

Gynecological aspects that may affect the risk of preterm birth and the success of embryo transfers after uterus transplantation

Gynekologické aspekty, které mohou ovlivnit riziko předčasného porodu a úspěšnost embryotransferů po transplantaci dělohy

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Summary: Absolute uterine factor infertility is conditioned by the congenital or acquired absence of the uterus or the presence of a nonfunctioning uterus in women who wish to become biological mothers. Uterine transplantation along with assisted reproductive techniques can provide this option for women without a uterus. In the early research period, to minimize the risk of preterm birth and other pregnancy-related complications, the uterus of a donor with a history of one to three successfully completed pregnancies was recommended for transplantation. We believe that insisting on a singleton pregnancy is necessary to reduce the risk of premature birth in uterus recipients, rather than insisting on donating a uterus from a woman with a history of at least one birth. Mild post-transplant narrowing of the vaginal-neovaginal anastomosis was expected; however, the first severe vaginal stricture revealed soon after transplantation was an unpleasant surprise. To prevent post-transplant vaginal stricture, gynecologic surgeons should evaluate the shape and size of the donor's cervix, compare it with the size of the recipient's neovagina and vaginal vault, and perform a vaginal-neovaginal anastomosis to ensure free access for post-transplant cervical biopsies to reveal signs of subclinical rejection and smooth insertion of the embryo transfer catheter into the uterine cavity.

Key words: absolute uterine factor infertility – nulliparity – preterm delivery – uterus transplantation – vaginal stricture

Souhrn: Absolutní uterinní faktor infertility je podmíněn vrozenou nebo získanou absencí dělohy či přítomností nefunkční dělohy u žen, které se chtějí stát biologickými matkami. Osobní reprodukční zkušenost může dnes ženám bez dělohy poskytnout transplantace dělohy v kombinaci s metodami asistované reprodukce. V raném období výzkumu byla v zájmu minimalizace rizika předčasného porodu a dalších komplikací souvisejících s těhotenstvím doporučena k transplantaci pouze děloha od dárkyně s anamnézou jednoho až tří dokončených těhotenství. Ke snížení rizika předčasného porodu by se u příjemkyň dělohy mělo trvat spíše na jednočetném těhotenství než na darování dělohy od ženy s alespoň jedním porodem v anamnéze. Mírné zúžení v místě anastomózy vaginální manžety děložního štěpu a neovaginy příjemkyně jsme předpokládali, ale rozsah první vaginální stenózy časně po transplantaci dělohy byl přesto nepříjemným překvapením. Gynekolog by měl pro prevenci potransplantační vaginální striktury zhodnotit tvar a rozměry děložního čípku dárkyně, porovnat je s rozměry neovaginy a poševní klenby příjemkyně a provést anastomózu děložního hrdla k neovagině tak, aby byl zajištěn volný přístup k děložnímu hrdlu pro provedení cervikální biopsie kvůli kontrole rejekce štěpu a pro hladké zavedení katétru pro transfer embrya do děložní dutiny.

Klíčová slova: absolutní uterinní faktor infertility – nulliparita – předčasný porod – transplantace dělohy – vaginální striktura

Introduction

Absolute uterine factor infertility (AUI) is the congenital (primary) or acquired (secondary) absence of the uterus, or the presence of a nonfunctional uterus in women who wish to be biological mothers in the social and gestational sense.

Adoption and gestational surrogacy are potential routes to motherhood for women with AUI in countries where it is legally permitted. Both gestational carrier identification and adoption are long-term processes with unpredictable outcomes [1]. In addition, for many women,

compensatory surrogacy is not feasible because of financial constraints.

Contemporary society places great emphasis on an individual's experience with pregnancy and childbirth. Uterus transplantation (UTx) together with assisted reproduction techniques can provide this

exceptional personal reproductive experience to infertile women with congenital, e.g., Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, or acquired (post-hysterectomy conditions) absence of the uterus, although motherhood can be achieved after complex transplant/gynecological surgery using immunosuppressants [2]. The risk-benefit ratio of this complex infertility treatment is unknown. Therefore, its effectiveness and safety require further investigation. Several interim results of human UTx trials have been described over the last decade, but only one, the first Swedish trial, has been completed with published results [3,4]. Specialists in many medical disciplines are involved in this promising treatment method for female infertility, with gynecologists and assisted reproductive specialists responsible for the ultimate reproductive success. Several risks are associated with this treatment for mothers, fetuses, and neonates. Therefore, maternal-fetal experts involved in UTx trials should clearly understand the principles, strengths, and weaknesses of this complex treatment method. Detailed knowledge of these issues will help experts ensure that uterine recipients, as well as their fetuses and newborns, will have a strong protection required by scientific research protocols [5].

This article aimed to highlight two maternal-fetal pitfalls of treating AUI with UTx from the perspective of gynecology, maternal-fetal medicine, and assisted reproduction: the risk of preterm delivery with regard to the parity of the donor's uterus and post-transplant stenosis of the vaginal-neovaginal anastomosis.

Risk of preterm birth and parity of the donor's uterus

Preterm birth accounts for 75% of perinatal mortality and > 50% of long-term morbidity in children. The causes of preterm birth at less than 37 weeks of gestation include the following: spontaneous labor with intact membranes, premature rupture of membranes, and other maternal or fetal causes, such as multiple pregnancies.

Generally, a minority of preterm births occur at less than 28 weeks of gestation (extreme preterm birth), with the majority occurring at 34–36 weeks of gestation (near-term birth). Most births after UTx have been preterm, and only some occur around gestational week 37 [3]. Unfortunately, several babies were born at gestational weeks 31–33 with respiratory distress syndrome. The original recommendation to perform elective cesarean section close to week 36 of gestation to avoid possible complications arising from potential risks associated with prolonging pregnancy to term has been modified owing to the growing experience with dozens of pregnancies after UTx worldwide. Unless unexpected complications arise, cesarean section can be performed even after gestational week 37.

In the early stages of human UTx research, to reduce the difficulty of becoming pregnant and minimize the risks of preterm birth and other pregnancy-related complications, the uterus of a donor with a history of at least one to three successfully completed pregnancies is recommended for transplantation. Ten years after the first birth from a transplanted uterus, there are questions on whether there should be insistence on the higher risk of preterm birth when using a uterus from a nulliparous woman rather than when donating a uterus from a woman with at least one completed pregnancy. The course of the first pregnancy and cesarean delivery of a healthy infant at 34 weeks and 6 days of gestation in the uterus of a young nulliparous deceased donor in 2019 may justify the use of this type of uterus in the future [6]. With regard to premature birth and difficulties in conception, the use of a uterus from a donor after a cesarean section or after three or more births may seem questionable. History of cesarean section, especially in a living donor, may contribute to a technically demanding dissection of the bladder from the uterus, as well as uterine vessels and ureters in the parametria, and failure of graft procurement surgery; however, an

effect on preterm birth is unlikely. History of more than three births could contribute, for example, to cervical incompetence and premature rupture of membranes during pregnancy after UTx. However, these hypotheses need to be verified.

Transfers of two or more embryos have contributed to a significant increase in multiple pregnancies and premature births. To reduce the risk of preterm birth in uterus recipients, transferring a single embryo to achieve a singleton pregnancy appears to be more important than insisting on using only a uterus from a donor with a history of one to three completed pregnancies. We strongly believe that the transfer of only one embryo to the transplanted uterus, which was proposed in previous UTx studies, should continue to be followed [7].

Stenosis of neovaginal-vaginal anastomosis

Mild narrowing of the vaginal-neovaginal anastomosis we expected before severe post-transplant vaginal stenosis of the uterine graft-to-neovaginal anastomosis was confirmed [8]. Compared with the soft nature of the vaginal vault in post-hysterectomized women, a firm neovaginal vault in women with MRKH syndrome appears to be a risk factor for vaginal stricture after UTx. The neovagina of a woman with MRKH syndrome created using surgical and dilational approaches is usually shorter than a normal vagina and has a narrow and rigid vaginal vault [9]. Therefore, if a bulky cervix is anastomosed to the neovaginal vault of a recipient with MRKH syndrome, partial transverse resection of the solid vault using a sharp technique should be considered to create a large opening into the neovagina before performing the anastomosis suture. The goal of this procedure is to perform anastomosis without tension, thereby reducing the risk of postoperative stricture. However, resection of the vaginal vault can shorten the already short neovagina.

A high-degree post-transplant vaginal stricture 2 cm distal to the cervix is always an obstacle to the smooth transcervical insertion of a soft embryo transfer

catheter into the uterine cavity. Technically demanding post-transplant embryo transfers can affect the embryo transfer/pregnancy success rate. Repeated dilation of a post-transplant vaginal stricture using various techniques, such as long-term vaginal insertion of metal stents for the treatment of strictures in gastroenterology, may contribute to the gradual worsening of the stricture [8]. In addition, the risk of uterine infection and intrauterine adhesions may increase due to repeated manipulations near the cervical canal. Prolonged vaginal stenting during pregnancy may increase the risk of septic abortion, particularly during the second trimester. The risk of complications during and after surgical incision or non-surgical dilation of strictures is high. A serious complication occurred in a uterus recipient with severe vaginal stricture when the bladder was injured, and a vesicovaginal fistula was formed during repeated electro-surgical incisions of the scarred ring of the vaginal stricture seven months after UTx. Subsequently, a laparotomy with closure of the fistula and excision of the vaginal stricture had to be performed [10].

Vaginal strictures can also cause deterioration of blood flow during menstruation, long-term sexual dysfunction or at least temporary interruption of coital activities, difficulties during spontaneous or instrumental abortion, and increased risk of incomplete evacuation of lochia if the transplanted uterus is left *in situ* for another pregnancy. Swedish pioneers in UTx performed surgical correction of vaginal strictures in two uterus recipients [11]. Researchers from four centers in the United States have frequently encountered post-transplant vaginal strictures, the majority of which had to be treated with either dilation or electro-surgical incision of the scarred ring [12].

Conclusion

The goal of AUFI treatment using UTx and assisted reproduction techniques is the birth of a healthy child after early post-transplant initiation of embryo transfer with uterine graft explantation soon after reproductive plans have been met to discontinue immunosuppressant treatment. To avoid vaginal stricture, which can be a risk factor for conception and premature birth, gynecologists should evaluate the shape and size of the donor's cervix (using ultrasound and direct visualization), compare it with the size of the recipient's neovagina and vaginal vault, and perform a tension-free vaginal-neovaginal anastomosis to ensure free access for post-transplant cervical biopsies to reveal signs of subclinical rejection and smooth insertion of the embryo transfer catheter into the uterine cavity.

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