

University of Groningen

Protect pregnant women by including them in clinical research

Browne, Joyce; van der Zande, Indira; van Smeden, Maarten; van der Graaf, Rieke

Published in:
BMJ-British Medical Journal

DOI:
[10.1136/bmj.k4013](https://doi.org/10.1136/bmj.k4013)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Browne, J., van der Zande, I., van Smeden, M., & van der Graaf, R. (2018). Protect pregnant women by including them in clinical research. *BMJ-British Medical Journal*, 362, Article 4013.
<https://doi.org/10.1136/bmj.k4013>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



LETTERS

STOPPING OF VIAGRA TRIAL

Protect pregnant women by including them in clinical research

Joyce Browne *physician and clinical epidemiologist*¹, Indira van der Zande *ethicist*^{1,2}, Maarten van Smeden *statistician*³, Rieke van der Graaf *ethicist*¹

¹University Medical Center Utrecht, Heidelberglaan 100, 3584CX, Utrecht, Netherlands; ²University of Groningen (Campus Fryslân), Fryslân, Netherlands; ³Leiden University Medical Center, Leiden, Netherlands

The decision to stop the STRIDER trial with sildenafil (better known as Viagra) to improve uteroplacental blood flow, fetal growth, and infant outcomes for fetuses with severe growth restriction was disappointing for all involved.¹ International media extensively reported on this trial, triggering debates in academic journals and (social) media.²⁻⁴ But one aspect remains neglected: although results of the trial were undesirable, conducting clinical research in pregnant women is crucial. The importance of clinical trials with pregnant women has been argued and defended for decades, and these efforts should not be abandoned.^{5,6}

The response to the STRIDER trial shows the paradox in research with pregnant women—wanting to protect women and fetuses from harm, physicians, midwives, and researchers are reluctant to include them in clinical research, but it is the only way to increase the evidence base about safety and efficacy of drugs in pregnancy. Moreover, we must consider the risks of not conducting research in pregnant women: prescription of treatments for pregnant women without systematic assessment first. Sildenafil has been prescribed by doctors around the world for women with pregnancies with severely growth restricted fetuses.^{7,8} It is only because of this study that the potential adverse outcomes are now flagged.

Clinical research with pregnant women should not be prevented but encouraged. All stakeholders must encourage carefully designed and executed research, which observes normative considerations such as acceptable levels of risk and the optimal

use of safety and efficacy data from the non-pregnant population (fig 1).⁹ Ultimately, we need research like this to increase the evidence base and improve maternal and fetal health.

Competing interests: None declared.

Full response at: <https://www.bmj.com/content/362/bmj.k3247/rr>.

- Hawkes N. Trial of Viagra for fetal growth restriction is halted after baby deaths. *BMJ* 2018;362:k3247. 10.1136/bmj.k3247 30045911
- Paauw ND, Terstappen F, Ganzevoort W, Joles JA, Gremmels H, Lely AT. Sildenafil during pregnancy: a preclinical meta-analysis on fetal growth and maternal blood pressure. *Hypertension* 2017;70:998-1006. 10.1161/HYPERTENSIONAHA.117.09690 28893896
- UMC Amsterdam. Onderzoek gestaakt met medicijn tegen groeivertraging ongeboren baby. 2018. <https://www.amc.nl/web/nieuws-en-verhalen/actueel/actueel/onderzoek-gestaakt-met-medicijn-tegen-groeivertraging-ongeboren-baby-.htm>
- Peis A, Kenny LC, Alfirevic Z, et al. International STRIDER Consortium. STRIDER (Sildenafil TheRapy in dismal prognosis early onset fetal growth restriction): an international consortium of randomised placebo-controlled trials. *BMC Pregnancy Childbirth* 2017;17:440. 10.1186/s12884-017-1594-z 29282009
- Baylis F. Pregnant women deserve better. *Nature* 2010;465:689-90. 10.1038/465689a 20535185
- Little MO, Lyerly AD, Faden RR. Pregnant women & medical research: a moral imperative. *Bioethics Forum* 2009;2:60-5.
- Panda S, Das A, Md Nowroz H. Sildenafil citrate in fetal growth restriction. *J Reprod Infert* 2014;15:168-9.25202677
- Lin TH, Su YN, Shih JC, Hsu HC, Lee CN. Resolution of high uterine artery pulsatility index and notching following sildenafil citrate treatment in a growth-restricted pregnancy. *Ultrasound Obstet Gynecol* 2012;40:609-10. 10.1002/uog.11142 22350857
- Roes KCB, van der Zande ISE, van Smeden M, van der Graaf R. Towards an appropriate framework to facilitate responsible inclusion of pregnant women in drug development programs. *Trials* 2018;19:123. 10.1186/s13063-018-2495-9 29458400

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

Figure

Fig 1 Infographic developed by University Medical Center Utrecht, ZonMw, and Sticky Visuals