In utero surgery – current state of the art – part II

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Summary

Background: Fetal surgery, also referred to as in utero, prenatal or intrauterine surgery, consists of treatment of congenital malformations during the fetal period. The idea of treating malformations diagnosed in the course of intrauterine life dates back to 1963, when Lilly performed the first blood transfusion in a fetus. Since then it has been introduced as a treatment option in a series of lethal malformations. Efforts are being made to treat nonlethal malformations by means of fetal surgery.

Material/Methods: A comprehensive search of the literature using MEDLINE and PubMed between 1925 and February 2009 was performed. Search terms for MEDLINE and PubMed were: fetal surgery, foetal surgery, in utero surgery, prenatal surgery, and in utero treatment. In addition, information was obtained at Web sites of the International Medicine and Surgery Society and the University of California Fetal Treatment Centre.

Results: Authors' attention focused on the survey of indications to intrauterine operations. We outline potential directions of its development, quoting the groundwork of the most experienced researchers and clinicians. Moreover, owing to the authors' interest in plastic surgery, some remarks on the role of intrauterine medicine and surgery in this branch of medicine are made.

Conclusions: In utero surgery may be regarded as an efficient tool of preventive medicine. It offers some advantages that no other branch of medicine may offer. However, its implementation is more troublesome than in the past, therefore only selected cases may benefit from its advantages. Nevertheless, current tendencies are to include, after thorough evaluation of benefit-risk ratio, some new indications for fetal surgery.

key words: fetus • fetal surgery • congenital malformations • wound healing • prenatal diagnosis • risk

Abbreviations: **ABS** – Amniotic Band Syndrome; **CCAM** – Congenital Cystic Adenomatoid Malformation; **CDH** – Congenital Diaphragmatic Hernia; **CHAOS** – Congenital High Airway Obstruction Syndrome; **CLP** – Cleft Lip and Palate; **EXIT procedure** – Ex utero Intrapartum Treatment; **FETENDO** – fetoscopic techniques; **FIGS-IT** – Fetal Image – Guided Surgery; **IFMSS** – International Fetal Medicine and Surgery Society; **MMC** – myelomeningocele; **MOMS** – Management of Myelomeningocele Study; **NaCl** – sodium chloride; **NIH** – National Institute of Health; **OOPS** – Operation On Placental Support; **PPROM** – Preterm Premature Rupture of the Membranes; **RF** – Radiofrequency; **SCT** – Sacrococcygeal Teratoma; **TRAP** – Twin Reversed Arterial Perfusion syndrome; **UCSF** – University of California in San Francisco

IMPLEMENTATION OF INTRAUTERINE MEDICINE IN OBSTRUCTIVE UROPATHY

Obstructive uropathy occurs with frequency of 1 in 1000 live births [1]. In the course of the disease it leads to renal dysplasia, oligohydramnios and lung hypoplasia. Morbidity related to the last 2 symptoms is high, with rates up to 63% [2]. The majority of cases (up to 90%) do not require intrauterine intervention. Indication to in utero operations is diagnosed bilateral hydronephrosis connected with oligohydramnios [3]. Before performing the procedure it is necessary to define the fetus karyotype, conduct detailed ultrasound diagnosis and perform a urine examination in order to identify the level of fetal renal damage [4]. In case of lung immaturity, the urinary bladder can be decompressed with 1 of the following methods: transcutaneous application of vesical catheter under ultrasound supervision [3], vesicostomy via open method [4], or use of catheter reinforced with metal mesh [5]. Experience gained in treatment of the disorders mentioned above in several hundred fetuses has allowed for precise establishment of indications and contra-indications to the procedure, contributing to avoidance of unnecessary operations and reduction of complications to a minimum [3]. However, there are disagreements whether early decompression of the urinary system in utero facilitates inversion of degenerative changes on the renal level and restoration of normal dynamics of the urinary bladder [2–4].

CHAOS – CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME

Congenital High Airway Obstruction Syndrome (CHAOS) is either connected with tracheal atresia (the most frequent cause) [2] or with compression of the trachea by a neck tumor. Regardless of the nature of the disease, it leads to disturbance of amniotic fluid circulation and development of fetal hydrops. In mild cases the anomaly can be corrected surgically in the course of birth with application of the previously described EXIT procedure. In case of a greater degree of the disease (hydrops), correction can be conducted with the use of less invasive methods or the birth can be accelerated [2,4].

CONGENITAL CYSTIC ADENOMATOID MALFORMATION

Congenital Cystic Adenomatoid Malformation (CCAM) is a developmental anomaly consisting of bronchioli maturation disorder coexisting with hypertrophy of mesenchymal elements [2]. The majority of CCAM cases present a benign course and are revealed in the neonatal period or in early childhood. In some cases (up to 10%) [5], intensive changes result in lung hypoplasia, fetal hydrops and fetal death [2]. If the fetus is endangered, intrauterine lobectomy from open access can be a life-saving procedure. In the years 1990–1993 Harrison et al. operated on 9 such cases. Five of them responded to treatment favorably – pulmonary edema reduced, lungs began to decompress, and children were properly developing in the neonatal and infant period. In 2 cases presenting 1 dominant cyst, it was sufficient to use a decompressing pleuro-amniotic shunt (Harrison catheter) [2,6,7]. At present, CCAM is the most frequent indication for in utero surgery [8].

CONGENITAL DIAPHRAGMATIC HERNIA

The incidence of Congenital Diaphragmatic Hernia (CDH) is approximately 1 in 2200 live births and is burdened with high mortality, amounting to 80% [9]. The major pathology associated with this malformation is lung hypoplasia triggered by oppression of the hernia sac contents. Unfavorable prognosis refers to cases with translocation of the liver into the thorax [8]. Treatment can be either conservative or surgical. The former comprises application of precursors of nitric oxide, extracorporeal membrane oxygenation, and high frequency mechanical ventilation [8]. First treatment attempts were based on restoration of normal anatomical relations – translocation of shifted organs from the thorax into the abdominal cavity and closure of the foramen in the diaphragm [8]. However, their results were not satisfactory since the prognosis did not prove to be considerably different from the prognosis in the group of patients treated with conservative measures [8]. Further efforts were focused on triggering development of hypoplastic lung with the aid of temporary trachea occlusion. Tracheal defect was taken care of following the childbirth [10]. Initially, tracheal occlusion was achieved by endoscopic application of titanium clips onto the fetal trachea [11]. Implementation of this method in clinical practice was possible due to elaboration of the EXIT procedure (Ex Utero Intrapartum Treatment). This procedure uses clips removal in the course of childbirth while the baby is still fed through placental vessels [12]. To eliminate threats connected with endoscopic neck preparation (bilateral damage of recurrent laryngeal nerves), another method of respiratory tract obturation was advocated. It consisted in introduction of an expandible balloon directly into the trachea to close its lumen [13]. Biard et al. conducted experiments on sheep, in which 1 bronchus was selectively closed on the side where the diaphragmatic hernia appeared. Nevertheless, experimental results do not confirm the efficacy of the method mentioned above in restoration of the lungs' normal expanding potential [14].

Cases of CDH with liver lobe translocation into the thorax are connected with unfavorable prognosis following the intrauterine procedure. It is the result of umbilical vessels bending, caused by the liver re-translocation into the unextended abdominal cavity [3]. In these cases it is recommended to employ methods of temporary tracheal occlusion due to the less violent return of the liver into the abdominal cavity, providing time for the abdominal cavity wall to adapt to new conditions [8]. On the other hand, research results comparing the prognosis after in utero surgery in less complex cases with the prognosis following conservative treatment do not provide unequivocal evidence for the superiority of any of the above-cited methods [3,8]. Preliminary results indicate that correction of CDH in the course of fetal life does not improve the prognosis. The percentage of premature births is higher in the group subject to in utero procedure than in the control group treated with the conservative approach [15].

Salguero et al. comprehensively searched the literature for all methods of CDH treatment according to Evidence-Based Medicine principles. They concluded that there exists no evidence supporting the advantage of in utero surgery over other methods of treatment, including surgery in the neonatal period as well as the conservative approach [16].

TWIN-TO-TWIN TRANSFUSION SYNDROME

Twin-to-twin transfusion syndrome is the most frequent anomaly occurring in twin single-amniotic pregnancy; it is diagnosed in 10–20% of cases [17]. Its prevalence is conditioned by the existence of pathological connections of both fetuses' vessels on the level of placental circulation. Leak within their margins leads to underdevelopment of 1 of the twins (the "donor"), oligohydramnios and heart-failure of the other twin (the "recipient"). Diagnosis of disordered blood circulation, generalized fetal edema and deterioration of its general condition are indications to surgical intervention. Highly invasive methods involve multiple decompressing amniocenteses and application of a membrane separating both amniotic cavities. Minimally invasive methods include rupture of abnormal vessel connections within placenta – mainly with the use of laser rays [4,8]. Some authors recommend non-selective photocoagulation while others suggest a selective one [4]. Research outcomes comparing treatment results of serial amniocentesis and laser ablation of abnormal vessel connections emphasize the high efficacy of the laser therapy [18].

CARDIAC DEFECTS

The majority of fetuses with complete heart block survive without the necessity of surgical intervention. An in utero procedure can be considered in cases of significant bradycardia (<50 beats per minute) due to the threat of generalized fetal edema and subsequent heart failure. The course of action in such cases rests on cardiac pacemaker implantation by means of open or transcutaneous technique [3]. Assad et al. described experimental research conducted on animals (lambs), in which transcutaneous ablation of the atrioventricular node with liquid nitrogen followed by consecutive implantation of a cardiac pacemaker was performed due to difficult-to-abstain tachyarrhythmia [19]. In case of aorta and pulmonary artery stenosis, in utero operating techniques were invented on animal models with the use of less invasive methods [4], among others, the previously described fetal surgery supervised with ultrasonographic examination. The strategy seems to be particularly justified in reference to aortic valve stenosis occasionally leading to so-called hypoplasia of the left heart. It widens the heart aortic ostium with the aid of expandible balloons [15].

Bruch et al. elaborated their own experiences in surgical treatment of fetal pericardial teratomas using a procedure consisting of pericardiocentesis performed in order to reduce compression on the right atrium. Following the procedure, the fetus developed normally. The tumor was removed on the second day of life [20].

SACROCOCCYGEAL TERATOMA

In case of Sacrococcygeal Teratoma (SCT), unfavorable prognosis, similar to that of CCAM, is connected with development of generalized fetal edema. In this case it is caused by heart failure with high output volume, which is the direct cause of vascular leakage within the dynamically growing tumor [9]. Incidence of this anomaly is estimated at 1 in 35 000 live births [21]. In order to prevent fetal heart failure and improve SCT prognosis, open (resection of fetal tumor) or minimally invasive methods (thermo-coagulation or

ablation with the aid of radiofrequency waves of vessels supporting the tumor) are performed [22–24]. In the majority of cases it is sufficient to monitor the progress of the disease with regular ultrasound examination. Rapid tumor growth is connected with increased risk of fetal mortality [25].

MYELOMENINGOCELE

Myelomeningocele (MMC) was the first non-lethal fetal disease in which in utero surgery was used. Incidence of this malformation is estimated at 4.6 cases in 10 000 live births [8]. Spinal cord exposure to the unfavorable influence of amniotic fluid in the course of fetal life has a significant impact on child's further development, including paraplegia, hydrocephalus, neurogenic bladder, disturbances of sexual functions, deformations of skeletal system, and mental retardation. The worst prognosis is associated with occurrence of Arnold-Chiari malformation [26]. It was proven on an animal model that the degree of spinal cord destruction is proportional to the time of exposure to unfavorable conditions [27]. It was demonstrated that closure of the defect during fetal life can prevent both structural and functional damage of the spinal cord [28,29]. Meuli et al, on the basis of animal research, suggested a technique employing latissimus dorsi flap. Outcomes were evaluated as promising since in 3 cases out of 7 they managed to heal the flap above the defect and to preserve normal function of rear limbs [30]. Hasan et al, on the basis of research performed on chick embryos, discovered that complete regeneration of injured spinal cord is achievable. The degree of regeneration depends on the period of pregnancy in which the injury occurred. As soon as the defect was taken care of, in the animals that had the spinal cord resected in early fetal life, complete restoration of anatomical continuity and resumption of spinal function were observed [31].

Adzick found that fetal surgery in treatment of MMC is justified in selected cases. He confirms the opinion that it improves the prognosis and diminishes the risk of Arnold-Chiari malformation [32]. Serial fetal magnetic resonance imaging following MMC in utero showed decreased intensification of hindbrain herniation [33]. Research conducted by Danzer et al. in 2009 [34] found favorable surgical outcomes in 93% of 54 children subject to in utero surgery.

World-wide, by the end of 2008, 330 intrauterine corrective procedures of MMC had been performed [16]. Myelomeningocele was treated both with open methods as well as with minimally invasive techniques. Open methods are advocated as the standard approach in operating of presented this disorder in utero [8]. In the USA a prospective and multi-centered comparative study of MMC treatment results obtained with application in utero surgery and corrective procedures performed following the birth is being conducted [35]. Simultaneously, research to determine the period of pregnancy in which amniotic fluid has the most toxic impact on the spinal cord in the course of MMC has been launched.

In the USA, intrauterine reconstructive procedures in MMC are performed exclusively in 3 centers – the objective of this approach is to restrict unsupervised procedures in units lacking sufficient experience [16]. Based on clinical experience, Fichter et al. preliminarily recapitulated treatment

results. They reported reduction of Chiari malformation incidence and hydrocephalus, as well as decrease in frequency of ventricular-peritoneal valve application. Data concerning improvement of other disorders appearing in the course of MMC (urinary incontinence, motor-sensory disturbances of lower extremities) do not allow for clear conclusions. The thesis was advanced that performance of intrauterine procedures might carry lower risk of formation of postoperative adhesions resulting in so-called Symptomatic Tethered Cord; however, preliminary outcomes of clinical research do not support the theory. In the authors' opinion, particularly good results can be achieved in operations in utero of MMC cases fulfilling the following criteria:

- Fetus age below 26 Hbd
- Lateral chambers with vertical dimension under 14 mm
- Malformation location beneath the level of L2 [16].

In Poland, in utero operations in cases of MMC are performed as well. The first successful operation was performed by the Stoba team in Gdansk [36], and subsequent operations were performed in Bytom [37]. Zamłyński et al. summarized their experiences in treatment of myelomeningocele in utero [37], describing 10 cases treated with the open method. Procedures were performed between 22 and 27 weeks of pregnancy. Technique of open surgery was applied. The authors did not report serious complications or any cases of maternal, fetal or neonatal death. Due to the short period of observation no final conclusions have been put forth. The authors reinforce the significance of previously described prospective clinical research of MOMS conducted in the USA.

AMNIOTIC BAND SYNDROME

Amniotic Band Syndrome (ABS) has incidence ranging from 1 in 1200 to 1 in 15 000 live births. It is manifested by stenosis or rupture of continuity of a particular body structure. Intensification of deformity within the most frequent location of malformation – the limbs – comprises dermal stenosis, deep creases or even complete amputation of phalanx, finger or the whole limb [2].

The trial to discover the etiology of ABS was undertaken by Torpin [2]. In his opinion, partial rupture of amnion creates fibrous bands extending in the shape of strings in the amniotic cavity, which may cause mechanical injury of the fetal body. Amniotic band syndrome is regarded as another non-lethal dysmorphic syndrome in which potential benefits of in utero surgery are obvious to prove. In 1995 Crombleholme conducted the first experiments on animals [38]. Two years later Quintero performed surgery on the fetus [39], consisting of crosscutting amniotic bands tightened around the limbs, thus preventing spontaneous amputation.

Keswani et al. used a laser beam to release amniotic bands in 2 cases [40]. According to the latest data, 7 fetoscopic intrauterine procedures in amniotic band syndrome have been performed so far [41]. It is assumed that proving blood circulation in distal section to amniotic stenosis via Doppler examination is an indication to perform an in utero procedure.

PLASTIC SURGERY

The actual benefit of fetal surgery is a distinct – nearly scarless – mechanism of wound healing [42,43]. This is particularly significant in case of primary treatment of congenital malformations in the head area, especially the face, where the treatment result depends on proper reconstruction of functions, as well as on aesthetic considerations [44].

Wounds in children and adults heal with scar formation built from connective tissue with irregularly arranged thick collagen fibers. Scars within skin are deprived of appendages and are characterized by lower flexibility. Postoperative adhesions in the abdominal cavity may trigger obstruction; anastomosis within vessels, intestines, trachea and ureters may cause formation of annular narrowing [43].

The aftermath of tissue cicatrization is most clearly noticeable within body integuments. It may lead to contractures of joints, while extensive plane scars repeatedly result in inhibition of child growth [43].

Since Rowlatt et al. in 1979 reported the existence of mechanisms facilitating scarless healing of wounds in a fetus, the frame of experimental and clinical research on in utero procedures was gradually broadened with non-lethal wounds that also are of interest in plastic surgery. In the early stages of fetal life, wounds are repaired by regeneration, with reconstruction of normal architecture of histological skin with formation of appendages [45]. This process was defined as scarless wound healing. Its existence was demonstrated in animal models (rabbit, rat, mouse, sheep, monkey) by various authors [46]. The outcomes of subsequent studies [47], mostly from the first half of the 1990s, confirmed that such repair mechanism is maintained by the end of the second pregnancy trimester. Wound repair is not exclusively dependant on foetus age, but also on the type of wound (linear wound/ after the excision), and its extensiveness. Adzick noticed that the bigger and more extensive the wound, the lesser the likelihood of its repair without a scar – no matter what the age of the foetus is [47].

Authors agree that the less intense inflammatory response probably accounts for scarless fetal wound repair [42,43,48,49]. Some studies also addressed the impact of amniotic fluid, which is sterile and rich in growth factors [50]. Its role was not definitely determined; nevertheless, its advantageous influence was confirmed solely in the early pregnancy stage [51,52]. It was suggested that amniotic fluid is responsible for provision of unique conditions for healing, regardless of the properties of the injured tissue [50].

Based on the immaturity of the immune system in the early stage of fetus development (up to 77 days of pregnancy in sheep), resulting in the lack of allogenic graft rejection, Longaker et al. [50] conducted studies on the impact of intrauterine environment on wound healing within the skin grafted to a fetus. In the study the skin harvested from adults and from fetuses in the third trimester of pregnancy was used. Autogenous fetal skin grafts served as the control group. At 40 days following the procedure, skin was cut through its whole thickness – both within grafts (harvested from mother, 120 days old fetus, and autografts), as well as within adjacent skin. Results of histological and immunohistochemical examinations, which examined tissues were subject to 14 days after intrauterine injury, showed that wounds within autografts and fetal skin healed with restoration of original collagen fiber architecture and formation of normal skin

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appendages. On the other hand, wounds within grafts from mothers' skin and those harvested from120-day-old fetuses healed with formation of easily identified and deprived of appendages scar characterized with abnormal arrangement of collagen fibers, and disordered proportion of their subsequent types. What is more, the grafts maintained original phenotypical features. The authors proved that diversified skin cells of adult and mature fetuses cannot be modulated towards scarless healing through exposure to amniotic fluid. Lorenz et al. [46] examined mechanisms of scarless wound healing in reference to human fetuses. Skin harvested from human fetal cadavers subjected to abortion in various pregnancy periods (from 15 to 22 Hbd) was grafted to mice deprived of thymus (hairless graft nu/nu). Recipient sites were the following: skin defect in the crest region and subcutaneous pocket in the lateral region of the trunk. The control group consisted of skin grafts harvested from mature mice nu/nu or human adults. In the postoperative period another procedure was performed relying on wound formation within the graft. Scarless wound healing was noted in grafts inserted in a subcutaneous skin pocket. Skin grafted into skin lodge healed with scar formation. The authors suggest that their results are related to differences in blood flow within the recipient site. Along with better perfusion, the number of immunological system cells of an adult recipient reaching the graft increases, and then induces an inflammatory response that leads to occurrence and intensification of the cicatrization processes. The authors concluded that presence of amniotic fluid is not necessary for wound healing without scar formation. They present the thesis that elaborated phenomenon has a close relation to fetal skin properties. However, on the grounds of results of experiments they emphasize the conditions under which wound healing occurs (skin pocket of less intensified inflammatory response). Their conclusions correspond to other authors' reports on the pace of fetal skin differentiation to adult specimen skin. It was stressed that the process proceeds far more rapidly in the outer environment (skin surface) than in an aseptic and highly hydrated environment (subcutaneous tissue).

Not all of the tissues behave similarly to skin when responding to an injury during intrauterine life. Longaker et al. found that wounds formed within the diaphragm healed with scar formation [53].

Mechanisms of healing the wounds created in the course of fetal life within bone and mucosa were submitted to extensive examination while establishing foundations for the intrauterine operation of cleft malformations correction [54–59]. It was shown that wounds and minor bone losses are healed in the course of fetal life without formation of abnormal tissue – the equivalent of skin scar – callus. Moreover, it was demonstrated that early treatment of cleft malformation in utero does not handicap maxilla growth of an operated animal. Both outcomes of research on scarless wound healing and described observations bear essential clinical implications.

In the early 1980s, along with development of imagining techniques, the first reports of lip and palate clefts in fetuses were published [2]. In combination with information reported above referring to scarless wound healing, it paved the way for discussions about hypothetical advantages of in utero malformation treatment. Advocates of the

new technique drew attention to potential lip cleft healing without scar formation, prevention of mandible and median face undergrowth, and improvement of postnatal corrective procedures results [2].

Initial optimistic results of experimental in utero treatment of lip and palate clefts gained publicity in the 1980s, but then were succeeded by a period of questioning both the legitimacy and the usefulness of this research. The nature of these doubts can be best illustrated by the words of Trier from 1985: "The quality of conducted corrective procedure of cleft malformation cannot be evaluated solely in reference to scar appearance. The presence of a scar and its quality may present the slightest significance in comparison with other deformities characteristic for this disorder."[13]

Aiming at establishment of an appropriate course of action in case of lip and palate clefts treated in utero, experiments on sheep were conducted [2,54]. Their results were very encouraging – lip healing following cleft suture proceeded without visible scar formation. The authors highlighted the fact that due to fetus age during the procedure (third trimester), the scar histologically constituted a so-called 'naked area', deprived of skin appendages. The above quote is in agreement with previously quoted statement regarding the characteristics of fetal wound healing and so-called 'transitional wound healing' [18].

Weinzweg et al. performed operations on sheep [55–58]. They proved that the procedure of intrauterine cleft suture is technically possible and its execution does not impair mandible growth. Such an effect is the aftermath of scarless healing involving mucosa and periosteum. Fetal lip cleft operations ought to be performed in the period of scarless wound healing. As Hedrick states, this period is not precisely determined; most probably it lasts until 24 weeks of pregnancy [60].

Due to the fetus immaturity and because of skin consistency resembling gelatin, performance of the procedure with putting in stitches is extremely difficult [61]. As an alternative solution Sullivan suggests the use of a special type of clip joining the margins of the cleft lip [62]. Kerby et al. compared the outcomes of endoscopic in utero procedures performed with the use of standard technique and clips application [63]. They proved the advantage of the latter method in terms of time needed to close the defect (average time 2.7 min. and 24 min.), simplicity of operating technique and induction of less inflammatory response in tissues.

Results of reconstructive clefts operations conducted in utero on animals were independently evaluated with cephalometric means by various authors [64]. In operated rabbits, symmetric growth of median face was observed, avoiding induction of disorders in mandible growth in the coronal plane. In both groups of experimental animals (operated and not operated in utero) deviation of nasal septum was noted. Other research rabbits operated in utero did not show asymmetry of nose, lip and alveolar process characteristic of the control group.

On the basis of literature review, Papadopulos concludes that treatment of cleft malformation in the course of scarless wound healing does not impair mandible growth in experimental animals [54]. He suggests this result might be

Table 1. Questions referring to in utero procedures in cleft malformations.

1. What is the influence of lip cleft and palate operation in utero on cranium growth and development?
2. Is scarless healing in human a phenomenon with the course of action probable to predict?
3. On what stage of pregnancy in human occurs the transition period between scarless wound healing and the healing of adult type?
4. Is prenatal ultrasound examination reliable in identification of cleft malformation and elimination of other anomalies?
5. Can the major complication of in utero surgery – premature birth be brought under control?
6. Is fetal surgery safe both for fetus and mother ?
7. What are the technical requirements in order to perform in utero surgery?
8. Can nose deformities be prevented?

connected not only with scarless healing within soft tissues but within bones as well. The process proceeds without callus formation following conducted osteotomies and following bone grafts [42]. Experiments on sheep, where formed cleft fissure in palatal bones was filled with bone graft, confirmed this opinion [64].

Many authors highlight the issue of nasal deformities in cleft surgery. In this context they question to what extent intra-uterine correction of malformation is capable of preventing subsequent nasal deformities [2,61,65]. Levine et al. checked the possibility of non-operative intrauterine modeling of nasal skeleton in sheep [66], proving that modeling with the aid of hyperosmolar sponge fragments enables modification of nose shape without any risk of scar formation.

Another essential aspect of in utero operations in case of cleft malformations is the reliability of prenatal examination detecting the defect. Authors point out that it is unacceptable to decide to operate on both mother and fetus facing the fears of false positive results [2,61]. They quote examination results [67], according to which, out of 35 fetuses who were USG diagnosed with CLP, 2 children were born with normal lip and palate.

Until present the only case study of lip cleft operation in utero in a human is by Fernando Oritz-Monasterio [61]. The procedure was performed with open technique in a 19-week-old fetus. No post-operative scar was observed following the birth; unfortunately, the child died shortly after birth.

Another congenital malformation belonging of interest to plastic surgeons is the group of craniostenoses, in which trials of in utero correction were undertaken. For the time being there are only the reports on experiments on animals. Stepnicki et al. created an experimental craniostenosis model on an animal model (sheep) [68,69]. The procedure consisted of resection of obliterated suture and implantation of Gore-Tex® mesh. The authors examined to what extent mesh implantation between cranial vault and dura mater prevents occlusion of both structures. In the group of sheep subject to surgical treatment, cranium morphology was normal.

In the opinion of Hedrick and Longaker, with present state of knowledge and expertise employment of in utero methods by plastic surgeons excludes achievement of better treatment results in surgical methods other than traditional

approaches [2]. Longaker – one of the discoverers and explorers of scarless wound healing mechanisms over 10 years ago – stressed that long-term experimental and clinical research would be indispensable to unequivocally identify benefits coming from in utero surgery [70]. Nevertheless, he believed that in the future such opportunities would appear along with improvement of operating techniques.

Papadopulos writes that a contemporary plastic surgeon intending to enter the field of in utero surgery must remain focused not only on achievement of esthetically 'acceptable' treatment result but also on exploitation of scarless healing mechanisms. What is more, he must be aware that he operates in a subtle and fragile environment that must not be injured. In his opinion, in utero treatment of cleft malformations must be preceded by consideration of fundamental issues formulated in the list of questions [41] (Table 1).

TRANSPLANTATION OF MOTHER CELLS IN FETUS

Imitating the latest trends in medicine resting on walking away from highly invasive procedures in favor of less aggravating methods, the efforts of transplantation of mother cells and introduction of gene therapy already in fetal life are regarded as highly justified. The fetal immunological system is immature and it is unnecessary to apply either immunosuppression or marrow ablation in order to prevent the rejection phenomenon. Bone marrow is under-developed, and is consequently subject to 'homing' by new mother cells. The objective of prenatal therapy is to prevent the appearance of disease symptoms, consequently protecting the fetus from injury.

Hematopoietic cells can be harvested from 3 sources: bone marrow in adults, cord blood, or fetal liver [3]. Experimental procedures of hematopoietic cells transplantation on animal model were conducted [71,72]. Research outcomes are defined as encouraging. The range of clinical studies on human fetuses is constrained due to legal regulations. For the time being, lack of spectacular clinical effects of a few procedures performed on humans is connected with small amount of grafted cells [73].

SURGERY IN UTERO AROUND THE WORLD

Surgery in utero does not belong to the field of medicine available on the basic level of health service. It is practiced in a few selected reference centers, mainly in the United States.

Table 2. Range of in utero operations performed in selected cases in San Francisco center.

1. Congenital diaphragmatic hernia
2. Pulmonary cystic degeneration
3. Amniotic band syndrome
4. Selected congenital heart malformations
5. Cases of fetal thrombocytopenia
6. Spina bifida with myelomeningocele
7. Sacrococcyeagal teratoma
8. Obstructive uropathy
9. Selected complications of twin pregnancy

The birthplace of fetal surgery was the Fetal Treatment Center in San Francisco. For almost 30 years high standard intrauterine operations have been performed under the management of Dr Michael Harrison [15] (Table 2).

Apart from the Fetal Treatment Center in San Francisco, there are a few other centers offering in utero procedures: the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia founded in 1995, the Fetal Care Center of Cincinnati Children's – Good Samaritan – University Hospital in Cincinnati, the Texas Center for Fetal Surgery in Houston, and the Plastic Surgery Clinic (Klinikum Rechts der Isar) in Munich.

SURGERY IN UTERO IN POLAND

The most frequently performed operations in utero in our country are decompressing procedures in case of internal hydrocephalus. The majority of such cases are conducted in the Congenital Malformations Diagnostics and Prophylaxis Department of Institute-Center of Mother and Child's Health in Lodz (Zakład Diagnostyki i Profilaktyki Wad Wrodzonych Instytutu – Centrum Zdrowia Matki i Dziecka). The center also performs procedures with the method of thoraco-amniotic shunt in case of CCAM type I [74], and decompressing procedures of fetal hydrothorax [75]. Other in utero procedures conducted in Poland are MMC operations. The first successful procedure of this type was performed in the Obstetrics Clinic in Gdansk in 2004. The team of surgeons operated under the supervision of Professor Czeslaw Stoba [76]. Further procedures were performed in the Gynecology and Obstetrics Clinic in Bytom [35]. Doctors from Gdańsk center reported twin-to-twin perfusion syndrome treatment with the aid of fetoscopic, laser, and selective ablation of abnormal vascular links [77].

Cardiology is a well-developed branch of perinatal care. Centers of fetal cardiology in Poland mainly offer diagnostics of organic heart disease in neonates. Depending on the degree of malformation, both the patient's physician and parents have at their disposal a 3-tier system of certified centers of perinatal cardiology. There are approximately 80 such institutions [39,78].

At present in Poland a Ministry of Health program is being implemented, with the objective to raise the quality of prenatal care, that also involves expansion of the scope of in utero operations, and another goal is to upgrade qualifications of doctors performing routine ultrasound examinations. The main goals are the following:

- diagnostics and therapeutic employment of fetoscopy in cases of malformations and fetal diseases,
- implementation of laser-therapy in Twin-Twin Transfusion Syndrome to eliminate vascular anastomosis between donor and recipient existing on the level in placental stroma,
- elaboration of guidelines and therapeutic principles in cases of non-immunological fetal edema,
- application of vesico-amniotic shunt with use of fetoscopic techniques and elaboration of new prognostic criteria of kidneys functions,
- use of pharmacological and operative treatment of polyhydramnios of various etiology with consideration of TTTS and serial amnioreductions,
- establishment of course of action in cases of CCAM with use of intrauterine therapy and fetoscopic techniques,
- identification of guidelines and techniques of uterine cavity opening in cases of fetal malformations (internal hydrocephalus, spinal hernia, obstructive uropathy),
- employment of shunt in-line and uterine cavity opening techniques in cases of internal hydrocephalus,
- implementation of endoscopic methods in treatment of spinal hernia and anomalies such as fetal teratoma,
- establishment of guidelines and techniques of surgical therapy in fetuses presenting selected organic heart diseases, fetal tachycardia, complete heart block and circulatory failure [79].

PERSPECTIVES

Prenatal surgery has the character of preventive medicine. Procedures performed in the course of fetal development facilitate avoidance of disastrous consequences in extrauterine life. Left heart hypoplasia caused by narrowing of aortic ostium may represent a good example. The procedure performed in utero under the control of ultrasound imagining – expansion of underdeveloped valve with the use of a balloon – restores normal anatomical relations in the heart and gives opportunities for its proper development [15]. In this way the child can avoid at least 3 life-threatening operations in early childhood. The progress of modern medicine is closely related to prophylaxis. The forecast for medicine and prenatal surgery in this context means further dynamic development.

The main factor hampering both development and extension of indications to intrauterine medicine is the threat of premature birth [2]. As long as there exist no surgical or treatment methods eliminating this problem, development of fetal surgery will remain limited to anomalies posing a threat to fetus life, with a few exceptions concerning non-lethal anomalies (eg, myelomeningocele).

Harrison emphasizes the fact that thanks to development of fetal surgery, many other branches of medicine broadened their horizons and gained a new useful tool in everyday practice. Among the beneficiaries of "scientific splinters" of the above-cited narrow branch of medicine he includes pediatricians, neonatologists and dysmorphologists, who, owing to direct in utero observation of numerous, so far unknown

anomalies, had a better insight into their pathophysiology and their natural course. He adds to the list obstetricians, perinatologists and fetologists for whom the experience gained during experiments on animals became helpful in management of high risk pregnancies. Among new surgical techniques, improvement of which was connected with fetal surgery, he mentions radio-telemetric monitoring and video-telescopic techniques. The giant progress in the scope of research over new tocolysis methods forced by high risk of premature birth is extremely appreciated in contemporary obstetrics [3].

All the authors engaged in surgery in utero – both clinical and experimental – constantly underline the necessity of a cautious approach to this issue. They strongly advocate need for meeting rigorous criteria prior to any procedure on fetuses. Particular restrictions ought to be obeyed in case of non-lethal anomalies in which relation of benefits to potential risk is rather vague and eludes unequivocal definitions as favorable.

The opportunity to practice in utero surgery opened the door to a new chapter in medicine; a chapter whose fate depends not on the author and the surgeon, but on the main characters – the mothers and fetuses who have extremely difficult roles to play. We should foster hope for the future that the fruits of this progress will be available without any limitations all over the world and that every receiver will be able to enjoy this high class literature.

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