusting for older age (>37 years), day of embryo transfer, or IVF stimulation protocol. The authors stated that women in the highest quartile of exposure (specific gravity-adjusted urinary BPA, 3.80–26.48 μg/L) were almost twice as likely to experience implantation failure as women in the lowest quartile of exposure (≤1.69 μg/L).

Summary

Together, the findings of the above-mentioned studies suggest that exposure to BPA during the stages of oocyte maturation result in perturbation in prophase I, impairment of follicular growth, spindle and chromosomal abnormalities, and also impaired blastocyst formation and implantation failure. Higher serum and urinary BPA levels might be associated with decreased oestradiol levels and (according to some studies) impaired oocyte maturation, decreased ovarian reserve, and reduced implantation. As the quality of evidence for the negative effects of BPA on human fertility is still scarce, further studies are needed.

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