The Effects of Endocrine Disrupting Chemicals on the Outcomes of Pregnancy and Fertility Treatments Should Not Be Underestimated

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Disclosure:	The authors have declared no conflicts of interest.
Received:	30.06.23
Accepted:	05.07.23
Keywords:	Endocrine disrupting chemicals (EDC), infertility, *in vitro* fertilisation (IVF).
Citation:	EMJ Repro Health. 2023;9[1]:54-56. DOI/10.33590/emjreprohealth/10302417. https://doi.org/10.33590/emjreprohealth/10302417.

Infertility rates are rising. Infertility is generally defined as the failure to establish clinical pregnancy after 12 months of regular, unprotected sexual intercourse. Around the world, approximately one in six couples hoping to conceive are being diagnosed as infertile.[1] There are numerous well-established causes of infertility, including advanced age, polycystic ovary syndrome, and sexually transmitted infections. However, in more than 10% of couples the cause of infertility is unknown,[2] and the prevalence of this unexplained subfertility is increasing.[3] In parallel to this, the production of synthetic chemicals is increasing at dramatic rates across the globe, leading experts to question their effects on human health, including reproductive health. It is time to examine the evidence regarding endocrine disrupting chemicals (EDC) as a possible cause of infertility and subfertility in both males and females, and the detrimental impact they might have on consequential fertility treatments.

EDCs are exogenous chemicals with the ability to interrupt normal endocrine function in humans. They are used extensively throughout manufacturing, industrial, and agricultural sectors; however, most of us are exposed to them on a day-to-day basis through plastics, pharmaceuticals, cosmetics, and food preservatives. EDCs are pervasive chemicals, able to bio-accumulate within adipose tissue once ingested or inhaled. Their long-half lives and widespread use mean it is sadly impossible to escape these ubiquitous chemicals.

It has already been established that environmental pollution negatively impacts the fertility of all mammalian species,[4] and exposure to air pollutants, including carbon monoxide, is already associated with an increased risk of both miscarriage and stillbirth.[5] It is therefore simple to predict that EDCs might have a similar impact. Indeed, increasingly substantial evidence has shown negative associations between increasing EDC exposure and male and female fertility, chromosomal abnormalities, development and implantation problems within the embryo, and early pregnancy loss.[6]

The pathophysiological mechanisms behind these unwanted effects are poorly understood but are hypothesised to relate to the ability of some EDCs, such as bisphenol A (BPA) and triclosan, to competitively bind to hormone receptors and interfere with oestrogen signalling pathways.[6] BPA is also thought to inhibit aromatase activity, thereby inhibiting oestrogen synthesis and disrupting ovarian folliculogenesis and implantation.[7] The impact of this should not be underestimated. The presence of BPA in everyday products, including plastics, the lining of food and drink containers, as well as medical products, means that the general population are exposed to its effects on a daily basis.

Maternal exposure to EDCs is also an identifiable risk factor for several pregnancy complications, including recurrent miscarriage, hypertensive disorders such as pre-eclampsia, and pre-term birth.[8] A recent systematic review has examined convincing evidence to show that BPA exposure leads to foetal growth restriction and reduced birth weight, particularly when exposure occurs in the first 20 weeks of gestation.[9] Furthermore, other EDCs, including phthalates and perfluorooctane sulphonate, have been associated with a significantly increased chance of premature delivery.[10,11] These effects likely occur due to their accumulation within, or actions upon, the placenta, causing misregulation of trophoblastic signalling pathways and therefore altered cell viability.[8] These complications pose a significant risk to the health of both mother and child in the short and long term. Given that birth weight is such a significant predictor for future health outcomes, including obesity, diabetes, and cardiovascular disease, the downstream effects of EDC exposure are larger than we know.

Sadly, the patients who will feel the greatest impact from EDC exposure are those who are already more likely to have trouble conceiving and need to seek fertility treatment: older females. These females not only suffer from decreased ovarian reserve, as the number of oocytes is fixed from birth, with no way to replace them, but will have had longer exposure to the effects of various EDCs during their lifetime, which may well confound the effects of better-established risk factors, such as smoking, alcohol consumption, and air pollution, further reducing the chance of a successful pregnancy.

It is not just female fertility that is impacted by EDCs. Studies have shown male exposure to EDCs can impact normal testicular morphology and function. BPA has been associated with decreased sperm quality,[12] possibly via its oestrogenic and anti-androgenic effects,[13] whilst phthalate exposure is linked to hypospadias, cryptorchidism, and the development of testicular cancer.[14]

Unfortunately, EDCs can impact not just natural conception, but may also adversely influence the outcomes of fertility treatment. Several studies have shown relationships between increased exposure to BPA in females and poor outcomes of *in vitro* fertilisation (IVF) treatment. Specifically, serum BPA levels have been negatively associated with oocyte retrieval, oocyte maturation, fertilisation rates, and embryo quality.[15]

However, studying the impact of EDCs on fertility and IVF outcomes is hard to do. Human fertility is dependent on multiple factors, all underpinned by complex underlying processes such as folliculogenesis and spermatogenesis. One of the biggest challenges when studying their effects is that these chemicals are vast in number and have varying biochemical effects. The impact of one cannot, and should not, be generalised to be the impact of them all. Their ubiquitous nature further complicates matters, as they are nigh on impossible to avoid, and patients will be exposed to many different compounds at any one time. The presence of multiple different chemicals within the human body may therefore impact the effects seen by an individual chemical.

Research into how we can mitigate the harmful effects of EDCs is limited but ongoing. The most promising method appears to be via increased antioxidant intake. Oxidative stress has been shown to indicate BPA toxicity, and various antioxidants, including vitamins, herbs, and melatonin, may be useful to counteract its effects.[16] Other studies have shown a similar protective role, with vitamins C and E minimising the impact of phthalates and polychlorinated biphenyls.[17]

It is clear that EDCs pose significant risk to human reproductive health, with potential downstream effects lasting for years to come. Significant evidence has shown associations

between increasing EDC concentration, diminishing ovarian reserve, and poor fertility and IVF outcomes. The literature is occasionally conflicting, usually due to small sample sizes and a lack of control of possible confounding variables. However, the association between exposure to EDCs and poor reproductive outcomes is undeniable, and will have a substantial impact on public health. Further research is needed to examine the impact of EDCs in combination, and to understand their mechanisms of action, as identifying the risk of a single chemical is meaningless, given we are exposed to hundreds of these chemicals in combination from conception. Furthermore, research should also focus on how we can reduce their effects, possibly via a diet rich in antioxidants, or through alternative methods. In the meantime, a global strategy is urgently needed to prevent exposure to these chemicals, especially in females of child-bearing age, but ideally from birth, to mitigate their impact on the outcomes of pregnancy. Healthcare workers within reproductive medicine should be educated about the impacts of EDCs, and how to support patients to minimise their exposure and moderate their effects. At a population level, awareness campaigns should advise on the use of consumer products, particularly personal care products, and healthy diets, to avoid EDCs where possible. These methods will not only improve public health, but ensure as many parents as possible achieve the ultimate goal of reproduction: a healthy and happy baby.

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