European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

# VASCERN-VASCA Consensus Statement: Sirolimus and Fertility

Version 1 - 20/12/2023

# Introduction

This document is based on the statement elaborated by ASPHO SIG (The American Society of Pediatric Hematology/Oncology Special Interest Group) and CaNVAS (Consortium of iNvestigators of Vascular AnomalieS), USA in December 2023, and further revised by the VASCERN (European Reference Network for Multisystemic Rare Vascular Diseases) VASCA (Vascular Anomalies) working group.

# Sirolimus and Fertility: A Comprehensive Overview

Recent concerns have been raised about the impact of sirolimus (or rapamycin) treatment on fertility in both men and women with vascular anomalies. As international specialists in Vascular Anomalies, we aim to address this issue by examining the current knowledge. While animal studies have provided insights, human literature is limited, primarily relying on case reports and a small series of solid organ transplant patients. It is crucial to recognize the differences between these populations, considering that 1) organ transplant patients require association of different immunosuppressive therapies; 2) sirolimus or tacrolimus is given for life for organ transplant patients; 3) daily doses for organ transplant patients need to reach a sustained, important serum sirolimus level; and 4) organ transplant patients experienced a long-lasting organ failure period and multiple prior heavy treatments.

Here is a summary of the current literature on sirolimus and its effects on gonadal function:

**A) Reversible effect of sirolimus on gonadal function**

- In 2012, rat studies indicated that sirolimus reduced testosterone levels and blocked spermatogenesis, with complete recovery upon treatment withdrawal (1).
- In 2013, a publication summarized the impact of sirolimus on fertility, based on different case reports that suggested a reversible impact of sirolimus on fertility and pregnancy in male and female solid tumor transplant patients (2). These case reports described patients who experienced decreased spermatozoid function and number on sirolimus, as well as lower sex hormone levels, with normalization of these dysfunctions when sirolimus was discontinued (3-5). A report of one heart transplant patient on sirolimus noted a poor in vitro fertilization outcome, which improved with discontinuation of the drug (6).

- Women may experience menstrual cycle disturbances and ovarian cysts with sirolimus or everolimus (given in vascular anomaly or solid organ transplantation setting), but these symptoms improve with dose reduction or drug cessation (7).
- In the recent report from the European multicentric phase III trial VASE (vascular anomaly-sirolimus -Europe), the incidence of dysmenorrhea was low (less than 10%), and all were Grade I-II (mild effects). Dysmenorrhea was resolved when sirolimus was stopped (8).
- Based on various observations, the EMA stated in the Summary of product characteristics (Smpc) of Rapamune®: "Impairments of sperm parameters have been observed among some patients treated with Rapamune. These effects have been reversible upon discontinuation of Rapamune in most cases" (9). FDA stated "Azoospermia has been reported with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases" (10)

**B) Successful pregnancy is possible after sirolimus**

- Numerous reports highlight successful pregnancies in solid transplant patients and those with Lymphangioleiomyomatosis (LAM) on long-term sirolimus therapy (2, 10-13).
- Preliminary results from the European multicentric phase III trial VASE showed that pregnancy is highly and rapidly feasible during the follow up period after being treated for 2 years with sirolimus: 4 pregnancies occurred (including 1 fathered pregnancy) in 3 patients (8).

**C) Future directions**

It is important to remember that sirolimus has FDA and EMA approval for both use in organ transplant patients and for lymphangioleiomyomatosis (9,10). This means that extensive studies have been completed outside of the field of vascular anomalies to not only prove efficacy, but to assess safety of sirolimus.

Although the studies surrounding fertility and gonadal function for patients with vascular anomalies are few (but increasing), it is still very important for vascular anomaly experts to be aware of what has been evaluated in other disease states and what the unknowns are.

More retrospective and prospective data need to be collected to obtain accurate information related to vascular anomaly patients. This will also be important to follow for many of the newer targeted therapies.

**In conclusion, the current evidence suggests that the effects of sirolimus on gonadal function are generally small and reversible. It is imperative for vascular anomaly experts to stay informed about the upcoming findings, and patients should be informed of these discoveries for informed decision-making.**

**References:**


1. Rovira J, Diekmann F, Ramírez-Bajo MJ, et al. Sirolimus-associated testicular toxicity: detrimental but reversible. Transplantation. 2012 May 15;93(9):874-9. doi: 10.1097/TP.0b013e31824bf1f0. PMID: 22357177.

2. Framarino-dei-Malatesta M, Derme M, Manzia TM, et al. Impact of mTOR-I on fertility and pregnancy: state of the art and review of the literature Date: Aug. 2013 Expert Review of Clinical Immunology (Vol. 9, Issue 8)

3. Skrzypek J, Krause W. Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment. Andrologia 39(5), 198–199 (2007).

4. Deutsch MA, Kaczmarek I, Huber S *et al.* Sirolimus associated infertility: case report and literature review of possible mechanisms. Am. J. Transplant. 7(10), 2414–2421 (2007).

5. Boobes Y. Gonadal dysfunction and infertility in kidney transplant patients receiving sirolimus. Int. Urol. Nephrol. 42(2), 493–498 (2010).

6. Wald K, Cakmak H, Noel M. mTOR inhibitor sirolimus negatively impacts in vitro fertilization outcomes. J Assist Reprod Genet. 2019 May;36(5):947-950. doi: 10.1007/s10815-019-01439-4. Epub 2019 Mar 25. PMID: 30911930; PMCID: PMC6541660.

7. Braun M, Young J, Reiner CS, et al. (2012) Low-Dose Oral Sirolimus and the Risk of Menstrual-Cycle Disturbances and Ovarian Cysts: Analysis of the Randomized Controlled SUISSE ADPKD Trial. PLoS ONE 7(10): e45868. doi:10.1371/journal.pone.0045868.

8. Seront E, Van Damme A, Legrand C, et al. Preliminary results of the European multicenter phase III trial regarding sirolimus in slow-flow vascular malformations. JCI Insight 2023;8(21):e173095.

9. https://www.ema.europa.eu/en/documents/product-information/rapamune-epar-product-information_en.pdf.

10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021083s059,021110s076lbl.pdf.

11. Veroux M, Corona D, Veroux P. Pregnancy under everolimus-based immunosuppression. Transpl Int. 2011 Dec;24(12):e115-7. doi: 10.1111/j.1432-2277.2011.01356.x. Epub 2011 Sep 22. PMID: 21950359.

12. Chu SH, Liu KL, Chiang YJ, et al. Sirolimus used during pregnancy in a living related renal transplant recipient: a case report. Transplant Proc. 2008 Sep;40(7):2446-8. doi: 10.1016/j.transproceed.2008.06.015. PMID: 18790264.

13. Shen L, Xu W, Gao J, Wang J, Huang J, Wang Y, He Y, Yang Y, Tian X, Xu KF. Pregnancy after the diagnosis of lymphangioleiomyomatosis (LAM). Orphanet J Rare Dis. 2021 Mar 17;16(1):133. doi: 10.1186/s13023-021-01776-7. PMID: 33731151; PMCID: PMC7972207

European Reference Network

VASCERN

Gathering the best expertise in Europe
to provide accessible cross-border healthcare
to patients with rare vascular diseases

VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million concerned). These include arterial diseases (affecting aorta to small arteries), arterio-venous anomalies, vascular malformations, and lymphatic diseases.

VASCERN currently gathers 48 expert teams from 39 highly specialized multidisciplinary HCPs, plus 6 additional Affiliated Partner centers, coming from 19 EU Member States, as well as various European Patient Organisations, and is coordinated in Paris, France.

Through our 6 Rare Disease Working Groups (RDWGs) as well as several thematic WGs and the ePAG – European Patient Advocacy Group, we aim to improve care, promote best practices and guidelines, reinforce research, empower patients, provide training for healthcare professionals and realise the full potential of European cooperation for specialised healthcare by exploiting the latest innovations in medical science and health technologies.

More information available at: https://vascern.eu

Follow us on

Co-funded by
the Health Programme
of the European Union