https://doi.org/10.1038/s44294-025-00069-9

Can pharmaceutical use during pregnancy affect the reproductive health of the offspring?

Check for updates

Agnes Stefansdottir[1] ✉ & Norah Spears[2] ✉

Care is required when administrating pharmaceuticals to pregnant women, bearing in mind not only the mother-to-be's health but also that of the unborn offspring. Until now, studies of fetal outcomes have primarily focused on avoiding major effects, but some outcomes could become apparent only later. This perspective discusses whether fetal exposure to pharmaceuticals administered to a pregnant woman could affect the developing reproductive system, potentially resulting in fertility problems, even with consequences for subsequent generations. Different circumstances in which pregnant women can be administered pharmaceuticals are examined, some where there is a necessity for treatment, but others that may be dispensable.

Medical treatment for a patient who is pregnant is always approached with care, with the medical practitioner needing to consider not only the health and wellbeing of the patient but also that of the unborn fetus. If any pharmaceutical is to be prescribed, drug safety is paramount. Would a medicine cross the placenta so that the fetus would be directly exposed to it? If so, what effects might exposure have on the fetus? Even without direct fetal exposure, there could be downstream or indirect consequences to the fetus following maternal treatment. Where fetal development is affected, the consequences of any such effect might become apparent only later, with some harmful effects potentially resulting in lifelong consequences for the unborn individual. The most urgent concern is to determine if treatment could affect the viability of the fetus, leading to an increased rate of spontaneous abortions and/or congenital malformations. However, for any drugs where data indicate that these drastic consequences are highly unlikely, the more complex task is to determine if there will be downstream effects on the health of the unborn child; effects that are more subtle, perhaps not immediately apparent. However, for one aspect of the fetus, something even longer-term is at stake—not only the health of that unborn child but also her or his subsequent fertility, an aspect that could also potentially affect the health, well-being, or even existence of future generations (Fig. 1).

From around midway through pregnancy, fetal ovaries already contain all the germ cells that an individual will ever have. This means that any future eggs that an unborn female will ever ovulate, and that might one day be fertilized, are already sitting in the fetal ovary at that point, potentially exposed to any pharmaceuticals administered to the pregnant woman. For male fetuses, stem germ cells are already present from around that same stage of pregnancy, although no future sperm cells are yet present in the fetal testis. In contrast to the fetal ovary, the stem germ cells present in the fetal testis will continue to divide a number of times before undergoing meiosis and differentiating into sperm, with that final process starting only after puberty. In either case, if fetal drug exposure does impact gonadal development, the consequences of that disruption may well not become apparent for years, perhaps after puberty but potentially not until decades later, when an individual experiences sub-fertility or infertility. With the added potential of induction of epigenetic modifications in the fetal germ cells, we also need to consider the possibility of effects not only on the individual after birth, but of epigenetic transgenerational inheritance, effects on future generations not directly exposed to the medication[1].

It is now well established that the environment during development can affect the long-term health of individuals, a concept termed the Developmental Origins of Health and Disease (DOHaD)[2]. An environmental perturbation can be prior to parturition, even as early as around the time of conception. This, of course, includes effects on the developing reproductive systems, the consequences of which may not become apparent for some time[3,4]. Much of the focus of work on DOHaD has been investigating unavoidable stresses such as impaired nutrition or exposure to environmental disruptors, but there is a clear application to effects from pharmaceuticals. Probably the best-known example of this is from effects of the estrogen diethylstilbestrol (DES), a drug prescribed to pregnant women for several decades from the 1940s in order to prevent miscarriages: DES was later found to have a plethora of effects including increased rates of several reproductive cancers, with consequences sometimes apparent for several generations[5].

In this perspective, we discuss some of the situations in which pharmaceuticals administered to or taken by a woman who is pregnant could affect the reproductive systems of the unborn fetus, highlighting the need for a better understanding of these potentially several-generations-long effects.

[1]BMTO, Teviot Place, University of Edinburgh, Edinburgh, UK. [2]Biomedical Sciences, Hugh Robson Building, George Square, University of Edinburgh, Edinburgh, UK. ✉e-mail: A.Stefans@ed.ac.uk; norah.spears@ed.ac.uk

Overview of gonadal development

The reproductive systems in both sexes begin to develop during early embryonic development, with the formation of the genital ridge; the primordium of the gonad. From that point onwards the gonads continue to develop throughout pregnancy, thus potentially rendering them vulnerable to pharmaceutical drug exposure (Fig. 2).

During the fourth week of gestation, the primordial germ cells (PGCs) that will go on to form the mature gametes, oocytes and sperm, migrate to the genital ridge. During migration and after arrival at the genital ridge, PGCs proliferate rapidly, increasing their number as they populate the developing gonads, which at that stage are bipotential, still able to develop into either ovaries or testes. Where the SRY gene on the Y chromosome is expressed in males, bipotential gonads will then develop into testes, while absence of SRY expression will result in development of ovaries. At this point, PGCs are termed oogonia or gonocytes in the ovary or testis respectively.

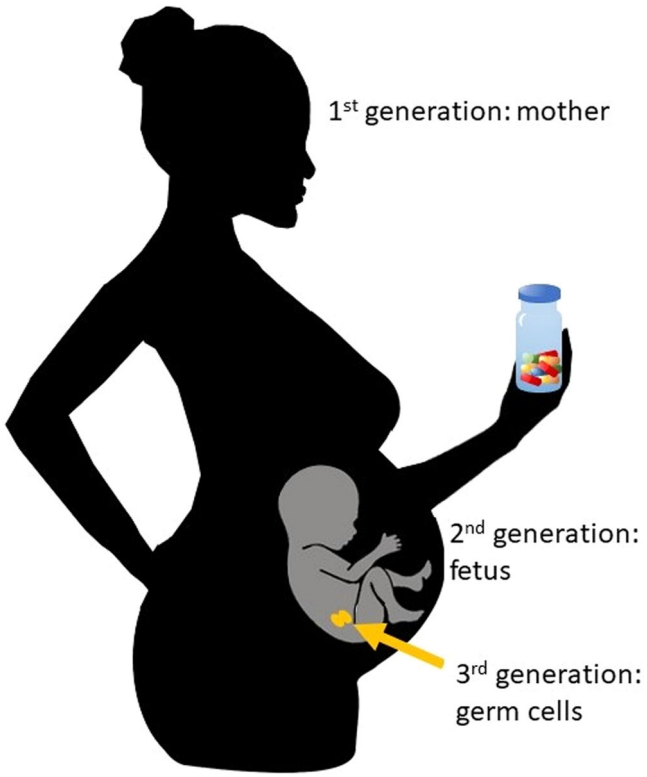


Fig. 1 | Treatment with pharmaceutical drugs during pregnancy can affect three generations, not only the mother and the fetus, who are both directly exposed to the drugs, but also a third generation, since the germ cells for that generation are laid down in the developing gonad during fetal development, with some changes potentially affecting generation(s) beyond that.

Ovarian development

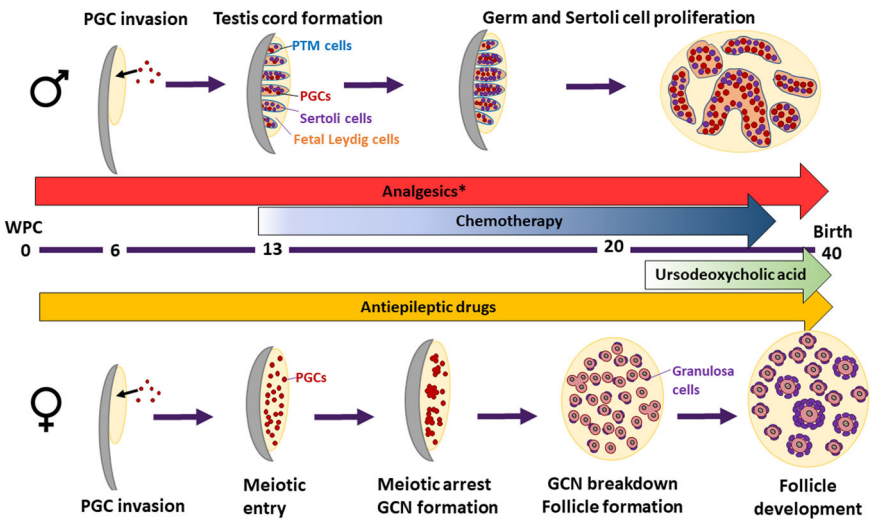
The developing ovary becomes populated by rapidly proliferating oogonia, increasing in number, reaching a peak of around seven million by the fifth month of gestation. Oogonia then form clusters surrounded by somatic cells that will differentiate into granulosa cells. At that point, oogonia undergo the first stage of the first meiotic division, prophase I, after which they enter meiotic arrest, now termed oocytes. As oocytes enter meiotic arrest, granulosa cells form a layer surrounding individual germ cells, forming a pool of resting primordial follicles. The oocytes remain in meiotic arrest until they ovulate several decades later. The majority of the seven million oogonia produced earlier do not go on to form follicles, but instead undergo apoptosis, leaving only around two million primordial follicles present in the human ovary by birth, comprising the non-renewable ovarian reserve of the female from which all future ovulated oocytes will derive[6,7].

From the point of follicle formation onwards there is a steady recruitment of dormant primordial follicles into the growth phase, and thus a continual reduction in the size of the resting follicle pool. Once a follicle has started growing, it will either continue to develop until reaching the pre-ovulatory stage (from puberty onwards) or die during the process of follicle development. Follicles reaching the pre-ovulatory stage can then ovulate, releasing a fully developed oocyte capable of fertilization. During adulthood, once the follicular pool has become too small to support ovarian cycles, a woman will enter the menopause. Consequently, the age at which a woman enters menopause is directly correlated with the size of her primordial follicle pool at birth: if a female fetus forms fewer follicles during ovarian development or loses more of the ones that she has formed, then, as an adult, she is likely to go through menopause at a younger age.

Testicular development

Within the developing testis, Sertoli cells, the first testicular cell type to differentiate, envelop, and support the differentiation of PGCs to male germ cells, termed gonocytes at that developmental stage. Sertoli and germ cells are contained within seminiferous cords, the primordium of the seminiferous tubules. Sertoli cells proliferate during fetal development: since each Sertoli cell is able to support only a set number of SSCs, the final size of the Sertoli cell population limits the future potential of sperm production throughout the male's reproductive lifespan[8]. The fetal Leydig cells, in the

Fig. 2 | Overview of gonadal development and potential periods of exposure to different pharmaceutical agents. (* Note that some non-steroidal anti-inflammatory drugs such as ibuprofen and diclofenac are not recommended after 20 weeks of pregnancy.) GCN—germ cell nest, PGCs—primordial germ cells, PTM cells—peritubular myoid cells, WPC—week(s) post-conception.



interstitial tissue, produce testosterone throughout fetal life, but eventually regress and are replaced by the adult Leydig cells during puberty[9]. After birth, gonocytes differentiate into spermatogonial stem cells (SSCs) and spermatogonia that will undergo meiosis to form spermatozoa. The presence of functional SSCs and their supporting Sertoli cells enable the production of new sperm throughout a male's lifetime.

Fetal testicular development has a critical period, the masculinization programming window (MPW), when it is highly sensitive to disruptions. The presumptive MPW occurs between 8–14 weeks of gestation and it has been hypothesized that testicular dysgenesis syndrome disorders, such as poor semen quality, testicular cancer and hypospadias, can result from disruptions following xenobiotic exposure during that period[3,10].

Use of pharmaceuticals during pregnancy

For women who are pregnant, differentiating between drug treatments that are necessary and the use of non-essential medications is crucial. In certain circumstances, treatment with pharmaceutical agents simply cannot be avoided, as is the case in the management of cancer or epilepsy. Treatment can be vital for managing life-threatening conditions, and so withholding or discontinuing treatment could have much more serious consequences than administering drug(s) to the pregnant patient. Depending on medical circumstances, this can be the case for administration of antibiotics. Some infections such as of the urinary tract are crucial to treat, with non-treatment incurring a significant risk to fetal health, although in other cases, risks and benefits need carefully weighed up, with some antibiotics having proven detrimental effects on fetal development[11]. In contrast, other pharmaceutical drugs such as analgesics are usually used for management of pain relief rather than to treat life-threatening conditions. They can, however, affect fetal development, and should therefore be used with caution.

Clear thinking about the distinction between necessary and non-essential pharmaceuticals by medical professionals and their patients is key for guiding clinical decision-making. This is particularly important given the distinct lack of follow-up studies, or even of research on animal models and/or human tissues, often leaving us without answers as to what extent different pharmaceutical agents taken during pregnancy could affect future fertility of individuals who have been exposed in-utero. There is a need for clear and transparent communication between doctors and pregnant patients about the risks and benefits of any medication. While the immediate needs of the pregnant woman are paramount, potential long-term effects on the fetus need to be acknowledged, including where follow-up data are limited. For conditions that require life-saving treatment, the priority should be on identifying the safest possible treatment regimen whilst acknowledging that there could be some degree of fetal risk involved. At the other end of the spectrum, there will be non-essential treatments, where a more conservative approach should be taken, and where medications, if needed, should always be taken for the shortest possible duration and at the lowest possible dose. Ultimately, balancing maternal treatment needs with the safety of the fetus requires some level of nuance, which will be personalized to each individual patient, at least until more research becomes available to permit better-informed treatment decisions.

This article explores four examples in detail, instances that fit within different categories of why pregnant women might be administered or self-administer pharmaceuticals. Firstly, for treatment that could be required regardless of the pregnancy, there is use of chemotherapy drugs to treat various cancers. Secondly, treatment that may be required but where it might be best to change the specific drug(s) administered, the use of sodium valproate (SV) to treat epilepsy is explored, with a current consensus that its use should be avoided in women of reproductive age, treatment for these patients switched to other anti-epileptic drugs (AEDs) that have a better safety profile in terms of effects on fetal development. The third instance is where treatment of a pregnant woman is primarily for the health of the fetus, exploring the example of the drug ursodeoxycholic acid (UDCA), which is administered to women with the liver condition intrahepatic cholestasis of pregnancy (ICP) primarily in order to protect the fetus from exposure to high levels of bile. Finally, to explore treatment that may not be essential, the use of analgesics during pregnancy is discussed: while these can be prescribed during pregnancy for the health of the pregnant woman and/or developing fetus, some use can at the very least be curtailed.

(i) Chemotherapy drug treatment

Although thankfully rare, around one in every thousand pregnant women receives a cancer diagnosis during her pregnancy, most commonly for breast cancer[12]. In Europe alone, this results in an estimated 3000–5000 diagnoses of cancer in pregnant women each year[13]. The treatment of a pregnant cancer patient is challenging, requiring consideration of both maternal and fetal well-being. Chemotherapy drug treatment during the first trimester of pregnancy is administered only where there is no option, since it is linked to increased rates of spontaneous abortions and of congenital malformations. Where deemed necessary though, these drugs are considered safe to administer during the second and third trimesters, although avoided immediately before birth. While there are some reported associations with negative neonatal outcomes such as being small for gestational age[14], it appears that fetal chemotherapy drug exposure at these later stages of pregnancy is broadly compatible with fetal health, with no noted association with severe congenital, neurological, or cardiac outcomes in any of the resulting births: as such, they are considered safe to administer[15]. Nonetheless, many chemotherapeutics can cross the placenta, and so enter fetal circulation[12]. This means that the potential exists for fetal development to be affected by these drugs, perhaps causing effects that either have a low level of severity or are not apparent until later in life. Any effects on the reproductive system could well fall into the latter category: a child may have affected ovaries, testes, or indeed other reproductive organs[16], but show no symptoms until after puberty, or even not until later, possibly not until those individuals begin trying to have children themselves only to discover that they are sub- or infertile.

What then is the likelihood that chemotherapy drugs administered to a pregnant woman and crossing the placenta would have a deleterious impact on ovarian or testicular development in the exposed fetus? Given that there is a large body of evidence showing that many of these drugs have deleterious effects on postnatal ovaries and testes, this could well be the case[17,18].

Postnatally, alkylating and alkylating-like agents such as cyclophosphamide and cisplatin are particularly damaging both to the ovary and to the testis: with chemotherapy treatment almost always involving administration of different drug combinations, it is not always clear yet just how damaging some other classes of drug are. In the ovary, exposure to many different chemotherapy drugs results in a loss of ovarian follicles from the primordial follicle stage onwards, but evidence to date indicates that the pathway to that damage can be variable, with some drugs initially targeting oocytes and others damaging surrounding somatic cells[19]. There is also an ongoing controversy as to whether the drugs result in the direct death of primordial follicles, or whether the drugs induce early growth activation of these resting follicles, which then die as a result of drug exposure while in the growth phase; these two possibilities are not exclusive, and it may well be that both processes occur[17,20]. In the testis, it appears that the germ cell population is particularly sensitive, with effects on numbers seen at all germ cell stages, from stem spermatogonial cells through to spermatozoa[9,18].

In contrast to the large body of evidence of damaging effects of chemotherapeutics on postnatal gonads, the extent of any damage to the developing fetal gonad is far from clear. Comparison of the fetal and the postnatal gonad may be instructive, to help determine likely effects. For the female, from around halfway through pregnancy, which is not far into the window during which chemotherapeutics are considered safe to administer to pregnant women, the ovary already contains its store of ovarian follicles. Given that both primordial and early growing follicles in the postnatal ovary are sensitive to chemotherapy drug exposure, it is highly likely that these same follicle stages are equally sensitive to drug exposure prior to birth. For the male, the situation is somewhat different, with the fetal testis containing earlier stages of germ cells, gonocytes. In addition, prior to birth the germ cells are contained within seminiferous cords, which will develop to tubules only later. Theoretically, therefore, it is possible that the sensitivity of the

testis to chemotherapy drugs could be different before birth compared to later. At the time of writing, though, there are only a handful of studies that have directly examined chemotherapy drug effects on fetal ovaries and testes. Of these, ovary studies all use the mouse as a model (see for example refs. 21–23), while testis work involves not only rodent models but also studies using human fetal testis biopsies[24–26]. In work on both the ovary and the testis, germ cell number is affected by chemotherapy exposure[21,22,25–27]: two studies also indicate deleterious effects on Leydig cell function in the testis[28,29].

(ii) Treatment of epilepsy with sodium valproate

Epilepsy is one of the most common neurological disorders, characterized by the onset of repeated, unprovoked, and debilitating seizures that can lead to the loss of consciousness and convulsions. It affects around 50–60 million people worldwide, with around 15 million of those being women of reproductive age, resulting in around one in every 200 pregnant women requiring treatment with AEDs. While some AEDs can cause problems for the developing fetus, in this circumstance pausing or changing AED medication could result in even more severe problems, such as intense seizures that might lead to serious detrimental consequences for the developing fetus. Consequently, the safest option for pregnant women with epilepsy is to continue taking their seizure medication throughout the pregnancy, perhaps adjusting dosage to minimize fetal exposure while still maintaining seizure control. In 2018, the AED SV was contraindicated for women of childbearing age due to its teratogenic risks, causing major congenital malformations including spina bifida and cleft palate, as well as minor malformations including hypospadias[30,31]. Furthermore, in January 2024, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) issued a national patient safety alert advising that SV prescriptions for all patients under 55 had to be signed off by two independent specialists (https://www.gov.uk/guidance/valproate-use-by-women-and-girls#valproate-should-not-be-used-in-pregnancy). However, even taking into account current policies limiting use in many countries, we need to consider the children born before such regulations were in place: in the UK alone, around 20,000 children are estimated to have been exposed to SV prenatally. Approximately 40% of these children are at risk of developmental disorders, yet assessment of effects on the developing fetal gonads has been limited. This is concerning given that both women and men with epilepsy have well-recognized reproductive symptoms, including an increased risk of infertility, while treatment with SV has been shown to cause endocrine side effects, causing menstrual disturbances, hyperandrogenism, and polycystic ovaries in women[32–35], and a reduction in sperm count and motility and increase in abnormal sperm morphology in men[36,37]. Given that AEDs can cross the placenta and impact organogenesis, more information is needed to determine whether AED exposure can detrimentally impact fetal gonadal development and hence the long-term reproductive health of the in-utero exposed fetus. Few epidemiological studies have examined the impact of in-utero AED exposure on the developing reproductive system and only a small number of experimental studies have examined their impact, with most of these conducted in rodent and/or in vitro models, and none on the fetal ovary at the time of writing[30,38,39]. Prenatal AED exposure has been shown to affect testicular steroidogenesis and germ and somatic cell survival, eventually leading to decreased sperm counts and increased rates of morphologically abnormal sperm[39].

(iii) Ursodeoxycholic acid

In some cases, drug administration during pregnancy is required not only to protect the mother but also—or even solely—to safeguard fetal health. This is particularly the case where maternal health conditions could be detrimental to fetal safety, such as with the liver condition ICP, a pregnancy-related ailment that can develop during the second or third trimester of pregnancy. Pregnant women with ICP suffer from impaired bile flow leading to an accumulation of circulating bile acids. These can cross the placenta and pose a risk to the fetus, including preterm birth, meconium-stained amniotic fluid, or miscarriage. Treatment with the drug UDCA is recommended here, not only to help alleviate maternal symptoms but also to lower the levels of circulating bile acids and hence improve placental function, mitigating the risks to the fetus. UDCA is considered a low-risk medication, with observational studies and randomized trials on its safety indicating that its use does not pose any significant risk to fetal development, whilst also improving outcomes for both the mother and her fetus[40,41]. However, while at this point there has been no reported effect on the developing gonads, it is still the case that more comprehensive and larger-scale studies are required, in order to better understand the full range of effects on long-term health outcomes of people who have been exposed to UDCA in utero, including effects on reproductive health.

(iv) Use of analgesics during pregnancy

Over-the-counter analgesics such as paracetamol (also known as acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen are amongst the most widely sold medications in the world. Paracetamol is considered the safest analgesic to take during pregnancy, with around 50–65% of pregnant women worldwide using it at some stage of their pregnancy[42–44]. Paracetamol is important for the treatment of fever and severe pain during pregnancy. If left untreated, fever could harm the mother and her developing fetus. However, less than 10% of pregnant women use paracetamol for management of fever, with the majority of use being for chronic pain and headaches. The popularity of paracetamol for treating various types of pain and fever is in part due to the recommendation against using NSAIDs such as ibuprofen and aspirin, both of which are contraindicated after week 28 of pregnancy due to a potential impact on fetal kidney and heart development (https://www.gov.uk/drug-safety-update/non-steroidal-anti-inflammatory-drugs-nsaids-potential-risks-following-prolonged-use-after-20-weeks-of-pregnancy). Over 25% of pregnant women do, though, take NSAIDs during the first trimester[45]. Furthermore, pregnant women who use analgesics are frequently unaware of the potential for adverse side effects of this medication, with analgesics therefore often taken inappropriately[46]. One study demonstrated that, unless specifically prompted, many pregnant women did not consider mild analgesics as medications[43]. This suggests that analgesic usage during pregnancy may be widely under-reported. Observational studies suggest an association between analgesic consumption during pregnancy and genital malformations, increasing the risk of congenital cryptorchidism[47–49]. In turn, cryptorchidism is itself a risk factor for poor semen quality, testicular germ cell cancer, and early puberty onset[50]. This potential risk from analgesic consumption during pregnancy is supported by evidence from animal model work. Animal model studies show that paracetamol can directly perturb hormone-dependent processes and cause urogenital tract reproductive disorders: impacts on male offspring include impaired masculinization, anti-androgenic effects, aberrations in testicular function, and increased occurrence of abnormal sperm[51,52]. Similarly, animal studies reporting effects on ovary development include reduced oocyte number, early ovarian insufficiency, and a reduction in fertility (reviewed in refs. 53,54). In 2021, a worldwide group of scientists, clinicians, and public health professionals raised concerns over this matter, highlighting developmental effects associated with maternal and perinatal use of paracetamol, including reproductive and urogenital disorders[47]. Their Consensus Statement urged caution, recommending that pregnant women should be advised from the start of pregnancy to avoid paracetamol unless its use is medically indicated, and to minimize exposure by using the lowest effective dose for the shortest possible duration.

The best way forward

In some instances, treatment of pregnant women with pharmaceuticals is unavoidable. Clearly, it is best if this is kept to an absolute minimum, ideally, medications taken where required for the long-term health of the pregnant woman and/or of the child yet to be born, and with consideration as to whether specific pharmaceuticals could or should be avoided. For non-essential medications, caution is required: use of pharmaceuticals should be reduced or even omitted where possible and appropriate, with more care needed before labeling medications as safe to take during pregnancy.

Where pharmaceuticals are taken during pregnancy, more information is needed, not only regarding immediate impacts on fetal health, effects that would be apparent by or shortly after birth, but also about longer-term effects such as those on the reproductive systems (Fig. 2). More animal model studies are clearly required, as are studies using human tissue through experimental models such as in vitro or transplantation work. Alongside such research though, there is a pressing need for longitudinal studies to monitor individuals who were exposed to drugs prior to birth as a consequence of their mothers' treatments. One of the most comprehensive studies to date investigated long-term effects of chemotherapy exposure in utero, following up the children of women diagnosed with hematologic malignancies during pregnancy and with a median follow-up of nearly 20 years, although reproductive and fertility outcomes were not included in that follow-up[55]. There are also organizations such as the International Network on Cancer, Infertility and Pregnancy (INCIP: https://www.cancerinpregnancy.org/), with one fairly recent paper from that group finding that offspring of mothers treated with chemotherapy during their pregnancies showed no impairment of cognitive, cardiac, or general development in early childhood[15]. However, to date, most studies generally focus on measuring major malformations, early developmental milestones, cognitive functions, and physical health, with little mention of fertility issues. Overall, more long-term studies are key to providing parents and their offspring with information on both short- and long-term complications of drug treatments during pregnancy. Such investigations need to be more comprehensive in terms of outcomes followed, including examination as to whether or not reproductive health and/or fertility are affected. When considering consequences of fetal gonadal exposure, including the possibility of epigenetic modifications to germ cells and thus the potential for epigenetic transgenerational inheritance, it should be borne in mind that effects could not only be on the unborn child but on generations to come.

Data availability

No datasets were generated or analysed during the current study.

Received: 13 November 2024; Accepted: 6 March 2025;
Published online: 21 March 2025

References

1. Thompson, R. P. Examination of generational impacts of adolescent chemotherapy: Ifosfamide and potential for epigenetic transgenerational inheritance. *iScience* **25**, 105570 (2022).
2. Jazwiec, P. A. & Sloboda, D. M. Nutritional adversity, sex and reproduction: 30 years of DOHaD and what have we learned? *J. Endocrinol.* **242**, T51–T68 (2019).
3. Skakkebæk, N. E., Rajpert-De Meyts, E. & Main, K. M. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects: opinion. *Hum. Reprod.* **16**, 972–978 (2001).
4. Johansson, H. K. L., Svingen, T., Fowler, P. A., Vinggaard, A. M. & Boberg, J. Environmental influences on ovarian dysgenesis - developmental windows sensitive to chemical exposures. *Nat. Rev. Endocrinol.* **13**, 400–414 (2017).
5. Al Jishi, T. & Sergi, C. Current perspective of diethylstilbestrol (DES) exposure in mothers and offspring. *Reprod. Toxicol.* **71**,71–77 (2017).
6. Hartshorne, G. M., Lyrakou, S., Hamoda, H., Oloto, E. & Ghafari, F. Oogenesis and cell death in human prenatal ovaries: What are the criteria for oocyte selection? *Mol. Hum. Reprod.* **15**, 805–819 (2009).
7. Kerr, J. B., Myers, M. & Anderson, R. A. The dynamics of the primordial follicle reserve. *Reproduction* **146**, R205–215 (2013).
8. O'Shaughnessy, P. J. & Fowler, P. A. Development of the human fetal testis. *Ann. Endocrinol.* **75**, 48–53 (2014).
9. Allen, C. M., Lopes, F., Mitchell, R. T. & Spears, N. How does chemotherapy treatment damage the prepubertal testis? *Reproduction* **156**, R209–r233 (2018).
10. Sharpe, R. M. Androgens and the masculinization programming window: human–rodent differences. *Biochem. Soc. Trans.* **48**, 1725–1735 (2020).
11. Bookstaver, P. B. et al. A Review of Antibiotic Use in Pregnancy. *Pharmacotherapy* **35**, 1052–1062 (2015).
12. Benoit, L., Mir, O., Vialard, F. & Berveiller, P. Cancer during pregnancy: a review of preclinical and clinical transplacental transfer of anticancer agents. *Cancers* **13**, 1238 (2021).
13. Van Calsteren, K. & Amant, F. Chemotherapy during pregnancy: pharmacokinetics and impact on foetal neurological development. *Verh. K. Acad. Geneeskd. Belg.* **73**, 105–121 (2011).
14. de Haan, J. et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol.* **19**, 337–346 (2018).
15. Amant, F. et al. Pediatric outcome after maternal cancer diagnosed during pregnancy. *N. Engl. J. Med.* **373**, 1824–1834 (2015).
16. Griffiths, M. J., Winship, A. L. & Hutt, K. J. Do cancer therapies damage the uterus and compromise fertility? *Hum. Reprod. Update* **26**, 161–173 (2020).
17. Spears, N. et al. Ovarian damage from chemotherapy and current approaches to its protection. *Hum Reprod Update* **25**, 673–693 (2019).
18. Duffin, K. et al. Impacts of cancer therapy on male fertility: Past and present. *Mol. Asp. Med.* **100**, 101308 (2024).
19. Morgan, S., Anderson, R. A., Gourley, C., Wallace, W. H. & Spears, N. How do chemotherapeutic agents damage the ovary? *Hum. Reprod. Update* **18**, 525–535 (2012).
20. Rosario, R., Stewart, H. L., Spears, N., Telfer, E. E. & Anderson, R. A. Anti-Mullerian hormone attenuates both cyclophosphamide-induced damage and PI3K signalling activation, while rapamycin attenuates only PI3K signalling activation, in human ovarian cortex in vitro. *Hum. Reprod.* **39**, 382–392 (2024).
21. Comish, P. B. et al. Fetal cyclophosphamide exposure induces testicular cancer and reduced spermatogenesis and ovarian follicle numbers in mice. *PLoS One* **9**, e93311 (2014).
22. Stefansdottir, A. Etoposide damages female germ cells in the developing ovary. *BMC Cancer* **16**, 482 (2016).
23. Chaqour, J. et al. Effects of maternal taxane chemotherapy exposure on daughters' ovarian reserve and fertility potential. *F&S Science* **5**, 141–153 (2023).
24. Matilionyte, G. Maintenance of sertoli cell number and function in immature human testicular tissues exposed to platinum-based chemotherapy-implications for fertility restoration. *Front. Toxicol.* **4**, 825734 (2022).
25. Matilionyte, G., Rimmer, M. P., Spears, N., Anderson, R. A. & Mitchell, R. T. Cisplatin effects on the human fetal testis–establishing the sensitive period for (Pre) spermatogonial loss and relevance for fertility preservation in pre-pubertal boys. *Front. Endocrinol.* **13**, 914443 (2022).
26. Matilionyte, G. Granulocyte-colony stimulating factor does not prevent in vitro cisplatin-induced germ cell reduction in immature human and mouse testis. *BMC Cancer* **23**, 251 (2023).
27. Tharmalingam, M. D. Cisplatin and carboplatin result in similar gonadotoxicity in immature human testis with implications for fertility preservation in childhood cancer. *BMC Med.* **18**, 374 (2020).
28. Hall, R. W. & Gomes, W. R. Testosterone levels in the serum and testes of growing rats following prenatal exposure to busulphan. *J. Reprod. Fertil.* **35**, 131–134 (1973).
29. Chilaka, K. N. & Namoju, R. Maternal supplementation of alpha-lipoic acid ameliorates prenatal cytarabine-induced mutilation in reproductive development and function in F1 male adult rats. *Naunyn Schmiedebergs Arch. Pharmacol.* **397**, 4035–4053 (2024).
30. Veroniki, A. A. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Med.* **15**, 95 (2017).

31. Jentink, J. et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N. Engl. J. Med.* **362**, 2185–2193 (2010).
32. O'Donovan, C., Kusumakar, V., Graves, G. R. & Bird, D. C. Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder. *J. Clin. Psychiatry* **63**, 322–330 (2002).
33. Isojärvi, J. I. et al. On the association between valproate and polycystic ovary syndrome: a response and an alternative view. *Epilepsia* **42**, 305–310 (2001).
34. Hu, X. et al. A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy. *Epilepsy Res* **97**, 73–82 (2011).
35. Morrell, M. J. et al. Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. *Ann. Neurol.* **64**, 200–211 (2008).
36. Tallon, E., O'Donovan, L. & Delanty, N. Reversible male infertility with valproate use: a review of the literature. *Epilepsy Behav. Rep.* **16**, 100446 (2021).
37. Hamed, S. A. et al. Seminal fluid analysis and testicular volume in adults with epilepsy receiving valproate. *J. Clin. Neurosci.* **22**, 508–512 (2015).
38. Blotière, P. O. et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. *Neurology* **93**, e167–e180 (2019).
39. Lesné, L. et al. Antiepileptic drugs are endocrine disruptors for the human fetal testis ex vivo. *Toxicol. Sci.* **195**, 169–183 (2023).
40. Cui, D., Zhong, Y., Zhang, L. & Du, H. Bile acid levels and risk of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy: A meta-analysis. *J. Obstet. Gynaecol. Res.* **43**, 1411–1420 (2017).
41. Ovadia, C. et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. *Lancet Gastroenterol. Hepatol.* **6**, 547–558 (2021).
42. Werler, M. M., Mitchell, A. A., Hernandez-Diaz, S. & Honein, M. A. Use of over-the-counter medications during pregnancy. *Am. J. Obstet. Gynecol.* **193**, 771–777 (2005).
43. Kristensen, D. M., et al. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum. Reprod.* **26**, 235–244 (2011).
44. Snijder, C. A., et al. Intrauterine exposure to mild analgesics during pregnancy and the occurrence of cryptorchidism and hypospadia in the offspring: the Generation R Study. *Hum. Reprod.* **27**, 1191–1201 (2012).
45. Welham, S. J., Sparrow, A. J., Gardner, D. S. & Elmes, M. J. Acetylsalicylic acid interferes with embryonic kidney growth and development by a prostaglandin-independent mechanism. *World J. Nephrol.* **6**, 21–28 (2017).
46. Wilcox, C. M., Cryer, B. & Triadafilopoulos, G. Patterns of use and public perception of over-the-counter pain relievers: focus on nonsteroidal antiinflammatory drugs. *J. Rheumatol.* **32**, 2218–2224 (2005).
47. Bauer, A. Z., et al. Paracetamol use during pregnancy - a call for precautionary action. *Nat. Rev. Endocrinol.* **17**, 757–766 (2021).
48. Gurney, J., Richiardi, L., McGlynn, K. A., Signal, V. & Sarfati, D. Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis. *Hum. Reprod.* **32**, 1118–1129 (2017).
49. Gurney, JKet al. Risk factors for cryptorchidism. *Nat. Rev. Urol.* **14**, 534–548 (2017).
50. Boisen, K. A., et al. Hypospadias in a cohort of 1072 Danish newborn boys: prevalence and relationship to placental weight, anthropometrical measurements at birth, and reproductive hormone levels at three months of age. *J. Clin. Endocrinol. Metab.* **90**, 4041–4046 (2005).
51. Pereira, M. R. F., et al. Can maternal exposure to paracetamol impair reproductive parameters of male rat offspring? *Reprod. Toxicol.* **93**, 68–74 (2020).
52. Hurtado-Gonzalez, P., Effects of exposure to acetaminophen and ibuprofen on fetal germ cell development in both sexes in rodent and human using multiple experimental systems. *Environ. Health Perspect.* **126**, 047006 (2018).
53. Arendrup, F. S., Mazaud-Guittot, S., Jégou, B. & Kristensen, D. M.EDC IMPACT: Is exposure during pregnancy to acetaminophen/paracetamol disrupting female reproductive development? *Endocr. Connect.* **7**, 149–158 (2018).
54. Wu, K., Lu, W. & Yan, X Potential adverse actions of prenatal exposure of acetaminophen to offspring. *Front. Pharmacol.* **14**, 1094435 (2023).
55. Avilés, A. & Neri, N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin. Lymphoma* **2**, 173–177 (2001).

Author contributions

A.S. and N.S. both wrote the manuscript and read and approved the final version.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Agnes Stefansdottir or Norah Spears.

Reprints and permissions information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025