Contraception in Kidney Transplantation: Advice on use of Mycophenololate

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University Hospital Birmingham, UK

Wmids Transplant Forum  5th July 2016
Contraception

• Do we routinely provide contraceptive advice to renal transplant recipients in fertile age range?

• Do we advise males transplant recipients treated with mycophenolate mofetil or mycophenolate sodium of MHRA advice?
SUCCESSFUL PREGNANCIES AFTER HUMAN RENAL TRANSPLANTATION*

Joseph E. Murray, M.D.,† Duncan E. Reid, M.D.,‡ J. Hartwell Harrison, M.D.,§ and
John P. Merrill, M.D.¶

BOSTON

THE NEW ENGLAND JOURNAL OF MEDICINE
Introduction

• Conception rare in women with ESRF
• Renal Tx restores fertility rapidly!
• 2-8 % women conceive
• Outcome Successful (usually) but complex
• Pre-conception & contraceptive counselling key
• In series only 1 in2 women are getting post transplant advice and up to half pregnancies unplanned
Graft Survival – Matched Analysis

567 UK transplant Pregnancies

P=0.032

Sarween, Knox, Day Lipkin 2016
# Maternal Complications in Transplants

567 UK transplant Pregnancies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Transplant Cohort (%)</th>
<th>General Population (%)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>IUGR**</td>
<td>9.2</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>15.0</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe UTI***</td>
<td>10.2</td>
<td>1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Puerperal Infection</td>
<td>5.1</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-eclampsia 1(^{st}) pregnancy</td>
<td>26.7</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVT or PE</td>
<td>0</td>
<td>0.07</td>
<td>-</td>
</tr>
</tbody>
</table>

*In those reaching 3\(^{rd}\) trimester (all pregnancies) **IUGR intrauterine growth restriction ***Required hospital admission

Sarween, Knox, Day Lipkin 2016
Pregnancy Rate

Mycophenolate

Gill. AJ Transplant 2009; 9:1541
Mycophenolate Fetopathy

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spont. Abortion</td>
<td>40</td>
</tr>
<tr>
<td>Live Birth</td>
<td>45</td>
</tr>
<tr>
<td>Congenital Anomalies</td>
<td>27</td>
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</tbody>
</table>

- Problems greater than expected
  - Microtia
  - Cleft lip/palate
  - EFMO

- Background congenital abnormality rate 2-3%
- Effective contraception for at least 6 weeks after stopping mycophenolate
- Ideally 3-6 months post conversion to ensure stability

Sifontis et al. Transplantation 2006:82;1698
Pregnancy Post Renal Transplant
Men

Post Transplant
• Recovery of ED
• Improved semen quality
• Offspring normal with CsA, tacrolimus

Safety of male transplant recipients taking MMF to conceive? MHRA advice

Sirolimus

**Renal Transplantation restores male fertility**
**Normal pregnancy outcomes**

Mycophenolate in Men

- SmPC for mycophenolate derivatives changed (FDA)

- Recent updates to the Summary of Product Characteristics (SmPC) for proprietary brands of mycophenolate derivatives (CellCept®, Roche and Myfortic®, Novartis) include new advice that sexually active men exposed to these agents should use condoms during treatment and for 90 days or 13 weeks (respectively) after discontinuation.

- Furthermore: ‘Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose’.

http://www.medicines.org.uk/emc/medicine/1680
http://www.medicines.org.uk/emc/medicine/14917
Mechanisms

In principle, paternal exposure to teratogenic agents may adversely affect pregnancy in two ways:

• genetic mutation in spermatozoa, or

• transmission of teratogenic agents in seminal fluid leading to local exposure of the ovum and systemic maternal exposure from maternal absorption.
But is there evidence of a problem?

• Defined risk of stopping/converting from MMF to alternative (2% in females)-previous rejection
• Background risk of congenital abnormalities 2-3%
• Registry series of male transplant recipients fathering children taking MMF-no increased risk
  • 3.1% vs 3%
  • 2.1% vs 1.9%
• Female exposure to seminal fluid of males taking MMF is very low (plasma level 1:1000)
• Miscarriage?

We recommend that potential fathers taking mycophenolate derivatives are informed of the *theoretical risks* of mycophenolate derivative exposure to a fetus and be made aware of contraceptive advice given by MHRA and contained in the SmPC. We advise that these theoretical risks should be balanced against the risks of conversion to alternative immunosuppressive regimes on their kidney transplant status in an individualised discussion.
Contraception in Renal Transplantation

Advise at discharge

Safe, tolerated, effective, minimal interactions

Focus on Long acting reversible contraception (LARC)

Personal preferences

Wide range of contraceptive options

Emergency Contraception
It’s safe?

- Emergency Contraception
  - Levonorgestrol 72h post unprotected intercourse (5 days)
    - Failure rate 2-3%

- Copper IUCD (ongoing contraception)
  - Failure rate 0.2%

- Much safer than an unplanned pregnancy

Krajewski-Transplantation, 2013;95(10):1183-6
Condoms (male/female)

- Safe, no interactions
- STD
- Spermicidal lubricant
- Failure rate: Peal index (pregnancies per 100 patient years) 20-25

Krajewski-Transplantation, 2013;95(10):1183-6
Depot Progestogens

• Variable interaction with tacrolimus ciclosporin: levels, irregular bleeding

• Depot Provera (DMPA)
  – Depot Provera: 3 monthly, bone density
  – Lasts 3 years
  – Failure rate: Pearl index 5

• Etonorgestrol implant
  – Lasts 3 years
  – Pearl score <1

Krajewski-Transplantation, 2013;95(10):1183-6
Progestogen only Pill

- Desogestrol: Cerezette or Cerelle
- 12 hour window to take
- Well tolerated
- Irregular bleeding in some
- CNI levels
- Failure rate 1

Krajewski-Transplantation, 2013;95(10):1183-6
Contraception

Incorporate contraceptive advice into all clinics
Signpost women-patient information

- Emergency contraception is safe in transplant recipients
- Desogestrol preferred POP (Cerezette, Cerelle)
- LNG-IUS (Mirena*) is safe & very effective
- Combined OCP 3rd line but suitable for some
- Be sensible about MHRA advice on MMF in men
- In women MMF Conversion at least 3-6 months pre-conception after pre-conception counselling

Baby joy for triple transplant patient

Brave Mary gives birth to baby she thought she’d never have after kidney transplant

Christmas will be double the fun this year for former transplant patient Mary Hibbs after giving birth to the baby she never thought she would have.

Five years ago this month (Dec), Mary was in theatre undergoing a third kidney transplant, thanks to her sister Donna who agreed to be a live donor.

Mary waited three years for her first kidney transplant after she was diagnosed with kidney failure when she was just eight years old.

However, in 1995, the 33-year-old went into renal failure once again and this time was given a kidney from her mum Elina, becoming the first person in the West Midlands to receive a live kidney transplant.

Mary was told her chances of survival were slim and she was warned that it could be a one-way ticket to dialysis.

But this year, on August 4th, Mary finally got the joy she never thought she would have.

Against all odds, Mary Hibbs gave birth to baby Levi on August 4th this year after a triple kidney transplant.

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