Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v26i1.544_ENG

REVIEW PAPER

Women After Solid Organ Transplantation: An Overview of Gynecological Health

Cássia Raquel Teatin Juliato[1,*], José Paulo Siqueira Guida[1], Fernanda Garanhani Surita [1]

1. Universidade Estadual de Campinas – Faculdade de Ciências Médicas – Departamento de Obstetrícia e Ginecologia – Campinas (SP), Brazil

*Corresponding author: cassia.raquel@gmail.com

Section editor: Ilka de Fátima Santana F Boin

Received: Nov. 13, 2023 | Accepted: Nov. 29, 2023

How to cite: Juliato CRT, Guida JPS, Surita FG. Women After Solid Organ Transplantation: An Overview of Gynecological Health. BJT. 2023.26 (01):e3923. https://doi.org/10.53855/bjt.v26i1.544_ENG

ABSTRACT

The increase in survival after transplantation and the growth of the female organ recipient population underscore the importance of carefully considering the reproductive and gynecological health of these women. One of the main concerns is the increased risk of cancer after transplantation, partly attributed to the use of immunosuppressive therapy. Gynecological cancers with a high association with viral infections, such as cervical cancer, should receive specific care and screening, especially among younger women. Additionally, the preventable nature of cervical cancer makes vaccination mandatory before undergoing transplantation. Breast cancer, another gynecological cancer of special interest due to its high prevalence, should be screened in the transplant population following guidelines for the general population. Fertility and family planning are also important considerations, as most women experience the return of ovulation and menstruation after transplantation. Contraception strategies, such as reversible long-acting methods, are recommended due to their effectiveness and low failure rate. The use of hormonal contraceptives and immunosuppressants should also be evaluated, emphasizing the need to carefully monitor potential drug interactions. An integrated approach to the gynecological health of women after solid organ transplantation enables better outcomes for both graft health and the gynecological health of the woman, resulting in improved outcomes for the patient. Ongoing follow-up, careful surveillance, cancer prevention, and effective management of fertility and contraception are crucial to ensure their quality of life and well-being.

Descriptors: Transplantation; Women; Primary prevention; Secondary prevention; Gynaecological malignancies; Contraception.

Mulheres após Transplante de Órgãos Sólidos: Um Olhar Sobre a Saúde Ginecológica

RESUMO

O aumento na sobrevida após o transplante e o crescimento da população feminina receptora de órgãos destacam a importância de considerar cuidadosamente a saúde reprodutiva e ginecológica dessas mulheres. Uma das principais preocupações é o risco aumentado de câncer após o transplante, atribuído em parte ao uso de terapia imunossupressora. Cânceres ginecológicos com alta associação com infecções virais, como câncer de colo uterino, devem receber cuidados e rastreios específicos, em especial entre mulheres mais jovens. Além disto, o caráter imunoprevinível do câncer de colo uterino torna a vacinação mandatória antes da realização do transplante. O câncer de mama, outro câncer ginecológico de especial interesse por sua alta prevalência, deve ser rastreado na população transplantada, seguindo as diretrizes da população geral. A fertilidade e o planejamento familiar também são considerações importantes, pois a maioria das mulheres apresenta o retorno da ovulação e da menstruação após o transplante. Estratégias de contracepção, como métodos de longa ação reversíveis, são recomendadas devido à sua eficácia e baixa taxa de falhas. O uso de contraceptivos hormonais e imunossupressores também devem ser avaliados, enfatizando a necessidade de observar cuidadosamente as possíveis interações medicamentosas. A abordagem integrada à saúde ginecológica das mulheres após um transplante de órgão sólido possibilita melhores resultados, tanto para a saúde do enxerto quanto para a saúde ginecológica daquela mulher, revertendo em melhores desfechos para a paciente. O acompanhamento e a vigilância cuidadosa, a prevenção do câncer e a gestão eficaz da fertilidade e contracepção são cruciais para garantir sua qualidade de vida e bem-estar.

Descritores: Transplante; Mulheres; Prevenção primária; Prevenção secundária; Neoplasias ginecológicas; Contracepção.

INTRODUCTION

The reproductive and gynecological health of women undergoing solid organ transplantation has become a concern during graft monitoring, essentially motivated by two reasons: the first is the increase in survival after transplantation, and the second is the increase in the prevalence of women among the receivers. Among people who received a liver graft in 2021, 38% were women, a higher number than that observed ten years earlier, which was 35%[1].

Of the aspects related to gynecological health, two stand out in the assistance to transplanted women: screening for the most common gynecological cancers and reproductive planning. There are no validated international guidelines for both topics[2-6]. However, it is essential to consider that transplanted women are at greater risk of tumors caused by viral infections, such as cervical cancer (cervix uteri), in addition to having fertility restored after correction of the underlying disease that led the patient to the transplant.

In this way, these topics become an essential part of care, which must be shared between the transplant and gynecological teams that provide clinical care to that woman. The objective of this article is to discuss screening and reproductive planning strategies for women after solid organ transplantation.

METHODS

The present was a narrative review study, which used as inclusion criteria articles whose results were related to women's gynecological health, including primary and secondary prevention, after solid organ transplantation. For the literature search, PubMed, Cochrane Library, and Scopus databases were used without language and time range restrictions. The following terms were used: transplant, solid organ transplant, vaccines, HPV, gynecological routine, gynecological cancer, or neoplasms (breast, ovarian, endometrial, vaginal and vulvar). The search strategy was carried out in English in November 2023. The main author evaluated the titles and abstracts of the retrieved articles. The articles selected in the first evaluation stage had their full text evaluated by the same reviewers. Data extraction and preparation of the article were carried out.

RESULTS

Cancer Risk After Transplant

Analysis of solid organ recipient registries suggests that there is a high incidence of cancer in the post-transplant population compared to the general population[7]. One study showed a 4-fold increased risk of developing cancer after kidney, liver, or other organ[8] transplantation, and another study showed that 22% of deaths occurring more than a year after liver transplantation were due to cases of cancer[9]. The increased prevalence of gynecological cancers in women after transplants can be explained by the immunosuppressive therapy commonly used after transplants and also due to the lack of specific protocols for screening this population.

Cervical Cancer

Cancers of the cervix, vulva and vagina are often caused by viral diseases, specifically Human Papillomavirus (HPV) infections. Post-transplant women usually use immunosuppressive therapy, which can increase the chance of developing cancers of viral origins, such as cancer of the cervix, vagina, and vulva. The increase in cases of these neoplasms is more impactful in the young population, which is outside the usual screening range, carried out from the age of 25 and repeated annually for two years and then every 3 years if negative results. In young women after transplantation, there is an increased risk of precursor lesions, such as third-degree intraepithelial neoplasia (CIN 3 or in situ neoplasia) of 4.7 times and of cervical cancer of 2.4 times when compared to older women after transplantation[10].

The American Society of Transplantation (AST) recommends an annual pelvic exam with an oncotic cytology exam (called Pap Smear) for post-kidney transplant patients[11]. The "Kidney Disease: Improving Global Outcomes" (KDIGO) recommends age-appropriate cancer screening in pre- and post-transplant patients in its latest guidance statement. However, there is no specific screening for ovarian, endometrial or vulvovaginal cancer[12]. Therefore, the screening strategies included are those suggested for the general population[13]. Consequently, it is essential that potential solid organ transplant recipients are adequately screened for the presence of colon cancer before transplantation. After transplantation, because of immunosuppression and considering the high prevalence of HPV in Brazil, it seems appropriate to collect oncotic cytology annually, avoiding longer intervals.

It is important to emphasize that cervical cancer is vaccine-preventable. There are currently vaccines to prevent infection with the main types of HPV. The vaccine is considered safe for post-transplant women but may have reduced effectiveness[13,14].

A study showed that after four weeks of the last dose of the vaccine, the immune response was observed in 63.2%, 68.4%, 63.2%, and 52.6% for HPV types 6, 11, 16, and 18, respectively.

The factors that led to reduced immunogenicity were early vaccination after transplantation, having had a lung transplant, and having higher levels of the drug tacrolimus[14]. Therefore, the vaccine to protect against HPV should be prioritized in women before solid organ transplants.

Breast Cancer

Breast cancer has a high incidence in the general population. Screening is carried out through mammography, which the Brazilian Ministry of Health recommends to be carried out from the age of 50 and should be carried out at least every two years. Mammography allows early diagnosis of lesions that are not yet palpable, allowing for less aggressive treatments with more significant survival potential. Due to this incidence, most transplant centers require breast cancer screening before listing a patient for transplant. Several studies have shown a lower risk of breast cancer, which is likely a consequence of pre-transplant screening methods[13,15-17].

An intensified surveillance protocol in women after liver transplantation was established, and the authors observed an improvement in the detection of *De Novo* cancers, from 4.9% to 13%. They also observed more malignancies, but again diagnosed at earlier stages[18]. The International Society for Heart and Lung Transplantation (ISHLT) recommends using the same general malignancy screening and surveillance methods used in the general population in pre- and post-heart and lung transplant patients related to breast and gynecological cancer[19].

Regarding kidney transplantation, there is no recommendation for screening earlier or at shorter intervals.

Fertility after Transplant and Family Planning

Reproductive capacity is often affected in women suffering from advanced diseases, with almost 75% of women awaiting a liver transplant not menstruate[20].

After solid organ transplantation, most women experience a return of ovulation and menstruation. Furthermore, there may be an increase in libido due to the increase in hormonal levels that were suppressed, the use of medications with teratogenic potential (used after the transplant), and the need not to get pregnant after the transplant, at least in the first 24 months[21]. All of this makes family planning essential in this population group - however, a study showed that only 28% of adolescents were using contraceptives after transplantation followed by the use of teratogenic immunosupressants[22].

It is important to emphasize that women should avoid returning to sexual activity for at least the first three months after the transplant, both due to the risk of surgical and immunological complications.

Methods called LARCs (Long-Acting Reversible Contraception methods) are considered the safest methods currently available as they have a failure rate 21.8 times lower than short-acting methods[23]. The available LARC methods are hormonal and non-hormonal intrauterine devices and contraceptive implants.

Intrauterine Devices (IUDs) are long-acting contraceptive methods widely used due to their low failure rates. What makes IUDs especially attractive is that their effectiveness is not dependent on patient compliance, making them a reliable option for women who want to avoid pregnancy. However, in the context of transplant recipients, there has been previous controversy over the use of IUDS.

This controversy was based on theoretical concerns, especially regarding the use of copper IUDs. There was concern that the use of IUDs in patients undergoing solid organ transplantation could increase the risk of pelvic inflammatory disease due to immunosuppression and a decreased inflammatory response. Additionally, there were concerns about the possibility of contraceptive failure due to this diminished inflammatory response.

However, more recent studies have shed light on this issue and have not confirmed the theoretical risks associated with the use of IUDs in transplant recipients. This research demonstrated that IUDs, including copper ones, can be safe and effective in women who have undergone a transplant as long as they are adequately evaluated by gynecologists at regular intervals in order to observe the presence of infectious signs or displacement of the IUD[24,25]. A study with 21 women after kidney transplantation showed that no cases of pregnancy or pelvic infection were observed during the average follow-up of 49.3 months[24,25].

There is concern about the possible reduced effectiveness of contraceptives due to interactions with drug metabolism. Both oral contraceptives and immunosuppressants are metabolized and can affect the activity of the cytochrome P450 3A4 (CYP3A4) enzyme, making drug interactions possible. The induction of CYP3A by immunosuppressants, such as glucocorticoids, could decrease the efficacy of oral contraceptives.

However, studies have shown that there were no changes in contraceptive hormone levels in transplanted women using immunosuppressants[26,27]. Conversely, inhibition of CYP3A4 by COCs may affect serum levels of concomitant immunosuppressive medications, such as cyclosporine, tacrolimus, and sirolimus, which could increase the risk of toxicity of graft rejection. Therefore, careful consideration of possible drug interaction is essential in the treatment of patients using both contraceptives and immunosuppressants.

Other studies have also shown the safety of contraception among transplant women. A systematic review evaluated the use of contraceptives in transplanted women. A total of 36 kidney transplant recipients using combined oral contraceptives (COCs) or the transdermal contraceptive patch showed no significant changes in biochemical measures after 18 months of use for both groups. A retrospective, non-comparative study of 15 liver transplant recipients who used COCs or the transdermal contraceptive patch found no significant changes in biochemical measurements, no interruptions or severe complications, and no pregnancies after a 12-month follow-up[24].

One study provided data on the safety of the etonogestrel contraceptive implant for women of reproductive age who are solid organ transplant recipients. The study evaluated 24 women after pelvic organ transplantation and the use of a contraceptive implant and compared them with 24 women after transplantation and without using hormonal contraception, matched in age and organ transplanted. Contraceptive implant users were not at greater risk of complications related to the transplant, infections, or the need for changes in immunosuppressive therapy[28].

Regarding liver transplantation, due to the need for the liver to metabolize hormonal contraceptives, some concerns may exist regarding their use after transplantation. A retrospective study aimed to evaluate the tolerability and safety of hormonal contraception in 15 women who underwent liver transplantation. Nine of these women used combined oral contraceptives, while six opted for the contraceptive patch. Biochemical concentrations, efficacy and continuation of the contraceptive method were monitored 3,6 and 12 months after starting treatment.

The results revealed no significant changes in biochemical measurements compared to reference values. Furthermore, there were no cases of graft rejection or serious complications related to contraceptive therapy. It is important to highlight that none of the patients discontinued contraceptive use for medical reasons, and there were no reports of pregnancy during the observation period. These findings suggest that hormonal contraception, whether through combined oral contraceptives, vaginal rings, or patches, appears to be well tolerated and safe in women who have undergone liver transplantation. This may be an effective option for these patients, offering contraceptive protection without compromising graft health or therapy efficacy[29].

Combined hormonal contraceptives include estrogens and progestins in the form of oral contraceptive pills, transdermal patches, or vaginal rings and are generally considered safe after transplants. Although, as previously presented, studies show that exposure to CHCs may be safe, Prudence recommends caution in the use of CHCs in patients who have undergone a liver transplant and show signs of graft failure due to concerns about possible increased risk of estrogen-related complications, such as venous thromboembolism[30].

On the other hand, progestogen-only methods such as oral contraceptive pills that contain only progesterone, medroxyprogesterone acetate injections, and subcutaneous implants are safe alternatives for liver transplant women, even in cases of graft failure, as they do not involve the associated risks to estrogen therapy[30].

It is important to mention that combined oral contraceptives have been associated with a worsening of hypertension and may influence cytochrome P450 metabolism. Therefore, it is advisable to review possible drug interactions and cardiovascular risks before starting treatment[30].

CONCLUSION

In a scenario of increasing post-transplant survival and the growing number of female organ recipients, crucial questions arise regarding the reproductive and gynecological health of women after transplantation. The lack of specific guidelines for gynecological or breast cancer screening in this population, combined with the need for family planning, makes a careful approach to ensuring their health essential. The risk of cancer after transplantation is significantly elevated, being attributed, in part, to the use of immunosuppressive therapies. Gynecological cancers, such as cervical cancer, are more common, especially in younger women, making adequate monitoring and screening important.

For the prevention of cervical cancer, HPV vaccination is recommended before transplantation. Furthermore, breast cancer screening and surveillance should follow general guidelines, while fertility and family planning should be addressed carefully and effectively, considering the return of ovulation and menstruation after transplantation. When it comes to contraception, it is essential to consider possible interactions between hormonal contraceptives and immunosuppressants, preferring estrogen-free options in case of liver graft failure and carefully evaluating drug interactions. Recent studies demonstrate the safety of combined oral contraceptives and implants in women who have had liver transplants, but appropriate monitoring and management are crucial. Overall, an integrated approach to the gynecological health of post-transplant women is essential to ensure their quality of life and well-being.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study:

CONCEPTION AND DESIGN:

Substantive scientific and intellectual contributions to the study: Juliato CRT, Guida JPS, Surita FG; **Conception and design:** Juliato CRT, Guida JPS, Surita FG; **Data analysis and interpretation:** Juliato CRT, Guida JPS, Surita FG; **Article writing:** Juliato CRT, Guida JPS, Surita FG; **Critical revision:** Juliato CRT, Guida JPS, Surita FG; **Final approval:** Juliato CRT, Guida JPS, Surita FG.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

FUNDING

Not applicable.

ACKNOWLEDGEMENT

To the Faculdade de Ciências Médicas da Unicamp.

REFERENCES

1. National data-OPTN. Organ Procurement and Transplantation Network. Available at https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/ . Acessed on 3 Sept 22.
2. Lucey M, Terrault N, Ojo L. Long-term management of the adult liver transplant. AASLD.org. Available at https://www.aasld.org/practice-guidelines/Long-term-management-adult-liver-transplant . Acessed on 1 Nov. 22.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016;64(2):433–485. https://doi.org/10.1016/j.jhep.2015.10.006
4. Adegunsoye A, Strek ME, Garrity E, Guzy R, Bag R. Comprehensive Care of the Lung Transplant Patient. Chest. 2017;152(1):150–164. https://doi.org/10.1016/j.chest.2016.10.001
5. Velleca A, Shullo MA, Dhital K, Azeka E, Colvin M, DePasquale E, et al.. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant.* 2023;42(5): e1–e141. https://doi.org/10.1016/j.healun.2022.10.015
6. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010;77(4):299–311. https://doi.org/10.1038/ki.2009.377
7. Brennan DC, Rodeheffer RJ, Ambinder RF. Malignancy after solid organ transplantation. UpToDate.com. Available at https://www.uptodate.com/contents/malignancy-after-solid-organ-transplantation#! Acessed on 11Sept 22.
8. Adami J, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, et al.. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer. 2003;89(7):1221–1227. https://doi.org/10.1038/sj.bjc.6601219
9. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant. 2010;10(6):1420–1427. https://doi.org/10.1111/j.1600-6143.2010.03126.x
10. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. Am J Transplant. 2013;13(12):3202–3209. https://doi.org/10.1111%2Fajt.12472
11. American Society of Transplantation. Guidelines for post-kidney transplant management in the community setting. 2017. Available at https://www.myast.org/guidelines-post-kidney-transplant-management-community-setting . Acessed on 22 Dec. 22.

12. Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V,et al.. Summary of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. *Transplantation.* 2020;104(4):708-714. https://doi.org/10.1097/tp.0000000000003137

13. Jones-Pauley M, Kodali S, Basra T, Victor DW. Women's health issues in solid organ transplantation: Breast and gynecologic cancers in the post-transplant population. World J Transplant. 2023;13(4):129-137. https://doi.org/10.5500%2Fwjt.v13.i4.129

14. Kumar D, Unger ER, Panicker G, Medvedev P, Wilson L, Humar A. Immunogenicity of quadrivalent human papillomavirus vaccine in organ transplant recipients. Am J Transplant. 2013;13(9):2411-7. https://doi.org/10.1111%2Fajt.12329

15. Jain AB, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, et al. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. Transplantation. 1998;66(9):1193–1200. https://doi.org/10.1097/00007890-199811150-00014

16. Oruc MT, Soran A, Jain AK, Wilson JW, Fung J. De novo breast cancer in patients with liver transplantation: University of Pittsburgh's experience and review of the literature. Liver Transpl. 2004;10(1):1–6. https://doi.org/10.1002/lt.20025

17. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891–1901. https://doi.org/10.1001/jama.2011.1592

18. Finkenstedt A, Graziadei IW, Oberaigner W, Hilbe W, Nachbaur K, Mark W,et al. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. Am J Transplant. 2009;9(10):2355–2361. https://doi.org/10.1111/j.1600-6143.2009.02766.x

19. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2021;40(11):1349–1379. https://doi.org/10.1016/j.healun.2021.07.005

20. Jabiry-Zieniewicz Z, Kaminski P, Bobrowska K, Pietrzak B, Wielgos M, Smoter P, et al. Menstrual function in female liver transplant recipients of reproductive age. Transplant Proc. 2009;41(5):1735-1739. https://doi.org/10.1016/j.transproceed.2009.03.073

21. Ritchie J, Seidman D, Srisengfa Y, Perito ER, Sarkar M. Family Planning in Liver Transplant: Patient and Provider Knowledge and Practices. Liver Transpl. 2020 ;26(10):1233-1240. https://doi.org/10.1002/lt.25835

22. Stancil SL, Miller M, Briggs H, Lynch D, Goggin K, Kearns G. Contraceptive provision to adolescent females prescribed teratogenic medications. Pediatrics. 2016;137(1):e20151454. https://doi.org/10.1542/peds.2015-1454

23. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med. 2012 May 24;366(21):1998-2007. https://doi.org/10.1056/NEJMoa1110855

24. Paulen ME, Folger SG, Curtis KM, Jamieson DJ. Contraceptive use among solid organ transplant patients: a systematic review. Contraception. 2010;82(1):102-12. https://doi.org/10.1016/j.contraception.2010.02.007

25. Juliato CRT, Stahlschmidt P, Fernandes A, Monteiro I, Bahamondes L. A case series on the use of levonorgestrel 52 mg intrauterine system after organ transplant. Contraception. 2018;98(3):252-254. https://doi.org/10.1016/j.contraception.2018.04.017

26. Estes CM, Westhoff C. Contraception for the transplant patient. Semin Perinatol 2007;31:372–7.

27. Gaston RS. Maintenance immunosuppression in the renal transplant recipient: an overview. Am J Kidney Dis 2001;38:S25–S35.

28. Lew J, Sheeder J, Lazorwitz A. Etonogestrel contraceptive implant uptake and safety among solid organ transplant recipients. Contraception. 2021;104(5):556-560. https://doi.org/10.1016/j.contraception.2021.06.007

29. Paulen ME, Folger SG, Curtis KM, Jamieson DJ. Contraceptive use among solid organ transplant patients: a systematic review. Contraception. 2010;82(1):102-12. https://doi.org/10.1016/j.contraception.2010.02.007

30. Bosch A, Daniel KE. Pregnancy and contraception in the post-liver transplant patient. Clin Liver Dis (Hoboken). 2023;21(6):187-190. https://doi.org/10.1097%2FCLD.0000000000000059