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REVIEW ARTICLE

## A review on pregnancy after intestinal transplantation

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### Abstract

The largest experience of pregnancy after solid organ transplantation is recorded in renal and liver recipients. Intestinal/multivisceral transplantation has shown steady improvements in graft and patient survival over the past 20 years and is rapidly becoming more established: the first pregnancy after this procedure was described 10 years ago, and so far eight cases of pregnancies with 100% successful live births have been reported worldwide. Specifically to this procedure, there are 2 factors to be considered in case of pregnancy: absorptive function of transplanted bowel and higher need of immune-suppressants. Close monitoring of renal function and of the graft by endoscopies and biopsies can be considered during the pregnancy to prevent episodes of rejection or enteritis, preserving the fetus by temporary malnutrition. As more intestinal transplant patients are surviving and regaining reproductive function, it is important to report this option to female recipients and to their health-care professionals.

### Keywords

Intestinal transplantation,  
immune-suppression, pregnancy

### History

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### Introduction

The largest experience of pregnancy after solid organ transplantation is recorded in renal and liver recipients. Data obtained from the U.S. National Transplantation Pregnancy Registry (NTPR) and other sources have shown a 71–76% live birth rate during pregnancies in kidney recipients and 50–86% for the other organs combined [1–4]. Intestinal transplantation (ITx) is the treatment modality for intestinal failure with life-threatening PN (parenteral nutrition) complications: the related nomenclature reports 4 graft types, namely isolated intestine, multivisceral, modified multivisceral and combined liver-intestine or intestine-pancreas (Figures 1–4). If the disease involves only the bowel, the transplanted graft type will be an isolated intestine, while the more the GI tract is affected by the disease, the more the number of transplanted organs will be required: combined liver-intestine or intestine-pancreas, modified multivisceral or full multivisceral graft. A modified multivisceral graft is represented by stomach-duodenum-pancreas and bowel (without the liver) while a full multivisceral graft is a modified multivisceral plus the liver. The procedure has shown steady improvements in graft and patient survival over the past 20 years and is rapidly becoming more established worldwide.

However, reports of successful pregnancies after ITx are still scarce. As more ITx patients are surviving and regaining reproductive function, it is important to report this option to female recipients in their reproductive age and to underline the care required for successful pregnancy in this unique population to health-care professionals.

### Historic notes and indications to transplant

The first bowel transplant was performed in a dog by Lillehei in 1958, followed a year later by the experimental work reported by Starzl and Kaupp regarding full multivisceral transplantation: the results were catastrophic due to the high incidence of rejection. In 1987 the first full multivisceral transplant on a human being was performed in Pittsburgh with a survival reported as 6 months after the procedure. In 1989, a baby girl was transplanted in Paris with an isolated bowel graft, and nowadays she represents the longest survivor worldwide. In the early '90s, the push towards the clinical application of intestine/multivisceral transplantation was aided by the introduction of tacrolimus, an immunosuppressant that changed dramatically the outcome of these recipients. Later on, the dawn of the new millennium saw the widespread use of preconditioning/induction immune-suppressive protocols based on anti-lymphocyte drugs, responsible for the improvement of the short-term survival comparable to other solid organ transplants. Currently, long-term outcomes are approaching the results reported by other transplanted solid organs, but there is still an enormous effort

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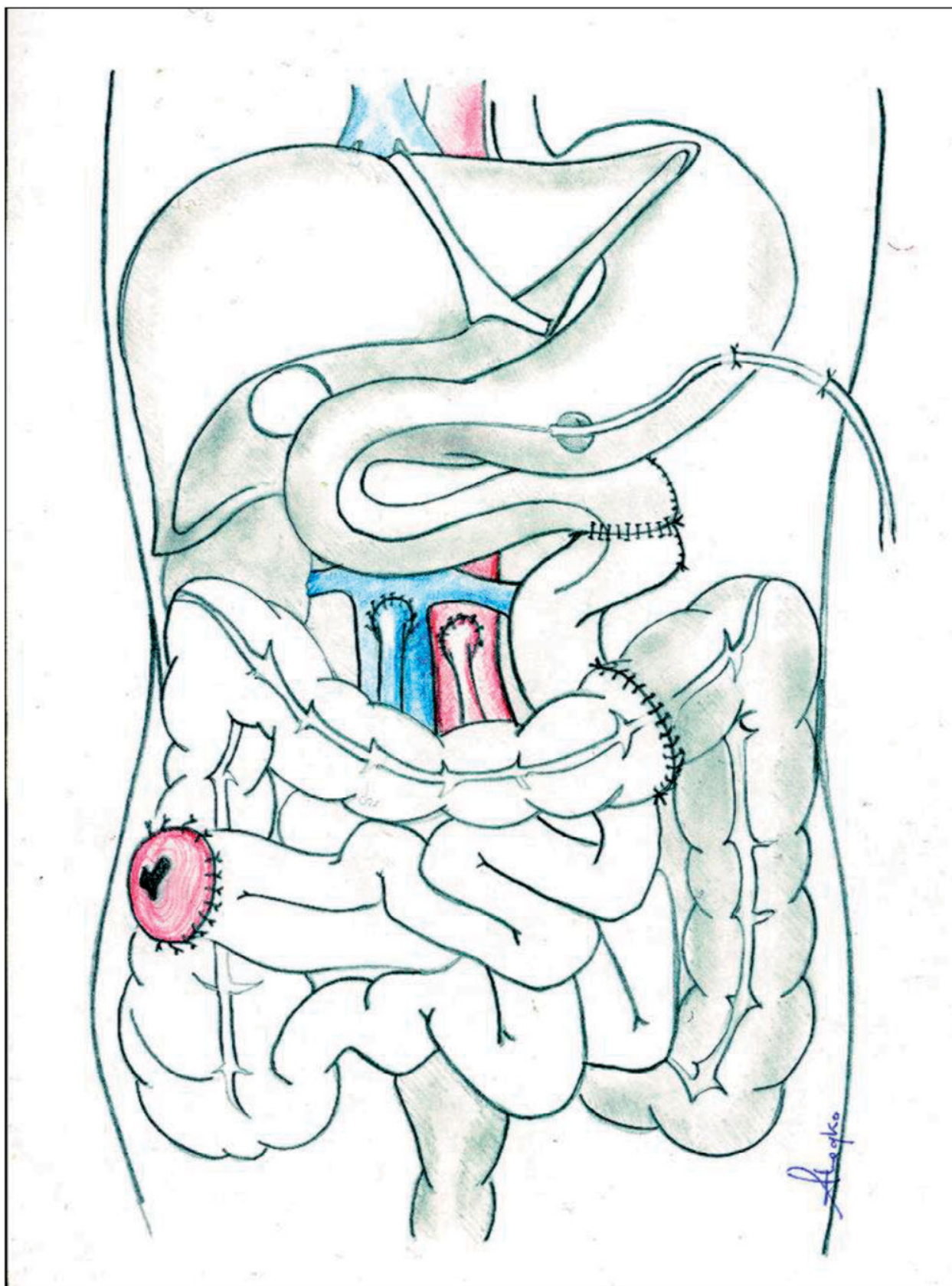


Figure 1. Isolated intestinal transplant.

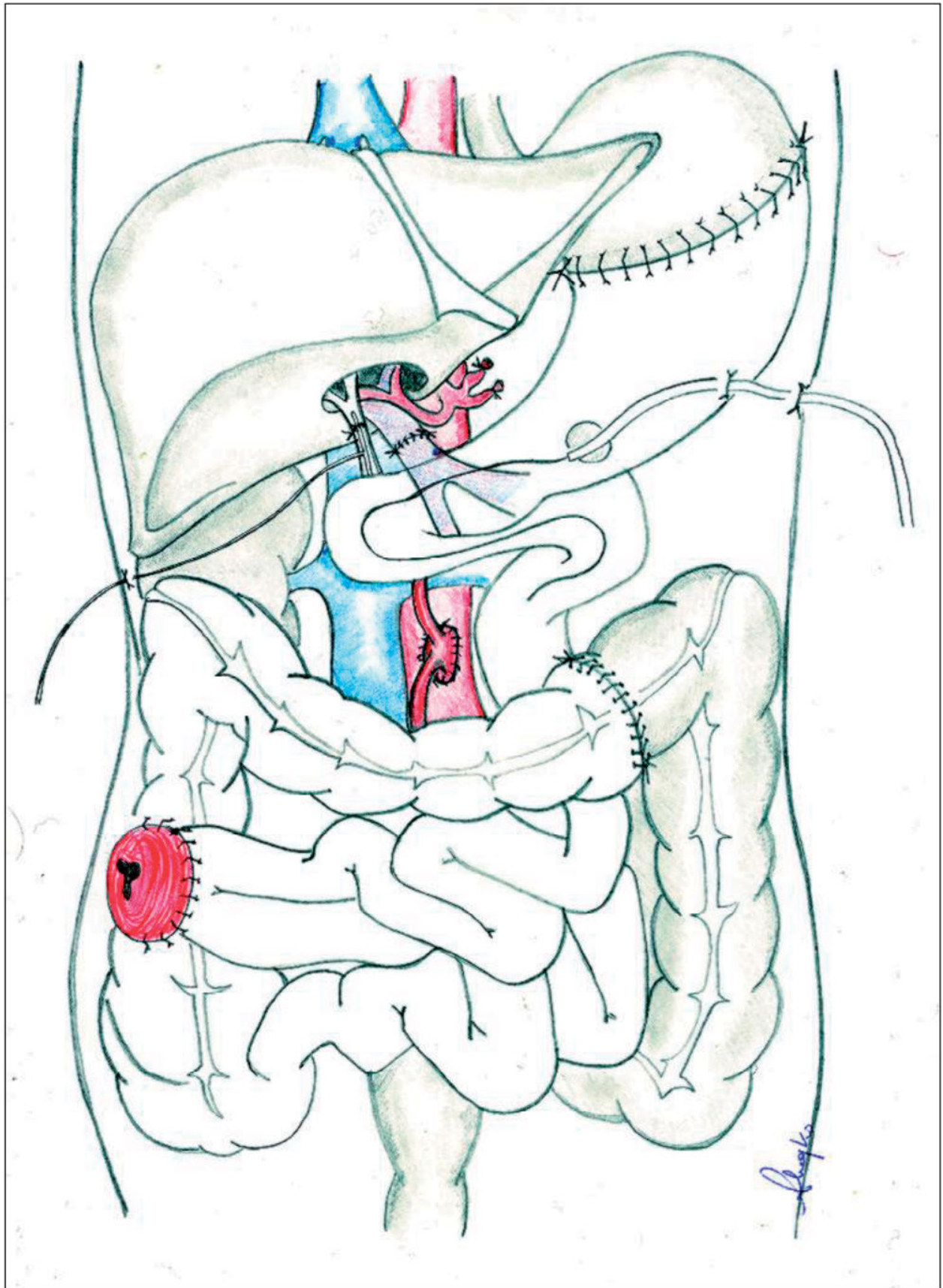


Figure 2. Modified multivisceral transplant (without liver).

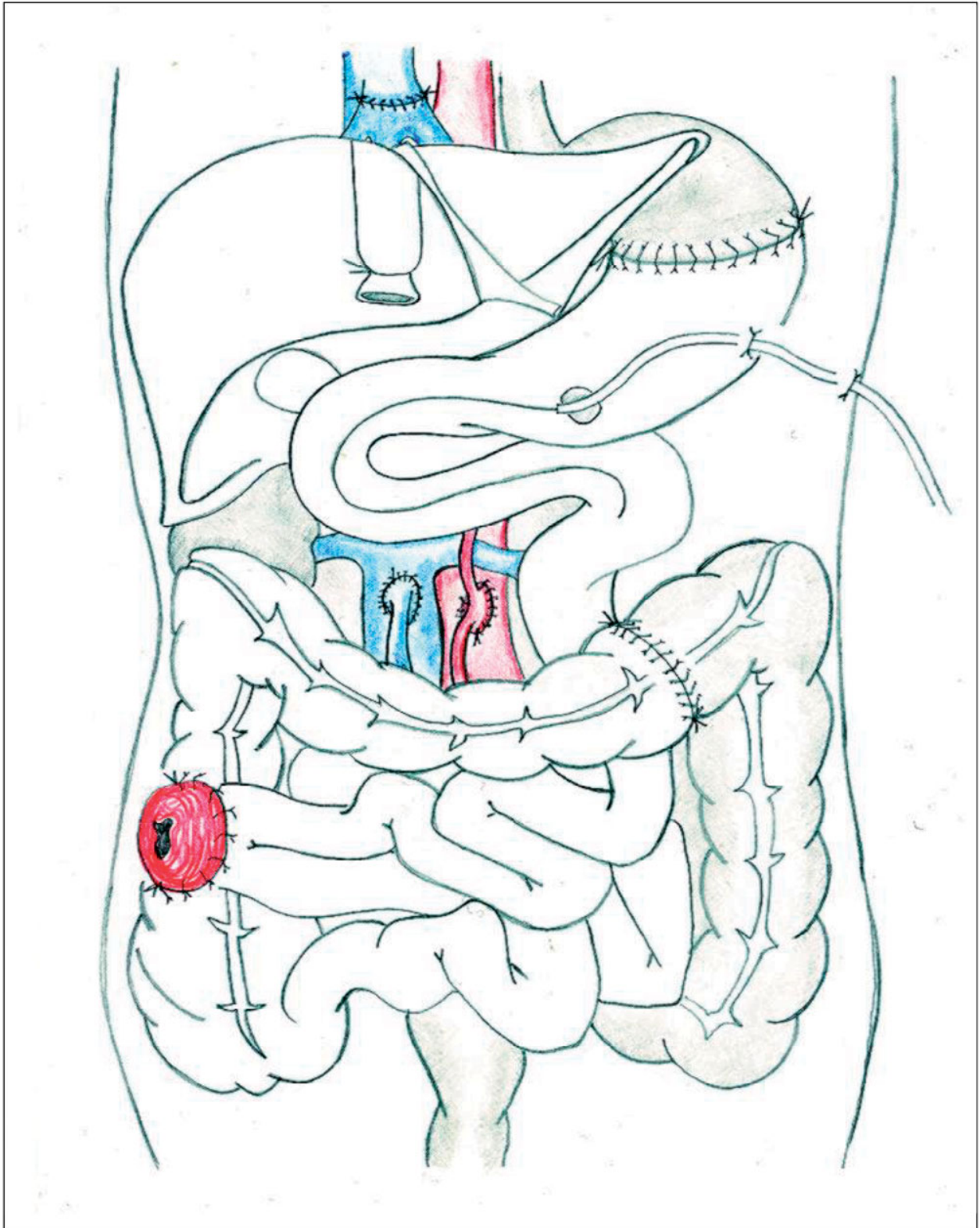


Figure 3. Multivisceral transplant (with liver).

in the form of ongoing research worldwide, in order to find the pitfalls and improve the long term outcomes of ITx [5]. PN still represents the gold standard therapy for patients with benign chronic intestinal failure (i.e. short bowel syndrome, motility disorders, etc.) and the transplant procedure is reserved for the complication of PN itself, such as line

infections or thrombosis, liver failure, dehydration, bacterial translocation.

The number of reported pregnancies after intestinal transplantation is limited. Therefore, it is worthwhile to describe in detail the single cases in order to discuss the whole issue in depth.

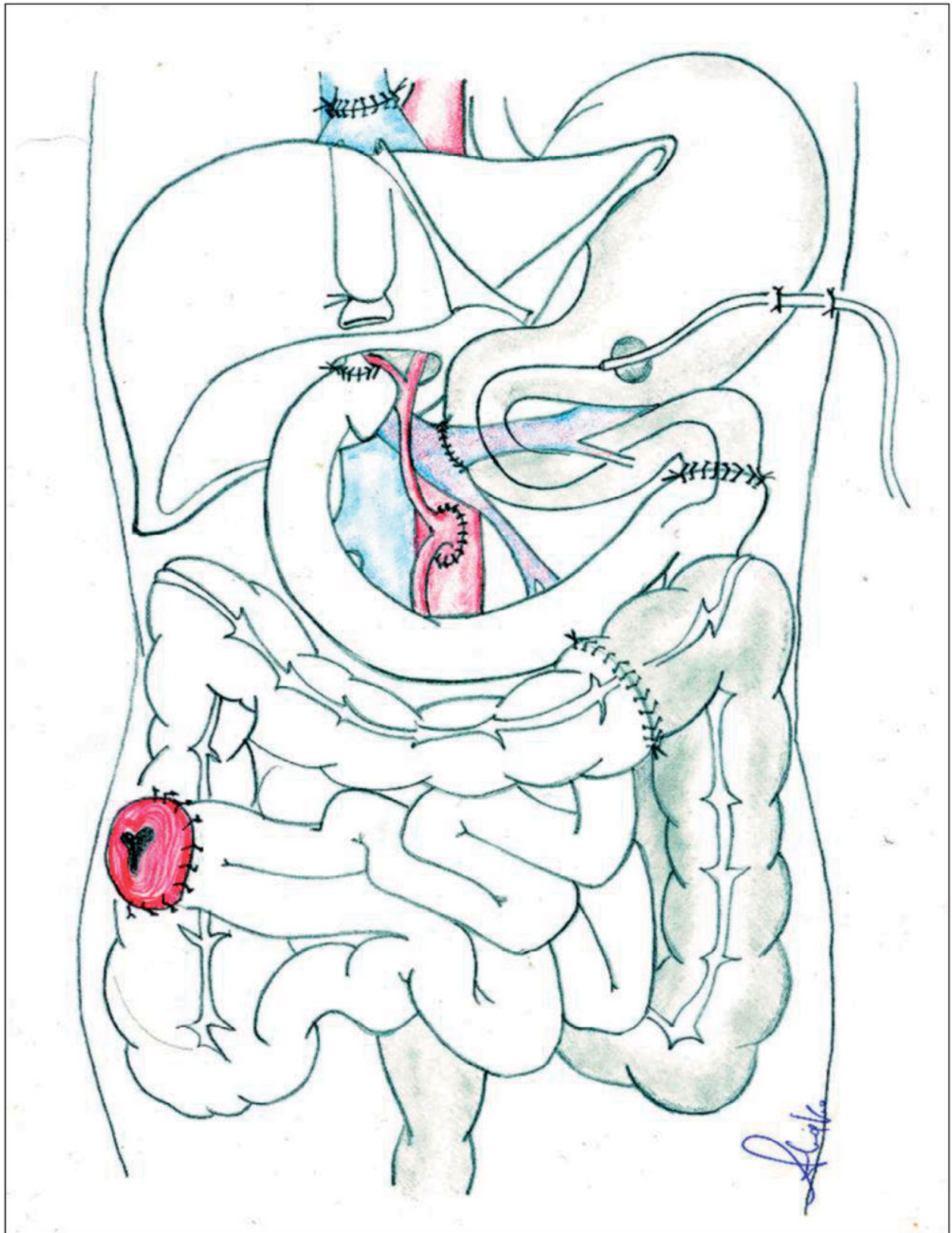


Figure 4. Combined liver-intestine transplant.

## Pregnancy after isolated intestinal transplant

### Case 1

Pregnancy after isolated ITx was first reported in 2006 [6], in a 23-year-old woman who had undergone liver transplant for biliary atresia at age 2.5 years, followed by small bowel herniation, intestinal failure, and intestinal transplant 11 years later, at 13 years of age. She suffered a spontaneous miscarriage in 2005, followed by a normal pregnancy and vaginal delivery in May 2006 (39 weeks) of a healthy full-term newborn girl. During the pregnancy immune-suppression was maintained with tacrolimus monotherapy, allowing trough levels to fall to an average of 3.8 ng/mL in the 3 to 6.3 range with stable bowel graft. Renal function remained normal as did the woman's blood pressure and glucose levels. She gained about 10.5 kg during the pregnancy. The baby girl weighed 7 pounds, 3 ounces (3.3 kg) at birth. She showed traces of tacrolimus in her blood until her third month postpartum. A surveillance endoscopy and biopsy of the mother at 3 months post-partum revealed no evidence of rejection at 11.5 year post-transplant. Tacrolimus dose was then increased to a trough level of 6 to 10.3 ng/mL.

### Case 2

In 2012, another case was described [7] of a 26-year-old woman who had extensive bowel resection following gastric bypass surgery, due to internal herniation that occurred during a pregnancy at 20 weeks gestation resulting in pregnancy loss. Obstetric history was significant for an uncomplicated term delivery in 2007 before her gastric bypass. She underwent successful isolated ITx and had stable graft function when she presented with an unplanned pregnancy at 13 weeks gestation. Immune-suppression at the time was with prednisone and tacrolimus. During the new pregnancy, the patient was evaluated weekly by the transplant team, every 1–2 weeks by the obstetric team and on a regular basis by the nephrology team, due to renal dysfunction. Fetal growth was normal and there was no evidence of preeclampsia. The patient had significant anemia, with a hematocrit of 25.4% at 21 weeks of gestation. She had no other evidence of nutritional deficiency. Pregnancy weight gain was 31 pounds (pre-pregnancy weight 175 pounds, final weight 206 pounds). Graft function remained stable and labor was induced at 39 weeks, leading to spontaneous vaginal delivery of a 6.83-pound (3.1 kg) healthy female infant. She elected to breastfeed her newborn for few weeks, and the newborn's tacrolimus level was less than 1.0 ng/mL at 1 week of life. She had an episode of rejection 3 months after delivery, treated with polyclonal anti-thymocyte globulin with restoration of normal graft function. The author's suggestion was that pregnancy should be considered a 'high immunologic risk' period. For the first 3 months after pregnancy, a return to surveillance endoscopy of the graft every 1 to 2 weeks should be considered, as would be performed early after transplantation or after an episode of rejection.

### Case 3–6

The Pittsburgh team [8] has then reported 4 additional successful births in 3 intestinal transplant patients with stable graft function. Indications for ITx were volvulus ( $n = 2$ ) and

pseudo-obstruction ( $n = 1$ ). Women's ages at ITx were 13.2, 22.2 and 26.9 years while at delivery they were 24.3 and 26.4 (same recipient, two pregnancies), 26.6 and 30.3 years respectively. All women received tacrolimus, mean levels during pregnancy ranged from 2.5 to 6.5 ng/ml. One patient received daily prednisone. Two patients had 3 previous episodes of acute cellular rejection, one moderate treated with OKT3 while another had 2 mild episodes treated with steroids. There were no significant complications that affected maternal outcomes with patients maintaining stable graft and kidney function. Mean BUN and creatinine levels during pregnancy were 16.1 mg/dL and 1.13 mg/dL respectively. Mean levels of nutritional markers and graft function were as follows: albumin 3.4 g/dL, protein 6.2 g/dL, magnesium 1.4 mg/dL. Recipients were normotensive and no incidences were observed of gestational diabetes. Polyhydramnios developed in one pregnancy and resolved without incident. There was fetal exposure to lithium during the first month of pregnancy in one patient being treated for depression and bipolar disorder. Ultrasounds revealed no structural abnormalities at 25 weeks gestation. Maternal outcomes were favorable with normal surveillance endoscopies at 1–6 months post-partum, stable graft function, no rejection and stable tacrolimus levels. One recipient reported new onset migraines following the birth of her son. Three females and 1 male were delivered at 35–39 weeks gestation (mean 37.7 weeks). Normal fetal growth, activity and development were reported during each pregnancy. Three infants were delivered by cesarean section (2 emergent, 1 planned). The infants' Apgar scores at 1 minute were 5–8, at 5 minutes was 9 for all. Birth-weights were 2270–3885 grams (mean=3105 grams). Tacrolimus levels were measured in 3 infants at 24 h after birth = 2.4, 3.7 and <5 ng/ml. None of the infants were breastfed due to concerns for low levels of tacrolimus in breast milk. Two infants were hospitalized for few additional days after birth, one for temperature instability and the other for poor feeding. Infant outcomes were excellent with all healthy and achieving developmental milestones at 3–7 years of age per maternal report.

## Pregnancy after multivisceral transplantation

In 2012 it was reported [9] the case of a woman undergone en-bloc intestine, liver, and pancreas (multivisceral) transplant in childhood, due to intestinal pseudo-obstruction and intestinal failure associated liver disease. Twelve years post-transplant, she presented at age 19 with an unplanned pregnancy at about 8 weeks' gestation. She had stable graft function at the time, maintained on tacrolimus, sirolimus, and prednisolone. Graft function was maintained throughout pregnancy. There was spontaneous onset of labor at 39 weeks gestation that resulted in an uncomplicated normal vaginal delivery of a live male infant, weighing 6.94 pounds (3.15 kg), with Apgar scores of 8 at 1 minute and 9 at 5 minutes. Sirolimus was held briefly after delivery to allow for labial laceration' healing.

## Pregnancy after intestinal transplant with chronic graft dysfunction

The L.A. group first reported [10] successful term pregnancy in an intestine-pancreas transplant recipient with chronic graft

dysfunction and dependence on both transplant immune-suppression and PN at the time of conception. A 23 year-old patient with two healthy children lost the majority of her small bowel from superior mesenteric artery injury during resection of a desmoid tumor. Later she became the recipient of a heterotopic en-bloc intestine and pancreas transplant with preservation of the remaining native pancreas. She had a complex post-transplant course, with chronic rejection necessitating long-term PN. At age 27 and age 28, she presented with intrauterine pregnancies at 8 and 14 weeks despite efforts to avoid pregnancy. She chose to terminate both pregnancies after extensive counseling regarding the risks. Due to the worsening of her clinical conditions, at age 33 she was placed on waiting list for liver/intestine/pancreas (multivisceral) transplant. A third pregnancy at age 34 was unexpected in the setting of chronic illness and menstrual irregularities, and discovered incidentally on abdominal ultrasound at approximately 18 weeks' gestation. Rapamune was held, tacrolimus continued, and PN adjusted to maintain consistent weight gain. Medical complications during pregnancy included anemia and need for tunneled catheter replacements. Ascites and edema were improved from baseline, with recurrence of large volume ascites shortly after delivery. A healthy female infant was delivered at term (39 1/7 weeks) by normal spontaneous vaginal delivery without complications. Apgar scores were 5 and 9. Thick meconium was noted. Birth weight was 6.81 pounds (3.090 kg). The mother required a 3-day hospital stay for delivery. Breastfeeding was decided by the delivering physician to be too high-risk for mother and baby.

## Discussion

Pregnancy after solid organ transplantation has been associated in the past with increased rates of gestational hypertension, preeclampsia, gestational diabetes, post-partum hemorrhage, cesarean delivery, prematurity, fetal growth restriction, perinatal complications and fetal mortality [1–3]. The American Society of Transplantation Consensus Group recommends planning a future pregnancy 1 to 2 years post-transplant, with stable graft function on reduced immune-suppression, stable blood pressure and kidney function, and absence of infectious complications [2]. Pregnancies after ITx are recently become more common (Table 1). However, specifically to this procedure, there are 2 factors affecting the transplant to be considered in case of pregnancy: absorptive function of transplanted bowel (as shown by L.A. case [10]) and higher need of immune-suppressants. Maternal nutritional status is critical during pregnancy to ensure the health of the developing fetus. Estimated needs during pregnancy are about 300 kcal/day and 30 g/day protein over basal requirements. Requirements for essential fatty acids also increase during pregnancy, to ensure proper brain development in the fetus. Intestinal transplantation is often affected by episodes of acute cellular rejection or enteritis, and the affected bowel could lose its absorptive capacity for a period of time: close monitoring by endoscopies and biopsies of the graft must be performed during the pregnancy, in order to prevent these episodes and to preserve the fetus by temporary malnutrition. In case of chronic dysfunction after ITx like in the L.A. case

[10], when the absorptive capacity is severely compromised, the use of PN should be always regarded as essential for mother/fetus safety. Moreover, during rejection episodes the need of immune-suppression is highly increased, often leading to episodes of infection or sepsis of the recipient subsequent to the treatment: the risk for the fetus is obviously to be considered. CMV infection is very frequent in intestinal/multivisceral recipients, and its recurrence – even long after the transplant – should always be kept in mind and monitored by health care professionals taking care of pregnant ITx recipients. Also, the increased need of immune-suppression negatively affects the kidney function of intestinal/multivisceral recipients (20% of them will develop chronic renal failure on a long term) and the risk of preeclampsia should always be considered and monitored carefully during pregnancy. Few complications were described in the reported literature, i.e. 2 cases of anemia [7–8] and one case of polyhydramnios [8]: mean gestational age at delivery was regular (only one preterm birth [8]) and no preeclampsia was noted. Before the widespread use of mycophenolic acid, there did not appear to be overall increase in anomalies between transplant recipients, when compared with the general population. Data from the U.S. National Transplant Pregnancy Registry, however, as well as post-marketing data, have revealed that mycophenolic acid compounds are associated with an increased risk of miscarriage and fetal anomalies [11]. Intestinal/multivisceral transplantation has become a clinical reality with the use of tacrolimus, still representing the gold standard maintenance immune-suppression: mycophenolic acid is less frequently used while there is an increased report of immune-suppression with sirolimus/everolimus (together with tacrolimus), to be held temporarily in the case of traumatic delivery or cesarean section as shown by Birmingham report [9].

## Conclusion

The cases reported in the literature have shown an increased confidence by patient/health care professionals towards intestinal/multivisceral transplantation. Over the last 10 years, 8 successful births after this procedure, once considered the transplant “frontier,” have been described with 100% live birth rate of pregnancies, low complication rate (anemia, polyhydramnios) associated with only one preterm birth and no preeclampsia. The pregnancies were reported as wished by recipients and approved by health care professionals, and it must be considered a further step towards a reasonable quality of life, comparable to other forms of solid organ transplant. Intestine is no longer regarded as the “forbidden” organ, and recent improvements in graft management have led the transplant community to face new challenges like pregnancies in this unique population. The need of deep counseling for the recipient and collaboration between medical teams in form of a multidisciplinary approach must be pursued together with close graft/patient monitoring during the whole pregnancy: immune-suppression should be minimized avoiding to worsen the kidney function, paying attention not to trigger episodes of rejection and/or infection affecting the recipient immune system and the graft absorptive capacity. If needed, a short PN course during the



Table 1. Reported successful pregnancies and births in intestinal/multivisceral recipients.

Reference	Type of graft	Age at ITx	Previous pregnancy	Age at pregnancy	Complication	Delivery	Outcome	Immune-suppression in pregnancy
Pittsburgh 2006 [6] Washington DC 2012 [7]	Isolated bowel Isolated bowel	13 yrs 23 yrs	1 miscarriage post ITx 1 delivery pre ITx 1 miscarriage pre ITx	23 yrs 26 yrs	None anemia	Vaginal Vaginal	1 full term female 1 full term female	Tacrolimus+ Prednisone+ Tacrolimus+ Sirolimus+
Birmingham 2012 [9]	Multivisceral	7 yrs	not reported	19 yrs	None	Vaginal	1 full term male	Prednisolone Tacrolimus (1 case plus Prednisone)
Pittsburgh 2013 [8]	Isolated bowel	13 yrs 22 yrs 26 yrs	not reported	24 yrs* 26 yrs* 26 yrs 30 yrs 34 yrs	1 polyhydra-mnios	3 cesarean and 1 vaginal	3 females and 1 male (1 preterm)	Tacrolimus (1 case plus Prednisone)
Los Angeles 2015 [10]	Combined bowel/pancreas	23 yrs	2 deliveries pre ITx 2 miscarriages post ITx	34 yrs	Anemia	Vaginal	1 full term female	Tacrolimus

\*Same recipient.

pregnancy must be regarded as supportive the fetal nutritional status, as shown by the Los Angeles report [10]. Finally, tacrolimus has been the milestone for intestinal transplantation and experience gained so far has shown this drug to be the most flexible during pregnancies to maintain good recipient/graft health and to obtain a successful birth.

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### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

### References

- Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. In: Cecka JM, Terasaki PI, eds. Clinical transplants 2010. Los Angeles, CA: UCLA Terasaki Foundation Laboratory. 2011:65–85.
- McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant* 2005;5: 1592–9.
- Armenti VT, Constantinescu S, Moritz MJ, et al. Pregnancy after transplantation. *Transplant Rev (Orlando)* 2008;22:223–40.
- Mastrobattista JM, Gomez-Lobo V, for the Society for Maternal-Fetal Medicine. Pregnancy after solid organ transplantation. *Obstet Gynecol* 2008;112:919–32.
- Abu-Elmagd K. The concept of gut rehabilitation and the future of visceral transplantation. *Nat Rev Gastroenterol Hepatol* 2015;12: 108–20.
- Kosmach-Park B, Doshi B, Seward L, et al. Successful pregnancy following intestine transplant in a long term survivor. *Am J Transplant* 2006;6:855. World Transplant Congress, Boston 2006).
- Gomez-Lobo V, Landy HJ, Matsumoto C, et al. Pregnancy in an intestinal transplant recipient. *Obstet Gynecol* 2012;120:497–500.
- Kosmach-Park B, Costa G, Mazariegos G. Reproductive health and outcomes following intestine transplantation. XIII ISBTS Annual Small Bowel Transplant Symposium, 2013; Oxford, UK.
- Srivastava R, Clarke S, Gupte GL, et al. Successful pregnancy outcome following triple organ transplantation (small intestine, liver and pancreas). *Eur J Obstet Gynecol Reprod Biol* 2012;163: 238–9.
- Marcus EA, Wozniak LJ, Venick RS, et al. Successful term pregnancy in an intestine-pancreas transplant recipient with chronic graft dysfunction and parenteral nutrition dependence: a case report. *Transplant Proc* 2015;47:863–7.
- Anderka MT, Lin AE, Abuelo DN, et al. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. *Am J Med Genet* 2009;149A:1241–8.