

Diminished Ovarian Reserve with Markedly Elevated BPA Exposure in One of Two Monozygotic Twin Sisters Married to Monozygotic Twin Brothers

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Case Report

Keywords: Bisphenol A (BPA), Ovarian reserve, Endocrine-disrupting chemicals, Identical twins

Posted Date: September 30th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11028225/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background:

Diminished ovarian reserve (DOR) in young women is commonly attributed to genetic factors; however, environmental endocrine-disrupting chemicals, particularly bisphenol A (BPA), have been increasingly implicated in ovarian dysfunction (1, 2, 4).

Case:

We report a unique case involving identical twin sisters married to identical twin brothers, minimising genetic, intrauterine, and partner-related confounding. One sister presented with infertility and DOR, while her genetically identical twin had preserved fertility. Environmental toxin analysis revealed a markedly elevated preconceptional urinary BPA level in the infertile woman, exceeding laboratory reference limits. In contrast, BPA concentrations in the other family members were within normal ranges.

Conclusion:

This uniquely controlled human model suggests that diminished ovarian reserve may not be explained solely by genetic aetiology; environmental endocrine-disrupting chemicals may contribute to ovarian reserve impairment at clinically meaningful exposure levels, underscoring the need for systematic investigation of such exposures (1–4).

Introduction

Diminished ovarian reserve (DOR) is an increasingly encountered clinical condition among women of reproductive age and directly affects the success of infertility treatments. While early-onset DOR is frequently attributed to genetic predisposition, accumulating evidence suggests that ovarian ageing is a multifactorial process influenced by both intrinsic and extrinsic factors, including environmental chemical exposures—particularly endocrine-disrupting chemicals (EDCs)—as potential contributors to impaired ovarian function (1, 2, 4). Among these, bisphenol A (BPA) holds particular relevance due to its widespread exposure and multifaceted effects on ovarian follicular dynamics (1, 3).

Bisphenol A (BPA) is a synthetic phenolic compound widely used in the production of polycarbonate plastics and epoxy resins, leading to ubiquitous human exposure through food packaging, plastic containers, thermal receipts, and occupational settings (1, 2, 13). BPA is primarily absorbed via the oral route, while dermal and inhalational exposure may also contribute, particularly in industrial environments (1, 13). Following absorption, BPA undergoes hepatic glucuronidation and sulfation and is predominantly excreted in urine. Although BPA has a relatively short biological half-life, continuous or repeated exposure may result in sustained internal exposure levels (1, 4). Urinary BPA measurements are

preferred over serum assessments because circulating BPA levels are transient and more susceptible to contamination, whereas urinary concentrations better reflect integrated recent exposure (1, 4).

BPA exerts endocrine-disrupting effects through interactions with oestrogen receptors, androgen receptors, and non-classical signalling pathways, thereby interfering with hypothalamic–pituitary–gonadal axis regulation (3, 11, 12). Experimental studies demonstrate that BPA disrupts granulosa cell function, increases oxidative stress, impairs mitochondrial integrity, alters steroidogenesis, and accelerates primordial follicle activation (3). In addition to its direct endocrine-disrupting effects, BPA has been shown to induce epigenetic alterations, raising concerns that its reproductive toxicity may persist beyond the period of active exposure (3, 11).

Human observational studies have reported inverse associations between urinary BPA concentrations and ovarian reserve markers such as antral follicle count (AFC) and anti-Müllerian hormone (AMH) (5–8). Moreover, recent evidence suggests that co-exposure to phenols and phthalates may further increase infertility risk, highlighting the relevance of mixture effects in real-life environmental exposure scenarios (9, 10). However, interpretation of these findings is complicated by genetic heterogeneity, differences in exposure assessment, and variability in study populations. In this context, investigation of BPA exposure in genetically identical individuals offers a uniquely powerful human model to disentangle environmental influences from genetic and partner-related confounding.

This case provides a uniquely controlled human model in which genetic, intrauterine, and partner-related confounding are minimised, allowing environmental exposure to be examined in relative isolation.

Case Presentation

A 33-year-old woman with a 9-year history of primary infertility presented for evaluation. She is an identical twin; her genetically identical sister conceived spontaneously and delivered two healthy children. Both sisters are married to identical twin brothers.

Baseline ovarian reserve assessment in the infertile woman revealed an anti-Müllerian hormone (AMH) level of 0.8 ng/mL, basal follicle-stimulating hormone (FSH) of 9 IU/L, and an antral follicle count (AFC) of 7 (total). The fertile twin sister demonstrated preserved ovarian reserve parameters, with an AMH level of 2.8 ng/mL and a total AFC of 18.

Semen analysis in the infertile woman's partner demonstrated a sperm concentration of 9 million/mL with 10% progressive motility and 1% normal morphology, whereas the fertile twin's partner had a sperm concentration of 23 million/mL with 39% progressive motility and 2% normal morphology. Although both results were above conventional IVF indication thresholds, semen parameters were quantitatively lower in the infertile couple. Notably, urinary BPA concentrations were within normal ranges in both male partners and in the fertile twin, with a markedly elevated BPA level observed exclusively in the infertile woman, supporting a sex-specific and individual exposure pattern rather than a shared household exposure effect.

The infertile woman reported smoking approximately 20 cigarettes per day. The fertile twin sister also reported smoking approximately 13 cigarettes per day, and both male partners were current smokers. The infertile woman had a substantial history of occupational exposure, having worked for approximately six years in a marble factory with potential exposure to epoxy resins, followed by approximately three years in agricultural field work with regular exposure to pesticides and other agrochemicals. Preconceptional urinary BPA sampling was performed before initiation of ovarian stimulation and before cessation of occupational exposure. These occupational exposures were terminated prior to initiation of fertility treatment. Karyotype analysis showed a normal 46, XX result; her partner's karyotype was 46, XY. Karyotypes were normal in all family members.

Environmental Toxin Assessment

Environmental toxin analysis included measurement of heavy metals and BPA levels in urine. Heavy metals—aluminium, manganese, cobalt, nickel, copper, arsenic, selenium, molybdenum, cadmium, and lead—were within laboratory reference ranges and comparable among all individuals.

In contrast, preconceptional urinary BPA concentration in the infertile woman was 629.1 µg/L (reference range: 0–15.9 µg/L), representing an approximately 50-fold higher level compared with the fertile twin and both male partners. According to information provided by the analytical laboratory, such BPA concentrations have not been observed in their previous routine or occupational monitoring measurements, including serial assessments performed in industrial workers with known BPA exposure.

Treatment and Reproductive Outcome

Controlled ovarian stimulation was performed using recombinant follicle-stimulating hormone (rFSH; Gonal-f®, Merck Serono, Darmstadt, Germany) at a daily dose of 375 IU for 10 days. To prevent premature ovulation, medroxyprogesterone acetate (MPA; Tarlusal®, Deva Holding A.Ş., Istanbul, Türkiye) was initiated when the leading follicles reached a diameter of 10 mm. Final oocyte maturation was triggered using a gonadotropin-releasing hormone agonist (triptorelin; Gonapeptyl®, Ferring Pharmaceuticals, Kiel, Germany).

Oocyte pickup yielded three metaphase II (MII) oocytes and one metaphase I (MI) oocyte. All mature oocytes fertilised successfully, resulting in three day-5 blastocysts (53BB, 52BB, and 52BC). In accordance with our clinic's routine freeze-all strategy applied to all IVF cycles; all embryos were cryopreserved.

A single blastocyst transfer using the highest-quality embryo (53BB) was subsequently performed in a later cycle.

The patient achieved an uncomplicated pregnancy and delivered a healthy male infant by caesarean section at 38 + 6 weeks of gestation, with a birth weight of 2750 g.

At 33 weeks of gestation, repeat urinary BPA measurement demonstrated complete normalisation of BPA levels in the patient, whereas her partner's BPA concentrations, which had already been within normal limits prior to pregnancy, remained within the normal range.

Methods – Environmental Exposure Assessment

Urinary bisphenol A (BPA) concentrations were determined according to the method described by Cunha et al. (17), using dispersive liquid–liquid microextraction (DLLME) followed by heart-cutting multidimensional gas chromatography–mass spectrometry (MD-GC/MS). Analyses were performed using an ISQ Trace 1300 Single Quadrupole GC-MS system (Thermo Scientific, Waltham, MA, USA).

Trace element concentrations were measured using an iCAP TQ ICP-MS system (Thermo Scientific, Waltham, MA, USA) in accordance with Thermo Scientific Technical Note 43283.

Discussion

BPA Exposure and Ovarian Reserve Parameters

The impact of bisphenol A (BPA) exposure on ovarian reserve has primarily been evaluated using clinically established markers such as antral follicle count (AFC) and anti-Müllerian hormone (AMH). A substantial proportion of human studies conducted in infertile populations report an inverse association between BPA exposure and ovarian reserve parameters (5–8). In a cross-sectional study of women attending an infertility clinic, Souter et al. demonstrated a significant inverse relationship between urinary BPA concentrations and AFC, providing early clinical evidence that increased BPA exposure may accelerate follicular depletion (5). Similarly, Zhang et al. reported negative associations between urinary BPA levels and both AFC and AMH in infertile women, supporting a potential adverse effect of BPA on ovarian physiology (7). In women undergoing assisted reproduction, Czubacka et al. identified significant negative correlations between urinary BPA concentrations and both AMH and AFC, further highlighting BPA exposure as a potential contributor to diminished ovarian reserve (6). Recent systematic and scoping reviews consistently emphasise these inverse associations, particularly in studies incorporating direct ovarian reserve markers rather than hormonal surrogates alone (1–4).

In the present case, BPA exposure was not inferred but quantitatively demonstrated. BPA concentrations were measured in all family members; however, an extraordinarily elevated preconceptional urinary BPA level—approximately 50-fold above the laboratory reference range—was observed exclusively in the infertile woman. In monochorionic monozygotic twins, derivation from a single zygote and a shared placental environment imply that both genetic background and intrauterine exposures are largely common, with more than 99% of the genomic sequence shared. Given that ovarian reserve is closely linked to genetic predisposition, a high degree of similarity would be expected between monozygotic twins. Accordingly, the marked divergence in ovarian reserve observed in genetically identical individuals points toward postnatal environmental exposures as a plausible contributor. Within this uniquely

controlled human model, minimising genetic, intrauterine, and partner-related confounding, the objectively demonstrated exposure contrast provides a biologically coherent framework for interpreting the observed ovarian reserve disparity. This configuration creates an exceptionally controlled human model that closely approximates a natural experiment for studying environmental effects on ovarian biology. Beyond BPA, cumulative exposure to endocrine-disrupting chemicals has been implicated in ovarian ageing; higher overall environmental exposure burdens, including BPA, have been associated with an increased risk of diminished ovarian reserve, suggesting that ovarian toxicity may reflect cumulative rather than isolated chemical effects (9–12). Moreover, emerging data on BPA analogues such as bisphenol S and bisphenol F indicate similar adverse trends on ovarian reserve and oocyte quality, reinforcing concerns regarding the bisphenol class as a whole (3, 7).

Interpretation of Conflicting Evidence

Studies reporting no significant association between BPA exposure and ovarian reserve predominantly involve fertile or general population cohorts characterised by lower exposure levels and younger age distributions (8, 9). The absence of detectable effects in low-risk populations does not negate BPA-related ovarian toxicity but suggests that clinically relevant effects may become evident primarily in susceptible or high-exposure subgroups.

Contribution and Novelty of the Present Case

This is, to our knowledge, the first report evaluating detailed environmental toxin exposure in genetically identical twin sisters married to genetically identical twin brothers. The approximately 50-fold difference in preconceptional BPA exposure between the twins closely parallels the divergent ovarian reserve profiles and aligns with prior epidemiological findings in infertile cohorts (5–7), strengthening the biological plausibility of BPA as a modifiable environmental contributor to diminished ovarian reserve.

Pregnancy-Related BPA Dynamics and Cumulative Toxicity

Although BPA has a short biological half-life, repeated or chronic exposure may sustain elevated internal exposure levels, allowing biological effects to accumulate (1, 4). The extraordinarily high BPA concentration observed is more consistent with chronic intensive exposure than with a single transient contact. The complete normalisation of BPA levels during pregnancy, coinciding with pregnancy-related physiological changes and cessation of occupational exposure, supports the modifiability of BPA exposure (13). Environmental toxicants have also been associated with adverse effects on sperm quality and male reproductive potential (14). While smoking was present in all family members and may contribute to cumulative oxidative stress (15, 16), the absence of parallel BPA elevations in the others suggests that smoking acted as a co-existing environmental burden rather than the primary determinant of the exceptional BPA elevation observed exclusively in the infertile woman. Dietary sources and plastic

use may also contribute; however, the magnitude of elevation points toward occupational exposure as the predominant source.

These findings highlight the potential clinical relevance of environmental exposure assessment in evaluating unexplained diminished ovarian reserve. Although routine screening for endocrine-disrupting chemicals is not currently recommended in infertility practice, this case illustrates that markedly elevated environmental exposures may represent a potentially modifiable contributor in selected patients. Increased awareness of occupational and lifestyle-related exposures may therefore support a more comprehensive evaluation of ovarian reserve impairment.

Conclusion

This case report involving genetically identical twin sisters married to genetically identical twin brothers provides clinical evidence supporting an environmental contribution to diminished ovarian reserve. The marked elevation of preconceptionally urinary BPA in the infertile woman, contrasted with reference-range levels in all other family members, is consistent with epidemiological data linking BPA exposure to impaired ovarian reserve (1–8). Although causality cannot be established from a single case, these findings indicate that diminished ovarian reserve may not be attributable solely to genetic aetiology and that environmental chemicals—particularly BPA—can exert clinically meaningful effects and should be systematically considered in the evaluation of ovarian reserve impairment.

Declarations

Funding

The authors received no specific funding for this work.

Author Contributions

Hande Antep TÖRE, Rovshan JABBAROV, Murat BERKKANOĞLU, Hasan BULUT, Kevin COETZEE, Muhittin SERDAR, and Kemal ÖZGÜR contributed to the conception and design of the work, acquisition and interpretation of the clinical and laboratory data, and preparation and critical revision of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Declaration

Ethics declaration: not applicable. Written informed consent was obtained from the patient for publication of this case report and accompanying data.

Data Availability Statement

The datasets generated during and/or analysed during the current study are not publicly available due to patient privacy and confidentiality but are available from the corresponding author on reasonable request.

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