











A Story of Health – Infertility: Reiko & Toshio's Story • 2021 Update

ACKNOWLEDGEMENTS



Primary Project Development Organizations

The Commonweal, the Office of Environmental Health Hazard Assessment (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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University of California, San Francisco: Program on Reproductive Health and the Environment

Videos – Speakers: Linda Giudice; Ulrike Luderer; Mark Miller; Lawrence Rosen; Tracey Woodruff; Marya Zlatnik

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A Story of Health HELP PAGE How to Navigate Our eBook

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: <u>underlined words</u> 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."



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.

Getting Started

Reunion

Help Page

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

Adobe Acrobat Tools

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

<u>Magnify</u> - 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.

Note: Navigation features may not work properly using other pdf reader platform



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A Story of Health 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.



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A Story of Health 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.



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A Story of Health 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.



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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:

A Story of Health

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



Cancer





Infertility





Diabetes

Infertility

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Asthma



Diabetes



Cognitive decline





Learning and developmental disabilities

A Story of Health **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.





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A Story of Health **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.



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.

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A Story of Health **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



Infertility stats source: CDC: National Center for Health Statistics.

Global and US infertility trends graphic: Sun H, Gong T, Jiang Y, Zhang S, Zhao Y, Wu Q. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990–2017: results from a global burden of disease study, 2017. Aging (Albany NY). 2019; 11:10952-10991

NSFG: Listing I — Key Statistics from the National Survey of Family Growth Ethnic and racial differences in the prevalence of infertility: national survey of family growth

(NSFG) — Fertility and Sterility.





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A Story of Health **INFERTILITY** Reiko & Toshio's Story

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. Women who are infertile are more likely to have endometriosis than the general population, with 30-50% of infertile women having endometriosis (of note, they may have other reasons for infertility in addition). 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. Giudice, 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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A Story of Health **INFERTILITY** Reiko & Toshio's Story

Dr. Lopez wants to explore other potential aspects of Reiko's infertility. 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 agrees that exercise is healthy 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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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





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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 gonads are the

reproductive glands (ovary or testis) that produce gametes/germ cells (i.e., sperm or egg). Initially, the gonads form near the kidney. During weeks seven and eight, the primitive gonads differentiate into ovary or testis based on whether or not a Y chromosome is present.

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

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

Mullerian duct **Metanephros** Ureter MALE Testes Kidnevs pididymi

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Vas deferens



- 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

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A Story of Health **INFERTILITY** Reiko & Toshio's Story

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

Resources:

CDC: Planning for Pregnancy

CDC: MTHFR Gene, Folic Acid, and Preventing Neural Tube Defects

CDC: Preconception care for women and men

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



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, <u>www.health.harvard.edu</u>.

Multigenerational nutrition graphic: Adapted and used with permission from Chan KA, Tsoulis MW, Sloboda DM. Early-life nutritional effects on the female reproductive system. J Endocrinol. 2015 Feb;224(2):R45-62.

Based on a mixture of human and laboratory animal data.





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

Resource: CDC: About **Folic Acid**

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Asthma

MORE INFORMATION:

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

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

Learning/







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A Story of Health **INFERTILITY** Reiko & Toshio's Story

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:

- TedX The Endrocrine Disruption Exchange
- Generations at Risk **Reproduction Health** and the Environment
- CDC's Lead and **Pregnancy**

KEY CONCEPT:

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



INFECTIOUS AGENTS such as:

Viruses: CMV, varicella, herpes Bacteria: syphilis, listeria Parasites: toxoplasmosis, Zika, rubella



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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.

> **TOXICANTS** including: pesticides, endocrine disruptors, metals, air pollution, solvents

> > RADIATION

STRESS

NUTRITION

CLIMATE **CHANGE**

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:

- <u>National environmental</u> health tracking program
- Pesticide Action Network <u>Database</u>

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

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- 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, absorbing contaminants through the skin, or via injection. 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.



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

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 <u>Society</u> 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.

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

Link: Infertility and psychological impact.

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.

Environmental History

Environmental History Form	11
What do you do for work?	Always wear Contact an O questions ab
Are you exposed to any of the following at work:	, C
Metals	
Solvents	
Chemicals (including those for cleaning)	1
Radiation	
Fumes	
Lead can cause brain damage, especially in babies and children	Eat foods en calcium (dair (oranges, gra
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 ho Chipping pair
Are there any plans to remodel your home?	Avoid remod Call 1-800-42
Have you ever lived outside the United States?	
Does your family use imported pottery or ceramics for cooking, eating, or drinking?	Imported po leach into fo
Have you used any home remedies such as azarcon, greta, pav-loo-ah?	Do not use le
Have you ever eaten any of the following:	Do not eat cl they may cor
Clay	
Soil or dirt	A.C
Pottery	17
Paint chips	-
Mercury is another metal that can damage the developing fetal brain. Small children are also sensitive.	It's importan https://www hg_spill_cl
Is there a mercury thermometer in your home?	Use a digital
In general, do you eat fish more than twice a week?	Eat a variety
Do you eat any of the following types of fish:	Do not eat st
Shark	
King Mackerel	111
Swordfish	
Tilefish	1
Orange Roughy	
Big eye tuna	
Marline	
Albacore tuna ("white" tuna)	Albacore tun tuna; do not tuna.
Air pollution is harmful to pregnant women who are "breathing for two" and also for fetuses, babies, and children.	

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proper personal protective equipment. Occupational and Environmental physician with out workplace exposures. www.aoec.org

riched with iron (lean red meats, chicken), ry, green leafy vegetables), and vitamin C apefruits, tomatoes, green peppers).

ome tested for lead if it was built before 1978. nt may release lead into the house. deling or hire a certified contractor. 24-LEAD for more information.

ottery or ceramics may contain lead, which can

ead-containing home remedies.

lay, soil, dirt, pottery, or paint chips because ntain high levels of lead.

nt to clean up mercury spills in a special way. w.atsdr.cdc.gov/mercury/docs/residential leanup.pdf

or mercury-free thermometer.

of fish low in mercury twice a week. Contact dept. about local fish advisories.

hark, swordfish, king mackerel or tilefish y contain high levels of mercury.

na contains more mercury than canned light eat more than 6 oz. per week of albacore



Learning/

A Story of Health **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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A Story of Health **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

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.

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A Story of Health **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

Air pollution and fertility, reproductive health

Link: 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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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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A Story of Health **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 Toshio.

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

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

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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A Story of Health **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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A Story of Health **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**

Introduction to the **PEHSU** network. For more information visit pehsu.net.

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 <u>Sheets</u> CHE Toxicant and Disease Database **Toxics Release Inventory**

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A Story of Health **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, and she recommends Toshio not hold his laptop on his lap while working on it.

Electromagnetic exposure and male fertility

Reference: Kesari KK, Agarwal A, Henkel R. **Radiations and male fertility.** Reprod Biol Endocrinol. 2018 Dec 9;16(1):118.

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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.

Bisphenol A (BPA) and how it can mimic estrogen

Bone disrupting chemicals: Fatty bones and osteoporosis

Parabens and reproductive health

<u>Watch</u>: Little Things Matter: The Impact of Toxins on the **Developing Brain**

Dr. Bruce P. Lanphear, MD MPH

Professor, Simon Fraser University

Endocrine disruptors and infertility/ reproductive health

Endocrine disruptors are chemicals that impact endocrine functions by interfering with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism).

These disruptions can cause cancerous tumors, birth defects, and other developmental disorders. As the cells begin to grow and differentiate, there are critical balances of hormones and protein changes that must occur. The Endocrine Society released a statement on **Endocrine-Disrupting Chemicals** (EDCs) specifically listing obesity, diabetes, female reproduction, male reproduction, hormonesensitive cancers in females, prostate cancer in males, thyroid, and neurodevelopment and neuroendocrine systems as possible effects of being exposed to EDCs.

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TESTICULAR DYSGENESIS SYNDROME

Ithough 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 AGD (anogenital distance) in boys

Phthalates and sperm quality

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.

Many of these same chemicals also cause a decrease in anogenital distance, a marker of anti-androgenic activity chemicals. 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.

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Humans are regularly exposed to a cocktail of endocrine disrupting

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 got 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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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 healthy weight.

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.

Link: Pesticide Safety Rules for Farmworkers — Cal. EPA

Female fertility diet Link to reference

Enlarge Table 2

Male diet and infertility

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Dr. Patel suggest treatment 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 an oral medication such as letrozole (a non-steroidal aromatase inhibitor that lowers estrogen production), 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.

Resource:

Guideline for the assessment and management of polycystic ovary syndrome

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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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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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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

Pesticides: EPA – Integrated Pest Management

Bio-integral Resource Center (BIRC)

<u>Pesticide Action Network</u> (PAN)

University of California - Pesticide Application Equipment

<u>Watch</u>: Epitaph for a Peach

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

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.

Both Toshio and Reiko decide to reduce red meat and eliminate highly processed food from their diets and emphasize intake of legumes, fruits, vegetables, whole grains, and nuts. When eating fish they will avoid species with elevated levels of mercury or other contaminants.*

Toshio will avoid high-fat dairy products. They will also avoid storing or microwaving food in plastic containers.

*FDA fish consumption guidelines are available at Advice about Eating Fish | FDA. State-specific guidelines vary and should also be followed.

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

Embryo development

The placenta – vital to human survival

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

<u>Watch</u>: The Epigenome at a Glance

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

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.

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A Story of Health **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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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.

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he Toolkit is an easy-to-use reference guide for health providers on preventing exposures to toxic chemicals and other substances that affect infant and child health. The new mobile device-ready online version of the PEHT includes links to many related online resources.

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Additional Resources

Pediatric Environmental Health Toolkit application for mobile devices

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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 Aquarium "Seafood Watch"

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

- Environmental Working Group's consumer guides
- EPA's Safer Choice
- <u>Silent Spring's</u> "Detox Me"

In the workplace:

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

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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).
- Encourage breastfeeding through health care and workplace policies.

- Increase access to healthy foods.
- Regulations and incentives can help existing stores increase the number and variety of healthy products they sell.

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► Cities and towns can change zoning and tax laws to make it easier to create new grocery stores, farmers' markets, and community gardens.

- 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.

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.

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Asthma

Childhood Leukemia

Learning/ **Developmental Disabilities**

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