American Journal of Transplantation 2009; 9: 820–824
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02427.x

Pregnancy and Birth After Kidney Donation: The Norwegian Experience

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Reports on pregnancies in kidney donors are scarce. The aim was to assess pregnancy outcomes for previous donors nationwide. The Medical Birth Registry of Norway holds records of births since 1967. Linkage with the Norwegian Renal Registry provided data on pregnancies of kidney donors 1967–2002. A random sample from the Medical Birth Registry was control group, as was pregnancies in kidney donors prior to donation. Differences between groups were assessed by two-sided Fisher's exact tests and with generalized linear mixed models (GLMM). We identified 326 donors with 726 pregnancies, 106 after donation. In unadjusted analysis (Fisher) no differences were observed in the occurrence of preeclampsia ($p = 0.22$). In the adjusted analysis (GLMM) it was more common in pregnancies after donation, 6/106 (5.7%), than in pregnancies before donation 16/620 (2.6%) ($p = 0.026$). The occurrence of stillbirths after donation was 3/106 (2.8%), before donation 7/620 (1.1%), in controls (1.1%) ($p = 0.17$). No differences were observed in the occurrence of adverse pregnancy outcome in kidney donors and in the general population in unadjusted analysis. Our finding of more frequent preeclampsia in pregnancies after kidney donation in the secondary analysis must be interpreted with caution, as the number of events was low.

Key words: Living donor transplantation, pregnancy, transplantation

Received 20 May 2008, revised 15 August 2008 and accepted for publication 20 August 2008

Introduction

The extensive and expanding use of living kidney donors calls for awareness of potential physical and emotional problems related to donation (1,2). Several studies have shown that it appears generally safe in terms of future health to donate a kidney in selected healthy persons (3–6). However, in meta-analysis (7–9), a marginal increase in blood pressure and some reduction of overall kidney function following uninephrectomy were found.

In many countries living kidney donors provide the majority of transplanted kidneys (10,11). A majority of chronic kidney failure patients are men, and most kidney donors are females (10,12). Many donors are women of childbearing age. Therefore, the impact of donation on future pregnancies and deliveries has been a matter of discussion. A normal pregnancy is characterized by a physiological increase in renal blood flow and glomerular filtration rate (13). In previous donors, the nephrons of the remaining kidney are already hyperfiltering, which has raised concerns about future pregnancies in female donors. It may be particularly relevant since it is conceivable that increase of blood pressure and loss of kidney function in donors may predispose for hypertensive pregnancy disorders and other complications. Available reports indicate that previous kidney donation is not detrimental to the course and outcome of future pregnancies (14–16). However, the reports are few and based on a low number of cases. Thus further studies are needed to address these issues.

By compulsory notification the Medical Birth Registry of Norway collects data on all pregnancies with gestational age of 16 weeks or more. Linkage of the Norwegian Renal Registry with the Medical Birth Registry identified all pregnancies in living kidney donors. The aim of this study was to assess the risks of adverse pregnancy outcome, in previous kidney donors in terms of gestational hypertension, preeclampsia, preterm delivery, low birth weight and perinatal mortality.

Materials and Methods

Medical Birth Registry of Norway

Since 1967, medical data on all pregnancies in Norway (total population of 4.5 million inhabitants) with a gestational age of 16 weeks or more are forwarded to the Medical Birth Registry of Norway (17). The attending

Table 1: Characteristics of births randomly selected from the Medial Birth Registry of Norway, births before and births after a kidney donation, Norway 1967–2002

		Donors		
Characteristics	Birth Registry ≈ 1% of births	Pregnancy before	Pregnancy after	p-Value[1]
Total N	21 511	620	106	
Primipara N (%)	8781 (41.2)	253 (40.9)	28 (27.2)	0.015
Mean (SD) age at delivery	27.1 (5.3)	25.0 (4.7)	31.9 (4.8)	< 0.001
Mean (SD) age at donation		37.0 (5.1)	26.9 (4.7)	< 0.001

[1]Chi-square, ANOVA and *t*-test, respectively.

obstetrician and midwife complete the forms. The notification form includes data on maternal disease, complications of delivery and the condition of the newborn. The form and set of data registered were revised in 1998. Data from 1967 through 2002 were integrated in the analysis resulting in a total of approximately 2.1 million pregnancies.

Donors and pregnancies

All living kidney donors had a thorough medical workup by their local nephrologist. Generally, only normotensive, nondiabetic, nonobese (BMI < 30 kg/m^2) and healthy persons with no sign of renal disease and adequate renal function were accepted as renal donors.

All solid organ transplantations in Norway are now performed at Rikshospitalet University Hospital. Until 1983 kidney transplantations were also performed at Ullevål University Hospital in Oslo. We have a complete record of all kidney transplantations performed in Norway. From 1967 to 2002, a majority of the living kidney donors in Norway were female (1097/1871, 58%). We identified 408 women who were 45 years or less of age at the time of kidney donation. The national identification numbers were used to link these donors to the Medical Birth Registry of Norway. Altogether 326 women were identified with pregnancies before and/or after donation.

The following three groups were subjected to analysis: Pregnancies after kidney donation, pregnancies before kidney donation and a control group from the Medical Birth Registry.

The control group

A random sample of mothers and their pregnancies were obtained from the Medical Birth Registry to constitute the control group of approximately 21 000 pregnancies (1%). We compared the complete registry and the control group on all variables presented in this study to ensure that they were identical (data not shown).

Outcome variables

In Norway, during the observation period, chronic hypertension in pregnancy was defined as BP ≥140/90 prior to pregnancy or gestational week 20. Gestational hypertension was defined as a BP of ≥140/90 mmHg or increase in diastolic BP of at least 15 mmHg or systolic BP of at least 30 mmHg from the woman's average BP before 20 weeks of gestation, without proteinuria in women without pregestational hypertension (18). The definition of preeclampsia was as for gestational hypertension above, but with proteinuria. Proteinuria was defined as excretion of ≥ 0.3 g per day, usually equivalent to ≥ 1+ on a standard urine test strip. Birth weight was measured immediately after birth. A fetus was recorded as stillborn if it died before or during labor. Gestational age was based on the last menstrual period.

Statistics

Frequencies and means of demographic variables were compared by chi-square, *t*-tests and analysis of variance (ANOVA). The donor group is small and the number of recorded events on many of the outcome variables is very low. Thus, approximative statistical methods like the chi-square test are not valid. Therefore comparisons of the controls and the two donor groups were performed with Fisher's exact test. This test does not allow for adjustments of neither confounding factors nor the fact that some mothers will contribute with more than one birth. When not limited by low numbers, we applied generalized linear mixed models (GLMM) (19). GLMM can be viewed as an advanced type of regression analysis, which additionally allows for adjustment for the fact that many mothers contribute with more than one birth. In the GLMM we also adjusted successively for maternal age, birth order (i.e. primipara or not) and year of birth.

In theory, GLMM could be applied for comparison of all three groups. However, due to the computational complexity of the method in combination with the rarity of events and the unbalanced sizes of the groups, we only compared the two donation groups to achieve stable estimates.

The analyses were done with SPSS 12.0 software and R 2.6.0 (20). The Regional Ethics Committee recommended the study and approval was given from the National Data Inspectorate and the Directorate of Health and Social Affairs.

Results

Altogether 726 pregnancies were registered in 326 donors, of which 106 occurred after donation in 69 of the donors. Mean (SD) time from donation to delivery was 5.0 (3.4) years. There was a lower proportion of primiparity and higher maternal age at delivery after donation (Table 1).

Gestational hypertension and preeclampsia

Chronic hypertension was infrequent in all groups (Table 2). The rate of gestational hypertension was not different between the three groups (Table 2). Gestational hypertension was observed in 3/106 (2.8%) pregnancies after donation and in 11/620 (1.8%) pregnancies before donation. All were live births with gestational age 37 weeks or more.

The rate of preeclampsia was not different between the groups in the unadjusted analysis ($p = 0.22$) (Table 3). However, in the adjusted GLMM analysis it was higher in pregnancies after kidney donation 6/106 (5.7%) than in pregnancies before donation 16/620 (2.6%) ($p = 0.026$). In this analysis we adjusted for participation with more than one pregnancy. The result remained valid when adjusting for maternal age ($p = 0.037$), birth order ($p = 0.017$) and year of birth ($p = 0.047$). The rate of preeclampsia in the control group was 3.1%. None of the living kidney donors with preeclampsia had chronic hypertension.

Table 2: Pregnancy outcome in births randomly selected from the Medial Birth Registry of Norway, births before and births after a kidney donation, Norway 1967–2002

Pregnany outcome	Birth Registry ≈ 1% of births	Donors		p-Value
		Pregnancy before	Pregnancy after	
	N = 21 511 (%)	N = 620 (%)	N = 106 (%)	
Mother				
Chronic hypertension	52 (0.2)	1 (0.2)	1 (0.9)	0.28
Gestational hypertension	314 (1.5)	11 (1.8)	3 (2.8)	0.26
Birth weight				
< 500 g	89 (0.4)	3 (0.5)	1 (0.9)	0.41
500–2500 g	1021 (4.8)	34 (5.5)	8 (7.5)	0.24[1]
> 2500 g	20340 (94.8)	581 (94.0)	97 (91.5)	0.19[1]
Gestational age				
< 22 weeks	59 (0.3)	2 (0.3)	1 (1.0)	0.26
< 37 weeks	1338 (6.6)	44 (7.5)	10 (9.8)	0.25
Mortality				
Stillbirths	227 (1.1)	7 (1.1)	3 (2.8)	0.17[1]
Death < 28 day after birth	134 (0.6)	3 (0.5)	0 (0.0)	1.00

The p-value = Fisher's exact test, calculated between all three groups.
[1]Generalized linear mixed models (GLMM) calculated between before and after donation groups. p = 0.28, 0.28 and 0.18, respectively.

There were no stillbirths or deaths within the first month after birth in the six preeclamptic pregnancies after donation. Only one woman was primipara. For the five other births, the intervals to the previous pregnancy were 4 years to 10 years. None of the women with pregnancies after donation had recurrent preeclampsia. The median (range) age of the mothers was 33.5 (28–37) years, the median (range) gestational age at delivery was 37 (36–39) months and the median (range) birth weight was 3065 (2750–3480) g.

Before kidney donation, 8 of 16 women with preeclampsia were primipara. For the other eight pregnancies the intervals to previous pregnancies were 1 year in three cases and 2, 3, 5, 8 and 18 years in five cases. Among preeclamptic births in the control group, 60% were primipara. Eclampsia was not reported during pregnancy in any of the kidney donors.

Preterm birth and low birth weight

The occurrence of preterm birth and low birth weight was not different between the groups (Table 2). There was no difference between the groups in preterm birth before 22 or 37 weeks (Table 2). Nor was there any difference between groups in the incidence of birth weight below 500 g, 500–2500 g and above 2500 g (Table 2). Also comparison of pregnancies before and after donation in GLMM analysis showed no differences.

Infant survival

There were no differences in stillbirths (p = 0.17) (Table 2). Also when comparing pregnancies before and after donation adjusted for participation with more than one pregnancy, no difference was found (p = 0.18). Adjustment for birth order and maternal age at delivery did not affect the result.

In 106 pregnancies after kidney donation, there were three (2.8%) fetal deaths. There was one late spontaneous abortion (week 19). One fetus suffered intrauterine growth restriction and died at gestational week 32 with a birth weight of 450 g. One term child died intrapartum after abruptio placentae. In 620 pregnancies before kidney donation 7 (1.1%) were late abortions or stillbirths. Of these three were late abortions and three were stillbirths with gestational age 30, 32 and 32 weeks, respectively. One term newborn with a weight of 3650 g died during labor due to umbilical cord strangulation. In the control group there were 1.1% stillbirths.

Table 3: Preeclampsia in births randomly selected from the Medial Birth Registry of Norway and births in kidney donors, Norway 1967–2002

	Birth Registry ≈ 1% of births	Donors		p^1	p^2
		Pregnancy before	Pregnancy after		
	N = 21 511	N = 620	N = 106		
Preeclampsia N (%)	666 (3.1)	16 (2.6)	6 (5.7)	0.22	0.026

[1]The p-value = Fisher's Exact Test, calculated between all three groups.
[2]Generalized linear mixed models (GLMM) calculated between before and after donation groups. The method adjusts for some mother's contributing with more than one birth causing dependence within the data. Adjusted for mother's age, birth order and year of birth: p = 0.037, 0.017 and 0.047, respectively.

In the births after donation, no deaths occurred during the first 28 days of life against 3 (0.5%) in the before donation births and 0.6% in the control group (Table 2).

Discussion

The study showed no differences in stillbirths and neonatal mortality between the groups of births after kidney donation, before kidney donation and the control group. The rates of preterm delivery and low birth weight were also similar in the three groups. Similarly, there was no increase in gestational hypertension or preeclampsia in pregnancies after kidney donation in the primary, unadjusted analysis. In the secondary analysis, there was a small, but statistically significant increase in the risk of preeclampsia after kidney donation.

Kidney donation results in hyperfiltration of the remaining kidney and reduction of overall renal function. Preeclampsia is associated with hypertension and microvascular kidney damage. Thus an increased risk of gestational hypertension and preeclampsia might be expected in previous kidney donors. On the other hand, long-term follow-up after renal donation has not shown serious adverse effects on blood pressure and renal function (5,7–9). These reports did not address the issue of pregnancies after kidney donation. Such reports are scarce, but the data available have not indicated an increased risk of adverse pregnancy outcome after unilateral nephrectomy (14–16,21).

Living kidney donors are strictly selected. An important question is whether the rate of adverse pregnancy outcomes is lower in this population than in unselected controls. In this study the control group was randomly selected from the Medical Birth Registry and represents an unselected population. Therefore, we also used pregnancies before kidney donation for comparison along with the randomly selected controls.

A strength of our study is that all births with gestational age of 16 weeks or more are reported to the Medical Birth Registry as enforced by law and all living kidney donors in Norway are listed in the Renal Registry. Thus, all births in kidney donors were captured to the extent they did not emigrate. The Norwegian population has a very low emigration rate.

The outcome variables are defined in the guidelines for the Medical Birth Registry of Norway. Inaccuracy in registration is a potential source of error and with a low number of events may become of importance. However, the report to the Medical Birth Registry has been routine at all births in Norway since 1967 and thus midwives are familiar with the definitions. Gestational hypertension and preeclampsia should resolve within 12 weeks of delivery, but The Medical Birth Registry does not include follow-up of the mother after delivery. However, the prevalence of preeclampsia as registered by the Medical Birth Registry is similar to the prevalence reported in clinical studies (22). Furthermore, any misclassification applies for all groups and would not affect the results.

Confounding might hamper the interpretation of our results. Low birth order and high maternal age are risk factors for preeclampsia (23,24). During the observation period, data from the Medical Birth Registry have shown a substantial reduction in perinatal mortality in Norway reflecting a general improvement in health standards (25). The unit of analysis was the pregnancy, not the mother. Therefore some women entered the analysis with more than one pregnancy, causing dependency. To adjust for the risk factors birth order, maternal age and year of birth and also dependency, generalized linear mixed model was the statistical method of choice. However, due to the low number of pregnancies and events in kidney donors this statistical analysis could only be performed for some of the outcomes. We observed that when adjusting the comparisons to account for mothers contributing with more than one pregnancy, outcomes related to the child were basically unaffected. The only maternal outcome for which we could perform the generalized linear mixed model analysis, preeclampsia, the outcome changed from clearly nonsignificant to statistically significant. However, the results must be interpreted with caution.

The rate of preeclampsia is 2–10%, depending on the population studied and definitions of preeclampsia (26). In Norwegian studies preeclampsia was found in 2.7% (22) and 2.5% (23) of the women. In our study the rate of preeclampsia in pregnancies after kidney donation was 5.7%, against 2.6% before and 3.1% in the control group, all within the range reported by others. The risk of preeclampsia has been shown to be increased in low birth order pregnancies (23,24), but the reverse was seen in this study. Out of six pregnancies after donation with preeclampsia, only one was a first-order pregnancy. However, the time interval between the pregnancies has to be considered. It has been shown that the risk of preeclampsia in a second or third pregnancy increases with time since the previous pregnancy (27) and in these cases the intervals were 4 years to 10 years.

Management of preeclampsia often culminates in delivery of a preterm infant. Analysis of data from the Medical Birth Registry of Norway (28) have shown that fetal survival in preeclamptic pregnancies has vastly improved over the last 35 years and the odds ratio for stillbirth for preeclamptic compared to nonpreeclamptic pregnancies is 1.3. The odds ratio for neonatal death is 2.0 and has shown little change. The six preeclamptic pregnancies in kidney donors in our study resulted in live births and no neonatal deaths.

Follow-up data for the mothers as regards renal function or mortality was not available from the Medical Birth Registry. A recent study showed that women who have

preeclampsia and give birth to offspring with low birth weight and short gestation have a substantially increased risk for having a later kidney biopsy (29). Studies have also shown an increased risk of cardiovascular morbidity and mortality among women with preeclampsia, low birth weight offspring and short gestation (30,31). Further studies on mother's health in kidney donors are necessary

There were no differences in outcome variables in the primary analysis. Our finding of more frequent preeclampsia in pregnancies after kidney donation in the secondary analysis must be interpreted with caution. The number of pregnancies at risk and the number of events was low. Most importantly, the outcome of the pregnancies was good for mother and child. In conclusion, this study support the clinical experience that pregnancy after kidney donation is safe and that women of fertile age should not be discouraged to become kidney donors. However, the pregnancies in kidney donors merit careful monitoring. Potential donors should be informed that there may be an increased risk of preeclampsia with reference to the possible effect on the infant. Any effect of preeclampsia on the donor's renal function and future health was not addressed in this study.

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