Hormonal contraception in female lung transplant recipients: a case series

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CASE SERIES

We present a case series of eight female lung transplant recipients who used combined hormonal contraception (CHC). Pregnancies after lung transplantation are rare[1] but can put the woman and the fetus at high risk. It has been reported that pre-eclampsia develops in approximately 25% of lung recipients, often leading to preterm delivery and low birth weight.[2] Little is known about the influence of pregnancy *per se* on the risk of transplant rejection, although the rejection rate seems similar to that in the non-pregnant population.[2] However, the National Transplantation Pregnancy Registry (NTPR) reported that 27% of woman in the lung transplant pregnancy cohort experienced a rejection episode, with 21% experiencing graft loss within 2 years after pregnancy. Thus, this group of women is considered high risk when compared with other solid organ recipients and are often advised against pregnancy.

Although it is recommended that women use a safe and reliable method of contraception, the safety of hormonal contraception in female lung transplant recipients might be problematic. Despite the fact that the effect of estrogens on the pulmonary vascular system remains poorly understood, higher estrogen levels in women may predispose them to having a more vulnerable pulmonary circulation, which could more easily foster the development of pulmonary arterial hypertension.[3] Hence, the aim of this study was to evaluate the safety of CHC in women after lung transplantation.

METHODS

From January 2009 to December 2012, eight women who were already using CHC following lung transplantation were referred to the Department of Gynecology and Obstetrics of the Medical University of Vienna, Austria for consultation about contraception and were included in this retrospective study. Table 1 shows details of the CHC. The women were asked about the duration of use, as well as about their general well-being, and possible complaints or side effects. All the women had undergone regular follow-up examinations. Surveillance bronchoscopies with transbronchial biopsy were performed at 2 weeks, and at 1, 2, 3, 6 and 12 months after transplantation. In addition, bronchoscopies with biopsy were performed as clinically indicated for suspected rejection, infection or other pulmonary problems. All diagnoses of acute rejection were confirmed with biopsy specimens, standard histological criteria and grading schemes. Pulmonary function tests were performed at regular intervals (every 2–3 months) and bronchiolitis obliterans syndrome was diagnosed according to the guidelines of the International Society for Heart and Lung Transplantation. Data on lung transplantation, graft function and concomitant medications, including immunosuppressive therapy, were retrieved by retrospective chart review. Data are presented as total numbers, as well as median and ranges.

RESULTS

The cases were a median of 34.0 (range 28–37) years of age when starting CHC, with a median body mass index of 19.8 (range 17.9–23.4) kg/m^2. None of the women had any comorbidities that required any long-term medication, apart from immunosuppressive therapy. They were all sexually active and did not use any additional contraceptive methods. Seven women had undergone bilateral lung transplantation for cystic fibrosis,

Table 1 Overview of first-line combined hormonal contraception

Hormonal contraception	Duration of use (months)	*n*
Transdermal: 0.75 mg EE+6.00 mg norelgestromin	27, 63, 70	3*
Intravaginal: 2.70 mg EE+11.70 mg etonogestrel	32	1
Monophasic oral: 0.03 mg EE+3.00 mg drospirenone	16	1
Monophasic oral: 0.02 mg EE+0.15 mg desogestrel	62	1
Biphasic oral: 0.04/0.30 mg EE+0.025/0.125 mg desogestrel	26	1
Triphasic oral: 0.03/0.04/0.03 mg EE+0.05/0.07/0.1 mg gestodene	47	1

*One patient switched from a transdermal to an intravaginal mode of delivery (see text for details).
EE, ethinylestradiol.

and one woman had undergone bilateral lung and heart transplantation for end-stage pulmonary hypertension due to transposition of the great vessels. When patients were seen at our Department they were using various combinations of at least three immunosuppressive agents (prednisolone, $n=7$; tacrolimus, $n=6$; mycophenolate mofetile, $n=4$; cyclosporine, $n=3$; everolimus, $n=3$; mycophenolate sodium, $n=2$). The median interval between transplantation and starting CHC was 12.5 (range 2–25) months. The median duration of CHC use was 39.5 (range 16–70) months. With regard to adverse effects, one woman with skin reactions to transdermal CHC, which she had used for 27 months, was switched to the vaginal ring, which she had used for 6 months before she was seen at our Department. Another patient using transdermal CHC reported a few episodes of mid-cycle spotting. One woman reported a slightly increased vaginal discharge while using the vaginal ring. None of the patients reported new side effects associated with immunosuppressive agents that occurred during CHC use. There were no cases of graft dysfunction or rejection during CHC use and none of the women became pregnant.

At the time of the referral appointment all the women were still using CHC. Since they had not experienced any major adverse events with their current contraception and did not want to change the regimen, they were all counselled to continue the method.

DISCUSSION

CHC was well tolerated in this case series of eight female lung transplant recipients. To the best of our knowledge, this is the first report on the safety of CHC use following lung transplantation. This issue has also been emphasised in a recent review on contraception in women with respiratory diseases.[4]

Although we did not identify any reported drug interactions between immunosuppressive drugs and progestogens, there are a number of potential drug interactions with estradiol. Estradiol may increase the levels of prednisolone by decreasing its breakdown, and prednisolone, tacrolimus and cyclosporin may influence the level of estrogens by affecting enzyme CYP450 3A4 metabolism. Further, estrogen levels may be increased by tacrolimus and cyclosporin by affecting P-glycoprotein (MDR1) efflux transporter. Mycophenolate decreases the effects of estradiol due to an unknown mechanism.[5] However, no increase in the rate of side effects associated with use of these medications was noted in our case series.

Ischemia-reperfusion injury is an extremely common complication after lung transplantation and is associated with both an increased risk of acute rejection and a high degree of morbidity and mortality in the early postoperative period. Although estradiol exerts antioxidant effects and reactive oxygen species are involved in the pathogenesis of ischaemia-reperfusion injury, a recent study in rats demonstrated that animals treated with estradiol had a poorer outcome than control animals. The authors hypothesised that this could have been the result of an increased relaxation of the lung vascular muscle, which would further counteract the increase in pulmonary vascular resistance by arteriolar and arterial contraction following reperfusion.[6] In our case series, none of the patients revealed graft dysfunction or rejection while using CHC. As stated in a recent review on the role of estrogen in pulmonary hypertension, the effects of estradiol on lung circulation are complex, often depend on the animal model in which they were tested, and cannot be reduced to their enhancing effect on the proliferation of smooth muscle cells *in vitro*.[3] Moreover, one has to distinguish between natural 17β-estradiol and ethinylestradiol, a derivative of 17β-estradiol. All patients in the present case series used CHC that included ethinylestradiol. Its effects on pulmonary circulation have not been evaluated in detail to the best of our knowledge.

In conclusion, despite the small sample size of this case series, our findings should encourage health care professions to consider CHC as a contraceptive option for female lung transplant recipients, at least in women without any comorbidities who have reached stable graft function. In our experience, use of CHC following lung transplantation is more common than anticipated. Larger multicentre studies should be performed in order to reliably evaluate the course of graft function in women using CHC.

Ethics approval The study was approved by the Medical University of Vienna ethics committee (IRB number 1099/2013).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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