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Preconception Pharmaceutical Care & Rare Diseases

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Abstract

The objective of this paper is to demonstrate how both individual family physicians and pharmacists, as well as larger primary care organisations can contribute to the implementation of preconception care delivery i.e. to establish the service, to reach the target population and to add sustainably and effectively to the primary goals of preconception care i.e. to modify the risks to the health of future children and more specifically with respect to rare diseases. This paper comprises a short introduction into the contents of preconception care and a structured debate in which implementation options are will be explored such as; seizing opportunities in daily practice, integration in contraception counselling and/or sexual and reproductive health programmes; selection of and outreach to, high risk subgroups defined for example by genetic predisposition, social economic deprivation, chronic diseases etc. The readers are expected to understand options to improve preconception pharmaceutical care applicable in their own healthcare system.

Community pharmacists are in a privileged position to implement pharmaceutical care to prevent rare diseases wherever possible by dispensing safe medicines and advising healthy life-style and genetic counselling before conception as well as occasionally referring to the possibility of assisted reproductive technology.

Keywords: Pharmaceutical care; Rare diseases; Preconception care; Assisted reproductive technology; Preventive medicine; Public health

Abbreviations: ACE: Angiotensin-Converting-Enzyme; CDC: Centre for Disease Control and Prevention; hCG: Human Chorionic Gonadotrophin; LHRH: Luteinizing Hormone-releasing Hormone; PCC: Preconception Care; WHO: World Health Organisation

Introduction

A hundred years ago (5 September 1919) the “Nationaal Werk voor Kinderwelzijn/Oeuvre Nationale de l’Enfance” (National Institute for Child Welfare) was established in Belgium to ensure child protection and to disseminate basic rules for better

hygiene in newborns and babies (“De morbis puerorum”). These were all measures to be taken after the birth of a child. Social regulations concerning maternity protection (noise, heat, chemicals, vibrations, infection) were installed much later. The concept of preconception care and its potential advantages began to grow only in the 1980s of last century.

Preconception care (PCC) is defined as: “A set of interventions and/or programmes that aim to identify and enable informed decision-making to modify biomedical, behavioural, and (psycho) social risks to parental health and the health of their future child, through counselling, prevention and management, emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact and/or choice (modified CDC-definition).” The WHO advocates that PCC should be delivered as an integrated service that reaches from pre-pregnancy to delivery, the immediate postnatal period unto childhood thus contributing to the realisation of the Millennium Development Goals for maternity, neonatal and child health care [1].

From the organisational point of view the challenges are how the Primary Care team including the family physician and the pharmacist can contribute to reaching the target population in the preconception period and how their role can be integrated in the broader spectrum of public education and services delivered by other providers like midwives, obstetricians, medical geneticists, genetic counsellors, family planning institutions and public health bodies [2].

Literature Review

Safe medicines before pregnancy

Community pharmacists are in a privileged position to deliver correct pharmaceutical care to couples with a wish to have children, as in many situations the pregnancy test is delivered in a community pharmacy. At this point, important actions need to be taken to optimise the fertility of the women and her partner as well as to protect the health of the future mother and her foetus [3]. The consumer organisation Test-Aankoop in Belgium discovered that half of the on-line pharmacies delivered unsafe medications to their pregnant customers [4]. Immunosuppressive drugs for example, taken by many patients

with a rare disease, may have deleterious effect on fertility [5]. Considering the safe use of (over the counter) medicinal products, herbs and supplements, there are several free accessible databases with scientific information on safe preconception drug use for males and females mainly for antiepileptic's, folate antimetabolites, warfarin and related anticoagulants, retinoic acid derivatives and ACE-inhibitors [6-12]. Mycophenolate mofetil is taken by many patients with rare inflammatory diseases and because of its teratogenic properties [10] it can best be switched before conception to another treatment [13]. Adherence to medication and diet for rare disease patients is very important in this period to keep levels (eg. phenylketonuria) within the required range to avoid congenital defects. Women with untreated phenylketonuria in the preconception period are at increased risk to have a foetus with multiple abnormalities [14]. Medication review and reconciliation can help the pharmacist to support adherence.

Men and women with rare genetic diseases are increasingly reaching the reproductive age thanks to better diagnosis and treatment and many have a wish to bear children [15]. The use of orphan drugs before conception and during pregnancy is mostly prescribed off-label [16]. However certain rare disorders place women at a higher risk for morbidity and mortality during pregnancy. Pregnancy is ill-advised and contraindicated in women with pulmonary arterial hypertension due to high maternal and foetal mortality [17]. Progestin-only implants and intrauterine devices are the preferred methods of contraception and are considered to be safe and effective in these patients. Also the outcome of pregnancy in women with systemic and cutaneous lupus erythematosus depends highly upon optimal systematic planning before the conception [18]. Women with sarcoidosis can carry out successful pregnancies but have a higher risk of venous thromboembolic events [19].

Healthy life-style and genetic counseling before pregnancy

In the field of lifestyle, community pharmacists need help prevent overweight/obesity and underweight, to reduce active and passive smoking, promote alcohol avoidance and stop substance abuse [20,21]. If medication could help achieve these goals, it could be considered. Strong scientific evidence shows that an adequate folate status in women before pregnancy is a protective factor for neural tube defects and other congenital malformations [22]. Folic acid supplements could be indicated: the usual daily dose is 0,4 mg but in certain conditions 4 mg could be needed. The ideal starting time is 1 to 3 months before conception and stopping time at least 12 weeks thereafter. Particular attention should also be given to vitamin B12 (vegetarians and vegans) and B6 (alcoholism) deficiencies, which is needed for proper metabolism of folate, and eventually to high doses of vitamin A and derivatives. Several commercial products are available for the correct intake of additives during pregnancy.

In the field of health services, genetic testing and counselling for families at risk should be advised before conception. Direct to consumer genetic testing is an option in carrier screening. Lab on a chip devices with multiple laboratory processes on a single

integrated circuit can provide fast analysis and response times with small human fluid volumes. Consanguinity, despite a decreasing trend [23], is still an important risk factor for the appearance of rare disorders [24]. Due to the overview of the medication, pharmacists are aware of rare genetic diseases in the families of their patients. Unfortunately, in many countries there is still a missing link between community pharmacy and hospital pharmacy drug use. Mothers with insulin-dependent diabetes, epilepsy and other chronic conditions need preconception pharmaceutical care to minimise the risk for birth defects. Maternal insulin-dependent diabetes is a well-established risk factor but this risk can almost be eliminated with good glycaemic control and 4mg daily dose of folic acid. Every diabetic future mother can easily be identified provided there is a proactive engagement by her pharmacist.

Protection against infectious diseases through vaccinations such as the measles-rubella-mumps vaccine before pregnancy are core elements in any primary preventive preconception strategy and two generations will benefit from this single injection. Community pharmacists can easily check the vaccination status of their patients thanks to centralised vaccination registries such as Vaccinnet [25] and E-Vax in Belgium. Additionally, current guidelines [26] recommend vaccination not before but during pregnancy (but not with live vaccines) to protect the mother and her foetus or new-born such as the diphtheria/tetanus/pertussis and flu vaccine during the season [27]. Vaccinations and other medical preventive measures against import pathology before conception are also important [28]. Ixiaro, a Japanese encephalitis antitoxin, was marketed as an orphan drug. Community pharmacists are aware of exotic destinations of their patients. Several countries now have travel clinics to help travellers to protect them when travelling to a (sub) tropical country [28].

Discussion

Assisted reproductive technology

Patients with non-genetic rare diseases such as congenital malformations of their productive genetic organs may suffer subfertility and need surgical intervention. Patients with genetic rare diseases may have disease-related subfertility [29] affecting males (e.g. Klinefelter Syndrome), females (e.g. Turner Syndrome) or both genders (e.g. Cystic Fibrosis). Assisted Reproductive Technology in patients with a rare disorder has resulted in successful pregnancies similar to other women [30]. By using Preimplantation Genetic Testing (screening and diagnosis), patients who are at risk of transmitting an inherited (rare) disease to their offspring can become pregnant without a foetus with the same genetic disease. Termination of the pregnancy is therefore prevented by this intervention. Artificial Oocyte Activation and In-vitro Maturation are techniques of the future probably indicated for patients with monogenic (rare) disorders (e.g. Fragile X and rare inherited cancers). In combination with in-vitro fertilisation this technique can induce pregnancies without ovarian stimulation. Cryopreservation of mature oocytes can be useful for patients who are at risk to lose their fertility (e.g. Turner Syndrome) and patients with rare

cancers before the start of their cytotoxic treatment: a well-known teratogenic [10] thalidomide is an orphan drug authorised for the treatment of multiple myeloma.

The dispensing of the medication for ovarian stimulation (LHRH agonists and antagonists, gonadotrophins, hCG and luteal medication) will be performed by the pharmacist connected to the in-vitro fertilisation centre. The dosage can be diverse and is related to age and weight, anti-Mullerian hormone, antral follicle counts and the local legal/reimbursement system. All these medications can be injected subcutaneously by the patient herself. Self-administration pens are now available for most of these medications. Pharmaceutical care by the pharmacist is crucial at this point (look-alike/sound-alike products). Inventory management (drug shortages) and cold chain handling is a constant concern.

Last but not least the community pharmacist is essential to bring evidence-based information to his patients. Millions of euros have been spent to develop a product but all that can be negated by dispensing the wrong dose at the wrong time to the wrong patient. With the help of the medical profession (including the community pharmacist), rare genetic disorders can be limited. Clairvoyance, the 1936 art work of the Belgian painter René Magritte (1898-1967) illustrates this (Figure 1) the appearance of an individual is defined when an embryo.



Figure 1: Clairvoyance (1936) by the Belgian painter René Magritte (1898-1967).

Conclusion

Community pharmacists are in a privileged position to implement preconception pharmaceutical care to prevent rare diseases wherever possible by dispensing safe medicines and advise healthy life-style and genetic counselling before conception and occasionally refer to the possibility of assisted reproductive technology.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflicting interests

The author declares that he has no competing interests.

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Authors' contributions

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