











ACKNOWLEDGEMENTS



Primary Development Organizations

The Agency for Toxic Substances and Disease Registry (ATSDR), the Center for Integrative Research on Childhood Leukemia and the Environment (CIRCLE) at the University of California, Berkeley, the Collaborative on Health and the Environment (CHE), the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA), the Science and Environmental Health Network (SEHN), and the Western States Pediatric **Environmental Health Specialty Unit (WSPEHSU)** teamed up to leverage our combined resources to develop and produce A Story of Health.

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Suggested citation: Miller M, Schettler T, Tencza B, Valenti M. A Story of Health. Agency for Toxic Substances and Disease Registry, Collaborative on Health and the **Environment, Science and Environmental** Health Network, Western States PESHU. PDF file online.

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We gratefully acknowledge the following people who reviewed draft sections of a Story of Health, noting that their review does not constitute an endorsement of the findings or conclusions. Any errors or misrepresentations that remain are entirely the responsibility of the authors.

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Boston University Superfund Research Project: Ann Aschengrau, Wendy Heiger-Bernays, Jennifer Schlezinger, Veronica Vieira

University of California, Berkeley: Berkeley/Stanford Children's **Environmental Health Center**

Center for Integrative Research on Childhood Leukemia and the Environment Educational Technology Services – Jon Schainker and Scott Vento

University of California, Davis:

Brenda M. Giddings, California Cancer Registry, Institute for Population Health Improvement, U.C. Davis Health System

University of California, San Francisco:

<u>Program on Reproductive Health</u> and the Environment

Videos - Speakers:

John Balmes; Patricia Buffler; Gary Dahl; Linda Guidice; Ulrike Luderer; Mark Miller; Catherine Metayer; Lawrence Rosen; Joseph Wiemels; Thomas Whitehead; Tracey Woodruff; Rosalind Wright; Marya Zlatnik

FUNDERS

In addition to significant in-kind contributions from all of the primary development organizations, we are grateful to the following funders who have made this project possible:

The Agency for Toxic **Substances and Disease** Registry (ATSDR)

The Center for Integrative **Research on Childhood** Leukemia and the Environment (CIRCLE) at the University of California, Berkeley

The John Merck Fund

The Jacob & Valeria **Langeloth Foundation** The Office of Environmental **Health Hazard Assessment**, **California Environmental Protection Agency (OEHHA) Western States PEHSU** The US Environmental

Protection Agency

DISCLAIMERS:

1. The Western States Pediatric Environmental Health Specialty Unit (PEHSU) prepared A Story of Health on behalf of the American College of Medical Toxicology (ACMT) and funded as part of the cooperative agreement award number 1U61TS000238-01 from the Agency for Toxic Substances and Disease Registry (ATSDR). CIRCLE is supported with funds from NIEHS grant P50 ES018172 and US EPA grant RD83615901, P.I. Catherine Metayer MD PhD.

- 2. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the organizations listed (above) as funders.
- 3. The ATSDR, US EPA, NIEHS, and Cal EPA/OEHHA do not endorse the purchase of any commercial products or services mentioned in this publication.

Help Page

Diabetes

Adobe Acrobat Tools

This interactive pdf document is best viewed on a laptop or desktop, downloaded and opened in a current version of Adobe Acrobat Reader. Refer to the top Adobe menu bar for features including:

Magnify - If you want to enlarge a diagram or some text, click (+) button.



Move through pages - You can use the up and down arrows to move through pages.

You can also move through pages using the scroll up and down feature to the right of your screen.

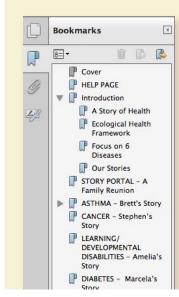


Table of Contents

HELP PAGE How to Navigate Our eBook

Use the sidebar **Bookmark Tools** as a table of contents to skip to a section of interest, find your place, or return to this Help page.

THE INDIVIDUAL STORIES OF HEALTH in this eBook are written to address many audiences. For example, some sections are more technical than others – you can skip sections if you wish.

(Note: underlined words or phrases link to online information, prompt down-loads or navigate to a related page.)

EACH OF THE EBOOK STORIES is embedded with a wide range of resources. These help further explain possible environmental and/or genetic "risk factors" -(contributors to the development of a disease, or factors that might make a disease worse) - and how these factors interact. We also provide links for additional resources, including actions you can take to prevent disease, and "tools you can use."

Our eBook Navigation: Click on selections in the bar at the top of each page to move between stories, navigate back to this 'Help Page', and to find out more in the References section.

If you lose your place, use the 'Go Back' selection in the navigation bar to return to your previous screen.

Icons

Click on icons that appear throughout the stories for pop-ups, videos, and links to more information as described.



key

concept



watch a

video



additional resources, tools



technical details for health professionals



skip this section

Skip this section - If you wish to skip a

technical section, choose the "Skip this section" arrow and you will jump to the

page after the technical sections ends.



definition

RESOURCES INCLUDE videos, slides with audio commentary, tables, charts, and graphics. Some 'popup' in the story, and some connect online. Through these links, you can choose to dig deeper and learn more. Refer to the icons (above) for guidance.

REFERENCES AND CITATIONS: Certain references are cited in the text where we believe they are most warranted. Full references by topic can be found at the end of each story.

You can skip this section and continue to the **Story of Health** introduction.



INTRODUCTION

This is a story about health.

It is a story of how our own health is intimately connected with the health of our families, friends and communities.

It is a story about how human health is interdependent with our surroundings.

Our overall story is told through the personal stories of a number of fictional people of various ages attending a family reunion.

These individual stories highlight the many ways our health is influenced by the complex environments where we live, eat, work, play, volunteer, gather and socialize.



Cognitive | References

INTRODUCTION

Our stories explore how many aspects of our lives, and what we are exposed to in our environments, influence health across the lifespan—from the beginning of fetal development to elder years—and how they can promote health and resilience, or disease and disability.

Important determinants of health come from the natural, built, chemical, food, economic, and social environments.

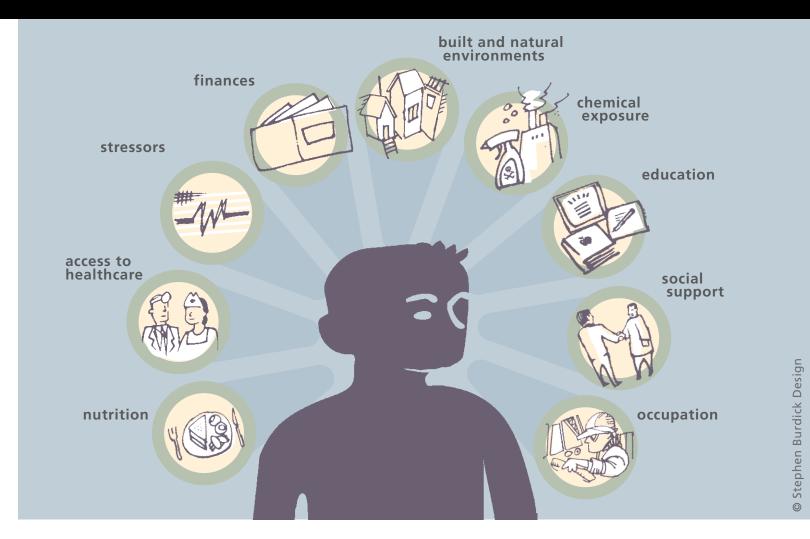
These environments are further expressed through such things as education, housing, nutrition, access to health care, social supports and more.

Many of them interact to create the conditions for health and wellness, or vulnerability to disease.



Watch: Pediatrician Larry Rosen addresses the environment and family health. (2 min.)

Lawrence D. Rosen MD is an integrative pediatrician and founder of the Whole Child Center.



Complex interactions occur among many variables and across individual, community, and societal levels.

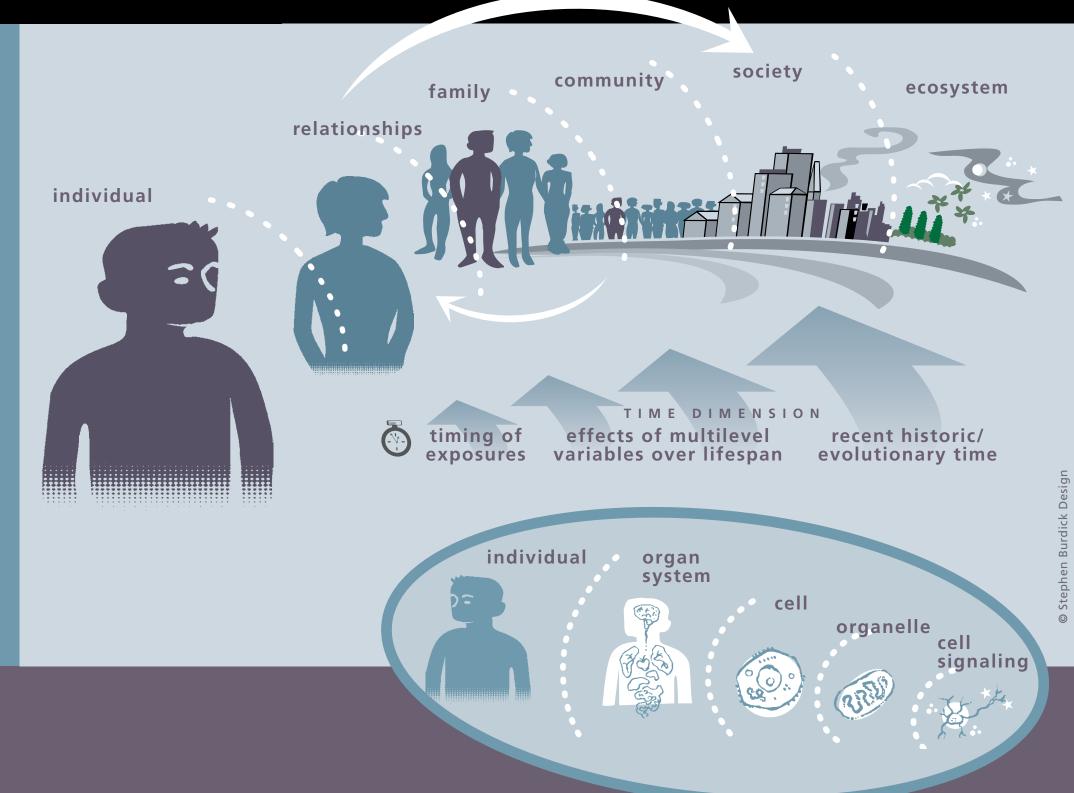
Rarely is one particular thing responsible for health or disease, so we refer to this as a multifactorial (or ecological) approach, the best way to promote health and prevent disease.

INTRODUCTION Ecological Health Framework

The ecological framework can include multiple levels from sub-cellular to societal.

It is not hierarchical in the sense that one level is more important than another, but rather in the sense that individual biology is progressively nested within the person, family, community, society and ecosystem.

The interactions and feedback loops within, across, and among these levels are complex and variable. They exert their influences on health across time.



The ecological health framework also extends to the sub-cellular level.

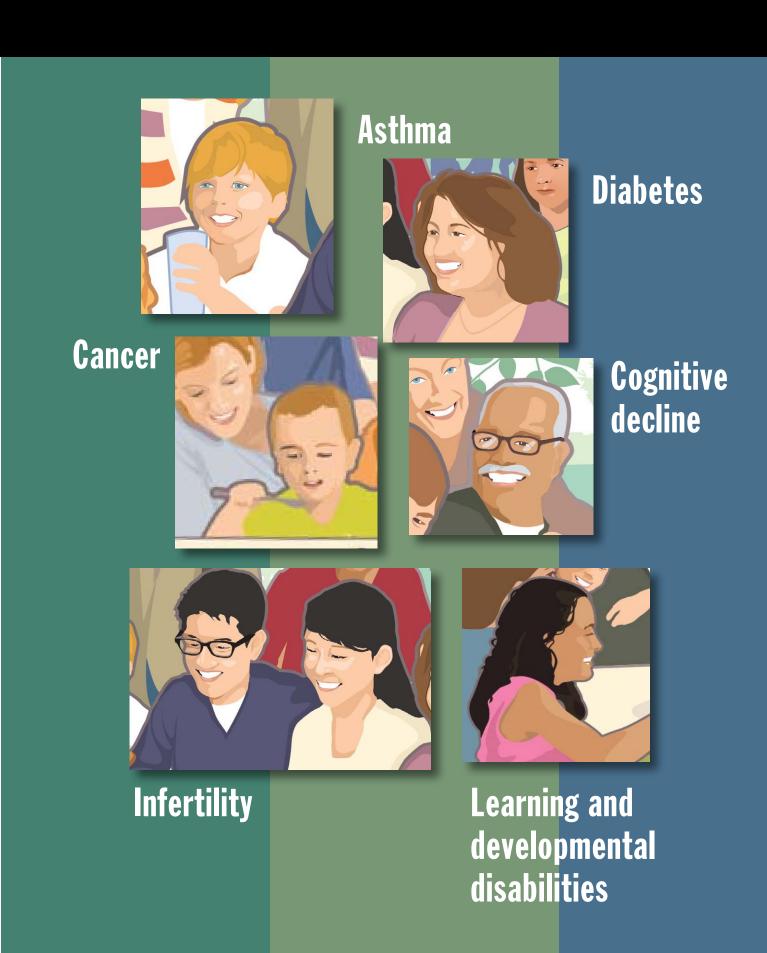
INTRODUCTION Focus on Six Diseases

Following are stories of people like you and me, our partners, families and friends, our mothers and fathers, sisters and brothers, children, grandparents, cousins, and aunts and uncles.

The personal health stories we will explore include some of the most common and troubling diseases and disorders of our time.

They include:

- Asthma
- Cancer (childhood leukemia)
- Diabetes
- Infertility
- Learning and developmental disabilities
- Cognitive decline



Cognitive | References

INTRODUCTION Our Stories

These stories are not meant to be an exhaustive accounting of every variation of a disease or every possible cause.

Rather, we present current, authoritative scientific evidence to enable you to better understand environmental contributors and make more informed decisions and take action to help improve your health, and the health of your family, friends, community, and patients.



Cognitive | **References**

A Story of Health

| Reunion | Asthma | Cancer | Learning/ | Diabetes | Infertility | Cognitive | References | Decline | Concer | Childhood | Developmental | Cancer | Childhood | Developmental | Cancer | Childhood | Developmental | Cancer | Cancer | Childhood | Developmental | Cancer | Canc

A FAMILY REUNION Six Stories

This page is your portal to six stories of health.

It is recommended that you read through the introduction first and then choose stories in the order you wish.



Health professionals can receive Continuing Education (CE) for completing *A Story of Health*. Click <u>here</u> for more details.



Choose stories in the order you wish. Select a disease term to highlight the affected person. Click the arrow button to read his or her fictional story of health.

Cognitive References

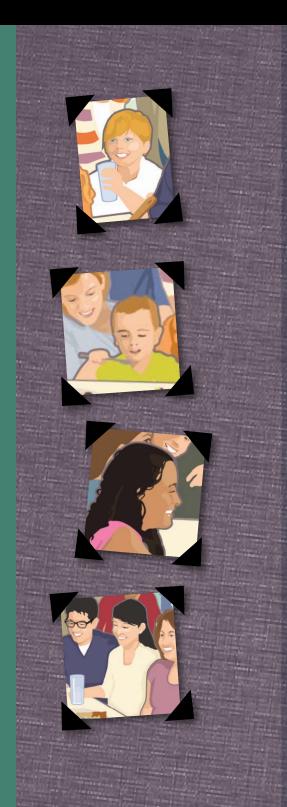
INTRODUCTION Free Continuing Education

Information on free Continuing Education offered from the Centers for Disease **Control and Prevention/Agency for Toxic Substances and Disease Registry**

Each of the fictional stories in A Story of Health offers free Continuing Education (CE). On the "Final Thoughts" page of the last story of the entire eBook, or of each story (if you download them separately), you will be prompted to register for CE through a hyperlink.

This hyperlink links to the CDC/ ATSDR CE page where you can register and take the test for CE for each story. Before you begin each story, please review the learning objectives at right. These will help you focus as you read each story, and prepare you for each CE test.

Review these learning objectives for each story:



FREE CONTINUING EDUCATION Continuing education available by specialty

- Continuing Medical Education (CME) for Physicians
- Continuing Nursing Education (CNE) for Nurses
- Continuing Education Units (CEU) for other professionals
- Continuing Education Contact **Hours (CECH) for Certified Health Education Specialists (CHES)**

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INFERTILITY Reiko & Toshio's Story

Reiko and Toshio are a Japanese-American couple in their early 30's who met in college and married five years ago. They have been trying to have a child for about a year and feel frustrated that Reiko is not yet pregnant. They are not alone – infertility is not uncommon.

US infertility statistics

Enlarge Table 1

Global and US infertility trends





At her annual exam, Reiko speaks with her gynecologist, Dr. Lopez, about the couple's frustration at not being able to conceive. Reiko says that they are now more than ready to start a family.

At an earlier appointment Dr. Lopez had explained that Reiko may have some degree of endometriosis due to her history of unusually painful menses. This could play a role in her difficulty conceiving. She tells Reiko that about 10% of women of reproductive age have endometriosis.

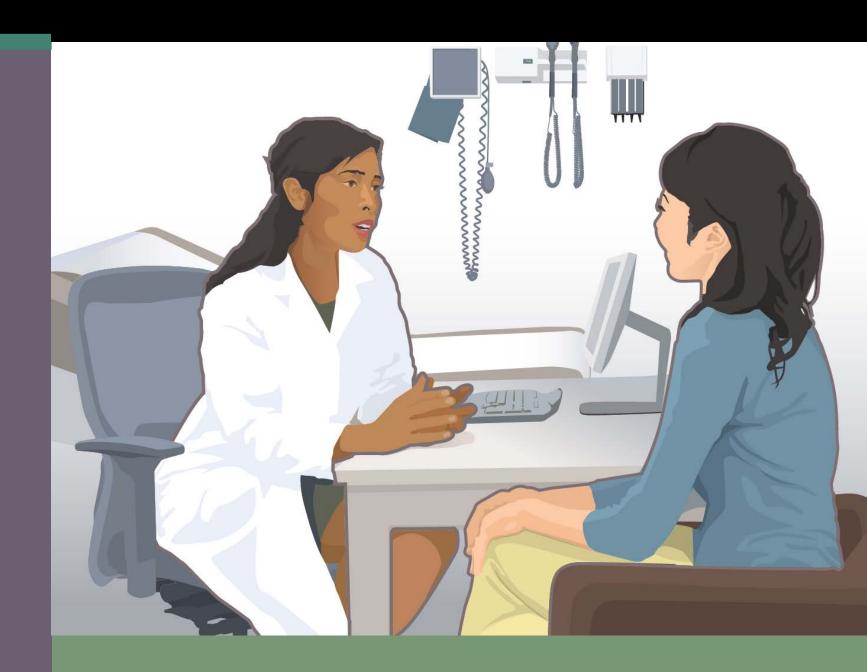
She also tells her that 30-50% of women with endometriosis are infertile and that about the same percentage who are infertile have endometriosis. Reiko is surprised at these percentages. Dr. Lopez tells Reiko she will discuss treatment options with her.



Definition: endometriosis and infertility

Endometriosis, infertility and the environment

Watch: Endometriosis and the Environment
Linda C. Guidice, MD,
PhD, MSc, Distinguished
Professor and Chair
The Robert B. Jaffe, MD
Endowed Professor in the
Reproductive Sciences,
University of California
San Francisco.



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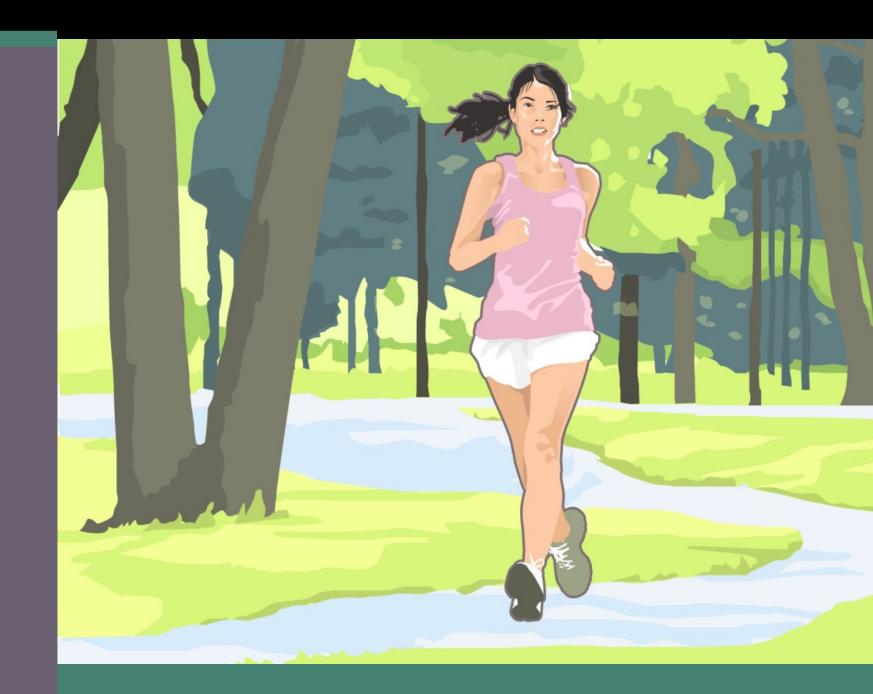
INFERTILITY Reiko & Toshio's Story

Dr. Lopez also notes that Reiko is quite thin at 5' 5" inches tall and 110 pounds, considered underweight based on her Body Mass Index or "BMI." She asks about Reiko's eating and exercise habits as she had lost weight since her last annual checkup.

Reiko says she has become an avid athlete and has started to compete in sprint triathlons. Her training routine before a race includes swimming a mile at least 2-3 times/week, biking around 50-75 miles/week, and running about 20-25 miles/week.

Dr. Lopez is impressed but explains that intense exercise combined with Reiko's thinness is likely causing her irregular menstrual cycles, which decrease the chance of pregnancy.

Intense exercise and infertility



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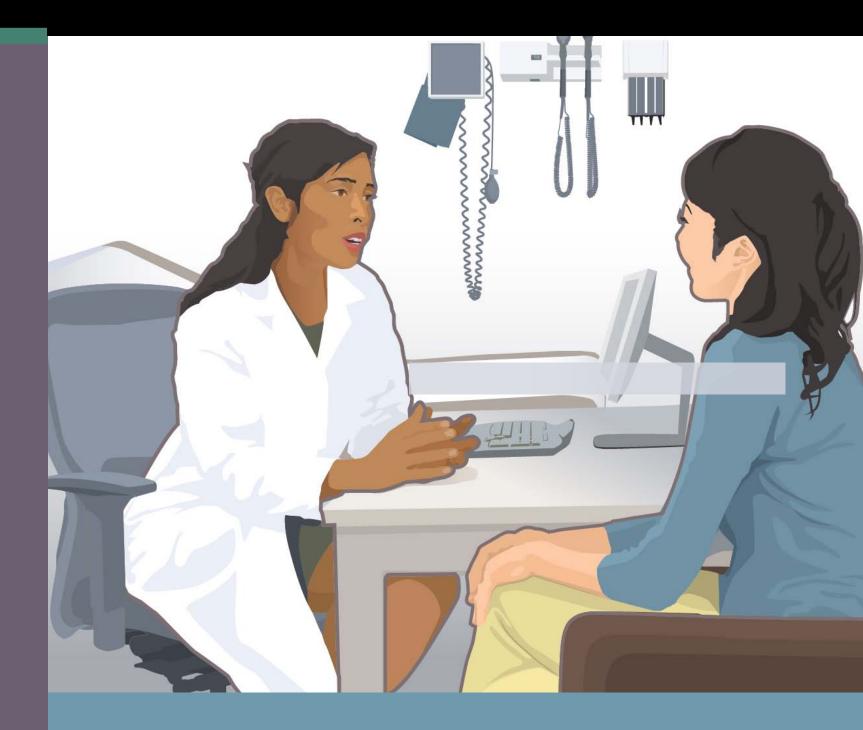
INFERTILITY Reiko & Toshio's Story

Dr. Lopez and Reiko discuss some of the ways that Reiko's reproductive system may be malfunctioning, including issues related to ovulation, egg fertilization, or implantation of the fertilized egg (blastocyst).

Dr. Lopez says that there may be more than one thing contributing to her inability to conceive, including issues related to her husband, Toshio, or a combination of factors from them both.

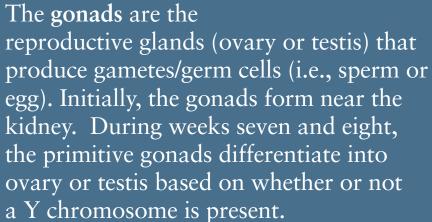
Let's leave our story for a moment to look at normal reproductive system development.

Classifications of infertility



NORMAL REPRODUCTIVE SYSTEM DEVELOPMENT

During embryonic life, the reproductive structures undergo remarkable transitions. Early on, (prior to six weeks of pregnancy), male and female reproductive structure of the fetus are identical.



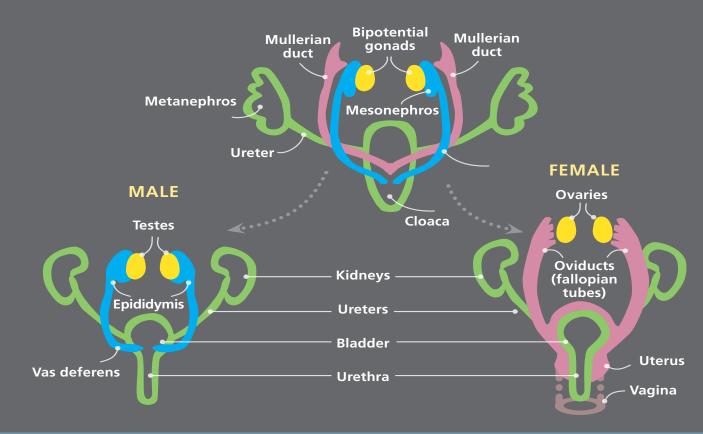
The Wolffian and Mullerian ducts develop into the internal genitalia. Prior to six weeks, the embryo has both types of ducts. After six weeks, in the male embryo, the Wolffian ducts develop into the ductus deferens, epididymis, and spermatic cords, while there is atrophy of Mullerian ducts caused by anti-Mullerian hormone (AMH) made in the gonads.



Hypothalamicpituitarygonadal (HPG) axis

Graphic used with permission from: Sex development: Genetics and biology by Peter Koopman, PhD, FAA

Normal Reproductive System Development



NORMAL REPRODUCTIVE SYSTEM DEVELOPMENT

In the female embryo, Mullerian ducts arise beside the Wolffian ducts and develop into the fallopian tubes, uterus, cervix and upper vagina, and the Wollfian ducts atrophy.

The external genitalia are also identical (or

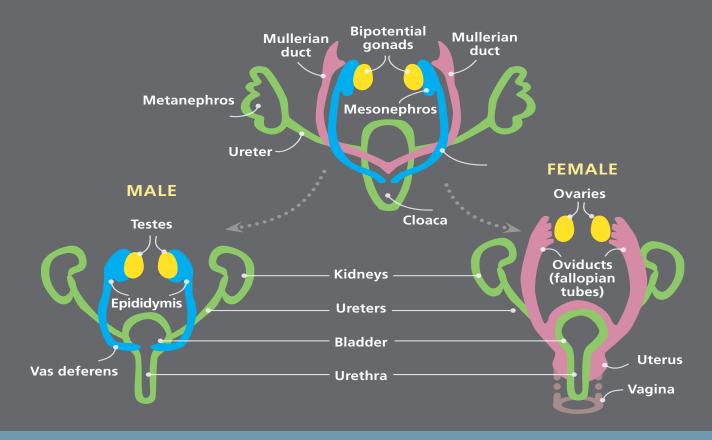
"ambiguous") until six weeks, consisting of a genital tubercle, genital swelling, and cloaca. In males, when the testes begin to secrete testosterone, the formation of male external genitalia is signaled. In females, the lack of hormone secretion results in female genitalia.

During embryonic development, not only do the male and female reproductive structures differentiate, there is sexual differentiation of the developing brain. The hormones produced by the developing male testis impact the fetal brain in sex-specific ways.



Life cycle of an ovarian follicle

Normal Reproductive System Development





Watch: Environmental Influences on the Developing Follicles

Ulrike Luderer, MD, PhD, MPH discusses environmental influences on the developing ovaries.

Ulrike Luderer, MD, PhD, MPH, Consultant, Western States PEHSU, Professor, School of Medicine, Director, Environmental Health Sciences Graduate Program, University of California, Irvine

Reiko and Dr. Lopez then discuss some general healthy habits for couples planning to have children.

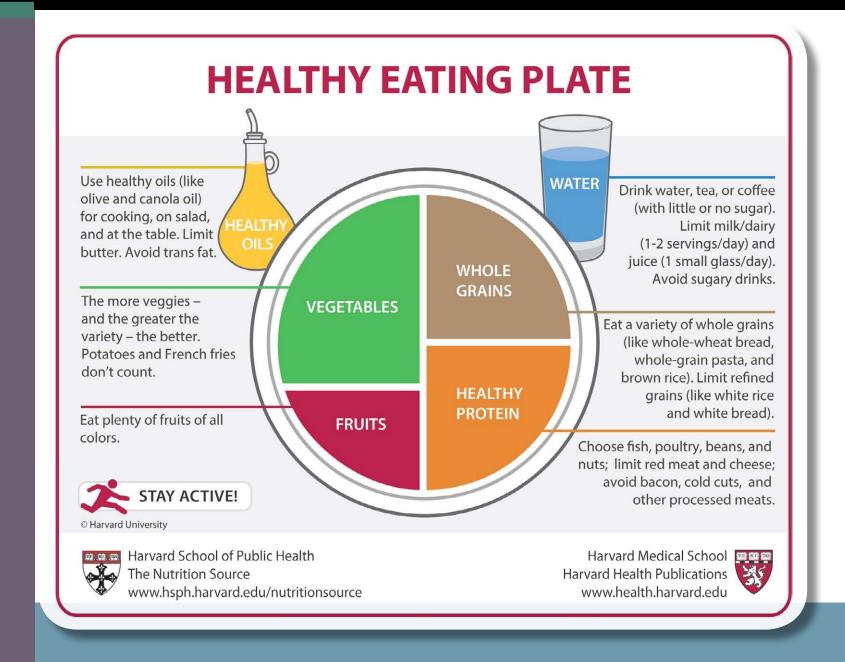
They discuss briefly that a healthy diet in general will also be beneficial for fertility. This includes eating lots of fruits and vegetables, whole grains, and healthy fats, as illustrated in the graphic at the right from the Harvard School of Public Health.

Some studies suggest that specific nutrients may increase fertility, including a daily multivitamin that contains folate and iron, and substituting high-fat for low-fat dairy. **Preconception** health

Key concept: Multigenerational nutrition

Link to graphic credit

Watch: Preconception **Counseling and Environment**, Marya Zlatnik MD, **Professor, UCSF School of Medicine**



Link:

More information: CDC's Preconception care for women and men

Healthy Eating Plate graphic copyright © 2011 Harvard University www.hsph.harvard.edu/nutritionsource/ healthy-eating-plate. Used with permission. For more information about The Healthy Eating Plate, please see The Nutrition Source, Department of Nutrition, Harvard School of Public Health, www.thenutritionsource.org and Harvard Health Publications, www.health.harvard.edu



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INFERTILITY Reiko & Toshio's Story

Dr. Lopez also gives Reiko some information on prenatal care for healthy child development, which she recommends Reiko incorporate into her life now that she is trying to become pregnant.

Prenatal Care for Healthy **Development**

Folate supplementation recommendations for women



MORE INFORMATION:

- CDC on pregnancy
- American Congress of Obstetrics and Gynecology (ACOG):
- Good Health Before **Pregnancy** (pdf)
- Prenatal Nutrition
- **Environmental Chemicals**

- Royal College of OB/GYN:
- Chemical Exposures During **Pregnancy**
- UCSF: Program on Reproductive **Health and the Environment**

Dr. Lopez includes information on the influence of toxic chemicals such as lead and the solvents in paints and other materials.

She again mentions the important nutrition issues they had discussed earlier.





Watch: Chemicals and Infertility
Tracey J, Woodruff, PhD, MPH
Director, Program on Reproductive
Health and the Environment;
Professor in the Department
of Obstetrics, Gynecology, and
Reproductive Sciences at the
University of California, San
Francisco

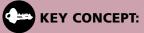
Reproductive health effects of solvents

Reproductive health effects of lead

Key concept:
Unintended adverse
consequences of
improvements to the
environment

Links:

- <u>TedX</u> The Endrocrine Disruption Exchange
- Generations at Risk Reproduction Health and the Environment
- CDC's Lead and Pregnancy

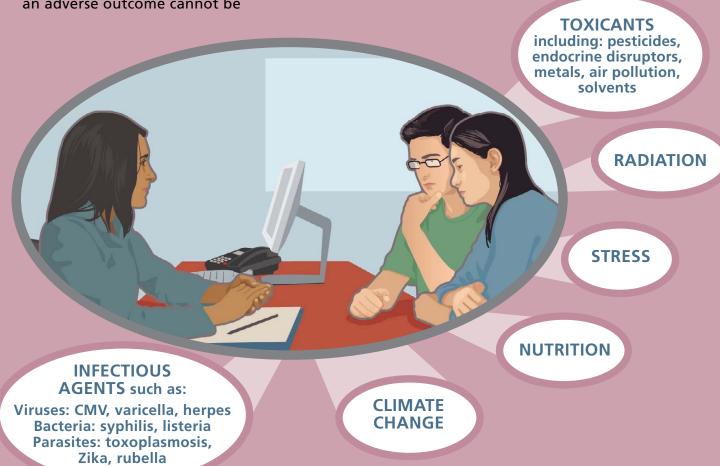


Multiple environmental factors can influence reproductive health.

Environmental factors, alone or in combination with other variables, can have adverse impacts on reproductive health, increasing the risk of infertility, miscarriage, abnormal fetal growth, fetal death, preterm birth, birth defects or other developmental abnormalities.

In many cases, a specific cause of an adverse outcome cannot be

identified. With the exception of birth defect registries in some states, lack of comprehensive data collection pertaining to most abnormal outcomes makes epidemiologic studies intended to identify causal factors difficult to conduct.



INFERTILITY Reiko & Toshio's Story



KEY CONCEPT:

CHALLENGES OF CONNECTING ENVIRONMENTAL EXPOSURES TO OUTCOMES



How can we measure exposure levels in the body or environment?

- By testing chemical concentrations in people's blood serum or urine.
- By testing chemicals in the environment of the home, workplace, or other place, for example, in the dust or air.

The higher the chemical levels in the environment, generally the higher the levels in the serum and/ or urine.

We know that exposure to environmental chemicals is widespread. For example, the National Health and Nutrition Examination Survey (NHANES) reported that BPA by-products were detected in over 90% of their urine samples from a representative population of the US (Calafat et al., 2008).

Knowing that exposures have occurred does not necessarily mean that they have caused a harmful effect.

People can be exposed to toxicants through air, water, soil, food and consumer and industrial products

RESOURCE LINKS:

- CDC–Reproductive and birth outcomes
- CDC–Tracking birth defects
- National environmental health tracking program
- Pesticide Action Network Database

Examples of issues that can complicate assessments of links between an exposure and health effects:

Help Page

- An exposure pathway must be completed. Exposure pathways are means by which hazardous substances move through the environment from a source to contact with people. A complete exposure pathway must have four parts: (1) a source of contamination; (2) a mechanism for transport of a substance from the source to a person through the air, water, food, or via direct contact; (3) a way by which people come in contact with contaminated air, water, food, or other products, and; (4) a route of entry into the body. Routes of entry can be eating or drinking contaminated materials, breathing contaminated air, or absorbing contaminants through the skin. If any part of an exposure pathway is absent, the pathway is incomplete and no exposure or risk is possible.
- We should know the dose, duration, and pattern of exposure necessary to cause a harmful effect but sometimes do not.
- Randomized controlled trials to conclusively establish the dose necessary to cause harms are unethical. So, we must use animal or basic science models in addition to observational data from exposed people.
- In observational studies, exact exposure levels over time are typically unknown and can only be estimated.
- The timing of exposure may be unclear or have occurred in the distant past.

• Different people can have different levels of sensitivity (stemming from nutritional status, life stage, metabolism, or genetics).

Infertility

Cognitive References

Decline

Evidence of Health Effects

Evidence comes from demonstrating health effects in experimental animal models and from human epidemiologic data. But epidemiologic studies require reliable collection of health outcome data. Unfortunately, except for fairly high-quality birth defect registries in a few states, and routine collection of birth weight data, ongoing tracking of reproductive and developmental abnormalities is generally lacking in the US. Periodically, an agency attempts to estimate the prevalence of various developmental disabilities in order to identify trends, but attempts to link cases with environmental exposures are usually not possible with these data. Improved tracking of reproductive health outcomes would help to link them to environmental exposures.

Tracking some adverse outcomes can be done through state vital records that include information on all births including the use of fertility drugs and assisted reproductive technology. These data can also be linked to a fertility database managed by the **Society** for Assisted Reproductive Technology to collect even more data about the patients and their individual treatment. With these types of data, the birth address could be used in statistical models to produce maps of areas where infertility may be higher. These maps could then be overlaid with environmental data to generate new hypotheses.

INFERTILITY Reiko & Toshio's Story

Dr. Lopez asks more about Reiko and Toshio's backgrounds and lifestyles to try to find some clues pointing to other possible reasons for the couple's infertility.



Taking environmental and psychosocial histories

Environmental history

Download a sample pdf

<u>Link</u>: Antenatal psychosocial health assessment

Multiple stressors and health risks

Link:

Centering Healthcare Institute Improving maternal child health by transforming care

Taking Environmental and Psychosocial Histories

Taking environmental and psychosocial histories can be routinely incorporated into clinical practice not only for couples with infertility but with all people of reproductive age. This will help identify opportunities for primary prevention of adverse reproductive outcomes prior to pregnancy.

Infertility | Cognitive | References

Diabetes

Environmental History

Help Page

Environmental History Form	
What do you do for work?	Always wear proper personal protective equipment. Contact an Occupational and Environmental physician witl questions about workplace exposures. www.aoec.org
Are you exposed to any of the following at work:	
Metals	
Solvents	
Chemicals (including those for cleaning)	
Radiation	
Fumes	
Lead can cause brain damage, especially in babies and children	Eat foods enriched with iron (lean red meats, chicken), calcium (dairy, green leafy vegetables), and vitamin C (oranges, grapefruits, tomatoes, green peppers).
Have you or anyone living in your house ever been treated for lead poisoning?	
Do you live in a house built before 1978?	Have your home tested for lead if it was built before 1978 Chipping paint may release lead into the house.
Are there any plans to remodel your home?	Avoid remodeling or hire a certified contractor. Call 1-800-424-LEAD for more information.
Have you ever lived outside the United States?	
Does your family use imported pottery or ceramics for	Imported pottery or ceramics may contain lead, which car
cooking, eating, or drinking?	leach into food.
Have you used any home remedies such as azarcon, greta, pay-loo-ah?	Do not use lead-containing home remedies.
Have you ever eaten any of the following:	Do not eat clay, soil, dirt, pottery, or paint chips because they may contain high levels of lead.
Clay	
Soil or dirt	
Pottery	
Paint chips	
Mercury is another metal that can damage the developing fetal brain. Small children are also sensitive.	It's important to clean up mercury spills in a special way. https://www.atsdr.cdc.gov/mercury/docs/residentia-hg-spill-cleanup.pdf
Is there a mercury thermometer in your home?	Use a digital or mercury-free thermometer.
In general, do you eat fish more than twice a week?	Eat a variety of fish low in mercury twice a week. Contact local health dept. about local fish advisories.
Do you eat any of the following types of fish:	Do not eat shark, swordfish, king mackerel or tilefish because they contain high levels of mercury.
Shark	
King Mackerel	
Swordfish	
Tilefish	
Orange Roughy	
Big eye tuna	
Marline	
Albacore tuna ("white" tuna)	Albacore tuna contains more mercury than canned light tuna; do not eat more than 6 oz. per week of albacore tuna.
Air pollution is harmful to pregnant women who are "breathing for two" and also for fetuses, babies, and children.	

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INFERTILITY Reiko & Toshio's Story

Reiko tells Dr. Lopez she was born and raised in the agricultural region of Okayama, Japan. She met Toshio when they were both attending college in California.

She says that Toshio has always been quite healthy. He grew up on his family's farm in the Central Valley of California during the 1980's, then moved to Los Angeles to attend college.



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INFERTILITY Reiko & Toshio's Story

Soon after graduating college the couple got married and settled in a suburb of Los Angeles. Toshio worked for a software development company for a few years. Reiko worked in a private nonprofit company designing their web products.

When Toshio's parents got older and needed help on the family farm, the couple decided to move there and help them. That was three years ago.

Toshio has been working on the farm to supplement their income while he launches a small business in web design. Reiko is able to continue her job remotely, driving into Los Angeles for monthly meetings.

Reiko knew that pesticides were used on the farm and asks whether that might be a problem. Dr. Lopez said yes and offered to send her information on this. Pesticides and fertility



Cognitive References

Photo: Copyright © 2000 The Regents of the University of California. Used by permission. Source: California Agriculture 54(6):14-19. DOI: 10.3733/ca.v054n06p14. November-December 2000

INFERTILITY Reiko & Toshio's Story

Dr. Lopez mentioned other environmental exposures that might affect fertility, such as air pollution, and says there are some good resources that she can also send to Reiko.

Reiko thinks about her training runs around some of the major roads, and remembers the emissions from the trucks and cars. She wonders how that might have affected her.

Dr. Lopez suggests that a fertility specialist may be able to provide even more information.



Vulnerable populations and environmental disparities

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Air pollution and fertility, reproductive health



<u>Link</u>: ACOG Evaluating Infertility

Links:

ACOG American Congress of Ob/Gyn: Vulnerable populations and environmental disparities

FIGO Opinion International Federal of Gyn/Ob:
Reproductive health impacts of exposure to toxic environmental chemicals



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INFERTILITY Reiko & Toshio's Story

Meanwhile, Dr. Lopez suggests that Reiko consider cutting down on intense exercise, but when she is training include a higher caloric intake of healthy food. She stressed that Reiko should return to her regular healthy diet when not in training.

Dr. Lopez recommends a diagnostic laparoscopy to determine if Reiko has endometriosis. If she does, Dr. Lopez says that Reiko could consider treating her endometriosis and describes what that might entail.

The usual next step would be for Reiko and her husband to see a reproductive endocrinologist/fertility specialist.

Dr. Lopez said she could recommend someone as Reiko got up to leave.

Endometriosis treatment



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INFERTILITY Reiko & Toshio's Story

When Reiko went home, her head was spinning. She thought that she was doing everything she could to get pregnant, so hearing Dr. Lopez's suggestions and concerns was a bit overwhelming. She couldn't wait to talk with

Reiko and Toshio spent a long while discussing the appointment with Dr. Lopez.

They then had a nice relaxing dinner with Toshio's parents.

Toshio.

Reiko was missing her family back in Japan but was going to call her sister that evening to tell her all about what was happening and ask her advice.



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INFERTILITY Reiko & Toshio's Story

In the next few days, after Reiko speaks more to Toshio and to her sister, she decides to have the laparoscopy. She calls Dr. Lopez and schedules it for a month later after she participates in her next mini-triathlon.

A month later...

When Reiko goes to Dr. Lopez for the laparoscopy she tells her that she placed second in her age group in the triathlon, the best she had ever done. Dr. Lopez congratulates her but reminds her about considering changes to her activity routine. Reiko says she had been thinking about that and had decided to get back to yoga on a regular basis, which she had practiced before.

Dr. Lopez performs the laparoscopy and informs Reiko that she does not have endometriosis. Reiko is happy to hear the news as is Toshio who is waiting for her in the reception area.

On the drive home they decide to make an appointment with Dr. Patel, the fertility specialist recommended by Dr. Lopez.



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INFERTILITY Reiko & Toshio's Story

Reiko and Toshio are able to get an appointment three weeks later with the fertility specialist Dr. Patel. The first thing Dr. Patel does is take a thorough medical history from Reiko and Toshio, including questions about occupations now and in the past. She orders lab tests as part of their initial visit.

Dr. Patel was recommended by Dr. Lopez because of her training in environmental influences on health, and because she regularly consulted with the regional Pediatric Environmental Health Specialty Unit (PEHSU) that also offered OB/GYN expertise.

Occupational influences on female reproductive health

Occupational exposures and male reproductive health Link to credit

For clinicians: Safety **Data Sheets**

More information about the **PEHSU** network

Link: the PEHSU network



Additional Resources:

SDS sheets are notoriously incomplete, use these additional resources to further understand the health effects of toxicants:

Proposition 65

New Jersey Hazardous Substance Fact **Sheets**

CHE Toxicant and Disease Database Toxics Release Inventory

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INFERTILITY Reiko & Toshio's Story

During the course of the history Toshio tells Dr. Patel that he spends a good deal of his time on the laptop each day.

Dr. Patel informs them, though controversial, there are some potential concerns related to low-frequency electromagnetic radiation.

Electromagnetic exposure and male fertility





They discuss a range of other possible environmental exposures including endocrine disruptors.

Dr. Patel says she will have the test results in about a week, so they set up another appointment.

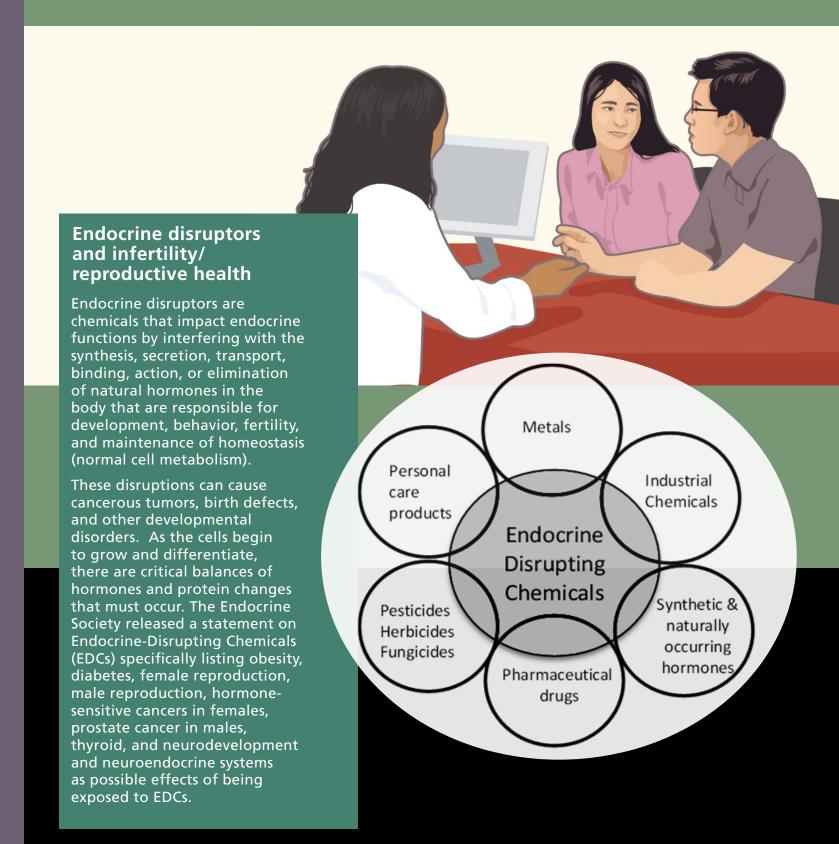
Watch: Little Things Matter: The Impact of Toxins on the **Developing Brain** Dr. Bruce P. Lanphear, MD MPH **Professor, Simon Fraser** University

Bisphenol A (BPA) and how it can mimic estrogen

Bone disrupting chemicals: Fatty bones and osteoporosis

Parabens and reproductive health





INFERTILITY Reiko & Toshio's Story

TESTICULAR DYSGENESIS SYNDROME

Although Toshio is not affected by this, a number of studies in the US and some countries in Europe have shown increasing trends in testicular cancer; declining semen quality, including lower sperm counts; and increases in hypospadias (an abnormality of the penis with the urethral opening along the underside of the shaft instead of at the tip) and cryptorchidism (undescended testes).



Testicular germ cell cancer arises from primordial germ cells that escaped fetal differentiation. Hypospadias and cryptorchidism result from incomplete masculinization of the reproductive tract during fetal development. It has been proposed that each of these represent different manifestations of the same underlying condition called testicular dysgenesis syndrome (TDS).

Clinical evidence of this syndrome comes from the observation that males with rare genetic abnormalities that cause testicular dysgenesis are at higher risk of testicular cancer, often combined with cryptorchidism and hypospadias.

But the majority of cases of these abnormalities occur in individuals without known underlying genetic abnormalities and the cause remains unclear. Moreover, countries with higher incidence of testicular cancer, such as Denmark, tend to have higher prevalence of cryptorchidism, hypospadias, and poor semen quality.

Thus, scientists have looked for environmental factors that may help explain the observations.

Prenatal
Phthalate
Exposure:
Effect on AGI
(anogenital
distance) in boys

Endocrine disrupting chemicals (EDCs) that interfere with normal testosterone production or androgen action are prime candidates. In laboratory animal studies, fetal exposures to various phthalates, the insecticide DDT, and the fungicide vinclozolin cause a TDS-like phenotype in rats although an equivalent to human male germ cell cancer does not exist in rodents.

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Many of these same chemicals also cause a decrease in anogenital distance, a marker of anti-androgenic activity that can be measured in laboratory animals and people. Humans are regularly exposed to a cocktail of endocrine disrupting chemicals including phthalates, bisphenol A, polybrominated diphenyls, polyfluorinated compounds, alkylphenol, and many others.

The shortened anogenital distance associated with prenatal exposure to phthalates previously described in humans, as well as with the endocrine disruptor bisphenol A, is consistent with an anti-androgenic effect and has been associated with lower sperm count and quality (Mendiola et al).

The animal and human studies, combined with trends in male reproductive health described above, support the hypothesis that exposure to EDCs may play a significant role in these findings.

Epidemiologic studies continue to identify environmental chemicals linked to adverse male reproductive tract development with the aim of identifying those that pose risk, including male infertility, in populations, helping to make the case for removing them from commerce.

Humans are regularly exposed to a cocktail of endocrine disrupting

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INFERTILITY Reiko & Toshio's Story

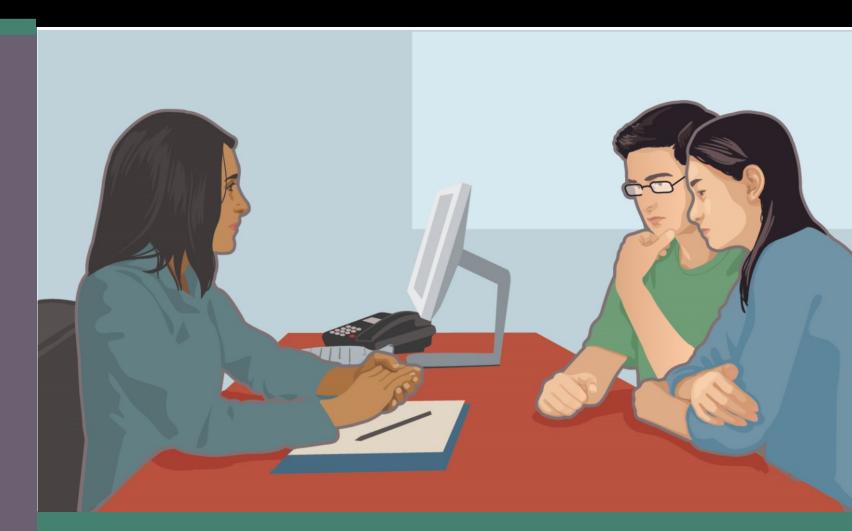
Even though Dr. Patel had done her best to reassure them, Reiko and Toshio were nervous as they drove to their next appointment. What if there was nothing Dr. Patel could recommend to help them?

When they get to her office she

tried to put them at ease and told

them about some key test results.

Key test results



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INFERTILITY Reiko & Toshio's Story

They discuss the meaning of the test results.

Dr. Patel makes some initial recommendations to Reiko and Toshio:

For Reiko:

- Decrease the amount of weekly exercise.
- Increase calorie intake with healthy foods, to achieve a weight of 120 pounds.

For Toshio:

- Be sure to use safe application practices when working with pesticides.
- Take an omega 3 fatty acid supplement such as fish oil and a multivitamin. Look for supplements that have been tested for contaminants and say "mercury free." Note: there is no regulation of these supplements.



<u>Link</u>: Pesticide Safety Rules for Farmworkers – Cal. EPA:

http://www.cdpr.ca.gov/docs/whs/pdf/hs1587.pdf

Fertility diet
Link to reference

Enlarge Table 2



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INFERTILITY Reiko & Toshio's Story

Dr. Patel also suggests Reiko needs therapy to begin ovulation.

The first step would be for her to change her exercise regimen, gain weight, and even see a therapist to deal with stress if that is an issue. If her weight increases she'll likely start ovulating.

For many women, including those with polycystic ovarian syndrome (PCOS), the next step would be to take the oral medication Clomiphene, or Clomid, a selective estrogen receptor modulator (or SERM) which increases the release of GnRH (Gonadotropin-releasing hormone) which stimulates ovulation.

Reiko, and other women with functional hypothalamic amenorrhea who have low estrogen levels, will likely need injectable gonadotropins (FSH injections) to produce ovulation, as their brain may not respond to GnRH.

She also suggests she undergo intrauterine insemination (IUI) and explains the procedure and also the costs, which she says may not be covered by their insurance.

In addition, she also suggests that Toshio see another clinician in the practice who is a urologist specializing in male infertility. She says he could probably see him within the next week.



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INFERTILITY Reiko & Toshio's Story

They ask Dr. Patel to set up an appointment with the urologist and explain that they'd like to discuss next steps and investigate insurance coverage before they make any decisions on how to proceed.

Toshio is indeed able to see the urologist Dr. Richardson within the week and undergoes a thorough history, physical exam and blood work to look for endocrine (hormonal) causes of a low sperm count.

The urologist offered a test to look for DNA damage in Toshio's sperm, but this test was not covered by his insurance.



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INFERTILITY Reiko & Toshio's Story

The next week after more discussion and research, they decide to go ahead with the injections. and to proceed with the intrauterine insemination.

Reiko calls Dr. Patel and asks when this might occur.

Dr. Lopez explains that in order to assess the response to therapy Reiko will need to undergo a series of ultrasounds to gauge follicular growth. Once follicles are mature, ovulation is triggered to time the intrauterine insemination. (Women on Clomid will use OTC ovulation prediction kits to time intercourse or IUI.)



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INFERTILITY Reiko & Toshio's Story

Meanwhile the couple does more research about infertility and afterward decide to take some additional steps.

Toshio talks with his parents and tells them his concerns about using pesticides on the peach farm, especially since they are trying to have a child. He shows them some studies about pesticides and health.

Toshio says that if he is going to be taking over the farm full time he wants to try to convert to organic production. He has been following trends showing that organic produce and fruit are popular with consumers and highly marketable, even though organic production presents new challenges.

His parents agree to introduce Integrated Pest Management (IPM) at the peach farm as a first step, and to work with him for a full transition.

Integrated pest management (IPM)

Links:

Source: What is Integrated Pest Management? University of California, Davis Image source: Wikipedia

More Resources:

Pesticides: EPA – <u>Integrated</u> Pest Management

Bio-integral Resource Center (BIRC)

Pesticide Action Network (PANNA)

University of California - Pesticide Application Equipment



Watch: Epitaph for a Peach

From Huell Howser California's Gold Archive, presented by **Chapman University** (long – 28 min.)



INFERTILITY Reiko & Toshio's Story

Toshio also starts using his laptop computer on a table, not on his lap, and starts to take fish oil supplements and a multivitamin.

Reiko commits to her yoga routine and also to practicing meditation, and decides to decrease her intense exercising.





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INFERTILITY Reiko & Toshio's Story

When the ultrasound indicates that the follicles have matured and Reiko is ovulating, Dr. Patel is able to proceed with the IUI.

Toshio's sperm is prepared and sterilely placed in Reiko's uterus with a syringe.

Dr. Patel assures Reiko she can resume her normal activities after the IUI.



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INFERTILITY Reiko & Toshio's Story

After two more cycles of IUI, and no pregnancy, they start to feel discouraged.

Toshio and her family urge her to continue.

After the fourth cycle she has a positive pregnancy test!

When they hear the good news, they rush to tell Toshio's parents, and Reiko is already texting her sister with the good news that she will be an aunt in the next year. They ask them to keep the news confidential until they are ready to tell others.

Over the next few weeks they spend time learning about the stages of growth of the fetus and review all the prenatal health recommendations that they can incorporate into both of their daily activities.

Watch: The Epigenome at a Glance

University of Utah, Genetic Science Learning Center (2 min.) **Embryo development**

The placenta – vital to human survival

Link: <u>NICHHD/NIH</u> *Human Placenta Project*

Links:

ARHP Environmental Impacts on Reproductive Health

CHAMACOS Environmental Health Kiosk

An interactive, touch-screen, audio-visual tutorial to learn about environmental hazards in English and Spanish.

Watch: Epigenetics
Mark Miller MD, MPH
(2 min.)



Cognitive References

INFERTILITY Reiko & Toshio's Story

KEY POINTS

Throughout the pages of Reiko and Toshio's story we've seen a wide range of interacting variables that may contribute to infertility or reproductive health problems.

These include exposure to toxic chemicals, diet, body weight/excessive exercise, socioeconomics, genetics, and gene-environment interactions.

We have also seen actions that can increase resilience and enhance healthy reproduction and development, such as avoiding toxic exposures and eating a healthy diet throughout life.

Although Reiko and Toshio's story is fictional, women, men and couples throughout the world may face a similar range of issues depending on their circumstances.

It is critical that we consider the multiple environmental influences associated with increased risks for infertility, reproductive harm, and impaired development, and their long term consequences when we design prevention strategies and treatments to address them.



SOME FINAL THOUGHTS

COMMON THEMES

Although the fictional narratives in *A Story of Health* describe the lives of children and adults with different conditions and diseases – infertility, asthma, developmental disabilities and childhood leukemia - common themes resonate. They include:

- Important environmental influences come from the natural, chemical, food, built, and social environments.
- Although there are exceptions, most diseases as well as good health are the result of complex interactions among multiple environmental influences and genetics.
- Early-life experiences, particularly during critical windows of development, can have profound beneficial or detrimental lifelong effects, even into elder years.
- Healthy people and healthy communities are interdependent. All people do not have equal access to nutritious food, clean air and water, safe workplaces, healthy housing, green spaces, peaceful neighborhoods or quality health care.
- Preventing disease and promoting health require actions and commitments from the individual, family, community and society. Health promoting public policies are necessary to make healthy living available to all people.

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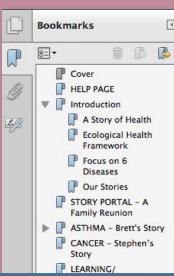
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Resources

We have linked to many useful resources in each story relevant to a wide range of audiences, including clinicians. To quickly access resources on specific topics in each story, use the **Bookmarks** toolbar on the left (which you can open or close), or return to the **Help page** for more details on other eBook features.



Additional resources to help prevent disease and promote health:

<u>Portal to Science Resources</u>: Hundreds of additional resources on environmental health including organizations, publications, videos and more.

Pediatric Environmental Health Toolkit application for mobile devices

Out of Harm's Way: Preventing Toxic Threats to Child Development: Fact Sheets in English and Spanish.

<u>Approaches to Healthy Living</u>: A 4-page guide on how to avoid toxicants, eat healthier, reduce stress.

Healthy Aging: The Way Forward: An ecological approach to policy level interventions for healthy aging across the lifespan.

Continuing Education

Register for Continuing Education (CE) for A Story of Health for a variety of health professions. Free credits are offered by the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry at this link.



Another free CE course on environmental health offered by the CDC/ATSDR is the <u>Pediatric Environmental Health Toolkit</u> online course.

Clinical and personal opportunities to support a healthy life and reproductive health

THINGS TO CONSIDER:

Learn to cook and eat a healthy diet

- Take recommended amounts of folic acid supplement (helps to prevent birth defects).
- Eat fresh fruits and vegetables, organic if possible.
- Never microwave your food in plastic (endocrine disruptors can leach from plastic).
- Avoid trans fats (in processed foods).
- Limit alcohol intake and avoid alcohol during pregnancy.
- Limit or eliminate sugary beverages.
- Eat more:
- monounsaturated fats (such as in olive oil, avocados, nuts);
- vegetable protein (such as in beans, peas, nuts, and soybeans or tofu);
- high-fiber, low glycemic carbohydrates (whole grains, vegetables, whole fruits, and beans);

- plant sources of iron such as leafy green vegetables;
- fish high in omega 3 fatty acids (but avoid eating fish high in mercury – see fish guide resources.)

Reduce exposure to toxic substances

- Reduce exposure to indoor and outdoor air pollution including cigarette smoke.
- Reduce exposure to toxic chemicals in products including those used for household cleaning and personal care. Replace with less toxic alternatives.
- Reduce exposure to lead in paints and water.
- Eliminate or reduce pesticide use in home and lawn/garden.

For clinicians: **Proposition 65** Links:

Proposition 65

Fact sheets for the public on Prop 65 chemicals

Additional Resources:

Reproductive health/infertility and the environment:

- <u>CHE</u> series of calls on infertility
- <u>PePH</u> The environment's role in infertility
- <u>TEDX</u> The Endocrine Disruption Exchange

Personal actions to protect your health:

• <u>UCSF</u> Program on Reproductive Health and the Environment "Toxic Matters"

Fish consumption guidelines including those based on health, sustainability:

- <u>EPA/FDA</u> fish consumption guidelines
- Physicians for Social Responsibility's "Healthy Fish, Healthy Families"
- Monterey Bay Aguarium "Seafood Watch"

Consumer product guides and apps including food, personal care, cleaning products:

- Environmental Working Group's consumer guides
- EPA's Safer Choice
- Good Guide
- Silent Spring's "Detox Me"

In the workplace:

- Occupational Safety and Health Administration: Reproductive Hazards/Possible Solutions
- A Guide for Nail Salon Workers



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INFERTILITY Reiko & Toshio's Story

POLICY RECOMMENDATIONS

In Reiko and Toshio's story we have discussed a range of risk factors that may affect fertility and reproductive health. Reducing those risk factors may involve personal choices, but many require public policy actions.

Policies include legislative and institutional actions to reduce exposure to toxic chemicals, improve access to healthy food, and encourage community solutions to reduce social stressors, among others. At right are a few policy actions recommended to reduce reproductive health risk factors.

These include exposure to toxic chemicals, diet, body weight/excessive exercise, socioeconomics, genetics, and gene-environment interactions.

Regrettable substitutions

LINK:
The Commons Principles
for Alternatives
Assessment



POLICY RECOMMENDATIONS

Reduce exposure to reproductive and developmental toxicants through federal, state and local policies.

- ► Legislate policies that keep air, water, food, and other sources of exposure free of pollutants.
- ► Ensure that consumer products, from household cleaning supplies to cosmetics, are free of harmful substances.
- ► Promote public transportation to reduce air pollution sources.
- ► Ensure that workers are not exposed to harmful substances on the job.
- ▶ Reduce the use of pesticides in public spaces, schools, homes, workplaces and promote Integrated Pest Management (IPM).

Increase access to healthy foods.

- ➤ Cities and towns can change zoning and tax laws to make it easier to create new grocery stores, farmers' markets, and community gardens.
- ▶ Regulations and incentives can help existing stores increase the number and variety of healthy products they sell.
- ▶ Maternal and child health programs, and food programs for low income families, young children, and elders, should prioritize optimum nutrition and include incentives and opportunities to purchase fresh, healthy foods.
- ► Local governments can create food policy councils to give residents a voice on how best to improve access to healthy food.
- ► Encourage breastfeeding through health care and workplace policies.

Support services and increase communication and education on preconception health and prenatal health.

All women and men can benefit from education on preconception health, whether or not they plan to have children as preconception health includes staying healthy throughout life. In addition, nearly half of all pregnancies in the United States are not planned.

- ▶ Provide support for pregnant women through innovative programs such as group prenatal care.
- ▶ Healthcare providers should include counseling on environmental influences on health and interventions to reduce risk in all specialties, from maternal and child health to elder care.

REFERENCES: Infertility

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Infertility Case References and Resources by Topic

Chemical Hazards Air pollution

Checa Vizcaino, M.A., M. Gonzalez-Comadran, and B. Jacquemin. Outdoor air pollution and human infertility: a systematic review. Fertil Steril. 2016.

Currie, J. and R. Walker. Traffic Congestion and Infant Health: Evidence from E-ZPass. American Economic Journal: Applied Economics. 2011. 3(1): p. 65-90.

Dadvand, P., et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect. 2013. 121(3): p. 267-373.

Devine, P.J., S.D. Perreault, and U. Luderer. Roles of Reactive Oxygen Species and Antioxidants in Ovarian Toxicity. Biology of Reproduction. 2012. 86(2): p. 27.

Gray, S.C., et al. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. Environmental Health. 2014. 13(1): p. 1-8.

Liu, S., et al. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect. 2003 Nov;111(14):1773-8.

Mahalingaiah, S., et al. Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. Hum Reprod, 2016. 31(3): p. 638-47.

Mohallem, S.V., et al. Decreased fertility in mice exposed to environmental air pollution in the city of Sao Paulo. Environ Res, 2005. 98(2): p. 196-202.

Nieuwenhuijsen, M.J., et al. Air pollution and human fertility rates. Environ Int, 2014. 70: p. 9-14.

Perin, P.M., et al. Impact of shortterm preconceptional exposure to particulate air pollution on treatment outcome in couples undergoing in vitro fertilization and embryo transfer (IVF/ET). L Assist Reprod Genet, 2010. 27(7): p. 371-82.



Perin, P.M., et al. Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in couples undergoing in vitro fertilization and embryo transfer. Fertil Steril, 2010. 93(1): p. 301-3.

Reproductive and Cancer Hazard Assessment Branch Office of Environmental Health Hazard Assessment California Environmental Protection Agency. Evidence on the developmental and reproductive toxicity of sulfur dioxide Feb 2011. oehha.ca.gov/media/downloads/ proposition-65//so2hid022511.pdf

Slama, R., et al. Short-term impact of atmospheric pollution on fecundability. Epidemiology, 2013. 24(6): p. 871-9.

Veras, M.M., et al. Chronic exposure to fine particulate matter emitted by traffic affects reproductive and fetal outcomes in mice. Environ Res, 2009. 109(5): p. 536-43.

Chemical Hazards Endocrine Disruptors

Bromer JG, Zhou Y, Taylor MB, Doherty L, Taylor HS. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 2010;24(7):2273-2280.

Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ Health Perspect. 2008;116(1):39-44.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009;30(4):293-342.

Ehrlich S, Williams PL, Missmer SA, et al. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Human reproduction (Oxford, England). 2012;27(12):3583-3592.

FitzGerald RE, Wilks MF. Bisphenol A--Why an adverse outcome pathway framework needs to be applied. <u>Toxicology letters.</u> 2014;230(2):368-374.

Furst P. Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk. Levels, correlations, trends and exposure through breastfeeding. Mol Nutr Food Res. 2006;50(10):922-933.

Gore AC, Chappell VA, Fenton SE, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015;36(6):E1-E150.

Grun F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. Endocrinology. 2006;147(6 Suppl):S50-55.

Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971;284(15):878-881.

Hernandez CJ, Beaupre GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporos Int. 2003;14(10):843-847.

Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med. 2011;365(14):1304-1314.

Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. Environ Toxicol Pharmacol. 2015;40(1):241-258.

Kannus P, Niemi S, Parkkari J, et al. Why is the age-standardized incidence of low-trauma fractures rising in many elderly populations? J Bone Miner Res. 2002;17(8):1363-1367.

Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol. 2010;24(3):526-539

Lees B, Molleson T, Arnett TR, Stevenson JC. Differences in proximal femur bone density over two centuries. Lancet. 1993;341(8846):673-675.

Min KB, Min JY. Urinary phthalate metabolites and the risk of low bone mineral density and osteoporosis in older women. The Journal of clinical endocrinology and metabolism. 2014;99(10):E1997-2003.

National Institute of Environmental Health Sciences. Endocrine Disruptors. 2010.

Palmer JR, Herbst AL, Noller KL, et al. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. Environmental health: a global access science source. 2009;8:37.

Pillai HK, Fang M, Beglov D, et al. Ligand binding and activation of PPARgamma by Firemaster(R) 550: effects on adipogenesis and osteogenesis in vitro. Environ Health Perspect. 2014;122(11):1225-1232.

Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone. 2010;46(2):294-305.

Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. The Journal of steroid biochemistry and molecular biology. 2011;127(1-2):27-34.

Swan SH, Main KM, Liu F. et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect. 2005;113(8):1056-1061.

Watt J, Schlezinger JJ. Structurallydiverse, PPARgamma-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells. <u>Toxicology.</u> 2015;331:66-77.

National Institute for Occupational Safety and Health. Workplace Safety & Health Topics: Lead: Information for Workers. 2013.

Chemical Hazards Pesticides

Abell A, Juul S, Bonde JP. Time to pregnancy among female greenhouse workers. Scandinavian journal of work, environment & health. 2000;26(2):131-136.

Harley KG, Marks AR, Bradman A, Barr DB, Eskenazi B. DDT exposure, work in agriculture, and time to pregnancy among farmworkers in California. Journal of occupational and environmental medicine/American College of Occupational and Environmental Medicine. 2008;50(12):1335-1342.

Lam T, Williams PL, Lee MM, et al. Prepubertal Serum Concentrations of Organochlorine Pesticides and Age at Sexual Maturity in Russian Boys. Environ Health Perspect. 2015;123(11):1216-1221.



Chemical Hazards

Lead and other metals

Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. The Lancet Neurology. 2014;13(3):330-338.

Rabito FA, Kocak M, Werthmann DW, Tylavsky FA, Palmer CD, Parsons PJ. Changes in low levels of lead over the course of pregnancy and the association with birth outcomes. Reproductive toxicology (Elmsford, N.Y.). 2014;50:138-144.

Sallmen M. Exposure to lead and male fertility. Int J Occup Med Environ Health. 2001;14(3):219-222.

Martenies SE, Perry MI. Environmental and occupational pesticide exposure and human sperm parameters: a systematic review. Toxicology. 2013;307:66-73.

Patel S, Zhou C, Rattan S, Flaws JA. Effects of Endocrine-**Disrupting Chemicals** on the Ovary. Biology of Reproduction, 2015;93(1):20.

Perry MJ. Effects of environmental and occupational pesticide exposure on human sperm: a systematic review. Hum Reprod Update. 2008;14(3):233-242.

Roeleveld N, Bretveld R. The impact of pesticides on male fertility. Curr Opin Obstet Gynecol. 2008;20(3):229-233.

Sanborn M, Kerr KJ, Sanin LH, Cole DC, Bassil KL, Vakil C. Noncancer health effects of pesticides: systematic review and implications for family doctors. Canadian family physician Medecin de famille canadien. 2007;53(10):1712-1720.

Sharpe RM, Fisher JS, Millar MM, Jobling S, Sumpter JP. Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. Environ Health Perspect. 1995;103(12):1136-1143.

Chemical Hazards Phthalates

Marsee K, Woodruff TJ, Axelrad DA, Calafat AM, Swan SH. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. Environ Health Perspect. 2006;114(6):805-809.

Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect. 2005;113(8):1056-1061.

Chemical Hazards Polybrominated Diethyl Ethers (PBDEs)

Johnson PI, Stapleton HM, Mukherjee B, Hauser R, Meeker JD. Associations between brominated flame retardants in house dust and hormone levels in men. The Science of the Total Environment. 2013;445-446:177-184.

Chemical Hazards Safety Data Sheets

Nicol AM, Hurrell AC, Wahvuni D, McDowall W, Chu W. Accuracy, comprehensibility, and use of material safety data sheets: a review. Am J Ind Med. 2008;51(11):861-876.

REFERENCES: Infertility, continued

Asthma

Childhood Leukemia

Learning/
Developmental
Disabilities

Diabetes

Infertility

Cognitive Decline

Chemical Hazards

Solvents

Aschengrau A, Weinberg JM, Janulewicz PA, et al. Prenatal exposure to tetrachloroethylenecontaminated drinking water and the risk of congenital anomalies: a retrospective cohort study. Environmental health: a global access science source. 2009;8:44.

Aschengrau A, Weinberg JM, Janulewicz PA, et al. Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. Environmental health: a global access science source. 2011;10:102.

Chiu WA, Jinot J, Scott CS, et al. Human health effects of trichloroethylene: key findings and scientific issues. Environ Health Perspect. 2013;121(3):303-311.

Elliott RC, Jones JR, McElvenny DM, et al. Spontaneous abortion in the British semiconductor industry: An HSE investigation. Health and Safety Executive. Am J Ind Med. 1999;36(5):557-572.

Kumar S. Occupational, environmental and lifestyle factors associated with spontaneous abortion. Reprod Sci. 2011;18(10):915-930.

Logman JF, de Vries LE, Hemels ME, Khattak S, Einarson TR. Paternal organic solvent exposure and adverse pregnancy outcomes: a meta-analysis. <u>Am J Ind Med.</u> 2005;47(1):37-44.

McMartin KI, Chu M, Kopecky E, Einarson TR, Koren G. Pregnancy outcome following maternal organic solvent exposure: a meta-analysis of epidemiologic studies. <u>Am J Ind Med.</u> 1998;34(3):288-292.

Schettler T, Solomon G, Valenti M, A. H. Generations at Risk: Reproductive Health and the Environment. <u>Boston, MA: MIT Press;</u> 1999.

Snijder CA, te Velde E, Roeleveld N, Burdorf A. Occupational exposure to chemical substances and time to pregnancy: a systematic review. <u>Hum Reprod Update</u>. 2012;18(3):284-300.

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental exposures and adverse pregnancy outcomes: a review of the science. Reprod Sci. 2008;15(7):631-650.

Climate change

Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. American journal of epidemiology. 2010;172(10):1108-1117.

Dadvand P, Basagana X, Sartini C, et al. Climate extremes and the length of gestation. <u>Environ Health Perspect</u>. 2011;119(10):1449-1453.

Khan AE, Scheelbeek PF, Shilpi AB, et al. Salinity in drinking water and the risk of (pre)eclampsia and gestational hypertension in coastal Bangladesh: a case-control study. PloS One. 2014;9(9):e108715.

Rylander C, Odland JO, Sandanger TM. Climate change and the potential effects on maternal and pregnancy outcomes: an assessment of the most vulnerable--the mother, fetus, and newborn child. Glob Health Action. 2013;6:19538.

Li DK, Yan B, Li Z, et al. Exposure to magnetic fields and the risk of poor sperm quality. Reproductive toxicology (Elmsford, N.Y.). 2010;29(1):86-92.

Liu K, Li Y, Zhang G, et al. Association between mobile phone use and semen quality: a systemic review and meta-analysis. <u>Andrology. 2014;2(4):491-501</u>.

Wang C, Cui YG, Wang XH, et al. transient scrotal hyperthermia and levonorgestrel enhance testosterone-induced spermatogenesis suppression in men through increased germ cell apoptosis. The Journal of clinical endocrinology and metabolism. 2007;92(8):3292-3304.

Zilberlicht A, Wiener-Megnazi Z, Sheinfeld Y, Grach B, Lahav-Baratz S, Dirnfeld M. Habits of cell phone usage and sperm quality - does it warrant attention? Reprod Biomed Online. 2015;31(3):421-426.



Electromagnetic radiation

Adams JA, Galloway TS, Mondal D, Esteves SC, Mathews F. Effect of mobile telephones on sperm quality: a systematic review and meta-analysis. <u>Environment international</u>. 2014;70:106-112.

Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertility and sterility. 2012;97(1):39-45.e32.

Gorpinchenko I, Nikitin O, Banyra O, Shulyak A. The influence of direct mobile phone radiation on sperm quality. <u>Central European journal of urology.</u> 2014;67(1):65-71.

Endometriosis

Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, Tayade C. Pathophysiology and Immune Dysfunction in Endometriosis. BioMed research international. 2015;2015:795976.

American College of Obstetrics and Gynecology Endometriosis. 2012.

American Society for Reproductive Medicine. Fact sheet - Endometriosis: Does It Cause Infertility?

Bruner-Tran KL, Osteen KG. Dioxin-like PCBs and endometriosis. Syst Biol Reprod Med. 2010;56(2):132-146.

Centers for Disease Control (CDC). Common Reproductive Health Concerns for Women: Endometriosis. 2015.

Crain DA, Janssen SJ, Edwards TM, et al. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. Fertility and sterility. 2008;90(4):911-940.

de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. Lancet. 2010;376(9742):730-738.

Hufnagel D, Li F, Cosar E, Krikun G, Taylor HS. The Role of Stem Cells in the Etiology and Pathophysiology of Endometriosis. Seminars in reproductive medicine. 2015;33(5):333-340.

Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am. 2012;39(4):535-549.

Naqvi H, Ilagan Y, Krikun G, Taylor HS. Altered genome-wide methylation in endometriosis. <u>Reprod Sci. 2014;21(10):1237-1243</u>.

Upson K, De Roos AJ, Thompson ML, et al. Organochlorine pesticides and risk of endometriosis: findings from a population-based case-control study. Environ Health Perspect. 2013;121(11-12):1319-1324.

Upson K, Sathyanarayana S, Scholes D, Holt VL. Early-life factors and endometriosis risk. Fertility and sterility. 2015;104(4):964-971 e965.

Wolff EF, Sun L, Hediger ML, et al. In utero exposures and endometriosis: the Endometriosis, Natural History, Disease, Outcome (ENDO) Study. Fertility and sterility. 2013;99(3):790-795.

Endometriosis

Endometriosis Treatment

Brown J, Farquhar C. Endometriosis an overview of Cochrane Reviews. The Cochrane database of systematic reviews. 2014(3):CD009590.

Lee HJ, Lee JE, Ku S-Y, et al. Natural conception rate following laparoscopic surgery in infertile women with endometriosis. Clinical and Experimental Reproductive Medicine. 2013;40(1):29-32.

Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N. Engl J Med. 1997;337(4):217-222.



Environmental disparities

ACOG. ACOG Committee Opinion No 575: Exposure to toxic environmental agents. <u>Obstet</u> <u>Gynecol. 2013;122(4):931-935</u>.

Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. Int J Gynaecol Obstet. 2015;131(3):219-225.

Environmental history taking

ATSDR. ATSDR Case Studies in Environmental Medicine: <u>Taking</u> an Exposure History. 2015.

Chicago Consortium for Reproductive Environmental Health in Minority Communities (CREHM). Prenatal Environmental Exposure History.

National Environmental Education Foundation. <u>Taking a Pediatric Environmental Health History</u>.

Infertility

Causes - General

Aiken CE, Tarry-Adkins JL, Ozanne SE. Transgenerational Developmental Programming of Ovarian Reserve. <u>Sci Rep.</u> 2015;5:16175.

de Kretser DM. Male infertility. The Lancet.349(9054):787-790.

Reiss HE. Population study of causes, treatment and outcome of infertility. Br Med J (Clin Res Ed). 1986;292(6522):761.

Richardson MC, Guo M, Fauser BC, Macklon NS. Environmental and developmental origins of ovarian reserve. <u>Hum Reprod Update.</u> 2014;20(3):353-369.

Evaluation

 $ACOG \ \underline{Infertility \ evaluation}.$

Trends

CDC/National Center for Health Statistics. <u>National</u> <u>Survey of Family Growth. 2012</u>.

CDC/National Center for Health Statistics. FastStats: <u>Infertility. 2015</u>.

Chandra A, Copen CE, Stephen EH. Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. Natl Health Stat Report. 2013(67):1-18, 11 p following 19.

Levine H, Jorgensen N, Andrade AM, Mendiola J, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. Human Reprod Update. 2017; 1-14.

Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012;9(12):e1001356.

Speroff L, Glass R, N K. Clinical gynecologic endocrinology and infertility. Baltimore: Williams and Wilkins; 1994.

Nutrition

American College of Obstetricians and Gynecologists. <u>ACOG state-ment on prenatal nutrition</u>. 2015.

Buck Louis GM, Sapra KJ, Schisterman EF, et al. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: The LIFE Study. Fertility and sterility. 2016;106(1):180-188.

Chan KA, Tsoulis MW, Sloboda DM. Early-life nutritional effects on the female reproductive system. The Journal of endocrinology. 2015;224(2):R45-62.

Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. <u>Human reproduction (Oxford, England)</u>. 2007;22(5):1340-1347.

Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. Obstet Gynecol. 2007;110(5):1050-1058.

Jacka FN, Ystrom E, Brantsaeter AL, et al. Maternal and early postnatal nutrition and mental health of offspring by age 5 years: a prospective cohort study. J Am Acad Child Adolesc Psychiatry. 2013;52(10):1038-1047.

U.S. Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. <u>Ann</u> <u>Intern Med. 2009; 150:626-631</u>.

Occupational health

Cloeren M, Gean C, Kesler D, et al. American College of Occupational and Environmental Medicine's Occupational and Environmental Medicine Competencies-2014: ACOEM OEM Competencies Task Force*. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2014;56(5):e21-40.

Luderer U, Hieb M, Diaz J, Baker B, American College of Occup and Environmental Med. Reproductive and developmental hazard management guidance: ACOEM Task Force on Reproductive Toxicology. Journal of Occupational and Environmental Medicine. 2011;53(8):941-949.

Schrader SM, Marlow KL. Assessing the reproductive health of men with occupational exposures. Asian Journal of Andrology 2014 16, (23–30).

Snijder CA, te Velde E, Roeleveld N, Burdorf A. Occupational exposure to chemical substances and time to pregnancy: a systematic review. Hum Reprod Update. 2012;18(3):284-300.

U.S. Equal Employment Opportunities Commission. EEOC Enforcement Guidance on Pregnancy Discrimination and Related Issues. In: U.S. Equal Employment Opportunities Commission, ed. 2015.

environmental exposures. Ma-

Metayer C, Milne E, Dockerty

JD, et al. Maternal Supplementa-

tion with Folic Acid and Other

Vitamins and Risk of Leukemia

Leukemia International Consor-

tium Study. Epidemiology. 2014

Roberts IR, Karr CI. Council on

Environmental Health. Pesticide

exposure in children. Pediatrics.

Schmidt RJ, Tancredi DJ, Ozonoff

S, et al. Maternal periconceptional

folic acid intake and risk of autism

spectrum disorders and devel-

opmental delay in the CHARGE

(CHildhood Autism Risks from

control study. Am J Clin Nutr

Surén P, Roth C, Bresnahan M,

Haugen M, Hornig M, Hirtz D, Lie

KK, Lipkin WI, Magnus P, Reich-

born-Kjennerud T, Schjølberg S,

Davey Śmith G, Øyen ÁS, Susser

between maternal use of folic acid

supplements and risk of autism

spectrum disorders in children.

Prenatal health

Care. 2015.

nancy. 2016.

JAMA. 2013 Feb 13;309(6):570-7.

American College of Obstetricians

and Gynecologists. Good Health

Before Pregnancy: Preconception

American Congress of Obstetri-

cians and Gynecologists. Toxic

(CDC). Pregnancy: During Preg-

Program on Reproductive Health

and the Environment, Univ of Cal.

San Francisco. Toxic Matters. 2015.

Royal College of Obstetrics and

Gynecology. Chemical Exposures

During Pregnancy: Dealing with

Potential, but Unproven, Risks to

Child Health. 2013.

Program on Reproductive

ment. Resources for health

care professionals to promote

environmental health. 2015.

Health and the Environ-

Centers for Disease Control

Environmental Agents.

E, Stoltenberg C. Association

2012;96:80-9

Genetics and Environment) case-

2012 Dec;130(6):e1765-88.

in the Offspring: a Childhood

Nov;25(6):811-22.

2006;10(5 Suppl):S123-128.

ternal and Child Health Journal.

REFERENCES: Infertility, continued

Asthma

Childhood Leukemia

Learning/ Developmental Disabilities

Diabetes

Infertility

Cognitive Decline

Parabens

Ahn HJ, An BS, Jung EM, Yang H, Choi KC, Jeung EB. Parabens inhibit the early phase of folliculogenesis and steroidogenesis in the ovaries of neonatal rats. Mol Reprod Dev. 2012 Sep;79(9):626-36.

Chen J, Ahn KC, Gee NA, Gee SJ, Hammock BD, Lasley BL. 2007. Antiandrogenic properties of parabens and other phenolic containing small molecules in personal care products. <u>Toxicol Appl</u> Pharmacol 221(3):278-284.

Fisher M, MacPherson S, Braun JM, Hauser R, Walker M, Feeley M, et. al. Paraben concentrations in maternal urine and breast milk and its association with personal care product use. Environ Sci Technol. 2017 Mar 20.

Lee JH, Lee M, Ahn C, Kang HY, Tran DN, Jeung EB. Parabens accelerate ovarian dysfunction in a 4-vinylcyclohexene diepoxideinduced ovarian failure model. Int J Environ Res Public Health. 2017 Feb 8;14(2).

Mínguez-Alarcón L, Chiu YH, Messerlian C, Williams PL, Sabatini ME, Toth TL, et. al. Urinary paraben concentrations and in vitro fertilization outcomes among women from a fertility clinic. Fertil Steril. 2016 Mar;105(3):714-2.

National Toxicology Program. 2005. Butylparaben [CAS No. 94-26-8]: Review of Toxicological Literature.

Smarr MM, Sundaram R, Honda M, Kannan K, Buck Louis GM. Urinary concentrations of parabens and other antimicrobial chemicals and their association with couples' fecundity. Environ Health Perspect. 2016 Jun 10.

Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R. Urinary paraben concentrations and ovarian aging among women from a fertility center. Environ Health Perspect. 2013 Nov-Dec;121(11-12):1299-305.

Vo TT, Yoo YM, Choi KC, Jeung EB. 2010. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. Reprod Toxicol 29(3):306-316.



Placenta

Barker DJ, Thornburg KL. Placental programming of chronic diseases, cancer and lifespan: a review. Placenta. 2013;34(10):841-845.

Barker DJP. Developmental origins of chronic disease. Public Health. 2012;126(3):185-189.

Barker DJP, Lampl M, Roseboom T, Winder N. Resource allocation in utero and health in later life. Placenta. 2012;33, Supplement 2:e30-e34.

Gundacker C, Hengstschlager M. The role of the placenta in fetal exposure to heavy metals. Wiener medizinische Wochenschrift (1946). 2012;162(9-10):201-206.

Januar V, Desoye G, Novakovic B, Cvitic S, Saffery R. Epigenetic regulation of human placental function and pregnancy outcome: considerations for causal inference. American Journal of Obstetrics and Gynecology. 2015;213(4, Supplement):S182-S196.

Maccani JZ, Koestler DC, Houseman EA, Marsit CJ, Kelsey KT. Placental DNA methylation alterations associated with maternal tobacco smoking at the RUNX3 gene are also associated with gestational age. Epigenomics. 2013;5(6):619-630.

Nelson DM. How the placenta affects your life, from womb to tomb. Am J Obstet Gynecol. 2015;213(4, Supplement):S12-S13.

Thornburg KL, Marshall N. The placenta is the center of the chronic disease universe. Am J Obstet Gynecol. 2015;213(4 Suppl):S14-20.

Polycystic ovary syndrome

Barrett ES, Sobolewski M. Polycystic ovary syndrome: do endocrinedisrupting chemicals play a role? Seminars in Reproductive Medicine. 2014;32(3):166-176.

Nilsson E, Larsen G, Manikkam M, Guerrero-Bosagna C, Savenkova MI, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. PloS One. 2012;7(5):e36129.

Preconception health

Centers for Disease Control (CDC). Preconception Health and Health Care. 2015.

Gerson M, Van den Eeden SK, Gahagan P. Take-home lead poisoning in a child from his father's occupational exposure. Am J Ind Med. 1996 May;29(5):507-8.

Fenske RA, Lu C, Negrete M, Galvin K. Breaking the take home pesticide exposure pathway for agricultural families: workplace predictors of residential contamination. Am J Ind Med. 2013 Sep;56(9):1063-71.

Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M. Suderman M, Hallett M, and Kimmins S. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. Nature Communications 4. 2013; Article number:2889.

Lvall K, Schmidt R, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int I Epidemiol 2014;43(2):443-464.

McDiarmid MA, Gehle K. Pre-**Group Prenatal Care** conception brief: occupational/

Ickovics JR, Earnshaw V, Lewis JB, et al. Cluster Randomized Controlled Trial of Group Prenatal Care: Perinatal Outcomes Among Adolescents in New York City Health Centers. Am Journal Public Health. 2016;106(2):359-365.

Ickovics JR, Kershaw TS, Westdahl C, et al. Group prenatal care and perinatal outcomes: a randomized controlled trial. Obstet Gynecol. 2007;110(2 Pt 1):330-339.

Ickovics JR, Reed E, Magriples U, Westdahl C, Schindler Rising S, Kershaw TS. Effects of group prenatal care on psychosocial risk in pregnancy: results from a randomised controlled trial. Psychol Health. 2011;26(2):235-250.

Virtanen H, Rajpert-De Meyts E, Main K, Skakkebaek N, Toppari J. Testicular dysgenesis syndrome and the development and occurrence of male reproductive disorders. Toxicol Appl Pharmacol. 2005. 207(2 suppl):501-505.

Tracking of reproductive disorders

Centers for Disease Control & Prevention. Reproductive and Birth Outcomes. 2012.

Centers for Disease Control & Prevention. Tracking Birth Defects. 2012.

Centers for Disease Control and Prevention. National Environmental Public Health Tracking Program.

Massachusetts Department of Environmental Quality Engineering. Status report on tetrachloroethylene contamination of public drinking water supplies caused by vinyl-lined asbestos cement pipe. Boston 1982.

EPANET modeling software:

Rossman L. EPANET users manual. Cincinnati, OH: Environmental Protection Agency, Risk Reduction Engineering Laboratory, 1994.

Birth defects:

Aschengrau A, Weinberg JM, Janulewicz PA, et al. Prenatal exposure to tetrachloroethylenecontaminated drinking water and the risk of congenital anomalies: a retrospective cohort study. Environmental health: a global access science source. 2009;8:44.

Stillbirths:

Carwile JL, Mahalingaiah S, Winter MR, Aschengrau A. Prenatal drinking-water exposure to tetrachloroethylene and ischemic placental disease: a retrospective cohort study. Environmental health: a global access science source. 2014;13:72.

Risky behaviors:

Aschengrau A, Weinberg JM, Janulewicz PA, et al. Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)contaminated drinking water: a retrospective cohort study. Environmental health: a global access science source. 2011;10:102.

Weight and Body Mass Index

Centers for Disease Control & Prevention. Body Mass Index (BMI) calculator 2015.

Jacobsen BK, Knutsen SF, Oda K, Fraser GE. Body mass index at age 20 and subsequent childbearing: the Adventist Health Study-2. J Womens Health (Larchmt). 2013;22(5):460-466.

Testicular dysgenesis syndrome

Mendiola J, Stahlhut RW, Jørgensen N, Liu F, Swan SH. Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York. Environ Health Perspect. 2011.

Skakkebaek N. A brief review of the link between environment and male reproductive health: lessons from studies of testicular germ cell cancer. Horm Res Paediatr. 2016. Feb 13. [Epub ahead of print]

Unintended adverse consequences of environmental improvements

Flint water crisis:

Bellinger DC. Lead Contamination in Flint--An Abject Failure to Protect Public Health. N Engl J Med. 2016;374(12):1101-1103

Vinyl-lined pipes and their installation:

Larson CD, Love OT, Reynolds G, McCallie SW, Moser RH, Calabrese EJ. Tetrachloroethylene leached from lined asbestoscement pipe into drinking water [with Discussion]. Journal American Water Works Association. 1983;75(4):184-190.