Maternal health and pregnancy outcome in Marfan syndrome: A register-based study

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May 12, 2020

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Abstract

Objective In Marfan syndrome, pregnancy is considered as high-risk due to connective tissue insufficiency and increased risk of aortic dissection. The objective was to demonstrate the consequences on maternal health, including aortic events in women with Marfan syndrome. Furthermore, to investigate outcome in undiagnosed with Marfan syndrome at the time of pregnancy. Design Information on aortic operations, aortic dissections, and pregnancy related outcome, from a national cohort of women with Marfan syndrome (n=195) were compared to an age-matched background population (n=19,500). The women with Marfan syndrome were divided according to whether the Marfan syndrome diagnosis was known at the time of pregnancy or not. Setting National health care registers Methods Main outcomes measures Registered events from the National Patient Registry in Denmark Results Significantly fewer women with Marfan syndrome gave birth, compared to the background population. In Marfan syndrome, complications related to cervix were increased (HR: 19.8 (95% CI: 2.2-177.5)) and the number of caesarean sections was higher (HR: 2.09 (95% CI: 1.41-3.08)). No women with known Marfan syndrome had a pregnancy related aortic dissection and the consequences of pregnancy and delivery on future aortic events seemed limited. Among undiagnosed women with Marfan syndrome there were more foetal deaths and all delivery-related dissections came from this subgroup. Conclusion The surveillance program for pregnant women with Marfan syndrome seems appropriate and only women with undiagnosed Marfan syndrome experienced a pregnancy-related aortic dissection. However, there is still an increased risk of complications during pregnancy, but the overall outcome data are quite reassuring.

Tweetable abstract

In Marfan syndrome, undiagnosed women have pregnancy-related aortic disease. Well controlled Marfan syndrome women do not.

Introduction

Marfan Syndrome (MFS) is an inherited disorder of connective tissue with multisystem involvement[1] and a reported prevalence of 6.5 per 100.000.[2] Mutations in FBN1 are found in more than 90% of MFS cases.[3] FBN1 encodes the extracellular matrix protein fibrillin-1 which contributes to the integrity and function of connective tissue.[4] The inheritance is autosomal dominant with a high penetrance and great clinical variability.[5]

MFS is associated with increased morbidity and mortality primarily due to progressive aortic dilatation, dissection and ruptures.[6, 7]

Pregnancy with the physiological cardiac stress (increased stroke volume, cardiac output and heart rate) [8, 9] remains a controversial topic in MFS. Several studies regarding pregnancy related cardiovascular complications in MFS have been conducted and data collated in a systemic review from 2017.[10] In this study, aortic dissection rate was 7.9% and the mortality rate 1.2% with a trend towards dissection occurring at pre-pregnancy aortic root diameter above 40 mm (p=0.0504). Until a recent UK multicentre study reported an aortic dissection of 1.9% in 221 live births,[11] most studies have been rather small and mainly case reports indicating possible publication bias.

Besides cardiovascular complications, other birth-related complications may affect women with Marfan syndrome. However, an overall description of such pregnancy-related complications still is not clear. Moreover, most studies are from tertiary centres including only diagnosed Marfan syndrome women but no controls. A prominent problem related to Marfan syndrome care is the frequent occurrence of late diagnosis, sometimes during pregnancy, or outright non-diagnosis, which complicates the precise description of obstetric complications.

We hypothesized that morbidity in pregnancy is significantly increased in women with Marfan syndrome, particularly due to cardiac complications, to uterine, cervical and vaginal complications, as well as due to preeclampsia and pre-term birth. Thus, our purpose was to estimate pregnancy outcome, the overall morbidity as well as the risk of aortic surgery and aortic dissection in relation to pregnancy in a nationwide MFS cohort, where we included diagnosed as well as pre-pregnancy in undiagnosed women with Marfan syndrome compared to age matched controls.

Population

In our previous study[2] we identified all patients registered with Marfan syndrome in Denmark in 1977 to 2014; in total 412 patients, whereof 197 were women (183 above 13 years at end of study). In brief, we verified the Marfan diagnosis after manual evaluation of their medical records and application of the Ghent-II criteria, and listed their civil registration number, given to all Danes at birth[2].

Methods

For registrations to all pregnancy related events, we retrieved information from Statistics Denmark. Statistics Denmark holds copies of several national registries including the National Patient Registry, which registers all in- and outpatient contacts in Denmark, including procedural codes and dates of contact, using International Classification of Diseases (ICD), 8^{th} or 10^{th} edition. Statistics Denmark utilized the civil registration number and identified our Marfan syndrome women in the registries and ensured identification of 100 age matched (year of birth) female controls as well as accurate linkage of data. For two Marfan syndrome women, no controls were given, thus, data were obtained for 195 Marfan syndrome women and their 19,500 controls, matched on age and region.

Statistics Denmark holds no clinical data, for instance on aortic size and blood pressure.

Main outcome measures

We defined the overall term "Maternal health" and divided all relevant International Classification of Diseases (ICD) codes into four main groups, namely "Pregnancy", "Delivery", "Pregnancy loss" and "Death", and further into subgroups (Figure 1/ Table S1). Supplementary table 1 shows how we defined the main groups and subgroups using the ICD 8^{th} and 10^{th} edition. Unless clearly stated elsewise, the results are only given in those Marfan syndrome women with at least one pregnancy registration (n=91) and in their matched controls who all had at least one pregnancy registration (n=6,801). For each registration within the main groups as well as the subgroups, we divided the women with Marfan syndrome into two categories according to whether the Marfan syndrome diagnosis was known at the time of registration or not. Thus, a woman with Marfan syndrome could have multiple registrations related to maternal health before being diagnosed

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and multiple registrations after being diagnosed with Marfan syndrome. For all main groups and subgroup registrations, we only utilized the first registration in each group, regardless of time of diagnosis.

To report the total number of new-borns, we excluded all registrations less than 270 days after a delivery registration, as each delivery could have multiple delivery related registrations within few weeks' intervals.

In order to study the relationship between maternal health and aortic disease, we defined aortic dissection and aortic operation as previously described.[7] In brief, aortic disease is either a registration of an aortic dissection, defined as a registration within the ICD system with a diagnosis of aortic dissection, or a registration of an aortic operation, defined as a registration in the Nomesco Classification of Surgical Procedure (NCSP) related to aorta (for details see Table S2).

The women with Marfan syndrome were diagnosed from 1977 to 2014 and the registrations of maternal health were from 1977 to 2017. Data were accessed using a secure remote access to Statistics Denmark. In order to avoid any possibility of personal identification of cases, Statistics Denmark prohibits specification of the exact number of cases with a given condition if less than three, and we therefore report these as "<3".

Statistics

Basic epidemiological data are given using median and range. Time to first registration in all main groups and subgroups was analysed using stratified Cox regression, where each Marfan syndrome woman and her matched controls constituting one stratum. For the overall analyses, time at risk started at birth of the Marfan syndrome woman, and ended at the date of relevant registration, date of death, end of study, or emigration, whichever came first. Time at risk *before diagnosis*started at birth of the Marfan syndrome woman and ended at the date of relevant registration, date of the Marfan diagnosis, or emigration, whichever came first. Time at risk *after diagnosis* started at date of diagnosis and ended at the date of relevant registration, end of study, date of death or emigration, whichever came first. Stata 15.1 for Windows (StataCorp LP, College Station, TX, USA) was used for all calculations.

Results

In total, 91 out of the 195 Danish women with Marfan syndrome (47%) and 10,188 out of their 19,500 (52%) controls, had at least one registration related to "Maternal health" and thus a pregnancy (Table 1), corresponding to a significantly decreased hazard ratio (HR) of 0.79 (95% CI: 0.64-0.97). Seventy-four women with Marfan syndrome (out of the 91) gave birth to 142 children, and their 6,185 controls gave birth to 12,088 children.

Fifty women with Marfan syndrome (55 %) were not diagnosed with Marfan syndrome at the time of their first registration related to "Maternal health" and 40 of these had one or more registrations of delivery and thus gave birth to one or more children.

Maternal health

Combined, "Maternal health" was significantly decreased in women with Marfan syndrome. This was due to the significantly decreased proportion of registrations in women diagnosed with Marfan syndrome (HR: 0.68 (95% CI: 0.50-0.92)), while among undiagnosed women with Marfan syndrome, the HR was comparable to controls (Figure 2).

Complications during pregnancy, pregnancy loss, and delivery

The following data include all women with Marfan syndrome regardless of being diagnosed with Marfan syndrome at the time of registration or not (Figure 3), compared with their controls. In the main group "Pregnancy", the only subgroup with a significant finding was "Complications related to cervix" (HR: 19.8 (95% CI: 2.2-177.5)). There were no significant differences in outcome in "Pregnancy loss". In the main group "Delivery", "Caesarean delivery" was significantly increased (HR: 2.09 (95% CI: 1.41-3.08)) and "No complications" was significantly decreased (HR: 0.52 (95% CI: 0.37-0.74)), indicating a somewhat more complicated pregnancy.

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Foetal death

The HR in "Foetal death" was significantly increased in women with Marfan syndrome (HR: 12.3 (95% CI: 1.51-99.8)), primarily due to registrations in women not yet diagnosed with Marfan syndrome, as there were no registrations of "Foetal death" among women already diagnosed with Marfan syndrome. As there was a limited number of registrations in "Foetal death" (MFS: n<3), no further data can be reported in this main group.

Pregnancy complications in relation to having diagnosed or undiagnosed Marfan syndrome

Before the Marfan syndrome diagnosis, "Pregnancy", "Pregnancy loss", and "Delivery" were not affected, whereas after the Marfan syndrome diagnosis "Delivery" was significantly reduced, HR: 0.60 (95% CI: 0.43-0.85) (Figure 2).

None of the subgroups had significant outcomes both in the undiagnosed as well as in the diagnosed women with Marfan syndrome.

However, before the Marfan diagnosis, the following subgroups was significantly increased: In the main group Pregnancy "Complication related to vagina", HR: 27.2 (95% CI: 2.3-315.0) and "Preeclampsia" (HR: 2.25 (95% CI: 1.11-4.60)), and in the main group Delivery "Complications, others" (HR: 1.57 95% CI: 1.04-2.36)) (Figure 4).

After the Marfan syndrome diagnosis, the main group Pregnancy "Complication related to cervix" HR: 17.5 (95% CI: 1.9-157.7) was significantly increased, as was in the main group Pregnancy loss "Late abortion" (HR: 3.90 (95% CI: 1.21-12.56)) and "Extra uterine pregnancy" (HR: 3.90 (95% CI: 1.58-9.59)), and in main group Delivery "Infection" (HR: 25.5 (95% CI: 2.6-247.1)), and "Sectio" (HR: 2.33 (95% CI: 1.52-3.57)).

Marfan diagnosis, aortic disease and death

Combined, 29 women with Marfan syndrome had a pregnancy registration and at least one registration with aortic disease during the study period. We did not register any women with known Marfan syndrome with an aortic dissection in close relation to delivery. Three women diagnosed with Marfan syndrome had prophylactic aortic surgery prior to a registration of delivery; none of them were registered with dissection. Twenty undiagnosed women with Marfan syndrome gave birth to 39 children.

Fifteen (out of the 29 women) had one or more aortic dissections. Their details are as follows: Nine women suffered from aortic dissection unrelated to their pregnancy registration, with the event occurring more than 15 years after the first pregnancy registration and more than 10 years after the last pregnancy registration. Three women with undiagnosed Marfan syndrome had an aortic dissection in close relation to delivery. The remaining three women each had a unique order of events, however, none dissected within 20 years after delivery.

No women with Marfan syndrome and a previous dissection had a pregnancy registration.

Six of the women with Marfan syndrome and a pregnancy registration and aortic disease died; all had a registration of an aortic operation and three had previously had a dissection. Five of these six women died more than 20 years after their first pregnancy registration. Due to the prohibited specification of single cases, we cannot report details on the sixth case. Three controls with a pregnancy registration had aortic surgery, but no dissections; none of them died.

Discussion

Main findings

For the first time, in an unbiased population of women with Marfan syndrome, including both pre-pregnancy undiagnosed and diagnosed cases, we show that pregnancy is relatively safe in diagnosed women with Marfan syndrome. However, undiagnosed Marfan syndrome is associated with birth-related aortic disease.

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We also identified a significantly decreased number of registrations related to maternal health, indicative of fewer pregnancies, relative to the background population among diagnosed females with Marfan syndrome, while women not yet diagnosed with Marfan syndrome had just as many pregnancies as in the background population. Thus, knowledge of the diagnosis seems to impact both women with Marfan syndromes decisiveness and how the health care system advices on pregnancy.

Strengths and limitations

Limitations of the current study are the lack of clinical data, especially cardiac data, including aortic size, in these women. Since this is a register study we cannot comment on the impact of clinical surveillance or of medical intervention, such as for example the use of beta blockers or ACE-inhibitors. Strengths of this study are the inclusion of diagnosed as well as undiagnosed women with Marfan syndrome and the nationwide approach with including all diagnosed Marfan syndrome women. Further, the possibility to utilize the registers with cross-linkage, which enable identification of the age-matched controls and the linkage to all hospital contacts, is of paramount importance.

Interpretation

It is well known that Marfan syndrome in general is associated with grossly increased risk of aortic disease[7]. Prior studies on Marfan syndrome and pregnancy have primarily been focusing on aortic events in pregnant women already diagnosed with Marfan syndrome and cared for in tertiary centres[12].

In accordance with previous research, we found an increased risk of aortic events in Marfan syndrome women, however all dissections during pregnancy or delivery were in undiagnosed Marfan women.

In the women diagnosed with Marfan syndrome, we identified a significantly decreased number of registrations of non-complicated deliveries as well as significantly more extra-uterine pregnancies and caesarean sections, indicating that a pregnancy in a woman with Marfan syndrome is indeed more complicated than a normal pregnancy. The findings related to caesarean section is expected due to the definition of pregnancy in Marfan syndrome being a high risk pregnancy and the recommendation of caesarean section at aortic diameter of [?]40 mm.[13] We consider the findings of a significantly reduced number of non-complicated deliveries a logic consequence hereof, as pregnancies and deliveries in women with Marfan syndrome per se are considered high risk.

Surprisingly, the findings related to the connective tissue component of the birth canal, here interpreted as findings related to uterine, cervical, and vaginal complications, were not as frequent as expected. Although complication related to the cervix was significantly increased, there was no significantly increased rate of complications related to the uterine cavity or the vagina. However, in women without a pre-pregnancy diagnosis of Marfan syndrome there was an increased risk of vaginal complications, and among women with a pre-pregnancy diagnosis there were an increased risk of cervical complications.

The significantly increased number of extra uterine pregnancies is an unexpected finding, not previously reported. Here, we identified an increased risk in Marfan syndrome women diagnosed at the time of registration, however the risk in women with Marfan syndrome not yet diagnosed was not increased. Combined, the association was not significant.

Preeclampsia was increased in women with Marfan syndrome, however only significantly in women not yet diagnosed with Marfan syndrome. The increased risk was also present among women diagnosed with Marfan syndrome, although this result did not reach significance. Reports of preeclampsia in a woman diagnosed with Marfan syndrome has been published previously.[14]Reassuringly, we found no association between having Marfan syndrome and experiencing preterm births. However, this is unexpected since insufficiency of connective tissue is associated with preterm birth.[15]

Foetal death was significantly increased among the undiagnosed Marfan syndrome women, however as none of the registrations were among women diagnosed with Marfan syndrome, the consequences of this finding

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in relation to Marfan syndrome is limited. We could not find any further information of this result in the registries.

In Denmark, legal abortion is a possibility until 12th week of gestation on mother's request and after 12th week of gestation if permission is granted from the regional abortion council. Indications for a late abortion are for instance mother's health, congenital malformations, and genetic indications including Marfan syndrome. The significantly increased proportion of late abortion in the diagnosed Marfan syndrome women suggests that a diagnosis of MFS in a foetus is followed by application of legal late abortion in pregnant Marfan women. This could be a contributing cause of the reduced birth rate among diagnosed Marfan syndrome women.

The level of cardiac surveillance of the diagnosed Marfan women during pregnancy in Denmark seems appropriate. It is even likely that some women with Marfan syndrome, perhaps unnecessarily when scrutinizing the present data, refrain from becoming pregnant, or choose abortion, due to careful guidance from the clinical and cardiac Marfan syndrome centres[16]. However, we do not have detailed information concerning the clinical status of the women with diagnosed Marfan syndrome that chose not to be become pregnant, and it may therefore be possible that some of these individuals, choosing not to become pregnant, and then voluntarily infertile, indeed are very high risk patients[17]. We anticipate that no cardiac surveillance program was instituted for the previously undiagnosed women with Marfan syndrome.

The difference in outcome shows the importance of a pre-pregnancy diagnosis. Whether some of the associations identified during pregnancy are driven by historical reports, thus emphasising the clinicians' need to observe and register the complications, can only be considered among the women diagnosed with Marfan syndrome, and not among those not yet diagnosed. However, there is a possibility that the musculo-skeletal symptoms, known to be present in Marfan syndrome, are already present in the undiagnosed women, and as such, the clinicians have an increased awareness and register these complications.

Whether affected connective tissue because of FBN1 mutations in the uterine system, also can explain the findings with cervical complications, remains to be determined. The understanding of the association of an increased risk of preeclampsia in the women not yet diagnosed, remains to be elucidated, and clinical vigilance is recommended. It is possible that the pregnant women diagnosed with Marfan syndrome are treated medically with antihypertensive drugs, thus reducing the risk of preeclampsia.

Conclusions

We present relatively reassuring data on the aspects of maternal health in Marfan syndrome and showed that aortic events only appeared in undiagnosed Marfan syndrome. However, we still consider pregnancy and delivery in women with Marfan syndrome as high-risk, and close surveillance during pregnancy and delivery at highly specialised obstetric centres are a cornerstone in the caretaking of women with Marfan syndrome.

Acknowledgements

Claus H. Gravholt and Kirstine Stochholm are members of the European Reference Network on Rare Endocrine Conditions (ENDO-ERN), Project ID number 739543.

Disclosure of interests

None of the authors have any conflicts of interest to declare

Contribution to authorship

All authors have equally been involved in the conception, planning, carrying out, analysing and writing up of the work.

Details of ethics approval

The board of the Danish Cytogenetic Central Registry and the Danish Data Protection Authority approved the project in 2011, with the registration number 2011-41-6986.

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Funding

This study is supported by Department of Clinical Medicine, Aarhus University Hospital and Aarhus University and the Novo Nordisk Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Peripartum type B aortic dissection in patients with Marfan syndrome who underwent aortic root replacement: a case series study. BJOG. 2018 Mar;125(4):487-493.

Table 1

Women with Marfan syndrome (n=195) and their controls (n=19,500), and age at first registration related to maternal health, and the year they were born.

		Number with [?]1 registration	Median age, years (range)	Year of birth (range)
Marfan syndrome	Combined	91	27 (14-40)	1969 (1939-1993)
	Not diagnosed with Marfan syndrome at the time of first registration	50	26 (17-40)	1961 (1939-1989)
Controls	Combined	10,188	27 (12-48)	1972 (1933-2001)
	Matched with a woman with Marfan syndrome	6,801	27 (13-40)	1971 (1939-1993)

Figure 1

Maternal health and other groups

Hierarchal configuration illustrating the combined group maternal health, the main groups and subgroups. For details, see supplementary table 1

Figure 2

Hazard ratios related to time of the Marfan syndrome diagnosis

Proportion of all first registrations in maternal health (combined) and the main groups, Pregnancy, Pregnancy loss, and Delivery. Data are presented as a) all women with Marfan syndrome b) before the Marfan syndrome diagnosis, and c) after the Marfan syndrome diagnosis. Data are presented as women with Marfan syndrome relative to their controls.

Figure 3

Hazard ratios in Marfan syndrome compared to controls

Proportion of all first registrations within the main groups Pregnancy, Pregnancy loss, and Delivery. Data are presented as women with Marfan syndrome relative to their controls.

Figure 4

Hazard ratios related to time of Marfan syndrome diagnosis, subgroups

Proportion of all first registrations in all subgroups in Pregnancy, Delivery and Pregnancy loss where a) combined data were informative, b) before the Marfan diagnosis, and c) after the Marfan diagnosis. Data are presented as women with Marfan syndrome relative to their controls.

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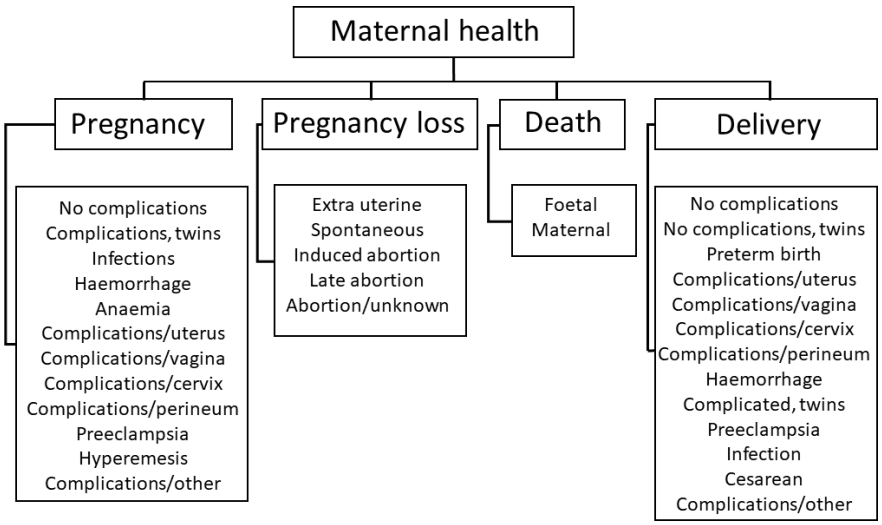

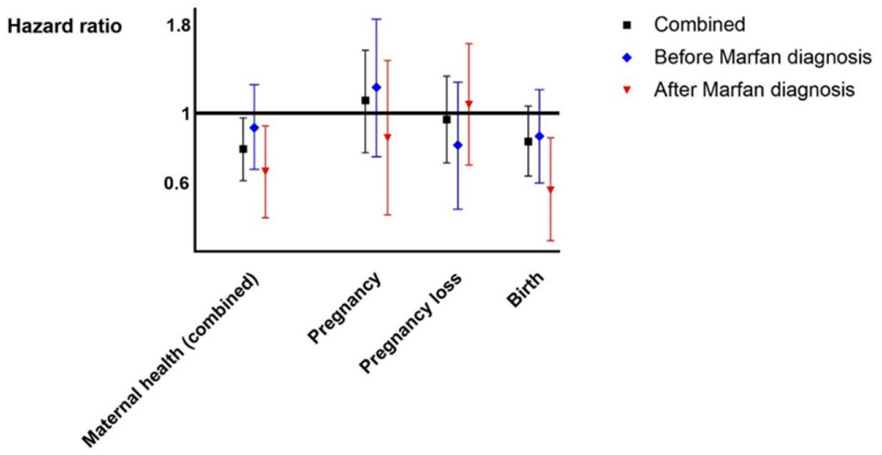

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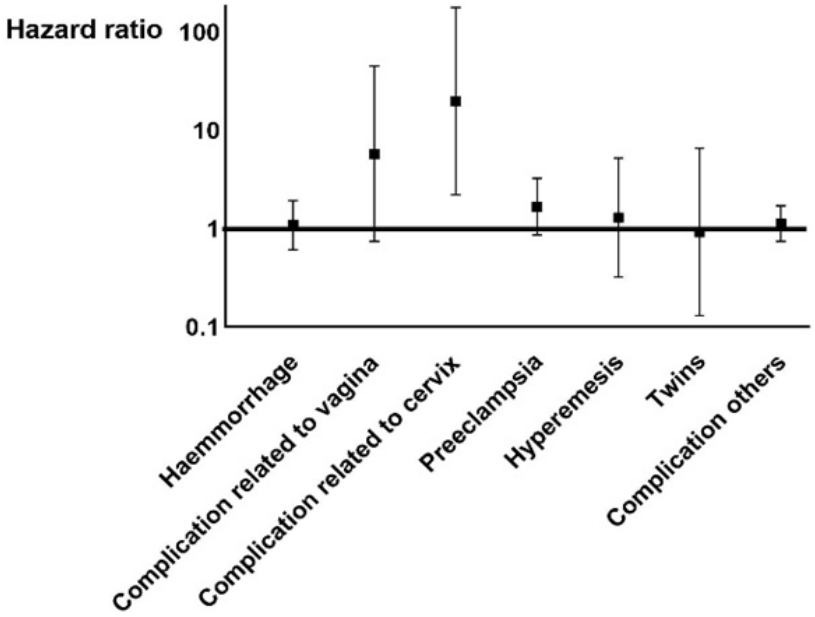

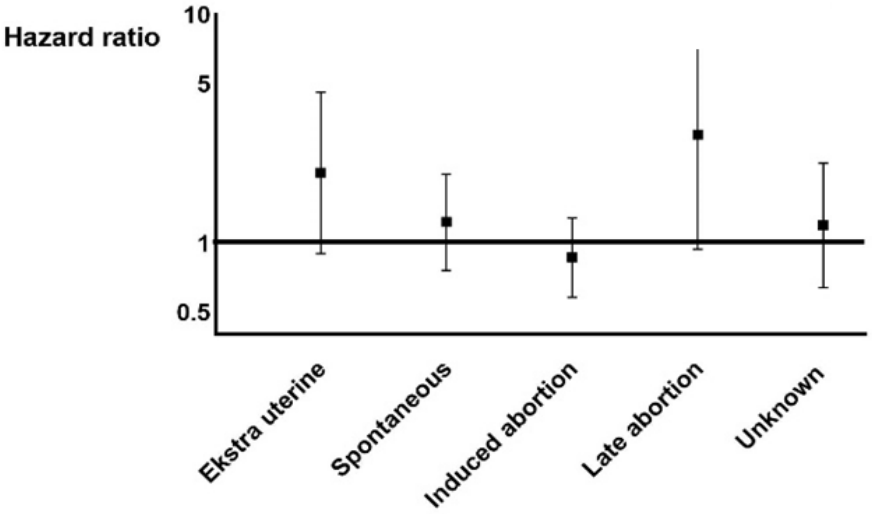

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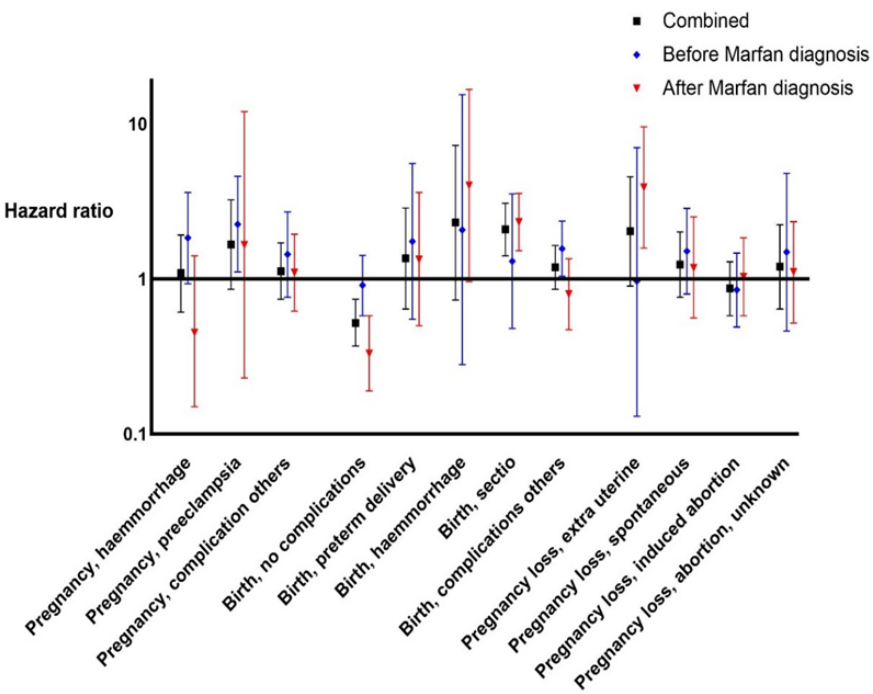

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