# Long-term maternal outcomes of pregnancy after orthotopic liver transplantation in the Netherlands: a retrospective multicenter cohort study

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## VISUAL ABSTRACT

### Long-term maternal outcomes of pregnancy after orthotopic liver transplantation in the Netherlands: A retrospective multicenter cohort study

#### Short-term outcomes

- 113 pregnancies in 70 women
  - Maternal outcomes
    - 20% hypertension
    - 12% preeclampsia
    - 0% graft failure during pregnancy
  - Fetal outcomes
    - 87% live birth
    - 33% preterm birth
    - 23% low birth weight
- Increased risk of complications if
  - Higher BMI
  - Higher maternal age

#### Long-term outcomes

- Median follow-up 10 years [IQR 4-14]

Stable graft function

Stable kidney function

23% of mother died median 8 years [IQR 4-12] after birth

#### Comparison overall survival

- No difference in survival between women with and without a pregnancy after transplantation

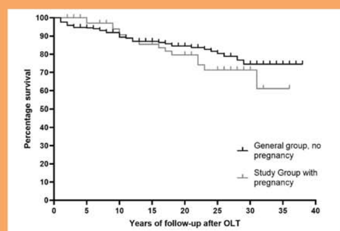


Figure 1. Kaplan-Meier survival curve of survival after OLT of women with an OLT <50 years with and without a pregnancy after OLT

#### Conclusion

**Pregnancy does not seem to influence long-term outcomes of graft, kidney function nor patient survival in most cases. However, 23% of children lost their mother early in life (<18 years). We believe this is important for pregnancy counseling of OLT patients and their partners.**

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ORIGINAL ARTICLE

# Long-term maternal outcomes of pregnancy after orthotopic liver transplantation in the Netherlands: A retrospective multicenter cohort study

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**Abstract**

Pregnancy after orthotopic liver transplantation (OLT) puts the mother, child, and transplanted organ at risk. Little is known about long-term outcomes. We performed a nationwide retrospective cohort study to evaluate short-term and long-term outcomes of post-OLT pregnancies. The secondary aim was to assess predictors for adverse pregnancy outcomes. A composite outcome of preeclampsia, preterm birth, low birth weight, and neonatal intensive care unit admission was made. Survival of women who received a transplant at $<50$ years of age with and without pregnancy after OLT were compared (Dutch Organ Transplantation Registry data). Descriptive statistics, regression analysis, Kaplan-Meier and log-rank analysis, and generalized estimating equation analysis were used. Among the included 70 women with 113 pregnancies $>20$ weeks of gestation, hypertension occurred in 20% and preeclampsia in 12%. The live birth rate was 87%; 33% were preterm, and 23% had low birth weight. Long-term follow-up (median 10 y [IQR: = 4–14]) showed small changes in serum creatinine and bilirubin ($p < 0.001$). Sixteen mothers (23%) died during follow-up (median 8 y [IQR: = 4–12]), with all their children aged $<18$ years. No difference in survival was found when comparing women with and without pregnancy after OLT. The composite outcome occurred in 43/98 of pregnancies. Higher body mass index (BMI) and maternal age at conception increased the composite outcome risk (OR: 1.24, $p < 0.01$, and OR: 1.25, $p = 0.01$, respectively). To conclude, pregnancy after OLT does not seem to influence long-term outcomes of graft, kidney function, or patient

**Abbreviations**: BMI, body mass index; GEE, generalized estimating equations; HELLP, Hemolysis Elevated Liver enzymes and Low Platelets; LBW, low birth weight.; OLT, orthotopic liver transplantation.

Preliminary results of the study were presented at the European Society for Organ Transplantation (ESOT) congress in 2021 and the Bootcongres in 2022 of the Dutch Transplantation Society.

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survival in most cases. However, although pregnancy does not seem to impact survival after OLT, we do show that a substantial number of children will lose their mothers early in life. We believe this is important for pregnancy couseling of patients with an OLT and their partners.

**Keywords:** graft function, kidney function, liver transplantation, long-term outcome, pregnancy, pregnancy complications, survival



## INTRODUCTION

Numbers of orthotopic liver transplantation (OLT) have increased substantially during the last decades,[1] and there is an increasing number of women with a liver transplant in their fertile years. Consequently, pregnancies after OLT are becoming more frequent. Pregnancy after OLT remains high risk, as indicated by higher rates of maternal complications, such as hypertension and preeclampsia,[2–5] and fetal complications such as prematurity and low birth weight (LBW).[2,6] Cholestasis of pregnancy also occurs more frequently in patients who underwent OLT.[2]

Knowledge of short-term outcomes of pregnancy after OLT is increasing as indicated by recent studies.[7–11] However, there remains a scarcity of literature regarding important aspects, such as the influence of pregnancy on both short-term and long-term graft function,[8,12] long-term kidney function, and maternal survival. Therefore, the primary aim of this retrospective multicenter cohort study was to assess short-term and long-term maternal and graft outcomes of pregnancy after OLT. The secondary aim was to assess predictors for adverse pregnancy outcomes.

## METHODS

### Study design

In this national retrospective cohort study, we included all consecutive recipients of OLT in the 3 Dutch liver transplant centers (University Medical Center Groningen [UMCG], Erasmus Medical Center Rotterdam, and Leiden University Medical Center) with a pregnancy term $>20$ weeks between January 1, 1987, and January 1, 2023. Exclusion criteria were age $<18$ years at the time of the study and not being able to read and speak Dutch or English.

During pregnancy, patients had frequent obstetric and hepatologic follow-ups according to local guidelines. We retrospectively collected data from patient records and through patient questionnaires. The questionnaire was sent through REDCap (Research Electronic Data Capture)[13,14] by e-mail after the informed consent form was returned. Participants who did not respond were contacted by phone up to 3 times to provide further explanation. The study was approved by the ethical review board (METC-201900482). All procedures were conducted in accordance with the Declarations of Helsinki and Istanbul.

### Data collection

Study data were collected and managed using REDCap electronic data capture tools hosted at UMCG.[13,14] Data were collected on demographics, information about the OLT, comorbidities present before pregnancy, obstetric history, and details on the pregnancy itself, including complications for both mother and fetus. Birth percentiles were calculated based on whole weeks of gestation and by using birth weight charts from the Dutch Perined registration.[15]

Liver enzymes, bilirubin levels, and serum creatinine levels were collected at several time points: 3 months and the last measurement before conception, each month during pregnancy, and the first measurement, 6 weeks, 3 months, and 1 year after delivery. Bilirubin and serum creatinine levels were also collected yearly during long-term follow-up for a maximum of 25 years after the birth of the first child. Furthermore, detailed information on long-term follow-up was collected about rejection, graft failure, retransplantation, and death.

To compare patient survival of women with a pregnancy after transplantation to women without a pregnancy after transplantation, we used data from the NOTR (Dutch organ transplantation registry) (source: Dutch Transplant Foundation). From NOTR data, all women who received a transplant at the age of $<50$ years were included. Women with a pregnancy after transplantation were removed from the reference group. From the NOTR data, all women with a follow-up $<1$ year after transplantation (deceased or not) were excluded from these analyses to allow for a fair comparison between women with and without a pregnancy after OLT because a significant proportion of the patients died within 1 year after transplantation and the vast majority of the pregnancies after transplantation do not occur within a year after transplantation. We compared survival after OLT in the pregnancy group to survival after the first OLT in the reference group. In the pregnancy group, we used the survival after the OLT with which the women got pregnant.

## Definitions

Pregnancy complications were included when mentioned in the patient record as such by the physician.

Furthermore, the following definitions were used:

- Preterm delivery: delivery before 37 weeks of gestation.[16]
- Very preterm delivery: delivery between 28 and 32 weeks of gestation.[16]
- Extremely preterm delivery: delivery before 28 weeks of gestation.[16]
- LBW: birth weight of $<2500$ g.[17]
- Very low birth weight: birth weight $<1500$ g.[17]
- Live birth rate: live-born infants divided by total pregnancies (including miscarriages and stillbirths) as mentioned in the patient records.
- Small for gestational age: birth weight $<10$th percentile for gestational age.[18]

## Statistical analyses

Statistical analyses were performed with SPSS version 28 (IBM). Descriptive statistics were used to characterize the study population. The normality of distribution was tested with the Shapiro-Wilk test. Normally distributed data were described as mean (SD), non-normally distributed data as median (IQR), and categorical variables as frequencies with percentages.

To identify variables associated with adverse pregnancy outcomes, that is, pregnancy complications for the mother or child, univariable logistic regression analysis was performed for the composite outcome and its components. The composite outcome of maternal and fetal adverse pregnancy outcomes was defined as the presence of at least 1 of the following: preeclampsia, preterm birth, LBW, and neonatal intensive care unit admission. To further analyze risk factors for adverse pregnancy outcomes, multivariable logistic regression analysis was performed with the composite outcome as dependent variable and significant univariable factors ($p < 0.10$) and factors based on literature (serum creatinine $>90$ μmol/L, preexistent hypertension, and age of the mother at conception) as independent variables.[19–21]

Kaplan-Meier analysis was used to compute and visualize maternal survival after delivery of the first child born after OLT, and to compare survival to women who received a transplant at an age of $<50$ years without a pregnancy after OLT. Log-rank analysis was used to assess if survival was significantly different. Generalized estimating equations (GEE) were used to analyze longitudinal data during pregnancy and during long-term follow-up. An exchangeable correlation matrix was used to account for the dependence of measurements within patients. The longitudinal data during pregnancy were analyzed with time as a categorical variable. Long-term follow-up bilirubin and serum creatinine levels were analyzed with time as a categorical variable starting 3 months before conception (time-point: −1), then 3 months after delivery (time-point: 0), and thereafter yearly. For the yearly follow-up, laboratory data dated closest to the month of birth of the child were used, which differed per patient and per follow-up visit. In both GEE analyses, estimated marginal means with SEM were calculated. To assess if the effect of time was dependent on other factors, the interaction of the effect of time with maternal age at conception, interval from OLT to conception, prepregnancy BMI, and the occurrence of a second pregnancy after OLT were separately analyzed in GEE analysis. In all analyses, a $p$ value $<0.05$ was considered statistically significant.

# RESULTS

## Population and demographics

We identified a total of 86 women with pregnancies $>20$ weeks of gestation after OLT between January 1, 1987, and January 1, 2023. After excluding 16 women based on the exclusion criteria (Figure 1), 113 pregnancies $>20$ weeks in 70 women were included in the analysis. In addition, 13 early miscarriages ($<12$ wk) and 8 elective terminations due to varying reasons were identified. The number of pregnancies after OLT increased over the decades, from n = 1 in the earliest years (1987–1989), n = 13 between 1990 and 1999, to n = 49 between 2010 and 2019 (Supplemental Figure S1, http://links.lww.com/LVT/A656).

Table 1 shows the demographics and clinical characteristics of the 70 patients. Metabolic disorders (n = 13, 19%) and immune-mediated causes (n = 12, 17%) were the most common reasons for OLT. Thirteen patients (19%) underwent 2 OLTs before pregnancy. Sixteen patients (23%) received a transplant before the age of 18 years, of which 5 were aged below 2 years. Four patients (5.8%) also had a kidney transplantation before their first pregnancy. Sixteen (24%) of the patients had preexistent hypertension, and 3 patients (4.3%) had preexisting diabetes mellitus.

## Maternal pregnancy outcomes

Table 2 describes characteristics per pregnancy. Mean age at conception was 30 years (SD: 4), and the median

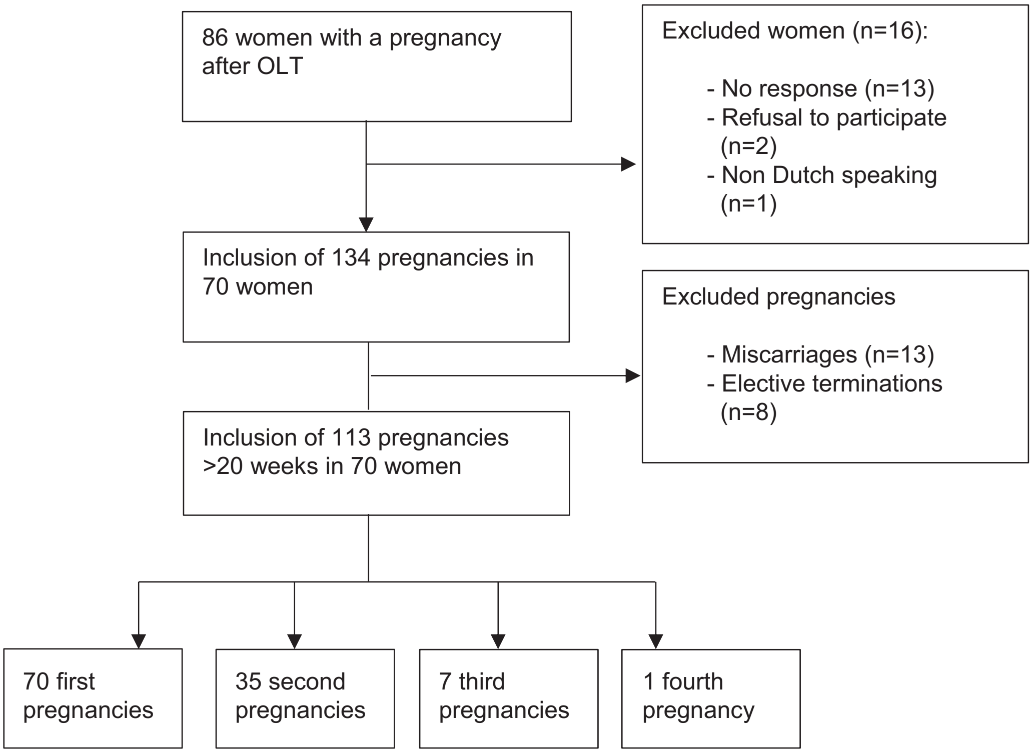



**FIGURE 1** Flowchart of inclusion and exclusion of pregnancies > 20 weeks after OLT in the Netherlands.

interval between OLT and conception was 6 years [IQR: 3–13]. In 41% (n = 34) of the pregnancies, the mother had a BMI ≥ 25 kg/m$^2$, of which 18% (n = 15) ≥ 30 kg/m$^2$. Mycophenolic acid was stopped or converted to azathioprine with or without prednisolone before pregnancy in 6 pregnancies, and around week 8 of gestation in 1 pregnancy. Tacrolimus monotherapy was the most frequently used immunosuppressive regimen (45%, n = 50 pregnancies). In 88% (n = 98) of pregnancies, a calcineurin inhibitor (tacrolimus or cyclosporine) was used. Antihypertensive medication was used in 26% (n = 25) of pregnancies.

Spontaneous pregnancy occurred in 87% (n = 90) of pregnancies. All deliveries occurred in-hospital. The majority (62% [n = 58]) were vaginal deliveries, 20% (n = 19) were planned cesarean sections, and 18% (n = 17) had emergency cesarean sections. Excluding the stillborn infants, hypertension complicated the pregnancy in 19% (n = 18), preeclampsia in 12% (n = 11), and HELLP in 2.1% (n = 2). In Supplemental Table S1, http://links.lww.com/LVT/A656, pregnancies with other severe complications are described.

## Short-term graft outcomes

In Table 2, graft outcomes during pregnancy are described. No cases of graft loss or new onset rejection during pregnancy occurred. However, 2 cases of graft loss shortly after pregnancy occurred. In 1 pregnancy, recurrent giant cell hepatitis led to emergency delivery at 27 weeks of gestation due to fetal distress. The patient was retransplanted 3 weeks after the delivery of her child. Two cases of chronic rejection that already existed before pregnancy were reported. One of these women developed severe HELLP syndrome and kidney function decline during pregnancy, possibly due to too high cyclosporine levels. She was successfully retransplanted a couple of months after delivery of a healthy son. Cholestasis of pregnancy occurred in 7.2% (n = 7). Furthermore, 9.3% (n = 9) of pregnancies were complicated by elevated liver enzymes, which mostly occurred in the last trimester of pregnancy or postpartum. In some cases, there were low whole-blood tacrolimus levels. In most cases, this was treated with an increase in immunosuppressive medication. No biopsies were performed.

## Fetal outcomes

In Table 3, the results of fetal outcomes are described. Two twin pregnancies were reported. Stillbirth occurred in 2.4% (n = 3) of pregnancies, 2 due to unknown causes at 21 and 26 weeks, and 1 in a woman with preeclampsia at 26 weeks of gestation. Of the 112 live-born infants, 2 infants died in the neonatal period and 2 infants thereafter. These 4 infants were born extremely preterm (n = 2) and very preterm (n = 2), and with very low birth weight.

**TABLE 1** Demographics and clinical characteristics

| | | | |
|---|---|---|---|
| Number of patients | n = 70 | | 70 |
| Number of pregnancies > 20 wk after OLT | n = 113 | | 113 |
| Indication for OLT, n (%) | n = 70 | Immune-mediated | 12 (17) |
| | | Metabolic disorders | 13 (19) |
| | | Acute liver failure | 9 (13) |
| | | PSC | 10 (14) |
| | | Biliary atresia | 7 (10) |
| | | Malignancy | 4 (6) |
| | | Secondary biliary cirrhosis | 4 (6) |
| | | Other | 11 (16) |
| Number of OLT, n (%) | n = 70 | 1 | 57 (81) |
| | | 2 | 13 (19) |
| Year of last OLT | n = 70 | | 2001 (9) |
| Age at last OLT (y) | n = 70 | | 23 [18–29] |
| | n = 70 | < 18 years old, n (%) | 16 (23) |
| | | ≥ 18 years old, n (%) | 54 (77) |
| Type of donor, n (%) | n = 58 | DBD | 51 (88) |
| | | DCD | 4 (7) |
| | | Living | 3 (5) |
| Preexisting diabetes mellitus, n (%) | n = 70 | | 3 (4) |
| Preexisting hypertension, n (%) | n = 67 | | 16 (24) |
| Kidney transplantation before pregnancy, n (%) | n = 70 | | 4 (6) |

*Note*: Data are given as mean (SD), median [IQR], or n (%) where appropriate.
Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; PSC, primary sclerosing cholangitis.

None of the children had congenital malformations, including the child from the pregnancy where during the first gestational weeks, mycophenolic acid was given. Excluding the stillborn infants, the median gestational age was 38 weeks [IQR: 36–39]. Preterm birth occurred in 33% (n = 32), and 8.3% (n = 8) was very preterm or extremely preterm. Median birth weight was 2925 g [IQR: 2500–3208]. Twenty-seven percent (n = 23) of the infants were born small for gestational age, of which 12% (n = 10) with a birth percentile < P3. In 1 child, there was a high suspicion of a congenital infection. The child was treated with ampicillin and amikacin and recovered without residual problems. Fifty-eight percent (n = 42) of the children were admitted to the hospital, of which 14% (n = 10) were in the neonatal intensive care unit.

## Biochemical parameters during pregnancy

Figure 2 shows results of biochemical parameters before, during, and after pregnancy until 1 year after delivery. Serum creatinine, bilirubin, ALT, and GGT significantly changed during pregnancy ($p < 0.001$, GEE analysis). Serum creatinine dipped from 78 μmol/L before pregnancy to 68 μmol/L at 5 months of gestation, and returned to 79 μmol/L at 1 year after delivery. Bilirubin levels decreased from 13 μmol/L before pregnancy to 9 μmol/L at 5 months of gestation, and to 26 μmol/L 1 year after delivery. GGT and ALT levels increased toward the end of pregnancy and decreased toward prepregnancy values at 1 year after delivery.

## Predictors for adverse pregnancy outcome

Univariable analysis of adverse pregnancy outcomes (pregnancy complications for mother or fetus) is depicted in Supplemental Table S2, http://links.lww.com/LVT/A656. The results show that prepregnancy BMI, preexistent hypertension, and serum creatinine > 90 μmol/L increase the OR for adverse pregnancy outcomes, although not significant in most complications. The presence of hypertension during pregnancy or preeclampsia did not significantly increase the risk for preterm birth, LBW, or neonatal intensive care unit admission, but a trend was seen.

Supplemental Table S3, http://links.lww.com/LVT/A656 shows the relation between prepregnancy variables and the composite outcome of adverse pregnancy outcomes. Univariable logistic regression analysis showed that a higher prepregnancy BMI significantly increased the risk for the composite outcome (OR: 1.12, 95% CI: 1.01–1.24). A similar trend as in the separate components was seen for preexistent hypertension and serum creatinine > 90 μmol/L.

**TABLE 2** Maternal pregnancy outcomes per pregnancy after OLT

| | | | |
|---|---|---|---|
| Age at conception (y) | n = 113 | | 30 (4) |
| Interval OLT-conception (y) | n = 113 | | 6 [3–13] |
| Year of birth of the offspring | n = 113 | | 2012 [2006–2018] |
| Conception, n (%) | n = 104 | Spontaneous | 91 (88) |
| | | Ovulation induction | 5 (5) |
| | | IUI | 3 (3) |
| | | IVF/ICSI | 5 (5) |
| Prepregnancy BMI (kg/m$^2$), n (%) | n = 82 | < 18.5 | 3 (4) |
| | | 18.5–24.9 | 45 (55) |
| | | 25–29.9 | 19 (23) |
| | | 30–34.9 | 10 (12) |
| | | > 35 | 5 (6) |
| Immunosuppressive regimen during pregnancy, n (%) | n = 111 | PRED + AZA + TAC | 11 (10) |
| | | PRED + AZA + CsA | 13 (12) |
| | | PRED + AZA | 11 (10) |
| | | PRED + TAC | 14 (13) |
| | | PRED + CsA | 3 (3) |
| | | AZA + TAC | 7 (6) |
| | | TAC | 50 (45) |
| | | CsA | 1 (1) |
| | | AZA | 25 (26) |
| Blood pressure medication during pregnancy, n (%) | n = 96 | Increased/changed during pregnancy | 14 (15) |
| | | Beta-blocker | 15 (16) |
| | | Calcium antagonist | 7 (7) |
| | | Methyldopa | 6 (6) |
| | | Diuretics | 2 (2) |
| | | ARB | 1 (1) |
| Anticoagulants, n (%) | n = 96 | | 17 (18) |
| | n = 96 | Heparin | 6 (6) |
| | | Trombocyte aggregation inhibitor | 8 (8) |
| | | Vitamin K antagonist | 3 (3) |
| Hypertension,[a] n (%) | n = 94 | | 19 (20) |
| Preeclampsia,[a] n (%) | n = 95 | | 11 (12) |
| HELLP syndrome,[a] n (%) | n = 95 | | 2 (2) |
| Eclampsia,[a] n (%) | n = 95 | | 0 (0) |
| Gestational diabetes,[a] n (%) | n = 95 | | 7 (7) |
| Delivery method, n (%) | n = 94 | Spontaneous vaginal | 50 (53) |
| | | Assisted vaginal delivery (vacuum or forceps) | 8 (9) |
| | | C-section planned | 19 (20) |
| | | C-section emergency | 17 (18) |
| Pregnancy outcome, n (%) | n = 113 | Live birth | 110 (87) |
| | | Stillbirth | 3 (2) |
| Graft outcomes, n (%) | n = 95 | Thrombosis | 1 (1) |
| | n = 95 | Bleeding | 3 (3) |
| | n = 103 | Graft failure during pregnancy | 0 (0) |
| | n = 96 | Biopsy proven rejection | 2 (2) |
| | n = 97 | Cholestasis of pregnancy | 7 (7) |

*Note*: Short-term maternal pregnancy outcomes per pregnancy after OLT. Twin pregnancies were considered as 1 pregnancy and therefore counted once. Data given as mean (SD), median [IQR], or n (%) where appropriate. All complications were scored if the diagnosis was mentioned in the patient record. Definition: Hypertension: preexistent or pregnancy-induced hypertension.

[a]Stillbirth pregnancies excluded.

Abbreviations: ARB, angiotensin receptor blockers; AZA, azathioprine; BMI, body mass index; CsA, cyclosporine; C-section, cesarean-section; HELLP, Hemolysis Elevated Liver enzymes and Low Platelets; ICSI, intracytoplasmic sperm; IUI, intrauterine insemination; IVF, in vitro fertilization; PRED, prednisolone; TAC, tacrolimus.

**TABLE 3** Fetal pregnancy outcomes

| | | | |
|---|---|---|---|
| Gender (female), n (%) | n = 106 | | 56 (53) |
| Gestational age (wk) | n = 96 | Gestational age | 38 [36–39] |
| | | Preterm birth, n (%) | 32 (33) |
| | | Very preterm birth, n (%) | 6 (6) |
| | | Extremely preterm birth, n (%) | 2 (2) |
| Birth weight (g) | n = 88 | Birth weight | 2925 [2500–3208] |
| | | Low birth weight, n (%) | 20 (23) |
| | | Very low birth weight, n (%) | 7 (8) |
| Birth percentile, n (%) | n = 85 | < P3 | 10 (12) |
| | | P3–P10 | 13 (15) |
| | | P10–P90 | 53 (62) |
| | | P90–P97 | 4 (5) |
| | | > p97 | 5 (6) |
| APGAR score | n = 68 | 1 min | 9 [8–9] |
| | n = 71 | 5 min | 10 [9–10] |
| | n = 26 | 10 min | 10 [9–10] |
| Death after delivery, n (%) | n = 112 | Neonatal death | 2 (2) |
| | | Death after the neonatal period | 2 (2) |
| Congenital malformation, n (%) | n = 84 | | 0 (0) |
| Congenital infection, n (%) | n = 83 | | 2 (2) |
| Hospital admission child, n (%) | n = 72 | Any admission | 42 (58) |
| | | NICU admission | 10 (14) |

*Note*: Short-term fetal pregnancy outcomes during pregnancy and up to 28 days after delivery. Data given as median [IQR] or n (%) where appropriate. Stillbirth pregnancies excluded. All complications were scored if the diagnosis was mentioned in the patient record. Definitions: neonatal death: death < 7 days after birth; preterm birth: < 37 weeks of gestation; very preterm birth: 28–32 weeks of gestation; extremely preterm birth: < 32 weeks of gestation; low birth weight: < 2500 g; very low birth weight: < 1500 g.
Abbreviations: APGAR, Appearance-Pulse-Grimace-Activity-Respiration; NICU, neonatal intensive care unit.

Multivariable regression analysis showed that higher prepregnancy BMI and higher maternal age at conception were significantly associated with the composite outcome after correction for potential confounding factors based on existing literature (OR: 1.24, 95% CI: 1.07–1.43, OR: 1.25, 95% CI: 1.05–1.49, respectively), Supplemental Table S4, http://links.lww.com/LVT/A656).

## Long-term follow-up of the mothers

The mean (and SE of the period average) of long-term yearly follow-up of bilirubin and serum creatinine are depicted in Figure 3. Follow-up was censored at 25 years after delivery, resulting in a median follow-up of 10 years [IQR: 4–14]. Serum creatinine levels changed over the years ($p < 0.001$). The estimated marginal mean of serum creatinine increased from 78 μmol/L (SEM: 2) before conception to 82 μmol/L (SEM: 4) at 15 years, 101 μmol/L (SEM: 21) at 20 years, and to 66 μmol/L (SEM: 8) at the 25-year follow-up (GEE analysis). Bilirubin levels significantly changed over the years as well ($p < 0.001$). The significant differences over time were independent of maternal age at conception, interval between OLT and conception, prepregnancy BMI, and the presence of a second pregnancy after OLT (data not shown).

None of the patients died during pregnancy. However, 16 of the 70 (23%) women died in the follow-up period (median 10 y [IQR: 5–15]) (Figure 4, Table 4, Supplemental Table S5, http://links.lww.com/LVT/A656). These mothers had given birth to 26 children after receiving transplants, of which 1 stillbirth and 1 child died at the age of 1.5 months. Median age of the 24 alive children at the time of their mother's death was 8 years [IQR: 4–12]. Figure 4A depicts the survival after delivery of the first child after OLT with a survival rate of 94% at 5 years, 80% at 10 years, 64% at 15 years, and 59% at 20 years. Two of the 16 patients died within 1 year after the delivery of their last child. One patient died 36 days after delivery due to pulmonary embolism, and the above-mentioned patient with acute liver failure due to recurrent giant-cell hepatitis, which led to retransplantation 3 weeks after delivery, experienced a recurrence of giant-cell hepatitis, resulting in the death of the patient 150 days after delivery. We found no evidence for causes other than pregnancy for these complications, and therefore assume that both deaths are likely pregnancy-related.

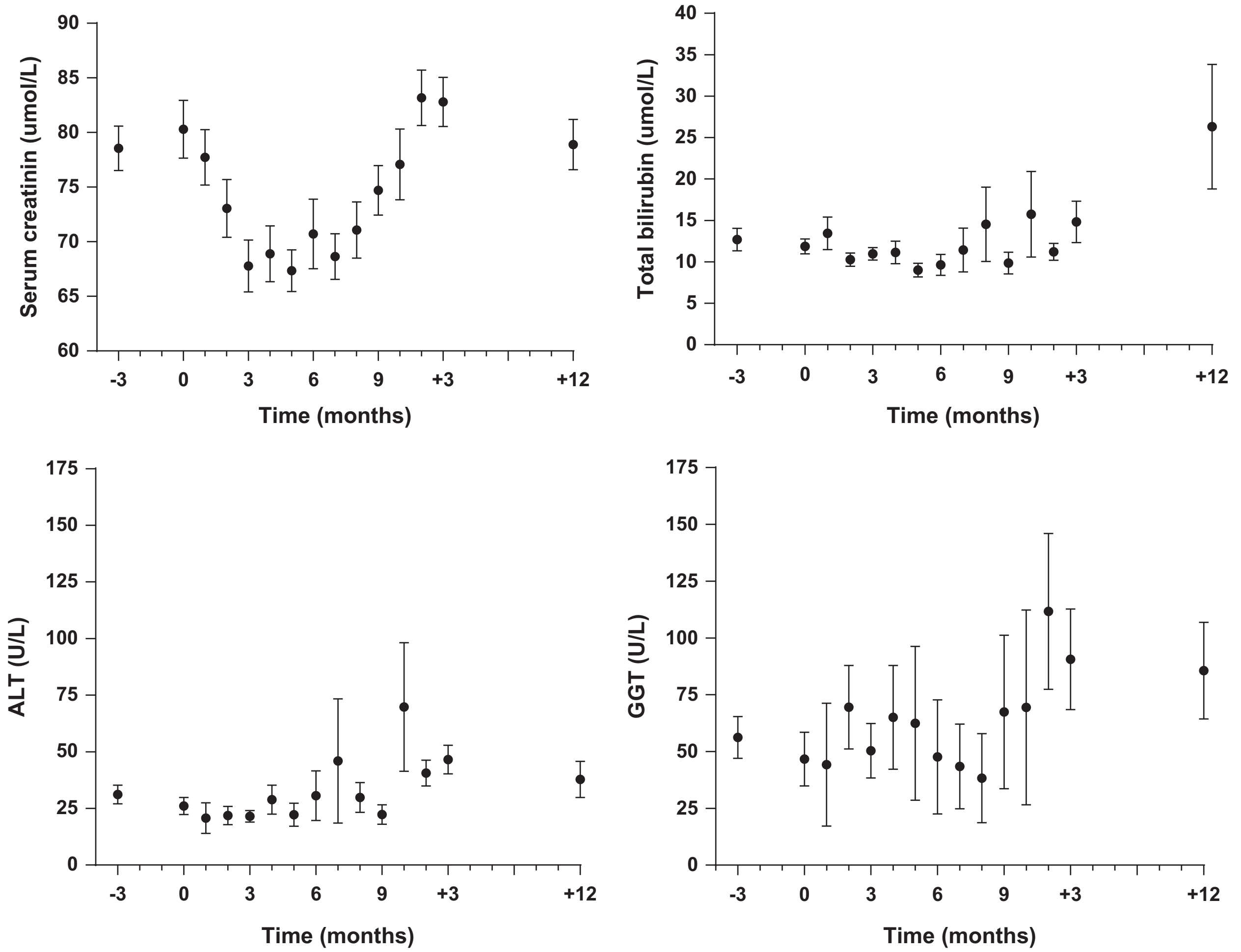



**FIGURE 2** Biochemical parameters during pregnancy after OLT. Estimated marginal means and SE of the period averages of serum creatinine (μmol/L) (884 measurements), total bilirubin (μmol/L) (789 measurements), ALT (U/L) (825 measurements), and GGT (U/L) (824 measurements) during pregnancy calculated with GEE analysis. Starting 3 months before conception (time point: −3) and ending at 3 months after delivery (time point: +3). Serum creatinine, bilirubin, ALT, and GGT significantly changed during pregnancy (overall effects of time: $p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$). Abbreviation: GEE, generalized estimation equation.



Rejection after pregnancy occurred in 5 patients. Two patients experienced 2 episodes of rejection. Besides the above-mentioned patient in which the rejection led to successful retransplantation, rejection occurred 1 year after delivery in 2 cases, and after 2, 3, 4, and 9 years in the remaining cases. Four episodes of rejection were chronic and 3 acute. Six patients experienced graft loss after pregnancy. Three of these patients died (patients 2, 9, and 11; Supplemental Table S2, http://links.lww.com/LVT/A656). Two patients first had a successful retransplantation but died 11 and 13 years after retransplantation (Supplemental Table S2, http://links.lww.com/LVT/A656).

## Comparison of survival in women with and without pregnancy after transplantation

In Figure 4B, the survival after OLT of women with (n = 70) and without (n = 390) pregnancy after OLT is depicted. No significant difference between the survival of women with or without pregnancy was found ($p = 0.39$). The survival rate at 5 years was 97% in the group with pregnancy after OLT and 94% in the group without pregnancy; at 10 years, this was 91% versus 89%; at 20 years, 80% versus 84%; and at 30 years 71% versus 75%.

# DISCUSSION

The primary aim of this retrospective multicenter cohort study was to assess the short-term and long-term maternal outcomes of pregnancy after OLT in the Netherlands. To our knowledge, this is the first study with detailed information on long-term follow-up in one of the largest cohorts on pregnancy after OLT. Although the vast majority of children were born healthy, we also show an increased risk for serious complications in the short term for both mother and fetus, in line with existing

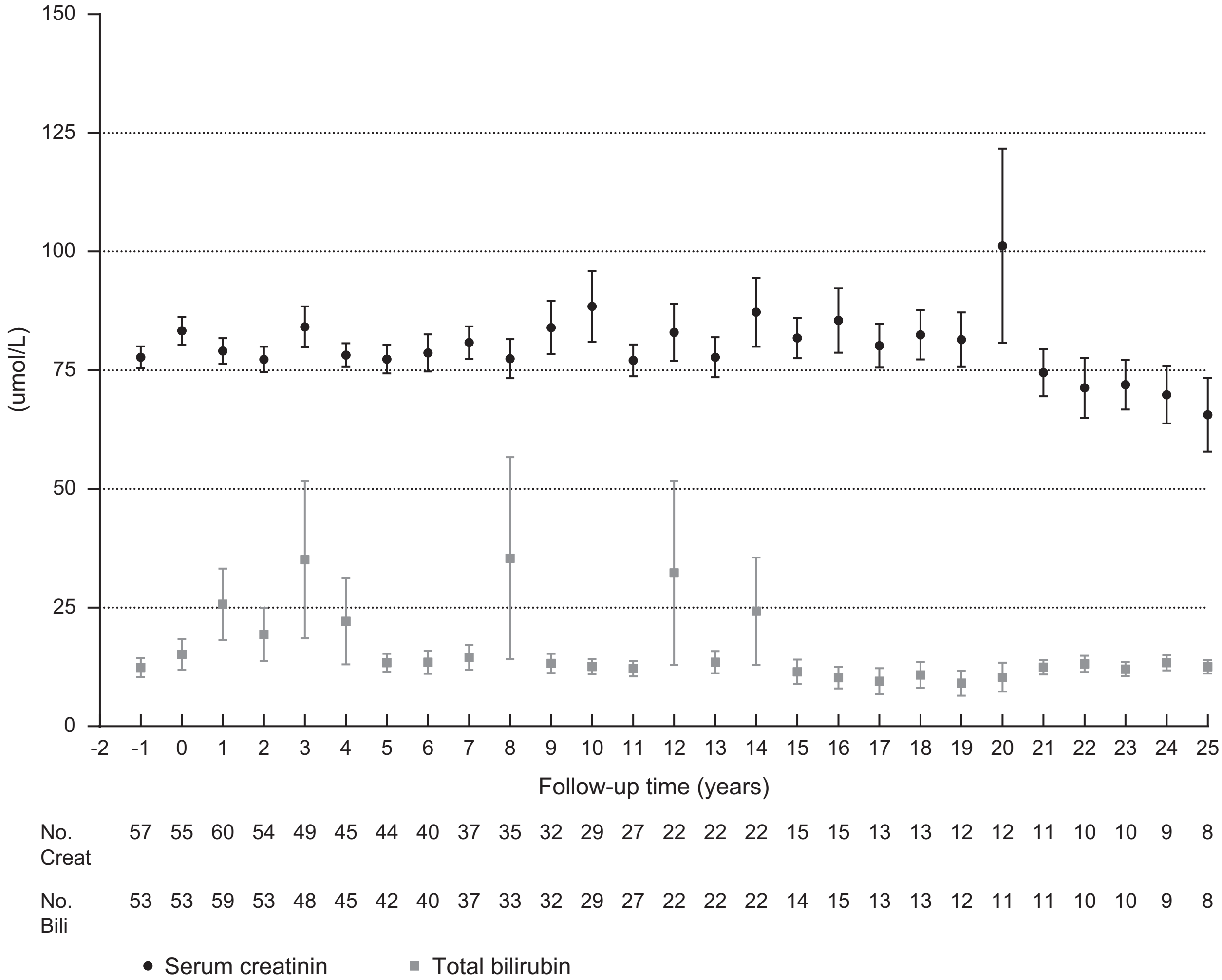
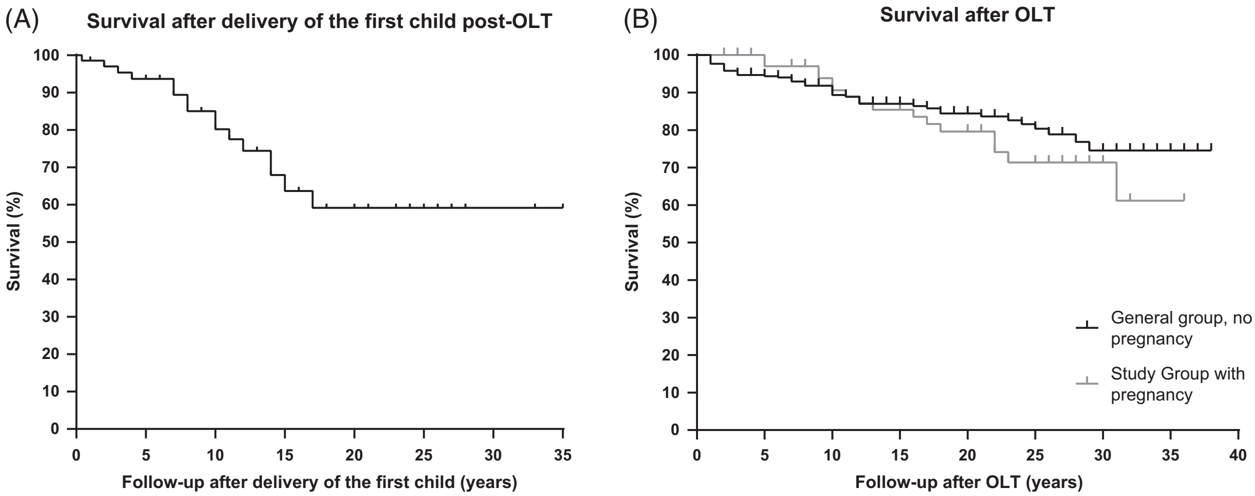



**FIGURE 3** Long-term yearly follow-up after pregnancy in patients who underwent OLT. Estimated marginal mean and SE of the period averages of serum creatinine (μmol/L) (756 measurements), and bilirubin (μmol/L) (743 measurements) levels calculated with GEE analysis. Starting 3 months before conception of the firstborn child after OLT (time point: −1), followed by 3 months after delivery (time point: 0), and then yearly till 20 years after delivery. Administrative censoring at a 25-year follow-up was performed. Creatinine and bilirubin significantly changed over time (overall effect of time: $p = 0.00$, $p < 0.001$, respectively). Abbreviation: GEE, generalized estimation equation.

literature.[2,8] In the long term, the pregnancy and the pregnancy complications seem safe for the transplanted liver in most cases. However, in line with general survival after OLT, we report that 23% of mothers did not see their child reach adulthood. The secondary aim was to assess predictors for adverse pregnancy outcomes. We found that, similar to the general population, a higher prepregnancy BMI and a higher maternal age at conception increased the risk for pregnancy-related complications.

Short-term fetal complication rates are higher than in the general population, which is in line with existing literature on post-OLT pregnancy.[2,5,10] We report a perinatal death rate (either stillbirth > 24 wk or neonatal death in the first 28 d) of 5.4%, which is substantially higher than the 0.5% in the general Dutch population.[22] This might be due to the increased incidence of preterm birth and very preterm birth in our population compared to the general population (33% vs. 7% and 6% vs. 1%, respectively). Moreover, the 4 fetal deaths after delivery were in extremely (n = 2) and very (n = 2) preterm infants.

Short-term maternal outcomes underline the increased risk of adverse pregnancy outcomes after OLT as well.[9,10] We found that 2 mothers died likely due to pregnancy-related complications, leading to a maternal death rate of 1.8% (2/113 pregnancies). This is substantially higher than the maternal death rate in the general Dutch population of 6/100,000. We do realize that our population is too small to make firm conclusions about the maternal death rate, but this finding does warrant further investigation. We found a trend toward an increased risk of pregnancy complications for preexistent hypertension and serum creatinine > 90 μmol/L as well, which might have been significant with higher numbers of patients. These results are therefore partly in line with a study from Lim et al[23] whereby they report that prepregnancy kidney function predicts the risk of




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No. at risk | 70 | 53 | 35 | 16 | 12 | 8 | 3 | 1 |
| No. events (cumulative) | 1 | 3 | 10 | 15 | 16 | 16 | 16 | 16 |

| Study group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No. at risk | 70 | 67 | 59 | 47 | 34 | 22 | 10 | 3 |
| No. events (cumulative) | 0 | 0 | 4 | 9 | 12 | 15 | 15 | 16 |

| General group after OLT | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No. at risk | 390 | 295 | 221 | 159 | 107 | 67 | 26 | 4 |
| No. events (cumulative) | 0 | 20 | 28 | 39 | 43 | 46 | 50 | 50 |

**FIGURE 4** Kaplan-Meier survival curves. (A) Kaplan-Meier survival curve after delivery of the first child after OLT. Survival (in years) after delivery of the first child born after OLT. (B) Kaplan-Meier survival curve of survival of women with an OLT $<50$ years with and without a pregnancy after OLT. Survival (in years) after transplantation. Exclusion of patients with a follow-up $<1$ year after transplantation. Cox regression: $p = 0.41$. Source: Dutch Transplant Foundation.

pregnancy complications in pregnancies after OLT. Increased prepregnancy bilirubin levels ($>17$ μmol/L) were not associated with an increased risk of pregnancy complications. However, bilirubin levels in our study were only mildly elevated (18–35 μmol/L) in all but 1 patient (bilirubin 114 μmol/L). This indicates that mild graft dysfunction does not increase the risk of complications, but does not exclude a risk associated with more severe degrees of liver dysfunction. Previous research has reported variable rates of graft rejection ranging between 0% and 20%.[5,8,24] No cases of acute cellular rejection during pregnancy occurred in our study, but 2 cases of graft loss occurred shortly after pregnancy. We did notice that patients with preexistent chronic rejection had complicated pregnancies, which indicates that that might be an important risk factor. Moreover, in recent years the importance of evaluating the presence of signs of portal hypertension has become an important factor in preconception counseling of patients with a pregnancy wish after OLT.[25] We did not have data on the presence of portal hypertension in our study, but this could be an important risk factor for adverse pregnancy outcomes.

Regarding long-term outcomes of pregnancy after OLT, we show that pregnancy, in most cases, does not seem to influence graft, kidney function, or patient survival. However, we believe that the risk that the child will lose its mother early in life is substantial and an important aspect in pregnancy counseling of patients OLT patients and their partners. Literature on long-term follow-up of graft, kidney, and general health of mothers after OLT is scarce.[26] We show that mean values of both bilirubin and serum creatinine only slightly change on long-term follow-up. This indicates that pregnancy does not have a direct harmful effect on the function of the graft or on kidney function in most patients. These findings are in line with research in women who underwent kidney transplantation, whereby no significant effect of pregnancy on kidney function was detected in the long term.[27] The mortality in our study of 23% is higher than in the study of Lim et al,[23] where 12% of the women died after pregnancy (median of 5.5 y after delivery), of which none of the deaths were pregnancy-related (median follow-up 16 y). The annual report of the TPR of 2022 reports that 15% of mothers who underwent OLT died after pregnancy with a mean age of 13.1 years of the children (mean follow-up: 9.6 y).[2] In contrast, an Italian multicenter study reported only 1 death out of 60 women with a pregnancy after OLT in a 30-year period.[12] To further assess whether pregnancy influenced patient survival, we compared the survival of women with and without a pregnancy after OLT, and we did not find a difference. This indicates that indeed it is not the pregnancy itself that directly influences survival in most women. The survival rates in our study group are better when compared to the general survival of patients who underwent OLT who

TABLE 4 Characteristics of deceased patients

| Case | Pregnancies (n) | Cause of death | Age at death (y) | Interval delivery-death (y) | Interval OLT-death (y) |
|---|---|---|---|---|---|
| 1 | 2 | Thyroid cancer | 51 | 15 ½ and 13 ½ | 22 |
| 2 | 2 | Liver failure after retransplantation | 28 | 2 ¾ and 150 days | 10 |
| 3 | 2 | Ruptured arterial conduit from aorta to hepatic artery | 44 | 11 ¼ and 6 | 23 |
| 4 | 2 | Bile duct complications with cirrhosis | 32 | 10 and 6 ½ | 31 |
| 5 | 1 | Massive pulmonary embolism | 30 | 0, 36 days | 16 |
| 6 | 2 | Respiratory insufficiency after metastatic lung cancer | 41 | 9 ¼ and 3 ¾ | 17 |
| 7 | 1 | Noncompliance of immunosuppressive therapy | 23 | 3 | 5 |
| 8 | 1 | GIT bleeding due to coagulation disturbances due to liver failure | 46 | 8 ¾ | 10 |
| 9 | 1 | Multiorgan failure due to pneumosepsis | 42 | 12 | 11[a] |
| 10 | 2 | Metastatic breast cancer | 45 | 14 and 11 ½ | 18 |
| 11 | 2 | Graft failure | 38 | 14 and 4 ¼ | 13[b] |
| 12 | 1 | Unknown, lost to follow-up | 34 | 7 | 9 |
| 13 | 1 | Unknown, lost to follow-up | 34 | 2 | 5 |
| 14 | 4 (2†) | Out-of-hospital cardiac arrest most probably due to intracranial bleeding | 43 | 17, 12†, 10 and 9† | 22 |
| 15 | 1 | Hemorrhagic shock after necrotizing pancreatitis | 45 | 8 | 12 |
| 16 | 1 | Metastatic breast cancer | 43 | 7 | 9 |

[a]Successful retransplantation after delivery of the child.
[b]Successful retransplantation 1 year after delivery of the first child (11a).
† indicates deceased.
Abbreviation: GIT, gastrointestinal bleeding.

received a transplant at $<45$ years of age in Europe, whereby survival rates of 75%, 66%, and 50% at 5, 10, and 20 years are reported,[28] compared to 97%, 91%, and 80% in our study group. This difference can probably be partly explained by the fact that a significant proportion of these patients died in the first year after transplantation and we excluded these patients. Moreover, the women who get pregnant after transplantation are a selected population of patients who do well. At the same time, it emphasizes again that the pregnancy itself probably does not affect the long-term survival but that is a consequence of the transplantation itself. The maternal survival after delivery of the first child was only 59% at 20 years. Of the remaining 54 patients, only 13 had a follow-up period of up to 18 years. Thus, it is possible that more children will lose their mother at a young age and will experience a period in which their mother is terminally ill, which will impact the offspring and the father of the child. Future research should, therefore, not only focus on the medical risks of a pregnancy after transplantation but also on the experiences of these families to understand better what the impact of a pregnancy after transplantation is on the whole family and if additional support is needed. Another important knowledge gap that should be addressed in future research is the long-term health outcomes for the offspring born after transplantation.[29]

An important feature of this study is that it is one of the first in pregnancies after OLT to report results on long-term follow-up, and the first with detailed information on graft function and kidney function on long-term follow-up. Moreover, it is one of the largest cohorts published on pregnancy after OLT.[8] The design of the study allowed for analysis in an unselected, relatively large population of pregnancies after OLT, and therefore prevented selection bias. However, even though the study population was relatively large, numbers are still small for firm statistical analysis. Another limitation is that the retrospective design of the study may lead to recall bias and, especially in the earlier pregnancies, there was missing data. By combining the results of medical files and questionnaires, missing data were minimized.

In conclusion, in pregnancies after OLT, we report a high live birth rate and, in line with the literature, a relatively high risk of adverse pregnancy outcomes, which was further increased by higher prepregnancy BMI and higher maternal age at conception. For the first time, we show that for most patients, pregnancy after OLT does not seem to influence long-term outcomes of graft, kidney function, or patient survival. However, even though pregnancy does not seem to impact survival after OLT in most cases, we do show that a substantial number of children will lose their mothers early in life.

We believe that this is an important aspect of pregnancy counseling for OLT patients and their partners.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## CONFLICTS OF INTEREST

Margriet F.C. de Jong is on the speakers' bureau for Alexion and Chiesi Pharma. She is on the speakers' bureau and received grants from Astellas. Stefan P. Berger received grants from Novartis, Chiesi Pharma, and Astellas. Bart van Hoek received grants from Chiesi Pharma and Sandoz Pharma and advises for Abacus Pharma. The remaining authors have no conflicts to report.

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