PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PRIMARY AND REPEAT SURGICAL TREATMENT FOR FEMALE PELVIC ORGAN PROLAPSE AND INCONTINENCE IN PAROUS WOMEN IN UK: A REGISTER LINKAGE STUDY.
AUTHORS	Abdel-fattah, Mohamed (contact); Familusi, Akinbowale; Fielding, Shona; Ford, John; Bhattacharya, Sohinee

VERSION 1 - REVIEW

REVIEWER	Dr Ian N Ramsay Consultant Urogynaecologist Forth Valley Health Board UK
REVIEW RETURNED	17/06/2011

THE STUDY	None
RESULTS & CONCLUSIONS	Non
REPORTING & ETHICS	None
GENERAL COMMENTS	I think this is an excellent and very important paper. The authors are to be congratulated

REVIEWER	Wael Agur, MB BCh MSc MD MRCOG Consultant Urogynaecologist Honorary Clinical Senior Lecturer, University of Glasgow Obstetrics & Gynaecology Department NHS Ayrshire & Arran Scotland, UK Competing interest: Working on research proposal with one of the authors of this article.
REVIEW RETURNED	21/06/2011

THE STUDY	None
RESULTS & CONCLUSIONS	None
REPORTING & ETHICS	None
GENERAL COMMENTS	This is a very valuable and original study in a UK population. Here are some comments: 1- Such statistical analysis may have involved looking at the data several times. This, in general, may produce false statistical significance known as the Bonferroni effect. Authors may wish to comment on this.

	2- Page 14 line 40. Authors seem to suggest that MUS has lower risk of reoperation compared to abdominal retropubic operations. There appear to be a 'temporal' bias here as the former is a relatively more recent operation and the former is older and was more likely to be 'tested' by time with apparantly more failures. 3- Page 18 line 15. Suggest remove the exclamation mark. 4- Page 18 line 18. Would a variation in the incidence of forceps deliveries (if any) explain the difference in results between the current study and the Australian one? 5- Page 17 line 39. European instead of Europe.

REVIEWER	Jan van der Meulen Professor of Clinical Epidemiology London School of Hygiene and Tropical Medicine United Kingdom
REVIEW RETURNED	29/06/2011

THE STUDY	The overall study design is inappropriate for a number of reasons. First, the design doesn't take into account that a number of women will have got lost to follow-up as they will have left Scotland. These women should have been treated as censored observations. Second, follow-up is from birth but the risk factors are "active" from different points in a woman's life. It is unclear how this has been taken into account in the analysis. For example, did the modelling also assume that the risk factor that a woman had two to four children increased the risk of surgical treatment before she had them? Third, the risk factors are defined in such a way that some are partially "nested" within others (e.g. "number of deliveries", "time between deliveries", "mode of delivery"). It is more likely for a women to have had at least one instrumental delivery if she had more children. The interpretation of the risk factors in the multivariable model is therefore problematic. A fourth issue is the representativeness of this group of women. The use of surgery for prolapse and incontinence is changing and the results described in this paper reflect a rather long period of practice. To what extent are these results relevant for today? Furthermore, given that it's likely that there are geographical variations in the use of surgery, it is inappropriate to refer to refer to the study population as a cohort of UK women. Fifth, proportional hazard regression modelling was used. I would have liked to see some exploration to what extent the proportional hazard assumption was met. Some time dependency in the effect of the risk factors seems very likely. The cumulative hazard to capture lifetime risk is presented as a percentage which is incorrect. The authors could have expressed it as the cumulative probability: F(t)= 1 - exp(- cum hazard(t)). The writing could have been better. The punctuation needs to be improved (with a reduced use of ";").

RESULTS & CONCLUSIONS	See above
REPORTING & ETHICS	None
GENERAL COMMENTS	None

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr Ian N Ramsay
Consultant Urogynaecologist
Forth Valley Health Board
UK

I think this is an excellent and very important paper. The authors are to be congratulated
We thank the reviewer for his encouraging comments and feel that no response is necessary.

Reviewer: Wael Agur, MB BCh MSc MD MRCOG
Consultant Urogynaecologist Honorary Clinical Senior Lecturer, University of Glasgow
Obstetrics & Gynaecology Department
NHS Ayrshire & Arran
Scotland, UK

Competing interest: Working on research proposal with one of the authors of this article.

This is a very valuable and original study in a UK population. Here are some comments:

1- Such statistical analysis may have involved looking at the data several times. This, in general, may produce false statistical significance known as the Bonferroni effect. Authors may wish to comment on this.

We thank the reviewer for raising a valid point however since we pre-specified a priori that we were going to analyse all operations and then each type (UI, POP, RP-FI) separately we do not feel an adjustment is statistically required.

2- Page 14 line 40. Authors seem to suggest that MUS has lower risk of reoperation compared to abdominal retropubic operations. There appear to be a 'temporal' bias here as the former is a relatively more recent operation and the former is older and was more likely to be 'tested' by time with apparently more failures.

The reviewer raises a good point as TVT has not been around for as long as retropubic colposuspension however in page 7 first paragraph we clarified that the median (IQR) time between index and repeat UI surgery was 2.80 (0.94, 8.07) years. The median time interval for repeat UI surgery varied according to the type of index operation; 0.93 years (0.27, 2.49) for mid-urethral slings compared to 4.20 years (1.73, 8.38) for retropubic abdominal procedures. Knowing that MUS have been performed since 1996 then it is reassuring that repeat surgery following MUS is likely to have been captured within the time frame of this study. This has now been clarified in Discussion section – (prior to strengths and limitations).

3- Page 17 line 15. Suggest remove the exclamation mark. We thank the reviewer for pointing this out and this has now been removed.

4- Page 17 line 18. Would a variation in the incidence of forceps deliveries (if any) explain the difference in results between the current study and the Australian one? Smith et al looked at age related prevalence and did not address other risk factors such as Forceps delivery so we would be unable to comment.

5- Page 17 line 39. European instead of Europe. Changed to European Countries

Reviewer: Jan van der Meulen
Professor of Clinical Epidemiology
London School of Hygiene and Tropical Medicine
United Kingdom

The overall study design is inappropriate for a number of reasons.

First, the design doesn't take into account that a number of women will have got lost to follow-up as they will have left Scotland. These women should have been treated as censored observations.

The study used data-linkage so by nature of the way it was undertaken, those who were not linked were not included and thus in a sense lost to follow up. We managed to link 73% of women eligible for our research question.
We recognise the potential for bias due to these exclusions and we have discussed this fully in the Discussion section under limitations. There are a number of possible reasons why health events for these women may not have been found. The first is a failure to match the health records for these women with the data on the maternity database. The second is that these women are alive and in good health. The third is that they are alive and have moved away from Scotland and, if so, their hospital admissions would not be recorded by the ISD in Scotland. The rates of exclusion in this study due to health records not being found were not significantly different between the different exposure groups, indicating that any bias is likely to be small.

Second, follow-up is from birth but the risk factors are "active" from different points in a woman's life. It is unclear how this has been taken into account in the analysis.
- For example, did the modelling also assume that the risk factor that a woman had two to four children increased the risk of surgical treatment before she had them?
- For example, did the modelling also assume that the risk factor that a woman had two to four children increased the risk of surgical treatment before she had them?'

We thank the reviewer for raising this issue. The initial lifetime risk analysis uses time from birth but thereafter the models use time from 1st delivery (for Tables 2-4) which is the start time of exposure. This was not made clear in the methods section before and has now been amended in the Statistical Analysis section to read "Unadjusted Cox regression models were carried out for various risk factors mentioned above; the adjusted models were then implemented to identify independent risk factors for primary surgery for UI, POP or RP-FI. Time for these models was calculated from date of first delivery to date of operation (or censored appropriately)."

Third, the risk factors are defined in such a way that some are partially "nested" within others (e.g. "number of deliveries", "time between deliveries", "mode of delivery"). It is more likely for a woman to have had at least one instrumental delivery if she had more children. The interpretation of the risk factors in the multivariable model is therefore problematic.

Thanks for raising this point – however these are "related" but not "dependant/ nested factors" i.e. they are unlikely to resemble the "weight and BMI model" often described to show how dependent risk factors should not be included in multivariate models.

Although mathematically sound yet not clinically true that if women had more than one child she is more likely to have a forceps delivery or CS – in-fact the most likely instrumental delivery/ CS would be in the first one. Inter-pregnancy intervals have never been shown to affect mode of

delivery.

Therefore we believe that multivariate modelling is the appropriate model to be used in this part of the analysis. The same model was used in all epidemiological studies addressing the risk factors for POP/ UI surgery.

A fourth issue is the representativeness of this group of women. The use of surgery for prolapse and incontinence is changing and the results described in this paper reflect a rather long period of practice. To what extent are these results relevant for today? Furthermore, given that it's likely that there are geographical variations in the use of surgery, it is inappropriate to refer to refer to the study population as a cohort of UK women.

We accept that the study reflects a long period of practice, but believe that including time in our models would take account of that.
With regard to geographical variation, we do not think that there is any threat to the external validity of the study. The main reasons are:
- There is only one Royal college for Gynaecologists in UK; this RCOG issues clinical guidelines that are followed by the vast majority of gynaecologists throughout UK and therefore any difference in surgical practice is likely to be minimal
- Data from British society of urogynaecology on surgical procedures for UI/ POP did not show any significant geographical variation in practice.
- Previous MRC study on epidemiology of UI in UK population has been done entirely within Leicester and has been accepted widely as true reflection of UK population
- Absolute representation of UK practice is impossible without studying the whole UK population.
- In the first paragraph of the discussion section we described the population for this study and why we believe it can be representative for UK.

Fifth, proportional hazard regression modelling was used. I would have liked to see some exploration to what extent the proportional hazard assumption was met. Some time dependency in the effect of the risk factors seems very likely.

Thank you for pointing this out. Plots of log survival time versus log (-log survivor function) were produced for each explanatory variable in each model and each showed parallel curves indicating the proportional hazards assumption was met. The text has been amended with the following sentence "The proportional hazards assumption for each covariate in each model was assessed using the log survival time versus the negative log of the survivor distribution function. Each covariate showed parallel curves indicating the proportional hazards assumption was met."

The cumulative hazard to capture lifetime risk is presented as a percentage which is incorrect. The authors could have expressed it as the cumulative probability: F(t)= 1 - exp(- cum hazard(t)).

Many Thnaks for this very valid point: using F(t) formula for the lifetime distribution function the probability of surgery by age 80 is:
Any pelvic floor surgery: 0.115
SUI: p = 0.035
POP: p = 0.091
RAP/FI = 0.007
However % was used to make clinical interpretation easier and also for comparability with previous papers.

We have now amended the first paragraph in the results section accordingly and it now reads:
Figure 2 shows the cumulative hazard function for women to undergo a pelvic floor surgery with age. Using this the lifetime distribution function can be calculated and we find that the probability of a women undergoing pelvic floor surgery by age 80 is 0.115. Further analysis showed that the probability of undergoing UI surgery was 0.036, a POP repair was 0.091 and a RP-FI operation was

0.007. In other words; the lifetime risk for women to undergo a pelvic floor surgery, by age 80, is 12.2%, while the lifetime risk of undergoing UI operation is 3.6%, POP repair is 9.5% and RP-FI operation is 0.7%.

The writing could have been better. The punctuation needs to be improved (with a reduced use of ";").
The manuscript has now been thoroughly proof read and corrected by an independent native English speaker.

VERSION 2 - REVIEW

REVIEWER	Wael Agur Consultant Urogynaecologist, Ayrshire, Scotland Competing interest: working within the same research network with one of the manuscript authors.
REVIEW RETURNED	05/09/2011

Reviewer made no further comments.