Gefitinib and methotrexate to resolve tubal ectopic pregnancy: the GEM3 RCT

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Disclosure of interests of authors

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/NNZF1037.

Primary conflicts of interest: Andrew W Horne reports grants from NIHR, grants from MRC, grants from Chief Scientist's Office, grants from Wellcome Trust, grants from Wellbeing of Women, grants and personal fees from Ferring, grants from Roche, personal fees from Nordic Pharma, personal fees from Roche Diagnostics, and personal fees from AbbVie, outside the submitted work. Jane P Daniels

is a member of NIHR CTU Standing Advisory Committee, 2016–2023. Arri Coomarasamy is a member of NIHR Efficacy and Evaluation Programme funding committee from January 2019 to present. Ben W Mol is supported by a NHMRC Investigator grant (GNT1176437). Ben W Mol reports consultancy for ObsEva and Merck and travel support from Merck. W Colin Duncan receives honoraria from Merck and Guerbet and research funding from Galvani Biosciences. Lucy H R Whitaker reports grants from NIHR and Roche Diagnostics. None declared by other authors.

Published June 2023
DOI: 10.3310/NNZF1037

Scientific summary

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Efficacy and Mechanism Evaluation 2023; Vol. 10: No. 1
DOI: 10.3310/NNZF1037

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Scientific summary

Background

Tubal ectopic pregnancy (EP) can cause significant morbidity or even death. Current treatment is with methotrexate (MTX) or surgery. However, MTX treatment can fail in approximately 30% of women. Preclinical studies have shown that tubal implantation sites express high levels of epidermal growth factor receptor (EGFR) and that gefitinib (an EGFR antagonist) augments MTX-induced regression of pregnancy-like tissue. Clinical evidence from uncontrolled phase I and II trials has raised the possibility that a combination of MTX and gefitinib could be a more effective medical treatment than MTX alone to treat stable tubal EP.

Objectives

To test the hypothesis, a combination of gefitinib with MTX can increase resolution of stable tubal EP without the need for surgery, compared with MTX alone.

Design

A randomised, double-blind, placebo-controlled, multicentre, superiority trial.

Setting

This trial took place in 50 hospitals in the UK.

Participants

A target of 328 women with a stable, tubal EP.

Intervention

Participants were randomly assigned in a 1:1 ratio to receive either gefitinib and MTX or matched placebo and MTX with the use of minimisation to balance trial-group assignments according to baseline human chorionic gonadotropin levels (<1500 IU/l, ≥1500 to <2500 IU/l, ≥2500 IU/l), body mass index (<25 kg/m^2, ≥25 kg/m^2), ectopic size (<2 cm, ≥2 cm) and by hospital centre.

Main outcome measures

The primary outcome, analysed by intention to treat, was surgical intervention for removal of the EP. Secondary outcomes included additional MTX doses, time to resolution of EP, number of treatment-associated hospital visits until resolution or scheduled/emergency surgery, safety/tolerability, acceptability of treatment, return to menses, adverse events and serious adverse events.

Results

Between 2 November 2016 and 6 October 2021, 328 women were randomly allocated to MTX and gefitinib (*n* = 165) or MTX and placebo (*n* = 163). Three women in the placebo group withdrew. Surgical intervention occurred in 30% (50/165) of the gefitinib group and in 29% (47/160) of the placebo group [adjusted risk ratio 1.15, 95% confidence interval (CI) 0.85 to 1.58; adjusted risk difference −0.01, 95% CI −0.10 to 0.09; *p* = 0.37]. Without surgical intervention, median time to resolution was 28.0 days in the gefitinib group and 28.0 days in the placebo group (subdistribution hazard ratio 1.03, 95% CI 0.75 to 1.40). The need for additional MTX doses and serious adverse events were similar in both groups. The proportion of women who experienced diarrhoea (75/160 vs. 39/161) and rash (97/159 vs. 36/160) were more common in the MTX and gefitinib group compared with the MTX and placebo group.

Conclusions

In women with a tubal EP, adding oral gefitinib to parental MTX does not offer clinical benefit over MTX alone and increases reported symptoms.

Limitations

We were unable to investigate how different gefitinib doses or modes of delivery would impact on the results.

Future work

Questions that remain unaddressed relate to the use of combination treatment for other extrauterine and uterine EP, such as caesarean scar pregnancies, or in the management of choriocarcinoma.

Trial registration

Current Controlled Trials ISRCTN 67795930 and EudraCT 2015-005013-76.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council (MRC) and National Institute for Health and Care Research partnership. Gefitinib and placebo were supplied by Astra Zeneca. This will be published in full in *Efficacy and Mechanistic Evaluation*; Vol. 10, No. 1. See the NIHR Journals Library website for further project information.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

Efficacy and Mechanism Evaluation (EME) was launched in 2014 and is indexed by Europe PMC, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and NCBI Bookshelf.

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 14/150/03. The contractual start date was in April 2016. The final report began editorial review in May 2022 and was accepted for publication in September 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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