Female Fertility and Environmental Pollution

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Terrestrial ecosystems are contaminated by heavy metals and organic chemicals that can be taken up by and accumulate in crop plants, and water tables are heavily contaminated by untreated industrial discharges. As deadly particulates can drift far, poor air quality has become a significant global problem and one that is not exclusive to major industrialized cities. The consequences are a dramatic impairment of our ecosystem and biodiversity and increases in degenerative or man-made diseases. In this respect, it has been demonstrated that environmental pollution impairs fertility in all mammalian species. The worst consequences are observed for females since the number of germ cells present in the ovary is fixed during fetal life, and the cells are not renewable. This means that any pollutant affecting hormonal homeostasis and/or the reproductive apparatus inevitably harms reproductive performance.

Keywords: ovary ; hormones ; endocrine disruptors ; environment

1. Introduction

Environmental pollution, which exerts potentially harmful effects on earth and atmospheric ecosystems, is caused by the presence of chemical, biological, and physical substances [1][2]. It is a global problem shared by all developed and developing countries, but measures to prevent it are considered too costly. However, reduced environmental quality has long-term socioeconomic consequences: people are exposed to too many environmental toxicants, and their overall health conditions may worsen due to the synergistic and still-unknown effects of these factors on human health.

One of the most important and underestimated negative consequences is infertility, generally defined as “a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse” [3]. It affects about 10–15% of couples aged 20–45 and affects women in 50% of cases. The most common direct or indirect causes of female infertility are advanced age, endocrine problems, and damage to reproductive apparatus (vaginal, cervical, uterine, tubal, and pelvic-peritoneal diseases). Premature ovarian insufficiency (POI), endometriosis, and polycystic ovarian syndrome (PCOS) or sexually transmitted diseases have widely recognized roles in fertility failure [4], although approximately 15–30% of cases remain unexplained [5].

In the last few decades, the increased age of first pregnancy can be considered the first cause of female infertility. Besides this, also the increasing incidence of cancer, the adoption of unhealthy lifestyles, and exposure to environmental stressors play a negative role on it. However, while anti-cancer therapies are necessary, the negative effects of poor lifestyle choices (e.g., smoking, alcohol and drug abuse, and excessive energy intake) and environmental pollution could be reasonably reduced, sometimes with easy changes of habits and better attention to our ecosystem.

2. How Environmental Pollution Affects Female Fertility

The impact of environmental pollutants has been extensively studied in recent years, and many papers have demonstrated how such chemicals impair human health (see for reviews: References [6][7][8].

Environmental pollutants can permanently affect male reproductive potential [9], although these negative impacts can be attenuated by the presence of spermatogonial stem cells (0.03% of all germ cells) that in the seminiferous tubules is sufficient for maintaining fertility throughout the male lifespan. By contrast, in the mammalian ovary, the oocyte pool is fixed at birth, and the absence of stem cells hinders their replacement. Women produce a very small number (about 400) of potentially fertilizable oocytes from menarche to menopause, since a process of follicular degeneration (atresia) occurs throughout fetal and adult life, reducing the number of ovarian follicles by more than 99.9%. Some researchers claim that female fertility is not fixed after all, because their studies support the presence of stem cells in adult ovaries [10][11]. Recently, Wagner et al. [12] confirmed the absence of ovarian stem cells in samples of human ovarian cortices by using single-cell transcriptome and cell-surface-marker profiling, but this evidence was considered inconclusive by others. This is a puzzling issue, and there is no simple answer to it. Whatever the different opinions, all researchers agree that the

production of fertilizable oocytes is a long and complex process dependent on strict collaboration between the germinal and somatic compartments of the follicle as well as on the coordinated interplay of several hormones. If this orchestration fails, there is no possibility to become pregnant.

3. Air Pollution

Every day, people living in industrialized countries breathe and ingest a mix of particles and chemicals present in the air, many of which may also enter the food chain via the contamination of soil and water. The list includes particulate matter (PM; diameters: 10, 2.5–10 and 2.5 µm), ground-level ozone (O_3), benzo(a)pyrene (BaP, the main marker of polycyclic aromatic hydrocarbon (PAH) presence), polychlorinated biphenyls (PCBs), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), organic compounds (organic solvents and dioxins) and HMs, all abundantly produced by transport and industries.

A key question is how unavoidable maternal exposure to contaminants during the pre- and peri-conceptional periods causes abnormalities in oocytes, embryos, and/or fetuses and is able to hamper the safe delivery of a baby and his/her overall health and mental activity.

During pregnancy, fetal growth is accompanied by morphological changes of the placenta such as extensive angiogenesis in uteroplacental and fetoplacental vasculatures as well as increases in uterine and umbilical blood flows [13]. These changes are essential for correct fetal development [14][15][16]. Thus, factors that affect vascular development and function will have impacts on fetal growth, development, and survival [15]. It has been shown that air pollution affects the functional morphology of mouse placenta [17] and the authors hypothesized that alterations in its functional morphology could at least contribute to the reduced fetal weights associated with exposure to air pollution. Recently, Segal and Giudice [18] proposed that reproductive endocrinologists and gynecologists should promote healthy pregnancies by educating fertile women to adopt safe lifestyles during the preconception period, including the indoor use of High-Efficiency Particulate Air (HEPA) filters, and to avoid outdoor activities when the air quality is poor due to heavy traffic.

In this context, smoking habit represents a serious problem. About half of the exposure to benzene in the United States results from direct or indirect exposure to tobacco smoke (U.S. Department of Health & Human Services, 2019). A recent report by the American Society of Reproductive Medicine [19] indicates that in the USA, about 15% of adult women are smokers but, at the same time, often unfamiliar with the consequences of smoking on their reproductive apparatus. More importantly, it is generally accepted that people exposed to secondhand smoke can suffer the same health risks of smokers [20]. A cigarette contains approximately 600 ingredients and, when burned, creates more than 7000 chemicals, of which at least 70 are known to cause cancer [21]: nicotine, NO_2, formaldehyde, CO, HMs, tar, and benzene are some examples.

Benzene, one of the chemicals produced by cigarette smoke, has been measured in the FFs of women undergoing IVF, and when it was present at >0.54 ng/mL, women showed higher basal FSH levels and significant reductions of E_2 and the numbers of oocytes retrieved, and embryos transferred [89]. Additionally, smoking stimulates follicular depletion, an increase in mean basal follicle FSH levels, and the bringing forward of menopause by 3–4 years [22][23]. More recently, Furlong et al. [24] found that cigarette smoke-induced ovarian dysfunction by dysregulating the expression of 152 miRNAs, five of which directly affect the MAPK pathway. It is noteworthy that the overexpression of the phosphorylated form of) MAPK is typical in ovarian cancers [25][26].

Finally, it is of interest to highlight the consequences on fertility of the use of sprayed pesticides. The dermal and inhalation routes of entry are typically the most common routes of farmers' exposure [27], although people living in areas treated with pesticides can also be subjected to direct spray diffused from neighboring fields. Some mechanisms of action of these pesticides can be explained by using laboratory animals. An interesting example is that of mancozeb [28][29][30], a fungicide used for the control of fungal plant pathogens and widely used to protect vegetables (tomatoes and potatoes), fruit (grapevines, apples, and bananas), and ginseng, as well as ornamental plants and golf courses. Since mancozeb is usually sprayed with aerial equipment, the general population can be easily exposed by inhalation and/or the ingestion of contaminated food. Despite its low acute toxicity, mancozeb impairs fertilization and embryo development in female mice exposed to high doses (500 mg/mL) during pregnancy and lactation [31]. In vitro, low doses of mancozeb (0.001–1 µg/mL) alter GC morphology [32][33] and mitochondrial metabolism [28]. Similar effects on fertilization have been observed for other sprayed pesticides [34].

References

1. Muralikrishna, I.V.; Manickam, V.. Science and Engineering for Industry. Environmental Management; Butterworth-Heinemann: Oxford, 2017; pp. 1-4.
2. Rai, P.K.. Particulate Matter and Its Size Fractionation; Elsevier: Amsterdam, The Netherlands, 2016; pp. 1–13.
3. Mélodie Vander Borght; Christine Wyns; Fertility and infertility: Definition and epidemiology. *Clinical Biochemistry* **2018**, *62*, 2-10, 10.1016/j.clinbiochem.2018.03.012.
4. Gianna Rossi; Valentina Di Nisio; Guido Macchiarelli; Stefania Annarita Nottola; Iman Halvaei; Lucia De Santis; Sandra Cecconi; Technologies for the Production of Fertilizable Mammalian Oocytes. *Applied Sciences* **2019**, *9*, 1536, 10.3390/app9081536.
5. Alexander Quaas; Anuja Dokras; Diagnosis and Treatment of Unexplained Infertility. *Reviews in obstetrics & gynecology* **2008**, *1*, 69-76, .
6. A. C. Gore; V. A. Chappell; S. E. Fenton; J. A. Flaws; A. Nadal; G. S. Prins; J. Toppari; R. T. Zoeller; EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews* **2015**, *36*, E1-E150, 10.1210/er.2015-1010.
7. Linda G Kahn; Claire Philippat; Shoji F Nakayama; Rémy Slama; Leonardo Trasande; Endocrine-disrupting chemicals: implications for human health. *The Lancet Diabetes & Endocrinology* **2020**, *8*, 703-718, 10.1016/s2213-8587(20)30129-7.
8. Alison E. Hipwell; Linda G. Kahn; Pam Factor-Litvak; Christina A. Porucznik; Eva L Siegel; Raina N. Fichorova; Richard F Hamman; Michele Klein-Fedyshin; Kim G. Harley; program collaborators for Environmental influences on Child Health Outcomes; et al. Exposure to non-persistent chemicals in consumer products and fecundability: a systematic review. *Human Reproduction Update* **2018**, *25*, 51-71, 10.1093/humupd/dmy032.
9. Niels E. Skakkebaek; Testicular Dysgenesis Syndrome. *Hormone Research* **2003**, *60*, 49-49, 10.1159/000074499.
10. Joshua Johnson; Jacqueline Canning; Tomoko Kaneko; James K. Pru; Jonathan L. Tilly; Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature* **2004**, *428*, 145-150, 10.1038/nature02316.
11. Kang Zou; Zhe Yuan; Zhaojuan Yang; Huacheng Luo; Kejing Sun; Li Zhou; Jie Xiang; Lingjun Shi; Qingsheng Yu; Yong Zhang; et al. Production of offspring from a germline stem cell line derived from neonatal ovaries. *Nature* **2009**, *11*, 631-636, 10.1038/ncb1869.
12. Magdalena Wagner; Masahito Yoshihara; Iyadh Douagi; Anastasios Damdimopoulos; Sarita Panula; Sophie Petropoulos; Haojiang Lu; Karin Pettersson; Kerstin Palm; Shintaro Katayama; et al. Single-cell analysis of human ovarian cortex identifies distinct cell populations but no oogonial stem cells. *Nature Communications* **2020**, *11*, 1-15, 10.1038/s41467-020-14936-3.
13. P. Kaufmann; Terry M. Mayhew; D. S. Charnock-Jones; Aspects of Human Fetoplacental Vasculogenesis and Angiogenesis. II. Changes During Normal Pregnancy. *Placenta* **2004**, *25*, 114-126, 10.1016/j.placenta.2003.10.009.
14. Graham J. Burton; Eric Jauniaux; Development of the Human Placenta and Fetal Heart: Synergic or Independent?. *Frontiers in Physiology* **2018**, *9*, 373, 10.3389/fphys.2018.00373.
15. John C.P. Kingdom; Berthold Huppertz; Gareth Seaward; Peter Kaufmann; Development of the placental villous tree and its consequences for fetal growth. *European Journal of Obstetrics & Gynecology and Reproductive Biology* **2000**, *92*, 35-43, 10.1016/s0301-2115(00)00423-1.
16. Catrin S. Rutland; Mallinath Mukhopadhyay; Suzanne Underwood; Norma Clyde; Terry M. Mayhew; Christopher A. Mitchell; Induction of Intrauterine Growth Restriction by Reducing Placental Vascular Growth with the Angioinhibin TNP-470. *Biology of Reproduction* **2005**, *73*, 1164-1173, 10.1095/biolreprod.105.043893.
17. Mariana Veras; Nilsa Regina Damaceno-Rodrigues; Elia Garcia Caldini; Antonio A. C. Maciel Ribeiro; Terry M. Mayhew; Paulo H. N. Saldiva; Marisa Dolhnikoff; Particulate Urban Air Pollution Affects the Functional Morphology of Mouse Placenta1. *Biology of Reproduction* **2008**, *79*, 578-584, 10.1095/biolreprod.108.069591.
18. Thalia R. Segal; Linda C. Giudice; Before the beginning: environmental exposures and reproductive and obstetrical outcomes. *Fertility and Sterility* **2019**, *112*, 613-621, 10.1016/j.fertnstert.2019.08.001.
19. Alan Penzias; Kristin Bendikson; Samantha Butts; Christos Coutifaris; Tommaso Falcone; Susan Gitlin; Clarisa Gracia; Karl Hansen; Sangita Jindal; Suleena Kalra; et al. Smoking and infertility: a committee opinion. *Fertility and Sterility* **2018**, *110*, 611-618, 10.1016/j.fertnstert.2018.06.016.
20. Health Effects of Secondhand Smoke . American Lung Association. Retrieved 2021-1-15
21. Harmful Chemicals in Tobacco Products . American Cancer Society. Retrieved 2021-1-15

22. Carlo Alviggi; Rossella Guadagni; Alessandro Conforti; Giuseppe Coppola; Silvia Picarelli; Pasquale De Rosa; Roberta Vallone; Ida Strina; Tiziana Pagano; Antonio Mollo; et al. Association between intrafollicular concentration of benzene and outcome of controlled ovarian stimulation in IVF/ICSI cycles: a pilot study. *Journal of Ovarian Research* **2014**, *7*, 67-67, 10.1186/1757-2215-7-67.
23. Donald R. Mattison; David Plowchalk; M. Meadows; Michael Miller; Antoine Malek; Steve London; The Effect of Smoking on Oogenesis, Fertilization, and Implantation. *Seminars in Reproductive Medicine* **1989**, *7*, 291-304, 10.1055/s-2007-1021411.
24. Hayley C. Furlong; Martin R. Stämpfli; Anne Gannon; Warren G. Foster; Identification of microRNAs as potential markers of ovarian toxicity. *Journal of Applied Toxicology* **2018**, *38*, 744-752, 10.1002/jat.3583.
25. Yan-Jun Guo; Wei-Wei Pan; Sheng-Bing Liu; Zhong-Fei Shen; Ying Xu; Ling-Ling Hu; ERK/MAPK signalling pathway and tumorigenesis (Review). *Experimental and Therapeutic Medicine* **2020**, *19*, 1997-2007, 10.3892/etm.2020.8454.
26. Lan Hong; Yifeng Wang; Wangsheng Chen; Shuying Yang; MicroRNA-508 suppresses epithelial-mesenchymal transition, migration, and invasion of ovarian cancer cells through the MAPK1/ERK signaling pathway. *Journal of Cellular Biochemistry* **2018**, *119*, 7431-7440, 10.1002/jcb.27052.
27. Christos A. Damalas; Spyridon D. Koutroubas; Farmers' Exposure to Pesticides: Toxicity Types and Ways of Prevention. *Toxics* **2016**, *4*, 1, 10.3390/toxics4010001.
28. R. Iorio; Annalisa Castellucci; Giovanni Ventriglia; Flavia Teoli; Valerio Cellini; Guido Macchiarelli; Sandra Cecconi; Ovarian toxicity: from environmental exposure to chemotherapy.. *Current Pharmaceutical Design* **2014**, *20*, 5388-5397, 10.2174/1381612820666140205145319.
29. Gianna Rossi; Maria G Palmerini; Guido Macchiarelli; Roberto Buccione; Sandra Cecconi; Mancozeb adversely affects meiotic spindle organization and fertilization in mouse oocytes. *Reproductive Toxicology* **2006**, *22*, 51-55, 10.1016/j.reprotox.2005.11.005.
30. Sandra Cecconi; Rita Paro; Gianna Rossi; Guido Macchiarelli; The Effects of the Endocrine Disruptors Dithiocarbamates on the Mammalian Ovary with Particular Regard to Mancozeb. *Current Pharmaceutical Design* **2007**, *13*, 2989-3004, 10.2174/138161207782110516.
31. Gianna Rossi; Roberto Buccione; Massimiliano Baldassarre; Guido Macchiarelli; Maria G Palmerini; Sandra Cecconi; Mancozeb exposure in vivo impairs mouse oocyte fertilizability. *Reproductive Toxicology* **2006**, *21*, 216-219, 10.1016/j.reprotox.2005.08.004.
32. Rita Paro; Gian Mario Tiboni; Roberto Buccione; Gianna Rossi; Valerio Cellini; Rita Canipari; Sandra Cecconi; The fungicide mancozeb induces toxic effects on mammalian granulosa cells. *Toxicology and Applied Pharmacology* **2012**, *260*, 155-161, 10.1016/j.taap.2012.02.005.
33. Maria G Palmerini; Manuel Belli; Stefania Annarita Nottola; Selenia Miglietta; Serena Bianchi; Sara Bernardi; Sevastiani Antonouli; Sandra Cecconi; Giuseppe Familiari; Guido Macchiarelli; et al. Mancozeb impairs the ultrastructure of mouse granulosa cells in a dose-dependent manner. *Journal of Reproduction and Development* **2018**, *64*, 75-82, 10.1262/jrd.2017-143.
34. Sandra Cecconi; Gianna Rossi; Gaspare Carta; Gianluca Di Luigi; Valerio Cellini; Rita Canipari; Roberto Buccione; Effects of trifluralin on the mouse ovary. *Environmental Toxicology* **2011**, *28*, 201-206, 10.1002/tox.20711.