PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The relationship between a uterine fibroid diagnosis and the risk of adverse obstetrical outcomes, a cohort study.
AUTHORS	karlsen, kamilla; Schiøler Kesmodel, Ulrik; Mogensen, Ole; Humaidan, Peter; Ravn, Pernille

VERSION 1 - REVIEW

REVIEWER	Ciavattini Andrea, MD Institute of Obstetrics and Gynecology Università Politecnica delle Marche, Ancona - Italy
REVIEW RETURNED	07-Jul-2019

GENERAL COMMENTS	I think this is an interesting large cohort study, which answers the question of whether uterine fibromatosis is a risk factor for preterm birth and deserves to be published with revision. Infact, the study has some limitations that the authors have partially highlighted but should try to improve and better discuss. In particular, the differences in terms of age, proportions of multiple pregnancies and fertility treatments are significant and they could make the interpretation of the results more difficult. Another important limitation is the low prevalence of uterine fibroids and the small number of events. In particular, the groups 2 and 4 that would best characterize the study population are the least numerous. I think the results should be better presented, especially in the preterm birth section. It is unclear what is the proportion of events in groups 2 and 4, compared to the stratification by fertility and by multiple pregnancies - it must be declared.

REVIEWER	ANDREA TINELLI Department of Obstetrics and Gynecology, Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Vito Fazzi Hospital, P.zza Muratore, Lecce, Italy; Laboratory of Human Physiology, Phystech BioMed School, Faculty of Biological & Medical Physics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia.
REVIEW RETURNED	14-Jul-2019

GENERAL COMMENTS	The manuscript is very well methodologically complete; the authors demonstrate considerable competence in the design and conduct of the study. The authors have carried out a complex work

	of evaluation and registration of the codes for data research and their analysis (including code biases in many Hospitals). The reduced number of patients with fibroids diagnosed and events in pregnancy, in 92,696 recorded pregnancies (retrospective analysis), reduce the effectiveness of conclusion that the association between uterine fibroid diagnosis and the risk of preterm birth in general and extreme preterm birth, in particular. But the great work done by the authors must be rewarded, in my opinion.

REVIEWER	Girault Aude Port Royal Maternity unit, Paris, France INSERM U1153
REVIEW RETURNED	18-Jul-2019

GENERAL COMMENTS	This retrospective study has multiple objectives but does not address one clearly. The methods, the results and the conclusion do not answer the objective.The article does not add to existing knowledge and the results are over-interperted.

REVIEWER	Shannon Laughlin-Tommaso Mayo Clinic, Rochester MN, USA
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	I appreciate the work that went into this manuscript as this is a difficult topic to address and as noted with the small event sizes, it requires a very large cohort. The findings are mainly consistent across gestational age and similar to prior findings. Overall, this is a well-written article with important findings. I have a few comments to address: 1. Can you describe the race/ethnicity of the cohort? 2. The limitations state that the codes could not be validated but have been validated before. I suggest going into more detail as this is a key factor in the paper. The prevalence noted of fibroid codes is about 1% which seems very low based on the average age of 30 years. How significant does a fibroid have to be to get a fibroid diagnosis code? Also, what is the validity of the codes for pathological tissue removed and how do you differentiate from polyps? 3. What kind of fertility treatments are included? it seems that this is very high in the fibroid code before pregnancy group and fibroid code with operation before pregnancy groups. I'm wondering if the fertility workup actually drives the fibroid diagnosis rather than the reverse. If this is true, then the fertility workup may be more related to the adverse outcomes than the fibroids alone. Do you think this is adequately addressed by the stratification or could there be residual confounding? what are the sample sizes in those categories? 4. I am not sure that the evidence supports the paragraph in discussion to remove fibroids before pregnancy. There is still a higher odds ratio of preterm birth for women who had fibroid surgery prior to pregnancy and it results in more cesarean sections which is where the higher percentage of uterine ruptures came from. Certainly it is reassuring that there were no uterine

	ruptures among the laparoscopic myomectomy patients but as mentioned, this was done by a very select group of surgeons. I think a deeper discussion into the results as well as the unknowns (fibroid size, location, etc) that can contribute to the decisions on surgery is warranted in that paragraph.

VERSION 1 – AUTHOR RESPONSE

Editorial Requests:	Authors comments:	Changes in the manuscript (Page):
Reviewer: 1 I think this is an interesting large cohort study, which answers the question of whether uterine fibromatosis is a risk factor for preterm birth and deserves to be published with revision. In fact, the study has some limitations that the authors have partially highlighted but should try to improve and better discuss.		
In particular, the differences in terms of age, proportions of multiple pregnancies and fertility treatments are significant and they could make the interpretation of the results more difficult.	Due to the differences in parity, and fertility treatment we made the stratified analyses and found the association persisted through all analyses.	
Another important limitation is the low prevalence of uterine fibroids and the small number of events. In particular, the groups 2 and 4 that would best characterize the study population are the least numerous.		Page 18 Our results cannot be used as an indicator of prevalence or incidence in the general population, but it is important to notice, that data are fully valid for analyses of associations. (Nohr, 2006)
I think the results should be better presented, especially in the preterm birth section. It is unclear what is the proportion of events in groups 2 and 4, compared to the stratification by fertility and by multiple pregnancies - it must be declared.	Group numbers have been added in the result section to present the results more clearly. The numbers of events have been added in the tables.	Table 1 Table 2 Table 3 Result section: groups have been added.
Reviewer: 2		

The manuscript is very well methodologically complete; the authors demonstrate considerable competence in the design and conduct of the study. The authors have carried out a complex work of evaluation and registration of the codes for data research and their analysis (including code biases in many Hospitals). The reduced number of patients with fibroids diagnosed and events in pregnancy, in 92,696 recorded pregnancies (retrospective analysis), reduce the effectiveness of conclusion that the association between uterine fibroid diagnosis and the risk of preterm birth in general and extreme preterm birth, in particular. But the great work done by the authors must be rewarded, in my opinion.	Thank you for the comment. There are no questions to answer or comments to address.	
Reviewer: 3		
This retrospective study has multiple objectives but does not address one clearly. The methods, the results and the conclusion do not answer the objective. The article does not add to existing knowledge and the results are over-interperted.	Thank you for the comment. There are no questions to answer or comments to address.	
Reviewer: 4 I appreciate the work that went into this manuscript as this is a difficult topic to address and as noted with the small event sizes, it requires a very large cohort. The findings are mainly consistent across gestational age and similar to prior findings. Overall, this is a well-written article with important findings.		

I have a few comments to address:		
1. Can you describe the race/ethnicity of the cohort?	The DNBC mainly consist of white women with middle or high social status (Jacobsen TN, 2010). Uterine fibroids have different pathophysiology for Afro-American and Caucasian woman (Parrazini, 1988), and our results can only reasonably be applied to the Scandinavian population.	The sentence has been added. Page 19
2. The limitations state that the codes could not be validated but have been validated before. I suggest going into more detail as this is a key factor in the paper. The prevalence noted of fibroid codes is about 1% which seems very low based on the average age of 30 years. How significant does a fibroid have to be to get a fibroid diagnosis code? Also, what is the validity of the codes for pathological tissue removed and how do you differentiate from polyps?	Our exposure registration was based on clinical diagnosis coding, which may be incorrect or lacking due to various work-related distractions and a variable individual interpretation of clinical cases, leading to exposure misclassification. The low prevalence of uterine fibroids in our study population is likely to be a result of underreporting. A potential bias will lead towards exposed women being categorized as unexposed, and hence attenuation of the association between exposure (uterine fibroids) and outcomes [32]. Since the potential underreporting is independent of the outcome due to the prospective nature of data collection in a cohort study, a potential misclassification could lead to non-differential information bias. Further, we found that some women had an operation code, but no diagnosis code, substantiating the hypothesis of risk of exposure misclassification. In Denmark, operation codes are more closely connected to hospital budgets than clinical diagnosis codes. A detailed validation of	The paragraph has been changed. Page 18-19

	data would most likely have solved discrepancies, but we did not have the possibility to validate the data from the DNPR, and we relied on previous studies, showing that reproductive gynecological coding in the DNPR is generally valid and suitable for clinical quality control [33]. Risk of misclassification related to the operation codes could have been cleared by post-operative histological diagnoses. As this data was not available, we minimized the risk by ensuring that none of the women in our exposure group had a diagnoses code for other uterine pathologies such as adenomyosis or polyps.	
3. a. What kind of fertility treatments are included? b. It seems that this is very high in the fibroid code before pregnancy group and fibroid code with operation before pregnancy groups. I'm wondering if the fertility workup actually drives the fibroid diagnosis rather than the reverse. If this is true, then the fertility workup may be more related to the adverse outcomes than the fibroids alone. Do you think this is adequately addressed by the stratification or could there be residual confounding? c. what are the sample sizes in those categories?	a. We included women in fertility treatment regardless of mode of ART. b. We used the diagnosis codes as measure of the presence of clinically relevant uterine fibroids, but we do not know the reason for the examination leading to the diagnosis. Typically, women would have an ultrasound examination because of relevant symptoms, and a uterine fibroid would then be diagnosed. One of the symptoms leading to examination could be infertility. It is probable that women diagnosed with infertility are diagnosed with a uterine fibroid at an earlier stage compared to women without infertility. The possible influence on our outcomes has been addressed by the stratification since fertility treatment has not been identified as a potential confounder.	a. Page 5 (regardless of mode of ART) b. The DAG's have been added as supplementary figures.  dags_preterm.svg c. Table 3

	(Directed Acyclic Graph) c. The sample size has been added in Table 3.	
4. I am not sure that the evidence supports the paragraph in discussion to remove fibroids before pregnancy. There is still a higher odds ratio of preterm birth for women who had fibroid surgery prior to pregnancy and it results in more cesarean sections which is where the higher percentage of uterine ruptures came from. Certainly it is reassuring that there were no uterine ruptures among the laparoscopic myomectomy patients but as mentioned, this was done by a very select group of surgeons. I think a deeper discussion into the results as well as the unknowns (fibroid size, location, etc) that can contribute to the decisions on surgery is warranted in that paragraph.	We agree that this paragraph should be changed. '' In the present study, the risk of preterm birth decreased whereas the risk of CS increased after myomectomy compared to the risks among women with untreated uterine fibroids. Our results contribute to the overall discussion about treatment prior to pregnancy, however, more studies are required.''	Page 18

Parazzini F, La Vecchia C, Negri E, et al. Epidemiologic characteristics of women with uterine fibroids: a case-control study. Obstet Gynecol. 1988;72(6):853-857.

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Kesmodel US. Information bias in epidemiological studies with a special focus on obstetrics and gynecology. Acta obstetricia et gynecologica Scandinavica. 2018;97(4):417-423.

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