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Uterus Transplantation: Potential Patients, Fertility in Animal Models and Ethics

C. Díaz-García^{1,2}, M. Brännström^{1,3}

Uterus transplantation (UTx) has been suggested as an alternative to surrogacy to achieve genetic motherhood. Extensive experimental research must be done before any kind of transplantation moves to the clinical field in order to guarantee its safety and effectiveness. Since the final aim of this kind of transplantation is to accomplish motherhood, the success of UTx should be evaluated not only in terms of organ/patient survival but also in terms of functionality, which means that full-term pregnancies with healthy offspring should be considered as the measure of success. In this review we summarize the experimental studies accomplished during the last decade, using fertility as the main outcome, which we consider as the base for further development of UTx towards a clinical setting. Characteristics of potential patients and ethical concerns are also discussed. **J Reproduktionsmed Endokrinol 2013; 10 (Special Issue 1): 72–81.**

Key words: uterus, transplantation, infertility, pregnancy, ethics

■ Introduction

During the last 2–3 decades the clinical fields of transplantation surgery and reproductive medicine have been the birthplaces of several clinical innovations, which have had profound positive consequences for large patient groups. Several of the novel treatments have as well affected the society at large and resulted in active media debate, in particular from the ethics perspective.

In reproductive medicine, the introduction of gonadotropin stimulation, in vitro fertilisation, intracytoplasmic sperm injection and oocyte donation have led to that most types of female and male infertility now can be effectively treated. The groups of infertile women that today, in spite of the developments in reproductive medicine, are untreatable are those that are irreversibly infertile due to uterine cause.

During the last decade, the discipline of transplantation surgery has introduced several organs/tissues for transplantation, which would enhance the quality-of-life of a patient rather than being necessary for a continued life. Examples of these novel types of procedures are transplantations of the hand [1], the abdominal wall [2], the larynx [3], and the face [4]. Uterus transplantation (UTx) may provide a chance for uterine infertile patients to experience pregnancy and to give birth, which naturally is a very

essential aspect of the quality-of-life [5] of a woman and her partner. Uterine infertile patients can today attain genetic parenthood by use of gestational surrogacy, which is permitted in some countries although most societies disapprove of its use because of ethical, religious or legal reasons [6].

The research field of UTx has advanced considerably during the last decade, research with activities and interest augmented by the human UTx case, which was performed in Saudi Arabia in 2000 [7]. The human UTx effort was partly successful since the surgery, involving a living donor and a 26-year old recipient, went uneventful. The uterus did not reject but had to be removed 3 months after transplantation due to uterine prolapse with thrombotic vessels.

The large amount of UTx research during recent years have used several animal models to study issues such as techniques for retrieval and transplantation surgery, uterine tolerance to ischemia-reperfusion, rejection mechanisms and tests of immunosuppressants to prevent rejection [8]. The ultimate goal of UTx research is to develop techniques that can enable long-term survival of a uterine graft with the potential to successfully implant an embryo and to carry a pregnancy to term.

The purpose of this review is to summarize the groups of uterine infertile patient

that may benefit from UTx and also to cover the animal-based UTx research that has tested the fertility potential of a transplanted uterus (Tab. 1). Additionally, the central ethical aspects of UTx will be discussed.

■ Uterine Infertility

Several groups of patients can be classified as infertile due to absence of the uterus or presence of a type of uterine dysfunction that cannot be corrected by surgery or hormonal/pharmacological treatment. This uterine infertility can either be acquired or occur as a consequence of a congenital malformation and include causes with no uterus present and those with a malfunctioning uterus (Fig. 1). The prevalence of uterine infertility among patients of childbearing age is not exactly known but it is likely to be significant, with a recent estimation of as many as 12,000–15,000 uterine infertile patients in the United Kingdom [9]. This estimation would indicate the presence of more than 150,000 uterine infertile patients in Europe, although obviously only a portion of these would have the firm desire to carry a pregnancy through UTx.

Numerically, the largest group of women with uterine infertility is that of women that have undergone hysterectomy during fertile age. Each year in the United States, around 600,000 women are hysterectomized and a substantial proportion

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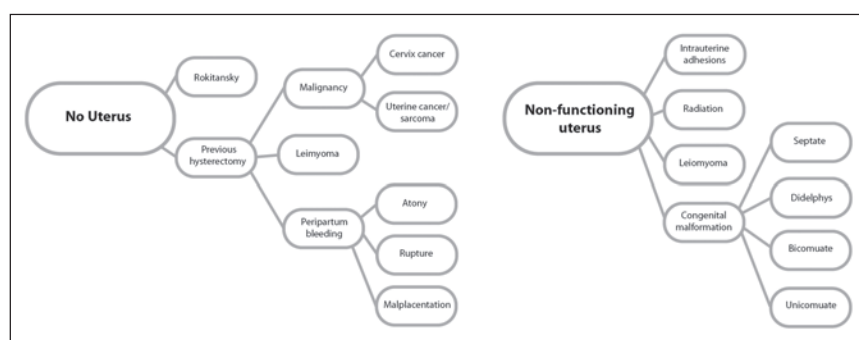
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Table 1. Results of the experimental models analyzing fertility after uterus transplantation.

Degree of histocompatibility	Study	Animal model	Position of the graft	Mode of conception	Pregnancy rate (per surgery)
Syn	Racho 2002 [59]	Mouse	Heterotopic	Embryo-transfer	*
	Racho 2003 [60]	Mouse	Heterotopic	Embryo-transfer	100%
	Racho 2003 [62]	Mouse	Heterotopic	Embryo-transfer	47.4%
	Wranning 2011 [63]	Rat	Orthotopic	Natural mating	40.7%
Auto	Enskog 2010 [71]	Baboon	Orthotopic	Natural mating	0%
	Wranning 2010 [67]	Sheep	Orthotopic	Natural mating	21.4%
Allo	Díaz-García 2010 [73]	Rat	Orthotopic	Natural mating	62.5%
	Ramírez 2011 [74]	Sheep	Orthotopic	Embryo-transfer	25%

* Only one animal underwent embryo-transfer as part of the graft evaluation protocol

**Figure 1.** Uterine infertile patients that may become treated by uterus transplantation. © M. Brännström

tion of these surgeries are performed in patients below 40 years of age [10]. In an IVF program, including surrogate gestation as a second step, around half of the enrolled women with uterine infertility had previously been hysterectomized [11], which give an indication of the relatively great size of this population among uterine infertile patients. The grounds to perform a hysterectomy at fertile age are numerous as described below in some cases, a hysterectomy; to remove a non-functional uterus, could also be an initial step in the UTx procedure.

Gynaecologic Cancer and Uterine Infertility

In women of fertile age, the ovary and the cervix are by far the most common primary sites of a gynecologic malignancy although primary malignant tumours of the uterus do also occur in women below the age of 40 years [12]. Cervical cancer is universally the most common gynecological malignancy [13], but with relatively low incidence in several developed countries after the introduction of effective screening programs to detect high grade cervical dys-

plasia [14]. Still, cervical cancer affects a large proportion of relatively young women, also in developed countries, with around > 30% being of fertile age at diagnosis [13, 15]. Since the average age of first-time motherhood is rising in the western world, a large portion of cervical cancer patients of fertile age will be nulliparous. Many of these young patients with cervical cancer have an early stage disease, with the tumour limited to the cervix and in some cases also involving the upper parts of the vagina. The 5-year survival rate for these women is above 75% [16]. In patients with early stage cervical cancer with stromal invasion of less than 3 mm, a cervical cone is the treatment of choice in women of fertile age. Larger tumours and those with greater invasion (stage Ib-IIa) should be treated with a surgical procedure that is more radical than conisation and also including pelvic lymphnode dissection. The ovaries are generally spared since the risk of ovarian metastasis is very low. Concerning squamous cell carcinoma of the cervix with a size < 2 cm and with invasion depth < 10 mm, a local radical fertility preserving procedure such as vaginal trachelectomy [17] or abdomi-

nal trachelectomy [18] should be performed. Larger tumours have to be surgically removed by a radical hysterectomy. In an analysis of cervical cancer patients who had undergone radical hysterectomy at a major cancer centre in the United States, during a time-era before introduction of the trachelectomy procedure, it was found that more than 40% were of fertile age at the time of diagnosis [15]. Out of these patients, about half of them would today still be, recommended radical hysterectomy because of a tumour size greater than 2 cm, in spite of the availability of trachelectomy surgery. These patients could in the future be candidates for UTx. Even if adjuvant radiotherapy over the pelvis or chemotherapy, which both may be toxic to the ovaries, are given after cervical cancer surgery, future fertility for these patients would be possible by gonadotropin stimulation followed by oocyte cryopreservation [19] or IVF and embryo cryopreservation prior to these adjuvant cancer therapies. More than 99% of cervical cancers are caused by an infection with an oncogenic strain of human papillomavirus [20] and it has to be ensured that the virus is cleared from the epithelia of the upper vagina, before transplantation. Clearance of cervical HPV infection usually occurs within 2 years after primary infection although HPV persistence is seen in around 15% of oncogenic HPV types [21].

Endometrial cancer of stage 1 and localized uterine sarcoma are rare in fertile-aged women, only around 2.5% of the cases occur during this life period [12]. The surgical treatment of these malignancies normally includes oophorectomy but sparing of the ovaries or cryopreservation of oocytes/embryos could be considered, so that UTx would be useful at a later stage.

Non-Gynecologic Malignancies and Uterine Infertility

Treatments of non-gynecological malignancies may result in uterine infertility. Cancer during childhood or early adult life affects around 1 in every 400 female and the long-term survival of these cancer victims is today above 70% [22]. Radiotherapy, given either as total body irradiation in preparation for bone marrow transplantation, abdominal irradiation (mostly for Wilm's tumor, rhabdomyosarcoma, Ewing's sarcoma) or total lym-

phoid irradiation causes considerable (around 60%) reduction in uterine volume [23] and this shrinkage is irreversible [24, 25]. Even though a small number of women with radiation-shrunk uteri will achieve pregnancies there will be a considerable risk for miscarriage and mid-trimester pregnancy loss [26]. Radiation is gonadotoxic and doses of 5–20 Gy administered to a field that includes the ovaries impairs gonadal function in most women [27]. Thus, post-pubertal females given radiation over the pelvis will become menopausal within a short time after radiation in > 90% [28] and pretreatment cryopreservation of oocytes, embryos or ovarian cortex would be a prerequisite for UTx in these women. In the situation of a radiation-damaged uterus in a prospective UTx-patient, the organ could be replaced in a combined procedure of hysterectomy and transplantation. At such hysterectomy of a radiation-injured uterus, the long proximal ends of the uterine arteries and veins could be spared to facilitate the transplantation surgery. A concern in this type of patient is however the surgical difficulties related to scarring, adhesions and impaired healing induced by radiation [29].

Myoma and Uterine Factor Infertility

The prevalence of uterine myoma increases with age [30] with a frequency of around 8% in a random sample of Scandinavian women between 33 and 40 years [31]. In the United States, a comparable prevalence was seen in Caucasian women but with a 2-fold higher prevalence in Afro-American woman [32]. Myoma and the related symptoms is a common cause of hysterectomy during the premenopausal period and in the United States approximately 1% of all women between 30 and 34 years and around 2.5% of those between 35 and 39 have been hysterectomized due to myoma [33]. In addition, myoma [34, 35] is a factor behind infertility, although the myoma-related infertility can be surgically treated to some extent [36]. Concerning surgical myomectomy of large/multiple intramural myoma, a prospective but non-randomized study showed fertility in around 60% of the operated patients [37]. The patients that remain infertile despite myomectomy and the large numbers that have undergone hysterectomy [10, 33] because of large

symptomatic myoma belong to the group of myoma-related uterine infertile patients that could be treated by UTx.

Intrauterine Adhesions and Uterine Infertility

Intrauterine adhesions (IUA), with a prevalence of around 1.5% among fertile-aged females [38], is another cause of absolute uterine infertility. Endometritis, especially that caused by genital tuberculosis, is the most common cause of severe IUA [39]. Other origins of adhesions inside the uterine cavity are surgical curettage at legal abortion or post partum [40]. In general, these adhesions results in infertility in around 50% of women and in the event of early pregnancy the miscarriage rate is around 40% [41]. The treatment of choice for intrauterine adhesions is hysteroscopic adhesiolysis which shows effectiveness to cure infertility in mild, moderate and severe IUA of around 90%, 70% and 30%, respectively [42]. From these data it can be estimated that around 1/3 of the patients with in this category are unreservedly uterine infertile and these women may in the future be treated by a combined hysterectomy-UTx procedure.

Emergency Peripartum Hysterectomy and Uterine Infertility

Emergency peripartum hysterectomy is performed to save the life of the mother in situations of severe bleeding due to uterine rupture/atony, invasive malplacentaion or uncontrolled bleeding at caesarean section. The incidence of hysterectomy in conjunction with birth is around 5 in 10,000 deliveries and will most likely increase in the future due to the escalating number of women having caesarean section [43].

Congenital Uterine Malformations and Uterine Infertility

Congenital uterine malformations, which occur because of disturbances during foetal life in the formation, development or fusion of the Müllerian (paramesonephric) ducts, represent a large group of uterine infertility, but these malformations may also increase the risk of premature birth and obstetric problems [44].

The factual prevalence of uterine malformations in the general population is uncertain, although prevalences of

around 6.7% in the general female population, 7.3% among infertile patients and 16.7% in women with recurrent miscarriage have been approximated [45]. As further pointed out in the paragraphs below, a majority of the total group of these patients are fertile. Nevertheless, a considerable portion of the patients will remain infertile, in spite of corrective surgery.

The most prevalent type of structural congenital uterine anomaly among infertile women is the septate uterus [45], which is the result of incomplete resorption of the central parts of the two fused Müllerian ducts. The septate uterus makes up around 1/3 of all uterine malformations [46]. Spontaneous abortion occurs in about 80% of pregnancies in untreated septate uteri [47] but hysteroscopic resection is an effective treatment and substantially decreases the miscarriage rate [47]. Even so, a small proportion of patients with surgically treated uterine septate will still remain infertile [48].

The second most common type of uterine malformation is the bicornuate uterus, where disturbed fusion of the two Müllerian ducts results in two fully developed uterine horns with a smaller common cavity. The bicornuate uterus represents around 1/4 of all uterine malformations [46]. The rate of spontaneous abortion among women with bicornuate uteri is around 35% [49]. Surgery decreases the rate of abortions [50], but a substantial number of women with bicornuate uteri will not be able to carry a pregnancy to the second or third trimester and there is also an increased risk of uterine rupture during the 3rd trimester.

The less common unicornuate and uterus didelphys comprise around 20% of uterine malformations [46]. Disturbed development of one of the Müllerian ducts will result in the unicornuate uterus, with or without a contralateral rudimentary uterine horn. A total failure of fusion of the Müllerian ducts results in uterus didelphys, i. e. two separate uterine horns without a common cavity. The potential to establish a pregnancy in these two types of malformed uteri is decreased and in case of pregnancy around 30% will end in miscarriage and the total live birth rate is only around 50% [46].

Surgery does not seem to improve the pregnancy potential of the unicornuate/didephys uterus [51]. Thus, a considerable proportion of these patients are unable to carry a pregnancy into the 3rd trimester.

The most extensive type of Müllerian anomaly is uterine agenesis, which on the other hand is fairly uncommon and representing only around 3% of all Müllerian anomalies [46] or one in every 1:4500 females [52]. Typically these women have a rudimentary solid bipartite uterus in combination with absence of the vagina above the hymenal ring. The syndrome is generally named the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome or only the Rokitansky syndrome. It is usually diagnosed around the age of 14–16, because of primary amenorrhea [53]. Girls with the MRKH syndrome develop into phenotypically normal female adults, with the exception of that there is no vagina above the hymenal ring. In general, a neovagina is surgically created in young adulthood by use of either split-thickness skin grafts, peritoneal lining, sigmoid colon or dilatation from the vulvar indentation [54].

Women with the MRKH syndrome have a normal female karyotype and the sporadic occurrence of the syndrome may be because of a highly variable expressivity of a single mutant gene [55] or epigenetic changes during fetal life. Familial aggregates of MRKH-cases have also been reported [56]. The outcome of gestational surrogate pregnancies with MRKH patients as the genetic mothers [57] does not demonstrate any increased malformation risk in the offspring. Fifty eight MRKH women underwent IVF stimulation with placement of embryos in surrogate mothers. These attempts resulted in 34 live births (17 female) and no genital malformation was seen among these.

Three distinct subtypes of the MRKH syndrome exist. The typical subtype, which goes without extrauterine malformations, is present in around 50% of MRKH-patients. The atypical subtype of the MRKH syndrome, with associated malformations in the renal system, is present in around 20% and the severe form of the MRKH syndrome, named MURCS (Müllerian duct aplasia, Renal aplasia, and Cervicothoracic Somite

dysplasia), is found in around 30% [58]. Women with the typical MRKH syndrome would be suitable patients for UTx in the future. Provided a neovagina of sufficient length exists, it could easily be surgically connected to the cervix of a transplanted uterus. Caesarean section would be the preferred mode of delivery at a future pregnancy since it is unclear whether a neovagina would have the capacity for dilatation at labour.

■ Fertility in Experimental UTx Models

A large number of studies on experimental UTx have been published during the last decade, but most of these studies have not involved fertility tests, which is a very important issue in UTx development. The reason for the scarcity of publications of fertility outcome after UTx, is that the development of each experimental model have been cumbersome, with the need to initially give special attention to the complicated surgery of UTx [8].

In general, one basic problem in evaluating results, including fertility outcome, of experimental transplantation is to separate the potentially harmful effects of ischemia-reperfusion and surgical trauma from the degenerative process of rejection. Auto-transplantation experiments and syngenic transplantation have commonly been used in initial animal-based developments of transplantation of new types of organs.

The knowledge from auto/syngenic transplantations, concerning surgical techniques and other related issues have then been used in the more complicated allogenic transplantation situation.

The research concerning fertility after UTx has also followed this pathway, as outlined below.

Syngenic Experimental UTx and Fertility

Experimental syngenic transplantation models can be used to isolate the effects of surgery, ischemic effect and the new anatomical placement of a transplanted organ from effects of rejection and immunosuppressive agents, which add to the complexity of experimental allogenic transplantation. The relationship between the donor and the recipient in

syngenic transplantation is that of being from the same inbred strain of a species. Therefore, the donor and recipient will then to a large extent be genetically identical. In the human situation this would be similar to transplantation between identical twins.

Concerning small experimental animals as the rodents, several inbred strains exist and can be used to avoid rejection in a transplantation situation. The mouse has the advantages of ample availability of gene-modified mouse strains and the accessibility of recombinant proteins and monoclonal antibodies in this species. The weight of these mice (20–25 g) is only about 10–15% of the weight of the rats used in UTx research (see below).

Thus, our primary rodent model, which was thoroughly explored concerning UTx and fertility, was the mouse model. In the initial study F1 hybrids of females of the inbred strains C57BL/6 and CBA/ca were used [59]. It was decided to use a model of heterotopic UTx, where the native uterus was kept in situ as an internal control (Fig. 2). The donor surgery (45 min duration) involved isolation of one uterine horn together with the common uterus cavity on a vascular pedicle containing all vessels and including the aorta and the vena cava. All branching vessels on this pedicle were ligated or coagulated with bipolar diathermy and the uterus was lifted out of the body after it had been freed from its attachments to the bladder, ureters and the broad ligament. The transplantation was end-to-side to vena cava and aorta of the recipient, with advanced microsurgical skills needed since the lumina of the aorta and vena cava were only about 0.7 mm and 1.5 mm, respectively. Notably with the cervix of the heterotopically transplanted uterus kept intra-abdominally to avoid ascending infections through the cervix of the graft. In this paper [59] the fertility potential of this first model of syngenic UTx was tested only in one of the transplanted mice. At about two weeks after UTx, blastocysts were retrieved from a naturally mated mouse. The blastocysts were transferred to the uterine graft of the transplanted mouse, which had been made pseudopregnant by mating with a vasectomised male. Since the complete uterine graft was positioned intra-abdominally, the embryo transfer was performed via a midline laparotomy and a

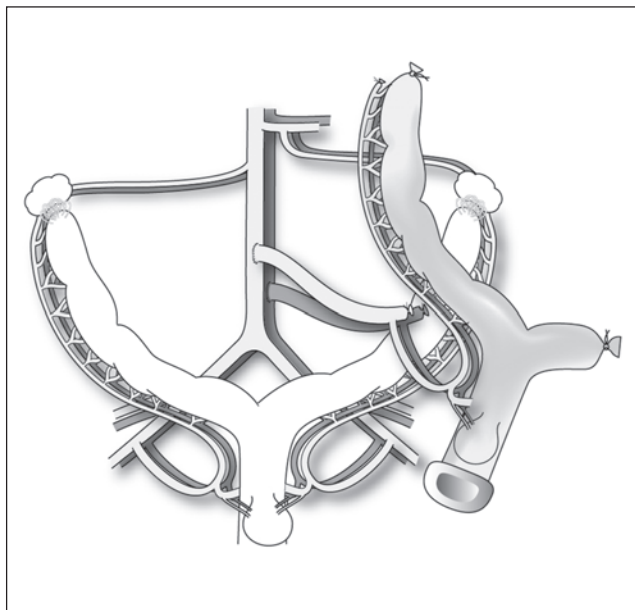


Figure 2. Schematic drawing of uterus transplantation in the mouse.
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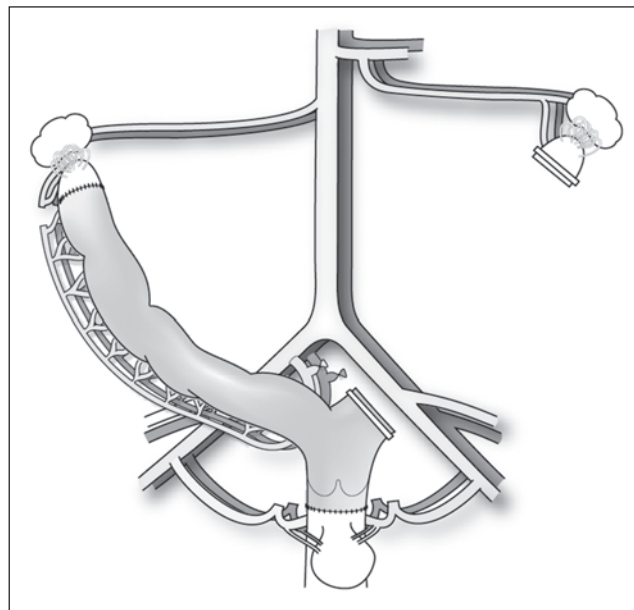


Figure 3. Schematic drawing of syngenic/allogenic uterus transplantation in the rat.
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thin cannula, which was inserted through the myometrium, provided a canal for transfer of the embryos to the lumen of the uterine cavity of the uterine graft but also to the native uterus. Out of the 6 transferred blastocysts, 3 were placed inside the native uterus and 3 inside the graft with pregnancy evaluated 10 days after embryo transfer. The results were that of 3 fetuses of normal size seen in the native uterus and one foetus in the transplanted uterus, which in addition exhibited an absorbed pregnancy. The paper [59], although limited concerning tests of fertility, represents the first important proof-of-principle study in relation to the fertility potential after UTx. However, it should be emphasized that the experiments were performed in a syngenic investigation situation.

In the follow-up paper, also involving the syngenic mouse UTx model the transplantation procedure was modified so that the cervix of the heterotopically placed uterine graft (Fig. 2) was attached to a cutaneous stoma [60], instead of being positioned intra-abdominally as in the initial method [59]. The reason for this modification was that the grafted uteri of the initial study [59] often presented with accumulated intraluminal mucus, which may have been caused by poor drainage of uterine/cervical fluid through the intraabdominal cervix.

Thus, the surgery was adapted so that cervix would be attached to a cutaneous

stoma to drain any uterine and cervical fluid (Fig. 2). In this larger series of animals, with the identical combination of inbred female mouse as described above, the modified transplantation model was used [60]. The pregnancy rate in 12 transplanted animals carrying both native and grafted uteri were compared with 13 animals undergoing sham surgery. The mice with transplanted uteri received embryos during the interval from 1-3 weeks after transplantation, with blastocysts (3-6 to each uterus) placed inside the uterine cavity by the well-established transmyometrial approach [61]. The experiments were divided into two series, where the first evaluated fertility at day 18 of pregnancy, a time which is about 2-3 days before anticipated parturition. The pregnancy rate was similar in the native and the grafted uterus of the transplanted animals as compared to control animals with pregnancy rates of 75% in the native uterus of transplanted animals, 66% in the grafted uterus of the transplanted animals and 66% in control animals. Importantly, the median numbers of foetuses in the pregnant animals were similar in the groups with 4, 4 and 3 in native, grafted and control uterus, respectively. Taken together, the results of this paper [60] points towards that the fertility potential and physiological environment to support a pregnancy is similar in a transplanted uterus as in a normal situation. The paper [60] also examined the weight of the foetuses at day 18 and that of the

placenta. There was no difference in weight or length of animals as well as of the placental weights between the groups. In the second series of the experiment in the same paper the pregnancies were allowed to go to full term and pups were delivered either spontaneously but caesarean section delivery was attempted from the grafted uterus, since poor dilatation of the birth canal would be anticipated in the transplanted uterus with its cervix passing through the collagen-rich skin of the mouse. In some cases spontaneous deliveries occurred from the heterotopically transplanted uterus and that was typically seen 6-12 hours after spontaneous vaginal delivery. This delay in spontaneous labour from the grafted uterus is most likely due to mechanical factors, with slow cervical dilatation at the point of passage through the skin but other mechanisms related to poor innervation of the uterine graft or the higher abdominal position of the organ cannot be ruled out. The growth trajectory of these offspring was followed for 8 postnatal weeks and growth was found to be normal, as compared to animals from native uteri and from control animals. In order to rule out that the native uterus would exhibit a positive effect on the grafted uterus, some animals underwent UTx with the native uterus removed [60]. These experiments also demonstrated pregnancies in the transplanted uteri, indicating that these pregnancies were not dependent on influences from the native, intact uterus. The

fertility of both male and female offspring from the grafted uterus was normal and the second generation offspring from these mice, with their foetal development inside a transplanted uterus, were also of normal birth weight. Taken together, this is the first study [60] ever to demonstrate live births from a truly transplanted uterus. It is of importance since it clearly shows that a denervated uterus with altered vascular connections and also devoid of proper lymphatic drainage as well as in a non-physiological position may act normally in a situation of embryo implantation and pregnancy.

In a follow-up study, identical transplantation and embryo transfer techniques, as discussed above, were used but the transplanted uterus was tested for tolerance to cold ischemic injury by being kept *ex vivo* for 24 h or 48 h in University of Wisconsin (UW) solution in between retrieval and transplantation [62]. Uteri that had been subjected to cold ischemia for 48 h became necrotic after transplantation. However, those with 24 h in UW showed normal morphology 2 weeks after UTx and in these six animals fertility was by embryo transfer (3–6 embryos in each graft) and pregnancies were seen in 5 out of six transplanted uteri with the growth trajectory of pups during an 8 weeks follow-up period being normal.

The fertility after UTx has also been tested in the other commonly used rodent model, the rat. The advantage of the rat, as compared to the mouse, is the larger (> 4 times) body size, which probably is one reason why this species is a popular animal model in transplantation research in general. In our syngeneic rat UTx model the uterus was orthotopically transplanted between inbred rats of Lewis strain [63]. The transplantation procedure involved retrieval of the right uterine horn together with the caudal common uterine component, the cervix and 2–3 mm of the upper vagina. The vascular tree of the graft included the uterine vessels, internal iliac vessels and around 4 mm of the common iliacs. The recipient underwent hysterectomy but the tip (3 mm) of the native right uterine horn was spared, to be anastomosed to the cranial part of the grafted uterus (Fig. 3). In this way the uterotubal junction and the oviduct was left undis-

turbed, which was an important component to allow for natural conception to occur. The pregnancy potential of this syngenic model of a uterine graft, with one uterine horn excised, was compared to sham operated rats. In the series of 19 animals of both transplanted and sham-operated animals, pregnancy rate was similar (11 rats in the UTx group versus 12 in the sham). The median numbers of pups were 3 in the UTx group and 3.5 in the sham group. However, the major difference, possibly of biological significance, between the sham group and the UTx group was that the UTx group had lower rate of successful deliveries. An explanation to this may be a protracted labour in the transplanted uterus, caused by denervation. This assumption was based on a previous paper showing that the sensory innervation of the uterus is necessary for a normal delivery in the rat [64]. The growth trajectory of the live births from the sham and the UTx groups was similar, although the number of live births in the UTx group was too low to draw any firm conclusions. This paper [63] represents the first UTx model of any species that has demonstrated live birth after natural mating.

The results of these syngenic rodent UTx models, as discussed above, are important as the first demonstrations of the principle of fertility potential in a transplanted uterus. An advantage of the rodent models is the existence of a vast knowledge of rodent reproductive physiology and also the possibilities to in the future to use gene modified models, with also possibilities to compare a native uterus with a gene-modified transplanted uterus or vice versa, within the same animal. However, being rodent models, the experimental situation is certainly different from a human situation concerning surgery and also pregnancy length as well as placentation.

Autologous Experimental UTx and Fertility

Autologous transplantation is a methodology that has been used traditionally in developments within solid organ transplantation in large animal models. In these experiments, the organ will be surgically removed from the animal and kept *ex vivo* for some time before it is transplanted back either to an orthotopic site or to a heterotopic site. The autologous transplantation situation will test

the surgical procedure of transplantation, the tolerance of a graft to ischemia and perfusion injury as well as effects of the altered vascular supply of the graft. The auto-UTx models that have been used in research are the sheep [65–67], the pig [68], the rhesus macaque [69], the cynomolgus macaque [70] and the baboon [71]. However, fertility has only been evaluated in the sheep, the rhesus macaque and the baboon UTx models.

The sheep auto-UTx model, also included a uterine graft with one of the uterine horn excised, in analogy with the rodent syngeneic models [65]. The reason for this surgical technique was to only use a vascular pedicle on one side, and thereby simplify both the retrieval surgery and the vascular anastomosis surgery. In view of the fact that there is a close physiological interplay between the uterus and ovary in regulation of luteolysis [72] possibly involving counter-current mechanisms it was decided to use a graft consisting of the common uterine cavity with one uterine horn and the ipsilateral oviduct and ovary (Fig. 4). This would also allow for minimal surgical trauma to the oviduct, which would be of importance to permit for natural conception. The vascular pedicle including the ovarian artery, the uterine artery and the ovarian uterine vein was dissected. The ovarian artery of the sheep is only about 1 mm wide and a direct anastomosis with good vessel patency, of this tiny vessel would require great microsurgical skills. Thus, to simplify the procedure a patch (diameter of about 7 mm) from the aorta including the origin of the uterine artery was included. The duration of surgery for the procurement was about 4 h. Vascular anastomosis of the anterior portion of the internal iliac artery, the utero-ovarian vein and the aortic patch with the ovarian artery were accomplished on the external iliac vessels (Fig. 4).

Initial animals were used to establish that the vaginal anastomosis was healed after 2 months and that cyclicity was re-established, which also was seen at this time-point. Five animals were subjected to natural mating some months after transplantation. They were compared to 5 control animals, not undergoing any surgery at all. All control animals mated and became pregnant with normal offspring. Four of the auto-UTx sheep

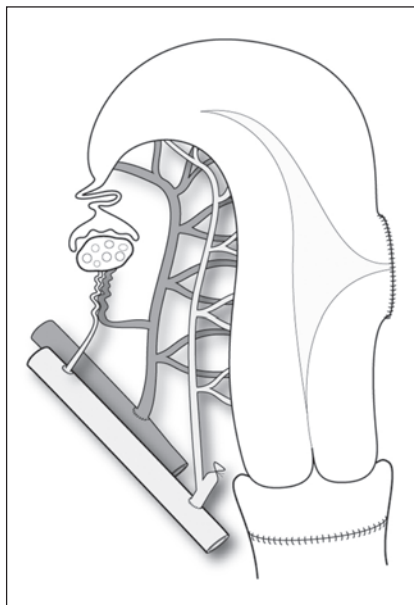


Figure 4. Schematic drawing of autologous uterus transplantation in the sheep. © M. Brännström

showed mating and pregnancies to full term were seen in 3 out of 5 animals. One of these pregnant ewes, showed contractions compatible with initiation of labour but they disappeared after 24 h. A caesarean section was made and a 360°-rotated uterus containing a twin pregnancy was found. The site of the torsion was the lower segment and both lambs were dead. Uterine torsion at labour is a well-known complication in sheep, but it may well be that inadequate fixation of the transplanted uterus contributed to the torsion.

In this study [67] the crown-rump lengths and the placental weights did not differ between the groups. In conclusion, this fairly small animal study represents the first report of fertility after transplantation in any large animal species.

Studies on fertility after UTx, was actually performed four decades ago when uterus and the oviducts were transplanted in the rhesus macaque by use of the omentum as a site for spontaneous neovascularisation [69]. The subtotal hysterectomy specimen was attached to the cervical stump of the recipient and the omentum was wrapped around and sutured to the uterus and oviduct in four monkeys as an auto-transplantation procedure. The auto-UTx uteri remained of normal size and with signs of satisfactory revascularization, since menstruation was resumed. However, no pregnancy occurred in any of these uteri al-

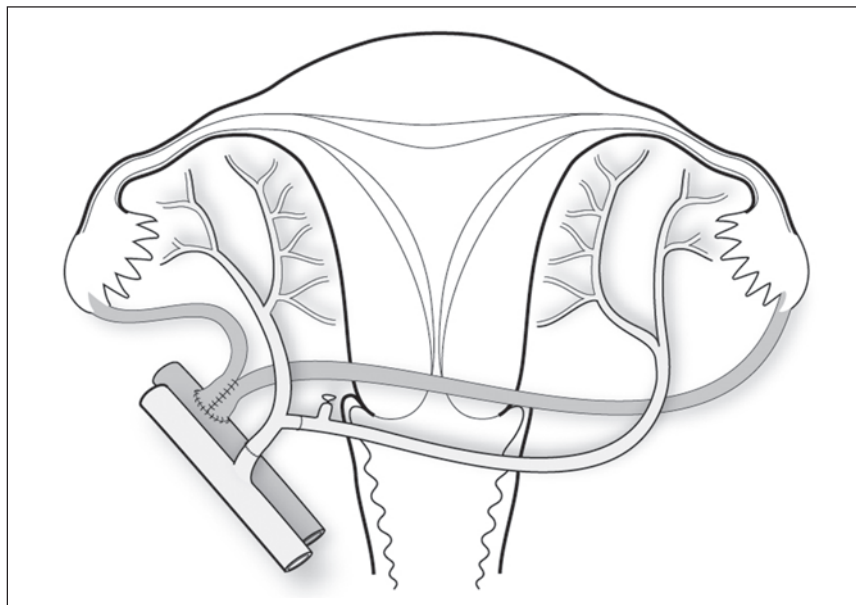


Figure 5. Schematic drawing of autologous transplantation in the baboon. © M. Brännström

beit several breeding attempts. It was speculated that postoperative adhesions prevented fertilization.

Our group has also explored a primate model (baboon) for autologous UTx [71]. In an initial study a surgical model to transplant the uterus together with the ovaries was developed [71]. The model was later modified, which enhanced the success rate in terms of restored menstruation from 20% [71] to 60% (our unpublished data). The modification included arterial vascular anastomosis end-to-end in the internal iliac artery (Fig. 5) instead of end-to-side to the external iliac artery and also more extensive flushing of the organ ex vivo. More than 50 occasions of timed mating occurred after UTx but no with pregnancy resulting. However, post mortem examination showed tubal occlusion in all animals and this tubal blockage may well be due to inflammatory changes secondary to transplantation associated ischemic damage.

Allogenic Experimental UTx and Fertility

The allogenic UTx situation is naturally more complex than syngenic and autologous UTx, since the effects of rejection and immunosuppressants are also added as extra factors that may affect the fertility potential of a transplanted uterus.

In 2010, our group described for the first time pregnancy after allogeneic UTx

[73] and this should be regarded as a major breakthrough in the research field of UTx. The surgical technique used in this study was essentially the same as for the syngenic rat model (Fig. 3). The uterus donor, of Dark Agouti (RT1av1) strain, was operated by a midline laparotomy to surgically isolate the uterus, with the right uterine horn excised. The vascular pedicle of the graft comprised all vessels from the uterine vessels up to and including the common iliacs. The graft was flushed ex vivo and preserved cold in preservation solution. The uterus recipient, of Lewis (RT1l) strain, was prepared for UTx by hysterectomy and dissections of the common iliac artery and vein on the right side, to be used as vascular anastomosis sites. Transplantation of the uterine graft was accomplished by end-to-side anastomosis (10–0 sutures) of the common iliac vessels of the graft to the common iliac vessels of the recipient. The vaginal rim of the graft was anastomosed end-to-end to the native vaginal vault and the top of the uterine graft was anastomosed end-to-end to a tiny remaining distal portion of the native uterus containing the utero-tubal junction, which was preserved to enable mating with natural conception. The immunosuppressant given to prevent uterine graft rejection was tacrolimus at a dose of 0.5 mg·kg⁻¹·day⁻¹. In addition to the transplanted group (UTx-Tac) 2 control groups were included in this study: (1.) rats undergoing just sham surgery (hemihysterectomy; Sham) and

(2.) rats undergoing sham surgery and the same immunosuppressive protocol as the transplanted group (Sham-Tac) [73]. After introduction of the experimental animals to males of proven-fertility, cesarean sections were performed on pregnancy day 17. The number of fetuses and implantation sites were counted. Pregnancy rates were slightly (but insignificantly possibly due to the small sample size [$n = 19$]) decreased in the groups undergoing immunosuppression: 62.5% in the UTx-Tac-group, 60% in the Sham-Tac-group, as compared to 83% in the Sham-group [73]. This study was only designed to prove that pregnancy was possible after allogenic UTx and to evaluate the possible impact on implantation rate. This is a step-by-step method we have used in studies on other aspects of experimental UTx.

Thus, we have continued with the research on fertility after allogenic UTx in the rat model, to add the next important step which is offspring health and development. In the follow up experiments in 2011 we used Lewis (RT1l) rats as donors and PVG (RT1c) rats as recipients (our unpublished observations). Similar groups as in the previous study [73] were used but the difference was that the pregnancies were followed until term (day 22). The pregnancy rates were similar to those previously described (50% in the UTx-Tac-group, 80% in the Sham-Tac group and 70% in the Sham) and the birth weights of the pups were similar in the groups (our unpublished observations). These pups are currently being followed-up and different physiological and behavioral aspects are analyzed.

There also exists some experience of allogenic UTx in a larger animal. In 2011, another group reported two pregnancies and one birth after allogenic UTx in the sheep [74]. In this experiment the authors used a surgical model previously described [75]. Via a small subumbilical incision the uterus and proximal parts of the uterine vessels were retrieved from one animal and placed in another animal that underwent the same surgical treatment [75]. The anastomoses were performed between the uterine arteries and veins bilaterally in an end-to-end fashion and the vaginal vault of the graft was anastomosed to the vaginal rim of the recipient. The experiment involved allogeneic transplanta-

tions between Sudanese and Ethiopian breeds with animals serving both as donors and recipients during simultaneous surgeries [74]. All the animals were treated orally with cyclosporine A and intramuscularly with prednisone, starting two days before allotransplantation of the uterus [74]. In this study prednisone treatment was discontinued after 2 weeks post-transplantation and satisfactory trough levels of cyclosporine were reached by day 5. Twelve animals underwent transplantation and four of them died during the immediate post-operative period. Only 5 out of surviving 8 animals were considered suitable for undergoing embryo-transfer based on the viability of the graft and the presence of corpus luteum [74]. Three pregnancies were reported within these five animals: one resulted in an ectopic pregnancy requiring removal of the uterus, one resulted in fetal demise at 105 days of gestation and the remaining one resulted in delivery of a fully developed lamb at 138 days via cesarean section. The lamb died 5 hours after delivery. A criticism of this study on supposedly allogenic sheep is that the use of sheep bred in farms may diminish the functional allogenicity of the transplantation [76].

■ Uterus Transplantation and Ethics

We think it is essential that UTx is discussed from an ethical perspective, in parallel with the animal UTx research. The ethics around UTx will naturally be influenced by the active bioethical debates surrounding both the field of transplantation surgery and that of reproductive medicine and in particular assisted reproduction [77].

Clinical introduction of any novel major surgical procedure should occur only after extensive experimental work in animal models to minimize the risk when introduced as an experimental procedure in the human. We are all aware of that several surgical procedures, also in gynecology, are introduced by enthusiastic doctors with a firm belief in the benefit of the new surgical intervention but with only minimal or none background data in animal models to support this. In transplantation surgery, there is a long tradition to optimize and test techniques in animal models before clinical intro-

duction, which was the case for heart transplantation [78] and liver transplantation [79]. In modern times, this is exemplified by the extensive research in rodent models on facial transplants [80] that preceded the first full facial transplant in the human that took place in the United States in 2009. In the UTx field, several research groups have used rodents, large domestic animals and non-human primates in their research towards clinical introduction of UTx [9, 60, 67, 68, 71, 73, 81–84]. It is also important that teams planning to carry out human UTx belong to a strong and comprehensive institution, so that expertise on all aspects before, during and after the procedure is provided in a professional way. The expertise needed for pre-transplantation work-up of both the patient and a live donor would be at least a gynecologist, transplant surgeon, psychologist, counsellor, reproductive medicine specialist, internal medicine specialist, radiologist and a specialist in maternal-fetal medicine. The gynaecologist would evaluate the prospects for UTx in the recipient, where considerations would have to be taken in regards previous surgery, vaginal length and position of the vaginal vault in relation to the bladder. In MRKH patients with only previous self dilation to obtain a vagina of sufficient length, the vagina may have to be lengthened before UTx by any type of neovagina surgery [85]. The gynaecologist would be most suitable to explain the surgery and risks involved with uterus retrieval from the donor. However, the transplant surgeon should also have these discussions independently with the potential donor. The best medical knowledge about the transplantation procedure, postoperative immunosuppression and follow up protocols is naturally among the transplantation surgeon. A psychologist and a counsellor should independently assess both the donor and the recipient well before the procedure, to assess that they are properly informed about the risk of the procedure and the chances for a success in the initial experimental situation of UTx. The recipient should be evaluated by a specialist in reproductive medicine at an initial state of the pre-transplantation work up to ensure that the ovarian function of the patient is normal and that the ovarian reserve is reasonable so that the couple would have a reasonable chance to conceive at IVF. We would

recommend the patient to undergo IVF treatment before UTx, to ensure fertility within the couple but also to obtain and cryopreserve enough embryos that later can be used at single embryo transfer, which should occur at earliest 12 months after UTx. The internal medicine specialist would be an independent doctor, well suited to evaluate the medical risks for the donor and the recipient in a UTx situation. A radiologist with a special interest in magnetic resonance and angiography would be essential for preoperative evaluation of the uterus and pelvic vascular system of the donor as well as the pelvic vascular system of the recipient. In a human UTx situation, pregnancy by embryo transfer should be attempted a year of post-transplantation stabilization of the organ, since immunosuppressive doses usually can be lowered after this initial period. Any pregnancy after UTx should in the initial stage be considered a high risk pregnancy and be taken care of by a specialist in high risk obstetrics/maternal-fetal medicine and this doctor should have long-standing experience of pregnancies of other organ transplanted women.

An institutional stability would also be important in a situation of human UTx. Thus, the procedure should only be carried out in a large hospital with long standing and extensive programs in organ transplantation and advanced retroperitoneal surgery. The latter expertise is carried by gynecology surgeons. There should be an overall assessment of the institution regarding ability and dedication to care for a living donor, the recipient, the recipient's partner and future children for several years

Indispensable in bioethics is that there should be a dominance of benefits over risks [86], and this should be analyzed for UTx. This type of transplantation would be a unique situation since there are at least four subjects involved; the uterus donor (living or deceased) and its immediate family, the uterus recipient, the partner of the uterus recipient who is also the prospective father, and the future child.

With reference to the risk-benefit of the donor, there is of course no added surgical risk in a situation of a deceased donor with retrieval of many organs, including the uterus. It should be noted that in the

initial stages of UTx, a multiorgan donor that have consented to organ donation may not have considered the uterus as an organ that would be donated, besides the classical organ such as the heart, lung and kidneys. Concerning a live donor, suitable donors would be a mother, sister or aunt. The surgical risks of the donor would probably be similar to that of an ordinary abdominal hysterectomy [87], taking into account that the risks related to the more extensive dissection of uterine vessels at hysterectomy for UTx would be compensated by that this hysterectomy would be carried out expert gynaecology surgeons.

The transplant patient, receiving the uterine graft and her partner should be extensively informed about other alternatives to motherhood than UTx and that this procedure would at its initial stage be fully experimental. The surgical risks would probably be similar to that of kidney transplantation, since the site for blood vessel anastomosis would be similar [71]. A somewhat longer surgical time at UTx than at renal transplantation would be anticipated because of the smaller diameters of the vessels of the graft and that bilateral vascular anastomosis would be performed. The patient should also be informed about the risks of immunosuppressive medication in relation to nephrotoxicity [88], viral infections [89] and certain malignancies after long-term use [90].

The risks for the foetus/prospective child are of course also extremely important to take into consideration. There does not seem to be any increased perinatal risk due to the mother's intake of immunosuppression during pregnancy, since similar risks for obstetric complications were seen in pregnancies of organ transplanted women before transplantation as after transplantation [91]. However, the disease that caused the transplantation may be a factor that negatively influences the pregnancy before transplantation and of course this negative influence is to a large extent abolished after transplantation. It is thus possible that immunosuppression may have some negative effects on pregnancies after transplantation, resulting in similar rates of pregnancy complications before and after. In this regard, it is of great importance to assess the pregnan-

cies and offspring after allogenic UTx in animal models, as has been done in the rat (see above).

Conflict of Interest

No potential conflict of interest to this article was reported.

References

- Dubernard JM, Owen E, Herzberg G, Martin X, Guigal V, Dawahra M, et al. [The first transplantation of a hand in humans. Early results]. *Chirurgie* 1999; 124: 358–65.
- Levi DM, Tzakis AG, Kato T, Madariaga J, Mittal NK, Nery J, et al. Transplantation of the abdominal wall. *Lancet* 2003; 361: 2173–6.
- Strome M, Stein J, Esclamado R, Hicks D, Lorenz RR, Braun W, et al. Laryngeal transplantation and 40-month follow-up. *NEJM* 2001; 344: 1676–9.
- Devauchelle B, Badet L, Lengele B, Morello E, Testelin S, Michallet M, et al. First human face allograft: early report. *Lancet* 2006; 368: 203–9.
- Aarts JW, van Empel IW, Boivin J, Nelen WL, Kremer JA, Verhaak CM. Relationship between quality of life and distress in infertility: a validation study of the Dutch FertiQoL. *Hum Reprod* 2011; 26: 1112–8.
- Catsanos R, Rogers W, Lotz M. The ethics of uterus transplantation. *Bioethics* 2011.
- Fageeh W, Raffa H, Jabbar H, Marzouki A. Transplantation of the human uterus. *Int J Gynaecol Obstet* 2002; 76: 245–51.
- Brannstrom M, Wranning CA, Altchek A. Experimental uterus transplantation. *Hum Reprod Update* 2010; 16: 329–45.
- Sieunarine K, Zakaria FB, Boyle DC, Corless DJ, Noakes DE, Lindsay I, et al. Possibilities for fertility restoration: a new surgical technique. *Int Surg* 2005; 90: 249–56.
- Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990–1997. *Obstet Gynecol* 2002; 99: 229–34.
- Goldfarb JM, Austin C, Peskin B, Lisbona H, Desai N, de Mola JR. Fifteen years experience with an in-vitro fertilization surrogate gestational pregnancy programme. *Hum Reprod* 2000; 15: 1075–8.
- Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *International Journal of Gynaecology and Obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2006; 95 (Suppl 1): S105–S143.
- Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *International Journal of Gynaecology and Obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2006; 95 (Suppl 1): S43–S103.
- Andrae B, Kemetli L, Sparen P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst* 2008; 100: 622–9.
- Sonoda Y, Aby-Rustum NR, Gemignani ML, et al. A fertility-sparing alternative to radical hysterectomy; how many patients may be eligible? *Gynecol Oncol* 2004; 95: 534–8.
- Nabuci S, Okazawa M, Matsuo K, et al. Impact of histological subtype on survival of patients with surgically-treated stage IA2–IIB cervical cancer: adenocarcinoma versus squamous cell carcinoma. *Gynaecol Oncol* 2012; 127: 114–20.
- Dargent D, Martin X, Sacchetoni A, Mathivet P. Laparoscopic vaginal radical trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients. *Cancer* 2000; 88: 1877–82.
- Ungar L, Palfalvi L, Hogg R, Siklos P, Boyle DC, Del Priore G, et al. Abdominal radical trachelectomy: a fertility-preserving option for women with early cervical cancer. *BJOG* 2005; 112: 366–9.
- Cobo A, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2011; 96: 277–85.
- Bosch FX, Castellsague X, de Sanjose S. HPV and cervical cancer: screening or vaccination? *BJC* 2008; 98: 15–21.
- Schiffman M, Herrero R, Desalle R, Hildesheim A, Wacholder S, Rodriguez AC, et al. The carcinogenicity of human pa-

- pillomavirus types reflects viral evolution. *Virology* 2005; 337: 76–84.
22. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr., Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol* 2001; 19: 3163–72.
23. Holm K, Nysom K, Brocks V, Hertz H, Jacobsen N, Muller J. Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. *Bone Marrow Transplant* 1999; 23: 259–63.
24. Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. *BJOG* 1999; 106: 1265–72.
25. Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004; 83: 96–102.
26. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. *J Natl Cancer Inst Monogr* 2005: 64–8.
27. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005; 62: 738–44.
28. Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* 1996; 87: 3045–52.
29. Edington HD, Sugarbaker PH, McDonald HD. Management of the surgically traumatized, irradiated, and infected pelvis. *Surgery* 1988; 103: 690–7.
30. Marino JL, Eskenazi B, Warner M, Samuels S, Vercellini P, Gavoni N, et al. Uterine leiomyoma and menstrual cycle characteristics in a population-based cohort study. *Hum Reprod* 2004; 19: 2350–5.
31. Borgfeldt C, Andolf E. Transvaginal ultrasonographic findings in the uterus and the endometrium: low prevalence of leiomyoma in a random sample of women age 25–40 years. *Acta Obstet Gynecol Scand* 2000; 79: 202–7.
32. Chen CR, Buck GM, Courey NG, Perez KM, Wactawski-Wende J. Risk factors for uterine fibroids among women undergoing tubal sterilization. *Am J Epidemiol* 2001; 153: 20–6.
33. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol* 1997; 90: 967–73.
34. Farhi J, Ashkenazi J, Feldberg D, Dicker D, Orvieto R, Ben Rafael Z. Effect of uterine leiomyomata on the results of in vitro fertilization treatment. *Hum Reprod* 1995; 10: 2576–8.
35. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, Abdelmassih R. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization-intracytoplasmic sperm injection. *Fertil Steril* 2004; 81: 582–7.
36. Fernandez H, Seftoui D, Virelizier C, Gervaise A, Gornel V, Frydman R. Hysteroscopic resection of submucosal myomas in patients with infertility. *Hum Reprod* 2001; 16: 1489–92.
37. Connolly G, Doyle M, Barrett T, Byrne P, De Mello M, Harrison RF. Fertility after abdominal myomectomy. *J Obstet Gynaecol* 2000; 20: 418–20.
38. Al-Inany H. Intrauterine adhesions. An update. *Acta Obstet Gynecol Scand* 2001; 80: 986–93.
39. Bukulmez O, Yerali H, Gurgan T. Total corporal synechiae due to tuberculosis carry a very poor prognosis following hysteroscopic synechialysis. *Hum Reprod* 1999; 14: 1960–1.
40. Friedler S, Margalioth EJ, Kafka I, Yaffe H. Incidence of post-abortion intra-uterine adhesions evaluated by hysteroscopy – a prospective study. *Hum Reprod* 1993; 8: 442–4.
41. Schenker JG, Margalioth EJ. Intrauterine adhesions: an updated appraisal. *Fertil Steril* 1982; 37: 593–610.
42. Fernandez H, Al-Najjar F, Chauveaud-Lambling A, Frydman R, Gervaise A. Fertility after treatment of Asherman's syndrome stage 3 and 4. *J Minim Invasive Gynecol* 2006; 13: 398–402.
43. Kwee A, Bots ML, Visser GH, Bruinse HW. Emergency peripartum hysterectomy: A prospective study in The Netherlands. *Eur J Obstet Gynecol Reprod Biol* 2006; 124: 187–92.
44. Heinonen PK, Saarikoski S, Pystynen P. Reproductive performance of women with uterine anomalies. An evaluation of 182 cases. *Acta Obstet Gynecol Scand* 1982; 61: 157–62.
45. Saravelos SH, Cocksedge KA, Li TC. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. *Hum Reprod Update* 2008; 14: 415–29.
46. Grimbizis GF, Camus M, Tarlatzis BC, Bontis JN, Devroey P. Clinical implications of uterine malformations and hysteroscopic treatment results. *Hum Reprod Update* 2001; 7: 161–74.
47. Homer HA, Li TC, Cooke ID. The septate uterus: a review of management and reproductive outcome. *Fertil Steril* 2000; 73: 1–14.
48. Pabuccu R, Gornel V. Reproductive outcome after hysteroscopic metroplasty in women with septate uterus and otherwise unexplained infertility. *Fertil Steril* 2004; 81: 1675–8.
49. Buttram VC, Jr. Mullerian anomalies and their management. *Fertil Steril* 1983; 40: 159–63.
50. Papp Z, Mezei G, Gavai M, Hupuczi P, Urbancsek J. Reproductive performance after transabdominal metroplasty: a review of 157 consecutive cases. *J Reprod Med* 2006; 51: 544–52.
51. Taylor E, Gornel V. The uterus and fertility. *Fertil Steril* 2008; 89: 1–16.
52. Folch M, Pigem I, Konje JC. Mullerian agenesis: etiology, diagnosis, and management. *Obstet Gynecol Surv* 2000; 55: 644–9.
53. Carson SA, Simpson JL, Malinak LR, Elias S, Gerbie AB, Buttram VC, Jr. et al. Heritable aspects of uterine anomalies. II. Genetic analysis of Mullerian aplasia. *Fertil Steril* 1983; 40: 86–90.
54. Davies MC, Creighton SM. Vaginoplasty. *Curr Opin Urol* 2007; 17: 415–8.
55. Guerrier D, Mouchel T, Pasquier L, Pellerin I. The Mayer-Rokitansky-Kuster-Hauser syndrome (congenital absence of uterus and vagina) – phenotypic manifestations and genetic approaches. *J Negat Results Biomed* 2006; 5: 1.
56. Jones HW, Jr. Mermut S. Familial occurrence of congenital absence of the vagina. *Am J Obstet Gynecol* 1972; 114: 1100–1.
57. Petrozza JC, Gray MR, Davis AJ, Reindollar RH. Congenital absence of the uterus and vagina is not commonly transmitted as a dominant genetic trait: outcomes of surrogate pregnancies. *Fertil Steril* 1997; 67: 387–9.
58. Oppelt P, Renner SP, Kellermann A, Brucker S, Hauser GA, Ludwig KS, et al. Clinical aspects of Mayer-Rokitansky-Kuester-Hauser syndrome: recommendations for clinical diagnosis and staging. *Hum Reprod* 2006; 21: 792–7.
59. Racho EI-Akouri R, Kurlberg G, Dindelegan G, Molne J, Wallin A, Brannstrom M. Heterotopic uterine transplantation by vascular anastomosis in the mouse. *J Endocrinol* 2002; 174: 157–66.
60. Racho EI-Akouri R, Kurlberg G, Brannstrom M. Successful uterine transplantation in the mouse: pregnancy and post-natal development of offspring. *Hum Reprod* 2003; 18: 2018–23.
61. Hogan B. Manipulating the mouse embryo: a laboratory manual. 2nd ed. Cold Spring Harbor Laboratory Press, Plainview, N.Y., 1994.
62. Racho EI-Akouri R, Wranning CA, Molne J, Kurlberg G, Brannstrom M. Pregnancy in transplanted mouse uterus after long-term cold ischaemic preservation. *Hum Reprod* 2003; 18: 2024–30.
63. Wranning CA, Akhi SN, Diaz-Garcia C, Brannstrom M. Pregnancy after syngeneic uterus transplantation and spontaneous mating in the rat. *Hum Reprod* 2011; 26: 553–8.
64. Martinez-Gomez M, Cruz Y, Pacheco P, Aguilar-Roblero R, Hudson R. The sensory but not muscular pelvic nerve branch is necessary for parturition in the rat. *Physiol Behav* 1998; 63: 929–32.
65. Dahm-Kahler P, Wranning C, Lundmark C, Enskog A, Molne J, Marcickiewicz J, et al. Transplantation of the uterus in sheep: methodology and early reperfusion events. *J Obstet Gynaecol Res* 2008; 34: 784–93.
66. Wranning CA, Dahm-Kahler P, Molne J, Nilsson UA, Enskog A, Brannstrom M. Transplantation of the uterus in the sheep: oxidative stress and reperfusion injury after short-time cold storage. *Fertil Steril* 2008; 90: 817–26.
67. Wranning CA, Marcickiewicz J, Enskog A, Dahm-Kahler P, Hanafy A, Brannstrom M. Fertility after autologous ovine uterine-tubal-ovarian transplantation by vascular anastomosis to the external iliac vessels. *Hum Reprod* 2010; 25: 1973–9.
68. Wranning CA, El-Akouri RR, Lundmark C, Dahm-Kahler P, Molne J, Enskog A, et al. Auto-transplantation of the uterus in the domestic pig (*Sus scrofa*): Surgical technique and early reperfusion events. *J Obstet Gynaecol Res* 2006; 32: 358–67.
69. Scott JR, Pitkin RM, Yannone ME. Transplantation of the primate uterus. *Surg Gynecol Obstet* 1971; 133: 414–8.
70. Kisu I, Mihara M, Banno K, Hara H, Yamamoto T, Araki J, et al. A new surgical technique of uterine auto-transplantation in cynomolgus monkey: preliminary report about two cases. *Arch Gynecol Obstet* 2011; 285: 129–37.
71. Enskog A, Johannesson L, Chai DC, Dahm-Kahler P, Marcickiewicz J, Nyachio A, et al. Uterus transplantation in the baboon: methodology and long-term function after auto-transplantation. *Hum Reprod* 2010; 25: 1980–7.
72. McCracken JA, Baird DT, Goding JR. Factors affecting the secretion of steroids from the transplanted ovary in the sheep. *Recent Prog Horm Res* 1971; 27: 537–82.
73. Diaz-Garcia C, Akhi SN, Wallin A, Pellicer A, Brannstrom M. First report on fertility after allogeneic uterus transplantation. *Acta Obstet Gynecol Scand* 2010; 89: 1491–4.
74. Ramirez ER, Ramirez Nessetti DK, Nessetti MB, Khatamee M, Wolfson MR, Shaffer TH, et al. Pregnancy and outcome of uterine allotransplantation and assisted reproduction in sheep. *J Minim Invasive Gynecol* 2011; 18: 238–45.
75. Ramirez ER, Ramirez DK, Pillari VT, Vasquez H, Ramirez HA. Modified uterine transplant procedure in the sheep model. *J Minim Invasive Gynecol* 2008; 15: 311–4.
76. Lehr EJ, Rayat GR, Desai LS, Coe JY, Korbut GS, Ross DB. Inbred or outbred? An evaluation of the functional allogenicity of farm sheep used in cardiac valve studies. *J Thorac Cardiovasc Surg* 2006; 132: 1156–61.
77. Dondorp W, de Wert G. Innovative reproductive technologies: risks and responsibilities. *Hum Reprod* 2011; 26: 1604–8.
78. Barnard MS. Heart transplantation: an experimental review and preliminary research. *S Afr Med J* 1967; 41: 1260–2.
79. Starzl TE, Kaupp HA, Jr, Brock DR, Linman JW. Studies on the rejection of the transplanted homologous dog liver. *Surg Gynecol Obstet* 1961; 112: 135–44.
80. Siemionow MZ, Demir Y, Sari A, Klimczak A. Facial tissue allograft transplantation. *Transplant Proc* 2005; 37: 201–4.
81. El-Akouri RR, Molne J, Groth K, Kurlberg G, Brannstrom M. Rejection patterns in allogeneic uterus transplantation in the mouse. *Hum Reprod* 2006; 21: 436–42.
82. Sieunarine K, Doumplis D, Kuzmin E, Corless DJ, Hakim NS, Del Priore G, et al. Uterine allotransplantation in the rabbit model using a macrovascular patch technique. *Int Surg* 2008; 93: 288–94.
83. Del Priore G, Stega J, Sieunarine K, Ungar L, Smith JR. Human uterus retrieval from a multi-organ donor. *Obstet Gynecol* 2007; 109: 101–4.
84. Avison DL, DeFaria W, Tryphonopoulos P, Tekin A, Attia GR, Takahashi H, et al. Heterotopic uterus transplantation in a swine model. *Transplantation* 2009; 88: 465–9.
85. Fedele L, Frontino G, Motta F, Restelli E, Candiani M. Creation of a neovagina in Rokitansky patients with a pelvic kidney: comparison of long-term results of the modified Vecchietti and McIndoe techniques. *Fertil Steril* 2010; 93: 1280–5.
86. Gillon R. Medical ethics: four principles plus attention to scope. *BMJ* 1994; 309: 184–8.
87. Spillsbury K, Hammond I, Bulsara M, Semmens JB. Morbidity outcomes of 78,577 hysterectomies for benign reasons over 23 years. *BJOG* 2008; 115: 1473–83.
88. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. *Transplantation* 1997; 63: 977–83.
89. Razonable RR. Management of viral infections in solid organ transplant recipients. *Expert Rev Anti Infect Ther* 2011; 9: 685–700.
90. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004; 4: 222–30.
91. Kallen B, Westgren M, Aberg A, Olsson PO. Pregnancy outcome after maternal organ transplantation in Sweden. *BJOG* 2005; 112: 904–9.

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