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Depot Medroxyprogesterone in Renal Transplanted Women: A Case Series

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Abstract

Introduction: DMPA has been reported to induce weight gain and changes in blood cell count (hemoconcentration). Also, there is no clinical trial investigating its use in renal impairment patients. The present study evaluated whether these changes occur in women after renal transplantation when DMPA was used as a contraceptive. Materials and methods: A single center retrospective cohort study of renal transplanted patients who initiated use of DMPA as a single contraceptive method with a follow-up of 6 months. We analyzed all women enrolled between October 2014 to July 2016 with functional renal graft. Data collection included demographics features, clinical parameters and laboratory tests (weight gain, hemoglobin, haematocrit, creatinine) in first appointment and six-months later. The primary outcome was if DMPA use impacts evolution of these data, compared to condom users. Results: After evaluation of 135 transplanted patients, we included 30 users of DMPA and 20 users of condom. There were no differences in demographics features, except in age, higher in the condom group. Evolution of weight gain, hemoglobin, hematocrit and creatinine were similar in both groups during six months follow-up.

Conclusion: Medroxyprogesterone acetate use did not interfere in analysed parameters, when compared to condom users.

Keywords: Contraception, Kidney Transplantation, Solid Organ Transplant, Clinical Performance

Abbreviations: BMI: Body mass index; CDC: Centers for Disease Control and Prevention; Cr: creatinine; DMPA: Depot medroxyprogesterone acetate; Hb: haemoglobin; Ht: haematocrit

Key Message: Depot medroxyprogesterone use in renal transplanted patients did not interfere in weight gain, blood pressure, creatinine and blood cell count, compared to condom users.

Introduction

The renal transplant improves significantly the quality of life of women in end-stage renal disease. Frequent symptoms such as irregular bleeding patterns and infertility are solved in few weeks after transplant [1]. Ovulation can happen in just one month after surgery, increasing the risk of an unplanned pregnancy [2]. Pregnancy outcomes like preterm labor and fetal death, besides complications such as pre-eclampsia and graft-loss are some of gestational risks associated in these women [3, 4]. Also, adjustment on immunosuppressive regimen can be required, avoiding the use of teratogenic mycophenolate and rapamycin [5].

Therefore, effective contraception must be discussed, oriented and initiated soon after surgery [6]. Less effective methods such as withdrawal and condom are frequently used by transplanted women [7]. Progestin-only methods are a reasonable choice and frequently recommended, however, specific studies assessing risks and side effects for them are limited to levonogestrel-releasing intrauterine devices [8, 9, 10].

The injectable contraceptive is a high efficacy, cheap and easy to use method, widely available in Brazil and most countries. It shows no drug interaction with main immunosuppressive, classified as a category 2 contraceptive for transplanted women by CDC [11]. Although current data shows depot medroxyprogesterone acetate (DMPA) as a safe option, no study evaluated possible adverse health effects in these women [8, 12-14]. Major concerns about DMPA use include irregular bleeding and weight gain [15, 16]. Also, some studies showed immunosuppressive effects linked to medroxyprogesterone use, that might interfere with acute rejection and graft survival [17]. Facing potential outcomes, we evaluated DMPA use in renal graft carriers, in comparison to condom users.

Materials and Methods

We designed an observational study, historical cohort type, included renal transplanted women enrolled in the Family Planning Sector of Federal University of Sao Paulo from October 1, 2014 to July 30, 2016; collecting data from their first appointment and six months later.

All sexually active women admitted in the period were included. We selected those who initiated DMPA as a single contraceptive method and also condom-only users (reference group). The exclusion criteria were non-functional renal graft, menopaused women (clinical or laboratory diagnosed) and those who changed methods between appointments.

Service routine started with an educational activity, where all patients were presented and informed about main contraceptive methods. Nursery evaluation, before all appointments, included height and weight assessment, using a mechanical scale. Medical appointments were conducted with detailed anamnesis and physical examination. All transplanted patient's follow-up in same institution (Transplantation Clinic of São Paulo Federal University), collecting routine laboratory tests every 3 months.

The baseline characteristics collected were age, height, number of gestations and labors and time of transplant, referring to first appointment. We also collected data from both appointments such as weight, hemoglobin (Hb), hematocrit (Ht), creatinine (Cr), and also occurrence of pregnancy and graft acute rejection during follow-up. The primary outcome was if DMPA use impacted analysed parameters.

Statistical analysis included Fischer's exact test for categorical data, Student's t test for baseline data and ANOVA for means along 6-month follow-up. Linear regression was used to evaluate contraceptive effects in all dependent variables (Hb, Ht, Cr), controlled by age. Kolmogorov–Smirnov test verified normal distribution and, if broken, Mann-Whitney test replaced Student's t.

Data was analyzed using SPSS version 20 (IBM, Armonk, NY, USA) and STATA 15 (Stata Corp LLC, College Station, TX, USA) with a significance level of 5%. The study was approved from local Ethics Committee (CEP UNIFESP – reference number 1.692.348) approved on Aug20th,2016. All collected data was anonymous and informed consent was exempt.

Results

During the follow-up period, 135 renal transplanted women were admitted in the Unit. However, 46 of them did not return and 13 medical records have failures on filling, making analysis impossible. A total of 50 patients were included for the study: 30 DMPA users and 20 condom users. The remaining 26 patients were users of other methods: 12 combined hormonal contraceptives, 8 intrauterine devices and 6 progestin-only pills.

From baseline characteristics, age was higher in condom group (35.8ys vs. 30.4ys, P=0.033) (Table 1). Nulliparous was predominant in both groups (63.3% vs. 45%) and no

difference was found in mean and distribution of gravity and parity (Tables 1 and 2). Mean time between transplant and first appointment was prolonged in both groups, but not statistically different (3.4ys vs. 4.2ys, P=0.522) (Table 1).

For linear regression analysis, condom group was used as a reference. No difference was found in all parameters, including age (Table 4).

Table 1: Baseline Patients Characteristics

	Mean ± SD	Minim	Maximum	Median	Range*	N	P
Age (years)	**32.5 ± 8.8**	**16.0**	**47.0**	**33.0**	**35.8 - 40.0**	**50**	0.033
DMPA	30.4 ± 9.4	16.0	45.0	32.5	21.0 - 37.3	30	
Condom	35.8 ± 6.8	24.0	47.0	33.0	31.0 - 42.3	20	
							0.562
BMI (kg/m²)	**24.6 ± 5.2**	**17.0**	**40.0**	**23.0**	**20.0 - 27.0**	**50**	
DMPA	24.3 ± 4.6	18.0	40.0	23.0	20.8 - 27.0	30	
Condom	25.2 ± 6.1	17.0	38.0	24.0	20.0 - 30.8	20	
							0.268[a]
Number of gestations	**1.0 ± 1.3**	**0.0**	**5.0**	**1.0**	**0.0 - 1.3**	**50**	
DMPA	0.7 ± 0.9	0.0	3.0	0.0	0.0 - 1.0	30	
Condom	1.3 ± 1.6	0.0	5.0	1.0	0.0 - 2.0	20	
							0.164[a]
Parity	**0.7 ± 1.1**	**0.0**	**5.0**	**0.0**	**0.0 - 1.0**	**50**	
DMPA	0.5 ± 0.8	0.0	3.0	0.0	0.0 - 1.0	30	
Condom	1.1 ± 1.4	0.0	5.0	1.0	0.0 - 1.8	20	
							0.522
Time of graft surgery (years)	**3.7 ± 4.3**	**0.0**	**15.3**	**2.0**	**0.4 - 4.8**	**50**	
DMPA	3.4 ± 3.9	0.0	13.9	2.0	0.4 - 4.4	30	
Condom	4.2 ± 4.8	0.2	15.3	2.3	0.4 - 5.6	20	
							0.472

SD - Standard deviation

Range* – Interquartile range

P – Student t or Mann-Whitney([a])

DMPA – Depot medroxyprogesterone acetate

BMI – Body mass index

BMI (weight/height²) was calculated of each included patient and no difference was found in mean values (24.3 vs. 25.3, P=0.562) (Table 1). Weight gain between appointments was also analysed, there was no difference in mean values (1.7kg vs. 1.3kg, P=0.685).

No case of pregnancy or acute rejection occurred in all 50-included patients, during follow-up. Creatinine variation analysis was stable in both groups (0.10 vs. 0.00, P=0.120) (Table 3). The same occurred in hemoglobin and hematocrit findings (0.53 vs. 0.11, P=0.503) (1.23 vs. 1.03, P=0.898) (Table 3).

Discussion

In our study, comparing medroxyprogesterone acetate and condom users for six months, we did not find changes in weight, red blood cell values and creatinine.

It is remarkable that the long-time difference between surgery and Family Planning Unit enrolment, more than three years for both groups. Also, 46 of 135 enrolled patients did not return to follow-up. In our opinion, it showed that contraception was not a relevant matter for them and for the doctors. This data was evaluated in a study already pub-

Table 2 – Number of Gestations and Parity Distribution

	Method				Total		P
	DMPA		Condom				
	N	%	N	%	N	%	
Number of gestations	**30**	**100.0%**	**20**	**100.0%**	**50**	**100.0%**	0.312
0	16	53.3%	8	40.0%	24	48.0%	
1	8	26.7%	6	30.0%	14	28.0%	
≥2	6	20.0%	6	30.0%	12	24.0%	
Parity	**30**	**100.0%**	**20**	**100.0%**	**50**	**100.0%**	0.463
0	19	63.3%	9	45.0%	28	56.0%	
1	7	23.3%	6	30.0%	13	26.0%	
≥2	4	13.3%	5	25.0%	9	18.0%	

P – Fisher's exact test

DMPA – Depot medroxyprogesterone acetate

Table 3 – Laboratory Tests Variations for Contraceptive Method

	Basel	6 months	Variation	P
Creatinine (mg/dL)				0.120
DMPA	1.26 ± 0.49	1.36 ± 0.55	0.10 ± 0.21	
Condom	1.36 ± 0.71	1.36 ± 0.64	0.00 ± 0.25	
Hemoglobin (g/dL)				0.503
DMPA	12.35 ± 1.83	12.79 ± 1.90	0.43 ± 1.94	
Condom	12.72 ± 1.95	12.82 ± 1.72	0.11 ± 1.21	
Hematocrit (%)				0.898
DMPA	37.31 ± 5.69	38.54 ± 5.53	1.23 ± 6.22	
Condom	38.88 ± 6.00	39.91 ± 5.89	1.03 ± 4.14	

Mean ± Standard deviation

DPMA – Depot medroxyprogesterone acetate

Table 4 – Linear Regression Results

	Creatinine		Hemoglobin		Hematocrit	
	Coefficient (CI95%)	**P**	**Coefficient (CI95%)**	**P**	**Coefficient (CI95%)**	**P**
DPMA (ref.=Condom)	-0.09 (-0.44 ; 0.26)	0.604	-0.17 (-1.25 ; 0.92)	0.765	-0.86 (-4.19 ; 2.48)	0.615
Basel (ref.=1° appointment)	0.00 (-0.10 ; 0.10)	0.937	0.11 (-0.63 ; 0.84)	0.781	1.03 (-1.38 ; 3.43)	0.404
Interaction DPMA x 6 months	0.10 (-0.02 ; 0.23)	0.114	0.33 (-0.63 ; 1.28)	0.500	0.21 (-2.9 ; 3.31)	0.897
Age	0.00 (-0.02 ; 0.02)	0.821	0.04 (-0.02 ; 0.09)	0.192	0.13 (-0.03 ; 0.3)	0.120
Constant	1.28 (0.54 ; 2.02)	0.001	11.41 (9.3 ; 13.53)	<0.001	34.16 (27.72 ; 40.61)	<0.001

DMPA – Depot medroxyprogesterone acetate

lished [7]. A multi-professional approach must emphasize the topic during routine follow-up, showing risks and opportunities for patients.

Our study has found weight gain in both groups, not statistically significant (P=0.68). The results were similar to systematic reviews that compared medroxyprogesterone acetate users to other methods [16].

We also found no difference in renal function (creatinine) in both groups (P=0.12), and also no case of acute rejection. The hepatic metabolism of medroxyprogesterone acetate and no description of drug interaction with main immunosuppressants supported its use in renal-transplanted patients. Our results showed the progestogen did not interfere with graft function.

Some evidence suggested immunosuppressive proprieties of DMPA, including rising risks for HIV and other STI infections, such as gonorrhoea and chlamydia [17]. Main findings were inhibition of interferon and interleucines (IL-2, IL-4, IL-6, IL-12) production by peripheral blood cells and activated T cells, in in-vitro studies. Women using DMPA displayed lower levels of interferon in plasma and genital secretions compared with controls with no hormonal contraception. Immunosuppressive effect of medroxyprogesterone acetate was observed in concentrations close to peak-concentration detected in plasma of women using DMPA (107M or 38ng/mL) [18]. Thus, DMPA may also be favourable to reduce the incidence of renal transplant rejection; however, the present study with a small population and short-term observation did not show data indicative of this effect.

In hematimetric analysis, we observed a little increase in hemoglobin and hematocrit values in both groups, not statistically significant (P=0.50/0.90), against expectations. DMPA is indicated for heavy menstrual bleeding disorders and its use is associated with high amenorrhea rates. The findings can be due to short follow-up time compared to method adjustment period, which courses with irregular bleeding [19]. Further studies could show more differences over a prolonged period between methods.

Conclusion

Our findings supported use of the injectable contraceptive for renal transplanted patients. However, limitations on sample size and short follow-up could interfere on results. We hope to expand studies and clarify the topic.

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