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Modern possibilities of prenatal therapy

Współczesne możliwości terapii prenatalnej

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INTRODUCTION

The beginnings of intrauterine treatment date back to the 1960s, when the global scientific environment focused on researching the issue of foetal haemolytic disease. However, the real development of prenatal therapy has been observed since the 1980s, which we owe to ultrasonography, which enabled real-time foetal imaging and intrauterine treatment monitoring. Prenatal treatment is used in a variety of diseases – from anaemia, through diaphragmatic hernia, spina bifida, to heart defects. The current intrauterine therapies can be classified into "needle" treatments, such as foetal

Summary

Many diseases and congenital defects can be detected already during foetal life due to the widespread use of prenatal ultrasonography and the implementation of routine prenatal diagnostics. An increasing number of abnormalities can be treated in utero, at early stages of pregnancy, long before birth. Since prenatal treatment involves some risk of complications that may even result in the loss of pregnancy, it is recommended only in the most severe pathologies. The therapy allows for a complete recovery (for example in foetal haemolytic disease) or, more frequently, is aimed at prolonging survival of the foetus until birth to enable its further postnatal treatment (e.g. diaphragmatic hernia and obstructive uropathies). Prenatal interventions are also increasingly implemented in defects that do not pose a direct threat to the life of the foetus, such as myelomeningocele and most cases of critical aortic stenosis, in order to minimise the consequences of the disease and improve further development of the child.

Streszczenie

Dzięki powszechnemu wykonywaniu u kobiet ciężarnych badań ultrasonograficznych i prowadzeniu systematycznej diagnostyki prenatalnej, możliwe jest obecnie wykrywanie wielu chorób i wad wrodzonych na etapie życia płodowego. Coraz więcej nieprawidłowości może być leczonych już w okresie ciąży, na coraz wcześniejszym jej etapie, często na długo przed urodzeniem dziecka. Ponieważ leczenie prenatalne jest obarczone ryzykiem powikłań, które w rezultacie mogą prowadzić nawet do utraty ciąży, dlatego rekomendowane jest jedynie w przypadku najcięższych patologii. Umożliwia ono całkowite wyleczenie, jak w przypadku choroby hemolitycznej, lub, częściej, przeżycie chorego dziecka do okresu porodu i dalsze jego leczenie po porodzie, jak to ma miejsce w przypadkach przepukliny przeponowej czy uropatii zaporowych. Coraz częściej leczenie wewnątrzmaciczne podejmuje się również w wadach, które nie stanowią bezpośredniego zagrożenia życia dziecka, takich jak przepuklina oponowo-rdzeniowa czy większość przypadków stenozy aortalnej, a głównym jego celem jest zmniejszenie konsekwencji choroby i poprawienie rozwoju dziecka w późniejszym okresie życia.

transfusions, paracentesis, inserting shunt catheters, foetoscopy and open uterus surgeries. The last achievement in prenatal therapy are foetal cardiac interventions. This paper presents the selected types of pathologies observed at a prenatal stage as well as prenatal treatment strategies.

FOETAL HAEMOLYTIC DISEASE

Rh incompatibility

Red blood cell incompatibility still remains one of the main causes of foetal anaemia despite widespread prophylaxis with anti-Rh immunoglobulin. Prenatal therapy

in foetal haemolytic disease involves repeated foetal RBC transfusions. The treatment is very effective and has remained relatively unchanged throughout the last decades. Although foetal transfusion belongs to routine procedures in fetal therapy centers, the therapy still requires much experience and precision (1). In recent years, much concern has been given to the fact that foetal transfusions should use maternal red blood cell preparations, if only possible, as mothers are safe RBC donors for their foetuses. Currently, we observe a huge breakthrough in the management of foetal haemolytic disease, which is possible due to the advances in both laboratory and ultrasonography diagnostics. At present, foetal anaemia, regardless of its cause, can be detected by Doppler assessment of peak systolic velocity in the middle cerebral artery (MCA PSV). This method, based on the use of hyperdynamic circulation in foetuses with anaemia, is characterised by almost 100% sensitivity in detecting at least moderate to severe anaemia (2). Its implementation at the beginning of the year 2000 considerably reduced the frequency of invasive diagnostic procedures (umbilical puncture-cordocentesis) aimed at the assessment of foetal blood count, and thus reduced the incidence of complications and intensification of immunisation in a pregnant woman (3). Similarly, a non-invasive determination of the foetal blood group is possible based on the assessment of foetal DNA (cfDNA) in the mother's bloodstream. It is particularly useful in immunised women with antibodies from previous pregnancies. Blood type assay for some of the most common antigens causing foetal haemolytic disease (in Poland the assayed genes are RhD, c E, K; the tests are performed at the Institute of Haematology and Transfusion Medicine in Warsaw) allows for determining the risk for the foetuses in subsequent (current) pregnancies. This test is characterised by very high sensitivity and specificity. In the case of results indicating the absence of risk for the foetus (if the foetus lacks the antigen against which the antibodies are directed), further monitoring of the patient can be discontinued.

Foeto-neonatal alloimmune thrombocytopenia (FNAIT)

Foeto-neonatal alloimmune thrombocytopenia, which is associated with the presence of maternal antibodies against foetal platelets, is the most common cause of deep thrombocytopenia in foetuses and infants. Deep thrombocytopenia (platelet count below 50,000/mm³) is dangerous for foetuses since it may cause spontaneous bleedings. Intracranial haemorrhages (ICH), which may lead to the infant's death or neurological complications of varying severity, are one of the most severe complications of foeto-neonatal alloimmune thrombocytopenia. Prenatal diagnosis of foetal thrombocytopenia is difficult as the disease shows no symptoms in ultrasonography. Unfortunately, the platelet antibody titres seem not be as helpful in assessing the severity of the dis-

ease as in RBC incompatibility. In some cases, in order to confirm or exclude foetal thrombocytopenia, diagnostic umbilical vessel puncture with complete blood count is performed. Foeto-neonatal alloimmune thrombocytopenia (FNAIT) still is unlike the Rh-Disease, a not fully known and underdiagnosed disease. Its diagnosis is usually based on the analysis of complications that occurred in already born infants and the ex post search for thrombocytopenia. The implementation of Polish screening program (PREVFNAIT) (4) targeted at the most common cause of FNAIT – presence of anti-HPA-1a antibodies, has allowed to diagnose pregnant women who are at risk of foetal thrombocytopenia before the symptoms occur in the fetus or newborn. This allows for implementing a therapy, whose principles usually differ between different centres, but which is currently considered the primary non-invasive therapy. So far, no uniform management strategy for the disease has been developed. However, contrary to RBC incompatibility, where the main therapeutic management involves RBC transfusion, foetal platelet transfusions in foeto-neonatal alloimmune thrombocytopenia (FNAIT) are sporadic. The therapy is based on regular, usually weekly, administration of human immunoglobulin infusions (IVIg) in a pregnant woman, combined with steroids in some cases (5).

MULTIPLE GESTATION COMPLICATIONS

The common placenta in monozygotic pregnancy can involve typical complications, like twin-to-twin transfusion syndrome (TTTS) and twin reversed arterial perfusion (TRAP), which often require prenatal treatment.

Twin-to-twin transfusion syndrome (TTTS)

Monozygotic placenta contains, under physiological conditions, balanced vessel connections (anastomoses) which bind circulatory systems of both foetuses. Transfusion syndrome, which involves disproportionate blood flow between foetuses, occurs in approximately 15% of monozygotic diamniotic pregnancies. It involves a disproportionate blood flow from one foetus (donor) to the other (recipient) through abnormal, mostly arteriovenous, connections in the placenta. As a result, anaemia, hypovolaemia and oligohydramnios/anhydramnion develop in the donor foetus who ceases to grow and becomes hypotrophic. The recipient foetus, in turn, develops hypervolaemia, polycythaemia, polyhydramnios and is usually much larger than the donor. Both foetuses are at risk of severe complications, including intrauterine death (mostly the donor), heart failure (the recipient), preterm delivery and other. The therapy of the twin-to-twin transfusion syndrome has evolved from purely symptomatic methods – drainage of polyhydramnios in the recipient foetus (serial amnioreduction), septostomy (creating an artificial connection between amniotic sacs of the twins), foetal transfusions into the donor foetus – to causal

treatment which currently involves foetoscopic laser ablation of vascular connections (6). Initially, vascular ablation was performed in a non-selective manner, coagulating all visible vessels connecting two placental poles along the amniotic septum. Nowadays, selective ablation of abnormal connections, which seem to be responsible for the complications, is preferred (7). Many studies have demonstrated the advantage of laser vascular ablation over other therapeutic methods in TTTS. Laser therapy, in comparison to amnioreduction, considerably reduces the number of distant complications in foetuses and infants, and it particularly improves their neurological condition. The main effect of amnioreduction, though, is to lengthen the duration of pregnancy in the absence of therapeutic effects on the increasing foetal hemodynamic disorders.

Twin reversed arterial perfusion (TRAP)

In the TRAP syndrome, one of the foetuses ceases to grow at a very early stage. Often, only the lower part of the body develops, while the heart does not in most cases. This is caused by the presence of arterial anastomosis (usually at the level of umbilical arteries), through which deoxygenated blood flows from very early stages of gestation from one foetus to the other, thus disturbing the development of the circulatory system. The affected foetus, referred to as the acardiac twin, is completely dependent on the circulation of the healthy foetus (pumping twin), and often comprises a considerable burden to the circulatory system of the latter. In extreme cases, when the size of the acardiac twin is large, heart failure and oedema occur in the pumping twin. Such a condition is a direct threat to its life and if this situation occurs before it is possible to safely deliver the pumping twin, then it is an indication for closing the umbilical cord of the acardiac twin. The procedure is usually performed by means of foetoscopic laser coagulation of the umbilical cord. This allows for further continuation of the pregnancy and the development of a healthy foetus.

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Congenital diaphragmatic hernia is a defect consisting in the presence of an opening in the diaphragm, through which organs of the abdominal cavity enter the thoracic cavity. It is one of the most severe congenital defects diagnosed in utero and is characterised by high postnatal mortality. Pulmonary hypoplasia and pulmonary hypertension, which lead to postnatal respiratory insufficiency and heart failure, are the main concern in foetuses with diaphragmatic hernia. These disorders persist despite drainage of the content of the hernia sac into the abdominal cavity. There are many prognostic factors for prenatal assessment, based on which the course of the infant's disease can be predicted. LHR (Lung to Head Ratio), which is calculated based on the measurement of the ratio of the lung area on the opposite side of the dia-

phragm to the foetal head circumference, is one of these factors. LHR is most commonly used in clinical practice. Since prenatal development of the lungs is much faster compared to that of the head, it was proposed that the LHR should be adjusted for the gestational age – O/E LHR (observed [O]/expected [E] LHR). The prognosis for the infant depends on the O/E LHR value: it is very poor for O/E LHR < 15 percent, severe at 15-25%, moderate at 26-35%, and relatively good for O/E LHR at 36-45%.

Diaphragmatic hernia can be treated before birth in order to improve the conditions for lung development. First attempts of prenatal treatment of diaphragmatic hernia consisted in surgical closure of the opening in the diaphragm in an open uterus, with the opening of the foetal abdominal cavity. Due to multiple complications, the surgeries were abandoned in favour of less invasive techniques. The current concept of prenatal CDH treatment originates in the natural pulmonary production of physiological secretion whose dynamics (excessive accumulation in cases of tracheal atresia or an increased discharge in oligohydramnios) has a significant impact on the development of lungs. In foetuses with a defect consisting in congenital obliteration of the upper respiratory tract, an increased accumulation of the fluid in the respiratory tract occurs, leading to the stimulation of growth and an increase in the volume of the lung tissue. This observation gave rise to therapeutic procedures that involve closing the foetal trachea using a balloon, which prevents fluid secretion and induces its accumulation under increased pressure in the lungs (8). This procedure is performed in foetuses with the most severe CDH, with the use of a thin foetoscope and a balloon with a diameter of several millimetres. So far, no final results of randomised studies that would confirm the effectiveness of such treatment have been obtained. However, the initial research outcomes are quite promising. There is an ongoing randomised multicenter trial (Eurofetus) that will allow for a clear evaluation of the therapeutic efficacy. The study (Fetal Endotracheal Occlusion – FETO) involves balloon insertion in two groups of patients – in cases of severe hernia between 26 and 28 weeks gestation, and between 30 and 32 weeks in moderate cases. The present results of the research indicate that the treatment improves the prognosis in prenatally treated infants – the average survival increases by 30-35% in comparison with infants receiving postnatal treatment. Due to the observed difficulties removing the balloon after the delivery, the balloon is currently removed prenatally after 34 weeks of gestation (9).

MYELOMENINGOCELE (MMC)

Myelomeningocele is one of the most common defects of the central nervous system. It involves the presence of the spina bifida and usually an opening in the skin, resulting in an exposure of both the spinal cord and meninges to the amniotic fluid. Until

the invention of a ventriculoperitoneal shunt in the 1950s, this defect was associated with high mortality due to hydrocephalus and neurological complications. Currently, the defect is not life-threatening, but it may cause chronic disability. It is believed that the spinal cord damage occurs already in the foetal life, according to the “two-hit” hypothesis – through the impact of the amniotic fluid on the spinal cord and mechanical trauma. First attempts of prenatal treatment, consisting in covering the hernia in order to prevent the leakage of the cerebrospinal fluid, were made in the 1990s. Prenatal surgery aims to prevent the development of hydrocephalus and the translocation of the rhombencephalon structures towards the spinal canal (Chiari II malformation) (10). A randomised trial was conducted in the USA between 2003 and 2010 to assess the justification of open uterine surgeries aimed at the closure of the spine. In the MoMs study (The Management of Myelomeningocele Study), one group of foetuses underwent intrauterine surgery between 18 and 25 weeks of pregnancy, while the other group received standard postnatal treatment. The study was discontinued as it was found that infants receiving intrauterine treatment showed better mental and motor development than those treated after birth. Also, the need for ventriculoperitoneal shunts was lower in the first group of patients (44 vs. 84%, respectively). The benefits of prenatal treatment were evident, despite complications associated with an open uterus surgery (prematurity and obstetric complications) (11). The meningocele repair is also performed in a foetoscopic mode, by covering the ports of the hernia with various types of materials. The outcomes of such a treatment are encouraging, though they seem to be beneficial only in the most experienced centres.

OBSTRUCTIVE UROPATHY

Bladder outlet obstruction, which may be due to the presence of posterior urethral valve in male foetuses (most common) or severe urethral stenosis/atresia, is one of the most common causes of prenatal obstructive uropathies (fig. 1). Regardless of the cause, if the urine does not exit from the kidneys and the bladder, the prognosis is poor due to irreversible kidney damage leading to oligohydramnios and lung hypoplasia at the prenatal stage. Most infants with obstructive kidney dysplasia secondary to urethral occlusion die immediately after birth due to respiratory failure. These infants fail to reach paediatric urologists, contributing to the so-called “hidden mortality” in this disease. Attempts to treat obstructive foetal uropathies were undertaken already in the 1980s. However, the effectiveness and justification of this therapy is still the subject of debates and experiments. Prenatal treatment may be considered in selected cases of obstructive uropathies, when it can be assumed, based on conducted tests (assessment of the karyotype, precise ultrasonography and echocardiography) that it is an isolated defect,

and the kidney function is still preserved (12). Criteria based on foetal urinalysis (serial bladder punctures) were developed for the prenatal assessment of kidney function. The following parameters were considered as qualifying for prenatal treatment: Na < 100 mmol/L, Cl < 90 mmol/L, osmolality < 210 mOsm/L and beta-2 macroglobulin level < 6 mg/L (13).



Fig. 1. Foetus with bladder outlet obstruction at 13 weeks gestation

Standard prenatal treatment in bladder outlet obstruction involves the insertion of shunts into the bladder. One end of the shunt is placed in the bladder, the other – in the amniotic cavity (fig. 2). This ensures urinary tract drainage and a simultaneous maintenance of normal amniotic volume. The causal diagnosis and the treatment of uropathy are performed only after the child’s birth. Vesicostomy is usually performed after delivery and removed after the elimination of the urine flow obstruction. The impossible detailed prenatal diagnosis of the cause of urethral obstruction is a disadvantage of this method. In the worst scenario, this may have consequences in the form of the lack of possibility to achieve physiological urination later in life. Bladder dysfunction that can generate high pressures and cause ureteral and renal refluxes, which induce secondary renal damages, is another problem. The third one is related to the potential coexistence of previously undiagnosed abnormalities (e.g. anal atresia). Therefore, prenatal treatment of obstructive uropathy is a very complex problem. Although it was demonstrated that inserting shunts into the bladder prevents pulmonary hypoplasia in an infant, no randomised study that would confirm that such treatment prevents renal insufficiency has been conducted so far. Unfortunately, most of infants treated with this method develop renal insufficiency of varying degree after their birth (14). The search for the method of causative treatment is aided by attempts of prenatal urethral dilation. Laser destruction of the urethral valves following foetoscopic visualisation is a relatively new method. Although this technique seems to be a very interesting therapeutic option, the first papers assessing its efficacy and safe-



Fig. 2. The same foetus with a visible shunt implanted into the bladder. The free end of the shunt in front of the foetal abdomen can be seen

ty have shown that the method involves a significant risk of foetal complications (relatively high mortality, formation of urethrocutaneous and rectourethral fistulas) (15).

CARDIOLOGIC INTERVENTIONS

The development of ultrasonography and the popularisation of foetal echocardiography, have allowed to track the dynamics of many heart pathologies at the prenatal stage. It was found that the image of most heart defects, such as the transposition of great arteries, defects in the septum or Fallot's syndrome, do not change significantly during foetal life. However, there are also prenatally dynamic defects with significant and rapid progression. Such defects include valvular stenosis of large vessels carrying the blood from the heart – aortic or pulmonary stenosis. By obstructing the blood outflow and generating high ventricular pressure, they may lead to a permanent damage of the right or the left ventricle, with the formation of a single-ventricle heart. The first foetal cardiac interventions, involving the dilation of the stenotic aortic valve with the use of a balloon, were undertaken in the 1990s. Still, most of them failed to bring the expected results. These attempts were abandoned several years later due to a simultaneous and rapid development of cardiac surgery, enabling survival of infants with a single-ventricle heart. The outcomes of cardiosurgical treatment, whose beginnings date back to the 1980s, improved significantly and increased the chance of survival in children with very severe defects, such as hypoplastic left heart

syndrome. This was enabled by multistage cardiac surgeries, adjusting the whole circulatory system to an abnormal anatomy. However, taking into account the risk of post-operative complications and the quality of life of children with only one heart ventricle, currently prenatal treatment attempts are more common. Prenatal therapy is aimed at preventing and minimising foetal heart damage as well as ensuring the highest possible quality of life in the future.

The dilation of aortic or pulmonary valve in the foetus is performed by puncturing the uterus of the pregnant woman and the chest of the foetus. The needle is inserted directly into the heart, and an adequate device is implanted. These are balloon catheters used in invasive cardiology in adult patients for dilating coronary vessels (fig. 3). The procedures are usually performed between 20 and 30 weeks of pregnancy, depending on the clinical situation – in practice, at the time of defect detection. A long-term effect of the treatment in the form of a two-ventricle heart can be achieved in approximately 30-50% of cases. Factors that adversely influence the prognosis after aortic or pulmonary valvuloplasty most likely include an overdue procedure and highly advanced changes in the ventricle (16). Prenatal treatments are not performed in the case of mild aortic or pulmonary stenosis, which do not involve the risk of ventricular loss or circulatory insufficiency and may be treated after delivery.



Fig. 3. Aortic valvuloplasty in a foetus – visible guide catheter passed through the aortic valve

Occlusion or considerable restriction of the foramen ovale is another type of pathology that can be treated prenatally. It can be found in fetuses with a critical aortic stenosis or hypoplastic left heart syndrome. This is a life-threatening condition as in the case of prevented blood outflow from the left ventricle into the aorta, the closure of the interatrial junction prevents blood outflow from the lungs and leads to the development of pulmonary hypertension. As long as the foetus is connected to the mother's body, the

presence of the placenta allows its survival, although the pulmonary hypertension causes irreversible damage of pulmonary vessels. Infants who develop this complication in the prenatal period, usually die soon after birth. In such cases, the only chance to improve the prognosis is to implant a stent (fig. 4) into the interatrial septum to allow for the blood outflow from the pulmonary veins, from the left into the right atrium and then through Botalli's duct into the descending aorta.

Cardiac procedures in foetuses constitute a new field of prenatal therapy. Although they are performed in an increasing number of centres, their global number is relatively small. At present, centres in Boston, Linz and Warsaw (2nd Clinic of Obstetrics and Gynecology at the Centre of Postgraduate Medical Education in Warsaw, the team performing foetal cardiologic surgeries, which includes Marzena Dębska and cardiologists – Professor Joanna Dangel and Adam Koleśnik, MD) boast the greatest experience in interventional foetal therapies in cardiovascular pathologies (17-19).



Fig. 4. Foetal heart with a critical aortic stenosis and the occlusion of the foramen ovale. Status after stent implantation into the interatrial septum

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