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Arguments for the introduction of preconception service as the new infrastructure of reproductive health

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ABSTRACT

Objective: To summarize the arguments for the introduction of preconception care based on the experience of the Hungarian Periconception Service (HPS), 1984–2011. **Methods:** This new health infrastructure, as part of primary health care is performed by qualified nurses/midwives after their special training. Couples at risk selected by nurses are referred to specialists to reject or confirm the supposed risks, in addition to treat them if necessary as part of the secondary care. The HPS includes counseling, examinations and medical interventions in three steps: (I) Reproductive health check-up as a preconception screening of reproductive risk factors. (II) The 3-month preparation for conception because the beginning of life is at conception, and the major events of life such as conceptus' sex, health and/or disease are determined at that time, therefore it is necessary to prepare it. (III) Better protection of early pregnancy. In general pregnant women visit prenatal care clinics between the 8th and 12th gestational week though the embryo has passed through his/her most sensitive and vulnerable period, thus it is too late to protect them from congenital abnormalities that occur before the 8th week of pregnancy. **Results:** The most important arguments for the introduction of pre/periconception care/service are the following: (1) The optimal infrastructure for periconception folic acid/multivitamin supplementation. (2) Preconception screening of sexually transmitted infections/disorders in women. (3) Avoidance of smoking and alcohol beverages. (4) Early diagnosis of infertility. (5) More effective participation in genetic counselling. (6) Selection of female participants at high risk. (7) Vaccination. (8) The benefits of early pregnancy diagnosis. (9) The more effective avoidance of teratogenic and other risks. (10) Long-term beneficial effects for children. **Conclusions:** Hungarian experiences show the feasibility and usefulness of pre/periconception care/service in the prevention of preterm births and congenital abnormalities.

1. Introduction

Preconception or prepregnancy care has been advocated as a major opportunity for risk reduction and health promotion in preparation for pregnancy since the 1980s^[1–6]. However, as far as we know the Hungarian Periconception Service (HPS) established in 1984 was the first national network within the primary health care^[7] and here the main arguments for the introduction of this new health infrastructure of reproductive health are summarized based on 28 years of experience in more than 34 thousand couples.

We prefer the term periconception service because in general pregnant women visit prenatal care clinics between the 8th and 12th gestational week. By that time, the embryo has passed through his/her most sensitive and vulnerable period, thus it is too late to protect them from structural birth defects, *i.e.*, congenital abnormalities that occur before the 8th week of pregnancy. This concept explains that the time window of the HPS includes optimally 3 months before conception and 3 months after conception followed by prenatal care.

2. Materials and methods

The HPS is performed by qualified nurses/midwives after

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their special training. The HPS is a free of charge health service with three criteria of participation: (i) no infertility, (ii) not currently pregnant and (iii) voluntary decision. The basic level of the HPS is connected with the selection couples at risk by nurses. These couples are referred to specialists to reject or confirm the supposed risks as the part of second level of the HPS; of course couples with confirmed risks are treated by medical doctors. The HSP includes not only counseling but examinations and medical interventions based on three steps/stages. The details and experiences of the different components of these three steps of the HPS were presented recently^[8], here only these steps and components are shown.

2.1. Reproductive health check-up

This is a preconception screening of reproductive risk factors. (1) Family history of prospective parents; (2) The pregnancy history of females; (3) The optimal time interval to achieve conception after previous pregnancy outcomes; (4) Maternal and paternal age; (5) Maternal health conditions; (6) Preconception screening of sexually transmitted infections/diseases in women; (7) Sperm analysis of males; (8) Psychosexual assessment; (9) Protection against rubella; (10) Vaccination against varicella and influenza.

2.2. The 3-month preparation for conception

The explanation is simple: the beginning of life is at conception, and the major events of life such as conceptus' sex, health and/or disease are determined at that time, therefore it is necessary to prepare it. (1) Discontinuation of oral contraception and the use of intrauterine devices. (2) Protection of germ cells. (3) Avoidance of occupational hazards in prospective mothers. (4) Check-up of sex-hormonal status of females. (5) Start of preconception multivitamin supplementation. (6) Recommendation that dental status is checked. (7) Guidelines of healthy diet. (8) Guidelines of optimal physical exercise.

2.3. The achievement of optimal conception and better protection of early pregnancy

The main aim of this step is to provide a better protection for early embryos. (1) The evaluation of the results of requested medical investigations. (2) The continuation of multivitamin supplementation. (3) The achievement of "optimal" conception. (4) Confirmation of pregnancy. (5) The avoidance of teratogenic and other risks. (6) Important further information for pregnant women. (7) Invitation for the so-called farewell visit on the 10–12th gestational week.

In general there are four meetings between participants and nurses in the HPS. The first meeting involves the reproductive health check-up and the beginning of the 3 month preparation for conception. The second meeting has two parts: the evaluation of the available results of examinations and to prepare for the optimal conception. If more examinations are needed and/or the results of

treatments are not sufficient, there are more (second b, c, etc.) meetings. The aim of the third meeting is the confirmation of pregnancy with the necessary advice regarding the further part of pregnancy. The fourth meeting is the so-called farewell meeting when pregnant women are given their discharge summary of HPS and referred to the prenatal care clinics.

3. Results

3.1. The optimal infrastructure for preconception folic acid/multivitamin supplementation

There was a breakthrough in the primary prevention of neural-tube defects and some other congenital abnormalities by preconception folic acid/multivitamin supplementation in the 1990s. However, the requirement of preconception onset of this supplementation needs a wide education campaign without real success or mandatory flour fortification with folic acid. Our experiences showed that preconception service is the optimal health infrastructure for the effective use of this new primary preventive method of congenital abnormalities.

We performed a randomised double-blind placebo-controlled trial of a micronutrient combination: "multivitamin" containing 0.8 mg of folic acid, 1.6 mg of vitamin B2/riboflavine, 2.6 mg of vitamin B6/pyridoxine and 4.0 microgram of vitamin B12/cobalamin) in the female participants of the HPS to test the hypothesis whether the physiological daily dose of folic acid (less than 1 mg) as a component of a multivitamin can reduce the first occurrence of neural-tube defects if it is started at least one month before conception and continued until the end of third gestational month. This RCT resulted in a significant (about 90%) reduction in the first occurrence of neural-tube defects after the preconception supplementation of women with this multivitamin^[9–11].

However, the unexpected result was a very highly significant reduction of the total congenital abnormality rate from the expected 4.0% to 2.1% due to mainly the significant reduction of cardiovascular malformations and urinary tract defects^[12–14]. These unexpected findings stimulated us to continue this research project, however, the RCT could not be continued due to ethical reasons, therefore a cohort controlled trial (CCT) was performed^[15]. All female participants in the HPS were supplied with the same multivitamin, while control matched pregnant women were selected from the regional antenatal care clinics without multivitamins or folic acid before conception and until the 14th gestational week. These CCT confirmed the reduction of neural-tube defects and cardiovascular malformations. There was no significant reduction in the rate of urinary tract defects, but the differentiation of subgroups showed a significant reduction in obstructive type urinary tract defects. Both the RCT and CCT showed some reduction in cases with congenital limb deficiencies, but these decreases have not reached the level of significance due to the limited

number of subjects. However, these trials indicated that this multivitamin is not appropriate for the reduction of orofacial clefts and syndromic/multiple congenital abnormalities.

In conclusion, we have a good chance to reduce about one-third of major congenital abnormalities with this simple and morally not debated method (*i.e.*, in contrast prenatal diagnosis of fetal defects followed in general by the elective termination of pregnancy)^[16].

3.2. Preconception screening of sexually transmitted infections/disorders in women

The preconception screening for sexually transmitted infections/disorders (STI/D) showed vaginal candidiasis (19.4%), chlamydial (16.6%), trichomonas (15.1%), bacterial vaginosis (11.0%), genital herpes (6.7%), mycoplasma hominis (1.1%) and ureaplasma (1.9%) infections in female participants, gonorrhoea, syphilis and HIV infection did not occur.

Females with the preliminary diagnosis of STI/D based on the above screening procedures were referred to the gynaecologist for final diagnosis and specific treatment (both members of the couple are treated). The rate of preterm birth was 5.0% in the female participants of the HPS while the Hungarian population figure was 9.2% during the study period^[17]. In addition the rate ectopic pregnancies was 0.2% in female participants in the HPS compared to the 1.0% in Hungarian population.

3.3. Avoidance of smoking and alcohol beverages

Prospective smoker mothers were informed of the mechanism of oogenesis, and the high risk of this lifestyle hazard for germ cells and later their fetus, and the available methods of smoking cessation. In addition an educational course was organised for smokers including two group discussions per week under the direction of an expert during the 3 month preparation period. Previously 34% of females smoked, this figure was 17.9% at the first visit in the HPS but it was reduced to 7.9% at the time of conception. The information of females regarding their smoking cessation was checked by the measurement of urine cotinine, and their information was valid in 97% of females^[18]. A similar good result was not achieved in males; but there was a reduction in the rate of smokers as well (from 24.2% at the first visit to 18.0% at the time of conception).

The proportion of hard (one drink or more per day) and regular (more than one drink per week) was 0.2% and 5.4% among female participants. These figures were much higher in male partners. Participants were informed about the hazards of alcohol to their germ cells, particularly oocytes about the time of ovulation and for their fetus. Thus, total abstinence was recommended for females during these time periods. Later these women informed us of the significant reduction in their drinking habit; there were no hard and/or regular drinkers at the time of conception and only 0.8% of females mentioned occasional drinks. However, we could not check their information, but fetal alcohol syndrome/effect did not occur in the babies of female participants.

3.4. Early diagnosis of infertility

One of the main aims of the HPS was the incorporation of male partners into the preparation of childbirth because their participation may help the development of responsible fatherhood and understanding of the importance of family planning (in our terms: to prepare the conception). Thus nurses suggested a voluntary semen analysis in all males after obtained the sperm at home by withdrawal method after 3 days of sexual abstinence and provided for laboratory analysis within 1–3 hours. About 76% of male participants produced sperm for analysis during the study period, and the data on sperm analysis were unexpected. In the mid 1960s the sperm density (million/ml) was 74 millions in Hungary, at the start of the HPS, *i.e.*, in 1984 and 1985, this figure was 57 millions but after 1987 it decreased to fewer than 40 millions and since 1990 the mean value has been 31 millions without further decline. Thus 23% of male participants had less than 20 millions/mL of spermatozoa, and 12% of males were affected with asthenospermia, while 16% of males were screened out with pyosperm (some overlapping with the previous diagnoses)^[19]. Thus about 40% of males were referred to the andrologist for final diagnosis and specific treatment. These findings indicate the robust drop of male fertility^[20].

At the first visit data of female participants, regarding their menstrual history (time of menarche, regularity of their cycles), the previous medical examinations and treatments were obtained. In addition daily oral basal body temperature measurement was suggested for 5 minutes (immediately after awakening in bed, *i.e.*, without previous movement in the morning using mercury thermometer in the closed mouth with the end of thermometer under tongue) during 3 but at least 2 female cycles. The evaluation of these data was possible in 86% of female participants and 4.8% women had anovulation while 7.2% of them were suspected of luteal insufficiency due to short postovulatory phases^[21]. These women and those with previous obvious menstrual irregularities were referred to gynaecologists for further hormonal examinations and treatment.

Thus, most couples with infertility were recognized at the beginning of their participation in the HPS therefore the start of medical treatment was earlier and “the unsuccessful period” to achieve conception was shortened.

3.5. More effective participation in genetic counseling

Practically the so-called “genetic check-up” was based on the evaluation of the pedigree of prospective mothers and fathers including their first degree relatives and maternal second degree relatives. If genetic disorders, congenital abnormalities, disabilities were revealed, these couples were referred to genetic counseling clinic. The obvious cluster of common diseases (cancer, stroke, depression, *etc.*) in the families of prospective parents also needed their referral to genetic counseling clinics. Of course, women with previous unsuccessful pregnancies such as children/fetuses with congenital abnormalities and fetal death (miscarriages), in addition woman over 35 years were also referred to

geneticist. The number of participants referred to genetic counseling clinics increased from 8% in the 1980s to nearly 20% in 2000s.

This preconception selection of participants helped us to find the true candidates for genetic counseling, because a certain part of the clients who visit directly our Genetic Counseling Clinic had no high genetic risk while several couples at high risk visited genetic counseling clinic only after the suggestion of nurses in the HPS[22].

3.6. Selection of female participants at high risk

Some maternal disorders are associated with a higher risk of complications during pregnancy and adverse birth outcomes, thus the evaluation of the case history of prospective mothers is very important. There was a long list of past and present maternal diseases including height and body weight in order to calculate body mass index in the protocol of the HPS, data regarding their onset, severity and related drug treatments were obtained through a personal interview. Unfortunately there was an increasing trend of obesity and overweight within the study period[23]. Nurses in the HPS as good traffic policemen directed prospective mothers with epilepsy, diabetes mellitus, obesity, hypertension, depression, and other major diseases to specialists who could provide special preconception care them that continued with special prenatal care.

3.7. Vaccination

The rubella blood test showed that 10.6% of female participants were seronegative during the 1980s; they were subsequently vaccinated. However, rubella vaccination was introduced for children in 1989, thus this problem is very rare in the years of 2000s. Furthermore vaccination is recommended for all women without previous varicella-disease during the preconception period[24] and influenza vaccine is recommended for participants before expected or during flu season[25].

3.8. The benefits of early pregnancy diagnosis

Prospective mothers were asked to visit us immediately after the first missed menstrual period to confirm their pregnancy by the sensitive beta HCG pregnancy test, The so-called “O” ultrasound scanning (the usual time of the “first” ultrasound scanning is about the 12th gestational week in Hungary) was suggested on the 5–6th gestational week. In general it was possible to diagnose ectopic pregnancies followed by methotrexate treatment, thus later surgical intervention was prevented in most women[26]. In addition multiple pregnancies were diagnosed in 6% of women in this very early pregnancy though the rate of multiple pregnancies at the time of delivery was about 1% in Hungary. The question is whether we have a chance for better survival in these “vanishing or phantom twins” by special prenatal care. However, the major advantage of this O ultrasound scanning was that pregnant women could see her embryo and they were informed that their

next weeks included the critical period of major congenital abnormalities with the most sensitive and vulnerable period of their fetus’ life. Thus they had to do their best to protect their embryos from possible environmental hazards.

3.9. The more effective avoidance of teratogenic and other risks

The recognition of embryos in early pregnancy was a great help to reduce possible risks connected with (i) maternal diseases (epilepsy, diabetes mellitus, thrombophilias, etc.) due to appropriate medical care, by the help of (ii) exemption of pregnant women with occupational hazards, to check (iii) the lifestyle of pregnant women with strong repetitive arguments to avoid smoking, alcohol beverages, or illicit drug uses. (iv) The use of medicinal products needs some discussion, because at present their risks and benefits are unbalanced: the possible teratogenic risk is exaggerated while the benefit of certain drugs is underestimated [27]. Our studies showed that the lack of necessary drug treatments causes more adverse pregnancy outcomes than the rare human teratogenic drugs.. For example the teratogenic risk of high fever related to maternal diseases frequently is not reduced with antifever drugs[28] or the lack of appropriate anti-asthmatic drug treatments in pregnant women affected with asthma is associated with a higher risk of preterm birth[29].

3.10. Long-term beneficial effects for children

The studies of Barker showed the importance of optimal fetal development for the incidence of complex common diseases in the adult age[30]. Thus this expectation is one of the hoped benefits of the HPS, though we have not had the opportunity to verify this outcome. However, the follow-up of children at the beginning of school age born to mothers who participated in the HPS showed better developmental milestones than the reference groups[31,32].

4. Discussion

Hungarian experiences show the feasibility and usefulness of pre/periconception care/service in the direct prevention of adverse pregnancy/birth outcomes. There was a significant reduction in the rate of preterm births and congenital abnormalities, the two major factors of infant mortality and disabilities in the children of participants in the HPS. Periconception service may diminish the recent anxiety of women regarding pregnancy complications and fetal defects due to the feeling that they do their best to use all available methods to achieve their goal: a healthy baby. Thus indirectly this program may increase the number of births. In addition, this new health service may be an optimal starting point for general and specific health promotion, because the proper preparation for conception is the earliest and probably the most important method of health promotion in general, and particularly for the prevention of congenital abnormalities, preterm birth and intrauterine fetal growth

retardation. In the future periconception service may be the institutional basis of modern genetic methods such as predictive gene/DNA tests in prospective parents and preimplantation genetic diagnosis of severe monogenic and chromosomal diseases in their pre-embryos^[33]. On the other hand periconception screening of prospective parents may include the markers of common complex diseases such as coronary artery disease^[34] with an early prevention of these diseases in these families. Thus pre/periconception care/service may be the central infrastructure of genetic oriented prevention of disorders in the medical health system^[35].

Conflict of interest statement

We declare that we have no conflict of interest.

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