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Review

Associations between male reproductive health and exposure to endocrine-disrupting chemicals

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Abstract

The incidence of many male reproductive disorders, including cryptorchidism and testicular cancer has increased. Semen quality in several countries has declined. Exposure to endocrine-disrupting chemicals (EDCs) — both prenatal and postnatal — has been proposed to have a role in these trends based on experimental data and animal studies. There is epidemiological evidence for an association between prenatal exposure to EDCs and cryptorchidism, hypospadias, and decreased anogenital distance, as well as an association between an exposure to EDCs in adulthood and semen quality. However, some of these findings are inconsistent across studies. There is less evidence about the role of prenatal exposure to EDCs for semen quality, and only few studies have investigated the role of prenatal EDC exposure in testicular cancer occurrence. This is due to a lack of long-term follow-up studies linking prenatal exposures with male reproductive disorders in adulthood. More research is needed investigating the role of EDC exposure for male reproductive health, particularly long-term follow-up studies to assess the outcomes in adulthood.

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Introduction

Reports on increasing rates of male reproductive health problems, such as testicular cancer and undescended testis (cryptorchidism) or declining semen quality, have been published over last few decades [1–4]. According to the testicular dysgenesis syndrome hypothesis, cryptorchidism, hypospadias, testicular germ cell cancer, and poor semen quality have a shared origin in the fetal period [5]. Testicular dysgenesis syndrome may present also as reduced anogenital distance (AGD) in male individuals and reduced testosterone levels in adult men [6]. In addition to genetic factors, especially exposure to environmental and lifestyle factors has been suggested to influence testicular development and function [6](see Figure 1). In the following text, we will review the most recent literature on the association between exposure to endocrine-disrupting chemicals (EDCs) and selected topics of male reproductive health. We focused on original human studies, meta-analyses, and systematic reviews published between October 2016 and October 2018. More background information on EDCs and AGD, cryptorchidism, hypospadias, and testicular cancer is provided in recent reviews [7,8].

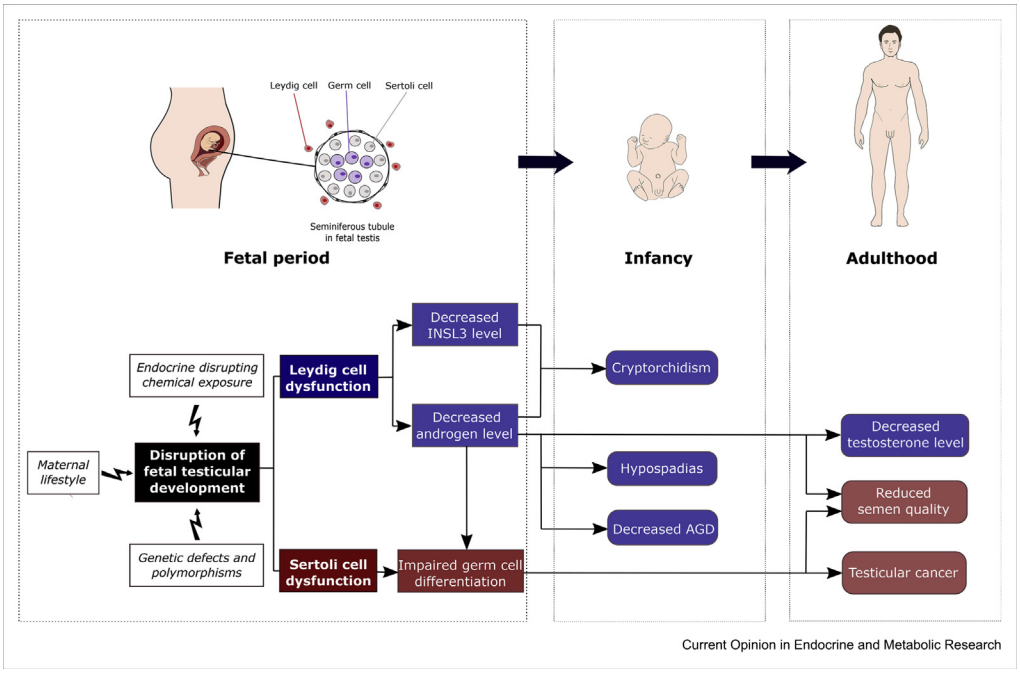
Anogenital distance

Mild analgesics and antifungal medication

The length of the AGD is considered a readout of the prenatal androgen action in males [9]. Three recent studies have investigated the association between the anogenital distance and maternal use of medication during pregnancy [10–12]. AGD was defined as anoscrotal distance (the distance between the center of the anus and the posterior base of the scrotum) or as anopenile distance (the distance between the center of the anus and the anterior base of the penis).

In a prospective baby cohort from Cambridge, UK, information on maternal medication during pregnancy was based on a perinatal questionnaire and sons were followed up until 24 months of age [10]. AGD measurements (anoscrotal distance) of over four hundred boys were available. Exposure to paracetamol during gestational weeks 8–14, but not during other periods, was associated with a reduced AGD (by 0.3 standard deviation [SD], 95% confidence interval [CI] 0.1–0.5) from birth to the age of 24 months [10].

Figure 1



Testicular dysgenesis syndrome. Adverse maternal lifestyle, exposure to endocrine-disrupting chemicals, genetic defects, and polymorphisms may affect the development of the fetal testis and disturb the function of the Leydig cells and Sertoli cells and the differentiation of the germ cells. This can result in a variety of male reproductive system abnormalities — both short-term and long-term manifestations. AGD, anogenital distance; INSL3, insulin-like peptide 3.

In two studies based on a Danish mother–child cohort, 557 and 812 duos, respectively, were included. Information on medication was collected via two questionnaires during pregnancy, and AGD (anoscrotal and anopenile distance) was measured three months after the expected delivery date [11](12). Maternal use of oral fluconazole tablets, but not vaginal antifungal medication, was associated with a significant decrease in AGD (anoscrotal distance) (6.4 mm, 95% CI 0.9–11.9) [11]. Prenatal exposure to mild analgesics (paracetamol and other analgesics) was associated with a significant decrease in AGD (anoscrotal distance) (4.1 mm, 95% CI 1.7–6.4), and exposure to paracetamol only showed a similar tendency [12]. No association between medications during pregnancy and the anopenile distance was found [11,12].

The results of the aforementioned human studies are consistent with some experimental data in rodents, which found a reduced AGD in male offspring after *in utero* exposure to ketoconazole and mild analgesics [reviewed in Ref. [13]].

Phthalates

Association between prenatal phthalate exposure (phthalate levels in maternal urine as a proxy) and AGD in infant boys was evaluated in a systematic review [14]. As phthalates are nonpersistent, exposure levels can vary considerably between and within individuals over time. Moderate evidence for an inverse association (supporting a hazard) between anogenital distance and exposure to di (2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) was reported [14]. For di-isononyl phthalate, di-isobutyl phthalate, butyl benzyl phthalate, and diethyl phthalate current data were not sufficient to reach a conclusion. A recent prospective cohort study from Canada that was not included in the systematic review found no statistically significant association between phthalate levels in a maternal first trimester spot urine sample and anoscrotal distance in the newborn sons (n = 198) [15]. The anopenile distance was positively associated with the level of mono-n-butyl phthalate and the molar sum of phthalates with low molecular weight [15].

Phenols

In a study from Cyprus, the association between cord blood levels of bisphenol A (BPA) and AGD (anoscrotal and anopenile distance) in healthy newborn boys (n = 72) was studied [16]. AGD (anoscrotal distance) was significantly shorter in boys whose cord blood BPA level was above the 90th percentile [16]. A previous study has suggested an association between shortened AGD (anopenile distance) in the sons and parental occupational exposure to BPA during pregnancy (8.1-mm shorter AGD with maternal exposure) [17]. Maternal urinary levels of BPA and triclosan during

pregnancy were also analyzed in the aforementioned prospective cohort study from Canada [15]. However, no statistically significant association between these chemical levels and AGD (anopenile or anoscrotal distance) in the newborn sons was found in the study [15]. In a longitudinal Chinese cohort study, association between BPA levels in maternal urine during pregnancy and AGD (anoscrotal and anopenile distance) in the sons at birth at 6 and 12 months of age was studied [18]. Maternal exposure to BPA was associated with a significantly reduced AGD (2.9 mm shorter anopenile distance and 4.1 mm shorter anoscrotal distance) in the sons only at the age of 12 months [18].

Pesticides, polychlorinated biphenyls, and flame retardants

In a study based on the aforementioned Danish mother–child cohort, associations between AGD in the sons at three months (n = 419) and maternal urine levels of pesticide metabolites (3-phenoxybenzoic acid, 3,5,6-trichloro-2-pyridinol, 2,4-dichlorophenoxyacetic acid, and dialkyl phosphates) during pregnancy were studied [19]. No consistent dose-related association between maternal pesticide metabolite levels and AGD (anoscrotal or anopenile distance) in the sons was observed in the study [19].

In a Spanish study based on a mother–child cohort, the anogenital index (anoscrotal distance divided by weight) of the sons at 18 months (n = 43) was recorded [20]. Associations between AGI and maternal serum levels of polybrominated diphenyl ethers (PBDEs) and organochlorine compounds (hexachlorobenzene, dichlorodiphenyltrichloroethane (DDT) metabolites, and polychlorinated biphenyls [PCBs]) during the first trimester of pregnancy were analyzed. Significant negative associations between AGI at 18 months and maternal levels of PBDE-99 and PBDE-153 were reported [20].

Cryptorchidism and hypospadias

Pesticides

The association between environmental exposure to pesticides and cryptorchidism or hypospadias was examined in a large Spanish population–based case–control study (963 and 678 cases with cryptorchidism and hypospadias, respectively, and 587,142 controls) [21]. The risk of cryptorchidism and hypospadias was increased (odds ratio [OR] 9.0, 95% CI 7.9–10.2 and OR 5.7, 95% CI 4.9–6.7, respectively) in areas of high pesticide use compared with areas of low use [21]. Some previous studies have also suggested positive or inverted U-shaped associations between the level of use of pesticides and the rates of cryptorchidism (e.g. OR for being a case 2.3, 95% CI 1.3–4.3 in the highest exposure category [22]) and hypospadias in the same area [22–24].

A case–control study (25 cases and 58 controls) from France evaluated the association between isolated hypospadias and meconium levels of pesticides or metabolites (organophosphates, carbamates, phenylurea, and phenoxyherbicides) [25]. The presence of the phenylurea herbicide isoproturon and phenoxyherbicide 2-methyl-4-chlorophenoxyacetic acid in meconium was associated with the risk of hypospadias (OR 5.9, 95% CI 1.0–34.1 with moderate exposure and OR 4.8, 95% CI 1.2–18.8, respectively) [25].

Flame retardants

A Canadian case–control study (137 cases, 158 controls) examined the association between operated congenital cryptorchidism and maternal hair levels of PBDEs as a proxy for fetal exposure [26]. The risk of cryptorchidism was positively correlated to maternal hair levels of BDE-99, BDE-100, and BDE-154 (OR 2.5, 95% CI 1.3–5.0, OR 2.5, 95% CI 1.3–4.6, and OR 1.9, 95% CI 1.1–3.3, respectively, for every 10-fold increase in BDE levels) [26]. Another case–control study (152 cases, 64 controls from Canada) evaluated the association between isolated hypospadias and PBDE levels in maternal hair as a proxy for fetal exposure [27]. Hair samples were collected when the child was 3–18 months old. Maternal hair total PBDE levels were significantly higher in boys with hypospadias as compared with the control boys [27]. A previous study reported a positive association between congenital cryptorchidism and the levels of PBDEs in maternal breast milk, but not in the placenta [28]. In another study, maternal serum levels of polybrominated biphenyls, as a proxy for *in utero* exposure to polybrominated biphenyls, were not associated with the risk of cryptorchidism or hypospadias in the sons [29].

Glycol ethers

A matched case–control study nested in two joint French mother–child cohorts studied the association of exposure to glycol ethers (GE, levels in maternal urine as a proxy) with the prevalence of cryptorchidism and hypospadias [30]. Cases had persistent or operated cryptorchidism (n = 14) or hypospadias (n = 15) confirmed by a specialist. Exposure to methoxyacetic acid, but not to phenoxyacetic acid, was significantly associated with the risk of hypospadias (OR 4.5 95% CI 1.4–23.7 in the highest tertile of exposure), but not with the risk of cryptorchidism [30]. This was in line with previous studies suggesting an association between parental exposure to solvents and the risk of male genital malformations (OR for cryptorchidism 2.0, 95% CI 1.0–3.9, OR for hypospadias 2.4, 95% CI 1.2–4.8,

significant only in univariate analysis [31], and OR for male genital malformations 3.6, 95% CI 1.1–11.4 [32]).

Analgesics

A systematic review and meta-analysis included ten studies that evaluated the association between cryptorchidism and the use of analgesia during pregnancy [33]. The analysis suggested a weak association between ever use of analgesia during pregnancy and risk of cryptorchidism (pooled crude OR 1.1, 95% CI 1.0–1.2). In addition, a weak evidence for a relationship of the risk with both the duration and timing of exposure was reported. However, meta-analyses of a dose–response relationship and timing of exposure to analgesics could not be performed because of data limitations [33]. The prospective baby cohort study from Cambridge, UK, did not find an association between testicular descent and exposure to paracetamol during pregnancy [10]. However, this result may have been influenced by the relatively small number of cryptorchid boys in the cohort (33 at birth, 62 at any age) [10].

Phthalates and perfluorooctane sulfonate

The systematic review of Radke et al. evaluated also the association between prenatal phthalate exposure and cryptorchidism or hypospadias [14]. The evidence for any association was, however, weak or uncertain for all six phthalates studied (DEHP, di-isononyl phthalate, DBP, di-isobutyl phthalate, butyl benzyl phthalate, diethyl phthalate) [14]. In a case–control study analyzing perfluorooctane sulfonate levels and levels of DEHP and DiNP metabolites in amniotic fluid during gestational weeks 13–16, no association between these chemical levels and cryptorchidism or hypospadias was found [34].

EDCs in general

In a French case–control study (57 cases, 162 matched controls), associations between hypospadias in the offspring and maternal occupational and household exposures was examined [35]. Information on maternal occupation and exposures during first trimester was collected postnatally via a questionnaire. Household use of hair care products was linked with a risk of hypospadias (adjusted OR 6.1, 95% CI 1.1–34.9, significant only after adjustment) [35]. Potential maternal occupational exposure to EDCs (based on a validated job-exposure matrix) was also associated with an increased risk of hypospadias (adjusted OR 9.6, 95% CI 1.4–66.1) [35]. Several previous studies have also suggested that maternal occupational exposure to EDCs in general is associated with the risk of hypospadias [36–39], but results concerning different chemical groups have been variable.

A meta-analysis aimed to evaluate the overall risk of exposure to EDCs for the development of genital malformations [40]. Different biological matrices were used in the studies to measure a variety of EDCs. Overall, the relative risk estimate for cryptorchidism (OR 1.0, 95% CI 0.7–1.5, 16 risk estimates included) and the risk estimate for hypospadias (OR 1.1, 95% CI 0.9–1.5, 18 risk estimates included) were not statistically significant. For hypospadias, the available data also allowed a meta-analysis for specific chemical groups, that is, for 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene and polychlorinated biphenyls (PCBs). However, also these summary estimates were statistically nonsignificant (OR 1.4, 95% CI 0.9–2.0 and OR 1.1 95% CI 0.6–2.0) [40].

Semen quality

There is evidence for a declining semen quality among men in North America, Europe, Australia, and New Zealand [1,41]. EDCs were proposed to have a role in this finding [42,43]. Most of the studies that investigated the relationship between EDC exposure and semen quality are focused on the exposure during adulthood. There are limited numbers of studies on prenatal exposure. Table 1 summarizes recent studies on the association between EDC exposure and the semen quality assessed by standard procedures of semen analysis.

Prenatal exposure to EDCs and semen quality

Hart et al. studied the relationship between prenatal maternal exposure to BPA or phthalates and semen quality of the sons at the age of 20–22 years in the Raine pregnancy cohort study. The main findings are summarized below.

Bisphenol A

The BPA levels were measured from the pooled serum of 284 mothers at 18 and 34 weeks of gestation. After adjusting for duration of sexual abstinence, varicocele, and maternal smoking, maternal BPA levels had a small positive association with sperm concentration and progressive sperm motility [44].

Phthalates

Maternal prenatal serum mono-ethyl phthalate concentration was negatively associated with semen volume, and the mono-carboxy-iso-octyl phthalate concentration was negatively associated with sperm motility [45].

To date, there are a small number of longitudinal studies assessing the association between prenatal exposure to EDCs and the semen quality [40,46]. The correlation is still unclear, except for some rare cases of occupational or environmental accidents where men with perinatal exposure to dioxin in Seveso, Italy [47], or prenatal exposure to PCBs and polychlorinated dibenzofurans in Taiwan (YuCheng accident) [48] have shown a reduced semen quality after prenatal exposure.

Table 1

List of articles on the association between exposure to endocrine-disrupting chemicals (EDCs) and semen quality published in October 2016–October 2018.

EDC Reference (year)	Country Study design Population	Exposure assessment	Samples for exposure Samples for outcome	Associations
BPA				
Adoamnei E (2017) [50]	Spain Cross-sectional 215 university students, aged 18–23 years	Concurrent	Urinary BPA One semen sample	Negative association (sperm concentration and total sperm count)
Hart RJ (2018) [44]	Australia Prospective pregnancy cohort 136 men, aged 20–22 years	Prenatal	Maternal serum BPA at 18 and 34 weeks' gestation One semen sample	Weak positive association (sperm concentration and motility)
Hu W (2017) [51]	China Cross-sectional 357 subfertile male volunteers, aged 18–43 years	Concurrent	Urinary BPA One semen sample	Negative association (total sperm count, only in obese men)
Radwan M (2018) [52]	Poland Cross-sectional 315 men, aged <45 years, with sperm concentration $\geq$ 15 million/ml	Concurrent	Urinary BPA One semen sample	Negative association (sperm motility)
PCBs				
Hsu PC (2016) [55] (PCBs and PCDFs)	Taiwan Cohort 2 study groups: 50 men exposed to PCBs and PCDFs and 34 neighborhood referents, aged 37–50 years	Adulthood	PCBs and PCDFs in blood in exposed men (not reported) One semen sample	Abnormal sperm morphology (%) was higher in the exposed men than the unexposed men.
Mínguez-Alarcón L (2017) [54]	Russia Cohort Healthy boys at the age of 8–9 years (n = 516) and 18–19 years (n = 133)	Childhood	Serum PCBs 1 or 2 semen sample(s) at 18–19 years of age	No associations
Paul R (2017) [57]	Spain Cross-sectional 2 groups of men from subfertile couples seeking infertility diagnosis aged 30–55 years - low semen quality (had at least 1 abnormal semen variable) (n = 24) - normal semen quality (all semen variables were above WHO reference limits) (n = 26)	Concurrent	Serum DL-PCBs 1 semen sample	Total PCB levels in the low semen quality group were higher than that in the normal semen quality group. *Among men with normal semen quality negative associations*: - PCB-118 (semen volume) - PCB-189 (progressive motility) *positive associations*: - PCB-77, -123, total nonortho PCBs (sperm with normal morphology) *Among men with low semen quality, positive associations*: - PCB-118, mono-ortho PCBs, $\sum$DL-PCBs (semen volume) - PCB-77, PCB-81 (sperm with normal morphology)

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Table 1. (*continued*)

EDC Reference (year)	Country Study design Population	Exposure assessment	Samples for exposure Samples for outcome	Associations
Petersen MS (2018) [53]	Faroe Island Cross-sectional 263 men aged 24–26 years	Concurrent	PCBs in blood One semen sample	No associations
PBDEs				
Albert O (2018) [59]	Canada Cross-sectional 153 healthy men aged 18–41 years	Concurrent	PBDEs in hair samples One semen sample	No associations
Yu YJ (2018) [60]	China Comparative cross-sectional Cases: 32 men (20–50 years) residing at an e-waste dismantling workshop Controls: 25 men (aged 24–46 years)	Concurrent	PBDEs in house dust PBDEs in seminal fluid One semen sample	Cases had lower total sperm count, progressive motility, and total motile spermatozoa than controls. Negative associations: - Seminal BDE-47 (sperm concentration and total sperm count) - BDE-100 in dust (sperm progressive motility and viability)
Phthalates				
Nassan FL (2016) [67]	USA Men with inflammatory bowel disease taking mesalamine aged 18–55 years Crossover–crossback prospective Arm 1: non-DBP–containing mesalamine at baseline, then crossover for 4 months to high DBP, followed by crossback for 4 months to non-DBP mesalamine (n = 26) Arm 2: high-DBP mesalamine at baseline, followed by 4 months non DBP, then 4 months high-DBP mesalamine (n = 47)	Concurrent	No measurement of DBP level One semen sample	At baseline, semen quality between the two groups was not different. Intervention period: *Arm1*: sperm motility decreased during crossover and crossback. *Arm 2:* no change of semen quality
Chen Q (2017) [69]	China Cohort 796 male students who moved to a different university campuses (median age: 20 years)	Concurrent	Urinary phthalate metabolites One urine and semen sample before and after relocation	Negative associations: - mEP (sperm concentration) - mEP, MnBP, MCPP, and sum of LMWP (sperm motility) - MnOP, MEHP, and sum of HMWP (sperm with normal morphology) Positive associations: - miBP and MEHP (semen volume) - MnOP (progressive motility) - MBzP (sperm with normal morphology) After relocation, levels of all phthalates metabolites, except MEHP, decreased along with increased semen volume and sperm with normal morphology.
Chang WH (2017) [64]	Taiwan Cross-sectional Male partners of subfertile (n = 253) and fertile (n = 37) couples (mean age: 33 years)	Concurrent	Urinary and seminal phthalate metabolites One semen sample	Negative associations: - Urinary MBzP and MEHP (sperm concentration and sperm motility) - Seminal MEHP and mono-2-ethyl-5-hydroxyl phthalate levels (sperm

				concentration), MEP level (sperm motility and normal morphology), DEHP level (sperm motility).
Albert O (2018) [59]	Canada Cross-sectional 153 healthy men aged 18–41 years	Concurrent	Urinary phthalate metabolites One semen sample	No associations
Broe A (2018) [68]	Denmark Case-control Danish men in the Danish IVF register (2006–2016) Median age: 34 years *Cases*: men with low semen quality *Controls:* men with normal semen quality In the past 3 months, 57 cases and 72 controls received a prescription for medication containing phthalates and 1421 cases and 2370 controls for phthalate-free drugs	Concurrent	No measurement phthalates level	Men who received phthalate-containing medications had an increased risk of poor semen quality as compared with men who received phthalate-free drugs (OR 1.3, 95% CI 0.9–1.9).
Hart RJ (2018) [45]	Australia Prospective pregnancy cohort 111 men, aged 20–22 years	Prenatal	Maternal serum at 18 and 34 weeks' gestation for phthalate diesters and metabolites One semen sample of the son at 20–22 years of age	Negative associations: - MEP (semen volume) - MCiOP (sperm motility)
Smarr MM (2018) [63]	USA Cross-sectional 339 male partners of couples discontinuing contraception to become pregnant, mean age 31.8 years	Concurrent	Seminal plasma phthalate diesters and monoesters Two semen samples	Negative associations: - monoesters metabolite (mEP, mBP, miBP, mBzP) (semen volume)
Dioxins				
Mínguez-Alarcón L (2017) [54]	Russia Cohort Healthy boys at the age of 8–9 years (n = 516) and 18–19 years (n = 133)	Childhood	Serum TCDD, PCDDs 1 or 2 semen samples at 18–19 years of age	Negative associations (sperm concentration, total sperm count, and total motile sperm count)
Perfluorinated compounds				
Petersen MS (2018) [53]	Faroe Island Cross-sectional 263 men, aged 24–26 years	Concurrent	Blood for PFASs levels (PFOA, PFOS, PFHxS, PFNA, and PFDA) One semen sample	No associations
Song X (2018) [58]	China Cross-sectional 103 men, aged varied	Concurrent	Blood and semen PFAAs	Blood: positive associations (PFBA, PFPeA, and PFBS and progressive sperm motility) negative associations (PFOA and PFOS and progressive sperm motility) Semen: negative associations (Sum of PFAAs, PFBA, PFPeA, PFHxA, PFBS, PFOA, PFHS, PFOS, and progressive sperm motility)
Insecticides/pesticides				
Cremonese C (2017) [72]	Brazil Comparative cross-sectional 99 rural and 36 urban men aged 18–23 years	Concurrent	No chemicals measurements One semen sample	Rural men, 60% were farmers and most reported use of pesticides > 1 year, had higher sperm concentration, but lower percentage of sperm with normal morphology.
Segal TR (2017) [70]	USA Cross-sectional	Concurrent	1–2 urine samples for DCBA levels ≥1 semen samples	No associations

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Table 1. (*continued*)

EDC Reference (year)	Country Study design Population	Exposure assessment	Samples for exposure Samples for outcome	Associations
	90 male partners of couples seeking for infertility treatment, aged 18–56 years			
Parabens				
Nishihama Y (2017) [71]	Japan Cross-sectional 42 male partners of couples who came for infertility consultation (mean age 37 years)	Concurrent	Urinary paraben concentrations One semen sample	No associations
Benzophenone-type ultraviolet filters				
Adoamnei E (2018) [73]	Spain Cross-sectional 215 university students, aged 18–23 years	Concurrent	Urinary benzophenone-type ultraviolet filters One semen sample	No associations
Medications				
Analgesics				
Høyer BB (2017) [74]	3 separate studies in England, Belgium, Italy, Denmark, Greenland, Poland, Sweden, and Ukraine Cross-sectional 1493 men Questionnaire about over-the-counter analgesics use during the past 6 months (paracetamol, NSAIDs, or combination drugs)	Concurrent	One semen sample	No association between over-the-counter analgesics use and semen quality
Statins				
Keihani S (2018) [75]	USA Retrospective Men attended fertility clinic Cases: 118 men who used statins $\geq$ 3 months (mean age 39 years old) Controls: 7698 men without any medication use during the past 3 months (mean age, 32 years old)	Concurrent	One semen sample	Statins use alone: no association with any semen variables. Statins use in combination with other nonspermatotoxic medications: association with lowered semen volume.

Persistent organic pollutants (POPs): DL-PCBs, dioxin-like polychlorinated biphenyl; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-p-dioxins; PCDFs, polychlorinated dibenzofurans; PFAAs, perfluoroalkyl acids; PFASs, perfluorinated alkylate substances; PFBA, Pentafluorobenzoic acid; PFBS, Perfluorobutanesulfonic acid; PFDA, perfluorodecanoic acid; PFPeA; PFHS, Perfluorohexane sulfonic acid; PFHxA, Perfluorohexanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Non-persistent EDCs: BPA, bisphenol A; BzBP, benzyl butyl phthalate; DBP, di-n-butyl phthalate; DCBA, 3-(diethylcarbamoyl) benzoic acid; phthalates; DEHP, di-(2-ethylhexyl) phthalate; HMWP, high-molecular-weight phthalates; LMWP, low-molecular-weight phthalates; MCiOP, Mono-carboxy-iso-octyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; mBP, mono-n-butyl phthalate; mBzP, mono-benzyl phthalate; mEP, mono-ethyl phthalate; MEHP, mono-2-ethylhexyl phthalate; miBP, mono-2-isobutyl phthalate; MnBP, mono-n-butylphthalate; MnOP, mono-n-octyl phthalate; parabens.

NSAIDs, nonsteroidal anti-inflammatory drugs; TEQs, toxic equivalents; OR, odds ratio; CI, confidence interval.

Postnatal exposure to EDCs and semen quality

There are a number of recently published studies, which investigated the association between postnatal EDC exposure (mainly in adulthood) and semen quality. These studies used different adjustment criteria, for example, age, body mass index, duration of sexual abstinence, time from ejaculation to start of semen analysis, smoking and alcohol drinking status and varicocele, for analyzing the correlation. This causes challenges to make direct comparisons between the studies. The key findings are described below.

Bisphenol A

Previous studies reported that the role of BPA exposure during adulthood on semen quality is inconclusive, because the data showed mixed results [49]. However, data from recent studies supported the potential link between BPA exposure and low semen quality.

Urinary BPA concentrations were found to have a significant negative association with sperm concentration and total sperm count in a study in 215 young university students in Spain [50] and in a subgroup of obese men (26 of 357 study men) in China [51]. A study in 315 men, aged below 45 years, with normal sperm concentration in Poland found a negative association between urinary BPA concentrations and sperm motility [52].

Polychlorinated biphenyls and dioxins

A cross-sectional study in 263 young Faroese men found no associations between serum PCBs and any semen variables [53]. A Russian cohort study followed boys from the age of 8–9 years (n = 516) until 18–19 years (n = 133). The serum samples were collected at the age of 8–9 years and semen samples at 18–19 years. The serum levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin, polychlorinated dibenzo-p-dioxins, furans, and PCBs were measured. Higher quartiles of 2,3,7,8-tetrachlorodibenzo-p-dioxin and polychlorinated dibenzo-p-dioxin toxic equivalents were negatively associated with sperm concentration, total sperm count, and total motile sperm count. In contrast, serum PCBs, furans, and total toxic equivalents did not show any associations with semen quality [54]. A study in Taiwan found that men who were exposed to PCBs and polychlorinated dibenzofurans by ingestion of contaminated rice oil during adulthood in 1978–1979 (YuCheng accident) had a higher percentage of sperm with abnormal morphology than unexposed men [55]. In summary, results of the recent PCB studies were different from previous studies, which showed a link between postnatal PCB exposure and lower sperm motility [56].

A study in men from subfertile couples in Spain showed that men with low semen quality (n = 24) had higher levels of dioxin-like PCBs than men with normal semen quality (n = 26). Positive associations between some dioxin-like PCBs and the percentage of sperm with normal morphology in both subgroups of men were found. Associations with other semen variables were also identified (Table 1) [57].

Perfluorinated compounds

A study in 263 young Faroese men found no associations between serum perfluorinated alkylate substances and any semen variables [53]. In contrast, a Chinese study, which measured the levels of perfluoroalkyl acids (PFAAs) in blood and semen in 103 men, found negative associations between seminal PFAAs levels and progressive sperm motility. However, the analysis of correlation between blood PFAAs levels and semen quality showed mixed results [58]. To date, studies on perfluorinated compounds have shown conflicting results.

Polybrominated diphenyl ethers

A cross-sectional study in 153 healthy young Canadian men found no association of the levels of BDE-47, BDE-100, and the sum of BDEs with sperm concentration or motility [59]. A study of 32 Chinese men, living close to an e-waste dismantling area, measured PBDE levels in house dust and semen samples. BDE-47 levels in semen samples were significantly negatively correlated with sperm concentration and total sperm count, whereas BDE-100 levels in dust had a significant negative correlation with the percentage of progressive sperm motility and sperm viability [60]. To date, studies investigating the role of PBDE exposure on semen quality have shown mixed results [61,62].

Phthalates

Several studies on the association between postnatal phthalate exposure and semen quality have recently been published. Of three cross-sectional studies, two demonstrated a negative association between urinary or seminal phthalate levels and semen quality [63,64], whereas one did not [59]. These findings suggest a link between postnatal phthalate exposure and lower semen quality, which are in line with results from the latest systematic reviews and meta-analysis [14,65,66].

A crossover–crossback study in US men diagnosed with inflammatory bowel disease and treated with mesalamine compared semen quality of the two intervention groups — men who were taking non-DBP–containing mesalamine (with crossover to high-DBP–containing mesalamine and crossback to non-DBP mesalamaine) and men who were taking high-DBP mesalamine (with crossover to non-DBP mesalamine and crossback to high-DBP mesalamaine). At baseline, semen quality of the men in the two groups was similar. However, the sperm motility decreased during crossover and continued to decrease even after crossback in the first group. The cumulative carryover effects during

crossback as compared with baseline were as follows: 7.6% lower total sperm motility (95% CI -13.1 to −2.2), 4.2% lower percentage of progressive sperm motility (95% CI -8.1 to −0.4), and 26.0% lower motile sperm count (95% CI 46.2 to 1.7). In contrast, semen quality did not change in the second group [67]. A case−control study in Danish men from the *in vitro* fertilization register reported an increased risk of low semen quality in men who used phthalate-containing medications as compared with men who used phthalate-free medications (adjusted OR 1.3, 95% CI 0.9−1.9) [68]. A cohort study in 796 male students in China observed associations between some urinary phthalate metabolites and semen quality [69] (Table 1).

Other EDCs

A study of 90 male partners of couples seeking infertility treatment in the USA showed no association between the level of urinary 3-(diethylcarbamoyl) benzoic acid, which is a metabolite of the insecticide N,N-diethyl-m-toluamide, and semen quality [70]. One study in 42 Japanese men did not find any association between urinary parabens and semen quality [71]. A Brazilian study showed that the men living in a rural area had higher sperm concentration but lower percentage of sperm with normal morphology and progressive sperm motility than men living in an urban area [72] (Table 1). Urinary levels of benzophenone-type ultraviolet light filters were not associated with semen quality in a study in 215 university students in Spain [73].

Medications

A combined data analysis of three occupational and environmental cohort studies of 1493 men in eight European countries showed no association between the use of over-the-counter analgesics (paracetamol, nonsteroidal anti-inflammatory drugs, or drugs containing both analgesics and other medications) and semen quality [74]. One study compared semen quality of the men attending a fertility clinic who used or did not use statins and found that semen quality of the men in two groups was not different. However, using statins together with other medications is associated with a 0.3-ml decrease of semen volume (95% CI 0.02−0.6, p = 0.04) [75].

Testicular cancer

The prevalence of testicular germ cell tumors (TGCT) has been increasing in several countries [2,76]. Experimental and epidemiological studies support the hypothesis that TGCT has an origin in fetal life [6]. However, there is no longitudinal follow-up study examining the relationship between prenatal EDCs exposure (by measuring the EDCs from the maternal samples during pregnancy, placenta, or cord blood) and testicular cancer in adulthood. This is most likely due to the long time lag between the two events, and the disease is not common.

The meta-analysis in 2016 included eight case-referent studies that investigated the prenatal exposure to EDCs and the risk of TGCT [40]. One study used maternal serum collected from the early postpartum period. Two studies measured persistent organic pollutants levels from the mothers' blood at the time of the sons' diagnosis of TGCT. The rest of the studies used serum persistent organic pollutants levels measured from the testicular cancer cases before or at the time of diagnosis as a proxy for prenatal exposure. The result showed that EDC exposure marginally increased the risk of TGCT (OR 1.2, 95% CI 0.8−1.9) [40].

Findings from the NORD-TEST study, which is a registry-based TGCT case−control study in Denmark, Finland, Sweden, and Norway, have recently been published. The first and second substudy included 8112 TGCT cases, aged 14−49 years, from 1978 to 2012, and 26,264 controls in Finland, Norway, and Sweden. The data on parental occupations before delivery were extracted from the censuses. The first substudy found no association between prenatal parental occupational exposure to organic solvents and TGCT in the sons. However, a subgroup analysis of mothers with available prenatal occupational data showed that maternal exposure to aromatic hydrocarbon solvents increased the risk of TGCT (OR 1.5, 95% CI 1.1−2.2) [77]. The second substudy found either no association between the parental exposure to heavy metals/welding fumes and the risk of TGCT in the sons except among fathers who were exposed to high chromium levels (compared with no chromium OR 1.4, 95% CI 1.1−1.8) [78]. The third substudy included 3421 cases and 14,024 controls from Denmark. Similarly, no significant association between parental exposure to solvents or heavy metals and the risk of TGCT in sons was found (OR for maternal exposure to both solvents and heavy metals 1.1, 95% CI 0.9−1.2, and OR for paternal exposure 1.0, 95% CI 0.9−1.2) [79]. However, the risk of TGCT was increased in the sons with paternal exposure to heavy metals other than lead (most of them were exposed to both chromium VI and toluene) (OR 1.5, 95% CI 1.0−2.2) [79].

Personal care products contain chemicals, some of which have endocrine-disrupting effects. One study evaluated the association between maternal use of personal care products during pregnancy and breastfeeding and the risk of TGCT in the sons. The study included 527 mothers of TGCT cases and 562 mothers of controls. The result showed that the maternal use of facial lotion more often than once per week was associated with an increased risk of TGCT in the sons (OR 1.4, 95% CI 1.1−1.9) [80].

The relationship between environmental exposure in adulthood and TGCT is not clearly demonstrated. This is consistent with the hypothesis that TGCT has a fetal origin [81].

Conclusions

An increasing number of studies suggest that there may be associations between the exposure to EDCs and cryptorchidism, hypospadias, reduced anogenital distance, and semen quality in man. However, there are also many studies showing no effects which leads to inconsistencies. Some of these may be caused by differences in study designs, sample sizes, methods of exposure assessment, and the timing of exposure. Furthermore, humans are exposed to a large cocktail of chemicals which may have additive effects and are still challenging to evaluate. Data on the relationship between exposure to EDCs and development of TGCT is still limited because of the long interval between fetal origin and adult cancer. More research is needed in particular of the association between prenatal and early life exposures to EDCs and semen quality in young adulthood.

Conflict of interest statement

Nothing declared.

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