NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Research Report on the Scoping Review of Prenatal Exposure to Progestogens and Adverse Health Outcomes

NTP RR 17

SEPTEMBER 2020

NTP Research Report on the Scoping Review of Prenatal Exposure to Progestogens and Adverse Health Outcomes

Research Report 17

September 2020

National Toxicology Program
Public Health Service
U.S. Department of Health and Human Services
ISSN: 2473-4756

Research Triangle Park, North Carolina, USA

Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

NTP reports the findings from many of its studies in the NTP Technical Report and Monograph series. NTP uses the Research Report series, which began in 2016, to report on work that does not fit readily into one of those two series, such as pilot studies, assay development or optimization studies, literature surveys or scoping reviews, and handbooks on NTP procedures or study specifications.

NTP Research Reports are available free of charge on the NTP website and cataloged in PubMed, a free resource developed and maintained by the National Library of Medicine (part of the National Institutes of Health). Data for these evaluations are included in NTP's Chemical Effects in Biological Systems database or the Health Assessment and Workspace Collaborative.

For questions about the reports and studies, please email NTP or call 984-287-3211.

Table of Contents

Tables

Figures

About This Review

National Toxicology Program[1]
[1]Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

Collaborators

Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Contributed to conception or design and contributed to drafting of protocol
Kembra L. Howdeshell, Ph.D., Project Lead
Andrew A. Rooney, Ph.D.
Michael D. Shelby, Ph.D.

Screened studies, extracted data, and contributed to conception or design and drafting of report
Kembra L. Howdeshell, Ph.D., Project Lead
Michael D. Shelby, Ph.D.

Contributed to conception or design and drafting of report
Brandiese E. Beverly, Ph.D.
Windy A. Boyd, Ph.D.
Andrew A. Rooney, Ph.D.
Kyla W. Taylor, Ph.D.
Vickie R. Walker, B.S.

ICF, Research Triangle Park, North Carolina, USA
Assisted with literature screening, data extraction, and design of figures
Alexandra E. Goldstone, M.P.H., Co-lead Work Assignment Manager
Christopher A. Sibrizzi, M.P.H., Co-lead Work Assignment Manager
Courtney Skuce, B.A.

Contributors

Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Conducted oversight of peer review
Elizabeth A. Maull, Ph.D.
Georgia K. Roberts, Ph.D.
Mary S. Wolfe, Ph.D.

Critically reviewed draft report and figures
Mamta Behl, Ph.D.
John Bucher, Ph.D.

Division of Intramural Research, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Critically reviewed draft report and figures
Annie Marie Z. Jukic, Ph.D.

Chemical and Pollutant Assessment Division, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA
Contributed to conception or design of the protocol
Kristina A. Thayer, Ph.D. (formerly of the Division of the National Toxicology Program, National Institute of Environmental Health Sciences)

Office of Research and Development, Center for Public Health and Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA
Critically reviewed protocol
Erin P. Hines, Ph.D. (formerly of National Center for Environmental Assessment, U.S. Environmental Protection Agency)

Office of Science Information Management, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Designed and executed preliminary literature search
Stephanie D. Holmgren, M.S.L.S., MBA

ICF, Research Triangle Park, North Carolina, USA
Assisted with literature screening and data extraction
Yousuf Ahmad, M.P.H.
Robyn B. Blain, Ph.D.
Kristin L. Bornstein, Ph.D.
Sorina E. Eftim, Ph.D.
Susan B. Goldhaber, M.P.H.
Joanna L. Greig, Ph.D.
Pamela A. Hartman, M.E.M.
Alex Lindahl, M.P.H.
Kristen Magnuson, M.E.S.M.
Johanna R. Rochester, Ph.D.
Pamela K. Ross, M.S.P.H.
Robert Shin, M.H.S.
Raquel Silva, Ph.D.

Designed and executed literature searches
Michelle A. Cawley, M.L.S., M.S.

Retrieved and managed references
Jeremy S. Frye, M.S.L.S.

Provided contract oversight
David F. Burch, M.E.M., Principal Investigator

Joshua Cleland, M.E.M.

Coordinated external peer review
Canden Byrd, B.S.
Lindsey Green, M.P.H.

Prepared, edited, and formatted report
Tara Hamilton, M.S.
Sophie Hearn, B.S.
Camryn Lieb, B.S.
Penny Kellar, M.S.
Kevin O'Donovan, B.A.

University of Lynchburg, Lynchburg, Virginia, USA
Assisted with literature screening and data extraction
Porscha Walton, M.P.H. (formerly an undergraduate intern of the Division of the National Toxicology Program, National Institute of Environmental Health Sciences)

University of Kentucky, Lexington, Kentucky, USA
Served as technical advisor on the selection of progestogen exposures
John O'Brien, M.D.

University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, USA
Served as technical advisor on the selection of progestogen exposures
Anne Steiner, M.D.

Peer Review

The National Toxicology Program (NTP) conducted a peer review of the draft *NTP Research Report on the Scoping Review of Prenatal Exposure to Progestogens and Adverse Health Outcomes* by letter in June 2020 by the experts listed below. Reviewer selection and document review followed established NTP practices. The reviewers were charged to:

(1) Peer review the draft *NTP Research Report on the Scoping Review of Prenatal Exposure to Progestogens and Adverse Health Outcomes*.

(2) Comment on the adequacy of the scoping review in identifying and summarizing the relevant literature.

NTP carefully considered reviewer comments in finalizing this report.

Peer Reviewers

Marian McDonagh, Ph.D.
Professor, Oregon Health and Science University School of Medicine
Associate Director, Pacific Northwest Evidence-based Practice Center
Portland, Oregon, USA

Catherine Spong, Ph.D.
Professor, Chief of Maternal Fetal Medicine
Vice Chair, Department of Obstetrics and Gynecology; The University of Texas Southwestern Medical Center
Dallas, Texas, USA

Publication Details

Publisher: National Toxicology Program

Publishing Location: Research Triangle Park, NC

ISSN: 2473-4756

DOI: https://doi.org/10.22427/NTP-RR-17

Report Series: NTP Research Report Series

Report Series Number: 17

Official citation: National Toxicology Program (NTP). 2020. NTP research report on the scoping review of prenatal exposure to progestogens and adverse health outcomes. Research Triangle Park, NC: National Toxicology Program. Research Report 17.

Acknowledgments

This work was supported by the Intramural Research Program (ES103316, ES103317) at the National Institute of Environmental Health Sciences, National Institutes of Health and performed for the National Toxicology Program, Public Health Service, U.S. Department of Health and Human Services under contracts HHSN316201200028W (Order No. HHSN27300006) and GS00Q14OADU417 (Order No. HHSN273201600015U).

Conflict of Interest

Individuals identified as collaborators in the About This Review section have certified that they have no known real or apparent conflict of interest related to progestogens.

Abstract

Introduction: Endogenous progesterone is a sex hormone, one role of which is to maintain the uterine lining to support pregnancy. Drugs that exert progesterone action, collectively called progestogens (or progestins), include bioidentical progesterone from plant sources and synthetic progestogens. Progestogens are administered to reproductive-aged women for a variety of reasons, including contraception, threatened miscarriage (or its prevention), and preterm birth (or its prevention), which create the potential for fetal exposure to these drugs. Case reports and case series of adverse reproductive development (e.g., virilization in female infants) have been documented after exposure to progestogens in the first trimester, and similar effects on reproductive development have been observed in nonhuman mammalian animal studies after in utero exposure to certain synthetic progestogens.

Objective: The objective of the scoping activities was to identify and characterize the literature on the possible association between exposure to progestogens (bioidentical progesterone or synthetic progestogens) during pregnancy and adverse pregnancy outcomes, congenital malformations, neurologic effects, cancer, and other health outcomes in offspring related to prenatal exposure.

Methods: The scoping review was conducted following the Office of Health Assessment and Translation's method for systematic review through an abbreviated data extraction step. A literature search was performed up to September 13, 2019, in PubMed, Cochrane Library, and Database of Abstracts of Reviews of Effects (through 2015) for references reporting on adverse neonatal outcomes, congenital malformations, neurological effects, and cancer incidence following in utero exposure to progestogens. Relevant references were characterized by evidence stream (e.g., animal, human, in vitro study), study design, exposure, and outcome, and by the indication for administration of the drug. An interactive evidence map was prepared to enable researchers to explore the health outcome data by exposure. Tables were developed to describe the human data on congenital malformations and neurodevelopmental outcomes.

Results: The literature search yielded 7,654 references of which 212 were relevant, including 123 epidemiological studies and 90 nonhuman animal studies and 1 that reported on both human and animal subjects. In these studies, 24 different progestogens were evaluated, and the most frequently reported exposures were bioidentical progesterone, 17-alpha-hydroxyprogesterone caproate (17OHPC), and medroxyprogesterone acetate. Congenital malformations were evaluated in 32 human studies with first-trimester exposure and in 32 animal studies. Genital organ malformations (e.g., hypospadias) were the most common congenital malformation evaluated. Exposures in studies reporting significantly higher rates of genital malformations primarily involved synthetic progestogens with known androgenic (e.g., allylestrenol, lynestrenol, norethindrone) or anti-androgenic (e.g., cyproterone acetate) activities. In contrast, 17OHPC did not appear to induce congenital malformations in either humans (five of five studies) or nonhuman mammalian animals (five of five studies) exposed during organogenesis. Anogenital distance (AGD) in animal studies followed a similar pattern with prenatal exposure to androgenic synthetic progestogens generally reported to be associated with a longer AGD in females (i.e., virilization), whereas prenatal exposures to anti-androgenic synthetic progestogens were associated with shorter AGD in males (i.e., demasculinization).

Discussion: The literature reporting on neurological outcomes (n = 61 studies) had several limitations, including few studies assessing similar endpoints and exposures or inconsistent

results. Studies evaluating sexually dimorphic behavior in animals reported the most consistent findings for neurological effects; 12 of 14 studies reported altered mating behavior following prenatal exposure to bioidentical progesterone, 17OHPC, cyproterone acetate, or allylestrenol. Other limitations in the body of evidence of this scoping review included inconsistently used nomenclature for bioidentical progesterone and the synthetic progestogens and an inability to evaluate the data across progestogens as a group because of the unique biological activities of the progestogens administered (e.g., androgenic, anti-androgenic).

This scoping review identified and characterized a limited body of evidence on potential adverse health effects associated with in utero exposure to progestogens. The evidence was not sufficient to recommend an evaluation by systematic review on the association of potential adverse health effects with prenatal exposure to progestogens due to limitations of the literature. These limitations included heterogeneity of the endpoints assessed within some outcome categories (e.g., neurological outcomes), inconsistent results, and inconsistently used nomenclature to identify bioidentical progesterone or the specific synthetic progestogens used. In addition, evaluating these exposures as a group was challenging because of the unique biological activities of the progestogens administered (e.g., androgenic, anti-androgenic). More research is needed to better understand the potential association of prenatal exposure to progestogens and adverse pregnancy outcomes, congenital malformation incidence, and longer-term health outcomes of prenatally exposed offspring (e.g., neurological effects and cancer).

Preface

NTP conducts scoping reviews to identify, categorize, and summarize the literature-based evidence evaluating whether exposure to environmental substances (e.g., chemicals, physical agents, and mixtures) may be associated with adverse health effects. These reviews serve as a foundational step in directing potential further inquiry by identifying areas that are data rich or data poor on project-specific key concepts such as: exposures, health effects, mechanisms, experimental model or study design, and evidence stream (human, experimental animal, in vitro models); however, they do not include a synthesis of the data. Depending on the goals and the available evidence, scoping reviews may include: (1) a summary of the research relating to specific questions or relatively broad topic areas, (2) a systematic evidence map—an interactive visual display of research relating to relatively broad topic areas that can be sorted, filtered, and categorized to illustrate the extent and types of evidence, or (3) both.

NTP conducts these health effects evaluations following the first three steps of the general methods outlined in the "Handbook for Conducting a Literature-Based Health Assessment Using the OHAT Approach for Systematic Review and Evidence Integration" [†]: (1) problem formulation, (2) literature search and selection of studies for inclusion, and (3) abbreviated data extraction to categorize published research by key concepts relevant to the goals of the review. The key feature in applying the systematic review approach to scoping reviews is the application of a transparent framework to document the methods.

[†]OHAT is the abbreviation for Office of Health Assessment and Translation, which is within the Division of the National Toxicology Program at the National Institute of Environmental Health Sciences.

Introduction

Endogenous progesterone is a steroid hormone that is involved in reproduction by inducing cellular differentiation and vascularization of the uterus to support the embryo during early pregnancy. It inhibits further ovulation and myometrium contractility throughout the pregnancy and suppresses the maternal immune response to allow for implantation and maintenance of the developing embryo and fetus. Similar to other steroid hormones, progesterone acts via both genomic (nuclear receptor) and nongenomic (extranuclear receptor) mechanisms [reviewed in Taraborrelli (2015)] The genomic action of progesterone is exerted via three known progesterone nuclear receptors that interact with DNA to produce proteins responsible for regulating female reproduction. The nongenomic action of progesterone occurs via cell-membrane-localized progesterone receptors, which induce many physiological reactions involved in reproduction (e.g., acrosome reaction in sperm, oocyte maturation) through activation of various signaling pathways (e.g., G protein activation, Ca^{2+} homeostasis, phospho-inositol-3-kinase activation) [reviewed in Gellersen (2009)].

Progestogens (also called progestins) are compounds that exert progestational activity. They include two broad categories of drugs: bioidentical progesterone and synthetic progestogens. Bioidentical (sometimes referred to as natural) progesterone is prepared from plant sources (e.g., Mexican yams). Synthetic progestogens (also called synthetic progestins) are structurally related to progesterone and testosterone. Synthetic progestogens also are reported to interact with other steroid hormone receptors leading to diverse biological activities among these agents (Hapgood et al. 2014; Louw-du Toit et al. 2017; Schindler 2015; Stanczyk et al. 2013).

Progestogens are most commonly administered to women for contraception and hormone replacement therapy. For example, medroxyprogesterone acetate, bioidentical progesterone, and norethindrone were among the top 300 most prescribed drugs in 2018 along with several combination progestin/estrogen contraceptives (Kane 2018). Progestogens are also prescribed to reproductive-aged women for treatment of infertility, menstrual disorders (e.g., amenorrhea, menorrhagia, premenstrual syndrome), and prevention or treatment of miscarriage and preterm labor, among other complications of pregnancy (Brucker and Likis 2010). Thus, fetal exposure to progestogens could occur due to intentional (e.g., treatment of miscarriage) or unintentional (e.g., contraceptive failure or an undiagnosed pregnancy) exposure. Early periods of development are sensitive to exogenous hormonal drug exposure, such as the period of sexual differentiation of the reproductive tract that occurs during the first trimester of pregnancy in humans.

Concerns about possible adverse effects of progestogens on the developing fetus stem from the observation that alterations in the normal levels of endogenous steroid hormones during development have been shown to cause adverse effects on offspring health and development. For example, congenital adrenal hyperplasia is a genetic disorder that causes a deficiency of the enzymes involved in steroidogenesis (e.g., 21-hydroxylase enzyme), which results in elevated progesterone and androgen levels. Health outcomes associated with classical congenital adrenal hyperplasia resulting in moderate 21-hydroxylase deficiency are ambiguous genitalia at birth, accelerated development of external genitalia during childhood, menstrual cycle irregularities, difficulties getting pregnant, and altered sexually dimorphic behaviors (Turcu and Auchus 2015; Witchel 2017). In addition, several case reports and studies have reported virilization of female

infants and hypospadias (opening of the penis on the underside of the penis, instead of the tip) in male infants of women administered different progestogens during the first trimester of pregnancy (Aarskog 1971; Grumbach et al. 1959; Wilkins et al. 1958). Similar effects have been reported in studies of animals exposed in utero to some synthetic progestogens, including the masculinization of external genitalia of female offspring, reproductive malformations in male offspring (e.g., hypospadias), and alterations in sexually dimorphic behavior.

Significance

In 2013, the association between prenatal exposure to progestogens and potential adverse health effects was identified as a potential candidate for systematic review or toxicology research by two separate groups of concerned public citizens with a special interest in neurological outcomes and transgenerational effects. The National Toxicology Program conducted this scoping review to characterize the extent of evidence from human and animal studies that focused primarily on the following four health outcome categories in exposed offspring: adverse neonatal health effects, congenital malformations, neurological effects, and cancer incidence. The literature on adverse health outcomes associated with prenatal exposure to progestogens was systematically collected and categorized to develop an interactive evidence map to enable individuals to explore published studies by the types of exposure, potential health effects, and evidence stream (e.g., human, animal) to identify bodies of evidence and data gaps in the available research. This scoping review, which includes an interactive evidence map of the data, was developed to support decision-making on whether the database is likely to support hazard characterization conclusions for one or more health effects in a full systematic review or for consideration of future research on prenatal exposure to progestogens and adverse health effects in offspring.

Objective and Specific Aims

Objective

The primary objective of this scoping review was to identify and characterize the literature relevant to prenatal exposure to progestogens (bioidentical progesterone and synthetic progestogens) during pregnancy and adverse health outcomes, including adverse neonatal health effects, congenital anomalies, neurological effects (e.g., neurodevelopmental and behavioral effects), and cancer incidence. This scoping review did not categorize adverse health effects associated with prenatal exposure to endogenous progesterone (e.g., congenital adrenal hyperplasia). Although assisted reproductive technologies represent a significant opportunity for exposure to natural (biological) progesterone drugs in the first trimester, these studies were not included in the current scoping review. The rationale for their exclusion was because the preliminary literature screening effort resulted in the observation that the studies often lacked reporting on the hormonal drug regimen used and often reported only the number of ongoing pregnancies or liveborn infants, without additional details on offspring health (see Limitations of the Scoping Review below).

Specific Aims

- Screen studies to identify relevant literature reporting on the association of prenatal exposure to progestogens and adverse neonatal health effects, congenital malformations, neurological effects (e.g., neurodevelopmental and behavioral

effects), and incidence of cancer from epidemiological, experimental animal, and in vitro studies relating to embryonic or fetal exposure.

- Extract data from relevant studies on health effects and the association with exposure to progestogens (i.e., the extent and types of health effects evidence available by individual progestogens).
- Create an interactive evidence map summarizing the characteristics of the data health effects by exposure to progestogens (i.e., the extent and types of health effects evidence available by individual progestogens) to identify data-rich and data-poor areas of the literature that could be addressed in future research or for which a systematic review might be useful.
- Summarize the reported conclusions available on the health effects.

Methods

The systematic review techniques in this scoping review adhere to the framework developed by the National Toxicology Program's (NTP's) Office of Health Assessment and Translation (OHAT) (Rooney et al. 2014). This report was restricted to the first three steps of the seven-step OHAT systematic review framework: (1) problem formulation, (2) literature search and selection of studies for inclusion, and (3) abbreviated data extraction. The data extraction step for the scoping review involves characterizing the studies to identify the areas of published research on the exposures by health outcomes of interest. The remaining four steps of the OHAT systematic review framework, which are relevant for assessing study quality and synthesizing evidence across evidence streams, were beyond the scope of the current report.

Problem Formulation and Protocol Development

Prenatal progestogen exposure and fetal germ-line (epigenetic) effects were nominated to NTP for possible literature evaluation and laboratory research studies in spring 2013. The first nomination was focused on the possible relationship between progestogen use during pregnancy and autism in the F_2 generation (grandchildren; exposed as germ cells). A second and related nomination was also received in 2013 with an interest in neurodevelopmental outcomes related to prenatal progestogen exposure. A preliminary, focused literature search of the PubMed database was conducted on progestogens (including both bioidentical progesterone and synthetic progestogens) and any adverse pregnancy outcome or health effects in prenatally exposed offspring. Informed by the results of the preliminary literature search, the final literature search was designed to identify literature reporting on the health outcomes evaluated in liveborn offspring, including adverse neonatal health effects, congenital malformations, and neurological effects (e.g., neurodevelopmental and behavioral effects). Cancer incidence following prenatal exposure to progestogens was included in the final literature search due to the listing of progesterone as reasonably anticipated to be a human carcinogen by NTP's Report on Carcinogens (NTP 2016). Known relevant references from the preliminary targeted search were used to train the machine-learning model used by SWIFT-Active Screener (Sciome, Research Triangle Park, NC) for the initial title-and-abstract screening of this scoping review (Howard et al. 2020). A protocol was developed and used to conduct this review (Appendix B). A brief summary of the methods is presented below.

PECO Statement

A PECO (Population, Exposure, Comparator, and Outcome) statement (Table 1) was developed to address and understand the adverse effects of prenatal exposure to progestogens reported in humans, animals, and in vitro model systems (Table 1). The following PECO statement was used to develop the specific research questions, search terms, and inclusion/exclusion criteria for the systematic review (Higgins et al. 2019). Of note, the exposures included in the literature search strategy were identified from the literature as progestogens prescribed to reproductive-aged women (Brucker and Likis 2010; Schindler et al. 2008).

Table 1. PECO (Population, Exposure, Comparator, and Outcome) Statement

Element	Type of Evidence
Population	Human: any population without restriction Animal: Nonhuman, vertebrate laboratory animal models, including but not limited to mice, monkeys, rats, fish, and amphibians In vitro: in vitro models using organs, tissues, cell lines, or cellular components relating to embryonic or fetal exposure
Exposure	Progestogens, including bioidentical (plant-based) progesterone or synthetic progestogens (e.g., 17-alpha-hydroxyprogesterone caproate) administered during pregnancy
Comparators	A comparison population exposed to lower levels (or no exposure) of progestogen; experimental studies should include an untreated or vehicle control
Outcomes	Adverse neonatal outcomes,[a] congenital malformations,[b] neurological effects (e.g., neurodevelopmental and behavioral effects), cancer, and other associated health outcomes (e.g., reproductive system effects)

[a]Adverse neonatal outcomes included those effects frequently associated with prematurity, such as apnea/bradycardia, bronchopulmonary dysplasia (also called chronic lung disease), respiratory distress syndrome, pneumothorax, pneumonia, patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, seizures, sepsis, hypoglycemia, and hyperbilirubinemia (IOM 2007).
[b]Studies reporting on congenital malformations in miscarried fetuses, stillborn, and liveborn infants were included.

Several health outcomes were not included in the scoping review. Mortality-related outcomes, such as miscarriage, stillbirth, or neonatal death, were not included because the focus of the scoping review was on adverse health outcomes of liveborn offspring (e.g., autism). Preterm birth was not included in the scoping review because progestogens often were administered to treat threatened miscarriage or preterm birth or to prevent these conditions from developing. Composite health outcomes (e.g., composite morbidity/mortality) and hospitalization-related endpoints (e.g., admittance or time in the neonatal intensive care unit) were not included because although they are general indicators of health, they were not usually informative of a specific health outcome. Furthermore, studies measuring composite health outcomes often included different combinations of health endpoints [e.g., composite morbidity/mortality (Palacio et al. 2016), global health rating (McNamara et al. 2015)].

Literature Search

The literature search strategy was designed to identify: (1) progesterone or synthetic progestogen as title-and-abstract search terms, (2) specific synthetic progestogen or progestin medical subject heading (MeSH) terms, and (3) specific progestogen drug names as title-and-abstract terms, each in combination with health outcomes of interest (e.g., pregnancy outcomes, congenital anomalies, neurological effects, cancer) associated with prenatal exposure (full details of the search strategy are presented in Appendix A). This scoping review considered two databases (PubMed and Cochrane Library) sufficient to map the major health effects categories for each evidence stream to identify in the literature and principal health effects categories that could be further evaluated by future research or a subsequent systematic review. PubMed and Cochrane Library databases were searched through September 13, 2019. The Database of Abstracts of Reviews of Effects (DARE), which stopped collecting records in 2015, was also searched for meta-analyses and systematic reviews addressing prenatal exposure to progestogens and offspring health. Although these types of studies were excluded from the scoping review, a list of the meta-analyses and systematic reviews was collated in the case of scientific interest in this

body of literature [see Relevant Literature tab in Tableau; (NTP 2020)]. No restrictions were placed on study design type or publication year. There were no language restrictions in the literature search; however, non-English language studies were excluded in the study selection step.

The reference lists of relevant studies and authoritative reviews or government-authored (state and federal) technical reports identified during the literature screening were hand searched for additional original research references not identified through the electronic searches. These additional studies were collated for use in a potential future systematic review and were not added to the current scoping review.

Study Selection

Evidence Selection Criteria

Studies were eligible for inclusion if they satisfied the eligibility criteria in the PECO statement. Inclusion and exclusion criteria used to screen articles for relevance and eligibility at both the title-and-abstract and full-text screening stages are summarized in Table 1. The reason for exclusion at the full-text review stage was recorded and is reported in the study flow diagram. A study was excluded if it was: (1) a review, commentary, or editorial with no original data; (2) an original research article that lacked relevant PECO characteristics (no relevant population, exposure, comparator, or health outcome information); (3) a conference abstract or thesis/dissertation; (4) not available in full text (as a PDF); or (5) not published in the English language. In addition, this scoping review excluded studies reporting on assisted reproductive technologies because they generally lacked information about the health outcome of the offspring (e.g., most studies reported on ongoing pregnancy or live birth), and they usually involved physical manipulation of the gametes and multiple hormone exposures (e.g., evaluating the effect of progestogens alone was not possible) or lacked information about hormone drugs administered. References reporting on livestock animal models were considered not relevant because most of these studies used natural (bioidentical) progesterone to understand the role of endogenous progesterone on establishing and maintaining pregnancy, or they evaluated assisted reproductive technologies with minimal reporting on offspring outcomes.

Title-and-abstract Review

Title-and-abstract screening was performed in SWIFT-Active Screener (Sciome, Research Triangle Park, NC) to identify references with exposure to bioidentical progesterone or synthetic progestogens during pregnancy; this software uses machine-learning and text-mining technology to prioritize the unscreened references in order of most relevant to least relevant on the basis of the results of manually screened references (Howard et al. 2020). In brief, title-and-abstract screening was conducted independently by two screeners per reference to determine whether the reference met the inclusion criteria and screening continued until the software predicted that at least 95% of the relevant references were identified. Screeners were trained using project-specific written instructions in a pilot phase undertaken to improve clarity of the inclusion and exclusion instructions and to improve accuracy and consistency among screeners. The project lead scientist resolved screening conflicts.

Full-text Review

After the title-and-abstract screening, references identified as potentially relevant or of unclear relevancy to the PECO statement were manually curated through full-text screening with the assistance of an online literature screening software database program (DistillerSR®, Evidence Partners, Ottawa, Canada). Screening at the full-text level were conducted independently by two screeners per reference to determine whether a reference met the inclusion criteria. The project lead scientist resolved screening conflicts.

Data Extraction

Relevant studies identified in the full-text screening were characterized by evidence stream, study design, exposure (e.g., progesterone or individual synthetic progestogen), and category of health outcomes. Due to the potential effect of confounding, the indication for administration of the progestogens also was characterized for all human studies. This data extraction step was conducted independently by two screeners per reference as part of the full-text level screening. The data extraction of the relevant studies was verified in a quality assurance step by the project lead scientist or a third member of the team in cases where the project lead extracted data. Because this was a scoping effort and not a systematic review, the quality of the relevant literature was not assessed.

The relevant studies were summarized in an evidence map of health outcomes by drug exposure using Tableau (Seattle, WA) and summarized in the text. These visualizations can be viewed online in Tableau, and the associated data file in Microsoft Excel format can be downloaded here: https://doi.org/10.22427/NTP-DATA-RR-17. The Read Me page in Tableau includes descriptions of each data tab and detailed instructions for how to expand and filter the data. Some figures in the scoping review were created by filtering the data (e.g., congenital malformations in human following first-trimester exposure, anogenital distance in animals); instructions on how to replicate these figures in Tableau are in the footnote of each figure. The Effect Significance filter allows for data to be sorted by statistical significance as reported by the authors (NTP 2020).

Data Availability

Interactive versions of each figure can be accessed directly using the link beneath each figure. In addition, all interactive figures and additional study details can be viewed online and data can be downloaded from Tableau in Microsoft Excel format here: https://doi.org/10.22427/NTP-DATA-RR-17 (NTP 2020).

Results

Study Selection Results

The screening results and reasons for exclusion are outlined in the study selection diagram (Figure 1). The electronic database searches retrieved 7,729 individual references. After duplicate removal, 7,650 unique references were screened for relevance and eligibility in the title-and-abstract screen using text-mining software. Of these references, 4,292 references were manually screened to achieve >95% recall on the basis of predicted relevance and 3,358 references were not screened (and assumed to be not relevant) as determined by the machine-learning algorithm. At the title-and-abstract level, 3,220 references were excluded manually because they were not relevant to the PECO criteria, did not contain original data, or were not written in English. In the title-and-abstract screening, 1,072 references were identified as potentially relevant to exposure to progestogens during pregnancy and were then reviewed in the full-text screen. After full-text review, 858 references were excluded and 212 studies were considered relevant, of which 123 were human studies and 90 were animal studies, including one study that evaluated both human and animal subjects (Li et al. 2018). No in vitro or mechanistic studies relevant to embryonic or fetal exposure were identified by the literature screening. Three relevant studies (Coomarasamy et al. 2016; Norman et al. 2018; Reinisch and Karow 1977) reporting on human subjects were excluded because the publications included data presented in more detail in a subsequent publication (Reinisch 1977) or were peer-reviewed government reports of data previously reported in journal publications (Coomarasamy et al. 2015; Norman et al. 2016). Some references excluded from the current scoping review were identified as potentially relevant to future research or systematic reviews on prenatal exposure to progestogens associated with pregnancy outcomes and offspring health; the references are collated in the interactive Tableau file [see Relevant Literature tab in Tableau; (NTP 2020)]. The potentially relevant reference categories included: meta-analyses and systematic reviews, narrative reviews, protocols or program descriptions, case report or case series, and original research studies of assisted reproductive technologies or livestock studies.

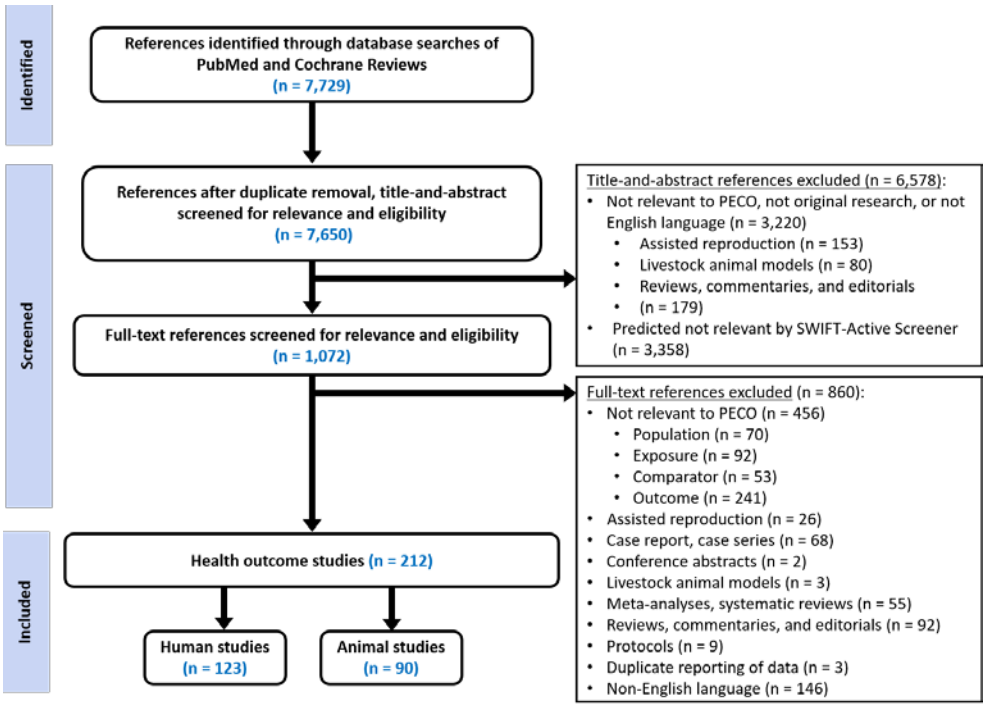


Figure 1. Study Selection Diagram

The number of relevant studies identified was 212, including 123 human studies and 90 animal studies, including one study reporting on both human and animal subjects (Li et al. 2018).

The reported data of the 212 relevant health outcome studies were mapped by exposure, evidence stream (e.g., human, animal), and outcome measured [see All Outcomes tab in Tableau; (NTP 2020)]. The studies reported on bioidentical progesterone, 23 individual synthetic progestogens, and two general categories of exposures: synthetic progestogens (i.e., exposure to one of many synthetic progestogens) progestogens (i.e., offspring exposed to either bioidentical progesterone or synthetic progestogens) (Figure 2). The most frequently reported exposures were bioidentical progesterone (86 studies), 17-alpha-hydroxyprogesterone caproate (17OHPC; 47 studies), and medroxyprogesterone acetate (MPA; 26 studies). More individual synthetic exposures were evaluated in animal studies (21 drugs) than were in human studies (9 drugs).

Exposure	Congenital Malformations	Endocrine System	Growth	Nervous System	Prematurity-Related Neonatal Outcomes	Reproductive System	Other Outcomes	Grand Total
	Health Outcome							
17OHPC	17	3	37	6	21	4	3	47
allylestrenol	2	2		3		2	1	10
chlormadinone acetate		1						1
cyproterone acetate	9	3	5	8		6		16
dienogest	1		1					1
drospirenone		1		2			2	4
dydrogesterone	4	1	4	1			2	9
ethynodiol diacetate	2							2
gestodene				1			1	1
levonorgestrel	4	4	5	4		2	1	10
lynestrenol	2		1					2
MDAP	1	1						1
megestrol acetate	1							1
melengestrol acetate	1	1						1
MPA	11	6	11	12		6	4	26
norethindrone	5	5	4	4		6	1	11
norethindrone acetate	1	1	1	2		2	1	4
norethynodrel		1		1				1
norgestimate		1		1				1
norgestrel	1	3	1			1	1	4
progesterone	21	15	51	28	27	8	10	86
progestogen	12	1	1	2		1	3	17
promegestone		1						1
quingestanol acetate			1			1		1
segesterone acetate		1		1				1
synthetic progestogen	1			3	1			5
Grand Total	79	32	109	61	47	29	21	212

Figure 2. Number of Studies Evaluating the Association between Prenatal Exposure to Progestogens and Adverse Health Outcomes

17OHPC = 17-alpha-hydroxyprogesterone caproate; MDAP = 16-methlyene-6-dehydro-17-alpha-acetoxyprogesterone; MPA = medroxyprogesterone acetate.
Progestogen indicates exposure to (bioidentical) progesterone or synthetic progestogen evaluated as a general category of exposure. Numbers in the grand total row and column refer to the number of unique studies per each exposure or health outcome; some studies might evaluate more than one exposure or health outcome. Cell shading indicates the number of studies available (i.e., darker shading indicates more studies, lighter shading indicates fewer studies, and a white space with no number indicates no studies identified). Interactive figure with study details are available on the Tableau All Outcomes tab (NTP 2020). In the interactive figure, the health outcomes can be expanded to view the number of studies per evidence stream (i.e., human or animal).

Among the human studies identified as relevant, the predominant indication for progestogen administration was the treatment (or prevention) of preterm birth or the treatment (or prevention) of miscarriage (79 studies; 64% of human studies). Twenty-five human studies did not state the reason for drug administration to the mother, and four studies evaluated the health of offspring born to a group of women treated for different individual health conditions. Other reasons these drugs were administered to women included contraception, preeclampsia, or preterm premature rupture of membranes.

The literature search strategy was tailored to retrieve adverse health outcomes in offspring prenatally exposed to progestogens informed by the results of a preliminary literature search. As expected, most of the relevant studies were related to growth (109 studies; predominantly measurements of birth weight), congenital malformations (80 studies), neurological outcomes (61 studies), adverse neonatal health outcomes related to prematurity (referred to as prematurity-related neonatal outcomes; 48 studies), and reproductive effects (30 studies) (Figure 2). Thirty-two studies (30 animal and 2 human studies) evaluated health effects related to the endocrine system, including primarily sex hormone-related endpoints (e.g., levels of hormones, receptors, steroidogenic enzymes) [see Endocrine tab in Tableau; (NTP 2020)]. Other health outcomes were evaluated in five or fewer studies, including cancer incidence in adults following developmental exposure [see Other Outcomes tab in Tableau; (NTP 2020)].

The sections that follow further describe the health outcome categories with 30 or more studies and provide additional study details for congenital malformations and neurological outcomes.

Growth and Prematurity-related Neonatal Outcomes

Human Studies

Growth was the most frequently measured outcome (76 studies) in offspring prenatally exposed to progestogens [see Growth tab in Tableau; (NTP 2020)]. Most of these studies tested the efficacy of bioidentical progesterone or 17OHPC for treating or preventing preterm birth, thus treatment occurred primarily in the second and third trimesters of pregnancy (data not shown). Birth weight was the most frequently reported growth outcome in humans (71 studies) and was measured in a variety of ways, including continuous measures (grams body weight), intrauterine growth restriction, low birth weight, very low birth weight, high birth weight, small for gestational age, and large for gestational age. Only six studies reported on infant and child growth endpoints in follow-up evaluations of prenatally exposed offspring (Jaffe et al. 1990; McNamara et al. 2015; Norman et al. 2016; Northern et al. 2007; Pardthaisong et al. 1992; Zhang et al. 2014). Most studies of growth outcomes reported no association with prenatal exposure to progestogens [see Growth tab in Tableau, Filter - Evidence type: Human, Filter - Evidence Significance (NTP 2020); see studies reporting significant findings for direction of effect].

Adverse neonatal health outcomes reported in the literature base were predominantly related to health conditions reported for premature infants. Thus, the scoping review categorized individual adverse neonatal health outcomes identified by the U.S. Institute of Medicine as outcomes commonly observed in premature infants (IOM 2007). These outcomes included apnea/bradycardia, bronchopulmonary dysplasia (also called chronic lung disease), respiratory distress syndrome, pneumothorax, pneumonia, patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, sepsis, hypoglycemia, and hyperbilirubinemia. In the 48 studies reporting on prematurity-related neonatal outcomes, respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage were the most frequently evaluated (Figure 3). Most studies of prematurity-related neonatal outcomes reported no association with prenatal exposure to progestogen [see Prematurity-related tab in Tableau, Filter - Evidence Significance (NTP 2020); see studies reporting significant findings for direction of effect].

	Exposure			
Specific Outcome	17OHPC	progesterone	synthetic progestogen	Grand Total
apnea/bradycardia		1		1
bronchopulmonary dysplasia	12	6		18
hyperbilirubinemia		7	1	8
hypoglycemia		3		3
intraventricular hemorrhage	19	17		35
necrotizing enterocolitis	20	18		37
neonatal infection		1		1
oxygen/ventilation/surfactant use	8	14		21
patent ductus arteriosus	8	4		12
periventricular leukomalacia	12	3		14
pneumonia	5			5
respiratory distress syndrome	18	21		38
retinopathy	9	7		16
seizures	7			7
sepsis	16	12		28
Grand Total	21	27	1	47

Figure 3. Number of Studies Evaluating the Association between Prenatal Exposure to Progestogens and Adverse Neonatal Outcomes in Humans Associated with Prematurity

17OHPC = 17-alpha-hydroxyprogesterone caproate.
Numbers in the grand total row and column refer to the number of unique studies per each exposure or health outcome; some studies might evaluate more than one exposure or health outcome. Cell shading indicates the number of studies available (i.e., darker shading indicates more studies, lighter shading indicates fewer studies, and a white space and no number indicates no studies identified). Interactive figure with study details available at Tableau Prematurity-related tab (NTP 2020).

Animal Studies

Growth outcomes evaluated in animal studies (32 studies) were predominantly fetal weight or birth weight. Most studies reporting on growth reported no effect of prenatal progestogen exposure [see Growth tab in Tableau, Filter - Evidence type: Animal, Filter - Evidence Significance (NTP 2020); see studies reporting significant findings for direction of effect]. No animal studies were identified as relevant to prematurity-related neonatal outcomes following prenatal exposure to progestogens.

Congenital Malformations

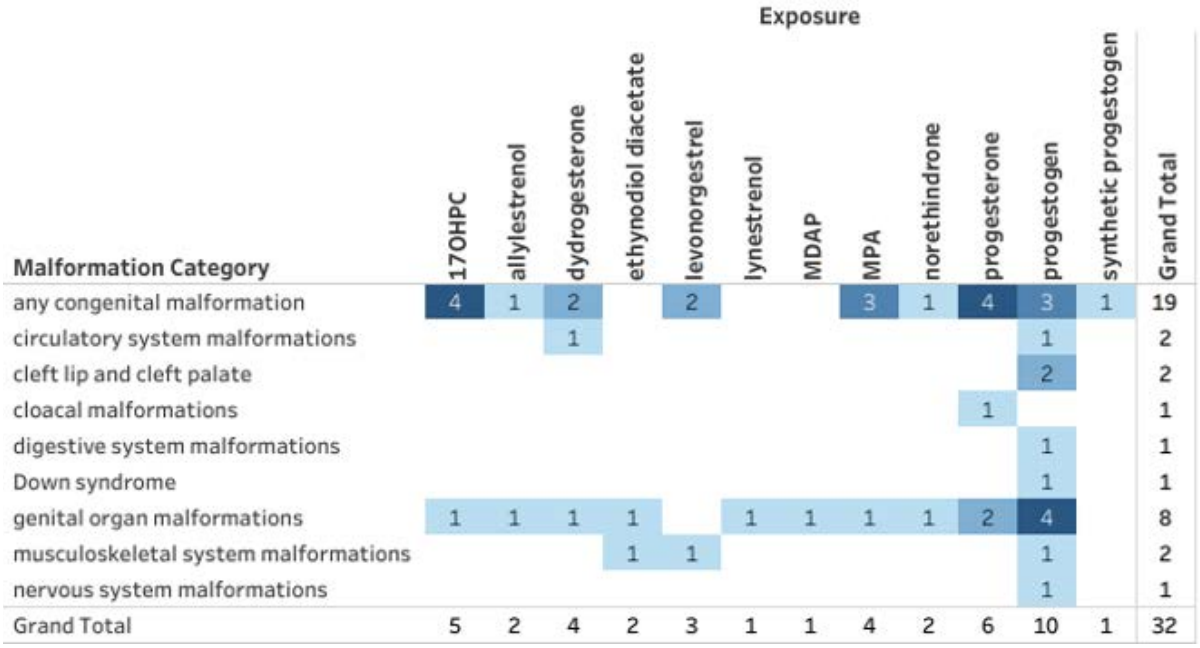
Human Studies

The scoping review identified 48 studies evaluating an association between congenital malformations and prenatal exposure to progestogens in humans. The critical period of organogenesis in humans occurs during the first trimester [from approximately 3 to 12 weeks

gestation (Moore et al. 2016)] and is particularly sensitive to chemical exposure (Shepard and Lemire 2004). Of the 48 studies, 32 evaluated the incidence of congenital malformations during the first trimester, including exposure to bioidentical progesterone, 1 of 9 different synthetic progestogens, or the general categories of synthetic progestogen or progestogen (bioidentical progesterone or synthetic progestogen) [Figure 4; see Malformations-Human tab, Filter - Exposure Timing in Tableau: select all categories with first trimester; (NTP 2020)]. Twenty studies measured any congenital malformation and 13 studies evaluated specific types of congenital malformations. The most frequently evaluated category of specific malformations was genital organ malformations (seven studies total).

Significant findings for congenital malformations were reported in 10 studies reporting first-trimester exposure to progestogens, including 3 studies evaluating any malformation (Colvin et al. 2010; Czeizel and Huiskes 1988; Hemminki et al. 1999) and 7 studies evaluating specific malformations (Calzolari et al. 1986; Carmichael et al. 2005; Corona-Rivera et al. 2018; Heinonen et al. 1977; Lammer and Cordero 1986; Mavrogenis et al. 2014; Zaqout et al. 2015) (Table 2). Two studies reported that the overall incidence of any congenital malformation was significantly higher following prenatal exposure to MPA (Colvin et al. 2010) or to the general category of progestogen (Colvin et al. 2010; Hemminki et al. 1999). The incidence of hypospadias, a genital organ malformation in which the opening of the penis is incorrectly positioned, was significantly greater in five studies; the exposures included allylestrenol (Czeizel and Huiskes 1988), lynestrenol (Mavrogenis et al. 2014), MPA (Colvin et al. 2010), and the general category of progestogen (Calzolari et al. 1986; Carmichael et al. 2005). A higher risk of cardiovascular defects was reported in three studies following exposure to dydrogesterone (Zaqout et al. 2015), MPA (Colvin et al. 2010), or the general category of progestogen (Heinonen et al. 1977). One study each reported a higher incidence of cleft lip with or without cleft palate (Corona-Rivera et al. 2018) and esophageal atresia (Lammer and Cordero 1986). Of note, an absence of congenital malformations was reported in six human studies evaluating first-trimester exposure to bioidentical progesterone (Coomarasamy et al. 2019; Coomarasamy et al. 2015; Gerhard et al. 1987; Hilgers et al. 2015; Keppler-Noreuil et al. 2017; Mavrogenis et al. 2014). Similarly, no significant association was reported for first-trimester exposure to 17OHPC and congenital malformations (five studies) (Table 2) (Dudas et al. 2006; Mavrogenis et al. 2014; Michaelis et al. 1983; Resseguie et al. 1985; Varma and Morsman 1982).

Studies reporting timing of exposure other than during first trimester were considered less informative of the association between progestogens and congenital malformations [see Malformations-Human, Filter - Exposure Timing in Tableau (NTP 2020)]. Eight studies reported exposure only as during pregnancy, which might or might not have included exposure during the first trimester. The studies reporting exposure only during the second and/or third trimester would have been less likely to detect malformations because exposure did not encompass the period of organogenesis.



Malformation Category	17OHPC	allylestrenol	dydrogesterone	ethynodiol diacetate	levonorgestrel	lynestrenol	MDAP	MPA	norethindrone	progesterone	progestogen	synthetic progestogen	Grand Total
	Exposure												
any congenital malformation	4	1	2		2			3	1	4	3	1	19
circulatory system malformations			1								1		2
cleft lip and cleft palate											2		2
cloacal malformations										1			1
digestive system malformations											1		1
Down syndrome											1		1
genital organ malformations	1	1	1	1		1	1	1	1	2	4		8
musculoskeletal system malformations				1	1						1		2
nervous system malformations											1		1
Grand Total	5	2	4	2	3	1	1	4	2	6	10	1	32

Figure 4. Number of Studies Evaluating the Association between Progestogen Exposure in the First Trimester of Pregnancy and Congenital Malformations in Humans

17OHPC = 17-alpha-hydroxyprogesterone caproate; MDAP = 16-methlyene-6-dehydro-17-alpha-acetoxyprogesterone; MPA = medroxyprogesterone acetate.
Progestogen indicates exposure to (bioidentical) progesterone or synthetic progestogen evaluated as a general category of exposure. Numbers in the grand total row and column refer to the number of unique studies per each exposure or health outcome; some studies might evaluate more than one exposure or health outcome. Cell shading indicates the number of studies available (i.e., darker shading indicates more studies, lighter shading indicates fewer studies, and a white space with no number indicates no studies available). Interactive figure available at the Tableau Malformations-Human tab; Filter - Exposure Timing and select all exposures that include first trimester (NTP 2020). To view the specific malformations evaluated, expand the Malformation Category column in the interactive Tableau figure (NTP 2020). To identify studies reporting significant effects, click "significant" in the Filter - Effect Significance in Tableau (NTP 2020). To identify studies that did not report statistical analyses, click "not reported" in the Filter - Effect Significance in Tableau (NTP 2020).

Table 2. Summary of Studies Evaluating the Association of Congenital Malformations in Humans Following Exposure to Progestogens in the First Trimester of Pregnancy

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
17OHPC	Case-control (Hungary) [22,843 cases, 38,151 controls]	250 mg, im injection	Any	No statistically significant difference in the prevalence of any congenital malformation in the offspring exposed to 17OHPC in gestational months 2 and 3 compared to matched controls (adjusted pOR = 1.2, 95% CI = 0.9–1.6).	Dudas et al. (2006)
	Prospective cohort (Germany) [186 progesterone exposed; 462 17OHPC exposed; 648 matched unexposed]	Not reported	Any	No increased risk for any congenital malformation in the 17OHPC exposed cohort compared to matched controls (OR = 0.66, 95% CI = 0.17–2.30).	Michaelis et al. (1983)
	Retrospective cohort (United States) [988 exposed offspring; 988 matched controls]	125–11,250 mg total dose, route not reported	Any	No association of congenital malformation with exposure to 17OHPC (HR not reported). Nonsignificant higher frequency of abnormal testes (primarily undescended testes) in 17OHPC exposed cohort compared to controls.	Resseguie et al. (1985)[a]
	Retrospective cohort (England) [150 exposed, 150 control pregnancies]	250–500 mg, im injection weekly	Any	No incidence of masculinization observed in liveborn female infants or female fetuses aborted before the 28th week of gestation in the 17OHPC exposed or control cohorts.	Varma and Morsman (1982)
	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	No statistically significant difference in odds of hypospadias in offspring exposed to 17OHPC during the critical period of development for hypospadias (7–16 weeks of gestation) compared to matched controls (similar rate of 0.7% reported for study groups; OR not reported).	Mavrogenis et al. (2014)

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
Allylestrenol	Case-control (Hungary) [7,686 congenital anomaly cases; 221 Down syndrome cases; 10,962 controls]	Not reported	Any	Significant difference ($p < 0.05$ by McNemar analysis) in the incidence rate of hypospadias of offspring exposed to allylestrenol during the second and third month of pregnancy (3–10 weeks of gestation), but not in the fourth month of pregnancy (11–14 weeks gestation), when compared to matched controls: the critical period of development for hypospadias (5–14 weeks of gestation).	Czeizel and Huiskes (1988)
	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	Positive association between isolated hypospadias in male infants and exposure to allylestrenol (specifically, medically recorded treatments) during the critical period of development for hypospadias (7–16 weeks of gestation) compared to population controls (adjusted OR = 1.55, 95% CI = 1.10–1.91) or matched controls (adjusted OR = 1.46, 95% CI = 1.09–1.39). Association disappeared when restricted to medically recorded allylestrenol treatments.	Mavrogenis et al. (2014)
Dydrogesterone	Randomized controlled trial (Jordan) [82 exposed, 48 controls]	10 mg, orally twice daily	Any	No statistically significant difference in the incidence of any congenital malformation in offspring exposed to dydrogesterone (n = 2, 2.8%) compared to controls (n = 1, 2.9%).	El-Zibdeh (2005)
	Randomized controlled trial (Malaysia) [96 exposed pregnancies, 95 unexposed pregnancies]	40 mg stat followed by 10 mg, twice daily	Any	No congenital malformations reported in offspring exposed to dydrogesterone or in controls.	Pandian (2009)
	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	No statistically significant difference in odds of hypospadias in offspring exposed to dydrogesterone in the first or second gestational months compared to population controls (adjusted OR = 1.11, 95% CI = 0.33–3.72) or matched controls (adjusted OR = 0.78, 95% CI = 0.22–2.72).	Mavrogenis et al. (2014)[a]

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
	Case-control (Palestine) [202 cases, 200 controls]	10 mg, orally twice daily	Congenital heart defects	Positive association between congenital heart defects in offspring and maternal usage of dydrogesterone during first trimester of pregnancy (adjusted OR = 2.71; 95% CI = 1.64–4.24).	Zaqout et al. (2015)
Ethynodiol Diacetate	Case-control (Hungary) [537 cases; 537 controls]	Not reported	Congenital limb reduction	Higher, but not statistically significant (p = 0.06), use of ethynodiol diacetate during pregnancy in cases with a terminal transverse defect.	Czeizel and Kodaj (1995)
	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	No difference in odds of hypospadias in offspring exposed to ethynodiol diacetate in the first or second gestational months compared to population controls (adjusted OR = 0.94, 95% CI = 0.29–3.12) or matched controls (adjusted OR = 1.22, 95% CI = 0.33–4.50).	Mavrogenis et al. (2014)[a]
Levonorgestrel	Retrospective cohort (Italy) [25 exposed, 80 controls]	0.75 mg, orally twice daily or 1.5 mg, orally once daily	Any	No statistically significant difference in the rate of congenital malformations in offspring exposed to levonorgestrel (n = 1, 4.0%) compared to controls (n = 1, 1.4%).	De Santis et al. (2005)
	Prospective cohort (China) [332 treated pregnant women (272 infants); 332 untreated controls (298 infants)]	≤1.5 mg (90.1% of cohort) or >1.5 mg (9.9% of cohort), orally	Any	No statistically higher incidence of congenital malformations in offspring exposed to levonorgestrel (n = 4, 1.5%) compared to controls (n = 4, 1.3%).	Zhang et al. (2009)
	Case-control (Hungary) [537 cases; 537 controls]	Not reported	Congenital limb reduction	No higher risk of congenital limb reductions in offspring exposed to levonorgestrel (also called D-norgestrel) compared to controls.	Czeizel and Kodaj (1995)
Lynestrenol	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	Significantly higher odds of isolated hypospadias in offspring exposed to lynestrenol during the first and second gestational month compared to population control (adjusted OR = 26.66, 95% CI = 8.69–81.80) or matched controls (adjusted OR = 47.68, 95% CI 6.23–364.64).	Mavrogenis et al. (2014)[a]

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
MDAP	Prospective cohort (Czech Republic) [5 exposed, 10 unexposed fetuses]	10 mg, orally daily	Genital organ malformations	No deviations in the development of the external genitalia observed in male or female fetuses exposed to MDAP compared to control fetuses. No statistical analysis conducted.	Uher et al. (1965)
MPA	Retrospective cohort (Western Australia) [106,074 births]	Not reported	Any	Higher odds of any malformations (OR = 1.8, 95% CI = 1.4–2.3), hypospadias (in male infants) (OR = 2.7; 95% CI = 1.3–5.8), cardiovascular malformations (OR = 1.9, 95% CI 1.1–3.1), gastrointestinal malformations (OR = 2.3, 95% CI = 1.2–4.2), congenital malformations of the integument (OR = 2.6, 95% CI = 1.1–5.8), and chromosome anomalies (OR = 3.3, 95% CI = 1.5–7.4) in exposed infants versus controls.	Colvin et al. (2010)
	Prospective cohort (Thailand) [1,229 exposed women; 4,023 unexposed women]	150 mg, im injection every 3 months or 450 mg, im injection every 6 months	Any	Significantly higher rates of any congenital malformations in offspring exposed to MPA compared to nonusers (RR = 1.7), due to higher rates of limb malformations (i.e., polysyndactyly) and chromosome anomalies.	Pardthaisong et al. (1988)
	Prospective cohort (Australia) [pregnancies of 508 exposed, 508 matched controls]	80 or 120 mg, oral capsule daily	Any	No statistically significant difference in incidence of congenital malformations in offspring exposed to MPA (4.1%) compared to matched controls (3.5%).	Yovich et al. (1988)
	Prospective cohort study (Israel) [74 exposed boys, 385 control boys]	150 mg, injection daily or ≥1 mg, oral tablet daily	Undescended testes and inguinal hernia[b]	Higher, nonstatistically significant, incidence of inguinal hernia (p = 0.20) and undescended left (p = 0.14) or right testicles (p = 0.11) in male offspring exposed to MPA compared to controls.	Jaffe et al. (1990)

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
Norethindrone	Retrospective cohort (Western Australia) [106,074 births]	Not reported	Any	No statistically significant difference in odds of any congenital malformation in offspring exposed to norethindrone compared to controls (OR = 2.2, 95% CI = 0.3–17.8).	Colvin et al. (2010)
	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	No statistically significant difference in odds of hypospadias in offspring exposed to norethindrone during the first and second gestational month compared to population controls (adjusted OR = 0.93, 95% CI = 0.33–2.63) or matched controls (adjusted OR = 3.66, 95% CI = 0.91–14.63).	Mavrogenis et al. (2014)[a]
Progesterone	Randomized controlled trial (United Kingdom and The Netherlands) [266 exposed, 276 control neonates]	400 mg, vaginal pessary daily	Any	Relative risk for genital anomalies was higher, but not statistically significant (RR = 1.04, 95% CI = 0.07–16.50), in the offspring exposed to progesterone versus controls. The risk of total congenital anomalies was similar between the two groups (RR = 0.75, 95% CI = 0.31–1.85).	Coomarasamy et al. (2015)
	Randomized controlled trial (United Kingdom) [2,025 exposed, 2,013 controls]	400 mg, vaginal pessary twice daily	Any	No statistically significant difference in the risk of congenital malformations in exposed (n = 53, 1.1%) versus control infants (RR = 1.0, 95% CI = 0.69–1.47).	Coomarasamy et al. (2019)
	Randomized controlled trial (Germany) [27 exposed, 29 controls]	25 mg, vaginal pessary twice daily	Any	No congenital malformations or virilization were observed in offspring exposed to progesterone compared to controls.	Gerhard et al. (1987)
	Retrospective cohort study (United States) [1,310 exposed; 453 unexposed]		Any	No statistically significant difference in the incidence of any congenital malformation in offspring exposed to progesterone (n = 10; 2.2%) compared to controls (n = 29; 2.2%).	Hilgers et al. (2015)

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
	Case-control (Hungary) [3,038 cases with isolated hypospadias; 24,814 population male controls with no defects; 11,096 malformed male controls with another isolated defect]	Not reported	Hypospadias	No statistically significant difference in odds of hypospadias in offspring exposed to progesterone during the first and second gestational month compared to positive controls (adjusted OR = 1.89, 95% CI = 0.54–6.62) or matched controls (adjusted OR = 1.57, 95% CI = 0.40–6.06).	Mavrogenis et al. (2014)[a]
	Case-control (United States) [101 cases, 11,829 controls]	Not reported	Cloacal malformations[c]	No statistically significant difference in odds of any cloacal malformation in offspring exposed to progesterone compared to controls following adjustment for child plurality and maternal age at delivery (adjusted OR = 1.9, 95% CI = 0.8–4.5).	Keppler-Noreuil et al. (2017)
Synthetic Progestogen	Prospective cohort study (Israel) [1,608 exposed, 1,146 controls]	20 or 30 mg, im injection daily (MPA) and/or 500 mg, im injection weekly (17OHPC)	Any	No statistically significant difference in incidence of any congenital malformation in offspring exposed to synthetic progestogens (specifically, 17OHPC or MPA) compared to controls.	Katz et al. (1985)
Progestogen[c]	Case-control (United States) [113 cases, 226 medical practice controls, 226 birth certificate controls]	Not reported	Undescended testes	No statistically significantly difference in odds of undescended testes in offspring exposed to synthetic progestogen as compared to either the medical practice control group I (adjusted RR = 0.9, 95% CI = 0.3–3.3), or the birth certificate control group II (adjusted RR = 0.7, 95% CI = 0.2–2.3).	Beard et al. (1984)[a]
	Case-control (Italy) [168 cases, 378 controls]	Not reported	Hypospadias	Significantly higher number of hypospadias cases were exposed to synthetic progestogen compared to controls ($X^2 = 5.68$, df = 1, $p < 0.05$).	Calzolari et al. (1986)[a]

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
	Case-control (United States) [502 cases, 1,286 controls]	Not reported	Hypospadias	Higher odds of progestogen exposure in hypospadias cases compared to controls. 42 case mothers (8.4%) and 31 control mothers (2.4%) reported any pregnancy-related progestogen intake from 4 weeks before through 14 weeks after conception (OR = 3.7, 95% CI = 2.3–6.0).	Carmichael et al. (2005)
	Case-control (Mexico) [105 cases, 315 controls]	Not reported	Cleft lip with or without cleft palate	Higher odds of first-trimester exposure to progestogen in cases with nonsyndromic cleft lip with or without cleft palate versus controls (adjusted OR = 6.8, 95% CI = 1.8–25.3).	Corona-Rivera et al. (2018)
	Retrospective cohort study (Finland) [1,484 exposed, 1,601 control offspring]	Not reported	Any	Significantly higher ($p < 0.001$) incidence of congenital malformations (major and minor) in offspring exposed to progestogen compared to controls, but no difference in the incidence of major congenital malformations, male genital organ malformations, or related reproductive or urinary system anomalies.	Hemminki et al. (1999)
	Prospective cohort (Egypt) [1,000 newborns total, 99 exposed]	Not reported	Genital organ malformations	No statistically significant difference in the incidence of genital anomalies in male neonates exposed to synthetic progestogens (2%) compared to controls (1.8%).	El Kholy et al. (2013)
	Retrospective cohort and nested case-control (Japan) [667 embryos with maternal genital bleeding: 130 exposed to hormone therapy, 537 unexposed; Nested case-control: 90 embryos with polydactyly and 38 with limb reductions matched 1:1 to controls (normal embryos)]	15–125 mg daily, route not reported	Any	Higher, but not statistically significant different, frequency of major malformations in embryos with progestogen exposure (19.2%) compared to matched control embryos (14.4%) ($X^2 = 1.03$, $p > 0.2$). The authors considered the association of progestogens with malformations secondary to genital bleeding (the indication for treatment with progestogens).	Matsunaga and Shiota (1979)

Exposure	Study Design (Location) [n]	Exposure Details	Congenital Malformation Measured	Results	Study
	Retrospective cohort (United States) [988 exposed offspring, 988 matched controls]	Not reported	Any	No statistically significant difference in the hazard ratio for any congenital malformation in offspring exposed to any progestogen exposure compared to matched controls [hazard ratio not reported].	Resseguie et al. (1985)[a]
	Prospective cohort (United States) [50,282 total, 1042 exposed]	Not reported	Circulatory system malformations	Higher risk of cardiovascular malformations in progestogen in exposed versus control offspring (adjusted RR = 1.5).	Heinonen et al. (1977)
	Case-control (United States) [1,091 cases, 1,055 controls (Note: for each malformation, infants with other malformations served as control)]	Not reported	11 non-genital organ malformations	Higher odds of esophageal atresia and maternal exposure to progestogen versus controls (OR = 2.87, 95% CI = 1.16–7.12); most cases were exposed to a progestogen hormonal pregnancy test (OR = 3.0, 95% CI = 1.07–8.46). No greater odds of progestogen exposure observed for any other congenital malformations evaluated, including anencephaly, spina bifida, encephalocele, Down syndrome, anterior abdominal wall defect, diaphragmatic hernia, small bowel atresia, and rectal anal atresia, limb reduction, and cleft lip ± palate, cleft palate.	Lammer and Cordero (1986)

17OHPC = 17-alpha-hydroxyprogesterone acetate; CI = confidence interval; df = degrees of freedom; HR = hazard ratio; im = intramuscular injection; MPA = medroxyprogesterone acetate; MDAP = 16-methlyene-6-dehydro-17-alpha-acetoxyprogesterone; OR = odds ratio; RR = relative risk; X^2 = chi-squared test.

[a]Study identified exposure as during pregnancy, but was inferred to include the first trimester because progestogens were administered to women for threatened abortion or a history of threatened abortion (Beard et al. 1984; Calzolari et al. 1986); in case of (Resseguie et al. 1985), 75% of offspring were exposed to progestogen in the first trimester.

[b]Study evaluated cloacal exstrophy and persistent cloaca (also called urorectal septum malformation sequence); these malformations include anorectal malformations that might also involve colon, bladder, gastrointestinal, skeletal, spinal, and genitourinary systems.

[c]Progestogen indicates exposure to (bioidentical) progesterone or synthetic progestogen evaluated as a general category of exposure. Note: First trimester of pregnancy is the first 13 weeks of gestation (weeks since last menstrual period).

Animal Studies

The available literature on congenital malformations included 32 studies in laboratory animals (Figure 5). Most of the studies used rats or mice, although a wide range of animal models were tested (e.g., primates, fish). Cyproterone and progesterone were the most commonly evaluated gestational exposures among the animal studies. Most animal studies evaluated the incidence of any congenital malformation (15 studies), while 14 studies specifically evaluated the incidence of genital organ malformations and 2 studies specifically evaluated neural tube defects. Ten of these studies were descriptive in nature and did not include statistical analysis (Foote et al. 1968; Forsberg and Jacobsohn 1969; Forsberg et al. 1968; Johnstone and Franklin 1964; Pamir et al. 2006; Prahalada et al. 1985b; Vega Matuszczyk and Larsson 1995; Ward and Renz 1972; Whalen et al. 1966; Wharton and Scott 1964).

	Exposure												
Malformation Category	17OHPC	cyproterone acetate	dienogest	levonorgestrel	lynestrenol	megestrol acetate	melengestrol acetate	MPA	norethindrone	norethindrone acetate	norgestrel	progesterone	Grand Total
any congenital malformation	4	1	1	1	1	1	1	6			1	3	17
genital organ malformations	1	8						1	3	1		3	13
neural tube defects												2	2
Grand Total	5	9	1	1	1	1	1	7	3	1	1	8	32

Figure 5. Number of Studies Evaluating the Association between Prenatal Exposure to Progestogens and Congenital Malformations in Animal Models

17OHPC = 17-alpha-hydroxyprogesterone caproate; MPA = medroxyprogesterone acetate.
Numbers in the grand total row or column refer to the number of unique studies per each exposure or health outcome; some studies might evaluate more than one exposure or health outcome. Cell shading indicates the number of studies available (i.e., darker shading indicates more studies, lighter shading indicates fewer studies, and a white space with no number indicates no studies available). Interactive figure with study details for studies evaluating nervous system effects at the Tableau Malformations-Animal tab (NTP 2020). To identify studies reporting significant effects, click "significant" in the Filter - Effect Significance in Tableau (NTP 2020). To identify studies that did not report statistical analyses, click "not reported" in the Filter - Effect Significance in Tableau (NTP 2020).

Higher frequencies of congenital malformations were reported in 18 animal studies, including 6 studies evaluating any congenital malformation (Andrew and Staples 1977; Eibs et al. 1982; Prahalada et al. 1985a; Prahalada et al. 1985b; Sannes et al. 1983; Silva et al. 2019) and 12 studies measuring specific congenital malformations (Dohler et al. 1986; Foote et al. 1968; Forsberg and Jacobsohn 1969; Forsberg et al. 1968; Graf and Neumann 1972; Iqbal et al. 2012; Johnstone and Franklin 1964; Pamir et al. 2006; Vega Matuszczyk and Larsson 1995; Ward 1972; Whalen et al. 1966; Wharton and Scott 1964). Of note, the animal studies reporting higher rates of congenital malformations included the 10, predominantly older, studies that were descriptive in nature and did not conduct statistical analyses [see Malformations-Animal, Filter - Effect Significance in Tableau (NTP 2020)].

Genital organ malformations were the most frequently observed malformations with effects reported in 11 studies, including 2 studies evaluating any congenital malformation (Prahalada et al. 1985a; Prahalada et al. 1985b) and 9 studies specifically evaluating genital malformations [see Malformations-Animal, Filter - Effect Significance in Tableau (NTP 2020)]. Demasculinizing effects on male reproductive development (e.g., hypospadias, undescended testes) were reported following exposure to cyproterone acetate (a synthetic progestogen with anti-androgenic action) (five studies) (Forsberg and Jacobsohn 1969; Forsberg et al. 1968; Graf and Neumann 1972; Vega Matuszczyk and Larsson 1995; Ward 1972), MPA (two studies) (Prahalada et al. 1985a; Prahalada et al. 1985b) and norethindrone (Wharton and Scott 1964). In addition, masculinizing effects on female development (e.g., clitoral enlargement, lack of vaginal opening) were reported with exposure to synthetic progestogens with known androgenic action, including norethindrone (three studies) (Foote et al. 1968; Whalen et al. 1966; Wharton and Scott 1964), norethindrone acetate (Johnstone and Franklin 1964), and medroxyprogesterone acetate (three studies) (Foote et al. 1968; Prahalada et al. 1985a; Prahalada et al. 1985b). Although not a congenital malformation, anogenital distance was reported to be altered in several nonhuman animal models after in utero exposure to the same synthetic progestogens, which were reported to induce genital organ malformations (see Reproductive System Effects section below for a complete description of this effect).

Except for genital organ malformations, very few types of malformations were reported to be induced by individual progestogen exposure. In studies evaluating any congenital malformation, significantly higher rates of cleft palate were reported following exposure to cyproterone acetate or MPA (two studies) (Andrew and Staples 1977; Eibs et al. 1982) as were central nervous system defects (other than neural tube defects), heart defects, and skeletal malformations following exposure to cyproterone acetate (Eibs et al. 1982) or lynestrenol (Sannes et al. 1983). Higher rates of neural tube defects were reported in chicks following a dose of progesterone reported to be 20 times the endogenous progesterone level for Stage 8 period of development in the chicken (157 ng), while the lower dose of progesterone (2 ng) had no effect (Iqbal et al. 2012; Pamir et al. 2006). Another study evaluating any malformation in zebrafish reported spinal and tail deformations following exposure to different forms of bioidentical progesterone (free and micronized forms) (Silva et al. 2019).

No congenital malformations were observed following prenatal exposure to 17OHPC (five studies) (Carbone and Brent 1993; Hendrickx et al. 1987; Johnstone and Franklin 1964; Schardein et al. 2012; Seegmiller et al. 1983), similar to its absence of effect in human studies. In contrast to the bird and fish models, no congenital malformations were reported in the studies evaluating progesterone in nonhuman mammalian models (Foote et al. 1968; Harini et al. 2009; Pointis et al. 1987; Wharton and Scott 1964) or in an amphibian model (Thomson and Langlois 2018).

Neurological Effects

Human Studies

The available literature on prenatal progestogen exposure associated with neurological effects was evaluated in 24 human studies (Figure 6). The literature base included 10 prospective cohort studies of 4 unique populations, 7 retrospective cohort studies with 6 unique populations, 6 randomized controlled trials of 5 unique populations, and 1 case-control study (Table 3). Most

studies evaluated neurological outcomes in humans following prenatal exposure to progesterone and MPA. Neurological effects were categorized into five domains: brain development (e.g., neurological handicap at discharge) and the neurobehavioral domains of learning and memory, sexually dimorphic behavior (i.e., gender roles/sexual identity), motor activity, and social/emotional measures. Several studies reported results relevant to more than one domain; for example, studies evaluating child development included assessments of learning and memory, motor activity, and social and emotional measure domains (McNamara et al. 2015; Norman et al. 2016; Northern et al. 2007; Rode et al. 2011; Vedel et al. 2016; Zhang et al. 2014).

The body of evidence for neurological development in human studies had a high degree of heterogeneity in the exposures and the neurological domains. Most of these studies were also older literature with publication dates between 1968 and 1989 (14 of 24 studies) [see Study Details and Timeline, Filter - Health Outcome in Tableau (NTP 2020)].

Significant effects were reported in 12 of 24 studies measuring neurodevelopmental and behavior effects in humans (Table 3). No evidence of consistent effects was observed across studies on an outcome basis or across an individual neurological domain considered broadly (e.g., learning, memory). Similarly, few studies focused on individual progestogen exposures and no evidence of consistent effects was observed among studies evaluating the same individual progestogen exposure with the largest literature bases. For example, the seven studies evaluating learning and memory associated with progesterone exposure assessed different endpoints (e.g., intelligence quotient, personality traits associated with good academic performance) with only three studies reporting significantly greater performance relevant to controls (Dalton 1968; 1976; Vedel et al. 2016).

Evidence Stream	Specific Outcome	17OHPC	allylestrenol	cyproterone acetate	drospirenone	dydrogesterone	gestodene	levonorgestrel	MPA	norethindrone	norethindrone acetate	norethynodrel	norgestimate	progesterone	progestogen	segesterone acetate	synthetic progestogen	Grand Total
		Exposure																
Animal	brain weight			2					2					6				10
	cholesterol levels													1				1
	DNA damage							1		1								2
	DNA levels													2				2
	enzyme levels/activity													2				2
	epigenetic modifications							1		1								2
	evoked potential													1				1
	fatty acid metabolism							1		1								2
	histology/immunohistochemistry			2										3				5
	learning and memory	1		1										5				7
	mitochondrial function							1		1								2
	motor activity	1		1	2	1	1	1	1		1			5				7
	motor sensory reflexes	1												1				2
	oxidative stress							1		1								2
	protein levels													1				1
	sexual dimorphic behavior	2	3	5						1				3				14
	social/emotional	1						2	2	3	1	1	1	6		1		9
	Total	3	3	8	2	1	1	3	5	4	2	1	1	19		1		38
Human	brain development	1												1				2
	learning and memory	1						1	1					7			2	12
	motor activity	1						1						6				8
	sexually dimorphic behavior	1							6					3			1	10
	social/emotional	1						1	1					4	2		1	10
	Total	3						1	7					9	2		3	24
Grand Total		6	3	8	2	1	1	4	12	4	2	1	1	28	2	1	3	61

Figure 6. Number of Studies Evaluating the Association between Prenatal Exposure to Progestogens and Nervous System Effects in Humans and Animals

17OHPC = 17-alpha-hydroxyprogesterone caproate; MPA = medroxyprogesterone acetate.
Progestogens indicates exposure to (bioidentical) progesterone or synthetic progestogens evaluated as a general category of exposure. Numbers in the grand total row or column refer to the number of unique studies per each exposure or health outcome; some studies might evaluate more than one exposure or health outcome. Cell shading indicates the number of studies available (i.e., darker shading indicates more studies, lighter shading indicates fewer studies, and a white space with no number indicates no available studies). Interactive figure with study details available at the Tableau Nervous System outcomes tab (NTP 2020). To view the specific outcome evaluated, expand the Specific Outcome column in the Tableau figure (NTP 2020). To identify studies reporting significant effects, click “significant” in the Filter - Effect Significance in Tableau (NTP 2020). To identify studies that did not report statistical analyses, click “not reported” in the Filter - Effect Significance in Tableau (NTP 2020).

Table 3. Summary of Studies Evaluating Neurological Effects in Humans Associated with In Utero Exposure to Progestogens

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
17OHPC	Randomized controlled trial (United States/neonates) [32 exposed and 28 unexposed]	250 mg, im injection weekly in second and/or third trimesters	Brain development (any neurological defect upon discharge from hospital)	No statistically significant difference in the incidence of neurological defects on discharge between exposed and unexposed neonates.	Briery et al. (2009)
	Retrospective cohort (United States/teenagers, age range 12–18 years) [25 exposed males, 25 unexposed males]	250 mg, im injection weekly in first, second and third trimesters	Sexually dimorphic behavior	Significantly more ($p < 0.05$) time spent watching television by exposed than unexposed males; however, no differences in aggression, gender identity, need to conform to group norms of social behavior, interest in play activity (sports, games, rough-and-tumble play), visual spatial ability, interest in reading and types of books, television program preferences.	Kester (1984)
	Prospective cohort (United States; follow-up to the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network study/children at age 48 months) [194 exposed, 84 unexposed]	250 mg, im injection weekly in second and third trimesters	Learning and memory, social/emotional, motor activity, and sexually dimorphic behavior	No statistically significant difference in the neurodevelopment or gender-specific roles scores between exposed and unexposed children.	Northern et al. (2007)
Levonorgestrel	Prospective cohort (China/infants and toddlers at ages 3, 6, 12 and 24 months) [195 exposed, 214 unexposed]	≤1.5 mg or >1.5 mg, orally in first trimester	Learning and memory, motor activity, and social/emotional	No statistically significant difference in the mental development of exposed infants or toddlers compared to unexposed children.	Zhang et al. (2014)

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
MPA	Prospective cohort (Israel/teenagers at age 18.6 ± 11.6 years) [73 exposed males, 97 exposed females; 377 unexposed males, 440 unexposed females]	150 mg per injection or ≥1 mg oral tablet, daily in first and second trimesters	Learning and memory	No statistically significant differences in verbal and spatial tests between the exposed and unexposed children.	Jaffe et al. (1988) [same cohort as Jaffe et al. (1989)]
	Prospective cohort (Israel/teenagers) [74 exposed boys, 98 exposed girls; 381 unexposed boys, 444 unexposed girls]	150 mg per injection or ≥1 mg oral tablet, daily in first and second trimesters	Aggression and sexually dimorphic behavior	No statistically significant differences in sex role or behavioral tests (aggressiveness, assertiveness, and physical activity levels) between the exposed and unexposed children.	Jaffe et al. (1989) [same cohort as Jaffe et al. (1988)]
	Prospective cohort (United States/female children, age range 8–12 years) [15 exposed, 15 unexposed]	140–2,020 mg total dose during pregnancy, im injection	Sexually dimorphic behavior	Significantly ($p < 0.05$) more females in the exposed group had a clear preference for feminine clothing styles and tended ($p = 0.06$) to show less tomboy-ism on a long-term basis than the control group.	Ehrhardt et al. (1977) [Preliminary study of Ehrhardt et al. (1984)]
	Prospective cohort (United States/ children, age range 8–12 years) [15 exposed, 15 unexposed]	140–3,900 mg total dose during pregnancy, im injection	Sexually dimorphic behavior	No statistically significant findings of greater frequency of stereotypic femininity in exposed females on the basis of reported less physical activity, and greater rates of playing with dolls and interest in feminine clothing than unexposed females.	Ehrhardt et al. (1984)
	Prospective cohort (United States/male children, age range 9–14 years) [13 exposed males, 13 matched unexposed males]	140–2,020 mg total dose during pregnancy, im injection	Sexually dimorphic behavior	No statistically significant difference in sexually dimorphic behavior in the exposed compared to unexposed male children. Slight tendencies of less interest in marriage and having children in the exposed group.	Meyer-Bahlburg et al. (1977) [Preliminary study of Ehrhardt et al. (1984)]

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
	Same as Ehrhardt et al. (1984)	Same as Ehrhardt et al. (1984)	Sexually dimorphic behavior	No statistically significant differences in sexually dimorphic behavior between the exposed girls and their controls. However, the children's interview suggested that boys in the exposed group appear more masculine on the general factor ($p = 0.016$) than their male controls.	Meyer-Bahlburg et al. (1984) [Reanalysis of Ehrhardt et al. (1984)]
	Same as Ehrhardt et al. (1984)	Same as Ehrhardt et al. (1984)	Sexually dimorphic behavior	Lower masculine nonathletic play behavior ($p < 0.05$) in exposed males after adjusting for pregnancy complications and age at time of study compared to unexposed. No statistically significant effects were observed in exposed compared to unexposed females.	Meyer-Bahlburg et al. (1988) [Reanalysis of Ehrhardt et al. (1984)]
Progesterone	Prospective cohort (United Kingdom/ infants and children) [infants: 29 exposed, 31 normal unexposed; children: 29 exposed, 21 normal unexposed, and 29 toxemia controls]	50–300 mg, im injection daily in second and third trimesters	Learning and memory, motor activity	At age 1 year, significantly ($p < 0.05$) more exposed infants were standing and walking than unexposed infants. More exposed infants were breast-fed than unexposed infants. At age 9–10 years, exposed children had significantly more above average school grades compared to unexposed children in all subjects except physical education.	Dalton (1968)
	Prospective cohort (United Kingdom/teenagers and young adults) [34 exposed, 37 normal unexposed, 12 toxemia controls]	500 mg, im injection during pregnancy, frequency not reported	Learning and memory	At ages 17–20 years, a significantly ($p < 0.05$) higher number of exposed teenagers and young adults achieved advanced grades and were accepted into university than unexposed groups.	Dalton (1976) [Same cohort as Dalton (1968)]

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
	Retrospective cohort (United States/adults, age range 19–24 years) [10 males exposed to progesterone, 13 males exposed to progestogens,[a] 23 unexposed males]	25–1,955 mg total dose during pregnancy, route not reported	Sexually dimorphic behavior	Significantly lower scores ($p < 0.05$) on the feminine and masculine scales of the Bem Sex Role Inventory in men exposed to higher doses of progesterone in utero, resulting in an undifferentiated score pattern. Significantly higher rate ($p < 0.05$) of erectile failure in men exposed to progesterone compared to unexposed men.	Kester et al. (1980)
	Retrospective cohort (United Kingdom/toddlers at age 2 years and teenagers at age 16 years) [toddlers: 19 exposed, 13 unexposed; and teenagers: 15 exposed, 11 unexposed]	50 mg on alternate days or 300 mg daily, im injection in second and third trimesters (16-year-old subjects)	Toddler: learning and memory, motor activity, social/emotional; teenager: learning and memory, sexually dimorphic behavior	Significantly lower ($p < 0.05$) scores for extroverted personality traits in exposed females than control females. No statistically significant effect on mental (learning and memory, social/emotional) or motor development in the age 2 group; no statistically significant enhanced intellectual and academic attainment in the age 16 group of exposed children compared to control group.	Lynch et al. (1978) [16-year old subjects in same cohort as Dalton (1968)]
	Randomized controlled trial (United Kingdom; follow-up to STOPPIT trial/neonates, infants, and preschoolers) [386 exposed, 395 unexposed]	90 mg, vaginal gel daily in second and third trimesters	Learning and memory, motor activity, social/emotional	No statistical differences in childhood development, emotion, or cognition at any life stage measured in exposed children compared to controls.	McNamara et al. (2015)

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
	Randomized controlled trial (United Kingdom and Sweden; the OPPTIMUM study/neonate and toddler) [neonates: 589 exposed, 587 unexposed; toddlers: 430 exposed, 439 unexposed]	200 mg, vaginal capsule daily in second and third trimesters	Neonate: brain development (brain injury diagnosed by ultrasound); toddler: learning and memory, motor activity, social/emotional	No statistically significant effect on incidence of neonatal brain injury or neurological developmental outcomes in toddlers, either as cognitive scores or neurological impairments, between exposed and unexposed subjects.	Norman et al. (2016)
	Retrospective cohort (Denmark/young adults) [34 exposed, 34 matched unexposed]	18.41 mg average, daily during third trimester, route not reported	Sexually dimorphic behavior	Lower rates ($p < 0.01$) of self-identification as heterosexual, and greater engagement in same-sex sexual behaviors ($p < 0.03$), attraction to the same or both sexes (e.g., ever attracted, $p < 0.02$), and higher scores on attraction to males ($p < 0.02$) for exposed men and women compared to controls.	Reinisch et al. (2017)
	Randomized controlled trial (Denmark and Austria; PREDICT trial/infants and toddlers) [664 exposed, 678 unexposed]	200 mg, vaginal pessary daily in second and third trimesters	Learning and memory, motor activity, social/emotional	No statistically significant difference in Ages and Stages Questionnaire scores between exposed and unexposed group.	Rode et al. (2011)

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
	Randomized controlled trial follow-up to PREDICT trial (Denmark/children at ages 48 and 60 months) [225 exposed, 212 unexposed]	200 mg, vaginal pessary daily in second and third trimesters	Learning and memory, motor activity, social/emotional	Mean Ages and Stages Questionnaire score was significantly higher ($p = 0.03$) (significant for total score and gross motor skills) in the exposed group compared with controls. In dichorionic twins, significantly lower risks of a low Ages and Stages Questionnaire score (<10th centile; (OR = 0.34, 95% CI = 0.14–0.86) or low gross motor skills score (OR, 0.43, 95% CI, 0.21–0.90) as well as higher communication ($p = 0.01$), gross motor skills ($p = 0.02$), and social/personality scores ($p = 0.04$) in the exposed versus control group.	Vedel et al. (2016) [Follow-up of the Danish cohort Rode et al. (2011)]
Synthetic progestogen	Retrospective cohort (United States/adults, age range 19–24 years) [10 males exposed to progesterone, 13 males exposed to progestogens, 23 unexposed males]	125–2,198 mg total dose, route not reported	Sexually dimorphic behavior	Higher scores ($p < 0.05$) on feminine scale, greater number ($p < 0.01$) of girls as friends in boyhood (based on timing of exposure during pregnancy), and a lower sex drive ($p < 0.01$) in exposed compared to control men.	Kester et al. (1980)
	Retrospective cohort (United States/children and teenagers at ages 5–18 years) [26 exposed, 26 unexposed]	525–9,890 mg total dose during pregnancy including first trimester (some were exposed to 1 mg estrogen), route not reported	Learning and memory, social/emotional	Significantly higher ($p < 0.05$) scores for independence and being self-assured, individualistic, and self-sufficient in exposed compared to unexposed siblings, but no statistically significant difference in IQ.	Reinisch and Karow (1977)

Exposure Measured	Study Design (Location/Subjects) [n]	Exposure Details	Outcome Measured	Results	Study
	Retrospective cohort (location not reported/children and adolescents, at ages 6–18 years) [25 exposed and 29 unexposed]	590–8,790 mg total dose in the first and second trimesters or first, second, and third trimesters, route not reported	Learning and memory, social/emotional	Significantly higher ($p < 0.01$) physical aggression scores in exposed children than their sex-matched unexposed siblings, especially with exposure to norethindrone. No statistically significant differences in verbal aggression or IQ.	Reinisch (1981)
Progestogen[a]	Case-control (China/children, ages ≤6 years) [235 cases and 37, 627 typically developing controls]	Not reported	ASD	Significantly higher odds of ASD with maternal use of progestogen to prevent threatened abortion (OR = 14.631, 95% CI = 5.103–41.952) or with use of progestogen contraceptives at time of conception (OR = 15.743, 95% CI = 7.610–32.568). Likewise, significantly higher odds of ASD with maternal consumption of progestogen-contaminated seafood during pregnancy (100–400 g/week, reference): 400–800 g/week (OR = 35.998, 95% CI = 16.589–78.115) or 800–1,200 (OR = 103.863, 95% CI = 30.128–358.057).	Li et al. (2018)
	Retrospective cohort (France; French Hhorages Association/children, ages not provided) [62 exposed, 18 unexposed firstborn siblings]	Not reported	Psychiatric disorders[b] and somatic disorders	Higher incidence of psychiatric disorders (79%) and somatic disorders (10%) in exposed children compared to firstborn unexposed siblings (0% for both types of disorder).	Soyer-Gobillard et al. (2019)

17OHPC = 17-alpha-hydroxyprogesterone caproate; Hhorages = Halt to Synthetic Hormones for Pregnancies; im = intramuscular injection; IQ = intelligence quotient; MPA = medroxyprogesterone acetate; n = number of subjects; OPPTIMUM = does progesterone prophylaxis to prevent preterm labor improve outcome; OR = odds ratio; PREDICT = prevention of preterm delivery in twin gestations; STOPPIT = study of progesterone for the prevention of preterm birth in twins; ASD = autism spectrum disorder.
[a]Progestogen refers to (bioidentical) progesterone or synthetic progestogens evaluated as general category of exposure.
[b]Psychiatric disorders included schizophrenia, manic-depressive psychosis, severe depression, behavior disorders, aggressiveness, or eating disorders.

Animal Studies

Thirty-seven studies of nonhuman animal models reporting on neurological effects were identified in the available literature (Figure 6). Similar to the human studies, progesterone was the most frequently evaluated exposure for nervous system effects in animals (19 studies). Neurobehavioral outcomes evaluated were grouped into five main categories: sexually dimorphic behavior (i.e., mating behavior; 14 studies), social/emotional skills (e.g., emotional reactivity, aggression; 9 studies), learning and memory (7 studies), motor activity (7 studies), and motor sensory reflexes (2 studies). Several non-neurobehavioral outcomes were assessed, including: brain weight (e.g., weight of whole brain or specific brain regions; nine studies), cholesterol levels (one study), DNA damage (two studies), DNA levels (two studies), enzyme levels and/or activity (two studies), epigenetic modification (two studies), evoked potential (one study), fatty acid metabolism (two studies), immunohistochemistry/histology (four studies), mitochondrial function (two studies), oxidative stress (two studies), and total brain protein levels (one study) (Figure 6). Among the studies, seven different animal models were tested, with rat the most commonly used (22 studies) [see Nervous System, Filter - Animal Model in Tableau (NTP 2020)].

Significant results were reported in 20 of the 28 studies evaluating nervous system effects; however, assessing the evidence for any potential pattern of effects for most outcomes was difficult due to too few studies per exposure and outcome pair, heterogeneity in the endpoints assessed within a domain, and/or heterogeneity in the results (Figure 6). The most consistent results were reported for studies evaluating sexually dimorphic behavior, with 10 of 12 studies reporting significant findings of alteration in mating behavior with apparent feminization of males and masculinization of females following exposure to progesterone (3 studies) (Hull et al. 1980; Pointis et al. 1987; Regestein et al. 1975), cyproterone acetate (4 studies) (Etzel et al. 1974; Perakis and Stylianopoulou 1986; Vega Matuszczyk and Larsson 1995; Ward 1972; Ward and Renz 1972), or allylestrenol (3 studies) (Csaba et al. 1993; Karabelyos et al. 1994a; Karabelyos et al. 1994b) in various animal models (e.g., rats, mice, guinea pig) [see Nervous System, Filter - Effect Significance in Tableau (NTP 2020)]. An additional study that did not conduct statistical analyses reported that 11 of 14 male guinea pigs prenatally exposed to cyproterone acetate did not display mating behavior toward females in estrus (Etzel et al. 1974). In contrast, a study of mating behavior following prenatal exposure to 17OHPC in a rat model reported a significantly greater number of copulation attempts (Pushpalatha et al. 2005). Studies reporting on other neurobehavioral domains yielded less consistent results or were assessed using a variety of tests measured in only a few studies each, which limited the ability to compare among studies. For example, of the five studies evaluating the effects of developmental exposure to progesterone on learning and memory, two studies reported apparent higher scores for learning and memory endpoints (Herrington et al. 2016; Snyder and Hull 1980), two reported lower scores (Herrington et al. 2015; Hull et al. 1980), and one study reported no effect (Coyle et al. 1976).

Reproductive System Effects

Human Studies

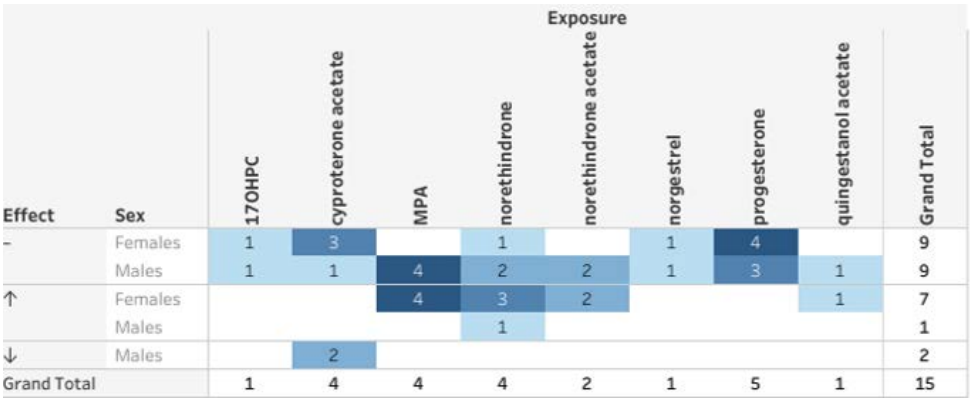
Three human studies addressed reproductive system effects associated with in utero exposure to progestogens evaluated in a single prospective cohort study and two retrospective cohort studies.

Only two reproductive effects were evaluated in humans: fertility and timing of puberty [see the Reproductive tab in Tableau; (NTP 2020)]. In the one study evaluating fertility, the authors reported no association of prenatal exposure to progestogens on fertility, which was measured as the number of women with a live birth (Hemminki et al. 1999). The appearance of pubic hair, a sign of onset of puberty, was reported delayed in girls exposed to MPA relative to controls in one study ($X^2 = 3.99$, $p = 0.05$ by Mantel-Haenszel weighted chi-square for all age strata, but not by another statistical method (RR = 0.61, 95% CI = 0.4–1.0) (Pardthaisong et al. 1992). Another study reported no statistically significant difference in timing of puberty in girls following multiple regression analysis (Jaffe et al. 1990). The timing of puberty for boys was not significantly different in either study (Jaffe et al. 1990; Pardthaisong et al. 1992).

Animal Studies

Reproductive system effects associated with in utero exposure to progestogens were reported in 26 animal studies. The most frequently evaluated reproductive outcome was anogenital distance (16 studies). Other outcomes reported included reproductive organ weights, reproductive organ histology, sperm parameters, timing of puberty, estrous cyclicity, fertility, fecundity, and gene expression (e.g., vitellogenin mRNA levels in fish).

Anogenital distance (AGD) is often measured in studies of humans and mammalian animal models to determine whether an exposure resulted in hormone disruption during the period of sexual differentiation in utero. In normal development, AGD in males is consistently longer than in females. Exposure to anti-androgenic chemicals or weak androgen agonists during pregnancy has been demonstrated to significantly shorten AGD in males. Significant findings were reported in 13 animal studies evaluating AGD following prenatal progestogen exposure and two studies that reported effects of progestogens but did not conduct statistics (Giannia et al. 1969; Johnstone and Franklin 1964) (Figure 7). The direction of the effect was consistent with in utero exposure to progestogens lengthening the AGD of female offspring (Foote et al. 1968; Gandelman et al. 1981; Giannia et al. 1969; Johnstone and Franklin 1964; Prahalada et al. 1985a; Prahalada et al. 1985b; Whalen et al. 1966) and shortening the AGD in male offspring (Gupta and Goldman 1986; Scouten et al. 1975). Similar effects were reported across species (mice, rats, guinea pigs, baboons, and cynomolgus monkeys) and across synthetic progestogen exposures with known anti-androgenic (e.g., cyproterone acetate) or androgenic effects (e.g., MPA, norethindrone, norethindrone acetate, quingestanol acetate). One exception was a report of greater AGD than controls in male guinea pigs prenatally exposed to norethindrone (Foote et al. 1968).



		Exposure								
Effect	Sex	17OHPC	cyproterone acetate	MPA	norethindrone	norethindrone acetate	norgestrel	progesterone	quingestanol acetate	Grand Total
-	Females	1	3		1		1	4		9
	Males	1	1	4	2	2	1	3	1	9
↑	Females			4	3	2			1	7
	Males				1					1
↓	Males		2							2
Grand Total		1	4	4	4	2	1	5	1	15

Figure 7. Reported Results of Animal Studies Evaluating the Association between Prenatal Exposure to Progestogens and Anogenital Distance by Sex

17OHPC = 17-alpha-hydroxyprogesterone caproate; MPA = medroxyprogesterone acetate.
Numbers in the grand total row and column refer to the number of unique studies per each exposure or health outcome; some studies might evaluate more than one exposure or health outcome. Cell shading indicates the number of studies available; i.e., darker shading indicates more studies; lighter shading indicates fewer studies; and a white space with no number indicates no studies available. Effect symbols: - = no effect (data similar to control), ↑ = greater than control, and ↓ = less than control. Interactive figure with study details available at the Tableau Reproductive outcomes tab (NTP 2020).

Discussion

Using systematic review methodology, this scoping review characterized the available published literature on adverse health outcomes in offspring associated with progestogen exposure during pregnancy in humans and in animal models. The comprehensive literature search and screening steps focused on identifying studies reporting on congenital malformations and the health outcomes of liveborn offspring. Among the 212 studies identified as relevant, a wide range of progestogens was evaluated, including bioidentical progesterone or 1 of 23 different synthetic progestogens. The most commonly reported outcomes were growth outcomes (primarily birth weight), prematurity-related neonatal outcomes, congenital malformations, neurological outcomes, and reproductive system outcomes.

Genital malformations were the most commonly induced group of malformations associated with prenatal exposure to progestogens**.** Of the studies reporting first-trimester exposure in humans, significantly higher rates of genital malformations were reported for 3 of 8 studies specifically evaluating genital malformations and 2 of 20 studies evaluating any malformation (Figure 4). Higher frequencies of genital malformations were also observed in animals in 10 of 12 studies specifically evaluating genital malformations and 2 of 17 evaluating any malformation (Figure 5). The exposures eliciting greater rates of reproductive tract malformations in males in these studies included 19-nortestosterone derivatives, allylestrenol, lynestrenol, norethindrone and norethindrone acetate, and 17-alpha-acetoxyprogesterone derivative MPA; these exposures are reported to have androgen agonist activity (Schindler et al. 2008), which might compete with the endogenous androgen levels. The 17-alpha-acetoxyprogesterone derivative cyproterone acetate was also associated with reproductive malformations in male animals consistent with inhibited testosterone (e.g., presence of a vaginal anlage, prostate agenesis); this exposure is reported to have anti-androgenic activity (Schindler et al. 2008). Consistent with the congenital malformation data, these agents also feminized the AGD of male animals (i.e., cyproterone acetate) or masculinized the AGD in female animals following developmental exposure to these same synthetic progestogens (i.e., MPA or the 17-nortestosterone derivatives). Of the remaining studies on congenital malformations reporting effects, findings for the type of malformations reported were inconsistent or different results were obtained for the same exposure (Table 2) [see Malformations-Animal Filter - Evidence Significance in Tableau (NTP 2020)].

Similar rates of congenital malformations were reported between control and exposed offspring following exposure during organogenesis to either 17OHPC (five human and five animal studies). First-trimester exposure to 17OHPC has been hypothesized to be without elevated risk for congenital malformations (Dudas et al. 2006; Hilgers et al. 2015) and might be a candidate for a future systematic review to evaluate a lack of effect. Progesterone exposure did not result in higher rates of congenital malformation in humans (four studies) and nonhuman mammalian animal models (five studies), but was reported to induce spinal and tail malformations in embryonic zebrafish (Silva et al. 2019) and neural tube defects when administered to chick embryos at reportedly supranormal levels (Iqbal et al. 2012; Pamir et al. 2006). Progesterone is regularly administered in the first trimester to aid in the maintenance of pregnancy in women undergoing infertility treatment and is generally accepted to have no risk of congenital malformations (Hilgers et al. 2015).

Although a large number of studies evaluated nervous system effects, relatively few studies evaluated the same exposure-outcome pair because of the large number of exposures (e.g., progesterone, 13 different synthetic progestogens) and the wide range of the neurological effects assessed (6 neurobehavioral domains and 12 morphological or functional domains) (Figure 6). Progesterone was the most commonly evaluated exposure across both human and animal studies. The reported results across the same outcome were, however, often inconsistent. For example in animal studies, whole brain (or a specific region of brain) weight was higher in some studies (Ahmad and Zamenhof 1979; Menzies et al. 1982; van Marthens et al. 1979) and unaffected in others (Coyle et al. 1976; Shaw et al. 2017; Snyder and Hull 1980). Some studies of prenatal progesterone exposure reported greater performance in the learning and cognition domain in exposed versus unexposed children (Dalton 1968; 1976), while other studies reported no difference from controls (Lynch et al. 1978; McNamara et al. 2015; Norman et al. 2016). One neurological outcome had more consistent significant findings: sexual behavior (e.g., mating behavior). Specifically, 11 of 14 animal studies reported a defeminization of mating behavior with exposure to allylestrenol (Csaba et al. 1993; Karabelyos et al. 1994a; Karabelyos et al. 1994b), cyproterone acetate (Etzel et al. 1974; Perakis and Stylianopoulou 1986; Vega Matuszczyk and Larsson 1995; Ward 1972; Ward and Renz 1972), or progesterone (Hull et al. 1980; Pointis et al. 1987; Regestein et al. 1975). Cyproterone acetate is used to treat hypersexuality in men, consistent with the effects reported in animal studies. Cyproterone acetate is administered to women as a combination estrogen/progestogen treatment for severe acne and hirsutism in women and is contraindicated for use during pregnancy. Several studies, mainly published in the 1970s and 1980s, evaluated the influence of progestogens on sexual behavior and sexually dimorphic behavior with inconsistent findings (Table 3).

Although many studies reported on growth and prematurity-related neonatal health outcomes for human infants, preterm birth was not commonly observed in unhandled laboratory animals. Thus, no studies reported on neonatal health outcomes in animal studies related to prematurity. In addition, the current scoping review did not include animal models of preterm birth because the models required additional exposures or physical manipulation to induce the condition (Elovitz and Mrinalini 2006). As stated in the methods, studies reporting premature birth were not included in the scoping review because threatened premature birth or the prevention thereof was the predominant reason for the administration of progestogens. Mortality (e.g., miscarriage and stillbirth) was not assessed in the current scoping review because it was often the reason for administration of drug and the focus of the current review was on liveborn offspring.

Limitations of the Evidence

Precise drug nomenclature is a major challenge in characterizing the literature available on the potential adverse health effects associated with the progestogens (Hilgers et al. 2015; Keith and Berger 1977; Romero and Stanczyk 2013). For example, the term progestin is defined as synthetic progestogens in some research groups (Stanczyk et al. 2013), whereas others have used the term progestin to refer to both the bioidentical progesterone and the synthetic progestogens (Carmichael et al. 2005; Heinonen et al. 1977; Li et al. 2018). In addition, some authors use the abbreviations of endogenous progestogens to refer to synthetic progestogen; for example, the abbreviation for the endogenous hormone 17-alpha-hydroxyprogesterone is 17P, but this abbreviation has often been used to refer to the synthetic progestogen 17-alpha-hydroxyprogesterone caproate [reviewed in Romero (2013)]. For the purposes of this scoping

review, the bioidentical (plant-based) progesterone drugs were referred to as progesterone, synthetic progestogens as synthetic progestogens, and progestogens as the general category for both bioidentical progesterone and synthetic progestogens.

One reason imprecision in the nomenclature is a challenge is that progesterone and the individual synthetic progestogens each have different biological properties (Hapgood et al. 2014; Schindler et al. 2008). Thus, for the 24 progestogens identified in the scoping efforts, the evidence base is smaller for any given progestogen due to their unique bioactivities. The common feature of the progestogens is that they all bind to the progesterone receptor to initiate development of the endometrial lining of the uterus to maintain a pregnancy, although they bind to the progesterone receptor with different relative binding affinities. Some synthetic progestogens also act as androgen agonists (e.g., many of the 19-nortestosterone derivatives like norethindrone and levonorgestrel), although the literature is inconsistent on progesterone. Other synthetic progestogens appear to have anti-androgenic properties (e.g., the pregnane derivatives such as cyproterone acetate, the spironolactone derivative drospirenone), although progesterone appears to be weakly anti-androgenic. Finally, a few synthetic progestogens are reported to act as glucocorticoid agonists (e.g., gestodene, drospirenone) or mineralocorticoid receptor antagonists (drospirenone), although the activity of progesterone on these receptors is inconclusive.

Many early reports of congenital malformations were associated with combined exposure to progestogens and estrogens [reviewed in Ferencz (1980) and Keith (1977)]. Determining the association of progestogens with an adverse health effect in some studies is not possible because individual progesterone or synthetic progestogen exposure is added to a general category called female hormones that includes combination drugs with progestogen and estrogen (Ferencz et al. 1980; Hadjigeorgiou et al. 1982; Nora and Nora 1975).

Limitations of the Scoping Review

Several limitations of the data hampered their utility to assess the association between progestogens with select adverse health outcomes:

- The current scoping review excluded an important population exposed to progestogens during pregnancy: offspring conceived with assisted reproductive technology. Many studies reporting on pregnancy outcomes and health of offspring conceived by assisted reproductive technologies do not detail the hormonal regimen followed, which made it challenging to identify relevant progestogen exposures, or the studies report limited information on the health of the offspring. Also, most treatments in assisted reproductive technology involve combinations of gonadotropins and steroid hormone drugs as well as physical manipulation of the gametes/embryo, which makes attributing an effect to progestogens alone difficult. The literature base evaluating the health of offspring conceived with assisted reproductive technologies is increasing, and systematic reviews and meta-analyses have been published in recent years on a number of health outcomes [e.g., adverse pregnancy outcomes (Qin et al. 2016); cancer (Wang et al. 2019); cardiovascular and metabolic profiles (Guo et al. 2017); genitourinary malformations (Massaro et al. 2015)].
- Studies exposing farm animals (livestock) to progestogens were also excluded from this scoping review as they often reported on methods of assisted reproduction or were investigating the role of endogenous progesterone on pregnancy through

hormonal and often surgical manipulation of pregnancy. In addition, these studies frequently had limited information on the outcome of the exposed offspring as the studies were focused on maintenance of pregnancy. A more refined literature search targeting mechanistic studies of progesterone might identify relevant studies in this literature base.

- The current scoping review did not exclude studies with co-exposure to tocolytics and associated drugs used during pregnancy or delivery. A subsequent systematic review might consider conducting a sensitivity analysis without offspring from pregnancies at high risk of preterm birth, to minimize the potential adverse health effects of co-exposures on the offspring.
- The current scoping review included only studies with exposure during pregnancy, yet some offspring in animal models are born precociously (e.g., mice and rats). Thus, the current scoping review could have missed some relevant animal studies of nervous system development, which are relevant to the period of in utero brain development in humans (Howdeshell 2002; Rice and Barone 2000).
- The literature search strategy was not sensitive to identifying in vitro or mechanistic studies with progestogen exposure relevant to miscarriage or preterm birth. Future scoping efforts or systematic reviews could be tailored to search for in vitro models or mechanistic targets for pregnancy outcomes and other adverse health outcomes in offspring, of interest.
- The current scoping review focused only on two databases (PubMed and Cochrane Reviews), which likely identified most but not all the relevant literature on the topic. In contrast, a systematic review evaluation would use multiple databases, perform snowballing (i.e., reviewing the reference lists of relevant studies and reviews to retrieve additional relevant papers), and conduct a risk-of-bias assessment of the quality of the literature to inform level of evidence conclusions on the body of evidence.

Research Needs

The scoping review identified several areas of research needed to address gaps in our knowledge of possible health effects associated with prenatal exposure to progestogens in humans, including neurobehavioral outcomes and cancer.

Relatively few studies evaluate the incidence of congenital malformations following first-trimester exposure to progestogen medication intended for use during pregnancy to ensure it is safe for both women and their fetuses.

Longer-term follow-up health evaluations of offspring prenatally exposed to progestogens are needed. For example, the few available studies of long-term evaluations of neurological outcomes associated with prenatal progestogen exposure only examined children up to age 60 months (Vedel et al. 2016). Similarly, very few studies have evaluated the association between cancer incidence in adulthood following prenatal exposure to progestogens. Progesterone was identified by the National Toxicology Program's Report on Carcinogens as reasonably anticipated to be a human carcinogen in accordance with evidence from experimental animal studies observing cancers of the breast, ovary, and uterus following postnatal exposure to

progesterone (NTP 2016); however, human data are not conclusive (IARC 1974; IARC 1979; IARC 1982). Early neonatal exposure to progesterone was reported to induce tumors of the mammary glands, vagina, and cervix in female rats (IARC 1974; IARC 1979; IARC 1982); however, information is lacking on cancer incidence in experimental animals following prenatal exposure. Even less information is available about synthetic progestogens.

As more literature on this topic is available, systematic reviews are needed that evaluate a specific progestogen (bioidentical progesterone or an individual synthetic progestogen) or class of synthetic progestogen (19-nortestosterone derivatives) to better understand the association between prenatal exposure to specific groups or individual progestogens.

On a related topic not covered in this evaluation, increased understanding is needed of the effects of early postnatal exposure to progestogens on the developing brain. Bioidentical progesterone is currently being explored as a neuroprotective treatment to reduce the effects of hypoxia and excitotoxic brain damage for preterm infants (Plunchino et al. 2016).

Summary

This scoping review identified and characterized a limited body of evidence on potential adverse health effects associated with exposure to progestogens during in utero development. The evidence was inadequate to recommend an evaluation of these potential health effects in a systematic review due to heterogeneity of the endpoints evaluated per health outcome and inconsistencies in the results. Also, the wide variety of synthetic progestogens administered and their biological properties unique from bioidentical progesterone limit the ability to assess the health effects of a general category of progestogens (bioidentical progesterone and synthetic progestogens) or synthetic progestogens. More research is needed to better understand the potential association between prenatal exposure to progestogens with adverse pregnancy outcomes, congenital malformation incidence, and longer-term health outcomes of prenatally exposed offspring.

References

Aarskog D. 1971. Intersex conditions masquerading as simple hypospadias. Birth Defects Orig Artic Ser. 7(6):122-130.

Ahmad G, Zamenhof S. 1979. The effect of progesterone on brain and body growth of chick embryos. Growth. 43(1):58-61.

Andrew FD, Staples RE. 1977. Prenatal toxicity of medroxyprogesterone acetate in rabbits, rats, and mice. Teratology. 15(1):25-32. http://dx.doi.org/10.1002/tera.1420150104

Beard CM, Melton LJ, 3rd, O'Fallon WM, Noller KL, Benson RC. 1984. Cryptorchism and maternal estrogen exposure. Am J Epidemiol. 120(5):707-716. http://dx.doi.org/10.1093/oxfordjournals.aje.a113938

Briery CM, Veillon EW, Klauser CK, Martin RW, Chauhan SP, Magann EF, Morrison JC. 2009. Progesterone does not prevent preterm births in women with twins. South Med J. 102(9):900-904. http://dx.doi.org/10.1097/SMJ.0b013e3181afee12

Brucker M, Likis F. 2010. Steroid hormones. In: King T, Brucker M, editors. Pharmacology for Women's Health. Burlington, MA: Jones & Bartlett Publishers.

Calzolari E, Contiero MR, Roncarati E, Mattiuz PL, Volpato S. 1986. Aetiological factors in hypospadias. J Med Genet. 23(4):333-337. http://dx.doi.org/10.1136/jmg.23.4.333

Carbone JP, Brent RL. 1993. Genital and nongenital teratogenesis of prenatal progestogen therapy: The effects of 17 alpha-hydroxyprogesterone caproate on embryonic and fetal development and endochondral ossification in the C57B1/6J mouse. Am J Obstet Gynecol. 169(5):1292-1298. http://dx.doi.org/10.1016/0002-9378(93)90296-U

Carmichael SL, Shaw GM, Laurent C, Croughan MS, Olney RS, Lammer EJ. 2005. Maternal progestin intake and risk of hypospadias. Arch Pediatr Adolesc Med. 159(10):957-962. http://dx.doi.org/10.1001/archpedi.159.10.957

Colvin L, Slack-Smith L, Stanley FJ, Bower C. 2010. Linking a pharmaceutical claims database with a birth defects registry to investigate birth defect rates of suspected teratogens. Pharmacoepidemiol Drug Saf. 19(11):1137-1150. http://dx.doi.org/10.1002/pds.1995

Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, Williams H, Eapen AK, Roberts T, Ogwulu CC et al. 2019. A randomized trial of progesterone in women with bleeding in early pregnancy. N Engl J Med. 380(19):1815-1824. http://dx.doi.org/10.1056/NEJMoa1813730

Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, Gupta P, Dawood F, Koot YE, Atik RB. 2015. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 373(22):2141-2148. http://dx.doi.org/10.1056/NEJMoa1504927

Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, Gupta P, Dawood F, Koot YE, Atik RB et al. 2016. PROMISE: First-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages-a randomised, double-blind, placebo-controlled,

international multicentre trial and economic evaulation. Health Technol Assess. 20(41):1-92. http://dx.doi.org/10.3310/hta20410

Corona-Rivera JR, Bobadilla-Morales L, Corona-Rivera A, Pena-Padilla C, Olvera-Molina S, Orozco-Martin MA, Garcia-Cruz D, Rios-Flores IM, Gomez-Rodrigues BG, Rivas-Soto G et al. 2018. Prevalence of orofacial clefts and risks of nonsyndromic cleft lip with or without cleft palate in newborns at a university hospital from West Mexico. Congenit Anom. 58(4):117-123. http://dx.doi.org/10.1111/cga.12276

Coyle IR, Anker R, Cragg B. 1976. Behavioral, biochemical and histological effects of prenatal administration of progesterone in the rat. Pharmacol Biochem Behav. 5(5):587-590. http://dx.doi.org/10.1016/0091-3057(76)90274-4

Csaba G, Karabelyos C, Dallo J. 1993. Fetal and neonatal action of a polycyclic hydrocarbon (benzpyrene) or a synthetic steroid hormone (allylestrenol) as reflected by the sexual behaviour of adult rats. J Dev Physiol. 19(2):67-70.

Czeizel A, Huiskes N. 1988. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. Clin Ther. 10(6):725-739.

Czeizel A, Kodaj I. 1995. A changing pattern in the association of oral contraceptives and the different groups of congenital limb deficiencies. Contraception. 51(1):19-24. http://dx.doi.org/10.1016/0010-7824(94)00008-K

Dalton K. 1968. Ante-natal progesterone and intelligence. Br J Psychiatry. 114(516):1377-1382. http://dx.doi.org/10.1192/bjp.114.516.1377

Dalton K. 1976. Prenatal progesterone and educational attainments. Br J Psychiatry. 129:438-442. http://dx.doi.org/10.1192/bjp.129.5.438

De Santis M, Cavaliere AF, Straface G, Carducci B, Caruso A. 2005. Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. Fertil Steril. 84(2):296-299. http://dx.doi.org/10.1016/j.fertnstert.2005.01.136

Dohler KD, Coquelin A, Davis F, Hines M, Shryne JE, Sickmoller PM, Jarzab B, Gorski RA. 1986. Pre- and postnatal influence of an estrogen antagonist and an androgen antagonist on differentiation of the sexually dimorphic nucleus of the preoptic area in male and female rats. Neuroendocrinology. 42(5):443-448. http://dx.doi.org/10.1159/000124484

Dudas I, Gidai J, Czeizel A. 2006. Population-based case-control teratogenic study of hydroxyprogesterone treatment during pregnancy. Congenit Anom. 46(4):194-198. http://dx.doi.org/10.1111/j.1741-4520.2006.00128.x

Ehrhardt AA, Grisanti GC, Meyer-Bahlburg HF. 1977. Prenatal exposure to medroxyprogesterone acetate (MPA) in girls. Psychoneuroendocrinology. 2(4):391-398. http://dx.doi.org/10.1016/0306-4530(77)90010-5

Ehrhardt AA, Meyer-Bahlburg HF, Feldman JR, Ince SE. 1984. Sex-dimorphic behavior in childhood subsequent to prenatal exposure to exogenous progestogens and estrogens. Arch Sex Behav. 13(5):457-477. http://dx.doi.org/10.1007/BF01541430

Eibs HG, Spielmann H, Hagele M. 1982. Teratogenic effects of cyproterone acetate and medroxyprogesterone treatment during the pre- and postimplantation period of mouse embryos. I. Teratology. 25(1):27-36. http://dx.doi.org/10.1002/tera.1420250105

El-Zibdeh MY. 2005. Dydrogesterone in the reduction of recurrent spontaneous abortion. J Steroid Biochem Mol Biol. 97(5):431-434. http://dx.doi.org/10.1016/j.jsbmb.2005.08.007

El Kholy M, Hamza RT, Saleh M, H E. 2013. Penile length and genital anomalies in Egyptian male newborns: Epidemiology and influence of endocrine disruptors. J Pediatr Endocrinol Metab. 26(5-6):509-513. http://dx.doi.org/10.1515/jpem-2012-0350

Elovitz MA, Mrinalini C. 2006. The use of progestational agents for preterm birth: Lessons from a mouse model. Am J Obstet Gynecol. 195(4):1004-1010. http://dx.doi.org/10.1016/j.ajog.2006.06.013

Etzel V, Schenck B, Neumann F. 1974. Influence of cyproterone acetate during pregnancy on the sexual behaviour of male guinea-pigs. J Reprod Fertil. 37(2):315-321. http://dx.doi.org/10.1530/jrf.0.0370315

Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R. 1980. Maternal hormone therapy and congenital heart disease. Teratology. 21(2):225-239. http://dx.doi.org/10.1002/tera.1420210213

Foote WD, Foote WC, Foote LH. 1968. Influence of certain natural and synthetic steroids on genital development in guinea pigs. Fertil Steril. 19(4):606-615. http://dx.doi.org/10.1016/S0015-0282(16)36735-8

Forsberg JG, Jacobsohn D. 1969. The reproductive tract of males delivered by rats given cyproterone acetate from days 7 to 21 of pregnancy. J Endocrinol. 44(3):461-462. http://dx.doi.org/10.1677/joe.0.0440461

Forsberg JG, Jacobsohn D, Norgren A. 1968. Development of the urogenital tract in male offspring of rats injected during pregnancy with a substance with antiandrogenic properties (cyproterone). Z Anat Entwicklungsgesch. 126(4):320-331. http://dx.doi.org/10.1007/BF00520797

Gandelman R, Howard SM, Reinisch JM. 1981. Perinatal exposure to 19-nor-17 alpha-ethynyltestosterone (norethindrone) influences morphology and aggressive behavior of female mice. Horm Behav. 15(4):404-415. http://dx.doi.org/10.1016/0018-506X(81)90005-2

Gellersen B, Fernandes MS, Brosens JJ. 2009. Non-genomic progesterone actions in female reproduction. Hum Reprod Update. 15(1):119-138. http://dx.doi.org/10.1093/humupd/dmn044

Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. 1987. Double-blind controlled trial of progesterone substitution in threatened abortion. Biol Res Pregnancy Perinatol. 8(1 1ST Half):26-34.

Giannia T, Steinetz BG, Rassaert CL, McDougall EA, Meli A. 1969. Biological profile of quingestanol acetate. Proc Soc Exp Biol Med. 131(3):781-789. http://dx.doi.org/10.3181/00379727-131-33977

Graf KJ, Neumann F. 1972. Influence of cyproterone acetate on sexual differentiation of male guinea pigs. Z Anat Entwicklungsgesch. 137(2):200-220. http://dx.doi.org/10.1007/BF00538791

Grumbach MM, Ducharme JR, Moloshok RE. 1959. On the fetal masculinizing action of certain oral progestins. J Clin Endocrinol Metab. 19:1369-1380. http://dx.doi.org/10.1210/jcem-19-11-1369

Guo X-Y, Liu X-M, Jin L, Wang T-T, Ullah K, Sheng J-Z, Huang H-F. 2017. Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis. Fertil Steril. 107(3):622-631.e625. https://doi.org/10.1016/j.fertnstert.2016.12.007

Gupta C, Goldman AS. 1986. The arachidonic acid cascade is involved in the masculinizing action of testosterone on embryonic external genitalia in mice. Proc Natl Acad Sci USA. 83(12):4346-4349. http://dx.doi.org/10.1073/pnas.83.12.4346

Hadjigeorgiou E, Malamitsi-Puchner A, Lolis D, Lazarides P, Nicolopoulos D, Kaskarelis D. 1982. Cardiovascular birth defects and antenatal exposure to female sex hormones. Dev Pharmacol Ther. 5(1-2):61-67. http://dx.doi.org/10.1159/000481008

Hapgood JP, Africander D, Louw R, Ray RM, Rohwer JM. 2014. Potency of progestogens used in hormonal therapy: Toward understanding differential actions. J Steroid Biochem Mol Biol. 142:39-47. http://dx.doi.org/10.1016/j.jsbmb.2013.08.001

Harini C, Sainath SB, Reddy PS. 2009. Progesterone administration induces preimplantation embryonic loss in mic. Fertil Steril. 91(5 Suppl):2137-2141. http://dx.doi.org/10.1016/j.fertnstert.2008.06.031

Heinonen OP, Slone D, Monson RR, Hook EB, Shapiro S. 1977. Cardiovascular birth defects and antenatal exposure to female sex hormones. N Engl J Med. 296(2):67-70. http://dx.doi.org/10.1056/NEJM197701132960202

Hemminki E, Gissler M, Toukomaa H. 1999. Exposure to female hormone drugs during pregnancy: Effect on malformations and cancer. Br J Cancer. 80(7):1092-1097. http://dx.doi.org/10.1038/sj.bjc.6690469

Hendrickx AG, Korte R, Leuschner F, Neumann BW, Poggel A, Binkerd P, Prahalada S, Gunzel P. 1987. Embryotoxicity of sex steroidal hormones in nonhuman primates: II. Hydroxyprogesterone caproate, estradiol valerate. Teratology. 35(1):129-136. http://dx.doi.org/10.1002/tera.1420350116

Herrington J, Vallian C, Lickliter R. 2015. Increased yolk progesterone interferes with prenatal auditory learning and elevates emotional reactivity in bobwhite quail (Colinus virginianus) chicks. Dev Psychobiol. 57(2):255-262. http://dx.doi.org/10.1002/dev.21274

Herrington JA, Rodriguez Y, Lickliter R. 2016. Elevated yolk progesterone moderates prenatal heart rate and postnatal auditory learning in bobwhite quail (Colinus virginianus). Dev Psychobiol. 58(6):784-788. http://dx.doi.org/10.1002/dev.21419

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. 2019. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 www.training.cochrane.org/handbook. [Updated July 2019]

Hilgers TW, Keefe CE, Pakiz KA. 2015. The use of isomolecular progesterone in the support of pregnancy and fetal safety. Issues Law Med. 30(2):159-168.

Howard BE, Phillips J, Tandon A, Maharana A, Elmore R, Mav D, Sedykh A, Thayer K, Merrick BA, Walker V et al. 2020. SWIFT-Active Screener: Accelerated document screening through active learning and integrated recall estimation. Environ Int. 138:105623. https://doi.org/10.1016/j.envint.2020.105623

Howdeshell KL. 2002. A model of the development of the brain as a construct of the thyroid system. Environ Health Perspect. 110 Suppl 3:337-348. http://dx.doi.org/10.1289/ehp.02110s3337

Hull EM, Franz JR, Snyder AM, Nishita JK. 1980. Perinatal progesterone and learning, social and reproductive behavior in rats. Physiol Behav. 24(2):251-256. http://dx.doi.org/10.1016/0031-9384(80)90082-7

Institute of Medicine (IOM). 2007. Preterm Birth: Causes, Consequences, and Prevention. Institute of Medicine U.S. Committee on Understanding Premature Birth and Assuring Health Outcomes Report. Washington, D.C.: National Academies Press. https://doi.org/10.17226/11622.

International Agency Research on Cancer (IARC). 1974. Progesterone. In: Sex Hormones IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer. p. 135-146.

International Agency Research on Cancer (IARC). 1979. Progesterone. In: Sex Hormones II IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer. p. 491-515.

International Agency Research on Cancer (IARC). 1982. Progesterone. In: Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. Lyon, France: IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. p. 202-203.

Iqbal I, Qamar K, Butt SA, Hayder O, Saeed I, Moor U. 2012. The role of folic acid in prevention of neural tube defects caused by high dose progesterone. Turk Neurosurg. 22(1):7-12.

Jaffe B, Harlap S, Baras M, Gordon L, Lieblich A, Magidor S, Sanchez M. 1988. Long-term effects of MPA on human progeny: Intellectual development. Contraception. 37(6):607-619. http://dx.doi.org/10.1016/0010-7824(88)90007-8

Jaffe B, Shye D, Harlap S, Baras M, Belmaker E, Gordon L, Magidor S, Fortney J. 1990. Health, growth and sexual development of teenagers exposed in utero to medroxyprogesterone acetate. Paediatr Perinat Epidemiol. 4(2):184-195. http://dx.doi.org/10.1111/j.1365-3016.1990.tb00637.x

Jaffe B, Shye D, Harlap S, Baras M, Lieblich A. 1989. Aggression, physical activity levels and sex role identity in teenagers exposed in utero to MPA. Contraception. 40(3):351-363. http://dx.doi.org/10.1016/0010-7824(89)90098-X

Johnstone EE, Franklin RR. 1964. Assay of progestins for fetal virilizing properties using the mouse. Obstet Gynecol. 23:359-362.

Kane S. 2018. The Top 300 of 2018, ClinCalc DrugStats Database, Version 18.0. ClinCalc. https://clincalc.com/DrugStats/Top300Drugs.aspx.

Karabelyos C, Csaba G, Dallo J. 1994a. Effect of treatment with contraceptive steroids on the sexual behaviour of rats pretreated with benzpyrene or allylestrenol in fetal or neonatal age. Horm Metab Res. 26(8):371-373. http://dx.doi.org/10.1055/s-2007-1001709

Karabelyos C, Dallo J, Csaba G. 1994b. Effects of benzpyrene and allylestrenol administered during pregnancy on the sexual behaviour of castrated and hormone treated adult rats. Acta Physiol Hung. 82(2):175-180.

Katz Z, Lancet M, Skornik J, Chemke J, Mogilner BM, Klinberg M. 1985. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol. 65(6):775-780. http://dx.doi.org/10.1097/00006254-198511000-00016

Keith L, Berger GS. 1977. The relationship between congenital defects and the use of exogenous progestional "contraceptive" hormones during pregnancy: A 20-year review. Int J Gynaecol Obstet. 15(2):115-124. http://dx.doi.org/10.1002/j.1879-3479.1977.tb00659.x

Keppler-Noreuil KM, Conway KM, Shen D, Rhoads AJ, Carey JC, Romitti PA. 2017. Clinical and risk factor analysis of cloacal defects in the National Birth Defects Prevention Study. Am J Med Genet A. 173(11):2873-2885. http://dx.doi.org/10.1002/ajmg.a.38469

Kester P. 1984. Effects of prenatally administered 17 alpha-hydroxyprogesterone caproate on adolescent males. Arch Sex Behav. 13(5):441-455. http://dx.doi.org/10.1007/BF01541429

Kester P, Green R, Finch SJ, Williams K. 1980. Prenatal 'female hormone' administration and psychosexual development in human males. Psychoneuroendocrinology. 5(4):269-285. http://dx.doi.org/10.1016/0306-4530(80)90032-3

Lammer EJ, Cordero JF. 1986. Exogenous sex hormone exposure and the risk for major malformations. JAMA. 255(22):3128-3132. http://dx.doi.org/10.1001/jama.1986.03370220090033

Li L, Li M, Ge X, Xie W, Wang Z, Li X, Li C, Wang Y, Han Y. 2018. Prenatal progestin exposure is associated with Autism Spectrum Disorders. Front Psychiatry. 9:611. http://dx.doi.org/10.3389/fpsyt.2018.00611

Louw-du Toit R, Perkins MS, Hapgood JP, Africander D. 2017. Comparing the androgenic and estrogenic properties of progestins used in contraception and hormone therapy. Biochem Biophys Res Commun. 491(1):140-146. http://dx.doi.org/10.1016/j.bbrc.2017.07.063

Lynch A, Mychalkiw W, Hutt SJ. 1978. Prenatal progesterone. I. Its effect on development and on intellectual and academic achievement. Early Hum Dev. 2(4):305-322. http://dx.doi.org/10.1016/0378-3782(78)90059-2

Massaro PA, MacLellan DL, Anderson PA, Romao RLP. 2015. Does intracytoplasmic sperm injection pose an increased risk of genitourinary congenital malformations in offspring compared

to in vitro fertilization? A systematic review and meta-analysis. J Urol. 193(5S):1837-1842. http://dx.doi.org/10.1016/j.juro.2014.10.113

Matsunaga E, Shiota K. 1979. Threatened abortion, hormone therapy and malformed embryos. Teratology. 20(3):469-480. http://dx.doi.org/10.1002/tera.1420200317

Mavrogenis S, Urban R, Czeizel AE, Acs N. 2014. Maternal risk factors in the origin of isolated hypospadias: A population-based case-control study. Congenit Anom. 54(2):110-115. http://dx.doi.org/10.1111/cga.12041

McNamara HC, Wood R, Chalmers J, Marlow N, Norrie J, MacLennan G, McPherson G, Boachie C, Norman JE. 2015. STOPPIT baby follow-up study: The effect of prophylactic progesterone in twin pregnancy on childhood outcome. PLoS One. 10(4):e0122341. http://dx.doi.org/10.1371/journal.pone.0122341

Menzies KD, Drysdale DB, Waite PM. 1982. Effects of prenatal progesterone on the development of pyramidal cells in rat cerebral cortex. Exp Neurol. 77(3):654-667. http://dx.doi.org/10.1016/0014-4886(82)90236-9

Meyer-Bahlburg HF, Feldman JF, Cohen P, Ehrhardt AA. 1988. Perinatal factors in the development of gender-related play behavior: Sex hormones versus pregnancy complications. Psychiatry. 51(3):260-271. http://dx.doi.org/10.1080/00332747.1988.11024401

Meyer-Bahlburg HF, Feldman JF, Ehrhardt AA, Cohen P. 1984. Effects of prenatal hormone exposure versus pregnancy complications on sex-dimorphic behavior. Arch Sex Behav. 13(5):479-495. http://dx.doi.org/10.1007/BF01541431

Meyer-Bahlburg HF, Grisanti GC, Ehrhardt AA. 1977. Prenatal effects of sex hormones on human male behavior: Medroxyprogesterone acetate (MPA). Psychoneuroendocrinology. 2(4):383-390. http://dx.doi.org/10.1016/0306-4530(77)90009-9

Michaelis J, Michaelis H, Gluck E, Koller S. 1983. Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformations. Teratology. 27(1):57-64. http://dx.doi.org/10.1002/tera.1420270109

Moore KL, Persaud TVN, Torchia MG. 2016. The Developing Human: Clinically Oriented Embryology. Philadelphia, PA: Elsevier.

National Toxicology Program (NTP). 2016. Report on Carcinogens, Fourteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/go/roc14

National Toxicology Program (NTP). 2020. Tableau data on the scoping review of prenatal exposure to progestogens and adverse health outcomes. https://doi.org/10.22427/NTP-DATA-RR-17

Nora AH, Nora JJ. 1975. A syndrome of multiple congenital anomalies associated with teratogenic exposure. Arch Environ Health. 30(1):17-21. http://dx.doi.org/10.1080/00039896.1975.10666626

Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ et al. 2016. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): A multicentre, randomised, double-blind trial. Lancet. 387(10033):2106-2116. http://dx.doi.org/10.1016/S0140-6736(16)00350-0

Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ et al. 2018. Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM). Health Technol Assess. 22(35):1-304. http://dx.doi.org/10.3310/hta22350

Northern AT, Norman GS, Anderson K, Moseley L, Divito M, Cotroneo M, Swain M, Bousleiman S, Johnson F, Dorman K et al. 2007. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 110(4):865-872. http://dx.doi.org/10.1097/01.AOG.0000281348.51499.bc

Palacio M, Cobo T, Antolin E, Ramirez M, Cabrera F, Mozo de Rosales F, Bartha JL, Juan M, Marti A, Oros D et al. 2016. Vaginal progesterone as maintenance treatment after an episode of preterm labour (PROMISE) study: A multicentre, double-blind, randomised, placebo-controlled tria. BJOG. 123(12):1990-1999. http://dx.doi.org/10.1111/1471-0528.13956

Pamir E, Ali D, Ismail C, Sanli E, Ali K, Mustafa T. 2006. The effects of high dose progesterone on neural tube development in early chick embryos. Neurol India. 54(2):178-181.

Pandian RU. 2009. Dydrogesterone in threatened miscarriage: A Malaysian experience. Maturitas. 65:Suppl 1:S47-50. http://dx.doi.org/10.1016/j.maturitas.2009.11.016

Pardthaisong T, Gray RH, McDaniel EB, Chandacham A. 1988. Steroid contraceptive use and pregnancy outcome. Teratology. 38(1):51-58. http://dx.doi.org/10.1002/tera.1420380108

Pardthaisong T, Yenchit C, Gray R. 1992. The long-term growth and development of children exposed to Depo-Provera during pregnancy or lactation. Contraception. 45(4):313-324. http://dx.doi.org/10.1016/0010-7824(92)90053-V

Perakis A, Stylianopoulou F. 1986. Effects of a prenatal androgen peak on rat brain sexual differentiation. J Endocrinol. 108(2):281-285. http://dx.doi.org/10.1677/joe.0.1080281

Plunchino N, Russo M, Genazzani AR. 2016. The fetal brain: Role of progesterone and allopregnanolone. Horm Mol Biol Clin Investig. 27(1):29-34X. http://dx.doi.org/10.1515/hmbci-2016-0020

Pointis G, Latreille MT, Richard MO, D'Athis P, Cedard L. 1987. Effect of natural progesterone treatment during pregnancy on fetal testosterone and sexual behavior of the male offspring in the mouse. Dev Pharmacol Ther. 10(5):385-392. http://dx.doi.org/10.1159/000457768

Prahalada S, Carroad E, Cukierski M, Hendrickx AG. 1985a. Embryotoxicity of a single dose of medroxyprogesterone acetate (MPA) and maternal serum MPA concentrations in cynomolgus monkey (Macaca fascicularis). Teratology. 32(3):421-432. http://dx.doi.org/10.1002/tera.1420320312

Prahalada S, Carroad E, Hendrickx AG. 1985b. Embryotoxicity and maternal serum concentrations of medroxyprogesterone acetate (MPA) in baboons (Papio cynocephalus). Contraception. 32(5):497-515. http://dx.doi.org/10.1016/0010-7824(85)90020-4

Pushpalatha T, Reddy PR, Reddy PS. 2005. Gestational exposure to hydroxyprogesterone caproate suppresses reproductive potential in male rats. Naturwissenschaften. 92(8):385-388. http://dx.doi.org/10.1007/s00114-005-0005-x

Qin J, Liu X, Sheng X, Wang H, Gao S. 2016. Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: A meta-analysis of cohort studies. Fertil Steril. 105(1):73-85.e76. https://doi.org/10.1016/j.fertnstert.2015.09.007

Regestein QR, Williams GH, Rose LI. 1975. Influence of perinatal progesterone on sexual activity in the male guinea pig. J Psychiatr Res. 12(3):149-151. http://dx.doi.org/10.1016/0022-3956(75)90022-9

Reinisch JM. 1977. Prenatal exposure of human foetuses to synthetic progestin and oestrogen affects personality. Nature. 266(5602):561-562. http://dx.doi.org/10.1038/266561a0

Reinisch JM. 1981. Prenatal exposure to synthetic progestins increases potential for aggression in humans. Science. 211(4487):1171-1173. http://dx.doi.org/10.1126/science.7466388

Reinisch JM, Karow WG. 1977. Prenatal exposure to synthetic progestins and estrogens: Effects on human development. Arch Sex Behav. 6(4):257-288. http://dx.doi.org/10.1007/BF01541201

Reinisch JM, Mortensen EL, Sanders SA. 2017. Prenatal exposure to progesterone affects sexual orientation in humans. Arch Sex Behav. 46(5):1239-1249. http://dx.doi.org/10.1007/s10508-016-0923-z

Resseguie LJ, Hick JF, Bruen JA, Noller KL, O'Fallon WM, Kurland LT. 1985. Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota, 1936-1974. Fertil Steril. 43(4):514-519. http://dx.doi.org/10.1016/S0015-0282(16)48490-6

Rice D, Barone S, Jr. 2000. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. Environ Health Perspect. 108(Suppl 3):511-533.

Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A. 2011. Prevention of preterm delivery in twin gestations (PREDICT): A multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. Ultrasound Obstet Gynecol. 38(3):272-280. http://dx.doi.org/10.1002/uog.9093

Romero R, Stanczyk FZ. 2013. Progesterone is not the same as 17alpha-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol. 208(6):421-426. http://dx.doi.org/10.1016/j.ajog.2013.04.027

Rooney AA, Boyles AL, Wolfe MS, Burcher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect. 122(7):711-718. http://dx.doi.org/10.1289/ehp.1307972

Sannes E, Lyngest A, Nafstad I. 1983. Teratogenicity and embryotoxicity of orally administered lynestrenol in rabbits. Arch Toxicol. 52(1):23-33. http://dx.doi.org/10.1007/BF00317979

Schardein JL, Birch R, Hesley R, Thorsrud BA. 2012. Multigeneration reproductive study of hydroxyprogesterone caproate (HPC) in the rat: Laboratory results and clinical significance. Birth Defects Res B Dev Reprod Toxicol. 95(2):160-174. http://dx.doi.org/10.1002/bdrb.21000

Schindler AE. 2015. Pharmacology of progestins. In: Progestogens in Obstetrics and Gynecology. Switzerland: Springer International Publishing. p. 33-40.

Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, Thijssen JH. 2008. Classification and pharmacology of progestins. Maturitas. 61(1-2):171-180. http://dx.doi.org/10.1016/j.maturitas.2008.11.013

Scouten CW, Groteleuschen LK, Beatty WW. 1975. Androgens and the organization of sex differences in active avoidance behavior in the rat. J Comp Physiol Psychol. 88(1):264-270. http://dx.doi.org/10.1037/h0076184

Seegmiller RE, Nelson GW, Johnson CK. 1983. Evaluation of the teratogenic potential of delalutin (17 alpha-hydroxyprogesterone caproate) in mice. Teratology. 28(2):201-208. http://dx.doi.org/10.1002/tera.1420280208

Shaw JC, Palliser HK, Palazzi K, Hirst JJ. 2017. Administration of progesterone throughout pregnancy increases maternal steroids without adverse effect on mature oligodendrocyte immunostaining in the guinea pig. Reprod Sci. 25(3):395-405. http://dx.doi.org/10.1177/1933719117715125

Shepard TH, Lemire RJ. 2004. Catalog of Teratogenic Agents. Baltimore, MD: The John Hopkins University Press.

Silva M, Silva JFD, Santon TP, Silva N, Santos ARD, Andrade ALC, Souza E, Sales Cadena MR, Sa FB, Silva Junior VAD et al. 2019. The complexation of steroid hormones into cyclodextrin alters the toxic effects on the biological parameters of zebrafish (Danio rerio). Chemosphere. 214(330-340). http://dx.doi.org/10.1016/j.chemosphere.2018.09.116

Snyder AM, Hull EM. 1980. Perinatal progesterone affects learning in rats. Psychoneuroendocrinology. 5(2):113-119. http://dx.doi.org/10.1016/0306-4530(80)90014-1

Soyer-Gobillard MO, Gaspari L, Courtet P, Puillandre M, Paris F, Sultan C. 2019. Neurodevelopmental disorders in children exposed in utero to synthetic progestins: Analysis from the national cohort of the Hhorages Association. Gynecol Endocrinol. 35(3):247-250. http://dx.doi.org/10.1080/09513590.2018.1512968

Stanczyk FZ, Hapgood JP, Winer S, Mishell DR, Jr. 2013. Progestogens used in postmenopausal hormone therapy: Differences in their pharmacological properties, intracellular actions, and clinical effects. Endocr Rev. 34(2):171-208. http://dx.doi.org/10.1210/er.2012-1008

Taraborrelli S. 2015. Physiology, production and action of progesterone. Acta Obstet Gynecol Scand. 94 Suppl 161:8-16. http://dx.doi.org/10.1111/aogs.12771

Thomson P, Langlois VS. 2018. Developmental profiles of progesterone receptor transcripts and molecular responses to gestagen exposure during Silurana tropicalis early development. Gen Comp Endocrinol. 265:4-14. http://dx.doi.org/10.1016/j.ygcen.2018.05.017

Turcu AF, Auchus RJ. 2015. The next 150 years of congenital adrenal hyperplasia. J Steroid Biochem Mol Biol. 153:63-71. http://dx.doi.org/10.1016/j.jsbmb.2015.05.013

Uher J, Jirasek JE, Cernoch A. 1965. On the activity of 16-methylen-6-dehydro-17-alpha-acetoxyprogesterone (MDAP) on human foetus. Gynaecologia. 159(6):377-383.

van Marthens E, Zamenhof S, Firestone C. 1979. The effect of progesterone on fetal and placental development in normal and protein-energy-restricted rats. Nutr Metab. 23(6):438-448. http://dx.doi.org/10.1159/000176290

Varma TR, Morsman J. 1982. Evaluation of the use of Proluton-Depot (hydroxyprogesterone hexanoate) in early pregnancy. Int J Gynaecol Obstet. 20(1):13-17. http://dx.doi.org/10.1016/0020-7292(82)90039-X

Vedel C, Larsen H, Holmskov A, Andreasen KR, Uldbjerg N, Ramb J, Bodker B, Skibsted L, Sperling L, Krebs L et al. 2016. Long-term effects of prenatal progesterone exposure: neurophysiological development and hospital admissions in twins up to 8 years of age. Ultrasound Obstet Gynecol. 48(3):382-389. http://dx.doi.org/10.1002/uog.15948

Vega Matuszczyk JV, Larsson K. 1995. Sexual preference and feminine and masculine sexual behavior of male rats prenatally exposed to antiandrogen or antiestrogen. Horm Behav. 29(2):191-206. http://dx.doi.org/10.1006/hbeh.1995.1014

Wang T, Chen L, Yang T, Wang L, Zhao L, Zhang S, Ye Z, Chen L, Zheng Z, Qin J. 2019. Cancer risk among children conceived by fertility treatment. Int J Cancer. 144(12):3001-3013. https://doi.org/10.1002/ijc.32062

Ward IL. 1972. Female sexual behavior in male rats treated prenatally with an anti-androgen. Physiol Behav. 8(1):53-56. http://dx.doi.org/10.1016/0031-9384(72)90129-1

Ward IL, Renz FJ. 1972. Consequences of perinatal hormone manipulation on the adult sexual behavior of female rats. J Comp Physiol Psychol. 78(3):349-355. http://dx.doi.org/10.1037/h0032375

Whalen RE, Peck CK, LoPiccolo J. 1966. Virilization of female rats by prenatally administered progestin. Endocrinology. 78(5):965-970. http://dx.doi.org/10.1210/endo-78-5-965

Wharton LR, Jr., Scott RB. 1964. Experimental production of genital lesions with norethindrone. Obstet Gynecol. 89:701-715. http://dx.doi.org/10.1016/0002-9378(64)90170-X

Wilkins L, Jones HW, Jr., Holman GH, Stempfel RS, Jr. 1958. Masculinization of the female fetus associated with administration of oral and intramuscular progestins during gestation: Non-adrenal female pseudohermaphrodism. J Clin Endocrinol Metab. 18(6):559-585. http://dx.doi.org/10.1210/jcem-18-6-559

Witchel SF. 2017. Congenital adrenal hyperplasia. J Pediatr Adolesc Gynecol. 30(5):520-534. http://dx.doi.org/10.1016/j.jpag.2017.04.001

Yovich JL, Turner SR, Draper R. 1988. Medroxyprogesterone acetate therapy in early pregnancy has no apparent fetal effects. Teratology. 38(2):135-144. http://dx.doi.org/10.1002/tera.1420380206

Zaqout M, Aslem E, Abuqamar M, Abughazza O, Panzer J, De Wolf D. 2015. The impact of oral intake of dydrogesterone on fetal heart development during early pregnancy. Pediatr Cardiol. 36(7):1483-1488. http://dx.doi.org/10.1007/s00246-015-1190-9

Zhang L, Chen J, Wang Y, Ren F, Yu W, Cheng L. 2009. Pregnancy outcome after levonorgestrel-only emergency contraception failure: A prospective cohort study. Hum Reprod. 24(7):1605-1611. http://dx.doi.org/10.1093/humrep/dep076

Zhang L, Ye W, Yu W, Cheng L, Shen L, Yang Z. 2014. Physical and mental development of children after levonorgestrel emergency contraception exposure: A follow-up prospective cohort study. Biol Reprod. 91(1):1-7. http://dx.doi.org/10.1095/biolreprod.113.117226

Appendix A. Literature Search Strategy

Tables

The literature search involved three databases: PubMed, Cochrane Library, and Database of Abstracts of Reviews of Effects (DARE). The literature search for PubMed included a separate set of search terms from the literature search for Cochrane Library and DARE databases (Table A-1 and Table A-2).

Table A-1. PubMed Database Search Terms

Set	Search Terms
Exposure/Progestogens	((Progesterone[mh] OR progesterone-congeners[mh] OR progestins[mh] OR exogenous-progesterone[tiab] OR Algestone[tiab] OR Algestone-acetophenide[tiab] OR Allylestrenol[tiab] OR Chlormadinone-acetate[tiab] OR cyproterone-acetate[tiab] OR desogestrel[tiab] OR dydrogesterone[tiab] OR Ethisterone[tiab] OR ethynodiol-diacetate[tiab] OR Flurogestone-acetate[tiab] OR Gestonorone-caproate[tiab] OR Gestrinone[tiab] OR Levonorgestrel[tiab] OR Lynestrenol[tiab] OR medrogestone[tiab] OR medroxyprogesterone-acetate[tiab] OR Megestrol-acetate[tiab] OR Norethindrone[tiab] OR norethynodrel[tiab] OR Norgestrel[tiab] OR Promegestone[tiab] OR 11-hydroxyprogesterone[tiab] OR 17-alpha-hydroxy-progesterone-caproate[tiab] OR 17-alpha-hydroxyprogesterone-caproate[tiab] OR 17-hydroxyprogesterone-caproate[tiab] OR Demegestone[tiab] OR Dienogest[tiab] OR Drospirenone[tiab] OR Etonogestrel[tiab] OR Gestodene[tiab] OR Nomegestrol-acetate[tiab] OR Norelgestromin[tiab] OR Norethindrone-acetate[tiab] OR Norgestimate[tiab] OR ST-1435[tiab] OR Trimegestone[tiab] OR 11-hydroxyprogesterone[nm] OR 17-alpha-hydroxy-progesterone-caproate[nm] OR Demegestone[nm] OR Dienogest[nm] OR Drospirenone[nm] OR Etonogestrel[nm] OR Gestodene[nm] OR Nomegestrol-acetate[nm] OR Norelgestromin[nm] OR Norethindrone-acetate[nm] OR Norgestimate[nm] OR ST-1435[nm] OR Trimegestone[nm] OR Algestone[mh] OR Algestone-acetophenide[mh] OR Allylestrenol[mh] OR Chlormadinone-acetate[mh] OR cyproterone-acetate[mh] OR desogestrel[mh] OR dydrogesterone[mh] OR Ethisterone[mh] OR ethynodiol-diacetate[mh] OR Flurogestone-acetate[mh] OR Gestonorone-caproate[mh] OR Gestrinone[mh] OR Levonorgestrel[mh] OR Lynestrenol[mh] OR medrogestone[mh] OR medroxyprogesterone-acetate[mh] OR Megestrol-acetate[mh] OR Norethindrone[mh] OR norethynodrel[mh] OR Norgestrel[mh] OR Promegestone[mh] OR progestogens[tiab] OR progestogen[tiab] OR Hydroxyprogesterone-caproate[tiab]) OR ((progesterone[tiab] OR progestins[tiab]) NOT medline[sb]))
Window of Exposure	AND (animals,-newborn[mh] OR child[mh] OR infant[mh] OR maternal-exposure[mh] OR Maternal-Fetal Exchange[mh] OR babies[tiab] OR baby[tiab] OR child*[tiab] OR embryo[tiab] OR embryonic[tiab] OR embryos[tiab] OR fetal[tiab] OR fetus[tiab] OR foetal[tiab] OR gestation*[tiab] OR infant*[tiab] OR in-utero[tiab] OR maternal[tiab] OR neonat*[tiab] OR newborn*[tiab] OR offspring[tiab] OR perinat*[tiab] OR postnat*[tiab] OR prenat*[tiab] OR progeny[tiab] OR pups[tiab])
Outcome	AND (pregnancy-outcomes[mh] OR prenatal-exposure-delayed-effects[mh] OR premature-birth[mh] OR premature-birth[tiab] OR abortion,-spontaneous[mh] OR spontaneous-abortion[tiab] OR live-born[tiab] OR still-born[tiab] OR stillborn[tiab] OR stillbirth[tiab] OR still-birth[tiab] OR Congenital-Abnormality[tiab] OR Congenital-Abnormalities[tiab] OR Congenital-Abnormalities[mh] OR Deformities[tiab] OR Deformity[tiab] OR Congenital-defect[tiab] OR Congenital-defects[tiab] OR birth-defects[tiab] OR birth-defect[tiab] OR Congenital-anomalies[tiab] OR Congenital-anomaly[tiab] OR hypospadias[tiab] OR Behavior-and-Behavior-Mechanisms[mh] OR Gene-Expression-Regulation[mh] OR Glucuronosyltransferase[mh] OR Intelligence-tests[mh] OR Malate-Dehydrogenase[mh] OR Mediator-Complex-Subunit-1[mh] OR

Set	Search Terms
	Mental-disorders[mh] OR Mental-processes[mh] OR Monocarboxylic-Acid-Transporters[mh] OR Myelin-Basic-Protein[mh] OR nervous-system[mh] OR nervous-system-diseases[mh] OR nervous-system-physiological-phenomena[mh] OR Neurogranin[mh] OR Oligodendroglia[mh] OR Peroxisome-Proliferator-Activated-Receptors[mh] OR Psychological-Phenomena-and-Processes[mh] OR Academic-performance[tiab] OR auditory[tiab] OR cortical[tiab] OR delayed-development[tiab] OR developmental-impairment[tiab] OR developmental-delay*[tiab] OR developmental-disorder*[tiab] OR euthyroid[tiab] OR gait[tiab] OR glia*[tiab] OR gliogenesis[tiab] OR hyperactiv*[tiab] OR impulse-control[tiab] OR IQ[tiab] OR ischemi*[tiab] OR locomotor[tiab] OR mental-deficiency[tiab] OR mental-development[tiab] OR mental-illness[tiab] OR mental-deficit[tiab] OR mobility[tiab] OR mood[tiab] OR morris-maze[tiab] OR morris-water[tiab] OR motor-abilit*[tiab] OR Motor-activities[tiab] OR motor-performance[tiab] OR nerve[tiab] OR neural[tiab] OR neurobehav*[tiab] OR Neurocognitive-impairment[tiab] OR neurodegenerat*[tiab] OR Neurodevelopment*[tiab] OR neurodisease*[tiab] OR neurologic*[tiab] OR neuromuscular[tiab] OR neuron*[tiab] OR neuropath*[tiab] OR obsessive-compulsive[tiab] OR OCD[tiab] OR olfaction[tiab] OR olfactory[tiab] OR open-field-test[tiab] OR passive-avoidance[tiab] OR plasticity[tiab] OR sociab*[tiab] OR speech*[tiab] OR spelling[tiab] OR stereotypic-movement*[tiab] OR synap*[tiab] OR tauopath*[tiab] OR visual-motor[tiab] OR Visuospatial-processing[tiab] OR water-maze[tiab] OR active-avoidance[tiab] OR ADHD[tiab] OR amygdala[tiab] OR antisocial[tiab] OR anxiety[tiab] OR anxious[tiab] OR asperger*[tiab] OR attention-deficit[tiab] OR autism[tiab] OR autistic[tiab] OR behavioral[tiab] OR behaviors[tiab] OR behavioural[tiab] OR behaviours[tiab] OR bipolar[tiab] OR cerebellum[tiab] OR cognition[tiab] OR cognitive[tiab] OR comprehension[tiab] OR cranial[tiab] OR dementia[tiab] OR dendrit*[tiab] OR dentate-gyrus[tiab] OR depression[tiab] OR down-syndrome[tiab] OR dyslexia[tiab] OR entorhinal-cortex[tiab] OR epilep*[tiab] OR ganglia*[tiab] OR ganglion*[tiab] OR hearing[tiab] OR hippocamp*[tiab] OR human-development[tiab] OR impulsiv*[tiab] OR Intellectual-disability[tiab] OR intelligence[tiab] OR language[tiab] OR learning[tiab] OR lewy-bod*[tiab] OR long-term-potentiation[tiab] OR long-term-synaptic-depression[tiab] OR memory[tiab] OR mental-disorder*[tiab] OR mental-recall[tiab] OR Motor-activity[tiab] OR motor-skill*[tiab] OR myxedema[tiab] OR Nervous-system[tiab] OR nervous-system[tiab] OR neurit*[tiab] OR optic[tiab] OR palsy[tiab] OR panic[tiab] OR parahippocamp*[tiab] OR paranoia[tiab] OR paranoid[tiab] OR perception[tiab] OR perforant*[tiab] OR personality[tiab] OR phobia[tiab] OR problem-solving[tiab] OR proprioception[tiab] OR psychomotor[tiab] OR reflex[tiab] OR risk-taking[tiab] OR schizophrenia[tiab] OR seizure*[tiab] OR sensation*[tiab] OR sleep[tiab] OR smell[tiab] OR spatial-behavior[tiab] OR substantia-nigra[tiab] OR child-development[mh] OR child-development[tiab] OR acanthoma*[tiab] OR acrochord*[tiab] OR acrospiroma*[tiab] OR adamantinoma*[tiab] OR adenoacanthoma*[tiab] OR adenoameloblast*[tiab] OR adenocarcin*[tiab] OR adenofibrom*[tiab] OR adenol*[tiab] OR adenom*[tiab] OR adenosquamous[tiab] OR ameloblast*[tiab] OR androblast*[tiab] OR angiofib*[tiab] OR angiog*[tiab] OR angiok*[tiab] OR angiol*[tiab] OR angiom*[tiab] OR angiomatosis[mh] OR angiosarc*[tiab] OR antibodies, neoplasm[mh] OR antigens, neoplasm[mh] OR apudom*[tiab] OR argentaffin*[tiab] OR arrhenoblast*[tiab] OR astroblast*[tiab] OR astrocytom*[tiab] OR astrogliom*[tiab] OR atypia[tiab] OR baltoma[tiab] OR barrett esophagus[mh] OR blastom*[tiab] OR cancer[tiab] OR cancero*[tiab] OR cancers[tiab] OR carcinog*[tiab] OR carcinogenicity tests[mh] OR carcinogens[mh] OR carcinoid*[tiab] OR carcinom*[tiab] OR carcinos*[tiab] OR cavernom*[tiab] OR cell line, tumor[mh] OR cementom*[tiab] OR cerumin*[tiab] OR chloroma*[tiab] OR cholangio*[tiab] OR chondrob*[tiab] OR chondrom*[tiab] OR chondros*[tiab] OR chord*[tiab] OR chorioa*[tiab] OR choriocarc*[tiab] OR chorioep*[tiab] OR chorionep*[tiab] OR chromaffinom*[tiab] OR collagenom*[tiab]

Set	Search Terms
	OR comedocarcinom*[tiab] OR condylom*[tiab] OR condylomata acuminata[mh] OR corticotrop*[tiab] OR craniopharyng*[tiab] OR cylindrom*[tiab] OR cystadeno*[tiab] OR cystoma*[tiab] OR cystosa*[tiab] OR dentinom*[tiab] OR dermatofibro*[tiab] OR dermoid[tiab] OR desmoid[tiab] OR desmoplastic*[tiab] OR dictyota[tiab] OR dysgerm*[tiab] OR dyskerat*[tiab] OR dysmyelopoiesis[tiab] OR dysplas*[tiab] OR ectomesenchym*[tiab] OR elastofibr*[tiab] OR enchondrom*[tiab] OR endotheliom*[tiab] OR ependymo*[tiab] OR epidermoid*[tiab] OR epitheliom*[tiab] OR erythrol*[tiab] OR erythropl*[tiab] OR esthesioneuro*[tiab] OR etiolog*[tiab] OR fibroaden*[tiab] OR fibrochond*[tiab] OR fibroe*[tiab] OR fibrofol*[tiab] OR fibroid*[tiab] OR fibrolip*[tiab] OR fibrom*[tiab] OR fibroodontom*[tiab] OR fibrosarcom*[tiab] OR fibrothecom*[tiab] OR fibroxantho*[tiab] OR ganglioblast*[tiab] OR gangliocytom*[tiab] OR gangliogliom*[tiab] OR ganglioneuro*[tiab] OR gastrinom*[tiab] OR genes, neoplasm[mh] OR germinom*[tiab] OR glioblast*[tiab] OR gliom*[tiab] OR glomangio*[tiab] OR glucagonom*[tiab] OR gonadoblastom*[tiab] OR gonocytom*[tiab] OR gynandroblastom*[tiab] OR haemangio*[tiab] OR hamartom*[tiab] OR hemangio*[tiab] OR hepatoblastom*[tiab] OR hepatom*[tiab] OR hibernom*[tiab] OR hidradenom*[tiab] OR hidrocy*[tiab] OR hodgkin*[tiab] OR hydatidiform*[tiab] OR hydradenom*[tiab] OR hypernephrom*[tiab] OR IARC[tiab] OR immunocytom*[tiab] OR insulinom*[tiab] OR leiomyo*[tiab] OR lesion*[tiab] OR leukaemia*[tiab] OR leukemia*[tiab] OR leukoplak*[tiab] OR leukostas*[tiab] OR leukostasis[mh] OR lipoadenom*[tiab] OR lipoblastom*[tiab] OR lipom*[tiab] OR liposarcom*[tiab] OR luteinom*[tiab] OR luteom*[tiab] OR lymphangio*[tiab] OR lymphoepitheliom*[tiab] OR lymphom*[tiab] OR lymphoscintigraph*[tiab] OR macroglobulinem*[tiab] OR macroprolactinom*[tiab] OR malignan*[tiab] OR maltom*[tiab] OR masculinovoblastom*[tiab] OR mastocyto*[tiab] OR mcf-7[tiab] OR medullo*[tiab] OR meigs syndrome[tiab] OR melanoa*[tiab] OR melanocytom*[tiab] OR melanom*[tiab] OR meningio*[tiab] OR mesenchymom*[tiab] OR mesonephrom*[tiab] OR mesotheliom*[tiab] OR metaplas*[tiab] OR metaplasia[mh] OR metastas*[tiab] OR metastat*[tiab] OR microgliom*[tiab] OR micrometastas*[tiab] OR mucositis[mh] OR mycosis fungoides*[tiab] OR myelodysplas*[tiab] OR myelodysplastic syndromes[mh] OR myelodysplastic-myeloproliferative diseases[mh] OR myelofibrosis[tiab] OR myelol*[tiab] OR myeloma*[tiab] OR myeloproliferat*[tiab] OR myeloproliferative disorders[mh] OR myelosuppression*[tiab] OR myoblastom*[tiab] OR myoepitheliom*[tiab] OR myofibro*[tiab] OR myolipom*[tiab] OR myoma*[tiab] OR myosarcom*[tiab] OR myxof*[tiab] OR myxom*[tiab] OR naevus[tiab] OR neoplas*[tiab] OR neoplasm proteins[mh] OR neoplasms[mh] OR neoplastic stem cells[mh] OR nephroblastom*[tiab] OR neurilem*[tiab] OR neurinom*[tiab] OR neuroblastom*[tiab] OR neurocytom*[tiab] OR neuroepitheliom*[tiab] OR neurofibro*[tiab] OR neurolipocytom*[tiab] OR neuroma*[tiab] OR neuronevus[tiab] OR neurothekeom*[tiab] OR nevus[tiab] OR non coding RNA[tiab] OR nonseminom*[tiab] OR odontoam*[tiab] OR odontom*[tiab] OR oligoastrocytom*[tiab] OR oligodendrogliom*[tiab] OR oncocytom*[tiab] OR oncogen*[tiab] OR oncogene fusion[mh] OR oncogene proteins[mh] OR oncogenic viruses[mh] OR oncolog*[tiab] OR oncolytic viruses[mh] OR oncoprotein*[tiab] OR opsoclonus-myoclonus[tiab] OR orchioblastom*[tiab] OR osteoblastom*[tiab] OR osteoch*[tiab] OR osteofibrosarcom*[tiab] OR osteom*[tiab] OR osteosarcom*[tiab] OR pancreatoblastom*[tiab] OR papillom*[tiab] OR parachordom*[tiab] OR paragangliom*[tiab] OR paraneoplas*[tiab] OR perineuriom*[tiab] OR phaeochromocytom*[tiab] OR pheochromo*[tiab] OR pilomatri*[tiab] OR plasmacytom*[tiab] OR pneumoblast*[tiab] OR pneumocytom*[tiab] OR polyembryom*[tiab] OR polyhistiom*[tiab] OR polyp[tiab] OR polyps[mh] OR porocarcinom*[tiab] OR porom*[tiab] OR pre-cancer*[tiab] OR precancer*[tiab] OR

Set	Search Terms
	preleukaem*[tiab] OR preleukem*[tiab] OR prelymphom*[tiab] OR pre-lymphom*[tiab] OR pre-malign*[tiab] OR premalignan*[tiab] OR preneoplas*[tiab] OR pre-neoplas*[tiab] OR prolactinom*[tiab] OR protooncogen*[tiab] OR pseudotum*[tiab] OR reninom*[tiab] OR retinoblastom*[tiab] OR rhabdo*[tiab] OR RNA, neoplasm[mh] OR sarcoma*[tiab] OR schwannom*[tiab] OR SEER program[mh] OR seminom*[tiab] OR sentinel lymph node[tiab] OR sentinel lymph node biopsy[mh] OR sertoli-leydig cell tumor[tiab] OR sezary syndrome[tiab] OR somatostatinom*[tiab] OR somatotropinom*[tiab] OR spermatocytom*[tiab] OR spiradenom*[tiab] OR spongioblastom*[tiab] OR subependymom*[tiab] OR thecom*[tiab] OR thymom*[tiab] OR trichilemmom*[tiab] OR trichoadenom*[tiab] OR trichoblastom*[tiab] OR trichodiscom*[tiab] OR trichoepitheliom*[tiab] OR trichofolliculom*[tiab] OR tricholemm*[tiab] OR tumor[tiab] OR tumor markers, biological[mh] OR tumorgen*[tiab] OR tumorig*[tiab] OR tumor-inhibit*[tiab] OR tumorog*[tiab] OR tumors[tiab] OR tumors[tiab] OR tumour[tiab] OR up-regulat*[tiab] OR vipom*[tiab] OR waldenstrom*[tiab] OR xanthoma*[tiab])

Table A-2. Cochrane and DARE (Database of Abstracts of Reviews of Effects) Database Search Terms

Set	Search Strategy
Exposure/Progestogens	(exogenous-progesterone OR Algestone OR Algestone-acetophenide OR Allylestrenol OR Chlormadinone-acetate OR cyproterone-acetate OR desogestrel OR dydrogesterone OR Ethisterone OR ethynodiol-diacetate OR Flurogestone-acetate OR Gestonorone-caproate OR Gestrinone OR Levonorgestrel OR Lynestrenol OR medrogestone OR medroxyprogesterone-acetate OR Megestrol-acetate OR Norethindrone OR norethynodrel OR Norgestrel OR Promegestone OR 11-hydroxyprogesterone OR 17-alpha-hydroxy-progesterone-caproate OR 17-alpha-hydroxyprogesterone-caproate OR 17-hydroxyprogesterone-caproate OR Demegestone OR Dienogest OR Drospirenone OR Etonogestrel OR Gestodene OR Nomegestrol-acetate OR Norelgestromin OR Norethindrone-acetate OR Norgestimate OR ST-1435 OR Trimegestone OR progesterone OR progestins OR progestogens OR progestogen OR Hydroxyprogesterone-caproate)
Window of Exposure	AND (babies OR baby OR child* OR embryo OR embryonic OR embryos OR fetal OR fetus OR foetal OR gestation* OR infant* OR in-utero OR maternal OR neonat* OR newborn* OR offspring OR perinat* OR postnat* OR prenat* OR progeny OR pups)

Appendix B. Supplemental Files

The following supplemental files are available at https://doi.org/10.22427/NTP-DATA-RR-17.

B.1. Protocol Information

NTP Protocol (Revised July 31, 2020)

NTP Protocol (September 26, 2018)

B.2. Tableau Dataset

Progestogens Dataset

National Toxicology Program
NTP Central Data Management, MD K2-05
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

http://ntp.niehs.nih.gov

ISSN 2473-4756