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Review

Assisted Reproduction and Live Births in Uterus Transplantation—The Swedish View

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Abstract

Objective: Uterus transplantation (UTx) has evolved as the first true infertility treatment for absolute uterine factor infertility (AUFI), caused by a lack (congenital or surgical) of the uterus or presence of a non-functional uterus. Ever since the proof-of-concept of UTx as an infertility treatment, by the first live birth in 2014, the field has evolved with a number of ongoing clinical trials in several countries. Results are now gradually building up to estimate the efficacy of the procedure in terms of outcome of assisted reproduction, including live births. An update of these results will be presented along with our own experience. **Mechanism**: PubMed search for research articles with human UTx procedures. **Findings in Brief**: We could identify 62 UTx cases with data from research articles in peer-reviewed journals. Out of these, 51 were live donor procedures and 11 were deceased donor UTx. Surgical success was 78% in live donor UTx and 64% in deceased donor UTx. Limited data indicate a pregnancy and live birth rate per embryo transfer (ET), somewhat lower that in the general IVF population. The 24 published live births were premature (<37 gestational weeks) in 83%, with a high frequency (37%) of respiratory distress syndrome. Gestational hypertension/preeclampsia was seen in 17% and gestational diabetes in 12% of pregnancies. Post-natal health of children was fine. **Conclusions**: Uterus transplantation has entered the scene as the first available treatment for women with absolute uterine factor infertility. The procedure is still in an experimental phase and through ongoing clinical trials, with modifications of procedures, this type of combined infertility treatment and major transplantation surgery will improve regarding outcomes, such as surgical success, rate of pregnancy/live birth per ET, rate of term pregnancy, and rate of live births with only a minor rate of neonatal and postnatal complications.

Keywords: uterus; infertility; transplantation; *in vitro* fertilization; embryo transfer; birth

1. Introduction

During the last half century, reproductive medicine has made great advancements and today a great majority of male and female infertility causes are treatable. The major events in these developments were introduction of *in vitro* fertilization (IVF) and intra-cytoplasmatic sperm injection (ICSI) in the late 1970s and early 1990s, respectively. In parallel, there has been a tremendous advancement in organ and tissue transplantation during the last three decades, with clinical introduction of advanced types of vascularized composite transplantations, such as hand and face transplantations. Women with no uterus or presence of a non-functional uterus has remained infertile until recently, but thanks to breakthroughs in gynecology surgery combined with transplantation surgery, these women with absolute uterine factor infertility (AUFI) now have the option to undergo uterus transplantation (UTx) as an infertility treatment. After systematic animal-based research studies in rodents, large domestic species, and non-human primate for more than 10 years [1] the Swedish group was the first to announce a live birth after UTx in the human and this occurred in 2014 [2]. After that, the Swedish team and groups in six other countries have further proved that UTx is a feasible infertility treatment for AUFI, by reporting several additional births, as reviewed below.

2. Patients for Uterus Transplantation

The condition AUFI is due to either uterine absence (surgical/congenital) or a uterine defect (anatomic/functional). It is estimated that the prevalence of AUFI is approximately 20,000 women of childbearing age in a total population of 100 million [3]. Hysterectomy in women of reproductive age is an unintended consequence, but may occasionally be required due to symptoms of myoma(s), or after surgery for cervical/endometrial cancer or atonic uterine bleeding. Congenital uterine absence is seen in the Mayer-Rokitansky-Küster-Hauser syndrome (MRKHs), a condition with uterine absence and upper vaginal aplasia in a female with normal karyotype and normal secondary sex characteristics [4]. Congenital causes of AUFI are also seen in women with uterine malformations, such as hypoplastic uterus, unicornuate uterus, or bicornuate uterus, which are associated with repeated pregnancy loss [5]. Acquired uterine conditions,

such as extensive adenomyosis and severe intrauterine adhesions may also cause AUFI [5].

3. Surgery for UTx

Uterus transplantation can be either from a live donor (LD) or a deceased donor (DD), the latter often referred to as a multi-organ donor. A LD is usually closely related to the recipient, and in a majority of cases of UTx is has been the mother of the recipient or an older sister. However, also altruistic, anonymous LDs have been included in UTx trials.

Surgery in a DD will follow the general principles of organ procurement in DDs, but with the uterus typically retrieved after the traditional transplantable within the thorax and abdomen. The uterus has often been flushed in situ with cannulations into the external iliac arteries. Detailed descriptions exist in the literature [6].

Surgery in the LDs has been through laparotomy or by minimal invasive surgery, in most cases robotic-assisted laparoscopy. The laparotomy technique is by a midline incision and extensive pelvic dissection, to acquire a graft with long vascular pedicles, including segments of the internal iliac arteries and veins. Detailed descriptions exist in the literature [7]. The robotic-assisted laparoscopy has been developed through a number of sub-steps and conversion to laparotomy for uterine extraction [8] and also been accomplished as a total robotic procedure with vaginal extraction of the graft, which was first done in China in 2015 [9].

Surgery in the recipient has so far solely been by laparotomy, through a midline incision. Anastomoses have been bilaterally and end-to-side to the external iliac arteries and veins [7,10].

4. Efficacy and Safety of ART and Obstetrical Outcomes in UTx

Concerning reproductive efficacy, the clinical pregnancy and live birth per embryo transfer (ET) should be used as outcomes. Since the uterine graft will only be carried for a restricted time, usually up to seven years, the cumulative clinical pregnancy/live birth rate per attempted UTx procedure, and the cumulative clinical pregnancy/live birth rate per surgically successful UTx procedure with ET attempt(s), should also be clearly stated. Safety of ART in UTx should be assessed by monitoring rates of severe ovarian hyperstimulation syndrome (OHSS), large bleeding and infections post oocyte pick-up. Regarding obstetrics after UTx, important measures are pregnancy duration, birth weight, rates of pregnancy complication, preterm birth, neonatal complications, as well as occurrence of any congenital malformation.

5. Experience of LD UTx

There are results concerning surgical outcome available from altogether 51 LD UTx cases (Table 1, Ref. [7–21]), with the initial taking place already in year 2000 [11]. The cases include eighteen published LD UTx cases from one trial in USA [12], seventeen in Sweden [7,8,10], five in the Czech Republic [13], four each in Germany [14] and India [15,16], as well as single cases in Saudi Arabia [11], China [9], Lebanon [17] and Spain [22]. As shown in Table 1, a majority of LD UTx cases have been by laparotomy technique in the donor but during recent years also robotics has entered the scene as a minimal invasive approach for donor hysterectomy. The surgical success, defined as uneventful surgery, established blood flow and regular menstruations, after LD UTx procedures is up until today 78%, with a slightly higher success rate in minimal invasive LD UTx (89%) than in laparotomy LD UTx (73%), as shown in Table 1. An explanation for this difference may be that LD UTx by laparotomy was the initial method in several LD UTx trials and after accrued experience and a learning curve, minimal invasive methodology was introduced.

6. Experience of DD UTx

There are results concerning surgical outcome available from altogether 11 DD UTx cases, with the first occurring already in year 2011 [18]. Five DD UTx have been conducted in the Czech Republic [13], four cases in USA [12,19,20], and single DD UTx cases have been reported from Brazil [21] and Turkey [18]. The accumulated overall surgical success in DD UTx procedures is so far 64%, which is lower than in LD UTx.

7. Evaluations before Assisted Reproduction

In all UTx cases performed in the world so far, except the original case from year 2000 [11], the oviducts have not been included in the graft. Thus, pregnancy would only be possible after IVF and ET. The reasons to not include the oviducts in the graft are several. There would be a high risk for injuries to the sensitive oviducts, caused by donor surgery, ischemia, and suboptimal blood flow after transplantation. The tubal injury-risk would be even more pronounced if the proximal parts of the utero-ovarian veins are used for outlet, which was performed bilaterally in one of the cases in USA [12] or if the entire utero-ovarian veins are used for outlet, as in the first robotic case, which was carried out in China in 2015 [9]. Partly damaged oviducts would in case of natural conception be a factor that would significantly increase the risk for tubal ectopic pregnancy. This condition would not be easily treated by laparoscopic salpingectomy in a patient that has undergone UTx, due to presence of adhesions, altered anatomic position of the uterus with continuation of oviducts, as well as that the graft vessels that are anastomosed to the external iliacs may be positioned in close proximity to such an ectopic pregnancy.

As an integral part of IVF prior to UTx, the initial evaluations should be carried out in an accredited reproductive medicine unit, with systems for electronic medical record and patient management as well as good experience in embryo cryopreservation. Most countries have requirements

Table 1. Published uterus transplantation (UTx) cases (n = 62), including data on surgical success.

Type of UTx	n	UTx year(s)	Surgical success	Country (ref.)
LD laparotomy	1	2000	0/1	Saudi Arabia [11]
LD laparotomy	9	2012–2013	7/9	Sweden [7]
LD laparotomy	5	2016–2018	4/5	Czech Rep. [13]
LD laparotomy	13	2016–2019	8/13	USA [12]
LD laparotomy	4	2016–2019	4/4	Germany [14]
LD laparotomy	1	2018	1/1	Lebanon [17]
LD robotics	1	2015	1/1	China [9]
LD robotics	8	2017–2019	6/8	Sweden [8,10]
LD robotics	5	2019	5/5	USA [12]
LD laparoscopy	4	2018–2019	4/4	India [15,16]
DD	1	2011	1/1	Turkey [18]
DD	5	2016–2018	3/5	Czech Rep. [13]
DD	2	2016–2017	1/2	USA [19,20]
DD	1	2016	1/1	Brazil [21]
DD	2	2017	1/2	USA [12]
Summary	62	2000–2019	47/62	

LD, live donor; DD, deceased donor.

concerning screening of all patients (females and partners) for transmittable infections of human immunodeficiency virus (HIV), hepatitis B and C, syphilis and for the woman, rubella immunity. For UTx patients and partners screening for Chlamydia trachomatis and Gonorrhea should be performed, since the female patient will be immunosuppressed after UTx. The male partner should undergo a complete sperm analysis.

Considering the ovarian reserve and the quality of the oocytes, we recommend individual consideration if tests of ovarian reserve (see below) indicate an acceptable pool of follicles. Chronological age remains the most reliable predictor of IVF treatment outcome, but measurements of blood level of anti-Mullerian hormone (AMH), and ultrasound imaging to estimate ovarian antral follicle count (AFC) and ovarian volume, should be used as additional markers of ovarian reserve. A great majority of UTx patients have so far been women with MRKHs and data indicate that women with type B (40% of MRKHs) have lower AMH levels and AFC compared to age-matched controls [23] and in a gestational surrogacy program it was reported that women with MRKHs type B form had decreased ovarian response to gonadotropins and lower fertilization rates, compared with women with MRHKs type A [24].

8. IVF Treatment Prior to UTx

In general, IVF with cryopreservation of good quality embryos is performed prior to UTx. This is in order to assure fertility within the couple before the major surgical intervention of UTx, which in the LD UTx situation also involves major surgery of a donor, who would have no direct benefit from the UTx procedure.

Controlled ovarian stimulation for IVF is composed of a mix of medications designed to stimulate multiple ovarian follicle development, aiming at the generation of a large pool of follicles with oocytes that can be initiated by an ovulatory trigger to cytoplasmatic and nuclear maturity, and thereby to become fertilizable. The central pharmaceuticals for controlled ovarian stimulation are either urinary-derived human menopausal gonadotropin (hMG) or recombinant follicle stimulating hormone (rFSH), which after daily administration will stimulate final follicular growth from a diameter of less than 9 mm to sizes above 17 mm. These gonadotropins are used in combination with either a gonadotropin-releasing hormone (GnRH) agonist in a long protocol or with a GnRH antagonist in a short protocol. The GnRH agonist will by desensitization, after around 10 days of administration, down-regulate the GnRH receptors on the gonadotrophs of the anterior pituitary and the GnRH antagonist will directly block the receptors in a classical receptor antagonistic fashion. Either of these approaches will inhibit premature LH surges during stimulation, which could result in premature ovulation and luteinization.

Because of lack of information of menstruation and thereby ovarian cyclicity in IVF before UTx in women with no uterus, different approaches for pre-UTx IVF have been used by us. In the initial UTx study of Sweden [7], with surgeries 2012 and 2013, we used a long GnRH agonist protocol with a gonadotropin combination of rFSH and hMG to avoid stimulation failure in case of low endogenous luteinizing hormone (LH) levels. The stimulation could not be planned by the menstrual pattern and the nine patients went through one or more months of assessments of hormone levels, including LH, FSH, estradiol and progesterone. It was established that all patients

had regular ovulatory cycles with identifiable LH peaks, that could also be detected as urinary LH. Treatment with GnRH agonist was commenced 8 to 9 days after the start of an LH peak, when clearly elevated progesterone levels indicated luteal phase. Since follicular measurements were occasionally uncertain, especially in some of the patients with latero-cranially placed ovaries, monitoring was based mainly on serial measurements of estradiol levels, until follicles could be measured either by abdominal or vaginal ultrasound scans. LH responsive oocytes in the largest follicles can be expected after an uninterrupted increase in serum estradiol levels over baseline for a period of at least one week. Final ovulatory follicle development and oocyte maturation were induced by recombinant human chorion gonadotropin (hCG) and aspiration of was done oocytes 36 h later, by vaginal route in five patients and by transabdominal approach in four women. In both scenarios of oocyte retrieval, moderate conscious sedation by alfentanil and local anesthesia, was used. In total, 19 cycles were performed in the nine women to accumulate more than eight embryos before IVF (personal communication L. Nilsson). No case of severe ovarian hyperstimulation syndrome (OHSS) occurred.

In our second Swedish trial, with robotic-assisted donor hysterectomy, and with surgeries performed 2017–2019 [8,10], we used a random-start ovarian stimulation protocol [25] in the eight patients included. We had no information on stage of ovarian cycle, when initiating controlled ovarian stimulation and used GnRH antagonist and gonadotropin, simultaneously. We always used hMG as the gonadotropin in the initial cycles of all patients and in a second stimulation cycle, we changed to rFSH if there was a suboptimal response to hMG in the previous cycle. In general, the stimulations were around two days longer than that of a classical GnRH antagonist stimulation protocol. One out of eight patients had transabdominal oocyte pick up and the rest retrieval by the vaginal route. In all patients, moderate conscious sedation, using alfentanil and local anesthesia was used at oocyte retrieval. No cases of OHSS were seen, which is not surprising since ovulation triggering was with GnRH agonist [26] in a great majority of cases. Two random-start ovarian stimulation protocols were needed in six patients and in two patients only one stimulation was needed, to acquire the cryopreservation pool of at least eight embryos, which was stated in the ethics application.

Today, cryopreservation of blastocysts, and not cleavage-stage embryos, are routinely performed in most UTx programs, since transfer of frozen-thawed embryos will give a high chance of implantation and clinical pregnancy. Concerning genetic testing of embryos, the use of pregenetic testing of aneuploidy (PGT-A) in an UTx setting has been discussed. In a comprehensive review from the Cleveland Clinic group, this topic is well covered, listing a number of pros and cons for PGT-A in UTx [27]. Proposed advantages in IVF and UTx are shortening the time from ET to pregnancy, since the implantation rate is improved, as well as decreasing miscarriage rate and thereby emotional burden of the patient. Proposed disadvantages of PGT-A in an UTx setting are possible harm of embryos with live birth potential, questionable improvement in live birth outcomes, and increased costs. Moreover, to achieve the desired number of embryos before UTx with PGT-A, the uterus recipient may have to undergo additional cycles of controlled ovarian stimulation, with the associated risks of OHSS and thromboembolic events.

9. IVF Treatment after UTx

Specific challenges with post UTx IVF may be the altered position of the ovaries after surgery and that the anatomy of the pelvic vasculature is different, which may pose problems at oocyte pick up. Moreover, the patient is more susceptible to pelvic infections in conjunction with oocyte pick up, due to the immunosuppressed state. An advantage of post UTx IVF, in comparison to pre UTx IVF, is that the woman has menstruations and that a stimulation protocol, whether short or long, can be started at the optimal times, which in our hands are the second day of menstruation and mid-luteal phase, respectively.

There exists limited experience of IVF stimulation with oocyte pick up after a UTx procedure. The reason to conduct post UTx IVF was exhausted pools of embryos that had been cryopreserved before UTx, which was due to recurrent implantation failures when using the pre-UTx accumulated embryos to acquire a live birth in one case in the German trial [14]. In another patient of the German trial, only oocytes had been cryopreserved before UTx and these did not survive the thawing procedure when they were to be used for fertilization post UTx. A short GnRH antagonist protocol was used in both cases with vaginal oocyte pick up, even though the ovaries had been relocated lateral to the external iliac vessels through ovariopexy during transplantation [14].

In one of our own cases of the original Swedish study [7], one woman separated from her partner after UTx, but before starting ETs. That specific patient then went through single mother IVF with donor sperms and had babies twice from two post UTx IVF treatments. This case would suggest that perhaps a mix of unfertilized oocytes and embryos should be cryopreserved before UTx, in case of separation from partner or if other reasons, such as partners death, take place so that the embryos cannot be used. In another patient, with post UTx IVF due to exhausted pool of pre UTx embryos, OHSS occurred in one of the three post UTx IVF stimulations, which was an agonist cycle. Even though she had 16 ETs and six clinical pregnancies, all pregnancies ended before 15 gestational weeks.

10. Embryo Transfer in UTx Patients

The time for the first ET post UTx was in the original Swedish study [7] decided to be 12 months after UTx,

in order to be reach a period with lower levels of immunosuppressive agents and since a great majority of the initial acute rejection episodes occur with the first 8–10 months after UTx [28]. The complete success of the combined UTx and IVF procedure would then be delivery of a healthy child, which could not be evident until at least around 18 months after UTx. This period for first ET has later in other trials in USA been shortened to 6 months and in some cases 3 months, with the justification being to reduce total recipient-graft time and thereby costs and exposure of immunosuppressant drugs [12,29].

Single embryo transfer (SET) should always be planned for UTx recipients, since transfer of multiple embryos, although increasing the chance of pregnancy, will substantially increase the risk of a pregnancy with multiple fetuses. Such pregnancy will increase the risk for maternal pregnancy complications, preterm birth and associated neonatal complications. Moreover, the pelvic fixation of the uterus and the vascular supply of a uterine graft are unphysiological and that fact may pose problem when the gravid uterus is expanding a lot more in a multiple pregnancy than in a singleton pregnancy.

We have performed a majority of the ET procedures of the Swedish patients in the natural cycle and relating on self-examination of urinary LH to detect the peak. In some patients with irregular cycles or non-detectable LH signals we have used programmed cycles, with sequential estrogen and gestagen, although being aware of the higher rates of hypertensive disorders, postpartum hemorrhage, post-term birth and macrosomia after ET in programmed cycles [30].

There are some challenges in ET in UTx patients which should be considered. Among them is the length of the cervix uteri, which can be over 10 cm in some patients. The cervical length and possible cervical curving should be evaluated using pre-transfer evaluation by ultrasound examination and/or hysteroscopy. It is also mandatory to do ET under abdominal ultrasonic guidance to assure the embryo is placed in an optimal position. Moreover, an ET catheter with greater length than normal may be needed. We speculate that an explanation for the elongation of the cervix after UTx, as seen in many cases, could be that there is increased uterine blood flow after UTx [31], as compared to the normal physiological situation and that the increase in blood, with oxygen and nutrients, may induce hypertrophic changes of the uterine cervix. The elevated blood flow is caused by that the arterial anastomosis sites of the graft are the distal part of the anterior portion of the internal iliac arteries, and the total flow from these high caliber vessels will then be directed into the uterine arteries, since all other branches, except the uterine artery, are ligated and transected at donor hysterectomy [7]. In some cases, we have also seen a slight increase in the size of the proper uterine body after transplantation. Moreover, the uterus has in some cases been attached to the abdominal wall and will then be in an extreme anteflexion position, and this will render the cervix to be curved. Thus, a guidewire may have to be used to get the outer ET catheter through the cervical canal, to reach the caudal portion of the uterine cavity. Another technical challenge in ET may be presence of vaginal strictures over the vaginal anastomosis, which was reported both after LD and DD UTx procedures in the trial out of the Czech Republic [13]. The ring-formed strictures, which may render the vagina to become formed as an hour-glass, may in several cases be less than 10 mm in diameter. In such a case, dilatation under anesthesia by forced manual dilation or by diathermy incision are recommended before any ET attempt. Additionally, use of a vaginal self-expanding stent has been reported as a treatment before ET [13].

Another ET-related consideration is the occurrence of endometrial polyps in the uterine cavity post UTx, which we have seen in some cases. In cases with a fairly thick endometrium just after menstruation or with irregularities, we advise use of either saline infusion sonography or hysteroscopy to assess the cavity in a cycle prior to ET. In some patients with recurrent implantation failure (RIF) we have performed endometrial receptivity array (ERA) test [32] in order to achieve information whether ET have been performed in the receptive phase, or has been asynchronous in the pre-o or post-receptive phase. Although we only have two cases in our UTx populations with RIF and secondary ERA test, we have adjusted ET time accordingly and achieved clinical pregnancies with live births after such an adjustment. Moreover, the team in Dallas used the ERA test in two patients with consecutive failed ETs, with results showing pre-receptive endometrium [33]. The ET day was adjusted 24 h and clinical pregnancies were then achieved.

11. Reproductive and Live-Birth Outcomes after UTx

There exist no full reports available that detail complete study cohorts concerning reproductive performance in relation to ART after UTx. Data are available from three trials that give some, although incomplete, data on pregnancy rates and live birth rates.

In the Czech trial [13] four LD UTx and three DD UTx were surgically successful. Fifty ETs were reported with a clinical pregnancy rate per ET of 14% and live birth rate per ET of 6%. The cumulative pregnancy rates so far have been 50% per attempted UTx and 71% per successful UTx [13]. In the German trial [14] all four LD transplants were successful and ETs were initiated and reported in two patients. A total of seven ETs were carried out in these two patients with a clinical pregnancy rate per ET of 43% and live birth rate per ET of 29%. The cumulative pregnancy rate in these two successful transplants were 100%. The US trial of Dallas, with 13 laparotomy LD UTx cases, five robotics UTx LD cases and two DD UTx had 14 surgically successful UTx procedures [12]. The published data give some indications on cumulative live birth rate per attempted

Table 2. Reported live births (n = 24) after uterus transplantation and reported complications.

Type (country)	Week of live birth	Pregnancy complication	Neonatal complication
LD Laparotomy (Sweden)	31 + 6	PE	RDS
	34 + 4	ICP	RDS
LD laparotomy (USA)	33 + 1	SCH	RDS
	36 + 6	-	-
	38 + 0	-	-
	35 + 6	GD	RDS
	30 + 6	-	RDS
	37 + 2	-	-
	37 + 0	PP	-
	36 + 6	PE	-
LD Laparotomy LD (Germany)	35 + 1	-	RDS
	36 + 3	-	-
LD Laparotomy (Czech Rep)	35 + 3	GD	-
	36 + 2	PH	-
LD laparotomy (Lebanon)	35 + 2	-	-
LD robotics (China)	33 + 6	SCH	-
LD robotics (Sweden)	36 + 1	-	RDS
LD robotics (USA)	37 + 0	GH, PH	RDS
	32 + 4	PP	RDS
	35 + 6	-	-
DD (Brazil)	35 + 3	PN	-
DD (USA)	34 + 2	PP, PA	-
	37 + 6	GH	-
DD (Czech Rep)	34 + 6	GD	-

LD, live donor; DD, deceased donor; GD, gestational diabetes; GH, gestational hypertension; ICP, intrahepatic cholestasis of pregnancy; PA, placenta accreta; PH, polyhydramnion; PN, pyelonephritis; PP, placenta previa; SCH, subchorionic hematoma; RDS, respiratory distress syndrome.

and per surgically successful UTx [12,28,33,34], but since the numbers of ETs are not presented, pregnancy/live birth rate per ET cannot be estimated. Noteworthy, one recent study from the Dallas center reports that all 14 transplanted women, where single embryo transfer of euploid blastocysts were performed, achieved clinical pregnancy, with 10 of the 14 women getting pregnant after the initial ET [33]. The clinical pregnancy per ET that has been reported so far is 63%. The median time, from UTx until first clinical pregnancy, was as low as 7.3 months. So far, the cumulative live birth rate per attempted UTx in the Dallas study is 55% and per surgically successful it is UTx 86 %. Additional live births from three recipients, who have not yet had a live birth are predicted to be reported in the future. In the original Swedish trial [7], the cumulative live birth rates after attempted and successful UTx were 67% and 86%, respectively (Bokström H, personal communication). The clinical pregnancy rate and live birth rate per ET were around 30% and 20%, respectively.

There are 24 published live births after UTx (Table 2) with births in Sweden [2,35,36], USA [12,28,34], the Czech Republic [13], Germany [14], Lebanon [17], Brazil [21], and China [37]. All deliveries have been by cesarean sections. There were four (17%) cases of hypertensive disorder of pregnancy, which suggests an increased rate of gestational hypertensive disease. Of note, three cases of placenta previa and three cases of gestational diabetes were seen. Only five out of the 24 deliveries were term ($\geq$37 + 0 weeks), with a majority of the preterm deliveries due to per protocol decisions. The preterm per protocol timing of the delivery most likely represents a compromise between achieving adequate maturation of the child, and avoiding possible UTx-related obstetric complications during late pregnancy. However, the high rate of respiratory distress syndrome (38%) is a clear indication that elective deliveries should be planned at $\geq$37 + 0.

12. Conclusions

Uterus transplantation has entered the scene as the first available treatment for women with absolute uterine factor infertility. The procedure is still in an experimental phase and through ongoing clinical trials, with adaptations of several procedures, this type of combined infertility treatment and major transplantation surgery will most likely improve

regarding outcomes such as surgical success, rate of pregnancy/live birth per ET, rate of term pregnancy and rate of live births.

Author Contributions

GH and MB equally searched the literature and discussed all papers. MB wrote the preliminary draft. The final article was written by GH and MB together. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. MB is serving as one of the Guest editors of this journal. We declare that MB had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to DHB & MHD.

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