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1. Introduction

Numerous studies have associated maternal tobacco exposure with adverse pregnancy, neonatal and infantile outcomes including spontaneous abortion, congenital malformation (cleft lip and/or palate), premature delivery and intrauterine growth restriction, sudden infant death syndrome, childhood cancer, neurobehavioural/neurodevelopmental problems, asthma, obesity, and diabetes.[1-9] As such promotion of tobacco use cessation for those patients who are either planning a pregnancy, or who have inadvertently become pregnant is commonplace.

A recently published Cochrane review reaffirmed the importance of a combination of interventional strategies which improve the efficacy of tobacco use cessation[10], particularly the combination of behavioural support strategies with the prescription of tobacco use cessation aids including nicotine replacement therapy (NRT), bupropion or varenicline.

Varenicline (ATC code N07BA03) is a partial agonist of the α2β4 nicotinic acetylcholine receptor. In non-pregnant patients, varenicline has been shown to be more effective in aiding tobacco use cessation in comparison with both placebo and other tobacco use cessation therapies (NRT and bupropion). There are however very limited data available concerning the maternal use of varenicline during pregnancy, and the effects which this may have on the exposed fetus. To date information is available from one small prospective cohort study[11] (varenicline exposed n=24) published in an abstract, and one retrospective case series[12] (varenicline exposed n=23). These data are considered too limited to provide any sufficient conclusions regarding the risks of varenicline use during pregnancy

In order to provide pregnant women and women of childbearing potential with evidence-based information concerning the risks and benefits of varenicline use in pregnancy, additional data is required.

2. Study Aims

The aim of this study is to assess some of the fetal risks posed by maternal use of varenicline during pregnancy.

The primary objectives are to evaluate the occurrence of congenital malformation (both major and minor) following varenicline exposure in the first trimester, spontaneous abortion (defined as spontaneous fetal loss prior to 24 weeks gestation) or intrauterine death/fetal demise or stillbirth (defined as fetal loss from 24 weeks gestation onwards). As a secondary objective we aim to perform an evaluation of the incidence of elective termination, including an assessment of the gestational age at which this occurred, and where sufficient details are available, the indication for elective termination.

3. Study Design and Analysis Methods

We aim to undertake a prospective observational cohort study utilising one matched comparison group. Only pregnancies which have been prospectively

reported to a collaborating TIS/pharmacovigilance centre are eligible for enrolment in this study. For the purpose of this study prospective pregnancies are defined as those which were reported to the TIS whilst the pregnancy was ongoing prior to 24 weeks gestation. Please note that for assessment of the congenital malformation risk we shall only include in the analysis such prospective cases where the course of pregnancy was uneventful prior to case identification, and where there was no pathology detected by prenatal diagnostics including ultrasound scan prior to case identification. For purposes of the study all prospective cases (including those with prenatal pathology identified) which meet the criteria of the following three groups should be provided:

> ***1. Exposed group*** – Cases of varenicline exposure at any time during pregnancy which do not meet the exclusion criteria
>
> ***2. Non-teratogen exposed control group*** – Cases which do not meet the exclusion criteria below and which were not exposed to varenicline at any time during pregnancy
>
> ***3. Tobacco use cessation therapy exposed comparator group*** – Cases of bupropion or nicotine replacement therapy exposure at any time during pregnancy where varenicline exposure was not documented and which do not meet the exclusion criteria below

Exclusion criteria: Exposed and control cases should be excluded where maternal use of acitretin, any cytotoxic or antiepileptic medication, isotretinoin, methotrexate, mycophenolate mofetil, thalidomide, warfarin or coumarin derivatives has been documented at any time in pregnancy. Similarly both exposed and control cases should be excluded where angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker use has been documented in either the second or third trimester.

Notes regarding control and comparator groups: Each participating TIS should provide three non-teratogen exposed control cases, and up to three tobacco use cessation therapy exposed comparator cases for each varenicline exposed case. All control/comparator cases should be selected randomly (outcome blinded at selection) and matched to an exposed case by year of TIS contact.

The above data will be provided to UKTIS who are coordinating the study and who will undertake the analysis. It is requested that study data is submitted via the excel workbook ("Varenicline Study Data") which consists of three separate sheets, one for each group of patients (exposed and the two control groups). Birth defects will be categorised as either major or minor using the EUROCAT malformation coding guide.[13] This shall be performed by at least two independent specialists blinded to exposure status.

Comparisons of incidence rates for the primary and secondary objective measures of this study shall be made between the exposed cohort and the matched control group using appropriate statistical techniques which shall be determined by the sample size. Multivariate explorations may be required to account for the possible role of important confounding factors, and if so shall be performed using logistic regression analysis. The cumulative hazard method is likely to be required for the assessment of spontaneous abortion, elective termination and live birth rate data.

4. Collaboration and Authorship

Any TIS with ENTIS affiliation that is able to provide cases of exposure and matched controls is invited to participate in this collaborative study. There is no minimum number of exposed pregnancies which any one TIS is required to provide.

All participating collaborators who review and provide comments on the research findings manuscript will be named as co-authors on this subsequent publication. Participating collaborators who do not wish to review the manuscript will be listed in the publication acknowledgments. First and last authors will be from the centre coordinating the study (UKTIS).

5. Study Timeline

Task	***Time***
Estimate of ENTIS exposure cases	June 2013
Study design/draft protocol	October 2013
Submission of protocol to the ENTIS scientific committee	November 2013
Confirmation of TIS participation & call for cases	May 2014
Deadline for submission of cases	End of July 2014
Data analysis & draft publication	August 2014
Circulation of draft publication to co-authors for comment	September 2014
Submission to a peer-reviewed journal	October 2014

Please note, details in this timeline may be subject to change

6. Ethical Considerations

This study only requires the provision of de-identified data. All data provided to UKTIS will be stored securely on an NHS server requiring password authorisation to access. Raw data provided to UKTIS will not be transferred to any other organisation.

Each participating TIS is responsible for ensuring that provision of information to this collaborative study is undertaken in accordance with their own local

data protection procedures, and without breaching agreements made under any participant informed consent process.

7. References

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