TRAINING FOR THE HEALTH SECTOR

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CASE STUDIES OF FEMALE REPRODUCTIVE HEALTH AND THE ENVIRONMENT

Training Module 3

Children's Environmental Health

Public Health and the Environment

World Health Organization

www.who.int/ceh

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October 2011

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<<NOTE TO USER: Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation in the space indicated.>>

<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the issue. Present only those slides that apply most directly to the local situation in the region. You should replace the case studies as well as the figures with those relevant to your area and your audience>>

<<NOTE TO USER: This module presents several examples of risk factors that affect reproductive health. You can find more detailed information in other modules of the training package that deal with specific risk factors, such as lead, mercury, pesticides, persistent organic pollutants, endocrine disruptors, occupational exposures; or disease outcomes, such as developmental origins of disease, reproductive effects, neurodevelopmental effects, immune effects, respiratory effects, and others.>>

<<NOTE TO USER: For more information on reproductive health, please visit the website of the Department of Reproductive Health and Research at WHO: www.who.int/reproductivehealth/en/>>

Case Studies of Female Reproductive Health and the Environment

LEARNING OBJECTIVES

To understand the importance of specific case studies involving toxicant exposure and the resulting endpoints for female reproductive health

1. Diethylstilbestrol (DES)
2. Methylmercury
3. Pesticides
4. Dioxins

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<<READ SLIDE.>>

This presentation will provide you with specific examples of environmental exposure scenarios and their impacts on female reproductive health.
By the end of the presentation, individuals will be able to understand and recognize the importance of specific case studies involving toxicant exposure and the resulting endpoints for female reproductive health. Specific case studies will be reviewed to emphasize unique pathways of exposure, the mechanisms of action of certain environmental agents, and documented health endpoints related to female reproductive health. These case studies will include an overview of exposure to diethylstilbestrol, methylmercury, pesticides, and dioxins.

<<NOTE TO USER: This module will present case studies of specific exposure scenarios, thus if you would like more background information about female environmental reproductive health, please reference Module 1: Reproductive Environmental Health and Module 2: Female Environmental Reproductive Health.>>

Ref:

•WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York, United States of America, *World Health Organization*, 1946.

Case Studies of Female Reproductive Health and the Environment

FEMALE REPRODUCTIVE HEALTH

- ❖ Disorders related to female reproductive health may develop during fetal development, childhood, adolescence, or adulthood
- ❖ Multiple causes for alterations in female reproductive functioning
- ❖ Recent focus on potential environmental causes

WHO

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Reproductive health involves all of the reproductive processes, functions and systems at all stages of human life. This definition implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so. Women should have access to appropriate health care services that will enable them to go safely through pregnancy and childbirth and provide couples with the best chance of having a healthy infant.

Reproductive health is a universal concern, but is of special importance for women particularly during the reproductive years.

Several female reproductive disorders may affect the health status and overall quality of life of a woman. Female reproductive disorders may develop during various life phases of the female. Alterations in proper reproductive functioning may be the result of various occurrences and experiences throughout fetal development, childhood, adolescence, or adulthood.

While much is known about the female reproductive system, its development, and many causes of specific disorders, the research pertaining to the mechanisms of action for certain pathologies is still largely unknown. However, exposure to environmental contaminants has been proposed in recent years to potentially contribute to female reproductive disorders. Research has been focused on exposures that occur during critical periods of development, however this is an emerging field of research that demands greater scientific investigation.

Refs:

•UNDP/UNFPA/WHO/World Bank. Social science methods for research on reproductive health topics. Geneva, Switzerland, *UNDP/UNFPA/WHO/World Bank Special Programme on Research, Development, and Training in Human Reproduction*, 2006. Available at *whqlibdoc.who.int/hq/1999/WHO_RHR_HRP_SOC_99.1.pdf* - accessed 22 June 2010.

•WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York, United States of America, *World Health Organization*, 1946.

Image: WHO

REPRODUCTIVE HEALTH AND THE ENVIRONMENT

- Focuses on exposure to contaminants found in the environment, specifically during critical periods of development.
- All the physical, chemical, biological and social factors that may affect the origin, growth, development and survival of a person in a given setting.

  Some examples include:
  - **Specific synthetic chemicals**
  - **Some metals**
  - **Air contaminants**

Still an emerging issue!

Reproductive health and the environment focuses on exposures to environmental contaminants during critical periods of human development. These periods are directly related to reproductive health throughout the life course, including the period before conception, at conception, fertility, pregnancy, child and adolescent development, and adult health. Exposures to different environmental contaminants may influence reproductive health status of the individual and its offspring, through the process of epigenetics.

Environmental toxins may potentially induce effects in human reproductive processes. However, the extent of this hypothesis must be supported through greater levels of research.

Currently, women's health care providers and gynecologists are growing increasingly aware of the potential for environmental factors to influence female health and reproductive status.

Refs:

•WHO. Global assessment of the state of the science of endocrine disruptors. Geneva, Switzerland, *WHO/PCS/EDC*, 2002. Available at *www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/* - accessed 23 June 2010.

•Woodruff T. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. *Fertility and Sterility,* 2003, 89 (2),1-20.

<< NOTE TO USER: For further information, please refer to the module on "Developmental and Environmental Origins of Disease">>

Case Studies of Female Reproductive Health and the Environment

Case Study 1:

Diesthylstilbestrol (DES)

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The first case study that will be presented will be about exposure to the drug diesthylstilbestrol (DES). This is a significant example, as DES was widely used several decades ago and has since become the model for estrogenic effects of endocrine-disrupting chemicals. Potential endocrine disruptors include chemicals, pesticides, disinfection by-products, plants, drugs, among others.

Case Studies of Female Reproductive Health and the Environment

CASE STUDY 1: DIETHYLSTILBESTROL (DES)

WHO

- Synthetic form of estrogen
- Used to promote fetal growth and block spontaneous abortion
- In the U.S, 5 to 10 million pregnant women were exposed to DES (from 1938 to 1971)
- In 1971, the Food and Drug Administration (FDA) advised physicians to stop prescribing DES to pregnant women because it was linked to a rare vaginal cancer in female offspring

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<<READ SLIDE.>>

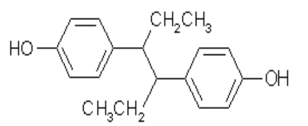
Diesthylstilbestrol (DES) is a chemical compound that acts a synthetic estrogen within the body. Throughout the United States, doctors prescribed diesthylstilbestrol (DES) to five to ten million pregnant women between around 1940 and 1970 as a medication to protect against adverse health effects during pregnancy, including protection from spontaneous abortion and in order to promote fetal growth. It was discovered after administration of this medication that children of mothers exposed to diesthylstilbestrol (DES) experienced developmental disorders and a greater risk for developing vaginal cancer.

Many others were exposed to diesthylstilbestrol (DES) through prenatal vitamins and in food supply because it was given to cattle until 1979 in the US.

Refs:
•CDC. About DES. *Centers for Disease Control*. Available at *www.cdc.gov/des/consumers/about/index.html* - accessed 21 March 2010.
•Baird DD, Newbold R. Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. *Reproductive Toxicology,* 2005, 20:81– 84 115.
•Diamanti-Kandarakis E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. 2009. *Endocrine reviews.* 30(4): 293-342.
•Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-365:1304-1314.
•McLachlan JA. Commentary: prenatal exposure to diethylstilbestrol (DES): a continuing story. *International Journal of Epidemiology,* 2006, 35:868 – 870.
•McLachlan JA et al. Reduced fertility in female mice exposed transplacentally to diethylstilbestrol (DES). *Fertility and Sterility, Sterility,* 1982, 38: 364 –371.

Image: WHO

WOMEN EXPOSED TO DIETHYLSTILBESTROL (DES) WHILE PREGNANT



4,4'-(1,2-diethyl-1,2,ethene-diyl)bisphenol
diethylstilbestrol
DES

www.chemistrydaily.com/chemistry/Diethylstilbestrol>

Women who took DES while pregnant face a 30% greater risk for breast cancer

Women who know that they were exposed to DES during pregnancy should follow a regular schedule for breast cancer screenings

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Women who took diesthylstilbestrol (DES) while pregnant are at an increased risk for developing breast cancer. Studies have consistently demonstrated a 30% increased risk for women prescribed DES while pregnant. A study conducted by Titus-Ernstoff in 2001 included more than 6,000 women and compared breast cancer rates of women exposed to DES with rates of women who were not exposed. This study followed participants over a longer period of time than earlier research on breast cancer risks associated with DES. The findings confirmed an increased breast cancer risk of approximately 30% for women prescribed DES while pregnant. Considering breast cancer risks across a lifetime, one in six women prescribed DES during pregnancy will get breast cancer. In comparison, only one in eight unexposed women will get breast cancer across their lifetime.
The 2002 National Cancer Institute recommends DES-exposed women follow the National Cancer Institute breast cancer-screening schedule for their age category. Mammography is recommended every 1 to 2 years for women in their forties.

Refs:

•CDC. About DES. Atlanta, Georgia, *Centers for Disease Control*, 2003. Available at *www.cdc.gov/des/consumers/about/index.html* - accessed 21 March 2010.

•Diamanti-Kandarakis E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. 2009. *Endocrine reviews.* 30(4): 293-342.

•Hoover RN et al. Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol. *N Engl J Med*. 2011; 365:1304-1314.
•Ma L et al. Abdominal B (AbdB) Hoxa genes: regulation in adult uterus by estrogen and progesterone and repression in mullerian duct by the synthetic estrogen diethylstilbestrol (DES). *Developmental Biology*, 2000, 197:141–154.
•McLachlan JA et al. Reduced fertility in female mice exposed transplacentally to diethylstilbestrol (DES). *Fertility and Sterility*, 1984, 38: 364 – 371.
•Newbold RR, Moore AB, Dixon D. Characterization of uterine leiomyomas in CD-1 mice following develop- mental exposure to diethylstilbestrol (DES). *Toxicol Pathology*, 2002, 30:611– 616.
•Titus-Ernstoff L et al. Long term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *British Journal of Cancer*, 2001, 84, 126–133.

From 1940 through the 1960s, diethylstilbestrol (DES), a synthetic oestrogen, was given to pregnant women to prevent pregnancy complications and losses. Subsequent studies showed increased risks of reproductive tract abnormalities, particularly vaginal adenocarcinoma, in exposed daughters. An increased risk of breast cancer in the DES-exposed mothers was also found in some studies. In this report, we present further follow-up and a combined analysis of two cohorts of women who were exposed to DES during pregnancy. The purpose of our study was to evaluate maternal DES exposure in relation to risk of cancer, particularly tumours with a hormonal aetiology. DES exposure status was determined by a review of medical records of the Mothers Study cohort or clinical trial records of the Dieckmann Study. Poisson regression analyses were used to estimate relative risks (RR) and 95% confidence intervals (CI) for the relationship between DES and cancer occurrence. The study results demonstrated a modest association between DES exposure and breast cancer risk, RR = 1.27 (95% CI = 1.07–1.52). The increased risk was not exacerbated by a family history of breast cancer, or by use of oral contraceptives or hormone replacement therapy. We found no evidence that DES was associated with risk of ovarian, endometrial or other cancer.

Image: www.chemistrydaily.com/chemistry/Diethylstilbestrol - accessed 22 March 2010. This image is public domain.

REPRODUCTIVE HEALTH ENDPOINTS OF DIETHYLSTILBESTROL (DES) DAUGHTERS

- **Clear cell adenocarcinoma**
  - A rare type of vaginal and cervical cancer. Approximately one in 1,000 (0.1%) of DES daughters will be diagnosed with clear cell adenocarcinoma
- **Reproductive tract structural differences**
  - T-shaped uterus, hooded cervix, cervical cockscomb, and pseudopolyp
- **Pregnancy complications**
  - Ectopic (tubal) pregnancy and pre-term (early) delivery
- **Infertility**

• Following the discovery of reproductive health effects in the daughters of the women who took diesthylstilbestrol (DES) during pregnancy, the term “DES daughters” was coined. DES daughters represent the women that were exposed *in utero* to DES.
• The first health problem identified as being associated with DES exposure was clear cell adenocarcinoma (CCA), a rare form of vaginal and cervical cancer. DES Daughters are 40 times more likely to develop CCA of the vagina and cervix than women not exposed to DES. Approximately one of every 1,000 women exposed to DES prenatally will be diagnosed with CCA of the vagina and/or the cervix. Before the use of DES, CCA of the vagina and cervix only occurred in women past childbearing age. In contrast, DES Daughters have been diagnosed with CCA of the vagina and cervix at as early as age 8 and up to their late teens and early 20s. In addition, recent studies have indicated that some DES Daughters have been diagnosed with CCA of the vagina and cervix in their 30s and 40s.
• Some studies have shown that up to one third of DES Daughters have had some form of reproductive tract abnormality of the cervix, uterus, or fallopian tubes, including vaginal adenosis or cervical changes (such as collars, hoods, septae, and cockscombs).
Research demonstrates that DES Daughters are at an increased risk for problems during pregnancy, specifically, increased risk for premature delivery. Approximately 20% of DES Daughters experience pre-term labor, compared with 8% of unexposed women.
• DES Daughters are also at an increased risk for ectopic (tubal) pregnancy and miscarriage. DES Daughter's risk for ectopic pregnancy are between 3-5 times higher than the risk for a woman not exposed to DES. Furthermore, almost 20% of DES Daughters have been found to have a miscarriage during their first pregnancy compared to 10% of unexposed women who experience miscarriage.
• An infertility study showed that 24% of DES Daughters were unable to become pregnant, compared with 18% of women not exposed to DES. DES exposure was most strongly associated with infertility caused by uterine problems (such as the shape of the uterus).
Recent research findings raise additional concerns about health problems associated with DES exposure for women exposed before birth.

Refs:

•Diamanti-Kandarakis E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. 2009. *Endocrine reviews.* 30(4): 293-342.
•Hatch EE et al. Cancer risk in women exposed to diethylstilbestrol in utero, *Journal of the American Medical Association,* 1998, 280, 630–634.
The association between in utero exposure to diethylstilbestrol (DES) and clear cell adenocarcinoma (CCA) of the vagina and cervix is well known, yet there has been no systematic study of DES-exposed daughters to determine whether they have an increased risk of other cancers. As many as 3 million women in the United States may have been exposed to DES in utero.
Objective.— To determine whether women exposed to DES in utero have a higher risk of cancer after an average of 16 years of follow-up.
Design. A cohort study with mailed questionnaires and medical record review of reported cancer outcomes.
Participants. A cohort of 4536 DES-exposed daughters (of whom 81% responded) and 1544 unexposed daughters (of whom 79% responded) who were first identified in the mid-1970s.
Main Outcome Measures. Cancer incidence in DES-exposed daughters compared with population-based rates and compared with cancer incidence in unexposed daughters.
Results. To date, DES-exposed daughters have not experienced an increased risk for all cancers (rate ratio, 0.96; 95% confidence interval [CI], 0.58-1.56) or for individual cancer sites, except for CCA. Three cases of vaginal CCA occurred among the exposed daughters, resulting in a standardized incidence ratio of 40.7 (95% CI, 13.1-126.2) in comparison with population-based incidence rates. The rate ratio for breast cancer was 1.18 (95% CI, 0.56-2.49); adjustment for known risk factors did not alter this result.
•Herbst AL et al. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). *Gynecology Oncology,* 1999,