Contraception in renal transplant recipient

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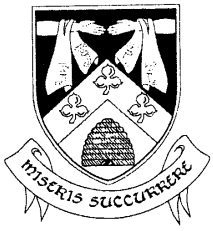

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<30th Nov 2010 ..... Page No 1....Number of Policy 29>

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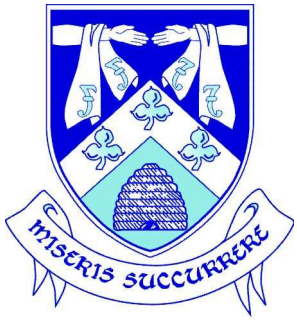

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CONTENTS

SECTION 1

INTRODUCTION:

Most patients with advanced renal failure have impaired reproductive function, mainly related to dysfunction in the hypothalamic-pituitary-gonadal axis. Sexuality and fertility are usually restored in these women 1 to 12 months after renal transplantation.

Reports show that pregnancy is common after renal transplantation and occurs in 5-12% of women who undergone kidney transplantation and are of childbearing age.

50% of these pregnancies are intended. Rate of congenital malformations reported as the same to general population which is 3%.
First reported successful pregnancy was 1958.Since then thousands of pregnancies has been reported with 60-80% success rate. Despite that the rate of complications indicates that such pregnancies is considered high risk therefore should monitored closely by medical team consists of transplant nephrologist, obstetrician, transplant surgeon, urologist and paediatrician.

SECTION 2

Important points to consider in renal transplant recipients:

Preconception counselling

- Fertility issues with patient and partner, preferably prior transplantation
- Vaccinated for HBV, strep pneumonia, tetanus and influenza pre transplantation
- Rubella vaccine pre transplantation due to live vaccine contraindicated post transplantation
- Discuss risk to patient and foetus to partner
- Prematurity and long term disability
- Patient and partner should be made aware about the stress of having children, especially if the mothers health deteriorates and if the children isn't healthy or both
- Fertility might be restored 1-6 months post transplantation therefore contraception should be initiated after surgery to prevent unintended conception
- Nutritional counselling is recommended to optimise nutrition for the mother and infant, with additional consideration to the recipient graft

Factors associated with favourable pregnancy outcome

- Good general health for about 2 years after transplantation
- No graft rejection in the last year
- Adequate and stable graft function
- No acute infection that might affect the foetus
- Maintenance immunosupression at the stable dose
- Patients compliance with treatment and follow up
- Normal blood pressure or blood pressure well controlled on one medication
- Normal allograft us

Co morbid condition associated with worse pregnancy outcome

- Etiology of the ESRF that necessitated transplantation
- Chronic allograft dysfunction
- Renal insufficiency
- Cardiopulmonary distress
- HTN
- Diabetes mellitus
- Obesity
- Maternal infection with HBV,HCV or CMV

Risk to the infant of a female Transplant recipient

- 12% risk of spontaneous abortion
- Premature up to 50% associated with increased risk of neonatal death, cerebral palsy, deafness, learning disability and low IQ
- IUGR up to 20%
- Infants born at low birth weight
- Immunosuppressant is noticed in this infants which should normalized by 6 months of life
- Increased risk of congenital infection
- Increased risk for autoimmune disease

SECTION 3

Most Effective Contraceptive Methods in Organ Transplant Recipients

Intrauterine Contraceptive Devices

-The most effective form of reversible birth control.

- The copper containing ParaGard® (Cu IUD, Duramed) and the levonorgestrel-releasing Mirena® (LNG IUD, Bayer). Both devices have similar levels of effectiveness and safety. The Cu IUD has an effective duration of 10 years, whereas the LNG IUD lasts for 5 years.

-Concerns:

- Effectiveness will be decreased in organ transplant recipients due to their chronic immune suppression. This theoretical risk is based on the assumption that an IUD's mechanism of action is dependent on a local inflammatory response in the uterus. Although IUD failure was reported in two renal transplant patients by Zerner in 1981, there have been no further reports of IUD failure in women with transplants in the contemporary literature. Evidence surrounding the mechanism of action of IUDs suggests that

macrophages play the most important role in destruction of ova and sperm. The immunosuppressive agents employed in transplant patients have minimal effects on the activation and function of macrophages. The calcineurin inhibitors, antimetabolites, rapamycin, daclizumab, and basiliximab all act by preventing the activation of T-cells. Rabbit antithymocyte myoglobulin works by destroying the host's T-cells, and muromonab-CD3 (OKT-3) works by directly inactivating CD-3-positive T-cells, whereas corticosteroids modulate immune response by decreasing the production of inflammatory mediators and decreasing intracellular transcription factors which up regulate the activity of immune cells. Interestingly, corticosteroids may actually increase the activity of macrophages by activating macrophage migration inhibiting factor (MIF), a pro-inflammatory substance which *increases* the activity of macrophages.

- Given these facts, there is no biological basis to assume that the effectiveness of an IUD would be decreased while an intrauterine device is in place. Moreover, no clinical evidence to date has demonstrated an excess of contraceptive failures among transplant patients using an IUD compared with normal women. Prospective data are needed to confirm the IUD's effectiveness in this population, but transplant patients should not be discouraged from using IUD for theoretical risks alone.

- Risk of infection due to immunosuppressive therapy. There is no literature demonstrating the risk of pelvic or cervical infection in women with transplants and IUDs. Morrison reported a prospective cohort study of 156 HIV-positive women and 493 HIV-negative women in Kenya who received a Cu IUD at a single clinic. Over an average of 24 months of follow-up (range 14-34 months), 16/150 (10.7%) HIV-positive women and 43/486 (8.8%) of the HIV-negative women experienced an infectious complication. Using a Cox regression model, there was no increase in infectious complications among the HIV-infected women (Hazard Ratio; 95% CI: 1.2; 0.6, 2.3). The proportion of women experiencing infectious complications was the same regardless of the severity of their disease as determined by CD-4 count (test for trend, P = 0.85). The incidence of pelvic inflammatory disease (PID) was very low for both groups: 3 cases in the HIV-positive women, 2 cases in the HIV-negative women. All cases of PID were managed in an outpatient fashion.

- Drug interactions are of no concern in the case of the Cu IUD. In the case of the LNG IUD, concerns are minimal. Systemic levels of levonorgestrel are minimal (357.3 pg/mL at 6 months), and interactions with common anti rejection drugs are unlikely. With regard to cervical and uterine infections, universal screening for gonorrhoea and chlamydia infection before IUD insertion is not required by the WHO. However, in immunosuppressed transplant recipients, there may be a benefit to screening and treating positive patients before the insertion of the IUD. If a patient screens positive for either infection, she and her partner(s) should be treated immediately and an alternative plan for contraception made. In 3 months, repeat testing to rule out re-infection should be performed. If this culture is negative AFTER treatment is negative, the patient may have an IUD placed.

In summary, there is no evidence to suggest that the efficacy or safety of the Cu IUD or LNG IUD would be compromised in the transplant patient. Given the special needs of a transplant patient, the IUD is truly the perfect option for several reasons:

1. It is long lasting.
2. It has a very low failure rate.
3. It is reversible, and the patient may get pregnant quickly on removal.
4. Interactions with other medications are nonexistent or unlikely.

Etonorgestrel Implant

- It is a single silastic rod which is implanted in the subcutaneous tissue of the upper arm. The system contains 68 mg of etonorgestrel and is associated with a typical use effectiveness greater than 99% and protection lasting for 3 years.
- Implanon shares a similar risk–benefit profile to DMPA, but has not been shown to cause the same decreases in bone mineral density. Its other contraindications and compatibility profile, however, are identical.
- Advantages;

1. A single-visit administration
2. Bleeding

There are no data regarding the use of Implanon among organ transplant recipients, but given its similarity to other drugs with long safety records, its use among organ transplant patients is likely safe.

Depot Medroxyprogesterone Acetate

-Depot medroxyprogesterone acetate (DMPA, DepoProvera®) is a synthetic progestin, formulated to be slowly released over a 12-week period of time.

-DMPA is a highly effective contraceptive with 1-year typical use failure rates of 2%. Most failures occur to delays in repeat injections.

-DMPA has no known drug interactions with common agents used in the immunosuppressive regimens of transplant patients. The drug is metabolized by the liver and should be avoided in the face of active liver disease, but its metabolism is not affected by concomitant administration of any drug. In patients with resolved liver disease (including viral hepatitis carriers, resolved schistosomiasis, cholestasis, and compensated cirrhosis), DMPA is considered to be safe. Following liver transplant, DMPA is not contraindicated in the setting of normal graft function.

- Adverse effects:

1. Delayed return to fertility up to 1 year or longer
2. Decreased bone mineral density. BMD back to baseline once stopped
3. Are irregular bleeding and amenorrhea with approximately 25% of women receiving DMPA reporting amenorrhea at 1 year and 80% reporting amenorrhea at 5 years.

<u>Modestly Effective Contraceptive Methods in Organ Transplant Recipients</u>

Combined Hormonal Contraceptives

Contraceptives containing oestrogen and progestin come in various formulations, including oral and transdermal delivery systems. Because of the risks associated with the oestrogen component of these formulations, combined hormonal contraceptives are contraindicated in the following patients:

1. Personal history of myocardial infarction, stroke, or deep vein thrombosis.
2. Smokers over the age of 35.
3. Migraine with focal aura.

4. Uncontrolled hypertension.
5. Active liver disease or hepatic adenoma.

- Metabolized primarily by the cytochrome P4503A4 system in the liver and thus careful attention must be paid to avoid drug interactions. Because the majority of anti rejection agents used in transplant patients are metabolized and excreted by the kidneys, interaction with COCs is unlikely. Some immunosuppressants, such as glucocorticoids, tacrolimus, sirolimus, and azathioprine, however, are metabolized by the liver and may interact the metabolism and effectiveness of COCs.
COCs are metabolized by the cytochrome P450 3A4 system in the liver. Although glucocorticoids are known to induce this enzyme, there is no clinical evidence that glucocorticoids impair the effectiveness of oral contraceptives. (Seidegard et all demonstrate that concentration and contraceptive efficacy are unchanged in the presence of glucocorticoids)
-Pietrzak published a series of 26 women who had kidney transplants who used COCs for at least 18 months and reported no pregnancies in this cohort. Although 2 patients discontinued COCs (one for a deep vein thrombosis, the other for deterioration in liver function), the study authors found that COCs did not influence serum transaminases, bilirubin, glucose, or cholesterol levels.

-In summary, COCs have a unique effect on the liver and should be considered carefully if they are to be used in a patient following transplantation. Expert opinion recommends that patients achieve a period of 6 to 8 months of graft stability and that there be no other contraindications to COCs before initiation of COC contraception. Because the oestrogen component of COCs can have a cholestatic effect, patients should be monitored for signs of biliary stasis.

Transdermal Contraceptive Patch

-This novel delivery system delivers oestrogen and progesterone transdermally through a patch placed on the maternal abdomen.
-Advantages:

- Three applications per month (one patch per week for each of 3 weeks, as opposed to one active pill per day for each of 21 days in the case of COCs).

Research has demonstrated that circulating levels of oestrogen among users of the patch are substantially higher than users of COC but in the absence of other risk factors, however, there is no definitive evidence to exclude the transdermal patch as a contraceptive option for transplant recipients at this time.

The Vaginal Ring-not available in Ireland

NuvaRing® (Organon) is a silastic ring impregnated with etonorgestrel and ethinyl estradiol. It has the benefit of a once-a-month application, and may safely be used in either a 21- or 28-day cycle safely. As circulating levels of ethinyl estradiol are lower than those seen among COC users, and first-pass metabolism in the liver is avoided, the vaginal ring is an appealing option for patients on anti rejection medications. Whether or not this makes it a safer or more effective option compared with other combined hormonal contraceptives is not known.

Progestin-Only Pills

-Side effects

- significant incidence of amenorrhea among women taking POPs.
- failure rate in the first year is 5%.

-Advantages

- Avoidance of the estrogen-related risks associated with combined hormonal methods.

POPs differ from DMPA and Implanon in that they are orally administered and undergo first-pass metabolism by the liver, whereas DMPA and Implanon avoid first-pass metabolism in the liver. Accordingly, concomitant administration of corticosteroids and POPs may be of a greater concern than when glucocorticoids are given with another progesterone-only contraceptive method.

<u>Less Effective Contraceptive Methods in Organ Transplant Recipients</u>

Barrier methods of contraception offer convenience and ease of use while also avoiding potential drug interactions.

-All barrier methods are acceptable forms of birth control for women with transplants. Given their relatively high failure rate and difficulty in achieving compliance, all of these barrier methods are best when combined with another method of birth control

for added protection against pregnancy. All of these devices are a reasonable first-line method for patients who have intercourse infrequently, or those who do not have a partner now but may become sexually active in the future.

SECTION

CONSULTANT SUMMARY	
Date PPPG issued for consultation	June 2010,
Number of versions produced for consultation	2
Committees/meetings where PPPG was formally discussed	Dates: Renal policy meeting September 2010, November 2010

Where Received	Summary of Feedback	Actions/Response

SECTION 5

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