HURGENT: toward a multi-country monitoring system of reproductive health in the context of EDC exposure

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Background

During the last decades, worrying trends regarding human reproductive endpoints (e.g. semen quality, reproductive cancers) have been reported and debated. In the meantime, evidences have considerably grown on the reproductive effects of endocrine disruptors chemicals (EDCs) and ubiquitous human exposure has been documented. Furthermore, the concept of the developmental origin of health and diseases (DOHaD) [6], with possible windows of exposure in fetal, perinatal, pubertal, or adult reproductive periods indicates that adverse changes in reproductive function/ organs fitting with a developmental hypothesis could be accumulative and result in a durable global impairment, if causal factors are still at work. However, there is a striking lack of human data, especially surveillance data, to fill the current knowledge gaps. To answer the crucial questions raised on human reproductive health, its relation with environmental changes and its future, there is an urgent need for a reproductive surveillance system to be shared across countries.

Methods

A multidisciplinary network named **HURGENT (HUman Reproductive health and Global ENvironment Network)** was created aiming at designing a European monitoring system for reproductive health indicators. Ten European and extra European countries are represented: France, Denmark, United Kingdom, Spain, Finland, Poland, Israel, USA, Hungary and Czechia. The network proposes the first steps of a strategy to design a multi-country monitoring system of reproductive health. Collaborative work allowed setting up the available knowledge to design such a system. Furthermore we conducted an overview of 23 potential indicators, based upon a weight of evidence (WoE) approach according to their potential relation with EDC exposure. The annex 1 of the report published by the European Commission for regulatory aims [1] was used to score WoE for linking the indicator or its variations to an endocrine mode of action from a mechanistic point of view, therefore focusing on the biological plausibility. The World Health Organization-United Nations Environment Program (WHO-UNEP) report [2] was used to estimate the WoE for the causal relationship with EDC exposure. It reflects a wider approach that used all available evidence obtained with biological, experimental, wildlife and epidemiological data, but only qualitative appraisals of the WoE.

Results

REPRODUCTIVE HEALTH

According to the WHO, reproductive health addresses the reproductive processes, functions and system at all stages of life [3]. Therefore, the framework to monitor reproductive health is not limited to fertility/fecundity outcomes (e.g. birth rate) which strongly depend on socio-economic issues, lifestyle and individual choices. Instead, it embraces reproductive organs attributes and pathologies like cancers (e.g. testicular, breast or prostate cancer), as well as biological characteristics (e.g. level of reproductive hormones), developmental reproductive endpoints and multigenerational reproductive effects.

PURPOSES OF A REPRODUCTIVE HEALTH MONITORING SYSTEM

Considering all uncertainties and potential threats about the evolution of reproductive health, the purposes of a human reproductive monitoring system at an international level would be:
- to quantify and compare reproductive health indicators within and among each participating country;
- to compare the actual observations of temporal trends with the hypothesis of human reproductive health impairment at a wider scale (global impairment);
- if observed temporal trends are consistent with the previous hypothesis, to appraise their scope and quantify them according to several characteristics, including the identification of susceptible populations;
- to provide data in support of, or against, current causal hypotheses, e.g. role of EDC exposure, and/ or to generate new hypotheses;
- to help estimating the health impacts and costs of EDC exposures and to identifying corrective measures (and their costs);
- to help anticipating and managing the ensued resulting public health problems;
- to assess the impact of public health interventions in the future.

THE BASES TO SET A MONITORING SYSTEM: REPRODUCTIVE HEALTH INDICATORS

Monitoring reproductive health requires the selection of suitable epidemiological indicators that are simple or aggregated variables, which then enable the estimation of temporal and geographical trends at the population level. These indicators can be constructed using health or biological endpoints. Harmonized data would allow comparative analysis of indicators across various regions and countries and pooled analyses would provide results that are more robust.

WHICH METHODS/CRITERIA TO SELECT SUITABLE INDICATORS?

We initially considered a wide range of indicators to avoid missing a potential useful endpoint. First, we addressed relevancy of endpoints, in order to then select among the relevant indicators those that had optimal feasibility.

Regarding relevancy, it is interesting to make a focus on indicators of syndromes fitting the DOHaD concept such as the testicular dysgenesis syndrome (TDS) [4] and the ovarian dysgenesis syndrome (ODS), that mirrors TDS in females [5].

Reproductive health indicators need to be relevant as regards the purposes of the monitoring system, thus in particular according to their sensitivity to environmental exposures such as EDCs exposure. In addition, they must be measurable, standardized, valid, and steady in time, in order to allow durable monitoring and comparisons. Eventually, they have to meet feasibility criteria. The indicators may be either already available in existing databases, either newly built using existing sources/ networks or newly collected easily in a cost/efficient way.

However other factors, such as changes shifts in diet and/lifestyle [7-9] or occupational exposures [10-13], together with parallel increases in the incidence of medical conditions that may influence reproductive health, such as obesity or diabetes (both also possibly linked to EDC exposure and to reproductive outcomes), could contribute to the observed increase in reproductive disorders. It is therefore pertinent to take them into account in future analyses.

In summary, the relevancy criteria used to assess reproductive health indicators should include relevancy to links with the general environment, comprising EDC exposure, and also public health and research issues.

TABLE 1 — OVERVIEW OF POTENTIAL INDICATORS

Indicators	Population	WoE for attributing effects/ variations to an endocrine disruption mode of action (total rank=8) (1)	WoE for the causal relation with EDCs exposure (2)	Main suspected EDCs (1) and (2)	Main data to be controlled	Potential sources
MALE ONLY						
Semen quality: Concentration Total count Morphology Motility	Adults	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE and phthalates	Age Abstinence delay Measurement methods	Health examination surveys Nationwide ART data bases Donor data bases
Birth defect: Cryptorchidism (Prevalence)	Children	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE, phthalates, DES	Shift in medical practices, coding	Hospital data Prospective cohort studies
Birth defect: Hypospadias (Prevalence)	Children	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE and phthalates, DES	Shift in medical practices, coding	Birth defect Registers Hospital data Prospective cohort studies
Testis cancer (Incidence)	Adults	2.25	Possible (TDS) (but animal data lacking)	Pesticides, fungicides, PBDE and phthalates	Age	Cancer registers Hospital data
Prostate cancer (Incidence)	Adults	7	Sufficient	Pesticides (occupational exposure), arsenic, PCBs	Age	Cancer registers Hospital/Insurance data
FEMALE ONLY						
Endometriosis (Incidence)	Adults	6.5	Likely	PCBs, phthalates, dioxins	To be explored	Hospital/insurance data to be explored
Uterine fibroids (Incidence)	Adults	6.25	Likely	PCBs, phthalates, dioxins	To be explored	Hospital/insurance data to be explored
Polycystic ovarian syndrome (PCOS) (Incidence)	Adults	4.75	Plausible but insufficient	BPA	To be explored	Hospital/insurance data to be explored
Premature ovarian failure (POF) (Incidence)	Adults< 40	N/A	N/A	2-Bromopromane (occupational exposure) (2)	To be explored	Hospital/insurance data to be explored
Breast cancer (Incidence)	Adults	6.25	Sufficient	Dioxins and furans, PCBs, organic solvants	Age, surveillance biases	Cancer registers Hospital/insurance data
Ovarian cancer (Incidence)	Adults	NA	Limited evidence	Triazine pesticides	Age	Cancer registers Hospital/insurance data
Endometrial cancer (Incidence)	Adults	NA	Limited evidence	DDT	Age	Cancer registers Hospital/insurance data
Age at menopause	Adults	N/A	Insufficient	DDE, dioxin, pesticides	Treatments	Health interview surveys
Preterm birth (Incidence)	Newborn	7 (adverse pregnancy outcomes)	Limited evidence	Organochlorine and organophosphate pesticides, metals	Medical condition	Perinatal data bases/ medical birth registers
COMMON MALE AND FEMALE						
Hormone levels: Anti-Müllerian hormone (AMH) Testosterone, Inhibin B…	Adults Children	N/A Theoretically 8	N/A	N/A	Measurement methods, sex dependent cofounders, health, nutrition…	Biomonitoring studies
Anthropometric measurement: Anogenital distance (AGD)	Newborns, children or adults	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE and phthalates	Measurement methods	Health examination surveys
Anthropometric measurement: 2D/4D ratio (3)	Adults	N/A	N/A	Pesticides, phthalates	Measurement methods	Health examination surveys
Pathology: Precocious puberty (Incidence)	<8 years old (girls) <9 years old (boys)	5.5 (female)	Plausible (female)	PBBs, cosmetics or hair care with estrogens	Medical practices, obesity, ethnicity	Hospital / insurance data
Age of puberty (e.g age at menarche for girls and voice changes in boys)	Teenagers	N/A	Plausible (female)	Lead (4)(delay) PBBs (5) (advance)	Nutrition, ethnicity, socio-economic factors	Health studies
Time to pregnancy	Couples desiring a child	5.75 (female sub fecundity)	N/A	PFOAs PFOs	Socio-economic factors	Health studies
Infertility (% >12 months of unsuccessful trial)	Couples desiring a child	5.75 (female subfecundity)	Likely but insufficient (female infertility)	N/A	Couple's age, previous fertility	Health studies
Sex ratio	Newborns	7 (adverse pregnancy outcomes)	Sufficient (in selected populations)	Dioxin and dibromochloro propane	Community customs	Demographic data, Perinatal data bases/ medical birth registers
Natural dizygotic twin ratio (6)	Newborns	N/A	N/A	N/A	ART treatments	To be explored

(1) The rank is based on the eight 2002-IPCS criteria (Damstra et al. 2002). For each criterion, the grade is 1 when the criterion is met, 0.5 when mostly met, 0.25 when partly met and 0 otherwise. The rank sums the grades for each eight criteria. (2) Beranger et al. 2012. (3) Auger et al. 2013; Auger and Eustache 2011; Dean and Sharpe 2013. (4) Naicker et al. 2010; Selevan et al. 2003. (5) Toppari and Juul 2010. (6) Tong and Short 1998.

Conclusion

As regard the weight of evidence for an endocrine mechanism of action and a causal link with EDCs exposure, the indicators with the highest cumulated scores are prostate and breast cancer incidence, sex ratio in selected populations, endometriosis and uterine fibroids incidence, indicators related to TDS and precocious puberty incidence. Hormone levels are not documented for the WoE in the WHO-UNEP report, but they are evidently highly relevant.

Hence, not only sentinel health endpoints, but also diseases with high burdens in public health are highlighted as prior indicators in the context of EDC exposure. Our work could help as a basis to construct, as soon as possible, the first multi-country reproductive monitoring system.

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