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European Recommendations for Primary Prevention of Congenital Anomalies: A Joined Effort of EUROCAT and EUROPLAN Projects to Facilitate Inclusion of This Topic in the National Rare Disease Plans

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Key Words

Congenital anomalies · EUROCAT · EUROPLAN · Genetic counseling · Health services · Lifestyles · Preconceptional care · Pregnancy · Primary prevention · Public health

Abstract

Congenital anomalies (CA) are the paradigm example of rare diseases liable to primary prevention actions due to the multifactorial etiology of many of them, involving a number of environmental factors together with genetic predispositions. Yet despite the preventive potential, lack of attention to an integrated preventive strategy has led to the prevalence of CA remaining relatively stable in recent decades. The 2 European projects, EUROCAT and EUROPLAN, have joined efforts to provide the first science-based and comprehensive set of recommendations for the primary prevention of CA in the European Union. The resulting EUROCAT-EUROPLAN 'Recommendations on Policies to Be Considered for the Primary Prevention of Congenital Anomalies in National Plans and Strategies on Rare Diseases' were issued in 2012 and endorsed by EUCERD (European Union Committee of Experts on Rare Diseases) in 2013. The recommendations exploit interdisciplinary expertise encompassing drugs, diet, lifestyles, maternal health status, and the environment. The recommendations include evidence-based actions aimed at

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reducing risk factors and at increasing protective factors and behaviors at both individual and population level. Moreover, consideration is given to topics specifically related to CA (e.g. folate status, teratogens) as well as of broad public health impact (e.g. obesity, smoking) which call for specific attention to their relevance in the pre- and periconceptional period. The recommendations, reported entirely in this paper, are a comprehensive tool to implement primary prevention into national policies on rare diseases in Europe.

Rare diseases include those disorders that affect a small fraction of the population, < 5 in 10,000 people according to the European Union definition [1]. Due to low prevalence, the vast majority of congenital anomalies (CA) have to be considered as rare diseases [2]. Whereas the majority of rare diseases are of genetic origin, most CA have a multifactorial etiology, with a number of environmental factors (often different for specific birth defects) triggering, in relation to specific genetic predispositions which are discovered recently with newest genomic technologies. Thus, the aetiopathogenesis of most CA involves a number of factors related to the parental living environment such as diet, lifestyle, or workplace, as well as maternal diseases and therapeutic treatments. Accordingly, CA are the paradigm example of rare diseases liable to be reduced by well-targeted primary prevention actions. Clinical, epidemiological, as well as experimental studies are providing a growing amount of information about recognized or potential risk factors for either individual or groups of CA. Nevertheless, little effort has been made till now to integrate such information into science-based, comprehensive, and consistent policies.

Effective protection of women and men during their fertile years and the fetus from teratogenic or mutagenic risk factors should be a priority public health target. Primary prevention actions can benefit the general population as well as afford a specific protection to the fetus at a particularly vulnerable life stage; they can also benefit a fraction of genetically vulnerable individuals. To build up a science-based and comprehensive approach, interdisciplinary expertise is required, encompassing drugs, diet, lifestyles, maternal health status, and the environment.

Rare diseases raise concern as an emerging public health issue. In 2008 the European Commission adopted the 'Communication on Rare Diseases: Europe's Challenges' proposing an overall strategy to support Member States [3]. In 2009 the European Council followed this by adopting the 'Council Recommendation on an Action in the Field of Rare Diseases' which recommends that Member States establish and implement national plans or strategies for rare diseases or explore suitable measures for rare diseases in other public health strategies [4]. Since the main core of rare diseases (approx. 80%) are genetic conditions, recommendations tackle approaches to guarantee early and accurate diagnosis and effective and affordable treatment. However, primary prevention is increasingly recognized as a relevant issue as well, in particular for CA. The specific aspects of CA as rare diseases have been thoroughly discussed in a EUROCAT (European Surveillance of CA) report published in 2012 [2].

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of CA. EUROCAT started in 1979 and currently surveys more than 1.7 million births per year, gathering data from 43 high-quality multiple source registries in 23 countries and covering 29% of the European Union birth population [5]. EUROCAT has more recently been funded by the EU Public Health Programme as a Joint Action (2011–2013) which includes a dedicated workpackage (Workpackage 7) on primary prevention. It is notable that in the 35 years since EUROCAT started in 1979, the total prevalence of major CA has not fallen, mainly indicating a lack of effective new interventions in primary prevention despite growing scientific knowledge.

EUROPLAN (European Project for Rare Diseases National Plans Development) has elaborated agreed tools for the development and implementation of national plans or strategies following the European Council Recommendations; in its second phase (2012–15), the project establishes an international and interactive network of policy makers and other stakeholders to speed up the implementation of national plans/strategies for rare diseases through scientific and technical assistance [6]. Within the frame of national plans/strategies for rare diseases, EUROPLAN has considered primary prevention as a priority target, with specific attention towards CA. Thus, EUROPLAN has joined efforts with EUROCAT in order to provide the first comprehensive set of recommendations for the primary prevention of CA in the European Union.

The resulting 'Recommendations on Policies to Be Considered for the Primary Prevention of Congenital Anomalies in National Plans and Strategies on Rare Diseases' were issued jointly by EUROCAT and EUROPLAN in 2012 and were endorsed by EUCERD (European Union Committee of Experts on Rare Diseases) in 2013 [7]. EUCERD is charged with aiding the European Commission with the preparation and implementation of

community activities in the field of rare diseases, in cooperation and consultation with the specialized bodies in Member States and the relevant European authorities in the fields of research and public health action. The recommendations point out areas in which public health policies are needed, whereas specific policies should be developed by Member States on the basis of national priorities and scenarios. As well as translating current evidence to effective interventions at the individual and population level, Member States need a targeted research policy. Research on the causes of CA has suffered from a similar fragmented approach as preventive actions, and there remains much scientific uncertainty relating to environmental causes that can and should be resolved.

In the context of these primary prevention recommendations, 'environmental' is used in its broadest sense as non-genetic (although interacting with genetic factors), encompassing physical, chemical, biological, and social factors and concentrating on factors which are potentially modifiable: this broad definition follows that of the US National Institute of Environmental Health Sciences [8–11].

The recommendations are entirely reported here in their original format and are a 'first step'. The next steps envisaged are to monitor their implementation in National Rare Disease Plans and by doing so to share experience regarding specific policy actions, to evaluate the impact of policy actions through continuing surveillance of CA by EUROCAT, and to periodically update the scientific evidence underpinning the recommendations as well as grow the evidence base regarding effective interventions.

How the Recommendations Were Formulated

The recommendations have been developed and shared through a multistep process.

A preliminary phase covered collection and analysis of relevant literature (peer-reviewed papers, reports from authorities from EU, EU Member States, and outside the EU) to define the main evidence-supported risk factors for CA.

Seven working groups were then established among EUROCAT and EUROPLAN partners in order to identify public health actions for the primary prevention of CA at several levels (regulatory, monitoring, pre- and periconceptional care). Namely, the following issues were considered: medicinal drugs, folic acid and other nutrition aspects, food safety, maternal lifestyles, maternal health and healthcare including chronic and infectious conditions, genetic factors and genetic counseling, and environment-related risk factors including the workplace. Working group participants were identified on the basis of specific expertise and declaration of interest.

In parallel, EUROPLAN performed a survey to collect the existing health policies, initiatives, and best practices regarding the primary prevention of CA from a selected panel of national experts from EU Member States. This step facilitated the exploitation of the added value from multidisciplinary expertise as well as the sharing of national experiences; moreover, this step provided support to a consensus approach for including the primary prevention of CA in national plans on rare diseases.

A consensus draft of the recommendations was prepared by the working groups in April 2012. This first draft was discussed in several joint sessions to be validated from both standpoints of scientific evidence and applicability. An advanced draft was then presented during a specific session at the EUROCAT Registry Leader Meeting (Budapest, June 13–15, 2012). The draft was revised taking into account the input of EUROCAT Registry Leaders and the comments of EUROCAT Project Management Committee (Ingeborg Barisic, Elisa Calzolari, Rhonda Curran, Helen Dolk, Ester Garne, Lorentz Irgens, Babak Khoshnood, Domenica Taruscio, Diana Wellesley) in June 2012. Upon approval by the EUROCAT Steering Committee (December 2012), the document was sent to the policy officer at the Directorate of Public Health at the European Commission in Luxembourg (Dr. Antoni Montserrat) and was finally endorsed by EUCERD in 2013.

Recommendations on Policies to Be Considered for the Primary Prevention of CA in National Plans and Strategies on Rare Diseases

Most CA are rare and form an important group of rare diseases for which EU Member States are developing national plans. The primary prevention of CA was identified as an important action in the field of rare diseases in the communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee, and the Committee of the Regions of November 11, 2008. However, it has not been included in the Council Recommendation on an action in the field of rare diseases of June 8, 2009. This document aims at providing an outline of evidence-based policy actions for the primary prevention of CA. It does not seek to recommend specific policy options but rather to indicate the areas that

Member States could target in their strategies for the primary prevention of CA. EUROPLAN [6] will support and facilitate Member States to incorporate the recommendations specified here in their national plans and will facilitate exchange of experience among Member States in collaboration with EUROCAT [5].

The causes of CA can be environmental, genetic, or an interaction involving both genes and environment [8–11]. Within the scope of this document, primary prevention includes any evidence-based action aimed at reducing environmental risk factors for CA and increasing protective environmental factors. Such factors act in the periconceptional period most often before the pregnancy has been confirmed. Whereas actions based on the precautionary principle fall mainly outside the scope of this document, in some cases precautionary actions have been quoted when they may bear significant public health and/or social benefits. Primary prevention also includes preconceptional counseling concerning genetic risks but does not include preimplantation diagnosis. The primary prevention of CA includes factors that are common to other diseases as well as factors specific to CA. Policies aimed at promoting safer foods and environment, healthy dietary habits and lifestyles, as well as reducing the health impact of chronic diseases are expected to reduce the prevalence of CA as well as many other diseases. However, elaboration of these policies needs to pay special attention to their relevance in the pre- and periconceptional period. Rather than pinpointing specific actions, which may have a limited impact in isolation, it is advisable that Member States would integrate the different recommendations within a strategy for primary prevention.

The Scope of Policy Actions Needed for the Primary Prevention of CA

In the Field of Medicinal Drugs

- To advise women taking medication to seek medical advice before trying to get pregnant [12];
- to ensure that guidelines are, or are going to be, made available for physicians regarding risk-benefit balance for use of medications in pregnancy, particularly those medications used for treating chronic diseases [13–17];
- to provide a teratogen information service where specialized advice can be sought by women and professionals [18];
- to conduct postmarketing pharmacovigilance to detect any risk of CA associated with the use of medications with the support of population-based CA registries [19].

Notes

Medications of particular concern include antiepileptics, folate antimetabolites, antiblastic agents, warfarin and related anticoagulants, retinoic acid derivatives, ACE-inhibitors, and AT1 receptor antagonists [13]. However, information on the human teratogenicity of most medications is limited [14, 15].

There is extensive literature investigating the relative teratogenicity of different antiepileptic medications [16]. For antiasthmatics and antidepressants, national guidelines need to take into account the growing evidence base [17].

In the Field of Food/Nutrition and Lifestyle

- To improve folate status through periconceptional supplementation with folic acid, promotion of the consumption of foods rich in natural folates, and the appropriate use of fortified foods [20–23];
- to prevent overweight/obesity and underweight [24–26];
- to promote effective information on diet and nutrition in women at childbearing age, minimizing the risks of deficiency and/or overdosing of vitamins and essential trace elements [27–31];
- to further the implementation of EU food safety strategies to prevent food contamination by recognized developmental toxicants [32–35];
- to reduce active and passive smoking [36, 37];
- to promote alcohol avoidance in women who are pregnant or wishing to get pregnant [38–41];
- to pay special attention to diet and lifestyles in communities with low socio-economic status or of recent immigrants.

Notes

Strong scientific evidence showed that folate-rich diets and periconceptional supplementation with folic acid (the synthetic form) are effective in reducing the prevalence of neural tube defects (NTD) and other congenital malformations. An adequate folate status in women before pregnancy is a protective factor toward these pathologies. In 2009 EUROCAT published a special report highlighting that the majority of women in Europe were still not taking folic acid preconceptionally and/or were beginning to take it too late to prevent CA after their pregnancy had been confirmed. As a result, the impact of policy on the rate of NTD in the population was minimal, and socioeconomic inequalities widen due to differences in knowledge. Furthermore, the dietary intake of folates may not be sufficient to protect vulnerable women [20].

Many non-European countries, such as USA and Canada, have instituted mandatory food (flour) fortification with folic acid as a way forward, with a positive impact in reducing NTD prevalence [21, 22]. However, fortification also raises concerns about the possible 'side effects' of high folic acid intake in non-target population groups which might be related to increased cancer promotion. In 2009 the scientific committee organized by EFSA (European Food Safety Authority) concluded that 'There are currently insufficient data to allow a full quantitative risk assessment of folic acid and cancer or to determine whether there is a dose-response relationship or a threshold level of folic acid intake associated with potential colorectal cancer risk. The current evidence does not show an association between high folic acid intakes and cancer risk, but neither do they confidently exclude a risk. The uncertainties in relation to cancer risk highlight the importance of ensuring monitoring systems are set up for assessment of folic acid intake and status and NTD and cancer incidence in countries that decide to introduce mandatory fortification' [23].

Particular attention should be given to (i) deficiency of vitamins B_{12} and B_6, since they are needed for the proper metabolism of folates, and (ii) zinc deficiency as a risk factor for NTD in communities from developing countries. In addition, pregnant women should avoid an excessive exposure to vitamin A associated to liver consumption and taking supplements containing vitamin A [27–31].

A recognized example of a food contaminant highly relevant to the safety of the unborn child is methylmercury in certain fish groups [32–34]. The developmental hazards (especially urogenital malformations) from dietary exposure to endocrine disrupters also deserve consideration (see also below 'Field of Environmental Pollution Including the Workplace') [35].

Active smoking is a risk factor for CA [36]. The evidence regarding passive smoking is more difficult to establish but is considered to be biologically plausible [37].

In the Field of Health Services

• To make available preconceptional care including genetic testing and counseling for families at risk [42–45];

• to ensure that women with diabetes, epilepsy, and other chronic diseases receive preconceptional care in order to minimize the risk of CA [46, 47];

• to ensure evidence-based vaccination policies to guarantee women are protected against infectious diseases associated with CA and avoid contraindicated vaccinations during pregnancy [48, 49];

• to include the awareness in school educational programs that CA may be caused very early in pregnancy, often before the pregnancy is confirmed, and hence, healthy practices should start preconceptionally;

• to include consideration of specific pregnancy-related actions in public health action plans on all the major health determinants.

Notes

Preconception health refers to the health of women and men during their reproductive years. It focuses on steps that women, men, and health professionals can take to reduce risks, promote healthy lifestyles, and increase readiness for pregnancy [42–44].

Proposed recommendations from published research and recommendations from the Centers for Disease Control and Prevention (CDC) [45]:

(1) Individual responsibility across the life span – each woman, man, and couple should be encouraged to have a reproductive life plan. Individuals identified as having a family history of developmental delays, CA, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy.

(2) Health professionals' responsibility – the challenge for health professionals is to reach women and men with these interventions at the time they will be most effective in reducing risks. Suspected genetic disorders might require further workup prior to conception. Known or discovered genetic conditions should be managed optimally before and after conception. As a part of primary care visits, provide risk assessment and educational and health promotion counseling to all women of childbearing age to reduce reproductive risk and improve pregnancy outcomes.

(3) Consumer awareness – increase public awareness of the importance of preconception health behaviors and preconception care services by using information and tools appropriate across various ages, literacy, including health literacy, and cultural/linguistic contexts.

(4) Research – increase the evidence base and promote the use of evidence to improve preconception health.

(5) Monitoring improvements – maximize public health surveillance and related research mechanisms to monitor preconception health.

Pearls for practice: women should also be informed that preconception care can improve health outcomes for both mother and baby. First, ask every women of reproductive age whether she intends to become pregnant in the next year. Asking every woman about her reproductive inten-

tions promotes the idea that pregnancies should be intended. Second, inform women that health conditions and medications can affect pregnancy outcomes [45].

During preconception screening visits, clinicians should focus on issues such as folate supplementation, hypothyroidism management, obesity control, hepatitis B vaccination for at-risk women, and rubella vaccination among previously unvaccinated women.

Maternal diabetes is a well-established risk factor for CA, but the excess risk can be almost eliminated with good glycaemic control. Health services must be organized to ensure that all women with diabetes have preconceptional care to achieve optimal glycaemic control [46, 47].

Vaccination against maternal rubella is a core element of any primary preventive strategy as rubella during pregnancy is a strong teratogen. Countries should consider their coverage of women, whether immigrant women are offered vaccination, and whether women found at a first pregnancy not to be immune are offered vaccinations to protect them in subsequent pregnancies. Other vaccinations should also be considered. Vaccination during the first trimester should only be given where there is evidence of safety or evidence of a favorable benefit-risk balance [48, 49].

In the Field of Environmental Pollution Including the Workplace

• To further the implementation of EU policies on high-concern chemicals, to ensure both regulatory actions and risk communication towards citizens in order to minimize exposure to pollutants identified as teratogens [50–60];

• to ensure a suitable surveillance system where environmental risks can be identified through the integration of CA registers with developments in biomonitoring [61];

• to minimize exposure of pregnant workers in their workplace to risk factors for CA (chemical, physical, and biological) [62–69].

Notes

The 'environment' as used here is all the physical, chemical, and biological factors external to the human host and all related behaviors but excluding those natural environments that cannot reasonably be modified. This definition excludes behavior not related to environment as well as behavior related to the social and cultural environment, genetics, and parts of the natural environment [50].

In the field of the environmental causes of CA, evidence is still limited and inadequate to show a causal association; however, the biological plausibility and special vulnerability of the fetus supports precautionary actions (Communication from the European Commission on the precautionary principle, Brussels, 2000). In particular, reduction of the level of exposure to hazards acting on a large scale, such as air pollutants, byproducts of drinking water disinfection, and pesticides, should be recommended [52–56].

Endocrine disrupters are recognized risk factors for reproductive disorders during puberty and adulthood; however, evidence indicates that higher exposure levels may increase the incidence of urogenital malformations such as cryptorchidism and hypospadias [57–60].

There is a general consensus that further elucidation of the links between environmental exposures and CA must come through linking biomarkers and CA surveillance approaches [61].

Pregnant women at work must be protected from teratogenic exposures. The challenge is to do this in early pregnancy, often before the pregnancy has been confirmed or employers are made aware. This issue should be addressed in occupational health policies. Occupational exposures of concern include pesticides, any endocrine disrupting exposure, and organic solvents [62–69].

Types of Primary Preventive Actions and Their Effectiveness

A number of types of primary preventive action can be identified:

(1) Advice to future parents by health professionals during individual preconceptional and early pregnancy consultations, tailored for high- and 'low'- (average population) risk couples.

(2) Health education campaigns targeted to potential future parents.

(3) EU-based and/or national regulatory actions which affect risk factors at source such as medicines, chemicals, infectious agents, foods, tobacco and alcohol, and other recreational drugs.

(4) Surveillance, research, and evaluation generating evidence for the initiation or updating of primary preventive measures. This includes also the establishment of expert committees to review evidence.

The effectiveness of targeted actions towards the primary prevention of CA is expected to be markedly improved by:

• An integrated primary prevention plan involving all relevant health professionals thus avoiding isolated and/or uncoordinated actions/recommendations;

• implementation and refinement of EU food and environmental control programs providing special attention to CA risk factors;

• proper evaluation and integration of new scientific knowledge into public health actions;

• ensuring preconception health care in local public health programs [70–74] while recognizing that many pregnancies are unplanned;

• availability of epidemiological surveillance data from population-based CA registers to monitor the effectiveness of services and interventions to build a sound evidence base for policy development planning and action;

• ensuring sustainability through national and international funding.

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