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MARIA INÊS VENTURA CABRAL

***Reproductive desire in women with infertility
uterine factor – what solutions?***

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***Reproductive desire in women with infertility uterine
factor – what solutions?***

Maria Inês Ventura Cabral¹; Ana Teresa Moreira de Almeida Santos^{2,3}

¹ Faculty of Medicine, University of Coimbra, Coimbra, Portugal

² Human Reproduction Department, Coimbra Hospital and University Centre (CHUC), EPE, Coimbra, Portugal

³ Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

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Abstract

Objective: Review and analyze the state of the art regarding gestational surrogacy and uterine transplantation.

Methods: A search was made in PubMed®, with the following inclusion criteria: articles published in English over the last 10 years. After analysing 98 abstracts, 27 articles were selected.

Results: AUI can be caused by several medical issues, such as Mayer-Rokitansky-Küster-Hauser syndrome, which is the congenital absence of uterus and upper two thirds of the vagina, being the most common cause of AUI, and by oncological disorders in fertile aged women when fertility sparing options are not a possibility. Living or deceased donors can both be used in UTx, each having advantages and limitations. After organ transplantation, permanent immunosuppression becomes part of the postoperative and maintenance care of a patient, to avoid graft rejection.

Discussion: A suggestion of a decisional algorithm is made aiming to help the decisional pathway of couples who suffer from AUI and wish to have children, and have to choose between adoption, GS or UTx. Step by step, we discuss the several issues involved with these options.

Conclusion: The availability of gestational surrogacy and uterine transplant has raised new options for patients with AUI. It is now imperative to discuss these alternatives in these patients, besides adoption or childlessness.

Keywords: infertility; uterus; transplantation; surrogate mothers; living donors; immunosuppression.

Resumo

Objetivo: Rever e analisar a literatura científica sobre gestação de substituição e transplantação de útero.

Métodos: Uma pesquisa na PubMed[®] foi feita de acordo com os seguintes critérios: artigos publicados em inglês nos últimos dez anos. Após analisar 98 resumos, 27 artigos foram selecionados.

Resultados: O factor absoluto de infertilidade uterina é causado mais frequentemente pelo síndrome de Mayer-Rokitansky-Küster-Hauser, caracterizado pela ausência congénita dos dois terços superiores da vagina e do útero. As neoplasias em mulheres em idade fértil são também uma causa frequente, quando tratamentos com preservação da fertilidade não são uma possibilidade. Dador cadáver ou dador vivo constituem dois tipos possíveis de dador em transplante de útero, ambos com diferentes vantagens e limitações. Após transplantação de órgão, a imunossupressão de manutenção faz parte do pós-operatório de um doente, para evitar rejeição do enxerto.

Discussão: Uma sugestão de um algoritmo decisional é feita com o objetivo de ajudar a tomada decisão em casais com factor absoluto de infertilidade uterina com o desejo de ter filhos. São discutidos os vários problemas levantados pelas opções de gestação de substituição, transplantação de útero e adoção.

Conclusão: A disponibilidade da gestação de substituição e do transplante de útero criou novas opções para doentes com factor absoluto de infertilidade uterina. É essencial discutir estas alternativas nestes doentes, para além da adoção e de não ter filhos.

Palavras-chave: infertility; uterus; transplantation; surrogate mothers; living donors; immunosuppression.

Introduction

Absolute uterine factor infertility (AUI) affects one in 500 (1) women in childbearing age, worldwide, corresponding to ~200 000 women in Europe (2), due to the lack of anatomical uterus or to the presence of a non-functioning uterus (such as congenital Müllerian malformations, Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, Asherman syndrome, pregnancy interfering myomas, oncological disorders) (1), not allowing a full term pregnancy. Women with AUI who wish to have children may consider other options such as adoption, gestational surrogacy (GS) or uterine transplantation (UTx), in accordance with the respective legal frame.

Tightening of international laws aiming to decrease child trafficking is making the process of adoption more difficult throughout Europe (3). For instance, in France, the average waiting time is 4 to 5 years. Couples prefer to adopt children of very young ages, which extends the waiting time. The increasing availability of options such as GS and UTx may be considered by couples with AUI (3).

Emotional and physical well-being, social support and patient adherence for all the involved parties, such as the intended parents, the surrogate, the uterus transplant recipient and her husband, the living donor (if the case) are crucial aspects of GS and UTx.

Gestational Surrogacy

Surrogacy happens when a woman, the surrogate, becomes pregnant with the goal of giving the child away to the intended parents (7). It can be a traditional surrogacy, where the surrogate has a genetic link to the child: the embryo resulting from the father's sperm and the surrogate's oocyte. It can also be a gestational surrogacy, in which gametes from the intended parents are used through IVF to create embryos that will be implanted in the surrogate, ergo having no genetic link to the child (8). Surrogacy can be commercial or altruistic. In commercial surrogacy, the surrogate receives financial benefit from the intended parents. Altruistic surrogacy, on the other hand, only involves the payment of surrogate pregnancy-related expenses by the intended parents (9).

In 1985, the United Kingdom was the first country in the world to have specific legislation regarding gestational surrogacy with the Surrogacy Arrangement Act and still has today the most complex legislation in the world (8).

International surrogacy is a reality. With different court systems and laws, a child can be born stateless and not eligible for entering the country of the intended parents. (8) More than 25 000 children are known to have been illegally born in India, through cross-border surrogacy, 50% being from the West (7).

Uterine Transplantation

More than 14000 babies born to transplanted and immunosuppressed women have been reported worldwide with no report of increased risk of fetal malformation (4).

A successful UTx requires an intimate articulation of a team of transplant surgeons, cardiologists, psychiatrists, obstetric and gynecologist physicians, reproductive medicine physicians, ethicists and patient advocates (5).

The first attempt of uterus transplantation occurred in 2002 by a Saudi Arabian team in a 26-year old woman who was submitted to a hysterectomy after uncontrollable bleeding during a cesarean section. The donor was a 46-year old woman who underwent a hysterectomy for a multiloculated ovarian cyst. Three months after the surgery, the transplanted uterus had to be removed (6). The second uterus transplant was performed in 2011, in a 21-year old woman with MRKH syndrome, using a uterus from a deceased donor. So far, 11 uterine transplants have been reported (1).

Methods

Review article. A search was performed in PubMed[®], with the following terms: “uterus transplantation”; “living donor uterus transplantation”; “deceased donor uterus transplantation”; “gestational surrogacy”; “immunosuppression”. The aim of the search was to collect information regarding the state of the art in gestational surrogacy and uterine transplantation, including the following topics:

- Mayer-Rokitansky-Küster-Hauser syndrome
- Gynecological neoplasms
- Living donor and deceased donor
- Immunosuppression

To narrow the search, only articles in English from the last ten years were included.

After a thorough abstract analysis, 23 papers were selected based on its possible inclusion on the area of research. Bibliographic references of these 23 papers were also analyzed based on the title to find potential additional relevant articles. A paper from 2002, one from 2006 and two from 2008 were thus found and included due to its relevance for this review.

Results

Mayer-Rokitansky-Küster-Hauser Syndrome

MRKH syndrome affects 1 in 4500 newborn girls, being characterized by the congenital absence of the uterus and the upper two thirds of the vagina, with normal breast and pubic hair development and mostly with normal ovarian function, in women with the 46,XX karyotype (10). Diagnosis is made in adolescents due to primary amenorrhea (11). This syndrome is frequently associated with unilateral renal agenesis (30%), skeleton (10-15%) and cardiac anomalies (2-3%) and deafness (2-3%).

There are two types of MRKH syndrome. In the typical form the Fallopian tubes, ovaries and renal system are present and normally developed. In the atypical form malformations of the ovaries and/or kidneys may be present. Furthermore, atypical MRKH patients have ovarian response and fertilization rates different from the typical MRKH (11).

MRKH syndrome is the most common indication for UTx. In the Turkish experience, 83% of the applicants had MRKH syndrome, while in the Swedish clinical trial eight of the nine women who participated had this condition (2).

Patients with MRKH syndrome may have renal and genitourinary abnormal development that contraindicates the reception of an UTx, whether with or without uterine absence. These alterations increase pregnancy risks for gestational hypertension, preeclampsia and growth restriction (12).

Gynecological Cancer

The most frequent cancers in reproductive age women are cervical, endometrial, epithelial ovarian and non-epithelial ovarian cancer; rarer disorders are leiomyosarcoma, endometrial stromal sarcoma and choriocarcinoma/placental site trophoblastic tumor with chemoresistance and solitary remaining tumor in the uterus can also occur (13).

All of these tumors have different approaches of treatment and prognosis, that can include radiation and chemotherapy. Fertility preservation options include oocyte cryopreservation, which is a technique used nowadays with improved efficiency (14). However, this and other fertility sparing options are not always a possibility. When a surgical approach with radical hysterectomy is the option, the patient is left with AUI.

So far only a UTx was successful in a patient with a previous gynecological malignancy, being the only reported patient with two baby deliveries after UTx, worldwide (13).

UTx: Living Donor VS Deceased Donor

The first clinical trial for living donor UTx was performed in Sweden, by the team lead by Dr. Mats Brännström, after working successfully for years with animal models of several species, including mammals and non-human primates (15-17). The nine women who were involved in this trial as recipients received transplants from family members with an average donor age of 53 ± 7 years old (12). Of the nine transplants, seven grafts proved viable; the other two were removed because of vascular thrombosis and severe graft infection (2).

Finding an organ donor, both living or deceased, is very complex. In table 1, a comparison is made between the two types of organ donor, underlining the main advantages and limitations of each one.

Table 1 – Comparison between living donor and deceased donor in Uterine Transplant

	Living donor	Deceased donor
Advantages	<ul style="list-style-type: none"> - Set the time when both donor and recipients are in optimal conditions (1) - Time to have a good medical history of the donor prior to transplantation (1) - Donor and recipient can be in close quarters, shortening the ischemia time and reducing post-transplant complication risk (12) 	<ul style="list-style-type: none"> - No medical risk associated with donor surgery (1) - Surgical dissection procedure is faster and vessels of a larger diameter can be used for the anastomosis, simplifying the transplantation procedure (1) - Surgical risks to the donor are non-existent and recovery time for the uterus is shorter (12) - Younger donors available (12)
Limitations	<ul style="list-style-type: none"> - Psychological strain the donor is exposed to (12) - Coercion, either intentional or unintentional, must be assessed (12) - Average age of donors will be higher and most donors will be women who have completed conceiving plans (12) - Use of hormonal replacement therapy in donors who become post-menopausal can increase the risk for thrombotic events (12). Before donation, a minimum of 3 months of combined oral contraceptive is mandatory to improve uterine vasculature (18). - Long duration of the surgery for live donors (1) - Potential hormonal dysfunction in a premenopausal woman (1) 	<ul style="list-style-type: none"> - Long term graft viability is reduced - The timing of deceased donors and recipients is hard to coordinate; when a person must sign to become an organ donor the availability of donors is smaller (12) - Bigger donor and recipients distance, increasing the time for ischemia and post-surgery complications (12) - Donors must be restricted to women in reproductive age with no history of infertility (5) - Recovery time is shorter (5) - Uterus is usually recovered after all lifesaving organs are retrieved (5)

Immunosuppression

Long term use of transplantation-related immunosuppression medication in cancer patients can lead to an increased risk of certain malignancies, such as skin cancer and hematological malignancies (13).

Immunosuppressive regimens are similar to the ones used in kidney transplantation, being based on antilymphocyte globulin and steroids. Maintenance immunosuppression is made with tacrolimus, mycophenolate mofetil (MMF) and corticoids. Six weeks prior to pregnancy attempt, MMF must be replaced with azathioprine, as MMF represents increased risk for abortion and congenital malformation (19).

Graft rejection monitoring is made with cervical biopsies. Initially, those are performed in the immediate postoperative period and then monthly, even during pregnancy, with no increased risk for the fetus. Doppler of the uterine arteries can also be performed to evaluate the presence of atherosclerosis (5).

Breast feeding in patients under immunosuppression with tacrolimus, azathioprine, prednisone and cyclosporine presents no danger to the baby. However, the use of MMF, sirolimus and everolimus is discouraged (19).

Discussion

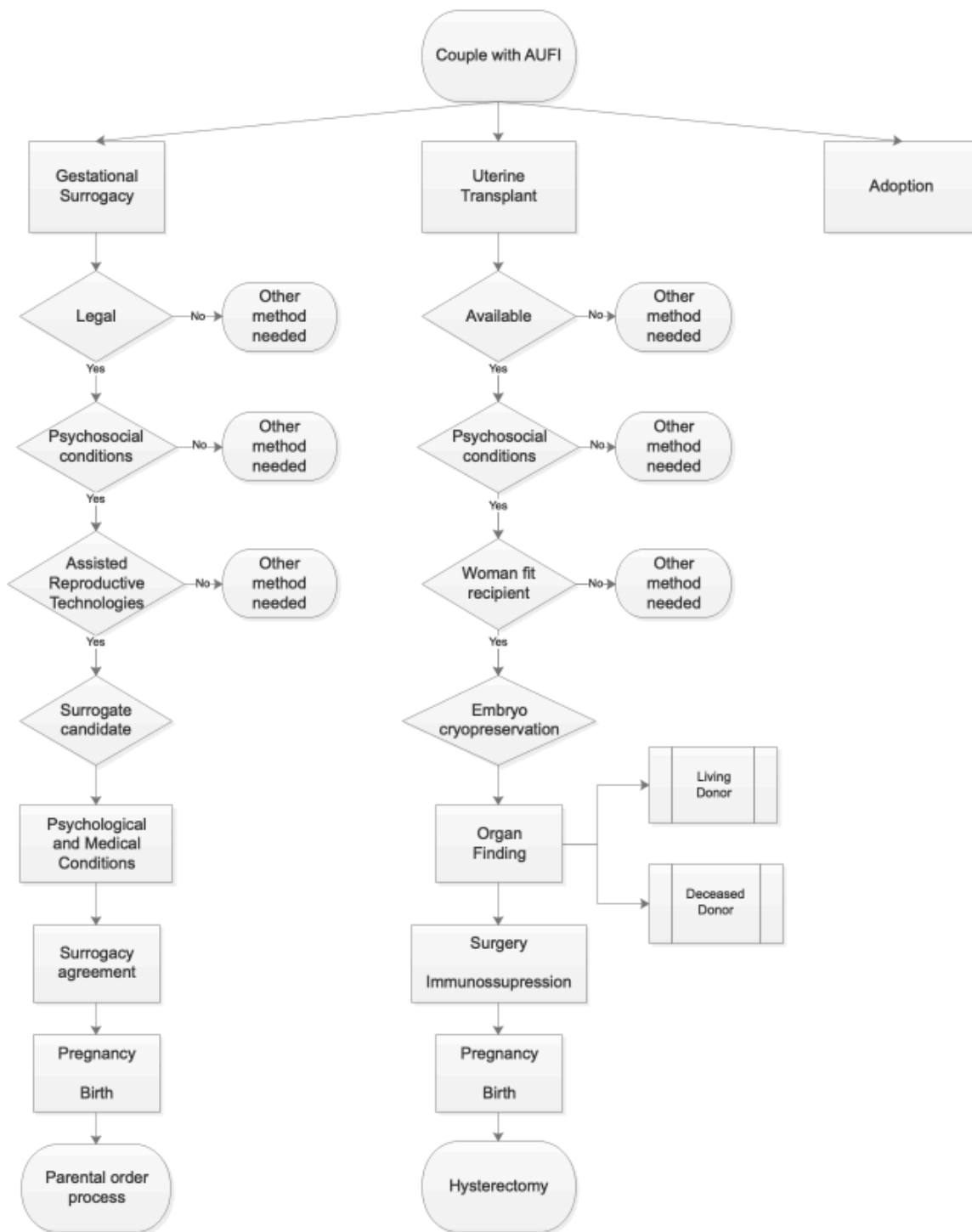


Figure 1 – Decisional algorithm for couples with AUI

The decisional algorithm we suggest in Figure 1 is aimed to be a guidance tool to help in the discussion in a couple with children desire who suffers from absolute uterine factor infertility. Three possible options are available to those patients: gestational surrogacy, uterine transplant and adoption. Only when adoption is excluded, should the couple consider GS or UTx.

According to the International Federation of Gynecology and Obstetrics committee report on surrogacy, only gestational surrogacy is now ethically and morally acceptable (20).

Gestational surrogacy legislation differs from country to country:

- It is not officially allowed in: Austria, Bulgaria, Denmark, Finland, France, Germany, Italy, Malta, Norway, Portugal, Spain and Sweden (7).
- It is allowed altruistic but not commercial: Belgium, Greece, the Netherlands, the United Kingdom, Australia, Canada, New Zealand, some states in the USA (7).
- There are no laws regulating GS: Poland and Czech Republic (7).
- GS is commercially allowed: Israel, Georgia, Ukraine, Russia, India, California USA (7).

The intended parents should go through assisted reproductive technology procedures in order to obtain viable embryos to be transferred to the surrogate candidate. According to the American Society of Reproductive Medicine, a surrogate should be a woman aged between 21 and 45 years old, having had a minimum of 1 child and a maximum of 5 children and a maximum of 3 caesarian sections. All those pregnancies must have been full-term and with no complications (21).

Both the intended parents and the surrogate, before an agreement contract is signed, must go through a very thorough psychosocial and psychiatric evaluations. Both parties should be mentally healthy. The intended parents must be evaluated alone and together as a couple, having good coping mechanisms and no psychological issues. They need to fully understand their role in this process, all the possible risks for them, the surrogate and the baby, both medical, ethical and legal. The process with the surrogate candidate and her partner is very similar. Furthermore, she needs to be aware of: a) the impact of the surrogacy pregnancy in her life; b) not getting pregnant at the first attempt; c) the possibility of pregnancy interurrences; d) and the risks associated with attaching with the child. To sum up, it is essential that the intended parents and the surrogate enter a balanced relationship, where boundaries are respected regarding pregnancy medical details and legal issues (21). In fact, a disagreement between the intended parents and the surrogate may happen, when, for example, fetal malformations exist and consequent abortion willingness (3).

Table 2 lists the main medical points the surrogate must go through in order to get approved to be a candidate.

In the final step of the surrogacy, there should be a parental order process, in which the intended parents file a formal adoption request to become the legal parents of the baby. This happens in countries such as the UK and the Netherlands, where the surrogate is the legal mother of the child as of the birth (8,9).

Uterine transplantation is still experimental, only possible in clinical trials in certain countries, such as Sweden. That is why availability is the first checkpoint of the algorithm.

Couples who look for UTx must consider the other possible options to have children, within the respective legal frame, before recurring to UTx. After the psychological assessment, they must be in agreement with all the risks that come from the transplant, immunosuppression and pregnancy (22) and after approval, they must go through a complete medical evaluation, as referred in Table 3, a modified from the one used in the Swedish clinical trial (2).

Generally, there are two types of laws for organ donors described as *opt-in* and *opt-out*. *Opt-in* countries are those where the person must register to be an organ donor. This is the case of Scotland, England, Northern Ireland, Denmark, Germany, Romania, Serbia and Malta. On the other hand, *opt-out* countries are those where everyone, after death, is a donor, except if they, during their life time, explicitly object. Countries such as Portugal, Spain, Austria, Wales, Greece, Poland and Sweden are included (23).

However, UTx is not included in organ donation in the UK and the USA. Donors, under normal circumstances, will not know that donating their uterus could even be possible (24).

The UTx recipient, after surgical and immunosuppression procedures, will be fit to go through pregnancy, with the same associated risks as kidney transplant recipients (19). After completion of family, the transplanted uterus is expected to be removed to prevent the consequences of long-term immunosuppression (13).

Table 2 – Surrogate applicant medical history and investigations. Modified from (21)

Medical history	Previous obstetric history; Past mental issues; Sexual history (risk behaviors); Smoking and drinking antecedents; Religion
Clinical	Pap smear
Blood parameters	Blood type and Rh factor; CBC
Microbiology	HIV, Hepatitis B and C, Syphilis, CMV. Chlamydia, Gonorrhoea, Varicella, Rubeola Urine drug screen
Radiology	Mammogram

CBC – Complete Blood Count; HIV – Human Immunodeficiency Virus; CMV – Citomegalovirus

Table 3 – Preoperative medical investigations in UTx recipients. Modified from (2)

Clinical	ECG, exercise ECG, Pap smear
Blood parameters	General (Haemoglobin, white blood cells, PTT, APTT, CRP); Liver function (ALT, AST, ALP, Albumin, Total protein, Bilirubin); Kidney function (creatinine, urea, electrolytes, dissolved salts); Thyroid function (TSH, Free T4)
Microbiology	CMV, EBV, HIV, Hepatitis A, B and C, Chlamydia, HPV, Gonorrhoea, Syphilis.
Radiology	MRI, Chest x-ray, Vaginal ultrasound scan

ECG – Electrocardiogram; PTT – Partial prothromboplastin time; APTT – Activated partial prothromboplastin time; ALT – Alanine transaminase; AST – Aspartate transaminase; ALP – Alkaline phosphatase; TSH – Thyroid-stimulating hormone; CMV – Citomegalovirus; EBV – Epstein-Barr virus; HIV – Human Immunodeficiency Virus; HPV – Human papillomavirus; MRI – Magnetic Resonance Imaging

Conclusion

Over this paper we analyzed uterus transplantation and gestational surrogacy as reproductive options for AUF1 people. We suggest a decisional chart for couples who suffer from AUF1.

The paradigm of cure, prevention and decrease of suffering is the main goal of medical sciences (25). Entering the field of GS and UTx, medicine may be turning on a “service on demand” with the final aim to decrease suffering.

Organ transplant has been practiced in the world for the past 50 years, considered to be lifesaving and life changing. Many people feel that if a transplant is not lifesaving or quality of life saving, it should not be performed (25). This argument might sound as subjective, because the meaning of quality of life depends on the person (25). A woman with AUF1 that will never have the chance to conceive naturally, may suffer from depression and other psychological issues. This could be considered deterioration of quality of life.

Coercion is one of the referred disadvantages of UTx with living donor. This concept can be more prevalent in some societies, such as the Islamic, where women really have scarce rights. The first UTx attempt happened in Saudi Arabia, almost 10 years before the second attempt (6). This may be explained by very intense social and familiar pressures to achieve one of women’s main role in society. Under those conditions, women may apply for UTx clinical studies, disregarding all the risks involved.

Concerning living donor UTx, it is suggested that better medical and moral judgements are required. When the desire to bear a child outweighs the negative effects, having an organ donation by a non-optimal donor can happen with partners being, for instance, mother-daughter or sister-sister (26). The genetic relationship between donor and recipient minimizes potential disputes regarding the patient’s principle of autonomy (3).

There was a survey made in the UK aimed to understand whether women are in favor or against uterus transplantation and their reasons. Those in favor argued that they would want to have their own genetic child, avoid legal issues that happen in GS and that the immunosuppression drug they would be exposed would only be temporary. Those against fear for the surgery, immunosuppression and risks for donors and recipients. They say that transplantation should only be reserved for vital organs (27). People against may also consider UTx a form of “reversed surrogacy”, where the donor acts as surrogate in the “foster mother’s” body (25).

Nowadays, UTx costs are completely covered by the clinical trials funding. In GS laws, the pregnancy is covered by the countries’ health system in force and the intended parents pay for pregnancy related expenses (3).

In the future, UTx may become a routine treatment of AUF1, as an alternative or a complement to GS (3).

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