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**ORIGINAL ARTICLE**

# Pregnancy in heart- and heart/lung recipients can be problematic

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**Abstract**

*Objective*. The first successful pregnancy after heart transplantation was reported in 1988. Worldwide experience with heart and heart/lung transplanted (H-HLTx) pregnant women is limited. To expand this knowledge the collaborating Nordic thoracic transplant centers wanted to collect information on all such pregnancies from their centers. *Design*. Information was retrospectively collected on all H-HLTx pregnancies in the Nordic countries. *Results.* A total of 25 women have had 42 pregnancies and all survived the gestation. Minor complications were increasing incidence of proteinuria, hypertension and diabetes. Major problems were two rejections (early post partum), two severe renal failures, seven pre-eclampsias and 17 abortions. Five women died two to 12 years after delivery. Of 25 live born children, one was born with cancer and one died early after inheriting the mother's cardiomyopathi. *Conclusion.* Pregnancy after H-HLTx can be successful for both mother and child. There are, however, many obstacles which should be addressed. Respecting the couple's desire for children the attitude should be carefully, not too optimistic, after proper pre-pregnant information and counseling. Delivery should preferably take place at the transplant center.

**Key words:** *heart transplantation, heart and lung transplantation, immunosuppression, pregnancy complications*

The first known successful pregnancy after heart transplantation was reported in 1988 (1). Case reports and small series describing experience with this special group of heart- and heart/lung transplanted (H-HLTx) pregnancies have later been published (2,3). Initially pregnancy was discouraged, but despite limited experience the risk has been considered as moderate, and a more optimistic view has evolved.

During pregnancy, the cardiovascular and respiratory systems adapts to the metabolic needs of mother and fetus in order to supply adequate perfusion. This normally induces an increase in circulating blood volume and cardiac output, and reduced vascular resistance (4–6). As a result of increased fetal and maternal tissue mass, and cardiac and respiratory work, maternal peak oxygen consumption can increase by 20–30% at term. Whereas most of the increase in cardiac output occurs early, the increase in oxygen consumption occurs progressively throughout the pregnancy (7). This induces stress to the cardio-respiratory system which has to be mastered by the transplanted organs, and is a potential risk factor for the fetus and the woman and may impose concerns regarding maternal longevity.

The number of female H-HLTx recipients of childbearing age has increased due to both an overall improved survival and to an aging pediatric transplant population. This situation puts focus on the desire to become a parent (8). Each transplant center has a limited number of pregnant H-HLTx women, and reports are basically case reports, center reports, and registry data such as Sibanda et al. from 2007 (3) and Coscia et al. from 2009 (9) and review articles like McKay et al. (10).

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Table I. Demographics for 25 women at last control before first pregnancy after transplantation.

| | |
|---|---|
| Heart- and heart/lung recipients | 19/6 |
| Indication for transplantation | |
| Cardiomyopathy | 15 (60%) |
| Congenital heart disease | 9 (36%) |
| Cystic fibrosis | 1 (4%) |
| Diabetes mellitus treatment | 1 (4%) |
| Hypertension treatment | 8 (32%) |
| Proteinuria | 2 (8%) |
| Creatinine (μmol/l, mean ± SD) | 93 ± 29 |
| Women with rejections before pregnancy | 15 (60%) |
| General health | |
| Good | 20 (80%) |
| Fair | 5 (20%) |

The Nordic population is relatively homogenous and the transplant protocols are practically equal. We therefore assumed that by collecting information from all the collaborating Nordic thoracic transplant centers we could contribute to the general knowledge and treatment of this rather unique patient population.

## Material and methods

### *Subjects*

Transplant recipients are subjected to yearly controls at the Nordic transplant centers where complete information of the patients is filed. Twenty-five women were identified with a total of 42 fetuses (including two pair of twins). Of these, 19 were heart (33 fetuses) and six heart/lung (nine fetuses) transplanted women.

Age at transplantation was 20 ± 6.6 (9–34) and time from transplantation to first pregnancy was 6.5 ± 3.2 (1–12) years, respectively. Other demographic information relates to the latest control before pregnancy (Table I).

### *Methods*

Information about the pregnancies, complications and outcome were retrospectively collected and analyzed. The women had been examined regularly at their transplant center in collaboration with the local physician and were also examined by an obstetrician.

Immunosuppression before, during and after the pregnancies followed the general local protocols. In 24 of the pregnancies a three drug regimen consisting of prednisolone, cyclosporine A and azathioprin was followed, and in 18 a 2 drug regimen without prednisolone was used. In five of the pregnancies tacrolimus was used instead of cyclosporine A and in two mycophenolate mofetil instead of azathioprin.

Blood concentrations of cyclosporine A and tacrolimus were followed closely during and after the pregnancies, together with graft function by eccocardiography and spirometry.

In this retrospective study there is only few lost data, mainly caused by that some information about an emigrated woman could not be obtained.

### *Statistics*

The data are presented as numbers (n), percent (%), mean value, standard deviation (SD) and range as appropriate. Statistical analysis was performed with SPSS statistical software version 13.0 (SPSS inc. Chicago, USA). $P < 0.05$ was regarded as significant.

## Results

### *Women*

The women had from one to five pregnancies, all surviving the pregnancy and the early post partum period. Major complications were two rejections (treated with methyl prednisolone and daclizumab) and two cases of serious renal failure. One of the patients with renal failure eventually recovered, while the other went into chronic dialysis and later renal transplantation. After renal transplantation, this woman (despite very serious warnings) got pregnant twice, and had two uncomplicated pregnancies, and delivered two healthy infants. Mean creatinine before pregnancy was 93 ± 29 μmol/l, which increased significantly during pregnancy to 109 ± 79 μmol/l ($p < 0.01$) with a minimal improvement to 106 ± 60 μmol/l 3 – 12 months after delivery ($p < 0.01$ before to after pregnancy).

Co-morbidities increased considerably; diabetes mellitus from one to four recipients, proteinuria from two to 12 and hypertension from eight to 21. Analyzing co-morbidities treated together there was a highly significant increase ($p = 0.001$) during pregnancy. After delivery hypertension persisted in 18 women.

Five of the women died relatively early after the pregnancy. One from rejection (two years post partum), one from heart failure (three years after induced abortion), one from lymphoma (one year post partum, twin pregnancy) and two from bronchiolitis obliterans (five and 12 years after induced abortion, respectively).

Complications appeared equally often among the heart- as among the heart/lung transplanted women.

Table II. Outcome of 42 pregnancies after heart or heart/lung transplantation.

| | |
|---|---|
| Spontaneous abortion | 11 (27%) |
| Induced abortion | 6 (15%) |
| Induction of delivery | 7 (17%) |
| Cesarean section | 12 (29%) |
| Indication for cesarean section | |
| Cholestasis | 2 (17%) |
| Preeclampsia | 3 (25%) |
| Maternal request | 3 (25%) |
| Twin pregnancy | 2 (17%) |
| Malformation | 1 (8%) |
| Preterm delivery | 1 (8%) |
| Spontaneous vaginal delivery | 6 (15%) |
| Pregnancy length (weeks) | $36.4 \pm 2.9$ |
| Birth weight (g) | $2726 \pm 655$ |

*Pregnancies*

A considerable number of the pregnancies resulted in abortions, either spontaneous or induced. The induced abortions were partly performed on the maternal request, and partly on medical/social indications (Table II). Regarding spontaneous abortion there was no advantage of a two drug regimen (n = 7) compared to a three drug regimen (n = 4). There were 12 cesarean sections, 11 elective and one acute because of preterm delivery. Cesarean section was performed on medical indications in nine of the women and three on maternal request.

There were six spontaneous vaginal deliveries without medical or surgical assistance (Table II).

*Children*

The 25 live born children were delivered after a pregnancy length of $36.4 \pm 2.9$ weeks, with a birth weight of $2726 \pm 655$ g. Of these there were 23 healthy infants. However, one was born with a non-specified malignant tumor which was treated, and the child is alive. Another died early from inherited cardiomyopathy. The rest of the children have developed normally without any complications, now to the age of $7.1 \pm 4.6$ years.

## Discussion

H-HLTx recipients in the Nordic countries are closely followed at the respective transplant centers where relevant information is filed. Pregnancies in this cohort are rare and involve unique circumstances not encountered in recipients of other solid organ transplants (11). Most of these women were therefore controlled by a multidisciplinary team at the transplant hospitals where also the delivery should preferably take place.

Fertility is regained early after transplantation (10), and since a large number of pregnancies are unintended (12) one should not wait to raise the issue until patients express concern. The relatively high number of therapeutic abortions, in our material, therefore emphasizes the need for prophylactic information.

*Contraception*

Counseling about contraception is important at an early stage, some recommend counseling already, during evaluation for transplantation (13). Traditionally among contraceptive approaches, the barrier methods have been favored by most centers. Intrauterine devices have an increased risk for infections and are less effective in the immunosuppressed recipients and should probably not be used (10). There is no information suggesting that estrogen-progesterin contraceptives should not be used under the same precautions as in other women. However, they inhibit the CYP 450 3A4 pathway and immunosuppression blood levels should therefore be monitored carefully when such therapy is started (14).

*Immunosuppression*

US Food and Drug Administration has published recommendations for medication during pregnancy. All the commonly used immunosuppressive drugs pass through the placenta and are secreted in breast milk and thus may carry some risk for the fetus and the newborn (15). The drugs used by our pregnant women, mainly a combination of predisolone, cyclosporine A (or tacrolimus) and azathioprin, have been the most commonly used drugs in H-HLTx recipients in the Nordic countries. This is probably the safest regime in pregnant recipients today and conforms to recently published guidelines (14). They are, however, only based on class I recommendation, level of evidence C. As the drugs pass through the placenta, we can not rule out that the high number of spontaneous abortions could, at least in part, be caused by their teratogenic side effect. In a study by Tendron et al. (16) most pregnancies in cyclosporine A.

Treated women had a favorable outcome and 60% of infants exposed to cyclosporine A antenatal had no neonatal complications.

Corticosteroids can in some recipients be stopped early after transplantation. In our cohort, near half of the pregnancies were on a two drug regimen. This would reduce the immunosuppressive burden, but did not have a significant effect on the number of spontaneous abortion. Mycophenolate mofetil has

been used for a shorter time than cyclosporine and experience in the pregnancy setting is scarcer.

It is, however, recommended that this drug should not be used during pregnancy (14). It is noteworthy that both pregnancies on this drug resulted in spontaneous abortion, while after change to azathioprin this later resulted in two successful pregnancies with healthy children.

*Maternal risks*

Two of our patients became pregnant within two years after transplantation. Guidelines recommend pregnancy no closer than one year after transplantation. Importantly there should not be any rejection the last year and the cardiopulmonary function should be good, as well as the physical condition in general (14).

The prevalence of systemic hypertension, diabetes mellitus and renal failure is high in transplant recipients, partly related to the immunosuppression (17). As observed among our patients the frequency increased during pregnancy, more than would be expected in healthy women. Co-morbidities should therefore be thoroughly evaluated before pregnancy, properly controlled and treated during pregnancy and in the post partum period.

Pre-eclampsia was frequent in our patient cohort, much higher than in healthy women (18) and even higher than reported earlier among heart transplant recipients (9). The exact pathogenesis of pre-eclampsia remains unknown and there is presently no proven strategy to consistently reduce the risk (19). However, since our study showed a doubled occurrence of pre-eclampsia among pregnant H-HLTx women compared to healthy women, blood pressure, proteinuria and immunosuppressive medication should be closely monitored and treated properly.

Coscia et al. reported 21% rejections in a series of 33 pregnancies; many were low grade and did not require additional treatment (9). This is in contrast to our experience as only two rejections were diagnosed, in both cases shortly after the delivery. Myocardial biopsy is at present the only reliable method to diagnose rejection and was used differently among our centers, but very few had a routine biopsy. One should, however, be aware of the problem and biopsy should be performed if rejection is clinically suspected.

In our study almost half of the live born deliveries were cesarean sections, some medically indicated and some on the maternal request. However, most centers agree that the indication for cesarean section should only be obstetrical reasons (20,21).

*Children's risk*

Although cyclosporine A passes the placenta there is limited experience concerning effects on the fetus. Among animals teratogenic effects are shown and there is an increased risk of preterm delivery and the drugs may cause spontaneous abortion as discussed above. On the other hand cyclosporine A is one of the main immunosuppressive drugs and the woman's blood concentration should be followed closely to be within therapeutic levels (14). The dose often has to be increased during pregnancy to keep blood concentration in the therapeutic range.

Apart from one child born with a malignant tumor that might have been caused by the immunosuppression and one with inherited heart disease all live born children were healthy at birth and during the observation period. This despite a shorter pregnancy length, however with a normal birth weight corresponding to the weeks of gestation (22). The possibility of inheritance of the mother's cardiac disease should call for special attention during the careful discussion with the couple before pregnancy should be attempted.

Life time prognosis of H-HLTx recipients is considerably shorter than for healthy women. If all the pregnancies had resulted in live born children a considerable percentage would have experienced the disaster of one parent dying during the child's early years, as shown by the post partum prognosis of the women in our cohort. Reported numbers from other studies vary, but our results are comparable with Scott et al. (23). However, mortality must be expected in this population taking into consideration the increased mortality among heart and specially heart/lung recipients compared to the general population (8). Ethical concerns have been raised about the wisdom of pregnancy for a woman who might have a limited life span or in whom serious medical complications might develop (13).

## Conclusion

Pregnancies in H-HLTx women can be successful for both the woman and the child. There are, however many obstacles that have to be taken into consideration as complications may be serious. Particularly it is worth noticing that there is a not negligible risk of early death leaving the child motherless.

Proper pre-pregnant counseling, by the transplant cardiologist and a gynecologist familiar with high risk pregnancies, to the woman and her partner, is mandatory. Respecting the couple's desire for children, the attitude should nevertheless not be too

optimistic. The delivery should preferably be at the transplant center.

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