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Motherhood of women with uterine factor infertility

Macierzyństwo kobiet z macicznym czynnikiem niepłodności

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STRESZCZENIE

MACIERZYŃSTWO KOBIET Z MACICZNYM CZYNNIKIEM NIEPŁODNOŚCI

Cel pracy. Celem pracy jest przedstawienie alternatywnych możliwości macierzyństwa kobiet z macicznym czynnikiem niepłodności.
Materiał i metody. Analiza fachowej literatury obejmującej problematykę macierzyństwa zastępczego, przeszczepu macicy oraz ektogenezy.
Wyniki. Niepłodność spowodowana czynnikiem macicznym dotyczy 3-5% kobiet na świecie. Istnieje grupa kobiet, które pomimo nieprawidłowej budowy macicy lub jej braku chcą posiadać dziecko z własnego materiału genetycznego. Medycyna, starając się wyjść naprzeciw potrzebom części społeczeństwa, umożliwia im zapłodnienie pozaustrojowe i wszczepienia zarodka do jamy macicy innej kobiety (macierzyństwo zastępcze), bądź – w szczególnych przypadkach – można dokonać u takiej pacjentki przeszczepu macicy w celu zajścia w ciążę. Inną kontrowersyjną ideą jest ektogeneza, czyli technologia, która pozwoliłaby na rozwój ludzkich embrionów poza organizmem kobiety, w sztucznej macicy. Opcja surogacji jest brana pod uwagę, gdy leczenie i inne metody rozrodu nie przyniosły zamierzonych efektów. Procedura ta w niektórych państwach jest legalna i akceptowana, w innych, natomiast spotyka się ze stanowczym sprzeciwem.
Wnioski. Wzrasta zapotrzebowanie na stosowanie odpowiednich i nowoczesnych metod diagnostycznych i leczniczych umożliwiających reprodukcję. Proponowane rozwiązania mogą wydawać się wręcz nierzeczywiste, jednak wyniki prowadzonych badań naukowych mających na celu ich ucieleśnienie wydają się być obiecujące.

Słowa kluczowe: **niepłodność, macica, surogacja, przeszczep macicy, ektogeneza**

ABSTRACT

MOTHERHOOD OF WOMEN WITH UTERINE FACTOR INFERTILITY

Aim. The aim of this paper is to present alternative ways for women with uterine factor infertility to achieve motherhood.
Material and methods. Analysis of professional literature including the issues of surrogate motherhood, uterine transplantation and ectogenesis.
Results. The infertility caused by uterine factor affects 3-5% of women in the world. There are also women who wish to conceive a baby out of their own genetic material, despite having a structurally abnormal uterus or lacking this organ altogether. Due to considerable advancements in reproductive medicine, the needs of such women can now be met via extracorporeal fertilisation and embryo implantation into the uterine cavity of another woman – surrogacy, or in special cases, via uterus transplantation. Another controversial concept is ectogenesis, i.e. technology which would allow for the growth of human embryos outside the mother's body in an artificial uterus. The surrogate is considered when treatment and other reproduction methods have not worked well. This procedure is legal and accepted in some countries, while in others it is strongly opposed.
Conclusions. There is growing demand for accurate and modern diagnostic and therapeutic methods allowing for successful reproduction. The proposed solutions may seem unreal, but the results of the research carried out to embody them seem to be promising.

Key words: **infertility, uterus, surrogacy, uterus transplantation, ectogenesis**

INTRODUCTION

Infertility is diagnosed in an ever-increasing number of men and women, denying them the possibility of having their own offspring. This makes reproductive failure a medical, social and demographic problem affecting nearly 20% of couples of reproductive age in Europe [1]. The etiopathogenesis of infertility may be related to genetic and epigenetic abnormalities, concomitant systemic and contagious diseases, lifestyle, and environmental or occupational factors [2].

Due to the considerable decrease in fertility, the only chance for some couples to have their own children is in vitro fertilisation (IVF). In 1978, the world's first IVF baby, Louise Brown, was born in the UK. Since then, the method has been widely used for selected medical indications [3]. Advances in medicine have brought improvements in the IVF process and embryo transfer. As a result, the effectiveness of the procedure has increased to 50% in women aged < 35 years [4]. Indications for the use of the method include fallopian tube obstruction, severe endometriosis or severe male factor. The IVF method is also useful in cases of structural uterine abnormalities, with the embryo being transferred to the uterus of a surrogate mother. The development of the IVF technique created the need for testing whether the embryo presents any genetic abnormalities. Pre-implantation testing used for this purpose includes pre-implantation genetic screening (PGS) and pre-implantation genetic diagnosis (PGD): qPCR, comparative genomic hybridization (CGH), SNP array, array comparative genomic hybridization (aCGH), fluorescence in situ hybridization (FISH), DNA sequencing, and whole-genome amplification (WGA) [5]. A significant role in the etiopathogenesis of reproductive disorders is played by the female infertility factor. Absolute infertility caused by uterine factors affects 3-5% of women worldwide [6,7]. There are women who wish to conceive a baby out of their own genetic material, despite having a structurally abnormal uterus or lacking this organ altogether. To meet their needs, reproductive medicine offers in vitro fertilisation and embryo implantation into the uterine cavity of another woman – surrogacy, or in special cases – uterus transplantation [8,9]. The aim of this paper is to present alternative ways for women with uterine factor infertility to achieve motherhood.

AIM

The aim of this paper is to present alternative ways for women with uterine factor infertility to achieve motherhood.

MATERIALS AND METHODS

Analysis of professional literature including the issues of surrogate motherhood, uterine transplantation and ectogenesis.

Uterine factors in infertility

Structural abnormalities of the uterus occur in situations where the organ has been irreversibly changed, e.g. following brachytherapy, which may lead to uterine malformations or obstruction of the cervical canal. Normal anatomical structures in the uterine cavity may also be damaged due to numerous factors leading to the obliteration of the uterine cavity (called Asherman's syndrome). Intrauterine adhesions may be a complication of surgical procedures in the uterine cavity, such as excessive D&C (dilation and curettage) during delivery or abortion, or following a C-section. Asherman's syndrome may be induced by endometrial ablation (surgical removal of the endometrium used to treat excessive uterine bleeding), endometrial infection (e.g. genital tuberculosis), and less frequently by schistosomiasis (a disease caused by blood parasites) or severe endometritis [10,11]. Uterine deformity may also be caused by fibroids which may lead to embryo implantation failure, miscarriage, or placental abruption, making pregnancy impossible in some cases. Risk factors for uterine fibroids include age, African descent, obesity and no history of pregnancy. Even though advancements in research have extended the knowledge about the pathology of fibroids, their etiology remains to be fully understood [12]. Structural abnormalities of the uterus may also stem from congenital uterine anomalies, uterine agenesis or hysterectomy (e.g. due to postpartum uterine atony) [6,12,13]. Congenital structural anomalies of the uterus constitute frequent malformations of the female reproductive system. Their actual prevalence is not known, but it is estimated to be about 3-5% in the general population. The etiology of these malformations remains unknown. However, their development may be influenced by genetic makeup, adverse environmental and mechanical factors, and also pharmacological agents [6,7]. Uterine anomalies are mostly sporadic, but there are also familial cases which have proven that the defects can be inherited. There are a number of genes whose mutations lead to uterine defects, i.e. uterine aplasia, unicornuate uterus – the *LHX1, WNT4, WNT5A, WNT7A, WNT9B,* and *TBX6* genes; bicornuate uterus – the *LHX1, WNT9B, EMX2, HOXA9, HOXA10, PAX2*, and *TBX6* genes; septated uterus – the *HNF1B, HOXA10, HOXA11*, and *TBX6* genes [14]. The Mayer–Rokitansky–Küster–Hauser syndrome (MRKH), on the other hand, usually develops in women with a normal karyotype (46,XX). However, it is believed that genetic factors play a role in its etiology. Of all genes, only WNT4 has been proven to be involved in the etiopathogenesis of MRKH. Other possible causative genes include: *GALT, CFTR, MIF, MHR, LHX1, HNF1B*, and *TBX6* [15,16].

Surrogacy

Surrogacy is taken into account when treatment and other reproductive methods have not delivered the expected results. Medical indications for surrogacy include: uterine factors in infertility; uterine defects caused by surgical intervention or cancer, which make it impossible to carry the pregnancy to term; severe somatic diseases, which would present a threat to the woman's life or health were she to carry the pregnancy to term; prior hysterectomy; repeated unsuccessful attempts at assisted reproduction [17]. Surrogacy may be considered a technique of assisted reproduction with three parties involved: the biological

mother, the biological father and the surrogate mother (surrogate). These parties usually enter into a formal agreement which includes the obligations of the surrogate during pregnancy, the way of giving up the child, her consent to post-birth adoption and the due remuneration for giving birth to the child. Pregnancy in the surrogate may be the result of in vivo or in vitro fertilisation with the intended father's sperm or the use of the intended mother's egg. In the latter case, there is no genetic relationship between the child and the surrogate. The two are only biologically related [18].

In Polish jurisdiction, the fact of giving birth to a child is essential to establishing maternity, i.e. the existence of a biological relationship, irrespective of whether the woman is the genetic mother of the child. Even though the child is genetically related to the intended parents, it is the surrogate, i.e. the woman who gave birth to the child, who is the child's biological mother. Ever since the Act on infertility treatment of 2015 came into force in Poland, there has been no possibility of using embryos with a targeted recipient and all forms of donation are anonymous. There is no possibility of targeted adoption, either [18,19].

Lack of unambiguous EU and international legislation and the rapid development of assisted reproduction techniques led to the emergence of surrogacy tourism. In order to fulfil their need of having children, infertile couples seek treatment in different European or non-European countries that allow surrogacy, both altruistic and commercial. These include Ukraine, Russia, Cyprus, Georgia, Thailand and several US States (Tab. 1) [9,18]. In India, where surrogacy was legalised in 2002, there used to be about 30,000 clinics offering help to childless, mostly foreign couples. In most cases, the women who decided to become surrogate mothers were financially motivated. However, the most frequent motivation given by the surrogates was altruism and the need to increase their self-esteem. After the surrogate mother gave birth, the child was handed over to the commissioning parents and the surrogate received financial remuneration. In the case of unsuccessful delivery, the surrogate did not receive any monetary compensation [17,20]. However, after years of criticism from Indian citizens and human rights defenders, the Indian authorities introduced "*The Surrogacy Bill*" in 2016, a regulation which completely banned commercial surrogacy, allowing only altruistic surrogacy [21].

Tab. 1. Surrogacy laws in the world [9,18]

Legal requirements	Selected countries
Surrogacy agreements are banned	Poland, Germany, France, Italy, Norway, Sweden, Switzerland, Slovenia, Austria, Iceland, Turkey, Canada (Quebec), Mexico (State of Querétaro), USA (e.g. Arizona, Columbia. Michigan), continental China, Saudi Arabia, Nepal, Cambodia
Surrogacy is regulated by a relevant legal framework	Denmark, Greece, the Netherlands, UK, Portugal, Israel, Canada (Alberta, British Columbia), New Zealand, Australia (Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria, Western Australia), RPA, India, China (Hong Kong Special Administrative Region)
All forms of surrogacy are legal	Ukraine, Russia, Georgia, Cyprus, USA (including California, Arkansas, Ohio, Texas), Uganda

Uterus transplantation

One alternative method of achieving pregnancy in the body of a biological mother with uterine dysfunction is transplantation of a uterus from a donor. Uterus transplantation (UTx) is a revolutionary way of treating women rendered infertile due to e.g. Müllerian agenesis, severe intrauterine adhesions or uterine fibroids [8,22].

The first attempt at UTx was made in Saudi Arabia in 2000. The recipient was a 26-year-old woman who had undergone a hysterectomy due to post-partum haemorrhage. However, three months after the transplant, necrosis developed in the uterus and it was necessary to remove the organ. The second UTx was performed in Turkey in 2011 in a woman with Mayer–Rokitansky–Küster–Hauser syndrome (MRKH). The organ had been harvested from a deceased donor. There were no complications during the procedure. However, the attempts to transfer an embryo to the uterus ended in spontaneous abortion before the 6th week of gestation. Uterus transplantations have been attempted in Sweden since 2012 [23,24].

The first case of a successful childbirth after UTx was announced in 2014 by doctors from Sahlgrenska Hospital (Goeteborg Universitet) in Sweden. An MRKH patient received UTx from a 61-year-old donor, who had given birth to two children. Both women underwent the surgery with no need for further intervention [8]. The recipient had her first menstruation period 43 days after the procedure. It lasted for 4 days. Subsequent periods occurred regularly every 26-36 days. A year after the transplantation, a transfer of an IVF embryo was conducted and the following pregnancy developed without complications until the 31st week. After 31 weeks and 5 days, the woman was hospitalised due to diagnosed preeclampsia, which necessitated a C-section. The baby was born in a good general condition, with a body weight of 1775 g and a body length of 40 cm. It stayed in hospital for 16 days. After the childbirth, the mother's condition normalised and did not require further treatment. Therefore, as soon as three days after the C-section, the woman was discharged [24].

There is also a case of a live birth following a transplant from a deceased donor. In the Brazilian Hospital das Clínicas (University of São Paulo), a uterus transplant was performed in a 32-year-old MRKH woman in 2016. The organ was harvested from a 45-year-old patient, who had died due to subarachnoid haemorrhage complications. The recipient had her first menstrual period 37 days after the transplant and the embryo transfer was conducted 7 months post-surgery. In December 2017, in the 35th week of gestation, the baby was born in a good general condition, with a body weight of 2550 g and a body length of 45 cm. The transplanted uterus was removed during the C-section. The newborn and the mother left hospital after three days of observation. This case of a live birth after UTx from a deceased donor significantly improves infertile couples' chances of having a baby, as the number of donors willing to donate their organs after death is much higher than the number of potential living donors, which at the same time makes it possible to avoid surgical intervention in healthy women [24,25].

During the surgery eligibility process, not only the benefits but also the risks should be discussed with the patient. Possible complications include organ rejection, infection or tissue necrosis. These are particularly dangerous when they occur during pregnancy. There is also a hypothesis which states that numerous feelings and sensations related to pregnancy and childbirth may be experienced differently by the recipient, as the surgery also involves pelvic nerve resection [22]. UTx is an ephemeral transplantation, which means that its purpose is to improve quality of life rather than extend human life. It is a surgery which requires numerous additional medical procedures to achieve the therapeutic outcome, i.e. successful treatment of infertility [26]. Since the transplanted uterus is not connected to the recipient's fallopian tubes, IVF is necessary and the pregnancy is concluded with a C-section [23]. The transplanted organ should be removed after the therapeutic outcome has been achieved, i.e. after childbirth, but this decision is to be made by the patient. Leaving the transplanted uterus in the body requires a lifelong use of immunosuppressants [24,27]. UTx also presents immunosuppression-related risks to the developing foetus: prematurity and low birth weight. On the other hand, there are currently no data on the risk of birth defects or any other possible complications [28].

In 2012, the "Montreal Criteria" were developed. They presented arguments for ethical feasibility of UTx. These criteria define general conditions for the recipient, the donor and the transplant team [29]. The criteria for the recipient are as follows: female (cisgender) of reproductive age, with no medical contraindications for the procedure, with documented infertility caused by congenital or acquired uterine factors; legal or personal contraindications for adoption/surrogacy and the need to have a baby; psychological/psychiatric assessment stating that the readiness to have UTx is not caused by any mental disorder. The criteria for the donor are as follows: female of reproductive age, with no medical contraindications for the donation; making an uncoerced decision to donate the uterus; being aware of the surgical risk and able to give "informed consent" for the procedure. As for the transplant team, it provides adequate information regarding the procedure to both parties so that they can make an informed and responsible decision; there is no conflict of interests; the team is obliged to protect the parties' anonymity, unless the donor and the recipient waive this right [29,30].

Uterus transplantation decidedly redefined the limits of reproductive surgery and the first post-UTx live birth documented in the literature confirms the success of this procedure [23,24,25].

Artificial uterus

Problems related to making a decision about having UTx or using a surrogate mother necessitate the development of new solutions. One controversial concept is ectogenesis, i.e. technology which would allow for the growth of human embryos outside the mother's body, in an artificial uterus. The term was coined by the geneticist J.B.S. Haldane. The scientist's vision has not been fully implemented yet. However, such a solution could present an opportunity for women who cannot carry the pregnancy to term, who do not have a uterus, or those for whom pregnancy is contraindicated due to medical reasons. Studies carried out in various countries in the world have demonstrated that in the future, foetus development outside the mother's body will be possible in the early stages of pregnancy. However, there are still problems related to hormone balance and foetal nutrition that remain to be solved [28,29].

An artificial uterus could be used as an incubator for newborns with extremely low body weight. The role of the system would be to provide an extracorporeal connection to the foetus, allowing for nutrient and oxygen supply, and waste product disposal. The system would require an artificial placenta serving as an interface in the necessary exchange between the foetal circulation and the unit replacing the maternal circulation. Other components necessary for the implementation of the idea include the endometrium and amniotic fluid [30]. To date, scientists have managed to grow endometrial cells and then engineer an entire uterus into which a human embryo was subsequently implanted. The latter developed for 6 days until the experiment was halted due to ethical reasons [30].

At the turn of the 1980s and 1990s, experiments on goats were carried out. Foetuses were incubated in an artificial amniotic fluid incubator with extra-corporeal membrane oxygenation for 494 and 543 hours. The animals survived for over a week off the incubator [31]. Scientists from Philadelphia developed a system of extra-uterine support to foetal lambs, which consisted of a pumpless arteriovenous circuit, a closed fluid circuit and an umbilical cord interface. The system was to serve as an incubator imitating the environment of the womb. This ‚*Biobag*' was used as a substitute for the amniotic sac. This was a flexible polyethylene bag, whose shape and size resembled that of the uterus. The *Biobag* was filled with amniotic fluid, which was continuously exchanged. Antibiotics were added to the fluid if needed. The fluid circuit was closed, which minimised the risk of contamination with microorganisms. The umbilical cord interface was used for parenteral nutrition and nutrient supplementation. A series of pilot studies conducted on extreme premature lambs demonstrated that the device may be used for extra-uterine support of foetal development even for up to 4 weeks without any physiological derangement [32].

Studies on improving an artificial placenta, its systems of gas exchange and conditions of the experiments have frequently been described in the literature. It has been proven that an artificial placenta utilising extracorporeal membrane oxygenation (ECMO) is efficient and safe [33]. The idea of an artificial placenta assumes gas exchange as a support for lung physiology, but it does not consider other functions of the human placenta. Thus, the progress achieved is not sufficient, which creates numerous new challenges for researchers [34].

Despite the many challenges, the concept of an artificial placenta offers extreme premature infants a chance of survival and constitutes an attractive alternative to preterm birth treatment. The use of artificial placenta

models in clinical practice could be another milestone in foetal medicine and neonatology. However, solutions such as foetal development in an artificial uterus outside the mother's body have the potential for abuse and constitute an introduction to the instrumentalisation of human life. On the other hand, they could solve the problems of women with UFI. They would also resolve the dilemmas of mothers whose life is threatened by the pregnancy, e.g. in situations where a woman must receive cancer treatment and has to choose between her own life and the life of her child. Moreover, these solutions would allow for abortion to be avoided; in cases like this the unwanted baby would be transferred to an artificial uterus and placed for adoption after birth [29,35].

CONCLUSIONS

The ever-increasing number of infertile or sterile individuals and aggravating problems related to reproduction set high expectations to be met by reproductive medicine. There is growing demand for adequate and modern diagnostic and therapeutic methods enabling successful reproduction. The birth of Louise Brown 40 years ago not only showed that there exists a remedy for infertility, but also promised new scientific discoveries and technological innovations [3]. The solutions proposed may sound unreal, but the results of scientific studies whose aim is to put them into effect seem promising.

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