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SYSTEMATIC REVIEW

Exposure to microplastics and human reproductive outcomes: A systematic review

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Abstract

Background: Microplastics, produced through degradation of environmental plastic pollution, have been detected in human tissues including placenta and fetal meconium. Cell culture and animal studies have demonstrated potential reproductive toxicity of these particles; however, their association with adverse fertility or pregnancy outcomes in humans is not known.

Objectives: To synthesise evidence for the presence of microplastics in human reproductive tissue and their associations with environmental exposures and reproductive outcomes.

Search Strategy: MEDLINE, Embase, Emcare, CINAHL, ClinicalTrials.gov and ICTRP were searched from inception to 03/02/2023.

Selection Criteria: Studies of human participants, assessing presence of microplastics in reproductive tissues, environmental exposures to microplastics, and fertility- or pregnancy-related outcomes.

Data Collection and Analysis: Two independent reviewers selected studies and extracted data on study characteristics, microplastics detected, environmental exposures and reproductive outcomes. Narrative synthesis was performed due to methodological heterogeneity.

Main Results: Of 1094 citations, seven studies were included, covering 96 participants. Microplastics composed of 16 different polymer types were detected in both placental and meconium samples. Two studies reported associations between lifestyle factors (daily water intake, use of scrub cleanser or toothpaste, bottled water and takeaway food) and placental microplastics. One study reported associations between meconium microplastics and reduced microbiota diversity. One reported placental microplastic levels correlated with reduced birthweights and 1-minute Apgar scores.

Conclusions: There is a need for high-quality observational studies to assess the effects of microplastics on human reproductive health.

KEYWORDS
environmental pollution, fertility, microplastics, pregnancy

1 | INTRODUCTION

Plastic pollution is a major and increasing global concern[1]: in 2019 alone, 22 million tonnes of plastic leaked into the environment and this is projected to double to 44 million tonnes a year by 2060.[2] Within healthcare settings, a huge rise in biochemical waste comprising single-use plastics, for example from face masks and other personal protective equipment, was seen in response to the global Covid-19 pandemic.[1,3]

Humans are exposed to plastic particles through inhalation, ingestion and skin contact,[4] and there is emerging evidence of multiple associated health threats.[5] Approximately 13 000

chemicals are used in plastics manufacture; these can leach from plastic products at all stages in their life cycle and include carcinogenic and endocrine-disrupting chemicals.[6] Exposure to plastic additives has been linked to infertility, miscarriage, obesity, diabetes, prostate and breast cancers, increased cardiovascular risk and neurodevelopmental disorders.[7–14]

Microplastics (plastic particles up to 5 mm diameter) and nanoplastics (those <1 μm) are derived from the degradation of plastic objects and have emerged as novel pollutants widely distributed in the environment.[15] There is increasing evidence for the ubiquity of microplastics in human tissues, including lung, blood, stool, kidney, liver and breast milk.[16–21] The first reports of microplastics detected in human placenta and meconium were published in 2021[22,23] and in recent years there has been an expansion in studies examining potential detrimental reproductive effects of these particles on a cellular level and in animal models.[24–29] Recent insights into the presence of microplastics in human tissues and evidence of their potential reproductive toxicity are summarised in Figure 1.

It is vital, from a clinical and public health perspective, to establish whether the toxicity of micro- and nanoplastics seen in cell culture and animal studies translates to adverse fertility, obstetric and fetal outcomes in human populations. This review therefore represents a timely attempt to evaluate the current evidence base for the impact of microplastics on human reproduction.

1.1 | Objectives

Aims of this systematic review are to: (i) describe the current evidence demonstrating the presence of micro- and nanoplastics in human reproductive tissues; (ii) synthesise the evidence for associations of lifestyle or environmental factors with micro- and nanoplastic particles in reproductive tissues; (iii) synthesise evidence about associations between presence of micro- and nanoplastics in reproductive tissues and adverse fertility or pregnancy outcomes in humans.

2 | METHODS

This report adheres to the PRISMA guidelines for systematic reviews.[30] Patients and/or members of the public were not involved in the development or conduct of this review.

2.1 | Registration

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (reference CRD42023397436, registered 13/02/2023).

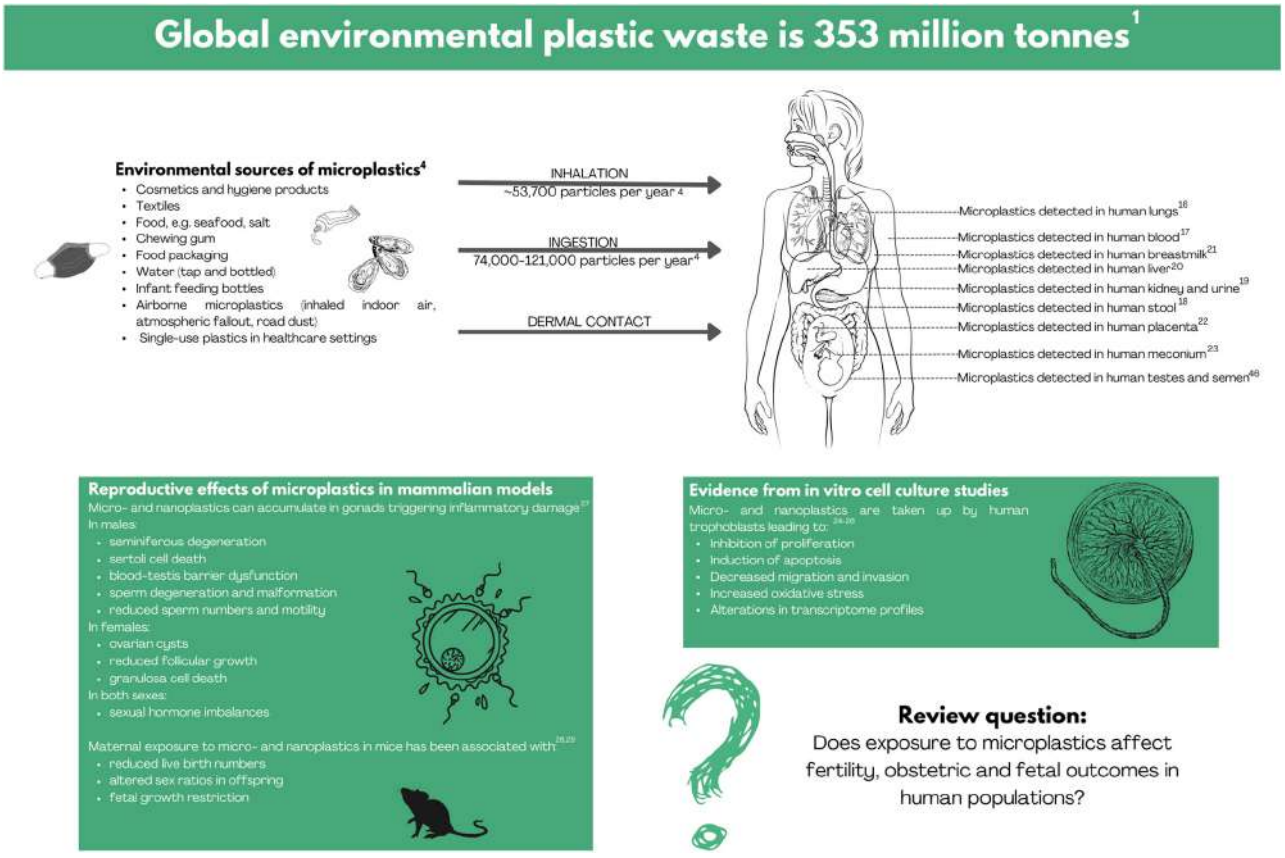

FIGURE 1 Insights into the presence of microplastics in human tissues and evidence of their potential reproductive toxicity.

2.2 | Search strategy

A search strategy combining keywords and subject headings for microplastics and fertility, pregnancy and premature infants was developed using the selection criteria below, in conjunction with a specialist medical librarian (KB) (see Appendix S1). Searches were conducted in MEDLINE (Ovid), Embase (Ovid), Emcare (Ovid) and CINAHL (EbscoHost) from database inception to 3 February 2023, with no language restriction and no limit on study design. Additionally, Clinicaltrials.gov and World Health Organization International Clinical Trials Registry were searched for clinical trials. References of retained articles were reviewed for studies not captured in the search.

2.3 | Selection criteria

We identified English-language, peer-reviewed studies meeting the following population, exposure, outcome and study design (PEOS) criteria[31]:

1. *Population*: Human subjects
2. *Exposure*: Environmental exposure to micro- or nanoplastics through inhalation, ingestion or dermal contact, assessed by least one of the following:
   a. data from questionnaires or structured interviews concerning plastic exposure in daily life in the time period preceding the study
   b. levels of micro- or nanoplastics in tissues sampled from study participants
3. *Outcome*: We searched the COMET database (https://www.comet-initiative.org/) and CROWN initiative to identify relevant Core Outcome Sets (COS).[32] We did not identify any COS relevant to studies of environmental pollutants and their effects on human reproductive health. Therefore, we identified studies assessing at least one of the following:
   a. The presence and/or levels of micro- and nanoplastics in tissues from human participants relevant to human reproductive function (e.g. placenta, ovaries, testes)
   b. Any clinical outcome relating to human fertility or pregnancy
4. *Study design*: observational study designs including prospective or retrospective cohort, case–control and analytical cross-sectional studies, in addition to randomised controlled trials, experimental or quasi-experimental studies. Animal and cell culture studies were excluded. Reviews, abstracts and protocols were excluded.

2.4 | Study selection

Citations were downloaded and screened using COVIDENCE software.[33] Two independent reviewers (KH and DB) screened titles and abstracts of citations to ensure eligibility. Full-text papers of retained citations were reviewed by both reviewers before final decisions regarding inclusion. Disagreements were resolved through discussion and recourse to a third author (AD), if necessary.

Where citations were trial registrations or protocols, the reviewers made efforts to identify whether the study had been published in a peer-reviewed publication.

2.5 | Data collection and analysis

2.5.1 | Data extraction

Data extraction was carried out by two authors (KH and DB) independently. Discrepancies were resolved through discussion. A standardised, piloted form was used to extract data. Extracted data were:

- Publication details.
- Study country.
- Study design.
- Number of participants.
- Participant characteristics (age, comorbidities, parity and, if pregnant, gestational age at birth, number of fetuses, mode of birth).
- Tissue types assessed for presence of microplastics.
- Methods for collection, processing and analysis of clinical samples for microplastics.
- Characteristics and levels of microplastics identified in reproductive tissues.
- Environmental exposures studied in relation to levels of microplastics in reproductive tissues. Where associations between potential exposures and the presence or levels of microplastics in reproductive tissues were reported, we extracted verbatim estimates of effect sizes, in addition to any confounding factors accounted for if adjusted results were reported.
- Any clinical outcome related to human fertility or pregnancy in relation to levels of microplastics in tissues. In addition to extracting data on (sub)fertility, pregnancy survival, maternal medical, obstetric, delivery, fetal and neonatal outcomes, we also considered related outcomes, for example menstrual cycle/ovulatory disturbances, relevant hormone levels, sperm count parameters, and chemical, structural and functional differences seen in reproductive tissues. Where associations between the presence of microplastics in reproductive tissues and reproductive outcomes were reported, we extracted verbatim estimates of effect size, in addition to any confounding factors accounted for if adjusted results were reported.

2.5.2 | Quality assessment

Our initial aim was to assess methodological quality (PROSPERO reference CRD42023397436). Existing risk of bias tools have not been well validated for pilot studies.

Included studies reported primarily pilot observational data from small number of participants; for this reason, risk of bias assessment was not appropriate.

2.5.3 | Data synthesis

We aimed to conduct meta-analysis (PROSPERO reference CRD42023397436). However, there was methodological and clinical heterogeneity across studies relating to detecting and measuring microplastic exposure of subjects and the outcomes measured, with only one study reporting on a clinical outcome. Therefore, a meta-analysis was not appropriate. A narrative synthesis is used to describe the evidence on epidemiological exposure to microplastics and human reproduction.

3 | RESULTS

3.1 | Study selection

The PRISMA flow diagram is provided in Figure S1.[34] Following de-duplication, 1094 studies were screened. Seven studies, representing six datasets, met the inclusion criteria. Table 1 summarises study characteristics and findings (our full data extraction is displayed in Table S1).

3.2 | Characteristics of included studies

3.2.1 | Design, settings and participants

Five studies were cross-sectional studies[22,23,35–37]: three of these assessed the presence/levels of microplastics in reproductive tissues without assessing exposures or outcomes,[22,23,37] one assessed the relation between levels of microplastics and microbiota in placental and meconium samples,[36] and one assessed the presence and localisation of placental microplastics as well as ultrastructural alterations in cell organelles.[35] One study was a prospective cohort study that assessed the relation between usage of plastic products and levels of microplastics in placenta and meconium,[38] and one was a case–control study that assessed levels of placental microplastics in relation to lifestyle factors (working conditions, drinking water and dietary habits) and fetal/neonatal outcomes (growth restriction, neonatal anthropometric measurements and 1-minute Apgar scores).[39]

There was a total of 96 participants across all studies; sample sizes in individual studies ranged between two and 43 participants (median 17, interquartile range 12). Studies were conducted in China ($n=3$),[36–38] Italy ($n=2$),[22,35] Germany ($n=1$)[23] and Iran ($n=1$).[39]

In five studies the participants were pregnant women only,[22,23,35,37,39] whereas two studies considered mother–infant pairs.[36,38] There were no studies of males or non-pregnant individuals. All studies described participants as 'healthy', as defined by the absence of specified exclusion criteria,[22,23,35–39] although one study included a woman with gestational diabetes and another with hypothyroidism among its participants.[35] Participants' age ranged from 23 to 42 years (reported in five studies).[21,36–39] In five studies, births were at term[22,23,36,38,39] and in two studies, gestation at birth was not reported.[35,37]

Three studies included only participants who had vaginal births,[22,36,38] one included only participants giving birth via caesarean[23] and one included participants regardless of birth mode.[35] Two studies did not report birth mode.[37,39] No study reported data on parity.[22,23,35–39]

3.2.2 | Clinical samples analysed, and methods of sample collection, processing and microplastic detection

Four studies analysed only placental samples for the presence of microplastics,[22,35,37,39] whereas three analysed both placental and meconium samples.[23,36,38] A total of 96 placentas were examined across all seven studies (ranging between two and 43 placentas).[22,23,35–39] In the three studies which examined fetal meconium, a total of 14 meconium samples were analysed (ranging between two and 12 samples).[23,36,38] All studies employed a plastic-free protocol for collection and processing of clinical samples, avoiding plastic-containing gloves, containers or instruments.[22,23,35–39]

Chemical digestion by different agents (KOH, H_2O_2 and NaOH, and NO) and filtration was used to process clinical samples in six studies.[22,23,36–39] Microplastic detection methods were: light microscopy and Raman microspectroscopy ($n=2$),[22,39] Fourier transform infrared microspectroscopy ($n=1$),[23] laser direct infrared spectroscopy ($n=3$)[36–38] and electron microscopy ($n=1$).[35]

Six studies used negative control samples to monitor for background contamination with microplastics.[22,23,36–39] One of these studies also analysed delivery room items and airborne fallout for microplastics to detect possible contaminants.[23]

3.3 | Synthesis of results

3.3.1 | Characteristics and levels of microplastics in clinical samples

Across the included studies, microplastics composed of 16 different polymer types were detected, and all 16 types were seen in both placental and meconium samples (see Table S1).[22,23,36–39] The size of detected microplastic fragments in studies varied from 2.1 to >150 micrometres.

Four studies, using data from three cohorts, measured the number of microplastic particles per gram of tissue.[22,36–38] Levels of placental microplastics detected using

TABLE 1 Characteristics and findings of included observational studies.

Paper and study setting	Participants	Clinical samples	Detection method for microplastics	Key study findings
Ragusa et al. (2021)[22] Italy	$n=6$ Vaginal births	Placenta	Light microscopy and Raman microspectroscopy	MPs detected in 4/6 placentas
Braun et al. (2021)[23] Germany	$n=2$ Caesarean births	Placenta Meconium Maternal stool	Fourier-transform infrared microspectroscopy	MPs detected in 2/2 placentas and 2/2 meconium specimens
Zhu et al. (2023)[37] China	$n=17$ Birth mode not reported	Placenta	Laser direct infrared spectroscopy	MPs detected in 17/17 placentas
Liu et al. (2023)[38] China	$n=18$ Vaginal births	Placenta Meconium	Laser direct infrared spectroscopy	MPs detected in 18/18 placentas and 18/18 meconium specimens Levels of total placental MPs and placental PA higher in women who drank >2 L water per day compared with those who drank ≤2 L water per day (total MPs: 82.3 vs. 17.9 particles/g, $p=0.038$, PA: 40.3 vs. 3.6 particles/g, $p=0.038$) Placental PE levels higher in women who used scrub cleanser or toothpaste ≥2 times a week, compared with those using these products less frequently (11.1 vs. 1.9 particles/g, $p=0.005$)
Ragusa et al. (2022)[35] Italy	$n=10$ 5 caesarean and 5 vaginal births	Placenta	Variable pressure scanning electron microscopy and transmission electron microscopy	MPs detected in 10/10 placentas Endoplasmic reticulum dilation, aggresomes, mitochondrial damage, mitochondrial granules and whorled membranous bodies observed in placental sections containing MPs Any association between placental MPs and these ultrastructural alterations was not quantitatively assessed
Liu et al. (2022)[36] China	$n=18$ Vaginal births NB: same study cohort as Liu et al. 2022 above	Placenta Meconium	Laser direct infrared spectroscopy	MPs detected in 18/18 placentas and 12/12 meconium specimens Negative correlation between PS levels and Chao diversity index of meconium microbiota (correlation coefficient −0.632, $p<0.05$)
Amereh et al. (2022)[39] Iran	$n=43$ (30 normal, 13 IUGR) Birth mode not reported	Placenta	Light microscopy and Raman microspectroscopy	In normal group, MPs detected in 4/30 placentas (6 MP particles in total from 30 placentas) In IUGR group, MPs detected in 13/13 placentas (302 MP particles in total from 13 placentas) Measured load of placental MPs was higher in individuals who used bottled rather than only boiled tap water (odds ratio 18.01, 95% CI 1.16–200.83, $p=0.01$) and in those eating takeaway, rather than only home-cooked, food (odds ratio 6.72, 95% CI 1.34–33.59, $p=0.02$) Negative correlation between MP levels and birth weight (correlation coefficient −0.82, $p<0.001$), length (correlation coefficient −0.56, $p<0.001$), head circumference (correlation coefficient −0.5, $p=0.001$) and 1-min Apgar scores (correlation coefficient −0.75, $p<0.001$) across all participants when studied as continuous variables

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; MP, microplastic; PA, polyamide; PE, polyethylene; PS, polystyrene.

laser direct infrared spectroscopy varied from a mean of 2.70 ± 2.65 particles/g (range 0.28–9.55 particles/g)[37] to a median of 18.0 particles/g.[36,38] Using light microscopy and Ramen microspectroscopy, Ragusa et al.[22] reported a level of 0.028 particles/g across all placental samples. Two studies, using data from the same cohort, reported levels of microplastics in meconium samples (median 54.1 particles/g).[36,38]

3.3.2 | Environmental exposures linked to the presence of microplastics in clinical samples

Two studies examined the association of self-reported plastic exposure-related habits and environmental exposures to plastics with the presence of microplastics in clinical samples.[38,39]

In one study, levels of total microplastics and of polyamides were significantly higher in placentas from women who drank over 2 L of water per day compared with women drinking less than 2 L.[38] Additionally, levels of placental polyamide were significantly higher in those who reported often using scrub cleanser or toothpaste in the previous year, compared with those who seldom or never did.[38]

The second study reported that measured load of placental microplastics was higher in individuals who used bottled water, compared with boiled tap water only, and found higher placental microplastic levels in those eating takeaway food compared with home-cooked food only.[39]

3.3.3 | Outcomes linked to microplastics in clinical samples

Three studies linked the presence of microplastics in clinical samples with physiological or clinical correlates including placental and meconium microbiota,[36] cell ultrastructural changes[35] and birth outcomes.[39]

One study reported a significant inverse relation between the level of polystyrene and Chao diversity index (an abundance-based estimator of species richness)[40] of microbiota in meconium, and associations between the levels of total and specific microplastics and placental and meconium microbiota genera.[36] In a second study, the authors report the presence of both microplastics and ultrastructural alterations of some cell organelles in placental tissue as observed by transmission electron microscopy; however, no test of association was carried out.[35]

Only one study reported an association between presence of microplastics and clinical birth outcomes.[39] The authors report that microplastics were identified in 100% of placentas from pregnancies with intrauterine growth restriction ($n = 13$) compared with 13% of placentas from normal pregnancies ($n = 30$). Higher levels of microplastics correlated with lower birthweight, length, head circumference and 1-minute Apgar scores across all study participants.

4 | DISCUSSION

4.1 | Main findings

Table 2 summarises our key findings, along with recommendations for areas where further research is needed, as identified from this systematic review.

Overall, we have identified only a handful of pilot studies in humans which report on microplastics in tissues relevant to reproduction and evaluate their associations with plastic exposure or with fertility and pregnancy-related outcomes. Sample sizes were very small in all included studies.

All seven studies reported the presence of microplastics in placental samples collected in a clinical setting, and three also detected microplastics in meconium samples. This adds to the emerging body of research which has found micro- and nanoplastics in a range of different human tissues.[16–23,41] Two studies reported findings suggesting that plastic exposure in pregnancy, for example food packaging, hygiene products, and volume and type of water intake, may influence levels of placental microplastics.[38,39] Only one study evaluated clinical outcomes, finding that higher loads of placental microplastics were associated with lower birthweight, length, head circumference and 1-minute Apgar score.[39] However, given the small sample sizes and heterogeneous methodologies across included studies, further high-quality research is needed involving larger cohorts of pregnant women to explore further the relation between microplastic exposure and pregnancy outcomes.

4.2 | Strengths and limitations

We used a registered, prespecified protocol, and a systematic, reliable process using multiple databases to identify relevant studies, from database inception to the present day, to ensure capture of all relevant data. Study selection criteria and data extraction were reliably applied by two researchers. We used an inclusive approach to identify as much relevant data as possible.

A potential limitation of this review is that we may not have identified all relevant studies; we did not identify grey literature, and our database search may have been limited by poorly indexed literature in the novel field of micro- and nanoplastics related to reproductive outcomes. We made efforts to mitigate this limitation by reviewing references of retained articles for studies not captured in the search.

4.3 | Interpretation

Our findings are consistent with a previous systematic review of microplastic exposure in non-pregnant human participants, which identified an absence of standardised

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TABLE 2 Key findings and recommendations for future research.

Key findings	Recommendations for future research
• We identified seven studies examining the presence of microplastics in human reproductive tissue, all with very small sample sizes. These studies included exclusively female participants, and were carried out in Italy, Germany, China and Iran. • Microplastics composed of 16 different polymer types were detected in placentas and fetal meconium. • All studies used plastic-free protocols for specimen collection and processing. • Studies varied in methods used to detect microplastics. • Environmental plastic exposure, e.g. through drinking water, hygiene products and food packaging, may influence levels of placental microplastics. • Higher loads of placental microplastics may be linked to fetal growth restriction.	• Future research on microplastics and human reproduction should be carried out in a range of geographical settings and in diverse populations. • There is a need for validated protocols to minimise microplastics contamination during specimen collection and processing. • Agreement on gold-standard methods for detecting microplastics in clinical samples is needed to enable comparison between studies. • Methods that allow accurate monitoring of environmental microplastics exposure should be developed. • Core outcome sets relating to adverse reproductive effects of microplastics should be agreed and implemented, to allow future studies to be compared and results collated. • High-quality observational studies, sufficiently powered to detect meaningful correlations, are needed to establish associations between microplastic exposure and human reproductive outcomes.

methods for establishing exposure to microplastics, and a paucity of studies of the effects of microplastic exposure on general populations, resulting in a lack of clear evidence for the effects of microplastics on health outcomes.[42] The aforementioned review predated the first published reports of microplastics in human placentas and did not consider reproductive outcomes. We demonstrate that validated methods and further well-designed and conducted studies are also needed in the field of microplastics and human reproductive health. A recent WHO report on dietary and inhalation exposures to nano- and microplastic particles and potential implications for human health further emphasises the need for development of standard methods to generate more robust data from environmental monitoring and studies of effect.[43]

Several methodological limitations within the current evidence base should be addressed in future studies. The small sample sizes within existing literature may not be representative of general pregnant populations, and limit the ability of authors adequately to match participants or adjust for confounding variables in comparative studies. High quality, larger-scale research, adequately powered to identify both determinants and clinically important consequences of exposure to microplastics, are needed.

Studies in this review varied with regards to the mode of birth of included participants, and not all reported this variable. Even if strict plastic-free protocols are employed, the degree of environmental microplastic contamination associated with vaginal or caesarean birth has the potential to vary considerably, for instance due to contamination from airborne fallout in operating theatres during caesarean birth, and from maternal stool during vaginal birth. Further work to quantify the degree of microplastic contamination associated with different birth modes, and to develop methods to mitigate and/or adjust for this contamination, is needed to enable selection of appropriate participant samples.

There were also differences between studies in methods used to process samples and detect microplastics. These differences may account for the variation in polymer types, sizes and levels reported in clinical samples from different studies (although differences in environmental exposures or demographic factors between the study cohorts may also have contributed). The creation of standardised, validated protocols for evaluating the microplastic load of clinical specimens is vital to produce high-quality evidence and to support future evidence synthesis.

The degree of microplastic exposure linked to environmental factors such as tap water, bottled water and food packaging may vary with local and regional differences in water treatment systems, waste management systems and food regulations.[44] Therefore, future studies examining environmental exposures in relation to microplastic levels in human tissues should take geographical and social context into account.

We are encouraged by ongoing research efforts in the field of microplastics and human reproduction. The MOMENTUM project is a collaborative initiative which aims to integrate and accelerate research to unravel the human health effects of micro- and nanoplastics, and to propose solutions to minimise their potential health impact.[45] Several currently registered trials (ClinicalTrials.gov IDs NCT05179993, ChiCTR2300070596) aim to examine the relation of these particles with fertility outcomes. Although this review did not identify any studies with male participants, the first reports of microplastics detected in human testes and semen were published within 5 months of our last search date, in June 2023.[46]

Given the growing body of evidence from cell culture and animal studies on the potential reproductive toxicity of micro- and nanoplastics,[24–29] we propose that establishing the effects of these pollutants on human fertility and pregnancy outcomes is a public health imperative. Evidence of potential harmful consequences could inform guidance and interventions to reduce plastic exposure preconception, during pregnancy and postpartum, as well as advocating for the reduction of unnecessary single-use plastics in healthcare settings.

5 | CONCLUSION

Only seven studies, all with small sample sizes, have evaluated the presence of microplastics in human reproductive

tissues, their associations with environmental exposures or implications for reproductive and pregnancy outcomes. Larger observational studies, performed using validated, evidence-informed methodologies, are needed to assess the effects of microplastics on human reproductive health, in addition to preclinical studies to determine relevant disease mechanisms. Given the current absence of robust evidence about the potential reproductive and developmental harms of microplastics, we advocate for further research and development of public health policy which seeks to reduce microplastic exposure throughout the life course, particularly during pregnancy, early infancy and childhood.

AUTHOR CONTRIBUTIONS

Conceived systematic review and developed protocol: KH, AD, AH, SH and DB. Developed search strategy and ran searches: KB. Screened studies for inclusion: KH and DB. Extracted data: KH and DB. Assessed study quality: KH, DB and AD. Drafted paper: KH, AD, AF, CB, and DB. All authors have read and approved the final paper.

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CONFLICT OF INTEREST STATEMENT

DB is a Trainee Scientific Editor for BJOG.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available provided in the article and its Supporting Information.

ETHICS APPROVAL

This study involved neither human or animal subjects or medical records, and therefore ethics approval was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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