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Phthalate Syndrome: From Disrupted Fetal Steroidogenesis to Neurobehavioural Demasculinisation. A Narrative Review

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Abstract
Background: Phthalates are diesters of phthalic acid used widely as plasticisers in plastics, food-contact materials, medical devices and personal-care products. As non-persistent endocrine-disrupting chemicals (EDCs), they may interfere with fetal androgen biosynthesis during the masculinisation programming window (MPW; 8–14 weeks' gestation) and have been associated with disorders collectively termed "phthalate syndrome".
Aim: To synthesise current evidence on the proposed pathomechanistic axis linking maternal phthalate exposure with disrupted fetal steroidogenesis, the phenotype of testicular dysgenesis syndrome (TDS) and longer-term neurobehavioural and andrological consequences.
Material and methods: PubMed/MEDLINE, Scopus, Web of Science and Embase were searched for original studies, reviews, meta-analyses and biomonitoring reports published 2000–2025, using "phthalates", "endocrine-disrupting chemicals", "Leydig cell", "INSL3", "anogenital distance", "testicular dysgenesis", "masculinisation programming window", "neurodevelopment", "autism" and "ADHD".
Results: Reviewed evidence indicates that maternal monoester metabolites cross the placenta and may suppress steroidogenic transcripts (StAR, TSPO, CYP11A1, CYP17A1, 3β-HSD) and INSL3 in fetal Leydig cells. Several cohorts associate higher prenatal biomarkers with shortened anogenital distance and, less consistently, with cryptorchidism and hypospadias. Higher in utero exposure has further been linked with diminished male-typed play, autistic traits, ADHD symptomatology and compensated Leydig cell failure in adulthood.
Conclusions: Prenatal phthalate exposure plausibly perturbs androgenic programming along a continuum extending from the gonad to the developing brain. Preventive public-health and preconceptional risk-reduction measures appear warranted.

Keywords: phthalates; endocrine-disrupting chemicals; testicular dysgenesis syndrome; anogenital distance; neurobehavioural demasculinisation; DOHaD.

1. Introduction

1.1. Prevalence of endocrine-disrupting chemicals (EDCs): sources of phthalates in the environment, consumer products and routes of exposure in the general population

Over the past several decades, the growing recognition that synthetic chemicals can interfere with the homeostatic machinery of the vertebrate endocrine system has reshaped both environmental medicine and reproductive epidemiology. The Endocrine Society's second scientific statement defined endocrine-disrupting chemicals (EDCs) as exogenous chemicals, or mixtures of chemicals, that interfere with any aspect of hormone action and may, in this way, contribute to adverse health outcomes across the human life course [1]. Among the several hundred substances that currently meet this operational definition, phthalates — diesters of phthalic acid (1,2-benzenedicarboxylic acid) — occupy a particularly conspicuous position because of their enormous global

production volume, their integration into virtually every category of plastic-containing product and the resulting near-universal human exposure documented in worldwide biomonitoring surveys [2].

Phthalates are conventionally subdivided into low-molecular-weight (LMW) congeners — chiefly dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DBP) and diisobutyl phthalate (DiBP) — and high-molecular-weight (HMW) congeners, the most widely studied of which are di-(2-ethylhexyl) phthalate (DEHP), butylbenzyl phthalate (BBzP), diisononyl phthalate (DiNP) and diisodecyl phthalate (DiDP) [2,3]. The LMW compounds are characteristically used in personal-care products (perfumes, lotions, nail varnishes, hair sprays) and as solvents or enteric coatings for pharmaceutical preparations, whereas HMW phthalates are predominantly incorporated as plasticisers into flexible polyvinyl chloride (PVC) used in flooring, food packaging, medical tubing, blood-storage bags and children's toys [2,4]. Because phthalates are not covalently bound to the polymer matrix, they may leach gradually into food, indoor air, household dust and surfaces during ordinary product use, with the rate of migration tending to be accentuated by heat, mechanical stress and contact with lipophilic media [3,5].
The dietary route appears to be the dominant pathway of exposure for HMW congeners, with DEHP and its metabolites correlating particularly closely with the consumption of fatty foodstuffs that have been packaged in or processed using PVC materials [2,5]. Critical reviews of food contamination have documented that virtually all categories of staple foodstuffs — dairy, edible oils, meat, fish and ready-to-eat meals — may contain measurable phthalate concentrations, and that the transfer from packaging is especially marked at elevated temperatures and during prolonged storage [5]. Personal-care products and cosmetics, by contrast, appear to constitute the principal source of LMW phthalate exposure, with diethyl phthalate frequently detected in fragrances, deodorants, hair products and skin lotions; women of reproductive age, who tend to use a greater number of such products, may consequently sustain comparatively higher LMW phthalate burdens [6]. More recently, growing attention has been devoted to the inhalation pathway, since indoor environments — particularly those containing PVC flooring, vinyl wall coverings, electronic equipment and soft furnishings — appear to act as long-term reservoirs of semi-volatile phthalate diesters; measurable internal exposures have been documented in school-aged children attending classrooms with elevated dust loadings of DEHP and DiNP, with some indices of pulmonary and anthropometric function also showing associations with these exposures [7].

Human biomonitoring (HBM) programmes have therefore been pivotal in quantifying real-world exposure and in tracking temporal trends. The European HBM4EU initiative aggregated phthalate biomarker data from harmonised studies across multiple countries and confirmed that virtually all sampled children, adolescents and adults excreted detectable concentrations of mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP) and the oxidative metabolites of DEHP and DiNP [8]. Subsequent harmonised analyses of European populations between 2005 and 2021 documented a progressive decline in exposure to the regulated congeners (DEHP, DBP, BBzP), running in parallel with rising biomarkers of substitute plasticisers, including di(2-ethylhexyl) terephthalate (DEHTP) and di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH) [9,10]. An umbrella review of meta-analyses concerned with plastic-associated chemicals concluded that phthalate exposure is consistently associated, across study designs and populations, with adverse reproductive, metabolic and neurodevelopmental endpoints, lending considerable public-health weight to the experimental and epidemiological literature [11].

1.2. The concept of early fetal programming: foundations of the DOHaD hypothesis

The conceptual framework most often invoked to interpret the long-latency consequences of intra-uterine phthalate exposure is the Developmental Origins of Health and Disease (DOHaD) hypothesis. DOHaD postulates that the in-utero and early-postnatal environments may calibrate physiological set-points — in glucose homeostasis, in the hypothalamic–pituitary–gonadal (HPG) axis, in immune competence and in neuronal circuitry — in ways that can remain phenotypically silent for years or even decades before manifesting as overt disease in adulthood [12]. EDCs are intrinsically well-suited to operate through this mechanism because the developing fetus is exposed precisely during the windows in which endogenous endocrine signalling sculpts tissue architecture and function; even brief perturbations of the hormonal milieu during such intervals may be sufficient to imprint a permanent functional deviation [13]. Several recent narrative reviews summarising the prenatal effects of EDCs on offspring development have emphasised that phthalates, bisphenols and related compounds can modify chromatin accessibility, micro-RNA expression and DNA methylation patterns in fetal somatic tissues, thereby providing a plausible molecular basis for the delayed-onset phenotypes that characterise the DOHaD paradigm [14].

Population-level evidence supportive of the DOHaD model has been accumulated by large prospective cohorts such as the United States Environmental Influences on Child Health Outcomes (ECHO) consortium, which has

assembled hundreds of thousands of mother–child pairs and demonstrated that even low-level prenatal chemical exposures, including those to phthalate metabolites, may co-vary with downstream measures of growth, cognition, behaviour and immune function [15]. The placenta itself is increasingly understood not as a passive barrier but as an active endocrine organ whose biology may be perturbed by maternal phthalate burden, with potential downstream consequences for the fetal hormonal milieu and for tissue-specific programming [16]. The DOHaD perspective therefore makes the prenatal period — and most particularly the first and second trimesters — the natural focal point for any mechanistic enquiry into the origins of phthalate-related morbidity.

1.3. The critical masculinisation programming window (MPW)

Within the broader DOHaD framework, male reproductive development possesses one especially well-characterised vulnerability window: the so-called masculinisation programming window (MPW). Seminal studies in rodents have shown that fetal exposure of male offspring to anti-androgens between embryonic days 15.5 and 18.5 — i.e., during a discrete interval immediately following testis differentiation — is sufficient to programme a constellation of reproductive disorders (cryptorchidism, hypospadias, reduced anogenital distance, subnormal Sertoli cell number, low sperm count in adulthood) that would not be induced by identical exposures occurring either before or after the window [17]. Extrapolation from animal models, from ultrasound studies of fetal genital development and from morphometric measurements of human abortuses has provisionally located the human MPW between approximately the 8th and the 14th week of gestation, coinciding with the emergence of male–female differences in anogenital distance (AGD) [17,18].

The fundamental physiological event of the MPW is the surge of androgen production by fetal Leydig cells, which provides the substrate for both testosterone-mediated and 5α-dihydrotestosterone-mediated masculinisation of the Wolffian ducts, urogenital sinus, external genitalia and central nervous system. Importantly, although the upstream control of fetal androgen production differs between rodents (where it is paracrine-regulated) and humans (where it is driven largely by placental human chorionic gonadotrophin acting on the LH receptor), the downstream tissue-level dependence on adequate androgen exposure during the window appears to be highly conserved across species [17]. AGD — the distance from the anus to the genital tubercle — has consequently emerged as a calibrated, lifelong anatomical readout of intra-MPW androgen action and is increasingly used in epidemiological studies as a non-invasive surrogate marker for fetal androgenisation [18]. Because the MPW falls largely within the first trimester — the period during which many women may not yet recognise their pregnancy, and during which placental protection of the conceptus is least developed — this interval represents both the most biologically relevant and the most pragmatically challenging window in which to characterise exposure–outcome relationships [19].

1.4. Aim of the review

Against the background outlined above, the aim of the present narrative review is to assemble and to systematise the evidence that has accumulated over the past two decades regarding the proposed pathomechanistic axis of "phthalate syndrome" in humans. The work is organised around a single, vertically integrated chain of reasoning that proceeds: from the cellular-level interference of phthalate monoesters with fetal steroidogenesis; through the anatomical phenotype of testicular dysgenesis syndrome (cryptorchidism, hypospadias, shortened AGD); to the more subtle neurobiological signature of brain demasculinisation manifested as altered sex-typed behaviour, atypical neurodevelopmental trajectories and changes in the dimorphic central nervous system; and finally to the long-term andrological and psychosexual consequences observable in adolescence and adulthood. The intention is not to provide a quantitative meta-analytic appraisal — several recent meta-analyses already exist for specific endpoints — but rather to offer an integrative mechanistic narrative that situates molecular, anatomical, behavioural and clinical observations within a single explanatory framework and that may inform clinical practice, public-health policy and the design of future research.

2. Methodology of the review

2.1. Inclusion and exclusion criteria

The present work was conceived and written as a narrative review rather than as a systematic review or meta-analysis, with the explicit intention of offering an integrative, mechanism-oriented synthesis of a literature that is methodologically heterogeneous and that is currently developing at distinctly different paces across its experimental, epidemiological and clinical components. A purely systematic approach, focused on a single PICO-style research question, would have been ill-suited to the bridging task required here, namely the assembly

of evidence linking molecular events in the fetal Leydig cell with anatomical phenotypes in the newborn boy and with neurobehavioural and andrological trajectories observable years or decades later.
Studies were considered eligible for inclusion when they (i) addressed at least one element of the proposed pathomechanistic axis linking maternal phthalate exposure with fetal steroidogenesis, with the testicular dysgenesis syndrome (TDS) phenotype, with neurobehavioural outcomes in childhood and adolescence, or with adult andrological and psychosexual function; (ii) reported original quantitative data — whether derived from in vitro models (cell lines, primary cultures, fetal testis explants, xenograft systems), in vivo rodent or non-human-primate experiments, human biomonitoring cohorts, observational epidemiological studies, randomised or quasi-randomised trials, or post-mortem and clinical case series; (iii) were peer-reviewed or, in the case of reviews and meta-analyses, were published in indexed scientific journals or as official reports of recognised public-health agencies and consortia; and (iv) were available in English in their full-text form. Earlier publications considered to be of historical or conceptual relevance — for instance the original formulations of the TDS hypothesis and the seminal masculinisation programming window (MPW) experiments in rats — were retained even when they preceded the principal time frame of the search.

Conference abstracts without subsequent full-text publication, opinion editorials lacking primary data, retracted articles, and reports in languages other than English were excluded. Studies whose outcome measures were not interpretable in relation to androgenic programming (for example, those focused exclusively on hepatic or renal toxicity unrelated to steroidogenesis) were excluded unless they provided mechanistic information complementary to the reproductive-developmental axis. Studies that used adverse-outcome-pathway (AOP) frameworks were specifically retained, since such approaches have been recommended for the integrative evaluation of EDC-related toxicological endpoints and the validation of biomarkers of effect for phthalate-induced reproductive toxicity [20]. Likewise, reports employing chemical-category and read-across methodology to group structurally related phthalate diesters were considered relevant when they informed the interpretation of mixture exposures or cross-congener extrapolations [21].

2.2. Databases and search terms

A comprehensive electronic search was carried out in the PubMed/MEDLINE, Scopus, Web of Science and Embase databases, supplemented by hand-searching of the reference lists of identified reviews and meta-analyses and by inspection of consortium and project reports from the European HBM4EU initiative, the United States Environmental Influences on Child Health Outcomes (ECHO) programme, the National Health and Nutrition Examination Survey (NHANES) and the U.S. National Toxicology Program. The principal time window of interest spanned January 2000 to December 2025, although seminal earlier publications were retrieved when cited in the more recent literature or when they provided foundational data on rodent reproductive toxicology, steroidogenesis or brain sexual differentiation that have not since been superseded.

Search syntax was constructed by combining controlled vocabulary and free-text terms across three logical domains. The exposure domain included the terms "phthalate", "phthalates", "DEHP", "MEHP", "DBP", "MBP", "DiNP", "DEP", "DiBP", "BBzP", "endocrine-disrupting chemical*", "EDC*" and "plasticis*". The developmental-window domain included "masculinisation programming window", "MPW", "first trimester", "prenatal", "in utero", "maternal exposure", "placenta" and "DOHaD". The outcome domain encompassed "testicular dysgenesis", "Leydig cell", "INSL3", "steroidogenesis", "StAR", "TSPO", "CYP11A1", "CYP17A1", "3β-HSD", "PPAR", "anogenital distance", "AGD", "cryptorchidism", "hypospadias", "spermatogenesis", "sex-typed play", "neurodevelopment", "autism spectrum disorder", "ADHD", "intelligence", "IQ" and "sexual differentiation of the brain". Within each domain the terms were combined with the OR operator, and the three domains were then combined with AND. Medical Subject Headings (MeSH) were used wherever the relevant database permitted, and the search was iteratively refined as further relevant terms emerged from the early body of retrieved literature.

Where multiple publications from the same research group overlapped substantially in their study population, sample frame or experimental design, the most recent and methodologically complete report was retained as the primary citation, while earlier work was acknowledged when it added complementary mechanistic or temporal information. The retrieved literature was organised around the manuscript's pathomechanistic chain (steroidogenesis → anatomical TDS phenotype → neurobehavioural demasculinisation → adult andrological outcomes), so that each piece of evidence could be located within the most biologically informative section of the narrative rather than being grouped purely by publication date or by study design.

3. Pharmacokinetics within the maternal–fetal compartment

3.1. Maternal metabolism: from biologically inert parent diesters to the reactive monoesters

The toxicological behaviour of phthalates is, paradoxically, governed less by the parent diesters than by the products of their metabolism in the maternal organism. The parent compound — for example DEHP, DBP or BBzP — is itself only weakly reactive at intracellular targets relevant to fetal endocrine programming, and its biological potency is largely acquired during first-pass intestinal and hepatic biotransformation in the pregnant woman [2,3]. After oral ingestion, which represents the dominant route of exposure for the higher-molecular-weight (HMW) congeners, parent diesters reach the duodenum and proximal jejunum in essentially unmodified form, where they encounter a population of non-specific carboxylesterases and pancreatic lipases that catalyse the rapid hydrolysis of one of the two ester bonds, releasing the corresponding bioactive monoester together with a free alcohol moiety [22]. The intestinal mucosa, salivary glands and hepatocytes all contribute to this first hydrolytic step, and the resulting monoester species — MEHP from DEHP, MBP (mono-n-butyl phthalate) from DBP, MEP from DEP, MBzP from BBzP, MiBP from DiBP — are the molecular entities measured in human urine and considered relevant for risk assessment [22].

For low-molecular-weight (LMW) phthalates such as DMP, DEP, DBP and DiBP, this single hydrolytic step accounts for the bulk of biotransformation, and the resulting monoesters are subsequently glucuronidated by hepatic UDP-glucuronosyltransferases and excreted predominantly in urine within hours [2,22]. For HMW phthalates — most importantly DEHP — the metabolic profile is considerably more complex. The initial gastrointestinal hydrolysis yields MEHP, which is then subject to sequential cytochrome P450-mediated oxidation of the 2-ethylhexyl side chain, predominantly through ω-1 and ω-oxidation, generating mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP, also denoted 5OH-MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP, 5oxo-MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP, 5cx-MEPP) [2,22]. These oxidative species typically exceed urinary MEHP concentrations by approximately four- to eight-fold and remain quantifiable for somewhat longer, in part because their increased hydrophilicity favours renal clearance over reabsorption [22]. Early epidemiological reliance on MEHP alone may therefore have substantially underestimated population DEHP burden, and contemporary biomonitoring programmes now routinely measure the secondary oxidative metabolites in parallel as the more sensitive and stable indicators of recent exposure [22].

The pharmacokinetic timescale of these processes is short relative to gestation. The biological half-life of DEHP itself, in the adult human compartment, has been estimated at approximately two hours, and within roughly 44 hours of an oral dose approximately half of the administered amount is recovered in urine in the form of MEHP, MEHHP and MEOHP, with the remainder presumed to be eliminated via the faecal route or sequestered, transiently, in lipid-rich tissue [23]. Similar rapid kinetics apply, with congener-specific differences, to the other phthalate diesters. Several physiological adaptations of pregnancy may further modify maternal kinetics, including the marked rise in cardiac output and hepatic blood flow, the gestational increase in glomerular filtration rate and the trimester-dependent changes in activity of CYP isoforms and UDP-glucuronosyltransferases that govern phthalate biotransformation; collectively these may amplify the dose of monoester delivered to the fetal compartment per unit of maternal intake [4]. From the analytical standpoint, the determination of phthalate metabolites in maternal biological matrices — whether by liquid chromatography–tandem mass spectrometry (LC-MS/MS) or by gas chromatography–mass spectrometry (GC-MS) — has matured considerably, and contemporary protocols permit reliable detection at sub-nanogram-per-millilitre levels. Methodological advances now allow direct gas-chromatographic separation of monoester metabolites without the derivatisation step previously needed for these polar and thermally labile species, which simplifies sample preparation, reduces toxic waste and may diminish the introduction of analytical artefacts [24].

A particular methodological caveat must, nevertheless, be acknowledged when interpreting pharmacokinetic data drawn from observational cohorts. Because the urinary half-life of phthalate metabolites is on the order of hours, a single spot urine sample obtained at one antenatal visit captures only a brief window of exposure and may systematically misclassify the time-integrated dose received during the biologically most sensitive period of pregnancy. Pooling of multiple urine collections across trimesters provides a more reliable exposure metric, and statistical standardisation methods that adjust for the hour of sampling, hydration status (creatinine concentration or specific gravity), pre-analytical storage time, and other sampling covariates have been developed; the application of such two-step residual-based standardisation to pregnancy cohorts has been shown to modify median metabolite concentrations by between −38% (for 2,5-dichlorophenol) and +80% (for a metabolite of

diisodecyl phthalate), while preserving the within-person ordering of exposure values [25]. The practical implication is that the biomarker-to-outcome associations reported in the published literature must be considered conservative estimates of the underlying biological signal, since random exposure misclassification, where present, biases effect estimates towards the null.

3.2. Crossing the placental barrier: transfer of metabolites and accumulation in amniotic fluid and umbilical cord blood

Phthalate diesters and, more importantly, their monoester and oxidative metabolites readily traverse the human placenta. Detection of MEHP, MBP, MBzP and the oxidative DEHP metabolites in amniotic fluid, in umbilical cord blood, in meconium and within placental tissue itself confirms that the maternofetal interface offers, at best, only partial protection against this class of compounds [23]. Phthalates have additionally been measured in maternal serum, semen, ovarian follicular fluid, breast milk and saliva, demonstrating that essentially all human biological compartments equilibrate, to a greater or lesser extent, with ambient exposure [23]. The physico-chemical properties of phthalates — moderate lipophilicity, comparatively low molecular weight in the case of the monoesters, and only partial plasma protein binding — are broadly compatible with passive diffusion across the syncytiotrophoblast, although facilitated transport via fatty-acid carriers and active uptake mechanisms cannot be definitively excluded [26]. DEHP and MEHP have been documented in fetal compartments at concentrations that correlate with maternal exposure indices, although absolute fetal levels are usually lower than maternal urinary metabolite concentrations, suggesting partial fetal clearance and progressive maternal-side equilibration over the course of pregnancy [26].

The contemporary view of the placenta departs decisively from the historical conception of a passive molecular sieve. The placenta is now recognised as a transient yet metabolically and endocrinologically active organ whose syncytiotrophoblast (STB), extravillous trophoblast (EVT) and cytotrophoblast (CTB) populations express CYP19A1 (aromatase), HSD17B1, the cholesterol side-chain cleavage enzyme CYP11A1, chorionic gonadotrophin α (CGA), the peroxisome proliferator-activated receptors PPARα and PPARγ, fatty-acid transport proteins (FATP1, FATP4), the thyroid-hormone carrier transthyretin (TTR) and several other transcripts whose expression appears to be modifiable by maternal phthalate exposure [23,27]. In urban birth cohort data from New York City, maternal urinary mono-n-butyl phthalate, mono-iso-butyl phthalate and mono-benzyl phthalate concentrations were associated with statistically significant changes in placental mRNA levels of CGA, CYP19A1, CYP11A1 and PPARG, and the direction of the association frequently differed between male and female placentas — for example, MnBP was associated with reduced CGA expression in male placentas and with slightly increased expression in female placentas (interaction $p \approx 0.01$) [28]. Such sex-specific placental responses to maternal phthalate exposure may, at least in part, mediate the sexual dimorphism of the downstream offspring phenotypes that constitute the phthalate syndrome, since the placenta itself is fetal in origin and shares the sex-chromosome complement of the conceptus [28].

In parallel with these molecular endpoints, structural and vascular outcomes have been characterised. A systematic review of 35 animal and human studies concluded that phthalate exposure is associated with detectable changes in placental morphology, cell composition, vascularisation, hormone production and histopathology, with the most reproducible findings concerning trophoblast invasion, spiral-artery remodelling and the syncytialisation process [27]. In vitro investigations using human trophoblast cell lines (BeWo, JEG-3, HTR-8/SVneo) and primary villous explants have additionally shown that MEHP, at concentrations within the range estimated for first-trimester exposures, may impair trophoblast differentiation, invasion and angiogenesis. MEHP at sub-micromolar concentrations has been reported to inhibit extravillous trophoblast invasion by suppressing matrix metalloproteinase-9 (MMP-9) and up-regulating its inhibitor TIMP1 through a PPARγ-dependent mechanism, to reduce hCG-β release from villous cytotrophoblasts with an apparently U-shaped (non-monotonic) dose–response, and to increase the production of reactive oxygen species, the expression of oxidative-stress responsive micro-RNAs (miR-17-5p, miR-155-5p, miR-126-3p) and the activity of apoptotic caspases [26]. DEHP and MEHP have also been shown to disrupt placental steroidogenesis through alterations in StAR and CYP11A1 transcription and to reduce intracellular thyroid hormone transport by suppressing transthyretin and downregulating DIO2 while up-regulating DIO3, all of which may translate into adverse trajectories of placental angiogenesis and fetal growth [26].

Epigenetic modifications represent a further mechanism by which phthalates may leave a persistent imprint on placental biology. In human cohort data, maternal urinary concentrations of DEHP metabolites have been associated with reductions in placental LINE-1 methylation, with altered methylation and allele-specific expression of the imprinted genes H19 and IGF2 (particularly in male newborns), with modified placental micro-RNA profiles (including the placenta-specific C19MC cluster member miR-518e) and with the expression of

multiple long non-coding RNAs — all changes that have themselves been linked, in other settings, to fetal growth restriction, preeclampsia and adverse neurodevelopment [23]. Such observations are biologically meaningful for several reasons that bear directly on the masculinisation programming window. First, placental disruption may compromise the supply of androgenic substrate generated by the placenta through the so-called "backdoor" steroidogenic pathway, a route that contributes appreciably to fetal androgen exposure in primates. Second, the documented suppression of placental hCG production may diminish the principal trophic signal that drives fetal Leydig cell testosterone secretion during the MPW, given that the human fetal testis depends on hCG/LH-receptor signalling rather than on the paracrine control that operates in rodents. Third, the placental perturbations elicited by phthalate exposure may contribute directly to obstetric outcomes — including intrauterine growth restriction, preeclampsia and preterm birth — that have themselves been associated, in observational studies of pregnant women, with elevated maternal phthalate metabolite concentrations [23,29].

The placenta, in short, is neither a passive nor an innocent participant in the phthalate-syndrome cascade: it is itself a target organ, an endocrine relay and a partial determinant of how much of the maternal exposure ultimately reaches the fetal endocrine and nervous tissues.

4. Molecular pathomechanism: disruption of fetal steroidogenesis

4.1. PPAR receptors and intracellular signalling pathways

The molecular cascade through which phthalates appear to compromise fetal androgen production has been the focus of intensive investigation over the past two decades, and a coherent — if still incomplete — picture has progressively emerged. An important observation, established early in the field and consistently replicated, is that neither the parent diesters nor their monoester metabolites function as direct androgen receptor (AR) antagonists at physiologically relevant concentrations. Transcriptional activation assays employing human or rodent AR have failed to demonstrate appreciable binding of DEHP, DBP, MEHP or MBP at concentrations up to 10 μM, distinguishing phthalates mechanistically from the prototypical AR antagonists such as flutamide or vinclozolin [30]. Phthalates therefore appear to operate through a more proximal mechanism — namely the disruption of androgen biosynthesis itself within the fetal Leydig cell — rather than through direct interference with downstream androgen signalling [31].

One of the most extensively explored upstream targets is the family of peroxisome proliferator-activated receptors (PPARs), ligand-activated nuclear transcription factors that belong, together with the steroid and thyroid hormone receptors, to the nuclear receptor superfamily. The PPAR family comprises three isoforms — PPARα, PPARβ/δ and PPARγ — each encoded by a separate gene and displaying a distinct tissue distribution; PPARα is predominantly expressed in the liver, PPARγ predominantly in adipose tissue, and PPARβ/δ more broadly across tissues [32]. Both PPARα and PPARγ have been detected in the fetal testis, with PPARα and PPARβ expressed in Leydig cells and seminiferous tubule cells (Sertoli and germ cells), while PPARγ appears predominantly in Sertoli cells with weaker expression elsewhere [32]. Crucially, the monoester metabolites of phthalates — most notably MEHP, mono-benzyl phthalate (MBzP) and mono-sec-butyl phthalate (MBuP) — are amphipathic carboxylates whose chemical structure broadly resembles long-chain saturated and unsaturated fatty acids, the endogenous ligands of the PPARs, and they have been shown to activate both human and rodent PPARα and PPARγ in transactivation assays; the parent diesters themselves are appreciably less potent, and the metabolic conversion to the monoester is therefore a prerequisite for receptor activation [32].

A coherent molecular model has accordingly emerged in which monoester phthalates suppress the expression of NR5A1 (steroidogenic factor 1, SF1)-regulated steroidogenic genes through an indirect, PPAR-mediated mechanism. Studies of DBP-exposed fetal rat testis have shown that the binding of NR5A1 to the promoters and introns of its target genes — including *Cyp11a1*, *Cyp17a1* and *Star* — is reduced in parallel with increased binding of PPARα to neighbouring regulatory elements, suggesting that PPARα may indirectly compete with NR5A1 for the common transcriptional co-activator CREB-binding protein (CBP), whose intracellular availability is limiting [31]. Notably, the binding of NR5A1 to the *Fshr* promoter is unaffected, and *Fshr* transcript levels are correspondingly preserved, consistent with the observation that phthalate exposure does not perturb FSH signalling in the same way it does the steroidogenic pathway [31]. Parallel evidence nevertheless suggests that PPARα may not be strictly required: PPARα-knockout mice still develop testicular and developmental toxicity after intrauterine DEHP exposure, and other isoforms — PPARβ and PPARγ — together with non-receptor-mediated mechanisms may also be involved [32]. Additional intracellular pathways implicated in the phthalate response include the aryl hydrocarbon receptor (AhR), whose downstream gene *Cyp1b1* is upregulated in phthalate-exposed fetal testis [33], and the gap-junctional connexin 43 (CX43), encoded by *Gja1*, whose marked down-regulation in fetal Leydig cells of DEHP-exposed rats may further

uncouple Leydig-to-Leydig cell communication and thereby distort the coordinated regulation of steroidogenic activity within the interstitial compartment [34]. Several lines of evidence further suggest that phthalates may interfere with the function of fetal Sertoli cells — which secrete the paracrine factors that drive Leydig cell differentiation — thereby setting up a complex network of indirect effects on overall fetal androgen output [35,36].

4.2. Effects on cholesterol transport: suppression of StAR and TSPO

Steroidogenesis depends on a continuous supply of cholesterol to the inner mitochondrial membrane, where it is converted to pregnenolone by cytochrome P450 side-chain cleavage enzyme (CYP11A1). This rate-limiting cholesterol-transport step is mediated principally by the steroidogenic acute regulatory protein (StAR), with additional involvement of the outer-mitochondrial-membrane translocator protein TSPO (formerly known as the peripheral benzodiazepine receptor) and the scavenger receptor class B type 1 (SR-B1, encoded by *Scarb1*), which mediates the selective uptake of cholesteryl esters from circulating high-density lipoproteins [32]. Within fetal Leydig cells exposed to phthalates, all three transporters appear vulnerable to suppression. Studies of intrauterine DEHP exposure in rats have reported a dose-dependent down-regulation of *Lhcgr*, *Scarb1*, *Star*, *Cyp11a1* and *Insl3* at both the transcript and the protein level, with similar findings for DPrP, DCHP, DBP, DiBP, DPP and DINP — i.e., for the entire class of phthalates whose alkyl side chains contain between three and nine carbon atoms [31]. Phthalates with one or two carbons (DMP, DEP) and those with ten or more (such as dioctyl terephthalate) appear to be inactive in this regard, a striking structure–activity relationship that mirrors the spectrum of PPAR activation and reproductive toxicity reported for the class [31].

The functional consequence of StAR suppression is a relative depletion of intramitochondrial cholesterol substrate available for the first enzymatic step of steroidogenesis, irrespective of whether the downstream enzymes are themselves directly inhibited. The convergence of reduced cholesterol uptake (via SR-B1 down-regulation), reduced intramitochondrial cholesterol delivery (via StAR and TSPO down-regulation) and reduced enzymatic processing capacity creates a multi-level bottleneck on testosterone biosynthesis [33]. Reviews of the fetal Leydig cell response to phthalates have consistently identified the cholesterol-transport step as one of the earliest and most reproducible targets, and the effect appears to be cumulative when several phthalates are administered together, with mixture studies in pregnant rats demonstrating dose-additive suppression of fetal testis testosterone even when individual congeners are present below their own no-effect levels [32,36]. Independent reviews of phthalate effects on reproductive processes have similarly emphasised the disruption of cholesterol handling and StAR expression as a unifying mechanistic feature across structurally diverse diesters [37].

4.3. Direct enzymatic inhibition: down-regulation of CYP11A1, CYP17A1 and 3β-HSD in fetal Leydig cells

Beyond the perturbation of cholesterol supply, phthalates appear to suppress the expression and/or activity of the cytochromes P450 and short-chain dehydrogenases that catalyse successive steps of testosterone biosynthesis. The two principal microsomal cytochromes involved — CYP11A1, the cholesterol side-chain cleavage enzyme that converts cholesterol to pregnenolone, and CYP17A1, the 17α-hydroxylase/17,20-lyase that converts pregnenolone or progesterone into androstenedione precursors — are consistently down-regulated at the mRNA level in fetal rat testis after maternal exposure to DEHP, DBP or their monoester metabolites. The magnitude of suppression follows a clear dose–response relationship and is detectable at exposure levels approaching, although generally above, those experienced by the general human population [31]. 3β-hydroxysteroid dehydrogenase type 1 (HSD3B1), which catalyses the conversion of pregnenolone to progesterone and of dehydroepiandrosterone to androstenedione, is similarly affected; the parallel suppression of HSD3B1, CYP11A1 and CYP17A1 effectively closes off both the Δ4 and the Δ5 pathways of fetal Leydig cell steroidogenesis [32,33].

Immunohistochemical and immunofluorescence studies of DEHP-exposed fetal rat testis at gestational day 21 have provided striking confirmation of these molecular findings at the protein level. After perinatal maternal DEHP exposure (300–900 mg/kg/day) in Wistar rats, CYP11A1 staining within fetal Leydig cells was markedly reduced and HSD3β staining marginally weaker, whereas the peritubular myoid cell marker SMA was unchanged, indicating relative specificity for the Leydig cell compartment [34]. Importantly, the same studies revealed an almost complete loss of the gap-junction protein CX43 within fetal Leydig cells after DEHP exposure, suggesting that the down-regulation of steroidogenic enzymes occurs alongside an uncoupling of Leydig-to-Leydig cell communication — a configuration that may amplify the functional impact of the enzymatic deficits, since CX43 itself contributes to coordinated steroidogenic output [34]. Studies of DBP at

gavage doses of 50–500 mg/kg/day administered from gestational day 12.5 to 21.5 have similarly documented parallel reductions in anogenital distance, histological testicular damage, apoptosis of seminiferous tubule cells, and dysregulation of proliferation- and apoptosis-related proteins (Rasd1, MEK1/2, Bcl-2/Bax ratio), suggesting that DBP-induced testicular dysgenesis involves a programme of impaired steroidogenesis combined with disrupted cell-fate decisions in the developing tubular compartment [38]. The experimental literature is consistent in its identification of a no-observed-adverse-effect-level (NOAEL) for DBP in the rat at approximately 50 mg/kg/day, with reproductive tract effects appearing reproducibly at 100 mg/kg/day and above [30].
Mixture studies add an important translational dimension to this picture. Where several phthalates with similar mechanisms of action have been administered together to pregnant rats, the suppression of fetal testosterone production and of the corresponding steroidogenic transcripts has been shown to be dose-additive — that is, the effects of individual compounds at sub-threshold doses may sum to a biologically meaningful suppression of fetal androgen output [31,37]. This observation has particular relevance for human exposure scenarios, given that pregnant women are typically exposed to several phthalates simultaneously rather than to any single congener in isolation, and given that biomonitoring data routinely detect five or more metabolites in essentially every sample examined.

4.4. Disruption of endocrine function: suppressed INSL3 secretion and impaired testicular descent

Although the dominant biochemical readout of fetal Leydig cell function is testosterone, the same cells are simultaneously the source of insulin-like peptide 3 (INSL3), a small heterodimeric peptide hormone of the relaxin family that is essential for the first, transabdominal phase of testicular descent. INSL3 is secreted constitutively by fetal Leydig cells under the transcriptional control of NR5A1 (SF1), through three functional SF1-responsive elements (SFREs) within its upstream promoter region; its expression in the human fetal testis begins immediately after gonadal sex determination at 7–8 weeks post-coitum, becomes detectable in amniotic fluid one to two weeks later and reaches a maximum at gestational weeks 12–16, i.e., within the MPW [39].

INSL3 acts through a unique G-protein-coupled receptor, RXFP2 (RelaXin-like Family Peptide receptor 2), expressed on the mesenchymal cells of the gubernacular ligament that anchors the fetal testis to the inguinal wall. The binding of INSL3 to RXFP2 induces a thickening of the gubernacular bulb, which retains the fetal testis in the inguinal region as the kidney and adrenal grow antero-dorsally — the so-called transabdominal phase of testicular descent — and this is later followed by an androgen-dependent inguinoscrotal phase in which the testis traverses the inguinal canal into the scrotum [39]. Genetic inactivation of either *Insl3* or *Rxfp2* in mice reproducibly produces bilateral cryptorchidism with failure of the first phase of descent, and pharmacological blockade of RXFP2 in pregnant rats reproduces the same phenotype; in humans, heterozygous mutations in either *INSL3* or *RXFP2* have been associated with an elevated population-level risk of (usually unilateral) cryptorchidism [39].

A substantial body of rodent experimental evidence has shown that maternal exposure to DEHP, DBP and other active phthalates may produce a dose-dependent reduction in fetal testis *Insl3* mRNA and INSL3 protein expression, paralleling the suppression of testosterone biosynthesis and the down-regulation of *Lhcgr*, *Scarb1*, *Star*, *Cyp11a1* and *Cyp17a1* [31]. Immunohistochemical studies of gestational day 17.5 fetal rat testis after maternal DBP exposure during embryonic days 12–16 have visualised this effect directly, with markedly attenuated INSL3 staining in the Leydig cells of exposed males relative to vehicle controls [39]. The structure–activity relationship for INSL3 suppression broadly mirrors that for testosterone suppression, with phthalates of three to nine alkyl carbons being active and those of one to two or of ten or more carbons being largely inactive [31].

Critically, human translational data have begun to corroborate the rodent observations. Measurements of INSL3 in amniotic fluid sampled at routine amniocentesis during gestational weeks 12–16 in a large Danish biobank have shown that INSL3 concentration — a population-level marker of fetal Leydig cell functional capacity that is undetectable in female fetuses — is reduced in proportion to the maternal phthalate metabolite load [39]. Comparable inverse correlations between phthalate biomarkers and INSL3 have been reported in umbilical cord blood at term, and a Danish case–control study has further documented that cord blood INSL3 is significantly lower in boys born with idiopathic cryptorchidism than in healthy controls [39]. A recent systematic review of early-life phthalate exposure and Leydig cell function in human male offspring has similarly reported a tendency towards reduced INSL3, alongside elevated LH and a reduced testosterone/LH ratio, suggestive of a compensated state of partial Leydig cell failure [40]. Together, the molecular, biochemical, anatomical and translational findings converge on a coherent picture: phthalate exposure during the MPW appears to disrupt fetal Leydig cell differentiation rather than merely modulating its acute output, and the resulting deficit in INSL3

secretion provides a plausible mechanistic bridge from the cellular events outlined in sections 4.1–4.3 to the anatomical manifestation of cryptorchidism considered in the next section [41,42].

5. Anatomical manifestation: the congenital testicular dysgenesis syndrome (TDS)

The molecular and biochemical events outlined in the previous section converge, at the level of the whole organism, on a recognisable clinical syndrome that has come to be referred to as the testicular dysgenesis syndrome (TDS). First articulated by Skakkebæk and colleagues in 2001 and progressively refined over the subsequent two decades, the TDS hypothesis proposes that cryptorchidism, hypospadias, reduced anogenital distance, low sperm counts in adulthood and testicular germ-cell carcinoma are not independent disorders but rather inter-related downstream manifestations of a common fetal-origin event — namely, suboptimal androgen exposure during the masculinisation programming window (MPW) [19]. In the specific context of in-utero phthalate exposure, three components of the syndrome that may be observable at or shortly after birth — cryptorchidism, hypospadias and shortened anogenital distance — are particularly informative for epidemiological enquiry, since they can be detected by standard neonatal examination and do not require the decades-long latency of low sperm count or testicular germ-cell cancer [17,19]. They are considered, in turn, in the following subsections.

5.1. Cryptorchidism: failure of testicular descent

Cryptorchidism, or undescended testis, is one of the most common urogenital anomalies in newborn boys, with a prospective clinical incidence reported between 1% and 8% in cohorts using standardised diagnostic criteria, and with a documented secular increase in some Northern European countries since the 1950s that has prompted speculation about an environmental contribution [43]. The condition reflects the failure of one or both fetal testes to complete the two-phase descent from a perirenal position into the scrotum. The first, transabdominal phase is driven principally by INSL3 secretion by fetal Leydig cells, which thickens the gubernacular bulb and retains the testis in the inguinal region while the kidney and adrenal grow antero-dorsally; the second, inguinoscrotal phase is largely androgen-dependent, requiring testosterone-mediated regression of the cranial suspensory ligament, calcitonin-gene-related peptide (CGRP) signalling from the genitofemoral nerve and adequate androgen-driven gubernacular migration through the inguinal canal into the scrotum [43]. Phthalate exposure during the MPW is therefore positioned to disrupt both phases simultaneously, since the same fetal Leydig cells are the source of both INSL3 and testosterone, and the suppression of either signal may translate into delayed or failed descent [17,39].

Rodent studies have consistently demonstrated that high-dose maternal exposure to DBP, DEHP or BBzP during the period of male reproductive tract development produces cryptorchidism in male offspring, often in combination with gubernacular hypoplasia or absence and with persistence of the cranial suspensory ligament — an anatomical configuration that broadly mirrors the histology of human cryptorchidism associated with INSL3 or RXFP2 mutations [43]. Translational evidence in humans is more nuanced. A 2024 systematic review and meta-analysis of 48 studies examining maternal endocrine-disruptor exposure during pregnancy and the incidence of male urogenital defects reported a pooled adjusted odds ratio for cryptorchidism of 1.37 (95% CI 1.19–1.57; $p < 0.001$) across all examined EDC classes, with significant subgroup associations for pesticides and PCBs; the specific subgroup for phthalates did not, however, reach conventional statistical significance for cryptorchidism in that analysis [44]. A complementary 2022 systematic review and meta-analysis focused exclusively on maternal phthalate exposure during pregnancy reported that exposure to DEHP and DiDP was associated with an elevated risk of cryptorchidism, although the authors emphasised that the modest number of available studies and the limited statistical power meant that their conclusions should be interpreted cautiously [45]. Several individual case–control studies have reported a tendency towards higher concentrations of phthalate monoesters in maternal breast milk or colostrum among cryptorchid boys than among controls, although such effects on individual congeners have only occasionally reached statistical significance and have not always survived adjustment for relevant confounders [43].

5.2. Hypospadias

Hypospadias is a congenital malformation in which the urethral meatus is displaced from the tip of the glans penis to a more proximal position along the ventral surface of the penis, the scrotum or, in the most severe forms, the perineum. Its incidence is approximately 0.3–0.7% at birth in many Western countries, making it the second most common congenital malformation of the male external genitalia after cryptorchidism, and registry data from several countries have suggested a progressive increase over recent decades, although changes in diagnostic and reporting practice may account for some of this trend [44]. The phenotype results from incomplete fusion of

the urethral folds during the differentiation of the male external genitalia in the first trimester, a process that depends critically on adequate exposure of the genital tubercle, urogenital sinus and developing penile tissues to 5α-dihydrotestosterone (DHT), the more potent androgen produced locally from testosterone by the enzyme 5α-reductase type 2 (SRD5A2) [17]. The local conversion of testosterone to DHT amplifies and extends the androgenic signal in target tissues; either insufficient substrate (testosterone) supplied by fetal Leydig cells or insufficient 5α-reductase activity may therefore predispose to hypospadias [17,31].

In line with the proposed molecular mechanism, phthalates have been identified as one plausible environmental contributor to the human phenotype. The same 2024 meta-analysis cited above reported a significant pooled adjusted odds ratio for hypospadias associated with maternal EDC exposure of 1.26 (95% CI 1.18–1.35; $p < 0.0001$), with significant subgroup contributions from pesticides, phthalates, alkyl-phenolic compounds and heavy metals [44]. The complementary 2022 phthalate-specific meta-analysis reported that maternal exposure to DEHP and DiDP was likewise associated with an increased risk of hypospadias, with the critical sensitivity window apparently lying in early pregnancy [45]. Mechanistically, the rodent literature has long demonstrated that intrauterine exposure to DBP and DEHP at doses sufficient to suppress fetal testis testosterone production is also sufficient to induce hypospadias in male rat offspring, with a clear dose–response relationship and a no-observed-adverse-effect level of approximately 50 mg/kg/day for DBP [30,42]. The molecular continuity from fetal Leydig cell dysfunction, through reduced testosterone substrate availability, to inadequate DHT signalling at the genital tubercle therefore provides a plausible mechanistic chain linking maternal phthalate burden to the clinical phenotype, even though the human exposure levels at which the effect emerges remain a subject of ongoing debate [17,31].

5.3. Reduced anogenital distance (AGD)

Of the anatomical manifestations of TDS, the most informative for population-level epidemiology has proven to be the shortened anogenital distance (AGD), defined as the distance between the centre of the anus and the proximal insertion of the external genitalia [18]. In males, two principal measurements are commonly recorded: the longer anopenile distance (AGDap), measured from the centre of the anus to the cephalad insertion of the penis where penile tissue meets the pubic bone, and the shorter anoscrotal distance (AGDas), measured from the centre of the anus to the base of the scrotum where the skin changes from rugated to smooth [18,46]. AGD is a sexually dimorphic trait — typically 50–100% longer in males than in females across mammalian species — that is established during the MPW under androgen control and that, in rodent studies, has been shown to provide a faithful lifelong readout of the level of androgen exposure within that critical window [17]. It has accordingly been adopted as a non-invasive surrogate biomarker of fetal androgenisation in human cohort studies, with the methodological advantage that it can be measured shortly after birth or in early childhood, well before any reproductive end-point becomes clinically manifest [18,46].

A series of prospective cohort studies has explored the relationship between maternal urinary phthalate metabolite concentrations and AGD in male offspring. The Study for Future Families (SFF), conducted in the United States, was the first to report inverse associations between maternal urinary metabolites of DEP, DBP, BBzP and DiBP and male AGD in infancy, with the strongest signal emerging in the subsequent SFF-II analysis for the DEHP metabolites MEHP, MEHHP and MEOHP [46]. The successor Infant Development and the Environment Study (TIDES), which prospectively followed 753 mother–infant pairs across four US clinical centres, found that first-trimester maternal urinary concentrations of MEHP, MEOHP and MEHHP were each inversely and statistically significantly associated with both AGD measures in male newborns, but not in female newborns. The reported regression coefficients (β with 95% CI) for AGDas in TIDES were −1.12 (−2.16, −0.07) mm for MEHP, −1.43 (−2.49, −0.38) mm for MEOHP and −1.28 (−2.29, −0.27) mm for MEHHP, with comparable but somewhat stronger associations for AGDap; an interquartile range increase in DEHP metabolite concentration corresponded to approximately a 2–5% reduction in mean AGD [46]. Crucially, the TIDES findings emerged at first-trimester exposure levels substantially lower than those used in rodent toxicity studies, suggesting either that the human fetal testis and genital tubercle may be more sensitive than rodent extrapolations would predict, or that simultaneous co-exposure to other anti-androgenic compounds is contributing additively.

Independent European cohorts have produced broadly concordant, though not uniform, findings. The Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy (SELMA) study examined first-trimester maternal urinary metabolites in 196 mother–boy pairs and reported a small but statistically significant inverse association between metabolites of DiNP (notably oh-MMeOP and oxo-MMeOP) and AGDas at 21 months of age, corresponding to an estimated 4% reduction in AGD across the interquartile range of DiNP exposure [47]. This finding has been considered noteworthy because DiNP has been progressively substituted for DEHP in

PVC products following regulatory action, and the SELMA data raise the possibility that anti-androgenic activity may extend to at least some of the substitute plasticisers, not only to the regulated congeners [47]. By contrast, the Odense Child Cohort (ODIN) in Denmark — a low-exposed cohort of 273 mother–boy pairs with urine sampled in late pregnancy — reported no statistically significant association between any of twelve phthalate metabolites and AGD at three months of age, although most point estimates were directionally negative; the authors noted that maternal exposures in this Danish population were considerably lower than those in the contemporaneous Swedish cohort, raising the possibility of a population-level threshold below which the AGD signal becomes difficult to detect, and noting that urine sampling occurred well after the presumptive MPW [48]. The negative Danish finding has therefore been interpreted as broadly compatible with — rather than as a refutation of — the cumulative AGD literature.

The biological meaning of AGD measurements obtained in infancy is supported by independent evidence from older male populations. In a clinic-based cohort of 116 adult men assessed at an andrology service, AGD was positively and statistically significantly correlated with serum testosterone ($r = 0.20$, $p = 0.03$), with each 1-cm increase in AGD corresponding, after adjustment for age, to approximately a 20-ng/dL increase in serum testosterone; men with hypogonadal testosterone (<300 ng/dL) had a significantly shorter mean AGD (31.6 mm) than men with higher testosterone (37.3 mm; $p = 0.02$) [49]. AGD has additionally been positively associated, in independent series, with sperm concentration, motility and morphology, and fertile men have been shown to have longer AGD than men attending fertility clinics for primary or secondary infertility [49]. Together these adult observations reinforce the interpretation of AGD as a calibrated, lifelong anatomical readout of intra-MPW androgenisation; they suggest that the maternal phthalate exposures associated with shorter AGD at birth may not be biologically trivial but may instead correspond, at the population level, to measurable deficits in adult Leydig cell function and fertility [50]. Although the effect sizes in individual studies are modest and meta-analytical summaries appropriately cautious, the overall pattern emerging across multiple cohorts on three continents appears to be broadly consistent with a phthalate-mediated, MPW-restricted contribution to the anatomical phenotype of TDS in male infants and boys.

6. Developmental neurobiology: demasculinisation of the central nervous system

The role of phthalates as putative disruptors of central nervous system development represents the second principal axis of the proposed "phthalate syndrome". The fundamental biological insight that connects this axis to the events at the level of the fetal Leydig cell described in section 4 is the recognition that the same fetal androgens that direct external genital masculinisation also drive — directly or through local aromatisation — the structural and functional masculinisation of the developing brain. A maternal exposure that suppresses fetal androgen availability during the masculinisation programming window (MPW) may therefore be expected to leave a measurable imprint not only on the urogenital tract but also on the dimorphic architecture of the central nervous system and on the behavioural phenotypes that emerge from it [17,19].

6.1. Physiological masculinisation of the fetal brain: testosterone, aromatisation and dimorphic nuclei

According to the classical aromatisation hypothesis, testosterone secreted by the fetal testes during the second half of pregnancy diffuses into the developing brain and is locally converted, by the cytochrome P450 enzyme aromatase (CYP19A1), into 17β-estradiol; this locally generated estradiol then acts on its cognate receptors to direct neurogenesis, regulated apoptosis and synaptic patterning within a series of sexually dimorphic nuclei [51]. Aromatase activity in the perinatal mammalian brain is regionally restricted, with the highest expression observed within the preoptic area, the hypothalamus and the amygdala — i.e., precisely those structures that subserve reproductive endocrine function and reproductive behaviour [51]. The most extensively studied target of this process is the sexually dimorphic nucleus of the preoptic area (SDN-POA), which is several times larger in male than in female rodents and is involved in the sex-typical organisation of copulatory behaviour and gonadotrophin secretion; its postnatal size appears to depend on intra-window estradiol exposure, and neonatal pharmacological inhibition of aromatase produces a significant reduction in the male SDN-POA [51].

The relative contributions of direct androgen-receptor signalling and of locally aromatised estradiol differ across mammalian species and across dimorphic structures [52]. In rats and mice, aromatisation appears to be the dominant route to brain masculinisation, whereas in non-human primates, sheep and possibly humans, direct androgen-receptor-mediated mechanisms may play a more prominent role [51,52]. In humans, the brain region thought to be homologous to the rodent SDN-POA is the third interstitial nucleus of the anterior hypothalamus (INAH-3); like its rodent counterpart, INAH-3 has been reported to be larger in males than in females, and its size has been correlated, in post-mortem case series, with self-reported sexual orientation and aspects of gender identity, although the functional inferences that can be drawn from such observations remain a subject of debate

[53]. The bed nucleus of the stria terminalis and the central component of the medial preoptic nucleus also display sex differences in volume and neurone density that have been attributed, with varying degrees of certainty, to the perinatal androgen surge [52,53]. Across rodent and primate models, the integrity of the perinatal androgenic signal — whether acting directly through the androgen receptor or indirectly via aromatisation — appears to be the principal determinant of subsequent sex-typical neural architecture and of the behavioural responses that emerge from it [54]. Phthalate exposure that suppresses fetal Leydig cell testosterone output during the MPW therefore has, on first principles, a biologically plausible route to the disruption of brain sexual differentiation [17].

6.2. Neuronal plasticity in conditions of reduced androgen exposure: synaptic density and dopaminergic pathways

Beyond their indirect effect through reduced testosterone substrate, phthalates and their monoester metabolites may operate on the developing brain through several additional, partially overlapping pathways. The endocrine programming of the central nervous system overlaps temporally with the so-called brain growth spurt — the period extending from the third trimester through approximately the first two postnatal years — during which neuronal proliferation, migration, differentiation, synaptogenesis and myelination proceed at their highest rates, and during which perturbations may translate into long-lasting deviations in brain structure and function [55]. Phthalate exposure within this window has been associated, in both human and rodent studies, with disturbances of thyroid hormone homeostasis — particularly suppression of free T4 — that may secondarily affect neurogenesis and synaptogenesis, given the recognised role of thyroid hormones in cortical and cerebellar maturation [55]. Within the hippocampus, an area especially sensitive to androgen and estrogen modulation, perinatal phthalate exposure has been linked with altered dendritic architecture, modified glutamatergic transmission and reduced expression of brain-derived neurotrophic factor (BDNF) in some — though not all — animal and observational human series [55].

A particularly active line of recent investigation concerns the dopaminergic system. Phthalates have been reported to interfere with the dopamine D2 receptor, with tyrosine hydroxylase activity and with BDNF expression, and dopaminergic neurons may be especially susceptible to phthalate-induced oxidative stress [55]. A harmonised analysis of European children from five HBM4EU-aligned studies related urinary phthalate metabolite concentrations to serum BDNF concentrations and to scores on validated behavioural scales, providing a population-level human counterpart to the experimental findings [56]. A systematic review and meta-analysis of phthalate-related neurotoxicity in children identified evidence — albeit of low or very low quality — for an association between prenatal and postnatal phthalate exposure and behavioural development, and between postnatal exposure and cognitive function [57]. Earlier systematic reviews of the human epidemiological evidence on phthalate-related neurodevelopment have reached broadly similar conclusions, with the strongest signals consistently emerging in early childhood and for behaviours that display a recognised sexually dimorphic component [58].

Epigenetic mechanisms may further mediate the persistence of the phthalate signal beyond the period of direct in-utero exposure. Reviews of transgenerational endocrine disruption have emphasised that phthalates, like other EDCs, may leave a heritable epigenetic imprint involving altered DNA methylation, histone modification and noncoding-RNA expression in tissues — including the central nervous system — that are relevant for sex-typical behaviour and neuroendocrine function [59]. Studies of human cord blood have shown that maternal phthalate exposure during pregnancy is associated with altered patterns of CpG methylation at loci of relevance to androgen signalling (e.g., MEG3, PA2G4, HMGCR, XRCC6) and to growth (e.g., LINE-1, H19, IGF2) [60]. Multi-omic analyses integrating methylome, transcriptome and metabolome data in mother–infant dyads have begun to refine these observations and to identify candidate mediator pathways linking maternal phthalate burden to offspring neurobehavioural outcomes, although the human transgenerational evidence remains preliminary [61].

6.3. Behavioural phenotype in childhood: sex-typed play and cognitive trajectories

The clearest behavioural correlate of intra-uterine androgenisation in humans is the constellation of sex-typed play preferences that emerges during the second and third years of life. Across cultures and across mammalian species, boys tend to engage more frequently in active rough-and-tumble play and to prefer male-typical toys (vehicles, construction items, weapons), whereas girls more often engage in nurturing play and prefer female-

typical toys (dolls, household objects); these differences are particularly large for toy preferences, with effect sizes substantially exceeding those of most sex differences in cognition or personality [62]. The use of the Pre-school Activities Inventory (PSAI), a validated parent-rated 24-item questionnaire that yields masculine, feminine and composite-score subscales, has been instrumental in quantifying these patterns and in relating them to prenatal hormonal exposure [62,63].

The clinical and toxicological literature has consistently associated lower intra-uterine androgenisation with reduced male-typical play behaviour. Girls with congenital adrenal hyperplasia (CAH), who experience supraphysiological intra-uterine androgen exposure, display elevated male-typical play behaviour in a dose-dependent fashion across the spectrum of disease severity; conversely, 46,XY individuals with complete androgen insensitivity syndrome display female-typical play patterns despite their Y chromosome [62]. A meta-analysis of nine amniotic-fluid studies in normally developing children reported a correlation between amniotic-fluid testosterone and male-typical play preferences in the theoretically expected direction ($r \approx 0.082$ unadjusted, $r \approx 0.166$ after trim-and-fill correction; $p = 0.014$ corrected), with the important caveat that within-typical-range effects appear to be modest in magnitude and somewhat heterogeneous across studies [62].

Against this background, several prospective birth cohorts have specifically examined the relationship between maternal urinary phthalate metabolite concentrations and PSAI-derived sex-typed play scores in offspring. The original Study for Future Families (SFF) analysis reported that higher prenatal urinary DEHP and DBP metabolite concentrations were associated with less male-typical play behaviour in boys at approximately four years of age, but not in girls [64]. The successor TIDES cohort — substantially larger, with carefully timed first-trimester urinary sampling and prospective PSAI assessment at 4–5 years — extended these observations: after adjustment for child age, race, maternal education, parental attitudes towards opposite-sex play and presence of a same-sex older sibling, first-trimester maternal urinary MnBP, MiBP and MBzP concentrations were inversely associated with masculine PSAI scores in boys ($\beta \approx -2.18$, -2.10 and -2.42, respectively), and first-trimester MBzP was also associated with lower masculine scores in girls ($\beta \approx -2.12$) [64]. Third-trimester urinary sampling, by contrast, did not reproduce the early-pregnancy signal, a finding consistent with the proposed timing of the human MPW and with the interpretation that demasculinising effects are most plausibly mediated by exposures occurring during the first trimester [64].

Postnatal androgen exposure during the so-called "mini-puberty" of the second to fourth month of life may further modulate the early behavioural trajectory. In one longitudinal cohort, higher salivary testosterone in male infants at 1–3 months of age, in interaction with harsher parenting, was associated with greater physical aggression at 12 months [65]. These observations underline the dual organisational and activational role of androgens in early postnatal behavioural development, and they identify an additional window — beyond the prenatal MPW — within which phthalate exposure could, in principle, alter behavioural trajectories.

6.4. Susceptibility to atypical neurodevelopmental phenotypes: autism spectrum disorder and ADHD

The behavioural shifts described above shade into a broader concern: that prenatal phthalate exposure may contribute to susceptibility to atypical neurodevelopmental phenotypes, most notably autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Both conditions display a male-predominant prevalence — suggesting a partial role for sex-related developmental factors — and both are increasingly understood as having an environmental component superimposed on a polygenic genetic background. A systematic review and meta-analysis of cohort studies on environmental pollutants and ASD identified several classes of compound, including phthalates, as plausible contributors to risk [66].

The empirical evidence for a phthalate–ASD link in humans is mixed. The MARBLES (Markers of Autism Risk in Babies — Learning Early Signs) study, which prospectively followed 201 mother–child pairs from high-risk (ASD-affected sibling) pregnancies with multiple second- and third-trimester urinary samples and gold-standard ADOS-based clinical assessment at three years of age, reported that most associations between individual phthalate metabolites and ASD or non-typical development were null, with the principal positive signal arising for mono-ethyl phthalate (MEP) and non-typical development (relative risk ratio 1.38; 95% CI 1.01–1.90 per 2.72-fold concentration increase); however, subgroup analyses by maternal prenatal vitamin use revealed both protective and risk associations across different metabolite–vitamin strata, illustrating the importance of effect modification by maternal nutritional status [67]. A substantially larger Chinese prospective cohort of 3,209 mother–child pairs found that exposure to a phthalate mixture was associated with elevated autistic-trait scores in children aged 1.5–6 years, with the exposure–response relationship being particularly evident among mothers with 25(OH)-vitamin D deficiency; the proposed mechanism implicated DEHP-mediated effects on GRIN2B expression and post-synaptic NMDAR function, and maternal vitamin D supplementation appeared to attenuate

this association [68]. Other observational studies have likewise reported associations between maternal phthalate concentrations and autistic-trait scores or related behavioural problems in children, although effect sizes have generally been modest and exposure–response relationships have not always been monotonic [69,70]. Phthalate mixtures appear to be associated, in some birth cohorts, with broader behavioural problems in preschool-aged children, including those with elevated likelihood of an ASD diagnosis [71].

The evidence for an association with ADHD has accumulated somewhat more consistently. In the Norwegian Mother and Child Cohort (MoBa), a population-based case–control analysis using clinical ADHD diagnoses ascertained from the Norwegian Patient Registry reported that children in the highest quintile of prenatal ΣDEHP exposure had approximately three-fold higher odds of an ADHD diagnosis than children in the lowest quintile, with the association appearing largely independent of maternal thyroid function [72,73]. Additional cohort data from the Odense Child Cohort have linked maternal urinary phthalate metabolite concentrations to ADHD-related symptoms in children aged 2–4 years [74]. The Childhood Autism Risks from Genetics and Environment (CHARGE) case–control study and its follow-on ReCHARGE analysis have further documented associations between early-childhood phthalate exposure and ADHD-relevant behaviours extending into middle childhood and adolescence, with some specificity for DEHP and high-molecular-weight metabolites [75,76]. Pooled-cohort and prospective analyses of prenatal phthalate mixtures in relation to broader neurodevelopmental outcomes have produced complementary observations [77]. Independent investigations linking phthalate biomarkers with reductions in non-verbal IQ in offspring, together with an emerging body of work on phthalate exposure and mental-health risk extending into older adulthood, further reinforce the picture of a chronic, lifelong vulnerability that may have its roots in the prenatal period [78,79].

Taken together, the convergence of mechanistic, animal, cohort and clinical evidence indicates that prenatal phthalate exposure during the MPW may contribute, in a modest but reproducible fashion, to a constellation of neurobehavioural deviations — reduced male-typical sex-typed play, altered cognitive trajectories, autistic traits and elevated ADHD risk — that collectively constitute the neurobehavioural arm of the "phthalate syndrome". The effect sizes appear to be smaller in magnitude than those documented for the anatomical phenotypes of Section 5, but their public-health significance is potentially substantial, given the very high prevalence of phthalate exposure in the general population [55,57].

7. Andrological and psychosexual consequences in adulthood

The pathomechanism outlined in the preceding sections does not terminate at birth. Several converging lines of evidence — partly mechanistic, partly cohort-based and partly clinical — suggest that in-utero phthalate exposure during the masculinisation programming window (MPW) may project a measurable shadow well into adult reproductive and psychosexual life [19,50]. The three principal manifestations considered below are: deficits in adult spermatogenesis that may be traceable to fetal Sertoli-cell injury; chronic perturbations of the hypothalamic–pituitary–gonadal (HPG) axis with a characteristic "compensated Leydig-cell failure" pattern; and the still-emerging evidence for effects on psychosexual function and gender-typical behavioural trajectories.

7.1. Spermatogenesis deficits: from fetal Sertoli-cell injury to adult oligozoospermia

The capacity of the adult testis to produce sperm is determined, to a substantial extent, by the absolute number of Sertoli cells that survive the late fetal and early postnatal proliferative phases. Each adult Sertoli cell supports a finite number of developing germ cells, and the pre-programmed adult sperm output of a given testis is therefore closely tied to the Sertoli-cell population set during this critical interval [19]. Experimental rodent data have demonstrated that maternal exposure to DBP during the MPW may produce up to a ≈40% reduction in Sertoli-cell number at the end of gestation, with corresponding reductions in seminiferous-tubule diameter, focal dysgenesis of the seminiferous cords, multinucleated gonocytes, and persistently reduced spermatogenic capacity in adulthood [30,38]. The mechanism appears to involve a combination of indirect effects, mediated by the impaired fetal Leydig-cell testosterone surge, and direct effects on the Sertoli cell itself, including altered FSH responsiveness and connexin-43-mediated gap-junctional uncoupling within the seminiferous epithelium [34,42].

A growing body of human evidence is broadly consistent with these experimental observations. A systematic review of human epidemiological studies on phthalate exposure and male reproductive outcomes concluded that there is robust evidence of an association between DEHP and DBP exposure and adult semen-quality parameters, with moderate evidence for DiNP and BBzP and slighter signals for DiBP and DEP [50]. A subsequent comprehensive review focused specifically on endocrine-disrupting chemicals and male reproductive health summarised the cumulative cross-sectional and prospective data and concluded that the human evidence supporting an adverse effect of phthalates on semen quality and circulating androgens is consistent and

reasonably strong, particularly for DEHP, DnBP and BBzP [80]. Earlier overarching reviews of environmental toxicants and male fertility have reached compatible conclusions, frequently invoking the "phthalate syndrome" / TDS framework to explain the temporal pattern by which an event in utero — Sertoli- and Leydig-cell injury during the MPW — is hypothesised to manifest decades later as reduced sperm count, oligozoospermia, asthenozoospermia or subfertility [81,82,83].

The clinical implications of these mechanistic and epidemiological observations are non-trivial. Sperm counts below the World Health Organization reference threshold (15–20 × 10^6/mL, depending on the version of the criteria used) are associated with longer time to pregnancy, reduced fecundity and a higher likelihood of recourse to assisted reproductive technologies; secular declines in semen quality reported in several Western populations over the past several decades have therefore prompted enquiry into modifiable, in-utero contributors that could plausibly explain this trend at the population level [80]. Phthalate exposure during the MPW satisfies several of the criteria — temporal precedence, plausible mechanism, biological gradient and broad consistency across rodent and human data — that would be required for it to be considered a contributory exposure within this picture, while a direct causal link in any individual case remains essentially impossible to establish given the latency involved [50,80].

7.2. Chronic alterations of the hypothalamic–pituitary–gonadal axis: compensated Leydig-cell failure

A complementary line of evidence concerns the HPG axis as an integrated regulatory system. The endocrine signature of partial primary testicular failure is a pattern of elevated LH (and, to a lesser extent, FSH) in the face of low-normal or low total testosterone, with a reduced testosterone/LH ratio reflecting the cost — in pituitary drive — required to sustain a given level of testicular androgen output. Several cross-sectional and prospective studies have reported precisely this pattern in adults with documented phthalate exposure.

In an early cross-sectional study of 74 Chinese PVC-flooring factory workers occupationally exposed to DBP and DEHP, compared with 63 age- and smoking-matched construction workers, urinary MBP and MEHP concentrations were dramatically elevated (MBP geometric mean 644 vs. 130 μg/g creatinine; MEHP 566 vs. 5.7 μg/g creatinine; both $p < 0.001$), and serum free testosterone was significantly lower in the exposed group (8.4 vs. 9.7 pg/mL; $p = 0.019$), with negative correlations between free testosterone and both MBP ($r = −0.25$; $p = 0.03$) and MEHP ($r = −0.19$; $p = 0.095$); the magnitude of the testosterone decrement scaled monotonically with a summary phthalate-exposure score ($r = −0.26$; $p = 0.002$) [84]. A subsequent study of 295 men recruited from a Massachusetts infertility clinic examined the relationship between urinary monoester metabolites and a broader reproductive-hormone panel, reporting an interquartile-range decrease in MBzP of approximately 10% in FSH concentration, alongside additional patterns consistent with subtle anti-androgenic effects [85].

The larger follow-on analysis of 425 men from the same infertility cohort extended these findings to oxidative DEHP metabolites and to a wider hormone panel: an interquartile-range increase in urinary MEHP was associated with a 4% (95% CI −7% to −1%) decrease in serum testosterone and a 7% (95% CI −11% to −2%) decrease in serum estradiol relative to the population median; the testosterone-to-LH ratio (a recognised index of Leydig-cell function) was likewise reduced, and the testosterone-to-estradiol ratio was positively associated with MEHP — pointing to concurrent suppression of aromatase activity in some men [86]. A complementary 17-study systematic review of early-life phthalate exposure and Leydig-cell function in human male offspring reported that, although the individual testosterone results were largely null, LH was positively and the testosterone/LH ratio negatively associated with early-life phthalate exposure, consistent with a compensated state of partial Leydig-cell failure in which acceptable testosterone is maintained at the cost of an increased pituitary drive [40]. Additional cross-sectional analyses of biomarker-based studies have reported hormone associations of broadly comparable direction, although the magnitude of the effect and the specific implicated congeners have varied across populations and across exposure ranges [87,88].

Taken collectively, the adult HPG-axis data support the interpretation that the cellular events documented in fetal Leydig cells (Section 4) may indeed translate into a measurable, life-long perturbation of the androgenic set-point — modest in magnitude in any single individual, but with potentially substantial implications at the population level given the ubiquity of phthalate exposure and the role of testosterone in cardio-metabolic, musculoskeletal and cognitive health across the life course [80,83].

7.3. Psychosexual function: available data and possible correlations between prenatal androgenisation and adult phenotype

The psychosexual dimension of "phthalate syndrome" in adulthood remains the most preliminary of the three considered here, but it is also the one with the greatest conceptual continuity with the neurobiological observations of Section 6. Animal studies of rodent reproductive behaviour following developmental exposure to EDCs — phthalates included — have documented persistent shifts in copulatory behaviour, sexual partner preference and sexually dimorphic mating activity, broadly compatible with the classic rodent literature on perinatal testosterone manipulation [89]. Such observations are mechanistically plausible: if intra-uterine phthalate exposure during the MPW reduces the androgenic input to the developing SDN-POA/INAH-3 homologues and to other sexually dimorphic nuclei (Section 6.1), and if the resulting structural deviations are stable, then adult libido, sexual partner preference and aspects of gender-typical behaviour might also be subtly modulated. Direct human data linking adult psychosexual phenotype with maternal phthalate exposure during the MPW are, however, scarce; most of the existing human evidence on prenatal androgen effects on adult psychosexual outcomes is drawn from the CAH/CAIS literature and from amniotic-fluid testosterone studies discussed in Section 6.3, rather than from phthalate-exposed birth cohorts per se [62].

That said, indirect evidence is accumulating from two adjacent directions. First, several studies have reported associations between adult AGD — itself a calibrated readout of MPW androgen exposure — and self-reported parameters of sexual function, including libido, erectile function and partner relationship variables, with shorter AGD generally tending to be associated with poorer scores [49]. To the extent that maternal phthalate exposure is associated with shorter AGD at birth (Section 5.3), it is at least plausible that the same exposure may project — in a small and currently under-documented proportion of individuals — into measurable variation in adult psychosexual phenotype. Second, the broader literature on EDC effects on male reproductive function has consistently invoked the framework of partial androgenic insufficiency, of which reduced libido, mood disturbance and altered cognitive function are recognised clinical features [90].

The current consensus, however, remains that the available human data are insufficient to establish a causal role for phthalates in adult psychosexual disorders, and that the relationship — if it exists at the population level — is likely to be modest, sex-specific, contingent on multiple co-exposures, and difficult to disentangle from the rich socio-cultural determinants of psychosexual phenotype [80]. This represents one of the more important areas for future prospective research, since the latency between fetal exposure and a clinically observable psychosexual outcome may exceed three decades, requiring the long-term follow-up of mother–offspring cohorts established in the 2000s and 2010s into mid-adulthood and beyond.

8. Methodological challenges and research perspectives

The body of evidence reviewed across Sections 3–7 supports a plausible — though not yet definitively established — causal chain linking maternal phthalate exposure during the masculinisation programming window (MPW) with a multidimensional offspring phenotype. Several methodological obstacles, however, qualify the strength of the inference that can presently be drawn at the population level, and these warrant systematic consideration if the next generation of studies is to refine the picture from association to mechanism and, ultimately, to causation. Three challenges are particularly salient: the "chemical cocktail" or mixture effect, the variability of exposure indicators that follows from the short biological half-life of phthalates, and the necessity of prospective long-term follow-up of mother–offspring dyads from fetal life into reproductive maturity.

8.1. The "chemical cocktail" effect: phthalate–co-pollutant interactions

A first and persistent challenge is that humans are not exposed to phthalates in isolation. Biomonitoring programmes have consistently documented the simultaneous detection of multiple phthalate congeners alongside bisphenols (BPA, BPS, BPF), parabens, perfluoroalkyl substances (PFAS), organochlorine pesticides, polychlorinated biphenyls and heavy metals in essentially every human matrix examined [1,11]. Many of these chemicals share, or partially overlap, the molecular pathways through which phthalates exert their anti-androgenic effects — including AR antagonism, PPAR activation, aromatase modulation and oxidative stress — and may therefore act in an additive, synergistic or, in some cases, antagonistic fashion on the developing organism [29,32].

Rodent mixture studies have shown that the simultaneous administration of several phthalates, often together with pesticides such as vinclozolin and procymidone or with bisphenol A, may produce reductions in fetal testosterone and reproductive-tract malformations that follow a dose-additive (rather than threshold) pattern, with adverse effects appearing even when each individual congener is present at concentrations below its own no-observed-adverse-effect level [37,43]. Human epidemiological data are, by their nature, less amenable to

clean mixture analysis: co-exposures are typically correlated, statistical adjustment for one chemical can introduce collider bias, and the dimensionality of the human "exposome" may exceed the resolving power of any single observational study. Recent meta-analytic syntheses have nevertheless documented that simultaneous exposure to several classes of endocrine disruptor is associated with cumulative increases in the odds of hypospadias and cryptorchidism in a sex- and class-specific manner, suggesting that the population-level "phthalate" signal documented in earlier sections may, in fact, partly reflect the broader EDC milieu in which phthalates are embedded [44,83].

Parabens — antimicrobial preservatives widely used in personal-care products — represent one such structurally related co-exposure that has received increasing attention. Their detection in prenatal urinary biomarker panels overlaps geographically and demographically with that of phthalates (both classes being enriched in users of multiple cosmetic products), and recent reviews of prenatal paraben exposure have documented associations with developmental endpoints partially congruent with those reported for phthalates, raising the possibility that some of the phthalate-attributed signal in the epidemiological literature may, in reality, be a paraben-or-phthalate (or paraben-and-phthalate) signal [91]. Sophisticated statistical methods for handling correlated exposure mixtures — including weighted quantile-sum regression, Bayesian kernel-machine regression and quantile-based g-computation — have been increasingly applied in this context, but each carries assumptions whose verification in observational human data remains demanding, and none can fully substitute for the kind of experimentally controlled mixture studies that ethical considerations preclude in pregnant women.

8.2. Variability of exposure indicators: the short-half-life problem

A second methodological challenge follows directly from the pharmacokinetic properties of phthalates outlined in Section 3. The urinary half-life of phthalate monoester and oxidative metabolites is on the order of hours, with DEHP-derived metabolites estimated to fall to half their initial concentration within approximately 10–12 hours and most monoester species being largely eliminated within 24–48 hours [22]. A single spot urine sample collected at any one antenatal visit therefore captures only a very brief window of exposure, and within-individual day-to-day and even hour-to-hour variability is correspondingly high, especially for the diet-driven higher-molecular-weight congeners. The practical consequence is that, when a single sample is used to characterise gestational exposure during the MPW (between approximately gestational weeks 8 and 14), the resulting biomarker concentration may misclassify the time-integrated dose received during that critical window by a substantial margin.

Such non-differential exposure misclassification ordinarily biases observational effect estimates towards the null, and may explain, at least in part, the heterogeneity of effect sizes reported across cohorts of comparable design — for example, the diverging anogenital-distance signals reported in the more highly-exposed Swedish SELMA cohort versus the lower-exposed Danish Odense Child Cohort discussed in Section 5.3 [25,47,48]. Two principal mitigations have been proposed. The first is statistical: residual-based two-step standardisation that adjusts metabolite concentrations for the hour of sampling, hydration status (creatinine or specific gravity) and pre-analytical storage time has been shown to substantially modify median concentrations while preserving the within-person ordering of exposure values [25]. The second is design-based: pooling of multiple spot samples collected across two or three pregnancy trimesters, ideally with at least one collection placed during the presumptive MPW, reduces within-person variability and may recover effect estimates that single-sample analyses fail to detect [9,27]. The recent individual-participant-data meta-analysis of the EU Child Cohort Network on prenatal phthalate exposure and childhood respiratory health — which combined 3,745 mother–child pairs from six European cohorts (EDEN, Generation R, Generation R Next, INMA, PELAGIE, Rhea) and used pregnancy-averaged maternal urinary phthalate concentrations standardised by within-cohort interquartile range — illustrates the methodological dividend of this approach, identifying associations of mid-childhood lung function with mono-iso-butyl, mono-n-butyl and low-molecular-weight metabolites, and an association of mono-benzyl phthalate with school-age asthma, that single-cohort analyses had not consistently demonstrated [92].

8.3. The importance of prospective long-term studies

A third challenge — and arguably the most consequential of the three — concerns the temporal mismatch between the proposed causal exposure (intra-uterine, restricted to a brief MPW) and the most clinically meaningful outcomes (reduced semen quality, subfertility, neuropsychiatric morbidity, psychosexual phenotype), which may not become measurable until 20–40 years later. The historical solution to this kind of latency problem has been the establishment of large prospective birth cohorts that follow mother–offspring pairs from pregnancy onward, with banked biological samples allowing retrospective biomarker analysis as new exposures of interest are identified. The Study for Future Families, TIDES, MARBLES, the Norwegian Mother and Child

Cohort (MoBa), the Odense Child Cohort, the Generation R study, the Spanish INMA cohort and the United States Environmental influences on Child Health Outcomes (ECHO) consortium are exemplars of this design, and several have now followed their participants from intra-uterine biomarker measurement to mid-childhood neurodevelopmental and respiratory endpoints [15,46,55].

Two further methodological priorities deserve emphasis. First, follow-up of these cohorts into reproductive maturity — i.e., into the late twenties and thirties of the index offspring — will be essential to test the central prediction of the phthalate-syndrome hypothesis: namely, that intra-uterine biomarker concentrations measured around the MPW prospectively predict adult AGD, semen quality, serum testosterone and LH, sexually dimorphic neurobehavioural outcomes and, ultimately, fertility. The individual-participant-data meta-analytic methodology demonstrated by the EU Child Cohort Network for respiratory outcomes [92] provides a template that can in principle be extended to reproductive endpoints once enough offspring reach adulthood with banked perinatal biomarker data. Second, the integration of exposure-reduction trials into the prospective design — for example, randomised dietary interventions during pregnancy aimed at reducing intake of high-phthalate foods, or behavioural interventions reducing the use of LMW-phthalate-containing cosmetics — would provide stronger causal inference than any further observational analysis. Complementary mechanistic and translational work on preventive antioxidant strategies, which have been proposed on the basis of the recognised oxidative-stress component of phthalate toxicity, may further refine the candidate interventions that could be tested in such trials [93].

In sum, the available evidence base for "phthalate syndrome" rests on a converging architecture of mechanistic, animal-model, biomonitoring and epidemiological studies, but its causal interpretation in humans is likely to continue to be limited by mixture co-exposure, exposure-biomarker variability and outcome latency. Methodological progress on all three fronts — multi-pollutant statistical models, pooled-trimester biomarker designs, and prospective follow-up into reproductive maturity supplemented by preventive trials — represents the most promising direction for the next decade of research [80,83].

9. Conclusions

The narrative of "phthalate syndrome" assembled in the preceding sections traces an internally coherent — though still imperfectly proven — pathological chain that may be initiated in the first and second trimesters of pregnancy and that appears to continue to shape male reproductive and neurobehavioural phenotypes for several subsequent decades.

9.1. The proposed pathological chain in synthesis

Maternal exposure to phthalates of medium chain length (DEHP, DBP, BBzP, DiBP, DiNP), occurring through diet, personal-care products, indoor air and household dust, has become virtually universal in industrialised populations [1,2,3]. Following ingestion, the parent diesters undergo rapid hydrolysis by intestinal and hepatic carboxylesterases and pancreatic lipases to their bioactive monoesters (MEHP, MBP, MBzP, MiBP); the higher-molecular-weight monoesters are further subjected to cytochrome-P450-mediated ω- and ω-1-oxidation to MEHHP, MEOHP and MECPP, with overall pharmacokinetic half-lives on the order of hours [22]. Both classes of metabolite readily cross the maternofetal placenta, accumulate in amniotic fluid, umbilical cord blood and meconium, and act not only on the developing fetal tissues but also on the placenta itself, where they may modify the expression of CYP19A1, CYP11A1, StAR, CGA and PPARG in a sex-specific manner — a level of biological complexity that departs decisively from the historical conception of the placenta as a passive sieve [23,26,27,28].

Within the fetal testis, the monoester metabolites appear to converge on the Leydig cell, where they suppress — through a partially PPARα-dependent and partially NR5A1-mediated indirect mechanism, and in some series through gap-junctional connexin-43 disruption — the expression of the cholesterol-handling machinery (StAR, TSPO, Scarb1) and of the steroidogenic enzymes CYP11A1, CYP17A1 and HSD3B1 [31,32,33,34]. The functional consequence is a dose-dependent suppression of fetal testosterone production and of INSL3 secretion within the human masculinisation programming window (MPW, 8–14 weeks' gestation) — an event for which the Sharpe–Skakkebæk testicular-dysgenesis-syndrome (TDS) framework provides a unifying interpretation [17,19,39].

The anatomical signature of this fetal androgen deficit appears shortly after birth in the form of a tendency towards shortened anogenital distance, with corresponding meta-analytic associations between maternal phthalate burden and the risk of hypospadias and (less consistently) cryptorchidism [44,45,46]. The

neurobiological signature emerges later in childhood, taking the form of reduced male-typical sex-typed play behaviour quantifiable on the PSAI scale, altered cognitive trajectories, and elevated risks of autistic traits and ADHD symptomatology — phenotypes that may plausibly be interpreted as the brain-level analogue of incomplete androgenic programming during the same MPW [51,55,62,64,66,73]. The adult andrological signature, finally, may take the form of reduced semen quality, a "compensated Leydig-cell failure" pattern (elevated LH, reduced testosterone/LH ratio), and an AGD that remains a calibrated lifelong readout of intra-MPW androgen exposure [40,49,50,80,84,86].

Two qualifications must be emphasised. First, the effect sizes documented in human cohorts are generally modest at the level of the individual, and the inferences drawn from observational data remain subject to the methodological limitations outlined in Section 8 — mixture co-exposure, biomarker variability and outcome latency. Second, and despite these limitations, the population-level public-health relevance is potentially substantial precisely because exposure to phthalates is essentially ubiquitous, and even a small per-individual shift in a continuous variable such as AGD, sperm count, total testosterone, or PSAI masculine score translates, at the population scale, into a non-trivial shift of the entire distribution of male reproductive and neurobehavioural health [11,80,83].

9.2. Public-health recommendations

From a public-health perspective, several priorities follow from the evidence summarised above. The continued regulatory restriction of the higher-priority phthalates (DEHP, DBP, BBzP, DiBP), already implemented through the European REACH framework, the EU Toy Safety Directive and the U.S. Consumer Product Safety Improvement Act, should be maintained and extended, while the substitute plasticisers (DEHTP, DINCH, DiNP) progressively replacing them should be subjected to rigorous toxicological scrutiny — particularly in view of preliminary signals that DiNP may share at least some of the anti-androgenic activity attributed to its predecessors [9,10,11]. Continued biomonitoring through programmes such as HBM4EU, NHANES, the EU Child Cohort Network and the ECHO consortium remains essential, both for tracking exposure trends over time and for the early identification of substitute-chemical signals before they become entrenched at the population level [8,9,10,15,92].

A second public-health priority is to extend the scope of regulation and consumer information beyond plastic products to include the personal-care, cosmetic and medical-device sectors, in which low-molecular-weight phthalate exposure remains substantial and disproportionately affects women of reproductive age [6]. Standardised labelling of phthalate content on cosmetic and medical-device packaging, equivalent to that already in place for some food additives and pharmaceutical excipients, would empower informed consumer choice and create market incentives for substitution.

9.3. Recommendations for obstetric care

From an obstetric perspective, the practical advice that can be offered to pregnant women is necessarily constrained by the unavoidable scientific uncertainty surrounding any individual exposure–outcome relationship; nonetheless, several broad recommendations are reasonable on the basis of the cumulative evidence. These include: limiting, where feasible, the consumption of foods packaged in flexible PVC and of foods stored or reheated in plastic containers; reducing the use of fragranced personal-care products (perfumes, scented lotions, certain hair products, nail varnishes) during pregnancy, particularly during the first trimester, when the MPW closes; preferring glass, stainless-steel and PVC-free food-contact materials; awareness on the part of clinicians of the contribution made by medical devices (intravenous bags, tubing, blood-storage bags, parenteral-nutrition systems) to phthalate burden in inpatient settings, especially in high-risk obstetric and neonatal care; and attention to dietary patterns rich in antioxidants and folate, which may partially attenuate oxidative-stress- and methylation-related downstream effects of phthalate exposure [55,67,80,93]. The integration of phthalate exposure into the broader patient education routinely delivered at preconceptional and early-pregnancy visits — alongside the established advice on alcohol, tobacco, dietary supplementation and infection prevention — would constitute a practical implementation of the DOHaD framework within mainstream obstetric care [12,13,14,29].

9.4. Environmental prevention in women of reproductive age

From an environmental-prevention perspective, the data reviewed in this work strongly support the principle that women of reproductive age — and particularly those in the planning, periconceptional and early-pregnancy

phases — represent the population subgroup in whom risk-reduction interventions are likely to produce the greatest health return. The DOHaD framework [12,13,14], combined with the specific vulnerability of the MPW [17,18,19], makes the first trimester a clinically actionable window: behavioural and exposure-reduction interventions taken in the periconceptional period have, in principle, the greatest leverage on lifelong offspring outcomes [16].

It is important to emphasise, however, that an exclusive focus on individual behaviour is neither equitable nor strategically sufficient, since the underlying determinants of phthalate exposure — food-packaging conventions, indoor-air quality, the chemical composition of cosmetics and medical devices, and the pricing differential between phthalate-free and phthalate-containing consumer products — operate predominantly at the regulatory and market level rather than at the level of individual choice. A coherent prevention strategy must therefore combine bottom-up patient education with top-down regulatory and industrial-policy action, and must be sensitive to the socio-economic gradients that may otherwise concentrate residual exposure in the most vulnerable mother–infant dyads [80,83].

9.5. Closing remarks

In closing, the phthalate-syndrome concept — first articulated as a rodent toxicological framework, subsequently extended through the TDS hypothesis to human male reproductive health, and now under continuing extension into the neurobehavioural and adult-andrological dimensions reviewed in Sections 6 and 7 — represents one of the more clinically translatable examples of the broader endocrine-disruption paradigm. The available evidence does not yet allow definitive causal claims at the level of any individual mother–child dyad, and several of the specific exposure–outcome associations reported in the literature await replication, refinement and mechanistic anchoring. Yet the convergence of mechanistic data on fetal Leydig-cell biology, of anatomical data on AGD, hypospadias and cryptorchidism, of neurobehavioural data on sex-typed play and atypical neurodevelopment, and of adult andrological data on semen quality and compensated Leydig-cell failure, supports a coherent, mechanistically grounded and methodologically tractable agenda for the next decade of research, regulatory action and clinical practice [1,19,80,83]. Phthalate exposure during pregnancy is best regarded not as an isolated environmental nuisance, but as one tractable target within the wider effort to protect the integrity of fetal endocrine programming — and, by extension, the reproductive and cognitive health of the generation now in utero.

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Author's contribution

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