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Review

Occupational exposures to chemicals as a possible etiology in premature ovarian failure: A critical analysis of the literature

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ABSTRACT

Premature ovarian failure (POF) is a cause of infertility that affects about 1% of women under 40, and is considered as idiopathic in 75% of cases. An occupational chemical origin has been identified at least once with 2-bromopropane, but human studies are rare and experimental data are sparse. This review aims to carry out a critical synthesis of knowledge of the chemical agents likely to affect follicular stock in humans and/or animals, by direct toxicity to follicles, or by increasing their recruitments. Of 140 chemical agents (or groups) studied, 20 have been identified as potentially damaging to the ovarian reserve. For the majority of toxic agents, only experimental data are currently available. At least four of these agents are likely to lead to POF in descendents (ethylene glycol methyl ether; 2,2-bis(bromomethyl)-1,3-propanediol; benzo[a]pyrene; dimethylbenzantracene). We propose a strategy aiming to encourage progress in identifying occupational factors responsible for POF.

Contents

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1. Introduction

1.1. Nosological context

Premature (or primary) ovarian failure (POF), now also known as primary ovarian insufficiency (POI), is a form of infertility that affects women under the age of 40. It is defined as a primary or secondary amenorrhea of more than 4 months duration, associated with an increase in serum levels of follicle stimulating hormone (FSH) to above 40 IU/mL, confirmed by a second measurement one month later, with decreased estrogen levels [1–4].

1.2. Epidemiology

Prevalence is generally estimated at 1% for women aged less than 40 years, ranging from 0.3 to 3% depending on the studies [2,3,5–7]. Prevalence is 1/1000 for women aged less than 30 years and 1/10,000 for women aged less than 20 years [4]. Changes in behaviors, such as increasing age at the first pregnancy, result in a shorter period available for procreation in these women.

1.3. Prognosis and comorbid disorders

Premature ovarian failure may be related to exhaustion of follicular stocks, or to a follicular stock that is refractory to maturation mechanisms [3,6]. It is associated with major morbidity (psychological impact, osteoporosis, increased cardiovascular risk, impaired cognitive function [2,5,8]) that requires specialized, multidisciplinary management. If pregnancy is desired, oocyte or embryo donation may be proposed. In addition, the associated risks, which are mainly cardiovascular if hormone replacement therapy is not given, increase with the early onset of the disorder (due to a longer period of estrogen privation) [2,5,8].

1.4. Known etiological factors

An etiology is found in only 25% of cases. Genetic forms account for the majority, usually Turner syndrome or a premutation of the *FMR1* gene implicated in the fragile X syndrome. More rarely, partial deletion of the long arm of the X chromosome, translocations between the X chromosome and an autosome, FSH receptor gene, *NOBOX*, *FOXL2*, *SF1* or *GALT1* gene mutations may be found. Acquired forms most frequently appear after radiotherapy or chemotherapy. Most genetic forms generally lead to primary amenorrhea and the secondary forms tend to lead to secondary amenorrhea [1–3,9]. There are however some exceptions, as certain mosaic Turner syndromes present forms of secondary amenorrhea [10], or anticancer treatments given in early childhood lead, on the contrary, to primary amenorrhea [9].

Other risk factors have been found in the literature: being the product of a twin pregnancy [3], tobacco use [11–13], ethnic group (in decreasing order of risk: Hispanic and African-American, Caucasian, Chinese, Japanese) [14], and probably a high body mass index [14].

1.5. POF and toxic exposures

The occurrence of a well-characterized cluster of POF in female workers exposed to 2-bromopropane (2BP or isopropyl bromide) illustrated the plausibility of an occupational chemical origin to the disorder. The women worked in an electric components factory in Korea and used 2BP, 97% pure, with no protection, as a solvent for cleaning electrical components. By FSH measurement, 16 of the 26 women employed were diagnosed with POF after exposure ranging from 4 to 16 months. Two of the women later resumed menstruation [15,16].

Human studies are rare [5,17], and subject to a certain number of biases, as limitations in diagnosis assessment (clinical assessment without biology, or even self-reported amenorrhea), limitations in exposure assessment (self-reported), and finally biases inherent to study design (cross-sectional). With regard to occupational origin, a case–control study (443 cases and 508 controls) suggested a link between work as a hairdresser and POF (relative risk 3.24 (95% CI 1.06–9.91) for the Caucasian population) [5]. With regard to the environment, a study using biomarkers of exposure to perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) in a very large female population (about 26,000 women) suggested a risk of menopause occurring several months earlier after exposure in women aged over 42 years [17]. Nevertheless reverse causation could be an explanation, because of lipid metabolism modification induced by menopause, which could impact on the serum concentrations of these perfluorocarbons. Certain occupational and environmental toxic agents have been shown to be potentially toxic to follicles, or even capable of inducing POF in the animal. Some of these are polycyclic aromatic hydrocarbons (PAHs) whose aryl hydrocarbon receptor (AhR) is present in oocytes [12,18], and it is also toxic for male gametes, as a receptor is present on the head of spermatozoa. In this study, men were more likely to have infertility when urinary concentration of PAHs metabolites were higher [19]. Moreover, tobacco is suspected to induce POF in animals, and PAHs are one of the toxic agents potentially involved [13]. 4-Vinylcyclohexene is also known to potentially alter the ovarian reserve [20–22].

1.6. Mechanisms involved in chemical induced POF

The first mechanism is that of a follicular stock that is initially normal, secondarily impaired by a *cytotoxic* external agent: alkylating agents in chemotherapy or 2-bromopropane in an occupational