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The impact of Bisphenol-A on human reproductive health

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A R T I C L E I N F O

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A B S T R A C T

Bisphenol-A (BPA) is a recognized endocrine-disrupting chemical used to produce several consumer goods and products. There has been widespread exposure to BPA because of increased industrial production and use of BPA-containing products. As a result of these exposures, BPA is found in several human body fluids and can cause endocrine disruption by interfering with hormone signaling pathways and epigenetic modifications. Therefore, human reproductive health and development have been adversely affected by BPA. This review aimed to consolidate existing knowledge on the impact of BPA on human reproductive health, examining its effects on both males and females. To achieve this, we systematically searched four databases for studies that associated BPA with reproductive health (male and female), after which we retrieved the important information from the selected articles. There was an association of reproductive health diseases with high BPA exposure. In males, BPA was associated with increased sperm alterations, altered reproductive hormone levels, and testicular atrophy. In females, there was an association of BPA exposure with hormonal imbalances, reduced ovarian reserve, and increased likelihood of conditions such as fibroids, polycystic ovarian syndrome, endometriosis and infertility. BPA's pervasive presence and its harmful effects on reproductive health underscore the need for global regulation and public awareness. Although substantial evidence from animal and *in vitro* studies supports the detrimental effects of BPA, there is a need for more human-focused research, particularly in developing countries, to confirm these findings. This review advocates for increased regulatory measures to limit BPA exposure.

1. Introduction

Endocrine-disrupting chemicals (EDCs) are environmental chemicals made up of one substance or a mixture of substances that can distort the endocrine system and lead to several developmental and reproductive effects [61]. They comprise a heterogeneous group of compounds utilized in producing consumables that are used daily, e.g. personal care products, food packaging materials, building materials, pesticides, etc. [5]. Research has shown that EDCs may affect several hormone signaling pathways by interacting with hormone receptors and interfering with the production, general metabolism or transport of hormones [39]. BPA is a recognized example of EDCs [5], and its consumption and production globally have been in very high quantities [7]. It is an organic compound of carbon, hydrogen and oxygen, comprises two hydroxyphenyl groups, and is a member of the class of diphenylmethane derivatives and bisphenols [144]. It was initially produced by a Russian chemist known as Aleksandr P. Dianin by mixing phenol and acetone with a strong acid acting as a catalyst [23]. It is primarily utilized in producing epoxy resins, polycarbonate plastic, and as a non-polymer addition to other plastics [1,30]. Human exposure to BPA is widespread and well-documented because of its use in the production of household goods and products, such as dental sealants, protective coatings, water supply pipes, polycarbonate food containers and utensils, some flame retardants, thermal paper, dental compounds and safety and medical device packaging [87,88,144]. As a result of these exposures, BPA has been demonstrated to have possible adverse effects on human reproduction and development [142].

BPA has been quantified in several body fluids, including blood, urine, breast milk, cord blood, and more. It can also easily and readily cross the blood-brain and placenta barriers because it is very lipophilic [43]. The digestive system (ingestion) [37,58], vertical transmission (maternofetal) [126], respiratory system (inhalation) [22], and integumentary system (skin and eye contact) [49] have all been described as potential routes of exposure to BPA (Fig. 2), with exposure through dietary routes being the most prevalent [7]. BPA acts by binding to estrogen receptors (ERs) located in the cytoplasm (cER), nucleus (nER), or cell membrane (mER) and stimulating several signaling pathways that induce changes in gene expression. BPA can also manipulate the cellular

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microenvironment directly because its detoxification leads to free radical formation, which can damage the DNA [8]. It can also bind directly to androgen receptors and act as an anti-androgen by inhibiting the effects of endogenous androgens [115]. The effect of this includes triggering alterations in the reproductive health of humans. Being exposed to a high amount of BPA in the developmental stages in males resulted in the feminization of male fetuses, disturbance of the sperm parameters, and reduction in the levels of testosterone and testicular and epididymal atrophy [60]. In females, high exposure to BPA affects the levels of estradiol (E2), which in turn causes irregular hormone balance and other metabolic abnormalities, e.g. early puberty, menstrual irregularities, increased risk of endometriosis as well as being at higher risk of embryo implantation failure [82]. BPA has influenced the pathogenesis of several reproductive health diseases, which include fibroids, polycystic ovarian syndrome (PCOS), endometriosis, female infertility, primary ovarian insufficiency (POI), etc., as well as led to an increase in the presentation of male infertility. Given the increasing pervasiveness of BPA exposure and its detrimental impact on reproductive health [129, 81], there is an urgent need to understand the full scope of its impact. Despite substantial evidence from animal and *in vitro* studies [35,43,94, 123], further research focusing on human populations is essential to confirm these effects and guide effective regulatory measures. This review provides a comprehensive analysis of BPA's effects on human reproductive health. It synthesizes findings from various studies to elucidate its role in reproductive disorders, focusing on both male and female perspectives. By consolidating and critically analyzing human-based research, this review offers a more applicable understanding of the impact of BPA, especially in comparison to the predominantly animal-centered and *in vitro* studies in the existing literature [93]. It addresses the variability of research findings, providing insights into how differences in study design, methodology, and population characteristics influence the observed effects of BPA. Furthermore, this review highlights the critical need for global regulations on BPA use, the promotion of safer alternatives, and the urgent necessity for increased research and regulation in non-developed countries, addressing a significant gap in the current literature.

2. Methodology

Articles were systematically retrieved through searches on EBSCO, Google Scholar, Scopus, and PubMed using an array of keywords: BPA, Bisphenol-A, Reproductive Health, Male Reproductive Health, Female Reproductive Health, Male Infertility, Endometriosis, Polycystic Ovarian Syndrome, Uterine Fibroids, Leiomyoma, Primary Ovarian Insufficiency, Cervical Cancer and Uterine Cervical neoplasms in the search. The search terms were adjusted according to the specific requirements of each database. We focused on articles between the years 2000–2023. Duplicate articles found across the four databases were removed before proceeding to the screening process. Following retrieval and removal of duplicates, two reviewers (OAR and EAS) screened the articles independently; initially, they screened the titles and abstracts and proceeded to screen the full-text articles. For inclusion, articles were required to provide quantitative data on BPA and its association with either male or female reproductive health (Fig. 1).

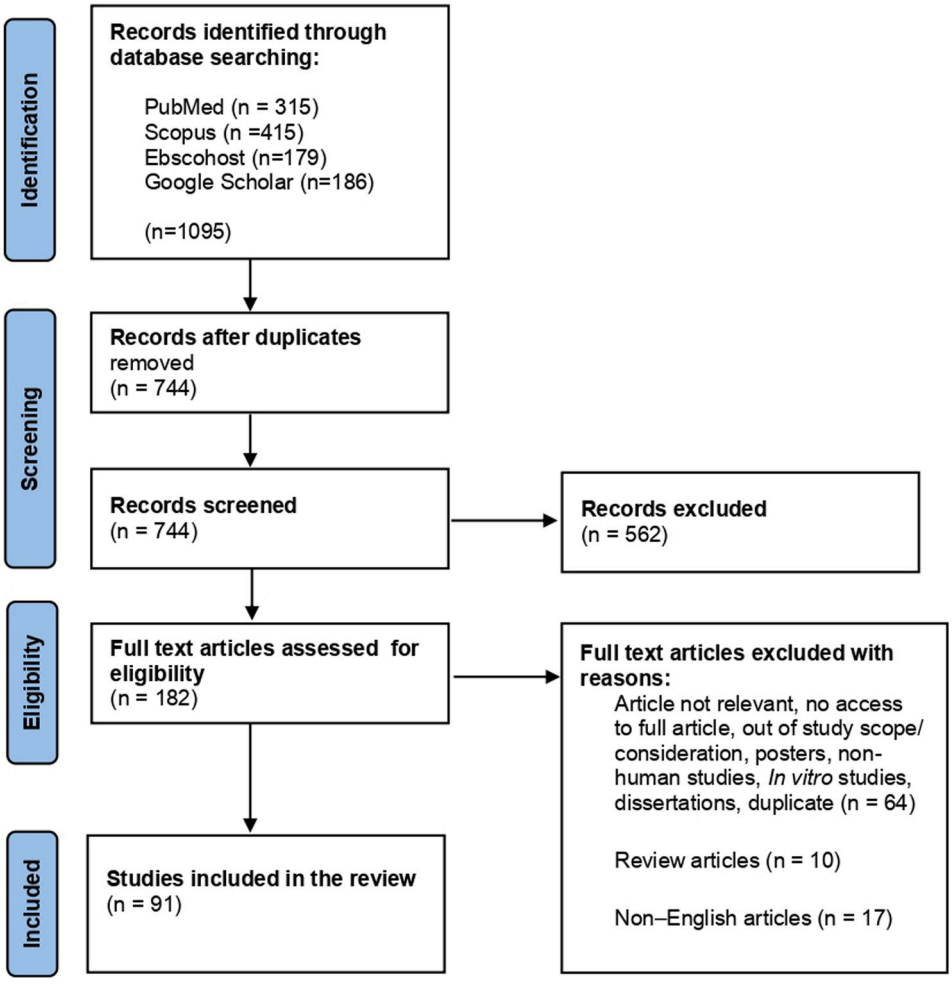

Fig. 1. Flowchart of search and selection process.

We excluded articles that were book chapters, not English, review/methods, and involved animal models from our review. We gathered information regarding the number and country of participants, type of study, BPA concentration, and method of BPA analysis. We retrieved the range/mean/median of BPA concentrations in the articles to depict the relationship between BPA and human reproductive health. The articles were then grouped based on male and female reproductive health (Tables 1–7).

3. Results and discussion

We systematically searched and reviewed articles examining the relationship between BPA and reproductive health in males and females. Among the 91 articles included in this review, 37.4 % discussed the impact of BPA on male reproductive health diseases, while 62.6 % addressed how BPA is involved in female reproductive health diseases. The studies originated from various continents, with the highest proportion conducted in Asia (42.9 %), followed by Europe (29.7 %), North America (19.9 %), Africa (5.5 %), and Australia and South America (1 % each). BPA was quantified in several body fluids, including urine,

Table 1
BPA and fibroids.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
1	Case-control study 495 women	GM (Cre) Cases: 2.09 μg/g Controls: 1.46 μg/g	HPLC-MS/MS	Urine	USA	No relationship was found between fibroids and BPA levels.	Pollack et al. [107]
2	Case-control study Cases: 100 Controls: 28	Range: ND-2.603 ng/ml.	LC-MS	Serum	Korea	Higher BPA levels were found in patients with larger leiomyomas.	Han et al. [42]
3	Case-control study Cases: 49 Controls:29	AM Cases: 13.9 ± 12.7 ng/ml Controls: 8.50 ± 12.2 ng/ml	HPLC–MS/MS	Urine	China	There was a difference between the mean levels and concentration distribution of urinary BPA between the two groups, but the BPA levels were not significantly different.	Zhou et al. [151]
4	Case-control study Cases: 214 Control:126	AM Urinary Control: 11.788 ± 1.738 ng/ml Cases: 17.586 ± 2.329 ng/ml AM Plasma Control: 7.062 ± 8.840 ng/ml Cases: 5.046 ± 5.911 ng/ml	HPLC-MS/MS.	Urine, Plasma	China	The mean levels, range of urinary BPA, and the number of participants with detectable BPA levels varied between the cases and controls, but no significant difference in urinary and plasma BPA levels of the cases and control group.	Shen et al. [120]
5	Case-control study 300 women	Cases Range: Urine: 1.06–59.6 ng/ml Plasma: 0.85–35.5 ng/ml Controls Urine: 1.17–57.4 ng/ml Plasma: 0.97–62.8 ng/ml	HPLC-MS/MS	Urine, Plasma	China	Plasma and urinary BPA levels did not differ significantly between the two groups. Urinary BPA was associated with fibroid incidence, whereas plasma BPA was not.	Shen et al. [118]
6	Case-control study Controls: 30 Cases: 101	AM Control: 0.557 ± 0.086 ng/ml Cases: 0.273 ± 0.052 ng/ml (mild) 0.336 ± 0.063 ng/ml (moderate), 0.636 ± 0.075 ng/ml (severe)	ELISA	Serum	Korea	The serum BPA levels between the two groups were not notably different.	Byun and Han [16]
7	Case-control study Control:30 Cases: 128	AM Control:0.558 ± 0.097 ng/ml Cases: 0.274 ± 0.063 ng/ml (mild) 0.346 ± 0.064 ng/ml (moderate) 0.647 ± 0.039 ng/ml (severe)	ELISA	Serum	Korea	There is no significant difference between the BPA levels of cases and controls.	Jeong et al. [55]
8	Case-cohort study 754 Black women	Median @ Baseline: 2.8 @20 months: 2.1 @40 months; 1.8 (μg/g creatinine)	SPE-HPLC/ID-MS	Urine	USA	There was a weak inverse association between BPA and fibroid incidence and growth.	Wesselink et al. [141]

GM (Cre), Creatinine adjusted geometric mean; LC/MS, Liquid chromatography-mass spectrometry; ELISA, Enzyme-linked immunosorbent assay; HPLC-MS/MS, High-performance liquid chromatography-tandem mass spectrometry; AM, Arithmetic mean; ND, Non-detection; SPE-HPLC/ID-MS, Solid-phase extraction coupled to high-performance liquid chromatography-isotope dilution mass spectrometry.

Table 2
BPA and endometriosis.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
1	Case-control study Cases: 50 Control: 50	AM Cases: 5.53 ± 3.46 ng/ml Controls: 1.42 ± 1.56 ng/ml	HPLC	Urine	Iran	Urinary BPA concentrations were positively associated with endometriosis. BPA concentrations of cases were significantly higher than controls.	Rashidi et al. [111]
2	Case-control study Cases: 143 Controls: 287	Median Cases: 1.02 μg/l Control: 0.86 μg/l	HPLC/MS	Urine	USA	BPA levels were significantly positively associated with non-ovarian pelvic endometriosis.	Upson et al. [132]
3	Cross-sectional study Cases: 160 Controls: 540	GM(Cre) Cases: 3.07 μg/g Controls: 2.21 μg/g	HPLC-MS/MS	Urine	Not stated	A positive relationship between BPA and endometriosis was observed, with levels in the cases being significantly higher than those in the controls	Lee and Eata [70]
4	Case-control study Cases: 35 Control: 89	GM Cases: 5.5 ng/ml Controls: 3.0 ng/ml	UHPLC-MS/MS	Urine	Spain	A strong positive correlation was observed between urinary BPA concentrations and endometriosis	Peinado et al. [105]
5	Matched cohort study Operative Cohort: 495 Population Cohort: 131	GM Operative Cohort Cases: 1.45 ng/ml Controls: 1.66 ng/ml Population Cohort Cases: 4.19 ng/ml Controls: 1.65 ng/ml	HPLC-MS	Urine	USA	No relationship between BPA and endometriosis. In the population cohort, BPA concentrations were higher in cases, compared to controls.	Buck Louis et al. [15]
6	Case-control study Cases: 120 Control: 100	Median Cases: 1.55 ng/ml Controls: 1.30 ng/ml	HPLC-MS	Urine	China	BPA was positively associated with peritoneal endometriosis, although BPA concentrations did not differ significantly between the two groups.	Wen et al. [140]
7	Case-control study Cases: 68 Controls:60	AM ± SD Cases: 5.31 ± 3.36 pg/μl Control: 1.64 ± 0.49 pg/μl	GC-MS/MS	Urine	Italy	Urinary BPA levels of the endometriotic women were higher than controls, and BPA was significantly associated with endometriosis.	Simonelli et al. [122]
8	Case-control study Cases: 58 Control: 11	AM ± SD Cases: 2.91 ± 1.74 ng/ml Range: 0.79 – 7.12 ng/ml	HPLC	Serum	Italy	BPA was not detected in the serum of any healthy woman. In contrast, it was found in 63.8 % of patients with endometriosis, suggesting a relationship between endometriosis and BPA levels	Cobellis et al. [25]
9	Case-control study Cases: 30 Controls: 22	AM Cases: 9.78 μg g^{-1} Control: 8.80 μg g^{-1}	GC-MS	Urine	Brazil	There was no relationship between urinary BPA concentration and endometriosis.	Moreira Fernandez et al. [95]
10	Cross-sectional study 140 women	Median: 1.6 μg/l	HPLC-MS	Urine	Japan	No significant association was found between urinary BPA levels and endometriosis.	Itoh et al. [54]

AM, Arithmetic mean; HPLC, High performance liquid chromatography; GC-MS, Gas chromatography mass spectrometry; HPLC-MS, High performance liquid chromatography mass spectrometry; UHPLC-MS/MS, Ultra-high-performance liquid chromatography with tandem mass spectrometry detection; SD, Standard deviation; HPLC-MS/MS, High performance liquid chromatography tandem mass spectrometry.

plasma, serum, follicular fluid (FF), semen, and saliva, with urine and plasma being the most frequently analyzed. The techniques used in these studies for quantifying BPA include high-performance liquid chromatography, liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry and enzyme-linked immunosorbent assay. In the majority of the studies reviewed, BPA levels were higher in patients with reproductive health diseases compared to controls, and BPA was associated with these diseases. This review discusses diseases and alterations of human reproductive health, highlighting the differences in reproductive health of individuals exposed to BPA and those who are not. It also clarifies which reproductive health diseases are significantly associated with BPA.

3.1. BPA and female reproductive health

The global incidence of reproductive health challenges among women has been on the rise, with exposure to artificial chemicals such as EDCs identified as a contributing factor [45]. Women are exposed to EDCs through various environmental factors, and this exposure can disrupt the endocrine system, leading to adverse effects on reproductive health. BPA, a prominent EDC, is a xenoestrogen, meaning it can mimic the properties of the estrogen hormone. BPA can activate alpha and beta ERs, functioning as both an estrogen mimic and an agonist of these receptors [115]. This disruption in hormonal balance can result in several reproductive health disorders in females. EDC exposure, including BPA exposure, has been associated with decreased female fertility and a range of ovarian and uterine disorders, such as PCOS, endometriosis, and fibroids [133], as described in Fig. 2.

3.1.1. BPA and fibroids

Fibroids are non-cancerous tumors that develop in the smooth muscle tissue of the uterus [16]. Although a lot of reproductive-aged women develop fibroids, only a subset experience symptoms. Fibroids are typically characterized by pain, heavy menstrual bleeding, subfertility and complications during pregnancy [118]. Notably, Black women are more likely to develop fibroids compared to women of other

Table 3
BPA and polycystic ovarian syndrome.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Ref.
1	Cross-sectional study 268 infertile women	Median: 2.35 ng/ml	HPLC-MS/MS	Urine	China	High urinary BPA levels led to a decrease in ovarian reserve, aiding infertility.	Zhou et al. [150]
2	Case-control study Cases: 60 Controls: 30	AM ± SE Cases: 167.04 ± 9.44 IU/ml Control: 31.94 ± 3.57 IU/ml	ELISA	Serum	Iraq	Serum BPA concentrations of both groups were significantly different.	Shaheed et al. [41]
3	Cross-sectional study Cases: 60 Controls: 60	Mean ± SD Cases: 3439.05 ± 2118.25 µg/ml Controls: 813.84 ± 584.78 µg/ml	HPLC	Urine	Egypt	BPA levels of cases were significantly higher than controls.	Fathy et al. [34]
4	Cross-sectional study Cases: 71 Controls:100	AM Cases: 1.05 ± 0.56 ng/ml Controls: 0.72 ± 0.37 ng/ml	ELISA	Serum	Not stated	BPA concentrations in the cases were higher than those of the controls.	Kandaraki et al. [59]
5	Cross-sectional study Cases: 80 Control: 80	Controls: Median: 5.63 ng/ml Range: 1.84–30.45 ng/ml Cases: Median: 24.49 ng/ml Range: 2.18–34.95 ng/ml	Not Stated	Urine	Egypt	Urinary BPA levels of cases and controls significantly differed.	Elkafrawy et al. [33]
6	Case-control study Cases: 51 Controls:51	AM ± SD Cases: 3.34±2.63 ng/ml Controls: 1.43 ±1.57 ng/ml	HPLC	Urine	Iran	BPA concentrations in the urine of women with PCOS were significantly higher than in the control group.	Rashidi et al. [111]

AM, Arithmetic mean; SE, Standard Error; ELISA, Enzyme linked immunosorbent assay; HPLC, High performance liquid chromatography; SD, Standard deviation; PCOS, Polycystic ovarian syndrome; HPLC/MS, High performance liquid chromatography mass spectrometry.

Table 4
BPA and primary ovarian insufficiency.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Ref.
1	Case-control study Cases: 159 Controls:186	AM Cases: 1.373 µg/l Controls:1.343 µg/l	UHPLC-MS/MS	Urine	China	Cases and controls urinary BPA concentrations were not significantly different.	Li et al. [72]
2	Cross-sectional and case-control study Cases: 30 Controls: 30	Cases: Median: 3.0 Range: 0.00–5.97 ng/ml Controls: Median:1.95 Range: 0.00–6.48 ng/ml	LC-MS/MS	Serum	Turkey	The levels of serum BPA concentrations between both groups were not significantly different.	Özel et al. [100]

UHPLC-MS/MS, Ultrahigh performance liquid chromatography tandem mass spectrometry; LC-MS/MS, Liquid chromatography tandem mass spectrometry.

racial backgrounds [11]. Fibroid growth is dependent on estrogen exposure; while early menarche increases the development of fibroids, reduction in estrogen levels during menopause decreases the growth of fibroids. This suggests that estrogen-like activity may contribute to leiomyoma growth [42]. Many women of reproductive age are exposed to a lot of EDCs, including BPA, which are implicated in fibroid development [11]. At low concentrations, BPA can increase fibroid cell proliferation by facilitating the transition of the cells from the G0-G1 to the S phase of the cell cycle. It can also upregulate expression of the ERα36 gene, thereby increasing the growth factor receptor bound (Grb2) and son of sevenless homolog 1 (SOS1) protein expression, which are key drivers of the MAPKp44/42/ERK1/2 signaling pathway [145].

Among the articles reviewed, eight focused on fibroids, revealing a correlation between BPA exposure and fibroids (Table 1). The findings across the studies varied, but most studies reported higher urinary, serum, and plasma BPA concentrations amongst women with fibroids compared to controls. Three studies compared the serum concentrations of BPA in fibroid patients and non-fibroid controls, finding no significant difference in serum BPA levels. However, patients with larger and more severe fibroids had higher BPA levels [16,42,55]. In a prospective study on reproductive-aged black women, a weak inverse association was observed between urinary BPA concentrations and the incidence and growth of fibroids [141]. In three other studies, urinary BPA mean concentrations and distribution range in the fibroid patients significantly differed from the controls. Although they didn't record a significant association between BPA exposure and fibroids, they suggested that BPA concentrations may be involved in the growth of fibroids [107, 120,151]. In a case-control study involving 300 fibroid patients, no significant differences were observed between the BPA levels of cases and controls. However, the incidence of fibroids was associated with urinary BPA but not plasma BPA in the women. The discrepancy may be due to the collection of plasma and urine samples at different time points, leading to fluctuations in metabolic status in the women [118]. Finally, in a case-control study on Chinese women by Shen and

Table 5
BPA and female infertility.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
1	Prospective cohort study 174 females	GM (SD) 1.50 (2.22) μg/l	HPLC-MS	Urine	USA	BPA levels were negatively associated with measures of ovarian response.	Ehrlich et al. [31]
2	Prospective study 301 married couples seeking ART treatment.	AM Blood: 1.29 ng/ml FF: 0.49 ng/ml	GC-MS	FF	Russia	Patients undergoing ART who had a higher level of BPA in FF than in their blood had a decrease in the number and quality of oocytes.	Syrkasheva et al. [128]
3	Comparative analytical study Cases: 48 sub-fertile women Controls: Not stated	Percentage BPA Cases: 70.8 % Controls: 30.7 %	HPLC	Serum	Pakistan	Serum BPA concentrations between cases and controls were significantly different.	Li et al. [72]
4	Case-control study Cases: 111 Controls: 44	Range Cases: 0.5–133.5 ng/ml Control: 0.5–60.9 ng/ml	HPLC-ESI-MS	Serum	Italy	The number of women with detectable BPA levels was significantly higher in cases than controls.	Caserta et al. [20]
5	Case-control study Cases:34 Controls: 45	AM Cases: 4.66 ng/ml Control: 2.64 ng/ml	GC-MS	Plasma	India	BPA concentrations of cases were higher than controls, suggesting a role of BPA in infertility.	Pednekar et al. [104]
6	Case-control study Cases: 110 Controls: 43	Median Cases: 14.9 ng/ml Controls: 0.5 ng/ml	HPLC-ESI-MS	Serum	Italy	There were significantly higher levels of serum BPA in infertile women than in fertile women.	Rocca et al. [113]
7	Case-control study Cases: 48 Control: 13	Percentage of patients with BPA Infertile patients: 72.9 % Fertile Patients: 23.1 %	HPLC-MS	Serum	Italy	The number of patients with observable serum BPA concentrations significantly differed between the case and control groups.	Caserta et al. [19]
8	Epidemiological study 111 women	GM: 4.32 μg/L	UHPLC-MS/MS	Urine	China	There was a relationship between urinary BPA and DOR.	Zhang et al. [149]
9	Prospective cohort study 256 women	Specific gravity-adjusted GM: 1.87 μg/l	HPLC-MS/MS	Urine	USA	There were no associations between high BPA and outcomes of IVF.	Minguez-Alarcon et al. [90]
10	Cross-sectional study 511 infertile women	AM ± SD 2.25 ± 4.77 ng/ml	GC-MS	Urine	Poland	There was a relationship between urinary BPA exposure and ovarian reserve reduction.	Czubacka et al. [29]
11	Prospective cohort study 420 women	GM: 1.14 ng/ml	ID-MS/MS	Urine	USA	There were no associations between BPA and IVF outcomes.	Mínguez-alarcon et al. [91]
12	Cross-sectional study 111 patients who had recurrent spontaneous abortion	Mean: 0.95 ng/ml Range: 0.48–1.87 ng/ml.	UHPLC-MS/MS	Urine	China	There was a potential association between BPA and the occurrence of oxidative stress and imbalance of the immune system in patients with URSA.	Liang et al. [74]
13	Cross-sectional study 44 women	Mean: 7.22 ng/ml Range: 0.3–67.36 ng/ml	HPLC	Serum	USA	Serum BPA was associated with a reduction in E2 response to gonadotropin stimulation during the process of IVF.	Bloom et al. [14]
14	Prospective cohort study 146 couples	AM urinary BPA: 3.7 ng/ml GM female plasma BPA: 0.049 ng/ml GM male plasma: 0.040 ng/ml GM FF: 0.033 ng/ml GM semen; 0.025 ng/ml	LC-MS	Urine, Plasma, FF, Semen	Korea	The levels of BPA in various body fluids (urine, plasma, FF, and semen) did not have a significant impact on fertility outcomes.	Kim et al. [64]
15	Cross-sectional study 351 infertile women	Median concentration 0.38 μg/l	SPE-LC-MS/MS	Urine	China	Urinary BPA exposure decreased the success rates of retrieving oocytes and implanting embryos in IVF women.	Shen et al. [119]
16	Cross-sectional epidemiological study 186 women	AM(Cre) ± SD Women in commerce: 1.10 ± 0.48 μg/g Cre. Women in non-commerce industries (0.45 ± 0.35 μg/g Cre. Median BPA concentration: 0.44 μg/g Cre	HPLC-MS	Urine	Italy	Women occupationally exposed to BPA had urinary BPA concentrations twice the levels of those unexposed, signifying that BPA played roles in diminishing reproductive health, particularly in women with RPL and unexplained infertility.	Caporossi et al. [18]
17	Cross-sectional study 307 women	Arithmetic Mean DOR group: 1.89 ± 2.17 μg/g non-DOR group: 1.58 ± 1.08 μg/g	HPLC-MS/MS	Urine	Korea	The BPA concentrations in women with DOR were higher than in the non-DOR group, suggesting that DOR and infertility are associated with BPA. .	Park et al. [103]
18	Cross-sectional study Exposed workers: 106 Unexposed workers: 250	GM Cases: 22.2 μg/g Cre Controls: 0.9 μg/g Cre	HPLC	Urine	China	Elevated BPA levels and E2 were positively correlated in the exposed workers.	Miao et al. [85]
19	Cross-sectional study 143 reproductive-aged women	Median: 2.8 ng/ml	HPLC-MS	Urine	USA	In reproductive-aged women, BPA was positively associated with E2 and P4.	Pollack et al. [108]

GM (SD), Geometric mean (Standard deviation); ART, Assisted reproductive technologies; FF, Follicular fluid; HPLC-ESI-MS, High-performance liquid chromatography with electrospray ionization tandem mass spectrometry; IVF, *In vitro* fertilization; UHPLC-MS/MS, Ultra high-performance liquid chromatography-tandem mass

spectrometry; URSA, Unexplained recurrent spontaneous abortion; RPL, Recurrent pregnancy loss; DOR, Diminished ovarian reserve; ID-MS/MS, Isotope-dilution tandem mass spectrometry; AM, Arithmetic mean; GC-MS, Gas chromatography-mass spectrometry; LC-MS, Liquid chromatography-mass spectrometry; SPE-LC-MS/MS, Solid phase extraction liquid chromatography-tandem mass spectrometry; HPLC, High-performance liquid chromatography; Cre, Creatinine.

Table 6
Prenatal exposure effects of BPA.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
1	Longitudinal cohort study 528 mother-child pairs	Median: 1.48 μg/g	UHPLC-MS/MS	Urine	China	BPA exposure in pregnancy resulted in changes in kisspeptin levels in pregnant women & their offspring.	Wang et al. [137]
2	Cross-sectional study 244 mother-child pairs	GM Maternal BPA 1.62 ng/ml	UHPLC	Urine	China	An inverse association between shorter penis length and prenatal exposure to BPA was observed.	Huang et al. [53]
3	Prospective preconception cohort study. 346 women and men	GM-SGA Paternal preconception: 1.6 ng/ml Maternal preconception: 1.5 ng/ml Maternal prenatal BPA: 1.2 ng/ml	SPE-HPLC	Urine	USA	There was a negative association between the BPA urinary concentrations in the mothers before conception and the weight and head circumference of their infants at birth.	Mustieles et al. [97]
4	Cross-sectional study 77 women (Guiyu -BPA exposed town) 60 women (Haojiang -BPA non-exposed town)	GM Guiyu: 2.72 ng/ml Haojiang: 0.62 ng/ml	GC-MS	Urine	China	Elevated levels of BPA in pregnant women in Guiyu were associated with distorted cord testosterone to E2 levels in male infants. However, no significant association was observed with AGD.	Liu et al. [77]
5	Prospective longitudinal birth cohort study 101 pregnant women	Range 0.3–21.0 ng/ml	LC-MS	Serum	Denmark	There was a correlation between high prenatal serum BPA levels in pregnant women and a decrease in Leydig cell function in their male children.	Holmboe et al. [46]
6	Observational study 913 men whose mothers were exposed to BPA	Median 0.25 μg/l	HPLC	Serum	Australia	There were no adverse effects of maternal serum BPA on testicular function in adulthood, but there was a weak positive relationship between BPA and some testicular function parameters (sperm concentration and sperm motility).	Hart et al. [44]
7	Prospective cohort study 1059 mother-child pairs	Median 1.66 ng/ml	HPLC-ESI-MS/MS	Urine	Netherlands	High maternal gestational BPA levels were associated with altered reproductive development in their children, particularly in boys.	Blaauwendraad et al. [13]
8	Prospective birth cohort study 514 pregnant women	GM 0.051 ng/ml.	ID- LC-MS/MS	Cord blood	Japan	Fetal cord blood BPA levels were associated with alterations in the levels of certain reproductive hormones of the children in a sex-specific manner.	Minatoya et al. [89]
9	Longitudinal cohort study 120 pregnant women	GM Overall prenatal exposure: 0.97 μg/l	ID-LC-MS/MS	Urine	Mexico	The development of the female reproductive system may be susceptible to the impact of exposure to BPA during in-utero development.	Watkins et al. [138]
10	Prospective cohort study 384 mothers and 211 fathers (203 couples) seeking infertility treatment	GM Mothers with partner: 1.12 ng/ml Mother without partner: 1.06 ng/ml	HPLC-ID-MS/MS	Urine	USA	The occurrence of preterm birth had a positive association with pre-conception urinary BPA.	Zhang et al. [148]
11	Cohort study 385 pregnant women	SGA Mean ± SD 1.8 ± 2.5 μg/l	HPLC/MS	Urine	USA	BPA exposure during the first trimester led to alterations in the hormonal environment of female fetuses had an association with a shorter AGD in the girls.	Barrett et al. [12]
12	Longitudinal cohort study 982 women	Median 1.26 μg/g	HPLC	Urine	China	Maternal urinary BPA was associated with a shortened AGDap and AGDas in males at 12 months of age but not in girls. This indicates that BPA exposure has a gender-specific impact on the development of offspring	Sun et al. [127]

GM-SGA, Specific gravity adjusted geometric mean; SPE-HPLC, Solid phase extraction-high performance liquid chromatography; AGD, Anogenital distance; AGDap, Anogenital distance (Anus-penis); AGDas, Anogenital distance (Anus-scrotum); GM, Geometric mean; UHPLC-MS/MS, Ultra high-performance liquid chromatography tandem mass spectrometry; UHPLC, Ultra high-performance liquid chromatography; LC-MS, Liquid chromatography-mass spectrometry; HPLC, High-performance liquid chromatography; ID-LC-MS/MS, Isotope dilution liquid chromatography-tandem mass spectrometry; GC-MS, Gas chromatography- mass spectrometry.

colleagues, it was observed that plasma BPA was not associated with the occurrence of fibroids. However, plasma BPA concentrations between cases and controls significantly differed [120].

The studies reviewed have presented varying views on the relationship between BPA and fibroids, therefore future prospective studies should be carried out to clarify the associations between BPA and fibroid tumorigenesis. However, since fibroids show increased expression of estrogen receptors (ERs), making them more sensitive to estrogen stimulation, they may be particularly vulnerable to endocrine disruption by xenoestrogens like BPA and susceptible to the agonistic effects of BPA on ERs, therefore signifying their role in driving fibroid progression [55]. Although causality is not yet established, most women with

Table 7
BPA and male reproductive health.

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
1	Case-control study Cases: 155 Infertile men Controls: 211 fertile men.	AM Cases: 0.47 μg/g creatinine Control: 0.69 μg/g creatinine	HPLC-MS	Urine	Italy	No significant difference between the urinary levels of BPA in cases and controls.	Caporossi et al. [17]
2	Cross-sectional study 375 husbands of pregnant women (fertile men)	GM: 1.5 μg/l	HPLC	Urine	USA	No significant associations between semen parameters and BPA levels.	Mendiola et al. [84]
3	Prospective cohort study 149 couples	GM: 1.55 ng/l	GC-MS	Urine	Slovenia	There was an inverse association between the quality of semen of male partners in subfertile couples and urinary BPA levels.	Knez et al. [66]
4	Occupational cohort study Cases: 72 exposed workers Controls: 86 non-exposed workers.	GM-Cre Cases: 158.41 μg/g Cr Controls: 0.84 μg/g Cr	HPLC	Urine	China	Occupational exposure to BPA was positively related to hydroxymethylation of sperm LINE-1 in human semen samples. BPA concentrations were significantly higher in cases than controls.	Tian et al. [130]
5	Case-control study Cases: 877 idiopathic infertile men Controls: 713 fertile men	GM Control: 0.621 ng/ml Cases: 0.612 ng/ml	UHPLC-MS/MS	Urine	China	Urinary BPA and male infertility were not associated.	Chen et al. [21]
6	Case-control study Cases: 281 BPA exposed male workers Controls: 278 BPA non-exposed male workers	Median Cases: 18.75 ng/ml Controls: 3.37 ng/ml	GC-MS	Serum	China	There was a relationship between occupational exposure to BPA and imbalances in male sex hormone levels. BPA concentrations were higher in cases than controls.	Zhuang et al. [152]
7	Cross-sectional study 158 healthy university students (18–23 years)	Median (Cre) 2.05 μg/g	UHPLC	Urine	Spain	Urinary BPA levels and SDF index among all the men were not associated. However, among the subset of males with a relatively high SDF index, there was a positive association.	Adoamnei et al. [2]
8	Cross-sectional study 191 men attending a fertility clinic Normospermic men: 89 Oligospermic men: 59 Teratospermic men:25 Azoospermic men: 18	Mean Plasma BPA: 0.019–0.072 ng/ml Seminal BPA: 0.075–0.153 ng/ml	LC-MS	Plasma, Semen	Germany	The presence of BPA in semen was associated with a decrease in sperm concentration and sperm quality.	Vitku et al. [134]
9	Cross-sectional study 462 men attending an infertility clinic	Median (Cre) 2.19 μg/g	LC-MS	Urine	China	Urinary BPA and reproductive hormones had a weak association.	Zeng et al. [147]
10	Cross-sectional study 172 peripubertal boys	GM 5.1 μg/l	LC-MS	Urine	Spain	Urinary BPA was negatively and significantly associated with serum cortisol concentrations in peripubertal boys.	Mustieles et al. [96]
11	Cross-sectional study 44 small-scale farmers (rural area) 37 townsmen (urban area)	Mean ± SD (Cre) 2.18 ± 1.97 μg/gCr	Radioimmunoassay	Urine	Cameroon	Associations between high urinary BPA and reduced levels of free testosterone in the men occupationally exposed to BPA were observed.	Tsague et al. [131]
12	Prospective study Cases: 100 infertile men Controls: 50 fertile men	Mean Cases: 10.07 ng/ml Control: 1.69 ng/ml	HPLC	Urine	Egypt	Urinary BPA levels in the cases significantly differed from controls.	Shokry et al. [121]
13	Case-control study Cases: 90 (men with different degrees of infertility) Control: 84 (normospermic men)	Range Plasma BPA: 33–137 pg/ml Seminal BPA: 66–179 pg/ml	LC-MS	Plasma, Semen	Germany	A negative relationship between seminal BPA, sperm concentration, and total sperm count was observed, with BPA concentrations in cases and controls significantly differing.	Vitku et al. [135]
14	Cross-sectional 223 factory workers	AM Petrochemical factory workers: 0.457 ng/ml Non-petrochemical workers: 0.628 ng/ml	HPLC-MS	Serum	Korea	The serum BADGE concentrations were high, which led to hormonal alterations in the cases.	Kim et al. [65]
15	Cross-sectional study 18 males who received two composite restorations.	Mean Serum: 1.42 ± 0.31 ng/ml Saliva: 0.29 ± 0.19 ng/ml	HPLC	Serum	Turkey	BPA exposure did not alter hormone levels in the participants.	Gul, Celik and Betul [40]
16	Case-control study Cases: 70 infertile men Controls: 83 fertile men	Mean Plasma Cases: 9.3 ng/ml Control: 5.7 ng/ml Semen	HPLC-ESI-MS	Plasma, Semen	Italy	An upregulation of all NRs, except PPARγ, and higher BPA levels were observed in cases compared to the controls.	Rocca et al. [114]

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Table 7 (*continued*)

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
		Cases: 1.1 ng/ml Control: 1.1 ng/ml					
17	Cross-sectional study Cases: 165 BPA exposed men Controls: 427 non-exposed	Median Cases: 685.9 μg/gCr Controls: 4.2 μg/gCr	HPLC	Urine	China	An increase in urinary BPA levels was related to alterations in reproductive hormones and may contribute to male infertility.	Liu et al. [76]
18	Case-control study 163 men Cases were male partners of couples with reduced semen quality. Controls were either male partners of couples with female causes of infertility or sperm donors.	Mean Control 1.5 μg/l Cases: 1.7 μg/l	GC-MS	Urine	Belgium	BPA was negatively associated with testosterone levels and increased subfertility in men.	Hond et al. [47]
19	Case-control study Cases: 77 BPA-exposed men Control: 72 non-BPA exposed men	Mean (Cre) Cases: 36.23 μg/g Cr Controls: 1.38 μg/gCr	HPLC	Urine	China	There was a significant decrease in the methylation level of sperm LINE-1 in cases compared to controls. BPA concentrations of cases were higher than controls	Miao et al. [86]
20	Cross-sectional study 357 subfertile obese men	GM 0.52 ng/ml	UHPLC-MS/MS	Urine	China	BPA concentration was significantly correlated with sperm count in obese men.	Hu et al. [52]
21	Prospective study 936 men in couples seeking infertility treatment at a fertility clinic	Median 1.12 ng/ml	ID-MS/MS	Urine	USA	Sperm concentration, total count, total motility, and per cent morphologically normal sperm decreased significantly, as urinary BPA concentration decreased in men over the study period.	Mínguez-alarcón et al. [92]
22	Case-control study Cases: 190 subfertile men Controls: 540 fertile men	GM Cases: 1.4 ng/ml Controls: 2.3 ng/ml	MS	Urine	USA	BPA levels in cases were lower than those of controls, but there may be associations of BPA with reduced semen quality and increased sperm DNA damage	Meeker et al. [83]
23	Cross-sectional, case-control and clinical study Cases: 55 men with infertility Controls: 25 fertile men	Median Cases: 0.19 ng/ml Controls: 0.18 ng/ml	ELISA	Serum	Greece	There was no difference in BPA concentrations between cases and control and no association between BPA and infertility, but very high levels of serum BPA were observed in infertile men, suggesting an influence of BPA in infertility.	Mantzouki et al. [80]
24	Prospective study Cases:98 boys with cryptorchidism Controls: 57 boys of the same age, without pathology of the testes	AM Cases: 5.3 ng/ml Control: 5.7 ng/ml	GC-MS	Serum	Poland	In boys with cryptorchidism, BPA levels were higher than controls, and BPA was associated with cryptorchidism.	Komarowska et al. [67]
25	Case-control study Cases: 66 Infertile men Control: 50 fertile men	Not specifically stated	UHPLC	Seminal Fluid	Poland	The levels of BPA in the seminal fluid were elevated in cases when compared to the controls. Additionally, there was a negative relationship between the levels of BPA and the quality of sperm.	Palak et al. [101]
26	Cross-sectional study 215 healthy students	Median 2.8 ng/ml	UHPLC-MS/MS	Urine	Spain	Reduced leydig cell capacity and sperm count in young men was associated with BPA exposure.	Adoamnei et al. [3]
27	Prospective cohort study 501 male partners of couples who discontinued contraception to become pregnant	GM 0.55 ng/ml	HPLC-ESI-MS/MS	Urine	USA	There was a negative relationship between urinary BPA and DNA fragmentation	Goldstone et al. [38]
28	Cross-sectional study 315 men attending an infertility clinic	Median 1.87 μg/l	GC-MS/MS	Urine	Poland	Urinary BPA was associated with lesser semen quality	Radwan et al. [110]
29	Cross-sectional study 308 young men	Median 3.25 ng/ml	ID-LCMS/MS	Urine	Denmark	Urinary BPA was linked to increased levels of reproductive hormones and a decreased amount of progressively motile sperm.	Lassen et al. [69]
30	Longitudinal birth and infancy cohort study 36 boys	Osmolality corrected AM 0.45 ng/ml	LC-MS/MS	Urine	Not stated	Urinary BPA was linked to changes in reproductive hormone levels in infant boys	Lærkeholm Müller et al. [68]
31	Case-control study Cases: 65 men with FLG loss of function mutation Control: 130 men without FLG loss of function mutation.	Median 3.5 ng/ml	LC-MS	Urine	Denmark	Among the men with FLG mutation, it was observed that BPA was associated with higher serum testosterone and E2 levels and a lower percentage of progressive motile spermatozoa as opposed to those without the mutation.	Nordström et al. [98]
32	Cohort study Cases: 130 men with BPA exposure in the workplace	Median (Cre) Exposed workers: 38.7 μg/gCr	HPLC	Urine	China	Increasing urinary BPA level was significantly associated with decreased sperm concentration, total sperm count, sperm vitality, and sperm motility.	Li et al. [73]

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Table 7 (*continued*)

S/N	Study type/no of participants	Levels	Quantification method	Matrix	Country	Findings	Refs.
	Controls: 88 men without BPA in the workplace	Unexposed workers: 1.4 μg/gCr					
33	Case-control study Cases: 50 infertile men attending a fertility clinic Control:50 fertile men	Median Cases: 24.2 μg/l Control: 20.9 μg/l	HPLC	Urine	Egypt	Total urinary BPA levels was negatively correlated with antioxidant levels and semen quality, while being positively associated with DNA damage. BPA concentrations were higher in cases than controls.	Omran et al. [99]
34	Cross-sectional study 167 subfertile men	Median 1.3 ng/ml	HPLC-MS/MS	Urine	USA	Urinary BPA was associated with altered hormone levels in men.	Meeker and Antonia M. Calafat [28]

AM, Arithmetic mean; GM, Geometric mean; SD, Standard deviation; LINE 1, Long interspersed nuclear element; SDF, Sperm DNA fragmentation; BADGE, Bisphenol-A diglycidyl ether; ID-MS/MS, Isotope dilution tandem mass spectrometry; FLG, Filaggrin gene; NRs, Nuclear receptors; PPAR, Peroxisome proliferator-activated receptor γ; UHPLC-MS/MS, Ultra high-performance liquid chromatography tandem mass spectrometry; UHPLC, Ultra high performance liquid chromatography; GC-MS, Gas chromatography-mass spectrometry; LC-MS/MS, Liquid chromatography tandem mass spectrometry; HPLC, High performance liquid chromatography; ID-LC-MS/MS, Isotope dilution liquid chromatography tandem mass spectrometry; HPLC-MS, High-performance liquid chromatography-mass spectrometry; MS, Mass spectrometry; ELISA, Enzyme-linked immunosorbent assay; GC-MS/MS, Gas chromatography tandem mass spectrometry; HPLC-ESI-MS/MS, High-performance liquid chromatography-electrospray ionization tandem mass spectrometry.

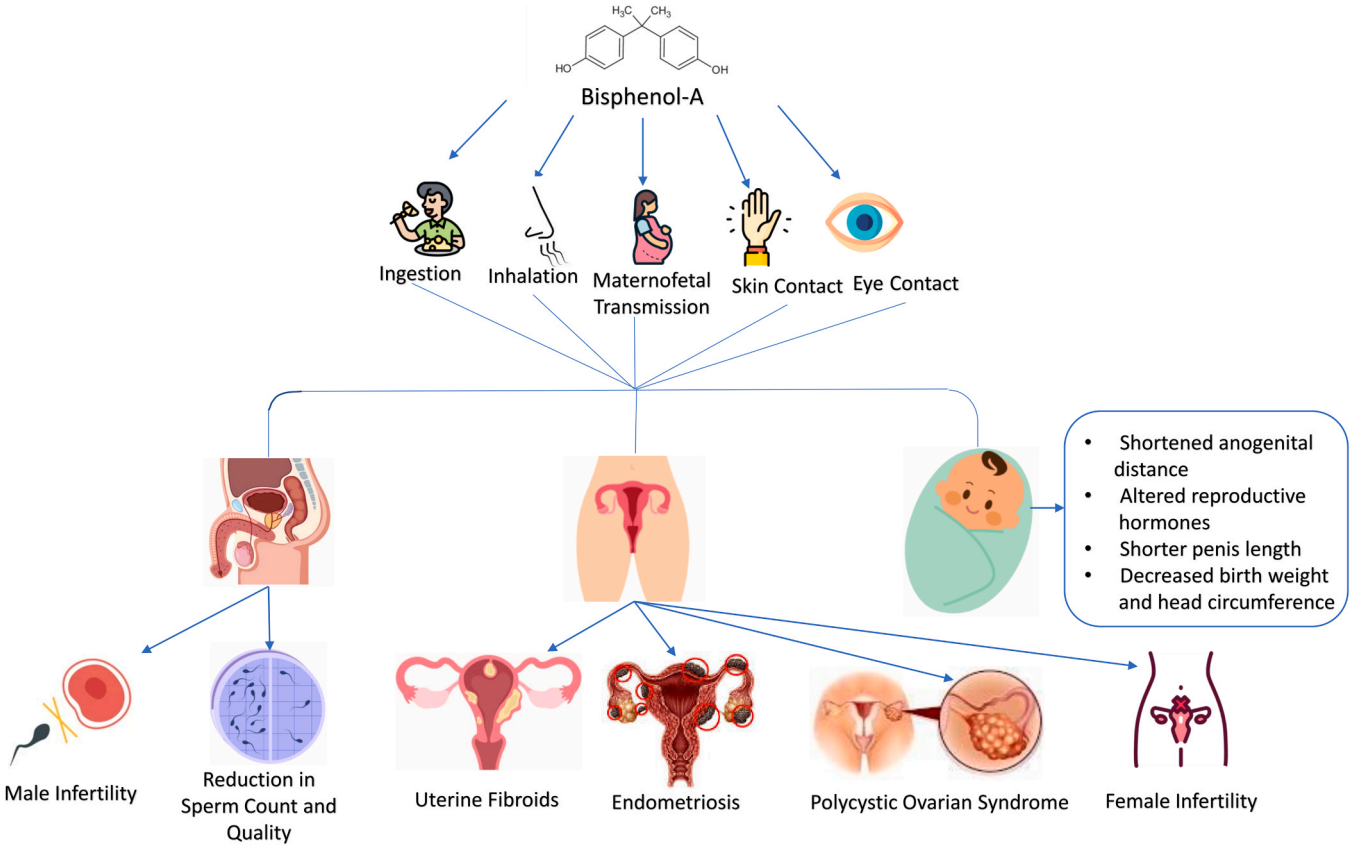

Fig. 2. Routes of exposure to BPA and the accompanying effect on human reproductive health.

fibroids had higher BPA levels than the control group, providing further evidence of BPA's influence in the pathogenesis of fibroids.

3.1.2. *BPA and endometriosis*

Endometriosis is a condition characterized by the inflammation of the uterus, and it presents as the implanting and development of endometrial tissue outside the uterus [124]. It is one of the most prevalent female reproductive health diseases, affecting approximately 10–15 % of women of reproductive age [102]. *In vivo* and *in vitro* studies have identified significant associations between endometriosis and BPA levels [4,57,62]. The accumulation of stromal and periglandular collagen, coupled with the development of endometrial gland nests, has been increased by exposure to low doses of BPA [62]. BPA also disrupts the normal physiology of the human endometrium by interfering with the cell cycle and upregulating the expression of proteins associated with the endometriotic phenotype, thereby promoting the progression of endometriosis [36]. Peroxisome proliferator-activated receptor gamma (PPARγ) is expressed in the endometrium and the ovarian tissue, where it plays a role in regulating folliculogenesis by modulating the activity of proteases involved in the remodeling of tissue and angiogenesis, which are essential processes in the progression of endometriosis [19]. BPA can dysregulate PPARγ expression, favoring the endometriotic phenotype.

We reviewed ten articles on endometriosis, and they demonstrated

significant associations between endometriosis and BPA exposure (Table 2). In 4 studies, urinary BPA concentrations were positively associated with endometriosis [70,105,112,122] and could significantly increase the risk of developing the condition [70]. Peinado et al. noted that urinary concentrations of BPA were significantly linked to a greater risk of endometriosis only after adjusting for variables such as urinary creatinine levels, age, BMI, parity, and residency [105]. Only one study suggested an association between serum BPA and endometriosis, as BPA was detected only in women with endometriosis and not in healthy controls [25]. Most studies measured BPA in the urine due to its short-lived nature in plasma or serum, as BPA is quickly metabolized and excreted through urine [136]. Overall, these studies found higher BPA levels in cases compared to controls [70,112,122].

One of the risk factors for endometriosis includes alterations in Matrix metalloproteinases (MMP) 2 and MMP9 levels in the endometrial tissue [146,26]. MMP2 and MMP9 are vital enzymes that facilitate cell invasion by degrading type IV collagen, the main component of the basement membrane. In a case-control study on 173 Chinese women, creatinine-adjusted urinary BPA was positively associated with peritoneal endometriosis, potentially due to the ability of BPA to upregulate MMP2 and MMP9 expression via the GPER-mediated MAPK/ERK signaling pathway, which could trigger an invasion of human endometrial stromal cells [140].

Nevertheless, no clear relationship between BPA and endometriosis was observed in some studies. For example, a case-control study by Upson et al., measured urinary BPA in relation to endometriosis disease subtypes (surgically visualized ovarian and non-ovarian pelvic endometriosis), found no relationship between BPA and overall endometriosis. However, total urinary BPA concentrations and non-ovarian pelvic endometriosis were significantly positively associated, suggesting a subset of endometriotic patients were more susceptible to BPA exposure [132]. Furthermore, the presence of undiagnosed endometriosis among the population-based controls might have caused the absence of an association between BPA and overall endometriosis. In another case-control study on Brazilian women, no association was found between BPA and endometriosis, possibly due to the time gap between BPA exposure and disease manifestation, which could limit the ability to establish an association [95]. Similarly, a matched-cohort study in Californian women and a cross-sectional study on infertile Japanese women found no association between endometriosis and BPA [15,54]. The studies' authors noted that using urine to measure BPA might limit the accuracy of exposure assessment, as urine reflects recent rather than cumulative exposure. The cross-sectional study design may have also contributed to the absence of association.

The reviewed studies indicated that BPA may induce the pathogenic mechanisms that drive endometriosis, as BPA was associated with the condition in most studies. Furthermore, the role of BPA in endometriosis was highlighted by the presence of elevated BPA levels in women with endometriosis compared to the controls. These deleterious effects of BPA were linked to its influence on facilitating cell invasion, leading to the degradation of the basement membrane in the endometrium, which favors the condition. Additionally, BPA was associated with the upregulation of several proteins (MMP2, MMP9, and PPARγ) involved in endometrial tissue remodeling, contributing to endometriosis.

3.1.3. BPA and polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age, with a prevalence ranging from 5 % to 10 % [109]. PCOS is a complex metabolic and endocrine disorder that exhibits a variety of phenotypes. According to the Rotterdam criteria, a woman is diagnosed with PCOS when she meets at least two of the three criteria, which include excessive circulating androgen levels, the presence of cysts in the ovary, and oligo-amenorrhea with oligo-anovulation [9]. BPA exposure can impact the phenotype of PCOS by influencing the release of gonadotropin-releasing hormone (GnRH), leading to increased luteinizing hormone (LH) levels and decreased follicle-stimulating hormone (FSH) secretion. This disruption affects follicle development and enhances ovarian androgen production, resulting in hyperandrogenism, anovulation, and ovulatory dysfunction—key drivers of PCOS [116,33].

We reviewed six articles on PCOS (Table 3), and BPA and PCOS were positively associated significantly [34,59,111]. In five of these studies, both serum and urinary BPA levels were notably higher in PCOS patients compared with controls [33,34,59,111,41]. BPA has also been detected in FF, indicating that BPA can alter oocytes during folliculogenesis. In a study involving Egyptian infertile women sub-grouped into PCOS and non-PCOS groups, all the infertile women had high levels of BPA; however, the cases had significantly higher BPA levels compared to the controls, which gave credence to the fact that BPA may be a cofactor in the development of PCOS [33]. The study also showed that BPA exposure decreased ovarian reserve and function, as evidenced by reduced antral follicle count (AFC) and anti-müllerian hormone (AMH) levels in PCOS women [33]. Similarly, a study of 268 infertile Chinese women found a negative association between urinary BPA and AFC concentrations [150]. BPA was observed to disrupt the LH/FSH ratio in a sample of 60 Iraqi PCOS women, contributing to the development of PCOS [41]. In another study of 60 Egyptian women with PCOS, urinary BPA had a direct relationship with serum LH and an inverse relationship with serum FSH [34]. Additionally, Kandaraki et al. found that higher BPA levels were associated with hyperandrogenism, as PCOS women exhibited elevated androgen levels and an altered LH/FSH ratio, with lower levels of sex hormone binding globulin (SHBG) compared to controls [59].

The studies reviewed revealed that BPA is associated with PCOS and is implicated in its development. In most studies, increased levels of BPA were seen in cases with PCOS compared to controls. These findings collectively indicate that BPA disrupts hormonal profiles in women thereby, leading to hyperandrogenism and other ovarian distortions, contributing to the development of PCOS.

3.1.4. BPA and primary ovarian insufficiency

POI is an endocrine disorder affecting approximately 1 % of women and is characterized by the loss of ovarian function before the age of 40. It is a significant cause of infertility. Although the exact pathophysiology of POI remains unclear, it is known to be influenced by various factors, including environmental factors [72]. POI, also referred to as idiopathic premature ovarian failure (POF), is diagnosed based on symptoms such as at least four months of amenorrhea and elevated FSH levels exceeding 25 IU/L in two separate tests conducted four weeks apart [100]. Our review of two studies on POI found no significant differences in serum and urinary BPA levels between cases and controls (Table 4) [72,100] and no clear association between BPA exposure and POI incidence. The specific role that BPA plays in POI is still poorly understood. Since both studies did not identify differences in BPA levels between POI patients and controls, it is difficult to infer an association. Therefore, we suggest that more prospective studies be conducted to understand the relationship better and confirm any association between BPA and POI.

3.1.5. BPA and female infertility

Infertility is typically defined as the inability to achieve pregnancy after engaging in unprotected sexual intercourse for 12 months. Infertility is of two types - primary and secondary infertility. Primary infertility occurs when a couple has never conceived, while secondary infertility arises when a couple cannot conceive again after a previous pregnancy [143]. The cause of infertility is sometimes unknown, but most times, what causes infertility in the female reproductive system include tubal, uterine, ovarian, and hormonal disorders. Lifestyle factors such as smoking, excessive alcohol and exposure to environmental toxins and pollutants can also be toxic to gametes and affect fertility [143]. BPA negatively impacts fertility by inducing autophagy in human granulosa cells (GCs) through the AMPK/mTOR/ULK1 signaling pathway, disrupting ovarian function and abnormal follicle

development [75]. BPA exposure has been linked with a higher likelihood of infertility in women, and this review provided further evidence to support EDC exposure as a factor that contributes to infertility in women. Our review of nineteen articles on female infertility (Table 5) found that BPA levels between fertile controls and infertile cases significantly differed [6,19,20,104]. Since it is well known that hormones are major drivers of processes that occur in the reproductive system, BPA can disrupt the hormonal profile in reproductive-aged women, leading to fertility issues. Studies involving infertile women in the United States undergoing *in vitro* fertilization (IVF) reported that higher BPA levels correlated with reduced peak serum E2 levels, fewer oocytes retrieved per IVF cycle, reduced metaphase II (MII) oocyte count and reduced number of normally fertilizing oocytes [14,31]. Additionally, negative associations were found between urinary BPA levels and blastocyst development [31], suggesting that BPA exposure may affect the response of E2 during gonadotropin stimulation as well as lead to a decrease in these ovarian response parameters, thereby affecting the outcome of an IVF treatment. In contrast, two other studies on reproductive-aged women exposed to BPA found that BPA levels were positively associated with serum E2, prolactin (PRL) and progesterone (P4) levels [108,85] confirming reproductive hormones in women can be altered by increased BPA exposure. Furthermore, in the prospective cohort study on women undergoing IVF by Shen and colleagues, elevated urinary BPA levels had a significant inverse association with the number of retrieved oocytes, clinical pregnancy, and implantation [119]. Syrkasheva et al., in their study on Russian infertile patients undergoing assisted reproductive technology (ART), measured BPA levels in the blood and FF and found no association between BPA levels in the blood or FF and the number of oocytes. In the study, the mean and maximum levels of BPA in the FF were significantly lower than that of the blood BPA. However, upon taking a closer look at the group of patients with detectable FF BPA levels, it was observed that half of the cases had a higher level of BPA in the FF compared to blood, and in this subgroup of patients, there was a decrease in the number of oocytes [128].

Conversely, some studies observed no association between hormones or IVF outcomes and BPA exposure. A study of 351 Chinese women undergoing infertility treatment found no association between BPA, E2 levels and endometrial wall thickness [119]. Likewise, three studies involving couples undergoing infertility treatments found no association between BPA and IVF outcomes such as pregnancy, good quality embryo, normally fertilized oocytes, number of retrieved oocytes, and peak E2 level [64,91,90]. The authors noted that the absence of associations may result from misclassifying BPA exposure based on spot urine samples because BPA is a short-lived chemical, and exposures are likely episodic in nature.

Diminished ovarian reserve (DOR) is defined as a reduction in the amount and/or quality of oocytes in the ovaries, resulting in decreased fertility. About 10 % of women seeking infertility treatments are affected by DOR [56]. AMH, AFC, FSH, and E2 levels are some key indicators of ovarian reserve. Though the specific mechanisms by which BPA exposure could affect ovarian reserve are not fully understood, the disruption of ovarian hormone (GnRH, FSH, and LH) production has been identified as one of the most significant mechanisms. BPA can mimic the activity of E2, affect hormone secretion and alter E2 feedback at the hypothalamus, thereby suppressing follicle development [149]. A cross-sectional study involving reproductive-aged women found that BPA levels in women with DOR were higher than that of non-DOR women, suggesting that BPA exposure may be related to DOR [103]. Higher levels of urinary BPA and an increased risk of DOR were significantly associated in two other studies on reproductive-aged women. Urinary BPA levels were inversely associated with AMH, which is an excellent predictor of oocyte yield [149,29], as well as with AFC, an important predictor of IVF outcomes [29]. A decrease in these ovarian reserve parameters is linked to an increased risk of DOR and reduced chances of fertilization [106]. However, BPA exposure and other indicators of ovarian reserve, such as FSH and E2 levels, had no association [29].

BPA also influences nuclear receptors (NRs) in hormone response pathways and steroid biosynthesis [20]. Peripheral blood mononuclear cells (PBMCs) of several NRs, including estrogen receptor α (ERα), estrogen receptor β (ERβ), androgen receptor (AR), aryl hydrocarbon receptor (AhR), and pregnane X receptor (PXR), which regulate endocrine pathways and are potential EDC targets were highly expressed in infertile patients compared to the control group [19,20]. Furthermore, another study that quantified BPA in women from rural, urban and metropolitan areas observed that infertile women from the metropolitan areas had higher BPA levels than fertile women in the same areas. Infertile women from metropolitan regions had a 10-fold increased expression of these NRs compared to fertile women [113]. From an occupational exposure perspective, women employed in the commerce sector exhibited urinary BPA levels that were more than twice that of women employed in other industries [18], showing that it is vital to consider the contribution of occupational exposure in BPA studies. Finally, oxidative stress and immune imbalance have been associated with BPA, particularly in women with unexplained recurrent spontaneous abortion (URSA). In a case-control study done on women with URSA, higher BPA levels correlated with increased biomarkers of oxidative stress, such as 8-isoprostane and 8-hydroxydeoxyguanosine (8-OhdG), and elevated inflammatory cytokines like IFN-g. The study revealed that the median urinary levels of BPA in women with URSA were greater than those of controls from the same geographical area [74].

Despite a few conflicting results, most studies reviewed showed that BPA levels in infertile cases were higher than in fertile controls. BPA exerted its effects by altering the concentrations of reproductive hormones, such as E2, P4, PRL, AMH, and AFC, and by reducing oocyte levels, quality, and development, leading to a diminished ovarian reserve in women. Additionally, BPA upregulated several nuclear receptors involved in endocrine signaling and regulation, disrupting the endocrine system. Finally, it is worth noting that occupational and locational exposure to BPA should be well studied, as the reviewed studies revealed that infertile women in BPA-exposed areas (metropolitan and BPA production industries) had higher BPA levels compared to fertile controls from the same areas. Together, these results indicate that BPA is strongly associated with infertility in the female reproductive system.

3.1.6. *Prenatal exposure effects of BPA*

Beyond its impact on the reproductive health of pregnant women, BPA exposure can significantly affect their offspring, leading to adverse pregnancy outcomes and negative changes in reproductive development [78]. BPA can easily diffuse across the placenta, and because the placenta's ability to conjugate and detoxify BPA is limited, it can exert adverse effects on the offspring [10]. We reviewed twelve articles on the effect of maternal exposure to BPA and its impact on the reproductive health of their offspring (Table 6). Hormones are important in regulating reproduction, growth, and development in humans, and BPA was observed to influence the proper synthesis of hormones. One study focused on kisspeptin, a peptide crucial for regulating reproductive health, which typically increases throughout pregnancy and peaks in the third trimester before dropping sharply after delivery [24,48]. During pregnancy, a reduced amount of circulating kisspeptin has been associated with an increased tendency of miscarriage, preeclampsia and small birth weight [51], and higher kisspeptin concentrations have been associated with the onset of puberty [27]. The study found that BPA exposure in pregnant women was associated with lower kisspeptin levels, while their prepubertal children had elevated kisspeptin levels, suggesting that BPA could affect pregnancy outcomes and offspring reproductive development [137].

In another study on female children, higher testosterone levels and higher odds of having a Tanner Stage > 1 for breast development was

associated with second trimester BPA exposure, indicating that BPA may affect reproductive development during critical periods of fetal growth [138]. PRL is vital in regulating immune and inflammatory responses through multiple immune signaling pathways [63]. BPA can mimic estrogen and trigger elevated PRL levels, leading to hyperprolactinemia [125]. A Japanese cohort study observed sex-specific associations of BPA with PRL levels: a weak inverse correlation in males and a weak direct correlation in females, with BPA also showing a weak positive relationship with testosterone, E2, and P4 concentration in boys [89]. Conversely, a cross-sectional study investigating the relationship between cord sex hormones and maternal BPA exposure found negative correlations between BPA and cord testosterone in male infants. Also, a disruption in the ratio of testosterone to E2 —a key indicator of prostate health— was observed, suggesting that BPA can reduce testosterone levels by distorting the pituitary system and inhibiting testosterone surge *in utero* [77]. Two studies reported no significant relationship between prenatal BPA exposure and offspring levels of E2, SHBG, and Inhibin B [44,138].

In another observational study, there was a weak association of prenatal BPA exposure with sperm motility and concentration but not with testicular volume, hormones, or total sperm output. The authors indicated that these findings might be due to chance and require confirmation in larger, prospectively designed studies [44]. A prospective longitudinal birth cohort study that measured the relationship between fetal exposure to BPA and markers of testicular function in adult men observed a reduced Leydig cell functionality in association with elevated BPA exposure as the offsprings had higher LH levels and a lower TT/LH ratio in adulthood [46]. Another prospective cohort study tracking reproductive development from infancy to age 13 found sex-specific associations: BPA exposure was linked to larger testicular volume and earlier puberty in boys but not to ovarian volume, breast development, or age of menarche in girls [13].

Anogenital distance (AGD) is the distance between the anus and the genitals, and it is an essential indicator in assessing reproductive toxicity caused by environmental toxins. Studies have shown that AGD is influenced by fetal androgen activity during early fetal development, implying that a shorter AGD may suggest low testosterone levels during the period of reproductive organ development [139,50]. The relationship between BPA and AGD showed conflicting results, as three studies observed that BPA was significantly associated with shortened AGD [12,53,127], while two other studies found that BPA was not associated with AGD in male newborns [77,46]. In the study by Liu et al., the urine and blood samples were collected outside the critical reproductive programming window (approximately 8–14 weeks of gestation), when AGD is believed to be most sensitive to environmental exposures [139], accounting for the lack of association. A cross-sectional study that investigated the interactive effects of prenatal BPA and oxidative stress on offspring reproductive development observed an inverse relationship between prenatal BPA exposure and penis length in infants in the high oxidative stress (8-iso-prostaglandin F2α) group but found no relationship with AGD, which may be because of the relatively small sample size in the study [53]. Finally, a preconception cohort study reported that higher maternal BPA levels were negatively associated with infant birth weight and head circumference [97].

From the diverse studies reviewed, it is clear that prenatal exposure to BPA can have complex effects on offspring, particularly on their reproductive development. The findings highlight that BPA exposure during critical periods of fetal growth, such as the reproductive programming window, is linked to disruptions in hormone levels, early puberty, and potential alterations in key reproductive markers like AGD, penis length, and testicular function. However, the results across different studies were not consistent, with some reporting significant associations between BPA exposure and reproductive outcomes while others found no direct effects. This inconsistency may be attributed to variations in study design, timing of sample collection, BPA exposure levels, and sample size across the studies. Overall, the evidence indicates that BPA exposure during early development and life stages predisposes offspring to an increased risk of altered reproductive health.

3.2. BPA and male reproductive health

Infertility impacts around 37–70 million couples globally, with men being the primary cause in 50 % of cases [17]. There is a decline in sperm count and concentration in humans on a global scale [71], and these changes may be attributed to the growing exposure of humans to EDCs [84]. Infertility and alteration in sperm parameters in men of reproductive age have been an increasing source of concern, thereby necessitating the need to properly understand the effects of environmental estrogen on male reproductive health. BPA exposure, even at low concentrations, can disrupt cellular and hormonal mechanisms critical for healthy sperm production, leading to impaired steroidogenesis [117]. BPA affects male reproductive health directly by targeting and inhibiting the proliferation of Leydig cells and disrupting normal steroidogenesis. This disruption occurs through the promotion of testosterone and 17-hydroxy-pregnenolone synthesis from cholesterol, and an increase in CYP19A1 expression, which converts testosterone into E2, leading to elevated E2 levels. Additionally, BPA reduces the expression of the enzyme 17α-hydroxylase/17–20 lyase involved in steroidogenesis. BPA also indirectly suppresses LH release from the pituitary through the upregulation of aromatase in the testes, thereby inhibiting testosterone synthesis [117].

We reviewed 34 articles focused on the reproductive health of males (Table 7). These studies showed that, compared to fertile men, infertile and subfertile men had higher BPA concentrations [80,99,101,114,121,135,152]. Epigenetic changes such as DNA hydroxymethylation and hypomethylation in semen have been linked to BPA exposure. The modification of 5-methylcytosine (5mC), associated with gene expression repression, and 5-hydroxymethylcytosine (5hmC), involved in the activation of gene expression, are notable among these alterations (Gan et al., 2013; [86]). Compared with controls, males who were occupationally exposed to BPA exhibited a higher degree of hydroxymethylation in their sperm long interspersed nucleotide elements 1 (LINE-1), and there was a direct relationship between BPA and sperm LINE-1 hydroxymethylation [130]. Also, Miao et al. observed that the degree of sperm LINE-1 methylation was notably lower in workers exposed to BPA compared to controls [86], showing that BPA can induce LINE-1 hypomethylation and hydroxymethylation, thereby inducing genomic alterations, and influencing sperm quality.

Elevated levels of BPA in males were also associated with several sperm alterations, which include reduced sperm count [3,52,66,73,135], concentration [66,92,101,135,134], vitality [66,73], and quality [83,92,99,110,134]. BPA exposure is also associated with abnormal semen morphology [101], reduced Leydig cell capacity [3], lower progressive motility [69,73,92,98], and increased sperm DNA damage and fragmentation [83,99,2]. However, in a prospective cohort study of 501 males, BPA was observed to be negatively associated with sperm DNA fragmentation, possibly due to lower BPA concentrations in that study [38].

BPA also correlated with alterations in reproductive hormones in males, and these alterations include reduced serum cortisol in peripubertal boys [96], decreased testosterone [47,98,99,131], increased PRL [76], increased E2 [65,76,98], increased SHBG [76,84,152], reduced androstenedione [152,76], reduced free androgen index [76,84], increased FSH ([65]; Meeker and Antonia, 2008), reduced inhibin B (Meeker and Antonia, 2008), increased AMH [68], and reduced dehydroepiandrosterone (DHEAS) levels [68].

Notably, Lassen et al., in their study on the associations between urinary BPA concentration and reproductive hormones in young men from the general population, observed that BPA was positively associated with testosterone, LH, and E2 [69]. In this study, BPA acted as an antiestrogen by competitively inhibiting the binding of E2 to ERs at the hypothalamus or pituitary level, thereby reducing the inhibitory effect

of circulating E2 on LH and FSH release, which resulted in increased LH levels in the bloodstream. This, in turn, causes an increase in the production of testosterone and E2 by the testes. Elevated BPA was associated with higher AMH and lower DHEAS in mini pubertal boys, indicating heightened sensitivity during mini puberty [68]. Some studies reported no significant associations between BPA and sperm quality, reproductive hormones, and fertility. This lack of associations may be because the BPA levels were below toxic doses, small sample sizes, and the demographic characteristics of participants in the study [84,21,40,147]. Additionally, men from metropolitan areas exhibited higher BPA levels and gene expression of various NRs (Erα, Erβ, AR, AhR, and PXR) than those from urban and rural areas [114].

Overall, the studies reviewed showed that BPA exposure levels in men with fertility issues were higher than those of fertile men. BPA was indeed directly or indirectly associated, with several alterations related to the amount, morphology, and quality of sperm due to changes in the levels of male reproductive hormones necessary for the proper development of the reproductive system. BPA was also associated with epigenetic modifications in the sperm of infertile men, contributing to their infertility. Additionally, at certain reproductive ages or stages of puberty (mini-puberty), growing boys were more sensitive to BPA exposure, highlighting the need for further studies in that area. These findings underscore the associations of BPA with male infertility and its detrimental effects on male reproductive health and function.

4. Limitations of the study

Since this review was based on a systematic search of EBSCO, PubMed, Google Scholar, and Scopus databases, we may have missed some papers that were not present in these databases.

5. Regulation of BPA

Given the documented risks associated with BPA, several alternatives like Bisphenol-F (BPF) and Bisphenol-S (BPS) have been developed. However, these substitutes have been shown to pose similar risks as BPA [32] and thus should be avoided. In response to the harmful effects of BPA, developed countries have implemented regulations to reduce the consumption of BPA through diet and mitigate exposure. For example, Canada, Malaysia, Colombia, Brazil, and the United States have banned BPA in producing baby food packaging and bottles [79]. Our review indicates a significant gap in research on BPA in developing countries, with only 5.5 % of the studies focusing on African populations. This lack of research may contribute to the absence of regulations in these regions. Despite some inconsistencies in the findings regarding BPA's effects on reproductive health, there is a strong case for adopting global regulations. In addition to implementing bans on BPA, it is crucial to transition to non-BPA-containing materials for consumer products. Consumers should prefer fresh food over canned items with epoxy resin linings and opt for glass or stainless steel containers to minimize BPA exposure worldwide.

6. Conclusion and future perspectives

BPA remains a significant concern due to its role as an EDC impacting reproductive health across various populations. This review underscores the widespread presence of BPA in body fluids such as serum, plasma, urine, FF, semen, and saliva and its potential adverse effects on reproductive health. Key findings from the studies reviewed reveal that BPA exposure is associated with a range of reproductive health issues. In females, BPA exposure is linked to several conditions, including fibroids, infertility, PCOS, and endometriosis. BPA's impact on reproductive health extends to adverse pregnancy outcomes, including altered kisspeptin levels and increased risk of miscarriage, preeclampsia, and low birth weight. In males, BPA exposure is associated with alterations in sperm parameters, hormonal imbalances, and increased DNA damage, which may contribute to infertility. The inconsistent findings across studies may result from variations in study design, methodologies, and population characteristics. Despite these discrepancies, it is clear that reducing BPA exposure is critical. It is, therefore, crucial to strengthen regulations and increase public awareness about the risks of BPA. This includes promoting BPA-free alternatives, such as glass and stainless steel, and reducing reliance on BPA-containing products. Future research should focus on conducting comprehensive epidemiological studies in diverse populations, including in developing countries, to better understand the full impact of BPA on reproductive health. Additionally, there is a need for standardized methodologies in BPA analysis to enable comparability across studies and enhance the reliability of findings. By addressing these research gaps and implementing effective regulations, we can work towards mitigating the reproductive health risks associated with BPA exposure.

CRediT authorship contribution statement

Esther A. Salami: Writing – review & editing, Writing – original draft. **Oluwakemi A. Rotimi:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] A. Abraham, P. Chakraborty, C. Staples, N. van der Hoeven, K. Clark, E. Mihaich, J. Woelz, S. Hentges, Distributions of concentrations of bisphenol A in North American and European surface waters and sediments determined from 19 years of monitoring data, Chemosphere 201 (8) (2018) 448–458, https://doi.org/10.1016/j.chemosphere.2018.02.175.
[2] Adoamnei, E., Kiwitt-c, J., Sarabia-cos, L., Vela-soria, F. & Fern, M.F. (2021) *Associations between urinary concentrations of bisphenol A and sperm DNA fragmentation in young men*. 199 (March). doi:⟨10.1016/j.envres.2021.111289⟩.
[3] E. Adoamnei, J. Mendiola, F. Vela-Soria, M.F. Fernández, N. Olea, N. Jørgensen, S.H. Swan, A.M. Torres-Cantero, Urinary bisphenol A concentrations are associated with reproductive parameters in young men, Environ. Res. 161 (October 2017) (2018) 122–128, https://doi.org/10.1016/j.envres.2017.11.002.
[4] L. Aghajanova, L.C. Giudice, Effect of bisphenol A on human endometrial stromal fibroblasts in vitro, Reprod. Biomed. Online 22 (3) (2011) 249–256, https://doi.org/10.1016/j.rbmo.2010.12.007.
[5] M.S.H. Akash, S. Sabir, K. Rehman, Bisphenol A-induced metabolic disorders: from exposure to mechanism of action, Environ. Toxicol. Pharm. 77 (December 2019) (2020) 103373, https://doi.org/10.1016/j.etap.2020.103373.
[6] N. Ali, S. Ghafoor, S. Zareen, F. Saleh, Z.-N. Qureshi, A. Sajid, Consequence of exposure to Endocrine disruptors chemicals on female fertility, Isra Med. J. 13 (3) (2021) 172–176. ⟨https://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=153490695&site=ehost-live&scope=site⟩.
[7] S. Almeida, A. Raposo, M. Almeida-González, C. Carrascosa, Bisphenol A: food exposure and impact on human health, Compr. Rev. Food Sci. Food Saf. 17 (6) (2018) 1503–1517, https://doi.org/10.1111/1541-4337.12388.
[8] S. Amjad, M.S. Rahman, M.G. Pang, Role of antioxidants in alleviating bisphenol a toxicity, Biomolecules 10 (8) (2020) 1–26, https://doi.org/10.3390/biom10081105.
[9] R. Azziz, Diagnostic criteria for polycystic ovary syndrome: a reappraisal, Fertil. Steril. 83 (5) (2005) 1343–1346, https://doi.org/10.1016/j.fertnstert.2005.01.085.
[10] B. Balakrishnan, K. Henare, E.B. Thorstensen, A.P. Ponnampalam, M.D. Mitchell, Transfer of bisphenol A across the human placenta, Am. J. Obstet. Gynecol. 202 (4) (2010) 393.e1–393.e7, https://doi.org/10.1016/j.ajog.2010.01.025.
[11] M.V. Bariani, R. Rangaswamy, H. Siblini, Q. Yang, A. Al-Hendy, A.R. Zota, The role of endocrine-disrupting chemicals in uterine fibroid pathogenesis, Curr. Opin. Endocrinol. Diabetes Obes. 27 (6) (2020) 380–387, https://doi.org/10.1097/MED.0000000000000578.
[12] E.S. Barrett, S. Sathyanarayana, O. Mbowe, S.W. Thurston, J.B. Redmon, R.H. N. Nguyen, S.H. Swan, First-trimester urinary bisphenol a concentration in relation to anogenital distance, an androgen-sensitive measure of reproductive

development, in infant girls, Environ. Health Perspect. 125 (7) (2017) 1–8, https://doi.org/10.1289/EHP875.
[13] S.M. Blaauwendraad, V.W. Jaddoe, S. Santos, K. Kannan, G.R. Dohle, L. Trasande, R. Gaillard, Associations of maternal urinary bisphenol and phthalate concentrations with offspring reproductive development, Environ. Pollut. 309 (January) (2022) 119745, https://doi.org/10.1016/j.envpol.2022.119745.
[14] M.S. Bloom, D. Kim, F.S. Vom Saal, J.A. Taylor, G. Cheng, J.D. Lamb, V. Y. Fujimoto, Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilization, Fertil. Steril. 96 (3) (2011) 672–677.e2, https://doi.org/10.1016/j.fertnstert.2011.06.063.
[15] G.M. Buck Louis, C.M. Peterson, Z. Chen, M. Croughan, R. Sundaram, J. Stanford, M.W. Varner, A. Kennedy, L. Giudice, V.Y. Fujimoto, L. Sun, L. Wang, Y. Guo, K. Kannan, Bisphenol A and phthalates and endometriosis: the endometriosis: natural history, diagnosis and outcomes study, Fertil. Steril. 100 (1) (2013) 162–169, https://doi.org/10.1016/j.fertnstert.2013.03.026.
[16] J.C. Byun, M.S. Han, Serum bisphenol-A concentrations from uterine leiomyoma patients, Korean J. Obstet. Gynecol. 53 (10) (2010) 915, https://doi.org/10.5468/kjog.2010.53.10.915.
[17] L. Caporossi, P. Vigan, E. Paci, S. Capanna, A. Alteri, D. Pigini, G. Tranfo, B. Papaleo, A Case – Control Study on the Effects of Plasticizers Exposure on Male Fertility, Int. J. Envir. Res. and Public Health 20 (1) (2023) 235, https://doi.org/10.3390/ijerph20010235.
[18] L. Caporossi, P. Viganò, E. Paci, S. Capanna, A. Alteri, G. Campo, D. Pigini, M. De Rosa, G. Tranfo, B. Papaleo, Female reproductive health and exposure to phthalates and bisphenol a: a cross sectional study, Toxics 9 (11) (2021) 1–15, https://doi.org/10.3390/toxics9110299.
[19] D. Caserta, G. Bordi, F. Ciardo, R. Marci, C. Rocca, La, S. Tait, B. Bergamasco, L. Stecca, A. Mantovani, C. Guerranti, E.L. Fanello, G. Perra, F. Borghini, S. E. Focardi, M. Moscarini, The influence of endocrine disruptors in a selected population of infertile women, Gynecol. Endocrinol. 29 (5) (2013) 444–447, https://doi.org/10.3109/09513590.2012.758702.
[20] D. Caserta, F. Ciardo, G. Bordi, C. Guerranti, E. Fanello, G. Perra, F. Borghini, C. La Rocca, S. Tait, B. Bergamasco, L. Stecca, R. Marci, G. Lo Monte, I. Soave, S. Focardi, A. Mantovani, M. Moscarini, Correlation of endocrine disrupting chemicals serum levels and white blood cells gene expression of nuclear receptors in a population of infertile women, Int. J. Endocrinol. (1) (2013) 510703, https://doi.org/10.1155/2013/510703.
[21] Chen, M., Tang, R., Fu, G., Xu, B., Zhu, P., Qiao, S., Chen,X., Xu, B., Qin, Y., Lu, C., Hang, B., Xia, Y. & Wang, X. (2013) Associationof exposure to phenols and idiopathic male infertility. 251, 115–121. doi:10.1016/j.jhazmat.2013.01.061.
[22] Y.H. Chung, J.H. Han, S.-B. Lee, Y.-H. Lee, Inhalation toxicity of bisphenol A and its effect on estrous cycle, spatial learning, and memory in rats upon whole-body exposure, Toxicol. Res. 33 (2) (2017) 165–171, https://doi.org/10.5487/TR.2017.33.2.165.
[23] I. Cimmino, F. Fiory, G. Perruolo, C. Miele, F. Beguinot, P. Formisano, F. Oriente, Potential mechanisms of bisphenol A (BPA) contributing to human disease, Int. J. Mol. Sci. 21 (16) (2020) 1–22.
[24] S.A. Clarke, W.S. Dhillo, Kisspeptin across the human lifespan:evidence from animal studies and beyond, J. Endocrinol. 229 (3) (2016) R83–R98, https://doi.org/10.1530/JOE-15-0538.
[25] L. Cobellis, N. Colacurci, E. Trabucco, C. Carpentiero, L. Grumetto, Measurement of bisphenol A and bisphenol B levels in human blood sera from healthy and endometriotic women, Biomed. Chromatogr. 23 (11) (2009) 1186–1190, https://doi.org/10.1002/bmc.1241.
[26] T. Collette, R. Maheux, J. Mailloux, A. Akoum, Increased expression of matrix metalloproteinase-9 in the eutopic endometrial tissue of women with endometriosis, Hum. Reprod. 21 (12) (2006) 3059–3067, https://doi.org/10.1093/humrep/del297.
[27] M.E. Cortés, B. Carrera, H. Rioseco, J. Pablo del Río, P. Vigil, The role of kisspeptin in the onset of puberty and in the ovulatory mechanism: a mini-review, J. Pediatr. Adolesc. Gynecol. 28 (5) (2015) 286–291, https://doi.org/10.1016/j.jpag.2014.09.017.
[28] E. Czubacka, B. Wielgomas, A. Klimowska, M. Radwan, P. Radwan, A. Karwacka, P. Kału, J. Jurewicz, Urinary Bisphenol A Concentrations and Parameters of Ovarian Reserve among Women from a Fertility Clinic, Int. J. Env. Res. Pub. Health. 18 (15) (2021) 8041, https://doi.org/10.3390/ijerph18158041.
[29] E. Czubacka, B. Wielgomas, A. Klimowska, M. Radwan, P. Radwan, A. Karwacka, P. Kału, J. Jurewicz, Urinary Bisphenol A Concentrations and Parameters of Ovarian Reserve among Women from a Fertility Clinic, Int. J. Env. Res. Pub. Health. 18 (15) (2021) 8041, https://doi.org/10.3390/ijerph18158041.
[30] D. Kyriacos, Polycarbonates, Elsevier Ltd, 2017. ⟨https://doi.org/10.1016/B978-0-323-35824-8.00017-7⟩.
[31] S. Ehrlich, P.L. Williams, S.A. Missmer, J.A. Flaws, X. Ye, A.M. Calafat, J. C. Petrozza, D. Wright, R. Hauser, Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF, Hum. Reprod. 27 (12) (2012) 3583–3592, https://doi.org/10.1093/humrep/des328.
[32] S. Eladak, T. Grisin, D. Moison, M.-J. Guerquin, T. N'Tumba-Byn, S. Pozzi-Gaudin, A. Benachi, G. Livera, V. Rouiller-Fabre, R. Habert, A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound, Fertil. Steril. 103 (1) (2015) 11–21, https://doi.org/10.1016/j.fertnstert.2014.11.005.
[33] M. Elkafrawy, S. Barghash, D. Mahmoud, Environmental Exposure of Bisphenol a and its Association with Polycystic Ovary Syndrome (PCOS) and Depletion of Ovarian Reserve among Infertile Women, Ann. Rom. Soc. Cell Biol. 25 (4) (2021) 7437–7447.
[34] M. Fathy, A. Elgazzar, M. Alalfy, M. Abd, Correlation study of urinary bisphenol-A in a sample of Egyptian women with polycystic ovary syndrome, The Egypt, J. Foren. Sci. App. Toxicol. 22 (4) (2022) 145–155, https://doi.org/10.21608/ejfsat.2023.152359.1263.
[35] J. Ferris, K. Mahboubi, N. MacLusky, W.A. King, L.A. Favetta, BPA exposure during in vitro oocyte maturation results in dose-dependent alterations to embryo development rates, apoptosis rate, sex ratio and gene expression, Reprod. Toxicol. 59 (2016) 128–138, https://doi.org/10.1016/j.reprotox.2015.12.002.
[36] M. Forte, L. Mita, L. Cobellis, V. Merafina, R. Specchio, S. Rossi, D.G. Mita, L. Mosca, M.A. Castaldi, M. De Falco, V. Laforgia, S. Crispi, Triclosan and bisphenol a affect decidualization of human endometrial stromal cells, Mol. Cell. Endocrinol. 422 (2016) 74–83, https://doi.org/10.1016/j.mce.2015.11.017.
[37] Y. Gálvez-Ontiveros, I. Moscoso-Ruiz, L. Rodrigo, M. Aguilera, A. Rivas, A. Zafra-Gómez, Presence of parabens and bisphenols in food commonly consumed in Spain, Foods 10 (1) (2021) 92, https://doi.org/10.3390/foods10010092.
[38] A.E. Goldstone, Z. Chen, M.J. Perry, K. Kannan, G.M. Buck, Urinary bisphenol A and semen quality, the LIFE Study, Reprod. Toxicol. 51 (2015) 7–13, https://doi.org/10.1016/j.reprotox.2014.11.003.
[39] A.C. Gore, V.A. Chappell, S.E. Fenton, J.A. Flaws, A. Nadal, G.S. Prins, J. Toppari, R.T. Zoeller, EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals, Endocr. Rev. 36 (6) (2015) E1–E150, https://doi.org/10.1210/er.2015-1010.
[40] P. Gul, N. Celik, F. Betul, Effects of Bisphenol A Released From Composite Fillings on Reproductive Hormone Levels in Men, Int. Dent. J. 71 (4) (2021) 343–351, https://doi.org/10.1016/j.identj.2020.12.008.
[41] H.S. Shaheed, W.A. Kareem, S. Yousif, Correlation between Serum Bisphenol-A Level, Luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH) In a Sample of Iraqi Women with PCOS, 13 (1) (2021) 1963 - 1966 .doi:/10.31838/ijpr/2021.13.01.290.
[42] M.S. Han, J.C. Byun, J.E. Park, J.Y. Kim, J.Y. Chung, J.M. Kim, Bisphenol-A concentrations from leiomyoma patients by LC/MS, Toxicol. Res. 27 (1) (2011) 49–52, https://doi.org/10.5487/TR.2011.27.1.049.
[43] K.G. Harnett, A. Chin, S.M. Schuh, BPA and BPA alternatives BPS, BPAF, and TMBPF, induce cytotoxicity and apoptosis in rat and human stem cells, Ecotoxicol. Environ. Saf. 216 (2021) 112210, https://doi.org/10.1016/j.ecoenv.2021.112210.
[44] R.J. Hart, D.A. Doherty, J.A. Keelan, N.S. Minaee, E.B. Thorstensen, J. E. Dickinson, C.E. Pennell, J.P. Newnham, R. McLachlan, R.J. Norman, D. J. Handelsman, The impact of antenatal Bisphenol A exposure on male reproductive function at 20–22 years of age, Reprod. BioMed. Online 36 (3) (2018) 340–347, https://doi.org/10.1016/j.rbmo.2017.11.009.
[45] S. Hassan, A. Thacharodi, A. Priya, R. Meenatchi, T.A. Hegde, T. R, H. Nguyen, A. Pugazhendhi, Endocrine disruptors: unravelling the link between chemical exposure and Women's reproductive health, Environ. Res. 241 (2024) 117385, https://doi.org/10.1016/j.envres.2023.117385.
[46] Holmboe, S.A., Henriksen, L.S., Frederiksen, H., Andersson, A., Priskorn, L., Jørgensen, N., Juul, A., Toppari, J., Skakkebæk, N.E. & Main, K.M. (2022) *Prenatal exposure to phenols and benzophenones in relation to markers of male reproductive function in adulthood.* (December), 1–13. doi:⟨10.3389/fendo.2022.1071761⟩.
[47] E.Den Hond, H. Tournaye, P. Sutter, De, W. Ombelet, W. Baeyens, A. Covaci, B. Cox, T.S. Nawrot, N. Larebeke, Van, T.D. Hooghe, Human exposure to endocrine disrupting chemicals and fertility: a case – control study in male subfertility patients, Environ. Int. 84 (2015) 154–160, https://doi.org/10.1016/j.envint.2015.07.017.
[48] Y. Horikoshi, H. Matsumoto, Y. Takatsu, T. Ohtaki, C. Kitada, S. Usuki, M. Fujino, Dramatic elevation of plasma metastin concentrations in human pregnancy: metastin as a novel placenta-derived hormone in humans, J. Clin. Endocrinol. Metab. 88 (2) (2003) 914–919, https://doi.org/10.1210/jc.2002-021235.
[49] A.M. Hormann, F.S. vom Saal, S.C. Nagel, R.W. Stahlhut, C.L. Moyer, M. R. Ellersieck, W.V. Welshons, P.-L. Toutain, J.A. Taylor, Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA), in: PLoS One, 9, 2014, p. e110509, https://doi.org/10.1371/journal.pone.0110509 (10).
[50] M.H. Hsieh, B.N. Breyer, M.L. Eisenberg, L.S. Baskin, Associations among hypospadias, cryptorchidism, anogenital distance, and endocrine disruption, Curr. Urol. Rep. 9 (2) (2008) 137–142, https://doi.org/10.1007/s11934-008-0025-0.
[51] K.-L. Hu, H.-M. Chang, H.-C. Zhao, Y. Yu, R. Li, J. Qiao, Potential roles for the kisspeptin/kisspeptin receptor system in implantation and placentation, Hum. Reprod. Update 25 (3) (2019) 326–343, https://doi.org/10.1093/humupd/dmy046.
[52] W. Hu, T. Dong, L. Wang, Q. Guan, L. Song, D. Chen, Z. Zhou, M. Chen, Y. Xia, X. Wang, Obesity aggravates toxic effect of BPA on spermatogenesis, Environ. Int. 105 (2017) 56–65, https://doi.org/10.1016/j.envint.2017.04.014.
[53] Y.F. Huang, P.W. Wang, L.W. Huang, M.H. Lin, W. Yang, H.C. Chen, K.P. Yu, M. L. Chen, Interactive effects of nonylphenol and bisphenol A exposure with oxidative stress on fetal reproductive indices, Environ. Res. 167 (155) (2018) 567–574, https://doi.org/10.1016/j.envres.2018.08.007.
[54] H. Itoh, M. Iwasaki, T. Hanaoka, H. Sasaki, T. Tanaka, S. Tsugane, Urinary bisphenol-A concentration in infertile Japanese women and its association with endometriosis: a cross-sectional study, Environ. Health Prev. Med. 12 (6) (2007) 258–264, https://doi.org/10.1265/ehpm.12.258.
[55] E.H. Jeong, G.Y. Hong, B.R. Kim, S.N. Park, H.-H. Lee, Y.-J. Na, J. Namkung, The relationship between uterine myoma growth and the endocrine disruptor in

postmenopausal women, J. Menopausal. Med. 19 (3) (2013) 130–134, https://doi.org/10.6118/jmm.2013.19.3.130.
[56] P. Jirge, Poor ovarian reserve, J. Hum. Reprod. Sci. 9 (2) (2016) 63, https://doi.org/10.4103/0974-1208.183514.
[57] R.L. Jones, S.A. Lang, J.A. Kendziorski, A.D. Greene, K.A. Burns, Use of a mouse model of experimentally induced endometriosis to evaluate and compare the effects of bisphenol A and bisphenol AF exposure, Environ. Health Perspect. 126 (12) (2018), https://doi.org/10.1289/EHP3802.
[58] R. Joskow, D.B. Barr, J.R. Barr, A.M. Calafat, L.L. Needham, C. Rubin, Exposure to bisphenol A from bis-glycidyl dimethacrylate–based dental sealants, J. Am. Dent. Assoc. 137 (3) (2006) 353–362, https://doi.org/10.14219/jada.archive.2006.0185.
[59] E. Kandaraki, A. Chatzigeorgiou, S. Livadas, E. Palioura, F. Economou, M. Koutsilieris, S. Palimeri, D. Panidis, E. Diamanti-Kandarakis, Endocrine disruptors and Polycystic Ovary Syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS, J. Clin. Endocrinol. Metab. 96 (3) (2011) 480–484, https://doi.org/10.1210/jc.2010-1658.
[60] S.S. Karnam, R.C. Ghosh, S. Mondal, M. Mondal, Evaluation of subacute bisphenol – A toxicity on male reproductive system, Vet. World 8 (6) (2015) 738–744, https://doi.org/10.14202/vetworld.2015.738-744.
[61] T.A. Katz, Q. Yang, L.S. Treviño, C.L. Walker, A. Al-Hendy, Endocrine-disrupting chemicals and uterine fibroids, Fertil. Steril. 106 (4) (2016) 967–977, https://doi.org/10.1016/j.fertnstert.2016.08.023.
[62] J.A. Kendziorski, S.M. Belcher, Strain-specific induction of endometrial periglandular fibrosis in mice exposed during adulthood to the endocrine disrupting chemical bisphenol A, Reprod. Toxicol. 58 (2015) 119–130, https://doi.org/10.1016/j.reprotox.2015.08.001.
[63] D. Kharrazian, The potential roles of bisphenol A (BPA) pathogenesis in autoimmunity, Autoimmune Dis. 2014 (2014) 1–12, https://doi.org/10.1155/2014/743616.
[64] H.K. Kim, D.H. Ko, W. Lee, K.R. Kim, S. Chun, J. Song, W.K. Min, Body fluid concentrations of bisphenol A and their association with in vitro fertilization outcomes, Hum. Fertil. 24 (3) (2021) 199–207, https://doi.org/10.1080/14647273.2019.1612104.
[65] S. Kim, Y. Yang, Y. Hong, S. Myung, S. Kim, Distribution of serum bisphenol A diglycidyl ether and its metabolite in Korean adult men and its association with reproductive hormone levels, Mol. Cell. Toxicol. 11 (2015) 71–78, https://doi.org/10.1007/s13273-015-0009-3.
[66] J. Knez, R. Kranvogl, B.P. Breznik, E. Vončina, V. Vlaisavljević, Are urinary bisphenol A levels in men related to semen quality and embryo development after medically assisted reproduction? Fertil. Steril. 101 (1) (2014) 215–221.e5, https://doi.org/10.1016/j.fertnstert.2013.09.030.
[67] Komarowska, M.D., Hermanowicz, A., Czyzewska, U., Milewski,R., Matuszczak, E., Miltyk, W. & Debek, W. (2015) Serum Bisphenol ALevel in Boys with Cryptorchidism : A Step to Male Infertility ? 2015.doi:10.1155/2015/973154.
[68] M. Lærkeholm Müller, A.S. Busch, M.L. Ljubicic, E.N. Upners, M.B. Fischer, C. P. Hagen, J. Albrethsen, H. Frederiksen, A. Juul, A.M. Andersson, Urinary concentration of phthalates and bisphenol A during minipuberty is associated with reproductive hormone concentrations in infant boys, Int. J. Hyg. Environ. Health 250 (March) (2023) 114166, https://doi.org/10.1016/j.ijheh.2023.114166.
[69] T.H. Lassen, H. Frederiksen, T.K. Jensen, J.H. Petersen, U.N. Joensen, K.M. Main, N.E. Skakkebaek, A. Juul, N. Jørgensen, A.-M. Andersson, Urinary bisphenol A levels in young men: association with reproductive hormones and semen quality, Environ. Health Perspect. 122 (5) (2014) 478–484, https://doi.org/10.1289/ehp.1307309.
[70] A.W. Lee, V. Eata, Association of environmental phenols with endometriosis and uterine leiomyoma: an analysis of NHANES, 2003–2006, Reprod. Toxicol. 113 (May) (2022) 30–34, https://doi.org/10.1016/j.reprotox.2022.08.003.
[71] H. Levine, N. Jørgensen, A. Martino-Andrade, J. Mendiola, D. Weksler-Derri, M. Jolles, R. Pinotti, S.H. Swan, Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries, Hum. Reprod. Update 29 (2) (2023) 157–176, https://doi.org/10.1093/humupd/dmac035.
[72] C. Li, M. Cao, T. Qi, X. Ye, L. Ma, W. Pan, J. Luo, P. Chen, J. Liu, J. Zhou, The association of bisphenol A exposure with premature ovarian insufficiency: a case–control study, Climacteric 24 (1) (2021) 95–100, https://doi.org/10.1080/13697137.2020.1781078.
[73] D.K. Li, Z. Zhou, M. Miao, Y. He, J. Wang, J. Ferber, L.J. Herrinton, E. Gao, W. Yuan, Urine bisphenol-A (BPA) level in relation to semen quality, Fertil. Steril. 95 (2) (2011) 625–630.e4, https://doi.org/10.1016/j.fertnstert.2010.09.026.
[74] F. Liang, X. Huo, W. Wang, Y. Li, Y. Feng, J. Zhang, Y. Wang, Association of bisphenol A or bisphenol S exposure with oxidative stress and immune disturbance among unexplained recurrent spontaneous abortion women, Chemosphere 257 (2020) 127035, https://doi.org/10.1016/j.chemosphere.2020.127035.
[75] M. Lin, R. Hua, J. Ma, Y. Zhou, P. Li, X. Xu, Z. Yu, S. Quan, Bisphenol A promotes autophagy in ovarian granulosa cells by inducing AMPK/mTOR/ULK1 signalling pathway, Environ. Int. 147 (2021) 106298, https://doi.org/10.1016/j.envint.2020.106298.
[76] X. Liu, M. Miao, Z. Zhou, E. Gao, J. Chen, J. Wang, F. Sun, W. Yuan, D. Li, Exposure to bisphenol-A and reproductive hormones among male adults, Environ. Toxicol. Pharm. 39 (2) (2015) 934–941, https://doi.org/10.1016/j.etap.2015.03.007.
[77] C. Liu, X. Xu, Y. Zhang, W. Li, X. Huo, Associations between maternal phenolic exposure and cord sex hormones in male newborns, Hum. Reprod. 31 (3) (2016) 648–656, https://doi.org/10.1093/humrep/dev327.
[78] Y. Ma, H. Liu, J. Wu, L. Yuan, Y. Wang, X. Du, R. Wang, P.W. Marwa, P. Petlulu, X. Chen, H. Zhang, The adverse health effects of bisphenol A and related toxicity mechanisms, Environ. Res. 176 (2019) 108575, https://doi.org/10.1016/j.envres.2019.108575.
[79] N.D. Mandel, B. Gamboa-Loira, M.E. Cebrián, Á. Mérida-Ortega, L. López-Carrillo, Challenges to regulate products containing bisphenol A: implications for policy, Salud Pública de México 61 (5) (2019) 692, https://doi.org/10.21149/10411.
[80] C. Mantzouki, D. Bliatka, P.K. Iliadou, A. Margeli, I. Papassotiriou, G. Mastorakos, E. Kousta, D.G. Goulis, Serum Bisphenol A concentrations in men with idiopathic infertility, Food Chem. Toxicol. 125 (December 2018) (2019) 562–565, https://doi.org/10.1016/j.fct.2019.02.016.
[81] M.F. Manzoor, T. Tariq, B. Fatima, A. Sahar, F. Tariq, S. Munir, S. Khan, M.M. A. Nawaz Ranjha, A. Sameen, X.-A. Zeng, S.A. Ibrahim, An insight into bisphenol A, food exposure and its adverse effects on health: a review, Front. Nutr. 9 (2022) 1047827, https://doi.org/10.3389/fnut.2022.1047827.
[82] A.A. Martínez-Peña, J. Rivera-Baños, L.L. Méndez-Carrillo, M.I. Ramírez-Solano, A. Galindo-Bustamante, J.C. Páez-Franco, S. Morimoto, L. González-Mariscal, M. E. Cruz, C.A. Mendoza-Rodríguez, Perinatal administration of bisphenol A alters the expression of tight junction proteins in the uterus and reduces the implantation rate, Reprod. Toxicol. 69 (2017) 106–120, https://doi.org/10.1016/j.reprotox.2017.02.009.
[83] J.D. Meeker, S. Ehrlich, T.L. Toth, D.L. Wright, A.M. Calafat, A.T. Trisini, X. Ye, R. Hauser, Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic,, Reprod. Toxicol. 30 (4) (2010) 532–539, https://doi.org/10.1016/j.reprotox.2010.07.005.
[84] J. Mendiola, N. Jørgensen, A.-M. Andersson, A.M. Calafat, X. Ye, J.B. Redmon, E. Z. Drobnis, C. Wang, A. Sparks, S.W. Thurston, F. Liu, S.H. Swan, Are environmental levels of bisphenol A associated with reproductive function in fertile men? Environ. Health Perspect. 118 (9) (2010) 1286–1291, https://doi.org/10.1289/ehp.1002037.
[85] M. Miao, W. Yuan, F. Yang, H. Liang, Z. Zhou, R. Li, E. Gao, D.K. Li, Associations between bisphenol a exposure and reproductive hormones among female workers, Int. J. Environ. Res. Public Health 12 (10) (2015) 13240–13250, https://doi.org/10.3390/ijerph121013240.
[86] M. Miao, X. Zhou, Y. Li, O. Zhang, Z. Zhou, T. Li, LINE-1 hypomethylation in spermatozoa is associated with Bisphenol A exposure, Andrology 2 (1) (2013) 138–144, https://doi.org/10.1111/j.2047-2927.2013.00166.x.
[87] J. Michałowicz, Bisphenol A – sources, toxicity and biotransformation, Environ. Toxicol. Pharm. 37 (2) (2014) 738–758, https://doi.org/10.1016/j.etap.2014.02.003.
[88] K. Mikołajewska, J. Stragierowicz, J. Gromadzińska, Bisphenol A – application, sources of exposure and potential risks in infants, children and pregnant women, Int. J. Occup. Med. Environ. Health 28 (2) (2015) 209–241, https://doi.org/10.13075/ijomeh.1896.00343.
[89] M. Minatoya, S. Sasaki, A. Araki, C. Miyashita, S. Itoh, J.M. Yamamoto, T. Mitsui, K. Moriya, K. Cho, K. Morioka, H. Minakami, N. Shinohara, R. Kishi, Cord Blood Bisphenol A Levels and Reproductive and Thyroid Hormone Levels of Neonates: The Hokkaido Study on Environment and Children's Health, Epidemiology. 28 (2017) S3–S9, https://doi.org/10.1097/EDE.0000000000000716.
[90] L. Mınguez-Alarcon, A.J. Gaskins, Y.-H. Chiu, P.L. Williams, S. Ehrlich, J. E. Chavarro, J.C. Petrozza, J.B. Ford, A.M. Calafat, R. Hauser, E. Study, Urinary bisphenol A concentrations and association with in vitro fertilization outcomes among women from a fertility clinic, Hum. Reprod. 30 (9) (2015) 2120–2128, https://doi.org/10.1093/humrep/dev183.
[91] L. Mínguez-alarcon, C. Messerlian, A. Bellavia, A.J. Gaskins, H. Chiu, J.B. Ford, A. R. Azevedo, J.C. Petrozza, M. Antonia, R. Hauser, P.L. Williams, E.S. Team, Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization, Environ. Int. 126 (2019) 355–362, https://doi.org/10.1016/j.envint.2019.02.025.
[92] L. Mínguez-alarcón, P.L. Williams, Y. Chiu, A.J. Gaskins, Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: identifying potential predictors, Environ. Int. 121 (2) (2018) 1297–1303, https://doi.org/10.1016/j.envint.2018.10.052.
[93] A.M. Molina-López, F. Bujalance-Reyes, N. Ayala-Soldado, R. Mora-Medina, A. Lora-Benítez, R. Moyano-Salvago, An overview of the health effects of bisphenol A from a one health perspective, Animals 13 (15) (2023) 2439, https://doi.org/10.3390/ani13152439.
[94] T.R. Moore-Ambriz, D.G. Acuña-Hernández, B. Ramos-Robles, M. Sánchez-Gutiérrez, R. Santacruz-Márquez, A. Sierra-Santoyo, B. Piña-Guzmán, M. Shibayama, I. Hernández-Ochoa, Exposure to bisphenol A in young adult mice does not alter ovulation but does alter the fertilization ability of oocytes, Toxicol. Appl. Pharm. 289 (3) (2015) 507–514, https://doi.org/10.1016/j.taap.2015.10.010.
[95] M.A. Moreira Fernandez, Z.L. Cardeal, M.M. Carneiro, L.C. André, Study of possible association between endometriosis and phthalate and bisphenol A by biomarkers analysis, J. Pharm. Biomed. Anal. 172 (2019) 238–242, https://doi.org/10.1016/j.jpba.2019.04.048.
[96] V. Mustieles, O. Ocón-hernandez, L. Mínguez-alarcón, C. Dávila-arias, R. Pérez-lobato, I. Calvente, J.P. Arrebola, F. Vela-soria, S. Rubio, R. Hauser, N. Olea, M. F. Fernández, Bisphenol A and reproductive hormones and cortisol in

peripubertal boys: the INMA-Granada cohort, Sci.Total Environ 618 (2017) 1046–1053, https://doi.org/10.1016/j.scitotenv.2017.09.093.
[97] V. Mustieles, P.L. Williams, M. Fernandez, L. Mnguez-Alarcn, J.B. Ford, A. M. Calafat, R. Hauser, C. Messerlian, Maternal and paternal preconception exposure to bisphenols and size at birth, Hum. Reprod. 33 (8) (2018) 1528–1537, https://doi.org/10.1093/humrep/dey234.
[98] U. Nordström, N. Jørgensen, J.P. Thyssen, P. Bela, S. Stender, Urinary excretion of phenols, parabens and benzophenones in young men: associations to reproductive hormones and semen quality are modified by mutations in the Filaggrin gene, Environ. Int. 121 (May) (2018) 365–374, https://doi.org/10.1016/j.envint.2018.09.020.
[99] G.A. Omran, H.D. Gaber, N.A.M. Mostafa, R.M. Abdel-Gaber, E.A. Salah, Potential hazards of bisphenol A exposure to semen quality and sperm DNA integrity among infertile men, Reprod. Toxicol. 81 (2018) 188–195, https://doi.org/10.1016/j.reprotox.2018.08.010.
[100] Ş. Özel, A. Tokmak, O. Aykut, A. Aktulay, N. Hançerlioğulları, Y. Engin Ustun, Serum levels of phthalates and bisphenol-A in patients with primary ovarian insufficiency, Gynecol. Endocrinol. 35 (4) (2019) 364–367, https://doi.org/10.1080/09513590.2018.1534951.
[101] E. Palak, W. Lebiedzińska, S. Anisimowicz, M. Sztachelska, P. Pierzynski, W. Wiczkowski, B. Żelazowska-Rutkowska, G.N. Niklińska, D. Ponikwicka-Tyszko, S. Wołczyński, The association between bisphenol A, steroid hormones, and selected micrornas levels in seminal plasma of men with infertility, J. Clin. Med. 10 (24) (2021) 55945, https://doi.org/10.3390/jcm10245945.
[102] P. Parasar, P. Ozcan, K.L. Terry, Endometriosis: epidemiology, diagnosis and clinical management, Curr. Obstet. Gynecol. Rep. 6 (1) (2017) 34–41, https://doi.org/10.1007/s13669-017-0187-1.
[103] S.Y. Park, J.H. Jeon, K. Jeong, H.W. Chung, H. Lee, Y.A. Sung, S. Ye, E.H. Ha, The association of ovarian reserve with exposure to bisphenol A and phthalate in reproductive-aged women, J. Korean Med. Sci. 36 (2) (2021) 1–9, https://doi.org/10.3346/jkms.2021.36.e1.
[104] P.P. Pednekar, R.K. Gajbhiye, A.D. Patil, S.V. Surve, Estimation of plasma levels of bisphenol-A & phthalates in fertile & infertile women by gas chromatography-mass spectrometry, Indian J. Med. Res. 148 (6) (2018) 734–742, https://doi.org/10.4103/ijmr.IJMR.
[105] F.M. Peinado, I. Lendínez, R. Sotelo, L.M. Iribarne-Durán, J. Fernández-Parra, F. Vela-Soria, N. Olea, M.F. Fernández, C. Freire, J. León, B. Pérez-Cabrera, O. Ocón-Hernández, F. Artacho-Cordón, Association of urinary levels of bisphenols A, F, and S with endometriosis risk: preliminary results of the EndEA study, Int. J. Environ. Res. Public Health 17 (4) (2020), https://doi.org/10.3390/ijerph17041194.
[106] C. Peluso, F.L.A. Fonseca, I.F. Rodart, V. Cavalcanti, G. Gastaldo, D. M. Christofolini, C.P. Barbosa, B. Bianco, AMH: an ovarian reserve biomarker in assisted reproduction, Clin. Chim. Acta 437 (2014) 175–182, https://doi.org/10.1016/j.cca.2014.07.029.
[107] A.Z. Pollack, G.M. Buck Louis, Z. Chen, L. Sun, B. Trabert, Y. Guo, K. Kannan, Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma, Environ. Res. 137 (2015) 101–107, https://doi.org/10.1016/j.envres.2014.06.028.
[108] A.Z. Pollack, S.L. Mumford, J.R. Krall, A.E. Carmichael, L.A. Sjaarda, N.J. Perkins, K. Kannan, E.F. Schisterman, Exposure to bisphenol A, chlorophenols, benzophenones, and parabens in relation to reproductive hormones in healthy women: a chemical mixture approach, Environ. Int. 120 (2018) 137–144, https://doi.org/10.1016/j.envint.2018.07.028.
[109] J. Qiao, Pay more attention to ethnic differences in polycystic ovary syndrome phenotypic expression, Chin. Med. J. 126 (11) (2013) 2003–2006, https://doi.org/10.3760/cma.j.issn.0366-6999.20130650.
[110] M. Radwan, B. Wielgomas, E. Dziewirska, P. Radwan, P. Kału, A. Klimowska, W. Hanke, J. Jurewicz, Urinary Bisphenol A Levels and Male Fertility, Am. J. Men's Health 12 (6) (2018) 2144–2151, https://doi.org/10.1177/1557988318799163.
[111] B.H. Rashidi, M. Amanlou, T.B. Lak, M. Ghazizadeh, F. Haghollahi, M. Bagheri, B. Eslami, The association between bisphenol a and polycystic ovarian syndrome: a case-control study, Acta Med. Iran. 55 (12) (2017) 759–764.
[112] B.H. Rashidi, M. Amanlou, T.B. Lak, M. Ghazizadeh, B. Eslami, A case–control study of bisphenol a and endometrioma among subgroup of Iranian women, J. Res. Med. Sci. 22 (1) (2017) 7–9, https://doi.org/10.4103/1735-1995.199086.
[113] C. Rocca, La, S. Tait, C. Guerranti, L. Busani, F. Ciardo, Exposure to endocrine disrupters and nuclear receptor gene expression in infertile and fertile women from different italian areas, Int. J. Environ. Res. Public Health 11 (10) (10) (2014) 10146–10164, https://doi.org/10.3390/ijerph111010146.
[114] C. Rocca, La, S. Tait, C. Guerranti, L. Busani, F. Ciardo, G. Bordi, D. Caserta, S. Focardi, M. Moscarini, Exposure to endocrine disruptors and nuclear receptors gene expression in infertile and fertile men from Italian areas with different environmental features, Int. J. Environ. Res. Public Health 12 (10) (2015) 12426–12445, https://doi.org/10.3390/ijerph121012426.
[115] J.R. Rochester, Bisphenol A and human health: a review of the literature, Reprod. Toxicol. 42 (2013) 132–155, https://doi.org/10.1016/j.reprotox.2013.08.008.
[116] A.Z. Rutkowska, E. Diamanti-Kandarakis, Polycystic ovary syndrome and environmental toxins, Fertil. Steril. 106 (4) (2016) 948–958, https://doi.org/10.1016/j.fertnstert.2016.08.031.
[117] J. Santiago, J.V. Silva, M.A.S. Santos, M. Fardilha, Fighting bisphenol a-induced male infertility: the power of antioxidants, Antioxidants 10 (2) (2021) 1–22, https://doi.org/10.3390/antiox10020289.
[118] Y. Shen, Y.M. Dong, Q. Lu, J. Xu, Y.T. Wu, S.S. Yun, M.L. Ren, Phenolic environmental estrogens in urine and blood plasma from women with uterine leiomyoma: epidemiological survey, J. Obstet. Gynaecol. Res. 42 (4) (2016) 440–445, https://doi.org/10.1111/jog.12928.
[119] J. Shen, Q. Kang, Y. Mao, M. Yuan, F. Le, X. Yang, X. Xu, F. Jin, Urinary bisphenol A concentration is correlated with poorer oocyte retrieval and embryo implantation outcomes in patients with tubal factor infertility undergoing in vitro fertilisation, Ecotoxicol. Environ. Saf. 187 (March 2019) (2020) 109816, https://doi.org/10.1016/j.ecoenv.2019.109816.
[120] Y. Shen, Q. Xu, M. Ren, X. Feng, Y. Cai, Y. Gao, Measurement of phenolic environmental estrogens in women with uterine leiomyoma, PLoS One 8 (11) (2013) 2–6, https://doi.org/10.1371/journal.pone.0079838.
[121] D.A. Shokry, M.I. Mohamed, M.F. Abdel-satar, N. El, S. Selim, M. Ahmed, A. El, Correlation between urinary bisphenol A (BPA) levels and male reproductive functions among sample of Egyptian population, Indian J. Forensic Med. Toxicol. 14 (3) (2020) 1857–1862.
[122] A. Simonelli, R. Guadagni, P. De Franciscis, N. Colacurci, M. Pieri, P. Basilicata, P. Pedata, M. Lamberti, N. Sannolo, N. Miraglia, Environmental and occupational exposure to bisphenol A and endometriosis: urinary and peritoneal fluid concentration levels, Int. Arch. Occup. Environ. Health 90 (1) (2017) 49–61, https://doi.org/10.1007/s00420-016-1171-1.
[123] J.S. Siracusa, L. Yin, E. Measel, S. Liang, X. Yu, Effects of bisphenol A and its analogs on reproductive health: a mini review, Reprod. Toxicol. 79 (2018) 96–123, https://doi.org/10.1016/j.reprotox.2018.06.005.
[124] B. Smolarz, K. Szyłło, H. Romanowicz, Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature), Int. J. Mol. Sci. 22 (19) (2021) 10554, https://doi.org/10.3390/ijms221910554.
[125] R. Steinmetz, N.G. Brown, D.L. Allen, R.M. Bigsby, N. Ben-Jonathan, The environmental estrogen bisphenol a stimulates prolactin release in vitro and in vivo, Endocrinology 138 (5) (1997) 1780–1786, https://doi.org/10.1210/endo.138.5.5132.
[126] C. Stoker, M.F. Andreoli, L. Kass, V.L. Bosquiazzo, M.F. Rossetti, G. Canesini, E. H. Luque, J.G. Ramos, Perinatal exposure to bisphenol A (BPA) impairs neuroendocrine mechanisms regulating food intake and kisspetin system in adult male rats. Evidences of metabolic disruptor hypothesis, Mol. Cell. Endocrinol. 499 (2020) 110614, https://doi.org/10.1016/j.mce.2019.110614.
[127] X. Sun, D. Li, H. Liang, M. Miao, X. Song, Z. Wang, Z. Zhou, W. Yuan, Maternal exposure to bisphenol A and anogenital distance throughout infancy: a longitudinal study from Shanghai, China, Environ. Int. 121 (August) (2018) 269–275, https://doi.org/10.1016/j.envint.2018.08.055.
[128] A.G. Syrkasheva, S.V. Kindysheva, N.L. Starodubtseva, V.E. Frankevich, N. V. Dolgushina, Bisphenol a in infertile patients: Impact on assisted reproductive technologies outcomes, Obst. Gyn. 2021 (5) (2021) 113–120, https://doi.org/10.18565/aig.2021.5.113-120.
[129] T.T. Schug, L.S. Birnbaum, Human Health Effects of Bisphenol A, In: Toxicants in food packaging and household plastics, (2014), pp. 1–29. ⟨doi:10.1007/978-1-4471-6500-2_1.
[130] Y. Tian, X. Zhou, M. Miao, D. Li, Z. Wang, R. Li, Association of bisphenol A exposure with LINE-1 hydroxymethylation in human semen, Int. J. Environ. Res. Public Health 15 (8) (2018) 1–10, https://doi.org/10.3390/ijerph15081770.
[131] F.P. Tsague, E.A. Nantia, H. Dechaud, N. Tchana, M. Pugeat, P.F. Moundipa, Bisphenol A differentially affects male reproductive function biomarkers in a reference population and agro pesticides users from Djutitsa, Cameroon, Toxicol. Ind. Health 35 (4) (2019) 324–335, https://doi.org/10.1177/0748233719838437.
[132] K. Upson, S. Sathyanarayana, A.J. De Roos, H.M. Koch, D. Scholes, V.L. Holt, A population-based case-control study of urinary bisphenol A concentrations and risk of endometriosis, Hum. Reprod. 29 (11) (2014) 2457–2464, https://doi.org/10.1093/humrep/deu227.
[133] M.B.M. van Duursen, J. Boberg, S. Christiansen, L. Connolly, P. Damdimopoulou, et al., Safeguarding female reproductive health against endocrine disrupting chemicals—the FREIA project, Int. J. Mol. Sci. 21 (9) (2020) 3215, https://doi.org/10.3390/ijms21093215.
[134] J. Vitku, J. Heracek, L. Sosvorova, R. Hampl, T. Chlupacova, M. Hill, V. Sobotka, M. Bicikova, L. Starka, Associations of bisphenol A and polychlorinated biphenyls with spermatogenesis and steroidogenesis in two biological fl uids from men attending an infertility clinic, Environ. Int. 89–90 (2016) 166–173, https://doi.org/10.1016/j.envint.2016.01.021.
[135] J. Vitku, L. Sosvorova, T. Chlupacova, R. Hampl, M. Hill, V. Sobotka, Differences in Bisphenol A and Estrogen Levels in the Plasma and Seminal Plasma of Men With Different Degrees of Infertility, Physiol. Res. 64 (2015) S303–S311, https://doi.org/10.33549/physiolres.933090.
[136] W. Völkel, T. Colnot, G.A. Csanády, J.G. Filser, W. Dekant, Metabolism and kinetics of bisphenol A in humans at low doses following oral administration, Chem. Res. Toxicol. 15 (10) (2002) 1281–1287, https://doi.org/10.1021/tx025548t.
[137] Z. Wang, M. Miao, J. Xu, Y. Chen, H. Liang, L. Yang, X. Liu, S. Wen, X. Tu, W. Yuan, Gestational exposure to bisphenol analogues and kisspeptin levels in pregnant women and their children: a pregnancy-birth cohort study, Sci. Total Environ. 848 (July) (2022) 157720, https://doi.org/10.1016/j.scitotenv.2022.157720.
[138] Watkins, D.J., Lee, J.M., Blank-goldenberg, C., Peterson, K.E., John, D., Evaluation, C.H. & Arbor, A. (2017) Phthalate and bisphenol A exposureduring in utero windows of susceptibility in relation to reproductive hormonesand pubertal development in girls. (734), 143–151.doi:10.1016/j.envres.2017.07.051. Phthalate.
[139] M. Welsh, P.T.K. Saunders, M. Fisken, H.M. Scott, G.R. Hutchison, L.B. Smith, R. M. Sharpe, Identification in rats of a programming window for reproductive tract

masculinization, disruption of which leads to hypospadias and cryptorchidism, J. Clin. Investig. 118 (4) (2008) 1479–1490, https://doi.org/10.1172/JCI34241.
[140] X. Wen, Y. Xiong, L. Jin, M. Zhang, L. Huang, Y. Mao, C. Zhou, Y. Qiao, Y. Zhang, Bisphenol A exposure enhances endometrial stromal cell invasion and has a positive association with peritoneal endometriosis, Reprod. Sci. 27 (2) (2020) 704–712, https://doi.org/10.1007/s43032-019-00076-7.
[141] A.K. Wesselink, D. Ph, J. Weuve, D. Sc, V. Fruh, D. Ph, T.N. Bethea, D. Ph, Urinary concentrations of phenols, parabens, and triclocarban in relation to uterine leiomyomata incidence and growth, Fertil. Steril. 02118 (2021) 1–10, https://doi.org/10.1016/j.fertnstert.2021.07.003.
[142] Y.B. Wetherill, B.T. Akingbemi, J. Kanno, J.A. McLachlan, A. Nadal, C. Sonnenschein, C.S. Watson, R.T. Zoeller, S.M. Belcher, In vitro molecular mechanisms of bisphenol A action, Reprod. Toxicol. 24 (2) (2007) 178–198, https://doi.org/10.1016/j.reprotox.2007.05.010.
[143] WHO, Infertility, 2024, 2024. ⟨https://www.who.int/news-room/fact-sheets/detail/infertility⟩ (Accessed 25 August 2024).
[144] Y.-Y. Yang, G.S. Toor, Contaminants in the urban environment: dioxins, Edis 2015 (5) (2015) 7, https://doi.org/10.32473/edis-ss642-2015.
[145] L. Yu, P. Das, A.J. Vall, Y. Yan, X. Gao, M.I. Sifre, C.D. Bortner, L. Castro, G. E. Kissling, A.B. Moore, D. Dixon, Bisphenol A induces human uterine leiomyoma cell proliferation through membrane-associated ERα36 via nongenomic signaling pathways, Mol. Cell. Endocrinol. 484 (2019) 59–68, https://doi.org/10.1016/j.mce.2019.01.001.
[146] H. Yu, Q. Zhong, Y. Xia, E. Li, S. Wang, R. Ren, MicroRNA-2861 targets STAT3 and MMP2 to regulate the proliferation and apoptosis of ectopic endometrial cells in endometriosis, Pharmazie 74 (4) (2019) 243–249, https://doi.org/10.1691/ph.2019.8881.
[147] J. Zeng, P. Chen, C. Liu, Y. Deng, Y. Miao, M. Zhang, Bisphenol A analogues in associations with serum hormone levels among reproductive-aged Chinese men, Environ. Int. 167 (July) (2022) 107446, https://doi.org/10.1016/j.envint.2022.107446.
[148] Y. Zhang, V. Mustieles, P.L. Williams, B.J. Wylie, I. Souter, A.M. Calafat, M. Demokritou, A. Lee, S. Vagios, R. Hauser, C. Messerlian, Parental preconception exposure to phenol and phthalate mixtures and the risk of preterm birth, Environ. Int. (2021) 151, https://doi.org/10.1016/j.envint.2021.106440.
[149] N. Zhang, Y. Zhao, L. Zhai, Y. Bai, L. Jia, Ecotoxicology and Environmental Safety Urinary bisphenol A and S are associated with diminished ovarian reserve in women from an infertility clinic in Northern China, Ecotoxicol. Environ. Saf. 256 (March) (2023) 114867, https://doi.org/10.1016/j.ecoenv.2023.114867.
[150] W. Zhou, F. Fang, W. Zhu, Z.J. Chen, Y. Du, J. Zhang, Bisphenol A and Ovarian reserve among infertile women with polycystic Ovarian syndrome, Int. J. Environ. Res. Public Health 14 (1) (2017) 6–12, https://doi.org/10.3390/ijerph14010018.
[151] F. Zhou, L. Zhang, A. Liu, Y. Shen, J. Yuan, X. Yu, X. Feng, Q. Xu, C. Cheng, Measurement of phenolic environmental estrogens in human urine samples by HPLC-MS/MS and primary discussion the possible linkage with uterine leiomyoma, J. Chromatogr. B: Anal. Technol. Biomed. Life Sci. 938 (2013) 80–85, https://doi.org/10.1016/j.jchromb.2013.08.032.
[152] W. Zhuang, K. Wu, Y. Wang, Association of serum bisphenol-A concentration and male reproductive function among exposed workers, Arch. Environ. Contam. Toxicol. 68 (1) (2015) 38–45, https://doi.org/10.1007/s00244-014-0078-7.