

Associations Between Pre-Pregnancy Chronic Health Conditions and Spontaneous Abortion: A Large Retrospective Cohort Study

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Abstract

Research question: To evaluate the associations between pre-pregnancy chronic health conditions and spontaneous abortion and, as a secondary exploratory objective, to derive a combined risk score based on the observed associations.

Design: his retrospective observational cohort study included documented singleton intrauterine pregnancies among women aged 21–45 years between 2010 and 2019. Pregnancies resulting in live birth were compared with pregnancies ending in spontaneous abortion. The primary outcome was spontaneous abortion. Demographic, reproductive, and chronic health factors were compared between groups, and adjusted associations were estimated using logistic regression.

Results: After application of the exclusion criteria, the final analytic cohort included 384,544 pregnancies: 346,222 live births (90.04%) and 38,322 spontaneous abortions (9.96%). Several pre-pregnancy chronic conditions were associated with higher odds of spontaneous abortion after adjustment for measured demographic and reproductive factors. An exploratory risk score incorporating demographic characteristics and the number of chronic conditions demonstrated an apparent area under the receiver operating characteristic curve of 0.70 (95% confidence interval, 0.69–0.71) within the derivation cohort.

Conclusions: Several pre-pregnancy chronic health conditions were associated with spontaneous abortion. The exploratory score demonstrated moderate apparent discrimination in the derivation cohort but requires calibration and independent validation before any potential clinical use.

Introduction

Spontaneous abortion is defined as the unplanned loss of a pregnancy before 20 completed weeks of gestation and occurs in approximately 12–15% of clinically recognized pregnancies.^{1,2} It is a multifactorial outcome arising from the interaction of embryonic or fetal factors, maternal characteristics, and environmental exposures. Chromosomal abnormalities are the primary cause of spontaneous abortion, accounting for more than 50% of miscarriages, particularly those occurring during the first trimester^{3–5}. Other recognized etiological pathways include uterine abnormalities⁶ maternal infections⁷, and acquired thrombophilia^{8–11}.

Several maternal characteristics may be associated with spontaneous abortion, either independently or in combination. These include advanced maternal age¹², a history of previous miscarriage¹³, obesity¹⁴, and lifestyle-related factors such as chronic psychological stress^{15,16} and smoking^{17,18}. However, the presence of a maternal risk factor does not necessarily indicate that it was the direct cause of an individual pregnancy loss, particularly because embryonic, maternal, and environmental mechanisms may coexist.¹⁹

Pre-pregnancy chronic health conditions may be associated with spontaneous abortion through several biological pathways. Endocrine and metabolic disorders may interfere with implantation, embryonic development, and early placentation; autoimmune and inflammatory diseases may alter maternal–fetal immune tolerance; and cardiovascular or vascular disorders may impair maternal adaptation to pregnancy and early placental perfusion^{19,20}. Chronic diseases may also serve as markers of disease severity, medication exposure, shared lifestyle factors, or other unmeasured characteristics rather than having a direct causal effect.

Previous studies have reported associations between spontaneous abortion and type 1 diabetes²¹, type 2 diabetes²², celiac disease²³ thyroid disorders²⁴, parathyroid disorders²⁵, and polycystic ovary syndrome²⁶. These conditions elevate the risk of spontaneous abortion due to their systemic impacts, which can disrupt the typical progression of a healthy pregnancy. Systemic effects include alterations in metabolic, immune, and vascular processes, all of which are crucial for maintaining a healthy pregnancy. However, many of these studies were limited by relatively small sample sizes or focused on a single chronic condition. A large registry-based study subsequently evaluated a broader spectrum of chronic diseases and identified associations with several cardiometabolic, endocrine, gastrointestinal, and gynecological conditions²⁰. Nevertheless, important potential confounders, including socioeconomic status, body mass index, smoking, fertility treatment, and previous spontaneous abortions, were not fully addressed.

The present study therefore aimed to evaluate the associations between a broad range of pre-pregnancy chronic health conditions and spontaneous abortion in a large healthcare database while adjusting for measured demographic and reproductive factors. As a secondary exploratory objective, we derived a combined risk score based on the observed associations. This score was intended for risk stratification and hypothesis generation rather than as a validated clinical prediction model.

Materials and Methods

Study Design

This retrospective, observational study was conducted using the electronic medical records of Maccabi Healthcare Services, a Israeli health maintenance organization that serves 2.3 million individuals²⁷.

Study Population

The study cohort included all documented singleton, intrauterine pregnancies, both births and spontaneous abortions, occurring in women aged 21 to 45 years between 2010 and 2019. Exclusion criteria were as follows: duplicate observations, abortions occurring less than 42 days from the last recorded abortion, abortions during pregnancy or within six weeks postpartum, and abortions occurring within the same pregnancy of the same woman. Additionally, women who had taken anticoagulant

(Clexane) or antiplatelet (aspirin) medications during pregnancy or within four weeks prior to conception were excluded. This decision was based on evidence from previous studies^{28–30} suggesting that these treatments may reduce the risk of spontaneous miscarriage, which could introduce bias and potentially skew the study results.

Outcome definition

The primary outcome was spontaneous abortion, identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 634.0–634.9. Spontaneous abortion was defined as a physician-diagnosed spontaneous loss of a documented intrauterine pregnancy occurring from the earliest clinically recognized gestation through 19 weeks and 6 days of gestation, based on post-menstrual age. No separate lower gestational-age cutoff was applied. Therefore, pregnancy losses occurring before clinical recognition, including biochemical pregnancies, were not captured. The outcome included missed, inevitable, incomplete, complete, and septic spontaneous abortions. Diagnoses were extracted from the electronic medical records.

Exposures and covariates

The primary independent predictor of interest was chronic diseases, diagnosed prior to the pregnancy of interest, and defined as a binary variable. Eleven categories of chronic diseases were identified: pre-gestational diabetes type 1 (ICD-9; 250), pre-gestational diabetes type 2 (ICD-9; 249), hypothyroidism (ICD-9; 244), hyperthyroidism (ICD-9; 242, 246), parathyroid disease (ICD-9; 252), cardiac diseases (including hypertension (ICD-9; 401, 402), ischemic heart disease (ICD-9; 410, 411, 412), angina pectoris (ICD-9; 413), coronary atherosclerosis (ICD-9; 414), heart failure (ICD-9; 428), neurologic diseases (including multiple sclerosis (ICD-9; 340), normal pressure hydrocephalus (ICD-9; 331.5)), depression (ICD-9; 311), rheumatologic diseases (including vasculitis (ICD-9; 446), systemic lupus erythematosus (ICD-9; 710), arthritis (ICD-9; 711), arthropathy (ICD-9; 713), rheumatoid arthritis (ICD-9; 714), osteoarthritis (ICD-9; 715), ankylosing spondylitis (ICD-9; 720), polymyalgia rheumatica (ICD-9; 725), polycystic ovary syndrome (PCOS; ICD-9; 256.4), primary ovarian insufficiency (POI; ICD-9; 256.3), hypertensive complications in past pregnancies (including gestational hypertension (ICD-9; 642.3), mild pre-eclampsia (ICD-9; 642.4), severe pre-eclampsia (ICD-9; 642.5) or eclampsia (ICD-9; 642.6) during past pregnancies), and a diagnosis of cancer (included if diagnosed up to one year before pregnancy, ICD-9; 140–239).

Information about smoking, pre-gestational body mass index (BMI), religious observance and socioeconomic status (SES) were retrieved from the electronic health records. SES was defined according to the poverty index of the woman's enumeration area, as determined by the 2011 national census³¹. The poverty index is based on several parameters, including housing type, household income, level of education, crowding, material conditions, car ownership, and the population census. SES levels

range from 1 (lowest) to 10 (highest). This study considered 1–5 to be low, 6–7 to be mid-range, and 8–10 to be high. Missing SES level values were replaced by median values.

Statistical Analysis

Demographic, reproductive, and chronic health characteristics were compared between pregnancies resulting in live birth and those ending in spontaneous abortion. Categorical variables were compared using chi-square tests.

Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the associations between chronic health conditions and spontaneous abortion. Models were adjusted for maternal age, BMI, SES, smoking, IVF treatment, and previous spontaneous abortion.

As a secondary exploratory analysis, factors associated with spontaneous abortion in the adjusted analyses were combined into a simplified risk score. Chronic disease burden was represented as the number of chronic conditions rather than as individual diagnoses. Regression coefficients were multiplied by 10 and rounded to the nearest integer to generate point values. The score was derived and evaluated in the complete study cohort; no separate temporal or external validation cohort was available. This score was derived by multiplying the regression coefficients by 10 and rounding the result to the nearest integer. The resulting scores ranged from – 3 to 53.

The score was calculated as:

$$\begin{aligned} \text{Score} = & 2 * \text{Age}_{36-40} - 1 * \text{Age}_{41-45} - \\ & 2 * \text{BMI}_{<18.5} + 1 * \text{BMI}_{31-36} + 1 * \text{BMI}_{36-40} + 2 * \text{Smoking} + 5 * \text{IVF} + \\ & 40 * \text{Past abortions} + 1 * \text{SES} + \\ & 3 * \text{One chronic disease} + 3 * \text{Two chronic diseases} \end{aligned}$$

The estimated probability (p) for experiencing a spontaneous abortion was calculated using the formula:

$$p = \frac{1}{1 + e^{-\text{score}}}$$

All statistical analyses were conducted using R, version 4.3.1. Statistical significance was defined as a p-value < 0.05.

Ethics

The study protocol was approved by the Maccabi Healthcare Services Institutional Review Board (0103-19-MHC) on February 16, 2020. All data were anonymized before analysis. Given the retrospective design and use of deidentified data, the requirement for informed consent was waived.

Results

The data included 427,136 pregnancies, of which 368,622 (86.3%) were live births and 58,514 (13.7%) were spontaneous abortions. Following the elimination of 42,592 cases that met the exclusion criteria, the final cohort consisted of 346,222 (90.03%) live births and 38,322 (9.96%) spontaneous abortions (Figure 1).

Table 1 presents a comparison of the demographic data between the study groups. Compared to normal pregnancies, women ages 36-45 had a higher spontaneous abortion rate (Figure S1) than those 21-35. The OR for ages 36-40 was 1.63 (95% CI: 1.59-1.67), and for ages 41-45 was OR 1.45 (95% CI: 1.38-1.52).

A clear trend emerged with BMI and abortion rates (Figure S2). Women with lower BMI had lower odds of spontaneous abortion (OR = 0.74 for BMI <18.5 (95% CI: 0.69-0.75), while higher BMI had higher odds, peaking at OR 1.36 for BMI >40. Smokers had an OR of 1.22 (95% CI: 1.17-1.28) for spontaneous abortion, and higher socioeconomic status slightly elevated the odds (OR = 1.06, 95% CI: 1.03-1.1). Fertility treatments significantly increased the abortion risk, with an OR of 1.83 (95% CI: 1.77-1.89), while a history of spontaneous abortion marked the highest risk with OR of 59.2 (95% CI: 56.6-61.9).

Table 2 presents the relation of chronic diseases to spontaneous abortion after adjusting for confounding variables. Hypothyroidism (adjusted odds ratio (aOR) = 1.29, 95% CI: 1.22-1.36), rheumatological disorders (aOR = 1.24, 95% CI: 1.06-1.44), cardiac diseases (aOR = 1.25, 95% CI: 1.16-1.34), pre-gestational type 2 diabetes (aOR = 1.16, 95% CI: 1.03-1.3) and neurology diseases (aOR = 1.78, 95% CI: 1.23-2.53) were linked to higher abortion rates.

Multivariable logistic regression analysis revealed risk factors that were independently associated with spontaneous abortions (**Table 3**). These variables were used to derive an exploratory risk score. (**Figure 2**) The apparent AUC within the derivation cohort was 0.70 (95% CI 0.69–0.71).

Discussion

Principal findings

In this large retrospective cohort, several pre-pregnancy chronic health conditions were associated with spontaneous abortion after adjustment for measured demographic and reproductive factors. Associations were observed with cardiometabolic conditions, including cardiac disease, chronic hypertension, and type 2 diabetes mellitus, as well as with thyroid and parathyroid disorders, neurologic and rheumatologic diseases, depression, PCOS, and cancer.

The exploratory risk score demonstrated moderate apparent discrimination within the derivation cohort, with an AUC of 0.70.

Interpretation in relation to previous research

These data augment the growing body of evidence of a possible association between cardiac diseases and spontaneous abortions²⁰. Nevertheless, this study may not have adequately considered key confounders such as SES, BMI, smoking habits, IVF treatments, and history of previous spontaneous abortions, all of which could influence the outcomes.

Profound physiological changes occur in the maternal cardiovascular system occur shortly after conception (27,28). Women with compromised cardiometabolic health who become pregnant may face challenges in adapting to these physiologic changes, which could result in a higher risk of miscarriage. Given the well-documented, increased likelihood of preeclampsia and premature births among women with cardiovascular risk factors³², it seems logical to consider that the risk of miscarriage could similarly be heightened for this group. Intriguingly, recent research³³ links spontaneous abortions to an increased risk of mortality from cardiovascular diseases. The relation between cardiovascular health and spontaneous abortions may be bidirectional; while cardiovascular disease may increase the likelihood of spontaneous abortions, occurrences of spontaneous abortions may also signal an elevated risk of future cardiovascular events.

Our findings, in conjunction with corroborating studies, confirm the association between hypertensive disorders during pregnancy and an elevated risk of spontaneous abortions^{20,34}. The results suggest that a history of hypertensive disease in a previous pregnancy also increases the risk for spontaneous abortions in subsequent pregnancies. Hypertension in an earlier pregnancy often foreshadows future chronic hypertension³⁵. It is linked with a recurrent pattern³⁶ and the development of related conditions, such as cardiovascular and kidney diseases, and diabetes mellitus^{37,38}. Furthermore, antiphospholipid syndrome (APLA), with severe pre-eclampsia as a diagnostic criterion, is associated with an increased incidence of spontaneous abortion^{39,40}. Collectively, this evidence indicates that a history of hypertension during pregnancy is linked to an increased likelihood of experiencing spontaneous abortions in subsequent pregnancies.

The association between cancer in women and an increased risk of miscarriage has not been well-established in previous studies. Much of the existing research has explored the reverse relationship, whether spontaneous abortions increase risk of developing breast cancer^{41,42} but found no significant association between the two. This emphasizes an area in medical research where further exploration is needed to understand the potential impact of cancer on the risk of miscarriage.

Our research confirms a link between depression and spontaneous abortions, showing that depression heightens the risk of spontaneous abortion regardless of antidepressant use. Past studies showed higher miscarriage risks in women with depression, whether on selective serotonin reuptake inhibitors^{43,44} or not⁴⁵. Chronic stress is linked to heightened cortisol production, which can trigger depression⁴⁶. Stress not only precedes depressive episodes but also affects their severity and recurrence⁴⁷. Furthermore, both short-term and prolonged stress have been identified as factors that increase miscarriage risk^{48,49}. The nexus of stress, elevated cortisol, and diminished immune function heightens

women's susceptibility to infections and health issues, raising the risk of pregnancy loss. In women with depression, this stress exacerbates the potential for these outcomes, highlighting the complex interplay between mental health and pregnancy outcomes^{15,16,50}.

The present study found a clear link between PCOS and spontaneous abortions. PCOS is known to be associated with a higher risk of pregnancy complications, including a 20%–40% increase in spontaneous abortion rates^{26,51}. However, a large study found that after adjusting for obesity and other factors, the risk of spontaneous abortion was reduced, suggesting that these factors, rather than PCOS itself, may contribute to the increased risk.⁵² After accounting for variables such as BMI, age, IVF, smoking and SES, we discovered an additional 15% risk. This increase might be linked to insulin resistance observed in the subjects in this group⁵³.

Women with pre-gestational type 2 diabetes are observed to have higher rates of spontaneous abortions, as supported by existing literature^{21,54}. Similarly, there is an established link between hypothyroidism and increased risk for spontaneous abortion^{55,56}. Additionally, our findings confirm that rheumatological diseases are also associated with a heightened risk of spontaneous abortions^{57–59}.

Neurological diseases, primarily represented by women with multiple sclerosis in our dataset, were significantly associated with a higher rate of spontaneous abortions. Multiple sclerosis is an autoimmune disorder that adds an intriguing dimension to pregnancy. During pregnancy, expectant mothers typically undergo a shift in their immune profile from Th1, which is often seen in autoimmune conditions, to Th2, more commonly found in allergic disorders. This shift plays a crucial role in establishing immune tolerance toward the developing embryo^{60,61}, contributing to the successful progression of pregnancy. However, in cases where this immune adaptation is insufficient during pregnancy, it may be linked to an increased risk of fetal loss⁶². This research is the first to identify a connection between neurological diseases and the occurrence of spontaneous abortion.

As a secondary exploratory objective, we derived a risk score incorporating maternal age, BMI, smoking, IVF treatment, previous pregnancy loss, and the number of chronic diseases. The score demonstrated moderate apparent discrimination within the derivation cohort, with an AUC of 0.70. This finding is broadly consistent with a previous study that developed a preconception miscarriage risk score⁶³. However, the score was derived and evaluated in the same retrospective dataset and was not independently validated. Its performance may also have been limited by unavailable factors, including maternal infections^{7,64,65}, chronic stress⁴⁹, embryonic chromosomal abnormalities, and other unmeasured determinants of pregnancy loss.

Strengths and limitations

This study adds to the existing literature by examining the associations between a broad range of chronic diseases and spontaneous abortion. We successfully accounted for a range of important confounders, including BMI, SES, history of IVF pregnancies, previous spontaneous abortions, and

smoking habits, to refine the assessment of spontaneous abortion risks across various chronic diseases. The study intentionally excluded women who had used anti-coagulation treatments^{28,29} or antiplatelets³⁰, as these were shown in some studies to reduce the risk of spontaneous abortions, potentially biasing the results. Furthermore, the study also omitted cases of induced abortions, considering them elective and outside the scope of the focus on spontaneous abortions. This approach ensures a well-defined cohort, providing clearer insights into the specific associations studied.

Several limitations should be considered when interpreting the findings. First, the retrospective nature of the study precluded assessment of several important etiological factors. Chromosomal abnormalities are the leading cause of spontaneous abortion and account for more than 50% of miscarriages, particularly those occurring during the first trimester. However, information regarding embryonic or fetal chromosomal abnormalities, products-of-conception testing, and parental genetic testing was unavailable. Consequently, we could not distinguish pregnancy losses primarily attributable to embryonic abnormalities from those potentially associated with maternal chronic conditions. This unmeasured heterogeneity may have contributed to residual confounding and limits the ability to infer causal relationships. Other unmeasured factors included uterine anatomical abnormalities, maternal infections⁷, lifestyle exposures such as night-shift work⁶⁶, and alcohol consumption⁶³. Information regarding medication use, disease control, and the severity and duration of the chronic conditions was also limited. Therefore, some of the observed associations may reflect disease severity, treatment exposure, or shared underlying risk factors rather than a direct effect of the chronic condition itself.

An additional limitation relates to the U.S. Preventive Services Task Force guidelines⁶⁷ issued in May 2014, which recommended low-dose aspirin for pregnant women at increased risk of preeclampsia, including those with chronic hypertension, autoimmune diseases, and type 1 or type 2 diabetes. Because women using aspirin were excluded, the composition of the cohort may have changed over the study period. Nevertheless, implementation of these recommendations was gradual, and widespread adherence was unlikely to have occurred immediately after their publication.

The diagnosis of a chronic condition at a specific point in time did not necessarily confirm its presence, absence, or severity during every previous pregnancy. Some chronic conditions may also have been underdiagnosed or incompletely documented in the electronic medical records. In addition, pregnancy losses occurring before clinical recognition, including biochemical pregnancies, were not captured. Information regarding pregnancy losses occurring before the study period may also have been incomplete, potentially resulting in misclassification of previous pregnancy history. Finally, the low prevalence of some chronic conditions limited statistical power and resulted in less precise estimates.

The exploratory risk score was derived and evaluated in the same retrospective cohort and was not subjected to independent temporal or external validation. Calibration was also not assessed. Therefore, its reported discriminatory performance may be optimistic, and the score should not be considered a validated clinical prediction tool or used for clinical decision-making without further development and independent validation.

Conclusion

Overall, the findings emphasize the multifactorial nature of spontaneous abortion and the complex interplay among demographic and maternal health factors. Several chronic conditions, particularly hypothyroidism, rheumatological disorders, and cardiac diseases, were associated with higher odds of spontaneous abortion. These findings may support increased clinical awareness and individualized preconception assessment, but they do not establish causality or provide evidence for a specific therapeutic intervention.

Declarations

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review board of Maccabi Healthcare Services health organization. All data were fully anonymized prior to analysis. Given the retrospective nature of the study and the use of de-identified data, the requirement for informed consent was waived by the ethics committee.

Consent for Publication

All authors consent to publication.

Availability of Data and Materials

The dataset used in this study is not publicly available due to restrictions by Maccabi Healthcare Services Healthcare Services.

Competing Interests

The authors declare no conflicts of interest.

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Declaration of generative AI and AI-assisted technologies in the writing process.

During the preparation of this work the authors used ChatGPT4 in order to help with English editing. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Author contributions

Hila SHALEV-RAM MD^{*} Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft

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Tables

Tables 1 to 3 are available in the supplementary files section

Figures

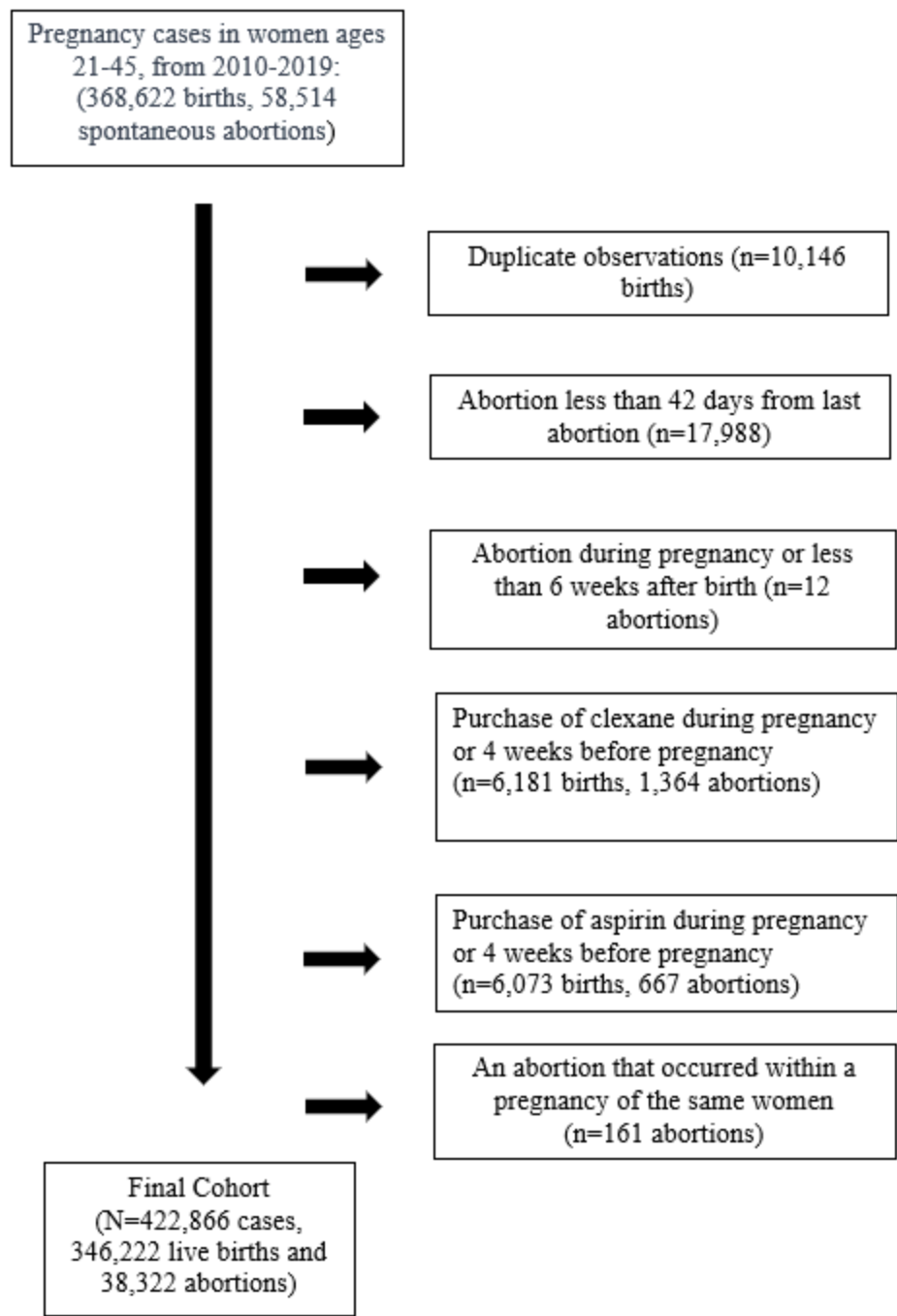


Figure 1

Flowchart describing study population.

^a Factors included in the multivariable regression model were independent variables found significantly different between groups in the univariate analysis.

^bBody mass index is calculated as weight in kilograms divided by the square of height in meters.^c Socioeconomic status levels range between 1-5 (low), 6-7 (medium), 8-10 (high)

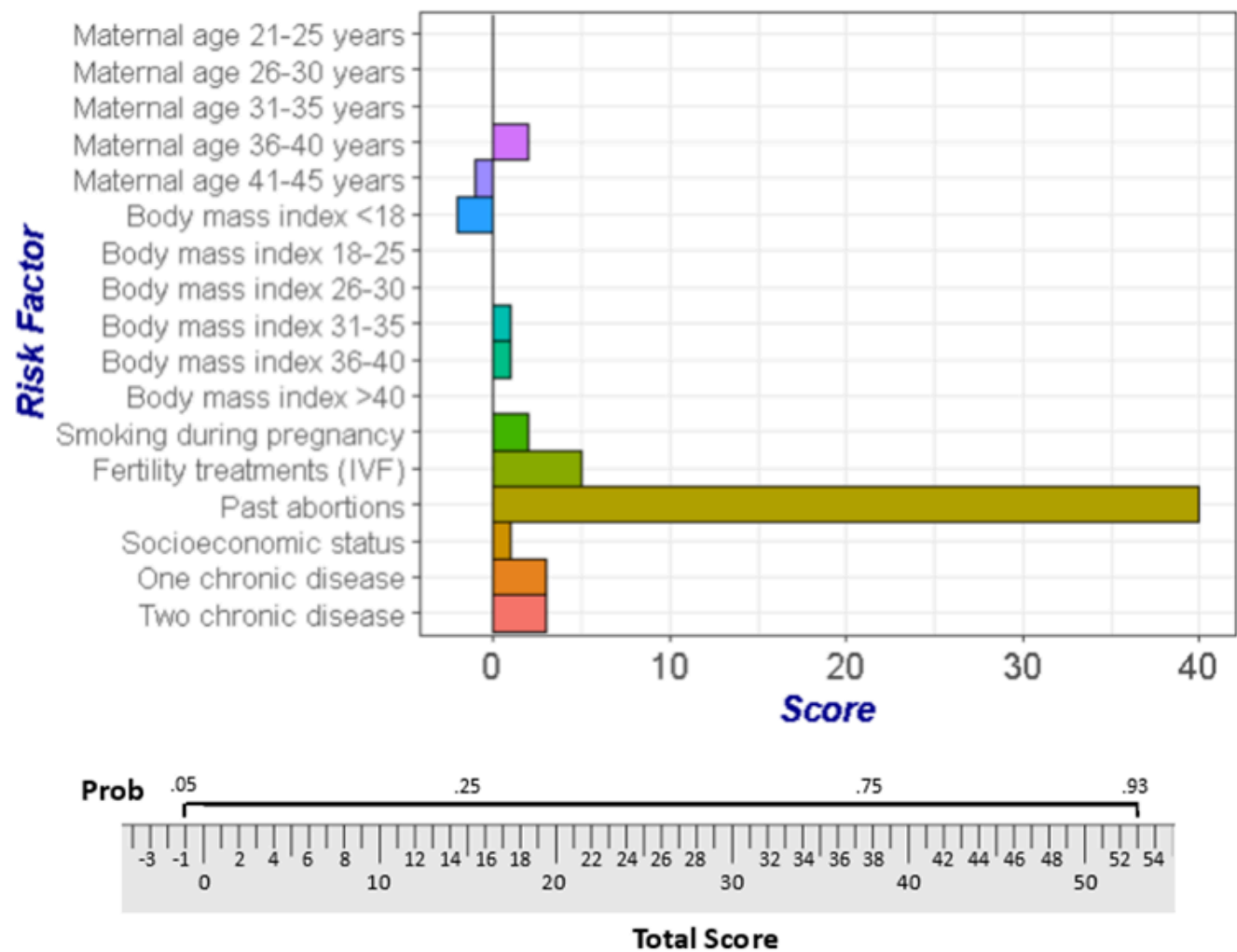


Figure 2

Risk Scoring for Spontaneous Abortions

Supplementary Files

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