ABSTRACT

INTRODUCTION

Congenital anomalies (CAs) represent one of the main cause of foetal death, infant mortality and morbidity, and long-term disability. CAs have been object of systematic registration activity for a long-time in many geographical areas in Europe and worldwide. CAs are often associated with disabilities of different types and severity, including the developed Countries worldwide. According to the World Health Organization (WHO), each year approximately 3,2 million of children worldwide are born with a CA and approximately 300,000 newborns with a diagnosis of birth defect die within the first 28 days of life. In Europe, CAs are the leading cause of perinatal mortality: the European Surveillance of Congenital Anomalies (EUROCAT) network estimated a perinatal mortality associated with CAs of 9.2 per 10,000 births in 2008-2012. In Italy, the Ministry of Health estimates that, on the average of 500,000 births each year, about 25,000 present at least one CA. Moreover, approximately 25% of infant mortality is due to CAs and about 50% of infant mortality is attributable to perinatal morbidity, almost always of prenatal origin. Regarding long-term survival, a recent population study conducted between 1985 and 2003 in the UK estimated a 20.5-year survival of 85.5% of children born with at least one CA. According to the Centre for Disease Control and Prevention, approximately 3.3% of live births in the United States have a severe birth defect. Since CAs represent a significant public health issue, an effective primary prevention strategy should be a priority for public policies and healthcare system.

Regarding aetiology, although in many cases the cause is still unknown, it has been hypothesized that CAs may be developed during the first trimester of pregnancy as a result of hereditary polygenic defects or of a gene-environment interaction. The aetiology is predominantly multifactorial, caused by complex interactions between genes and environment, which modify the normal embryo-foetal development, especially during the organogenesis phase.

In particular, environmental factors (e.g., chemical toxicants, infection agents, maternal disease, and exogenous factors) can have preconceptional mutagenic action, postconceptional teratogenic effects, periconceptional endocrine disruption or epigenetic action. Regarding genetic causes, there are genetic-chromosomal aberrations or dysgeneses. Furthermore, socioeconomic factors affect reproductive health by differentiating the exposure to the other risk factors as well as the access to prevention measures.

In recent years, the importance of the environment as a major factor of reproductive risk has been highlighted.

An individual may be exposed to pollutants present in the workplace and the population may be exposed to multiple sources of environmental contamination of water, soil, and air matrices. Pregnant women and the developing foetus are particularly sensitive to the effects of environmental exposure.

OBJECTIVE

The aim of the present working paper is to produce an updated review of the epidemiological evidence on the risk of CAs associated with environmental exposures, socioeconomic, and main individual risk factors, such as cigarette smoking and alcohol consumption, according to the approach proposed by Pirastu et al. 2010 in the framework of the SENTIERI Project (the Italian Epidemiological Study of Residents in National Priority Contaminated Sites).

DESIGN AND METHODS

Literature search was carried out in PubMed, following the SENTIERI project criteria to evaluate evidence, by selecting articles in English or Italian language published from 2011 to 2016 regarding human studies. For this review, descriptive and analytical epidemiological studies (cohort, case-control, cross-sectional, and ecological), systematic reviews, and metanalyses reporting association estimates between the outcome and at least one of the risk factors were selected.

As in Pirastu et al., the sources of environmental exposure have been classified into four macrocategories: industries, mines, landfills, and incinerators. The sources of individual exposure considered were: active and passive cigarette smoking, alcohol consumption, socioeconomic status (SES), occupational and environmental exposures related to air pollutants from vehicular traffic only. The obtained results were assessed according to the evaluation criteria on the epidemiological evidence related to the association between the outcome and exposures predefined and published by the SENTIERI working group (WG). For the evidence assessment, the SENTIERI WG criteria favoured firstly primary sources and quantitative metanalyses, secondly, consistency among sources. The evaluation of the epidemiological evidence for the association between outcome and the exposure has been classified into three categories: sufficient (S), limited (L), inadequate (I).

RESULTS

Industries: during the period under review, six single studies evaluating the association between industrial sites exposure and the risk of CAs were found. The epidemiological evidence of association between outcome and exposure has been considered limited.

Mines: from the bibliographic research, three single studies investigating possible cause-effect relationship between maternal residential proximity to mines and the risk of CAs have been collected providing inadequate epidemiological evidence.

Landfills: during the period under review, one systematic review and one literature review evaluating the causal associations between maternal residential proximity to landfills and CAs were identified. The epidemiological evidence is limited and concerns almost exclusively sites containing industrial or hazardous waste.

Incinerators: a systematic review has been selected; it concludes that the evidence for the association between maternal residential proximity to incinerators and CAs are inadequate.

Cigarette smoking: the literature search identified eight systematic reviews with metanalysis, five multicentre studies, and ten single studies assessing the causal association between maternal and/or paternal exposure to smoking and the risk of CAs in the offspring providing sufficient evidence for a causal association between maternal exposure to cigarette smoke and the risk of congenital heart defects, oro-facial clefts, neural tube defects, and gastrointestinal malformations.

Alcohol: three systematic reviews with metanalysis, two metanalyses, one multicentre study, and four single studies were collected for the period under review. The acquired literature has provided limited epidemiological evidence for associations between alcohol consumption and CAs in the nervous system, particularly for anencephaly and spina bifida.

Socioeconomic status: the evidence of an association with socioeconomic factors was inadequate due to an insufficient number of studies selected during the period under consideration.

Occupational exposure: the literature search collected one metanalysis, eight multicentre studies, and five single studies. The epidemiological evidence for associations between paternal occupational exposure to solvents and neural tube defects and between maternal pesticide exposure and gold-facial clefts were judged limited.

Air pollution: two systematic reviews with metanalyses, two multicentre studies, and nine single studies were selected by literature search; the epidemiological evidence for a causal association between air pollutants exposure and the risk of CAs is still to be considered limited.

CONCLUSIONS

For future epidemiological studies, a better exposure assessment, using in particular more accurate spatial measurements or models, a standardized case definition, a larger sample and more accurate control of the recognized or presumed confounding variables are needed.

Keywords: congenital anomalies, risk factors, epidemiological evidence