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Exposure to Mycophenolate and Fatherhood

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Stein Bergan collected the MPA exposer trough values and approved of the final manuscript.

Anna V. Reisæter critically evaluated and approved of the final manuscript.

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All authors declare no conflict of interest.

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Abstract:

Background: Mycophenolic acid (MPA) is the active immunosuppressive substance in both mycophenolate mofetil and mycophenolate sodium and it is widely used after organ transplantation. In females taking MPA is teratogenic and may also influence spermatogenesis. There is a lack of knowledge regarding outcome of pregnancies fathered by males exposed to MPA.

Methods: We compared outcomes in pregnancies fathered by renal transplant males per whether they had been exposed to MPA or not at time of conception. A nation-wide population-based retrospective cohort study was performed. Data from the Norwegian Renal Registry with all renal transplanted men alive between Jan. 1st 1995 and Dec. 31st 2015 were included and relevant outcome data were extracted from the Medical Birth Registry of Norway.

Results: During the given time, 230 immunosuppressed renal transplanted males fathered 350 children (155 on MPA/195 not on MPA). There were no significant increased risk of malformation (3.9% vs 2.6%, P=0.49) in MPA exposed vs unexposed cohorts of children. The average dose (±SD) of mycophenolate was 1.42 ± 0.3 g/day and the individual median MPA trough concentration in the time period of anticipated conception and pregnancy was 2.8 ± 1.6 mg/L. Birth weight was similar in exposed and unexposed cohorts of children; 3381±681 grams vs. 3429 ±714 grams (P=0.53).

Conclusions: Paternal exposure to MPA did not increase the risk of adverse birth outcomes in children fathered by male kidney transplanted patients. These results are reassuring and support the continuation of paternal MPA treatment before, during and after conception.

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Introduction

End stage renal disease (ESRD) patients commonly experience sexual disturbance and reduced fertility. Successful renal transplantation can restore these functions in both male and female patients (1, 2). Women are, in general, recommended to refrain from taking any medication during pregnancy. Transplant recipients, regardless of sex, must however take lifelong immunosuppressive medication to preserve their transplant function. It has therefore been a focus on pregnancy safety and outcome for immunosuppressed women (3-5). Mycophenolic acid (MPA) is the active immunsuppressive substance in both mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) and it reduces the incidence of acute rejection and benefits graft survival (6). From previous studies it is well known that exposure to MPA in early pregnancy of female transplant recipients has been associated with increased rate of miscarriages and birth defects in the live born (7, 8). Accordingly, common practice in female patients who wish to become pregnant is either to withdraw MPA or switch to azathioprine prior to conception. Recently, the manufacturers of MMF (CellCept; Roche, Basel) and MPS (Myfortic; Novartis, Basel) and the European Medicines Agency (EMA) recommended additional measurements to prevent MPA exposure in pregnancy(9). The warning states ; "sexually active men taking mycophenolate are recommended to use condom for sex during treatment and for 90 days thereafter; partners of childbearing potential are also recommended to use highly effective contraception for the same period" (9). There is very limited published data on the effect of MPA on human sperm and the possible effects of children whose fathers used MPA at time of conception. Actually the authors could only find 1 publication and the results published did not support the EMA recommendations (10). There is an increased risk of acute rejection and graft loss associated with withdrawal of MPA. The transplant community was therefore puzzled by the EMA warning (11, 12). Was this EMA recommendation solely due to precautionary measures? Obviously there was and is a need for

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more data. We therefore decided to perform a population-based nationwide retrospective study comparing outcomes in pregnancies fathered by renal transplant males either exposed to MPA or not at time of conception and/or pregnancy.

Materials and Methods

A national population-based study was designed with focus on the time-period from 1995-2015. Transplanted males alive between January 1st 1995 and December 31st 2015 were identified in the Norwegian Renal Registry (NRR). Data from the Medical Birth Registry of Norway (MBRN) was collected for the same time period. The registry was established in 1967 and was the 1st national medical birth registry in the world. It is based on compulsory notification of all live births and stillbirths from gestational week 16 initially (1967-2001) and since 2002 from week 12. To ensure medical notification of every newborn in Norway all records in the MBRN are matched with files of the Central Person Registry (13). Linkage between the Data from the NRR and MBRN were merged utilizing the unique 11-digit personal identification number given to every Norwegian citizen at birth.

Data on MPA exposure was extracted from NRR. Patients with registered use of MPA-drugs the year of birth or the year before were defined as "MPA-exposed". Trough concentrations of MPA for the same time period were searched for and obtained (when measured) from the hospital laboratory system for all patients in the MPA-exposed group. If no trough MPA-concentration was measured all patient charts were manually cross-checked for accuracy in reported MPA-usage to NRR in all patients defined as MPA-exposed above.

Data extracted from the MBRN included demographics on mother and father, previous births and spontaneous abortions of the mother, health status of the mother before and during pregnancy, pregnancy and birth outcomes including: birth complications, pregnancy duration, birth weight, stillbirths, perinatal death, APGAR score and malformations.

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Immunosuppressive protocols used by the patients included in the study have varied depending primarily on time period of engraftment. All recipients have received steroids and a calcineurin inhibitor (CNI) at time of engraftment. From 1995 to 2008 more or less all recipients received cyclosporine A. From January 1st 2009 recipients < 50 years received tacrolimus and from January 1st 2012 all recipients have received tacrolimus. Azathioprine was used from 1995 to December 31st 2000. After that all recipients have received MPA. Induction with basiliximab was started in 2000. Some patients have been included in clinical trials with either switch to mTOR (everolimus/sirolimus), use of JAK 3-inhibitor or belatacept. Data from these patients were not included in the final evaluation.

Statistical analyses: Differences between the MPA exposed and MPA not exposed groups were statistically compared with logistic and linear regression methods adjusting for repeated fatherhood both within and between groups by clustered sandwich estimator for adjusting the standard errors. R was used for data management and statistical analyses (14, 15).

Results

A total of 6032 renal transplant recipients were alive during this time, 3974 males/2058 females and a total of 4000 had been exposed to MPA (2681 M/1319 F). During the time period a total of 230 immunosuppressed renal transplanted males fathered 350 children. 136 males fathered 1 child, 73 males fathered 2 children and 21 fathered 3 or more children. At the estimated time of conception there were 112 different male transplant recipients that fathered 155 children under MPA exposure and 133 male recipients that fathered 195 children without MPA exposure. Fifteen males fathered children both as exposed and unexposed to MPA. In the early phase of MPA use trough measurements on stable maintenance patients were not always performed. We were, however, able to trace valid MPA

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trough concentration measurements for the actual time period for 117 of the 155 MPA exposed patients. The average dose (±SD) of mycophenolate was 1.42 ± 0.3 grams/day and individual median MPA trough concentration in the time period of anticipated conception and pregnancy was 2.8 ±1.6 mg/L. For the remaining 38 patients we found verification in hospital journals of MPA use at time of conception. There was no clinical differences between the age of the fathers on MPA vs not on MPA (36.1 ±5.6 vs 35.7 ±6.0 years, p= 0.59) or age of mothers to these children (31.9 ±4.7 vs 31.0 ±4.8 years, p= 0.12). Mean gestational age was also not different between the groups, 38.8 ±2.5 and 39.1 ±2.7 weeks, respectively (p= 0.30). When comparing other available data from the MBRN we could not detect any overall differences between outcomes in the 2 groups (Table 1).

There was no difference in malformations in children fathered by MPA exposed vs. nonexposed recipients. There were no significant differences with regards to mother's health before or during respective pregnancy or medication used during pregnancy (data not shown). Preeclampsia occurred in 7 (4.5%) and 14 (7.3%) births fathered by exposed and nonexposed to MPA, respectively.

Discussion

The results indicate no difference in congenital malformation or other unwanted outcomes when comparing pregnancies whether the father was exposed to or not exposed to MPA. This supports the previous findings published by Jones et al, and questions the validity of the EMA recommendations.

Following a successful organ transplantation recipients are faced with the need of lifelong immunosuppressive medication to preserve their transplant function. Kidney transplantation by far outnumbers other organs. Since approximately 40-50% of men receiving a kidney transplant are younger than 50 years of age the fertility and possibility of

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fatherhood of male renal transplant recipients is a concern. There have, however, been very few reports that have investigated the potential effect of immunosuppressants on the male fertility and on the offspring (10, 16). Currently the most common worldwide posttransplant immunosuppressive combination consists of glucocorticoids, tacrolimus and MPA. Additional concomitant medications are often needed. Many drugs may affect the spermatogenesis. This makes it impossible to pinpoint 1 specific drug used by the father at time of conception as "the sinner" causing possible adverse birth outcomes. There have been some animal studies and some very few human studies addressing a possible difference in the calcineurin inhibitors cyclosporine A and tacrolimus on the spermatozoa (2, 16, 17). Results are conflicting. Recently Nørgård et al, published a large study focusing on birth outcome in children fathered by men treated with azathioprine due to inflammatory bowel disease (18) ie, not using other immunosupprsive drugs. They found no increased risk of adverse birth outcomes. There is no such study addressing mono therapy with MPA. For ethical reasons randomized trials cannot be designed to evaluate the safety of drugs like MPA during conception. Therefore we have to base clinical decisions on evidence from observational registry studies.

In this evaluation we have not compared outcome of children conceived from immunosuppressed fathers with the outcome of the general population. This comparison was however recently performed by Morken et al, (19) but from a different time-interval and also including data from other organ transplant recipients. In their analysis, they compared data from 4614 pregnancies before and 474 after transplantation to the outcome in the general population and found an increased risk of preeclampsia. The risk of preeclampsia was increased (AOR: 7.4, 95% CI:1.1-51.4) after transplantation. They write that a "causal link between a specific immunosuppressive drug and preeclampsia is thus difficult to establish". Importantly no increased risk was found for congenital malformations or other outcomes

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when compared with pregnancies before transplantation or with the general population (2 511 506 births) i.e. findings not supporting the EMA recommendations. Number of fathers exposed to MPA was not specified.

A strength of the current study is its design being a nationwide population-based cohort study. Oslo University Hospital is the only transplant center in Norway serving approximately 5 million inhabitants and has kept complete life-long records of all transplanted individuals since 1969, including immunosuppressive drugs used. We do not have direct data on drug adherence but since MPA trough only is analyzed at the Oslo University Hospital laboratory we could verify a valid trough value around time of conception for the majority of the male recipients. Additionally, we could evaluate mother's health before or during respective pregnancy – finding no difference. A drawback is obviously the retrospective design of the study. Is is well known that most miscarriages occur during the 1st trimester and a caveat of our retrospective registration is that there may have been more miscarriages during the 1st trimester if the father was on immunosuprerssion. We are, however, not aware of any National registry capturing miscarriages this early.

In conclusion, the results indicate no difference in obstetrical and/or neonatal complications when the father is a transplanted male on MPA as compared to a transplanted male not on MPA. Obviously even more data is needed but in the mean time we once again urge the EMA to reconsider their current recommendations regarding MPA.

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Table 1. Birth outcomes between exposed (MPA+) and not exposed (MPA-) groups.

	MPA+ N=155	MPA- N=195	p value
Acute caesarean section	16 (10.3%)	24 (12.3%)	0.39
Normal placenta	121 (78.1%)	118 (60.5%)	0.32
Child weight (g)	3381 ±681	3429 ±714	0.53
Gestational age (weeks)	38.9 ±2.5	39.1 ±2.7	0.30
Child length (cm)	49.6 ±3.2	49.9 ±3.0	0.32
Child head circumference (cm)	34.7 ±2.1	35.1 ±2.1	0.12
APGAR score after 1 minute	8.6 ±1.5	8.6 ±1.5	0.97
APGAR score after 5 minutes	9.3 ±1.3	9.3 ±1.4	0.41
Stillborn	1 (0.6%)	4 (2.1%)	0.12
Born alive, dead within 24 hours	0 (0.0%)	1 (0.5%)	0.32
Congenital malformations	6 (3.9%)	5 (2.6%)	0.49
Respiratory distress syndrome	4 (2.6%)	2 (1.0%)	0.40
Neural tube defects	0 (0.0%)	0 (0.0%)	1.00
Icterus	11 (7.1%)	12 (6.2%)	0.33
Hip dysplasia	1 (0.6%)	1 (0.5%)	1.00

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