Time trends in antithrombotic therapy during pregnancy and maternal and perinatal outcomes in the Netherlands (2013-19) a nationwide cohort study

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Time trends in antithrombotic therapy during pregnancy and maternal and perinatal outcomes in the Netherlands (2013–19): a nationwide cohort study

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Summary

Background Considering the paucity of data, we aimed to describe nationwide time trends in antithrombotic therapy during pregnancy and risks of maternal and perinatal outcomes in the Netherlands.

Methods In this nationwide cohort study, all female individuals aged 16–45 years with delivery records in the Dutch perinatal registry between Jan 1, 2013, and Dec 31, 2019, and their infants, were included. Individually linked data from Statistics Netherlands on outpatient medication prescriptions, in-hospital diagnoses, and mortality were used to evaluate time trends in antithrombotic therapy during pregnancy, and risks of maternal and perinatal outcomes (including thromboembolism, bleeding, preeclampsia and eclampsia, and low birthweight).

Findings A total of 1122711 pregnancies and 1139116 infants were included (median maternal age 30·5 years [IQR 27·3–33·7]; 886085 [78·9%] White; median gravidity 2 (IQR 1–3); and median gestational age at delivery 39 weeks [IQR 38–40]). Low-molecular-weight heparin (LMWH) was the most commonly (more than 99%) prescribed anticoagulants during pregnancy, which slightly increased from 0·7% (1063 of 163 479) in 2013 to 0·9% (1352 of 158 654) in 2019. LMWH was generally started at 5–8 weeks' gestation when oral anticoagulant prescriptions dropped. Antiplatelet drug prescriptions increased from 0·7% (1129 of 163 479) to 4·8% (7671 of 158 654), which primarily initiated around week 12. Maternal risks of venous and arterial thromboembolism and bleeding remained constant from 2013 to 2019; the risk of preeclampsia and eclampsia gradually increased from 1·70% (95% CI 1·63–1·76) in 2013 to 2·05% (1·98–2·13) in 2017, after which it decreased to 1·83% (1·77–1·90) in 2019. There was a significant decrease (2019 *vs* 2013) in low birthweight (adjusted odds ratio 0·92 [0·90–0·94]; p<0·0001), whereas 28-day neonatal bleeding risk remained unchanged.

Interpretation Exposure to anticoagulants during pregnancy is not uncommon, and health-care providers and female individuals of reproductive age should be mindful of this to avoid unintended oral anticoagulant exposure. Adhering to guidelines for aspirin use to prevent preeclampsia might lead to a population-level reduction in disease burden and potential improvement in neonatal prognosis.

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For the Dutch translation of the abstract see Online for appendix 1

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Introduction

Antithrombotic therapy, including the use of anticoagulants and antiplatelet drugs, is not uncommon during pregnancy.[1–4] Anticoagulants are typically prescribed to prevent and treat thromboembolic complications, and antiplatelet drugs are frequently prescribed to prevent preeclampsia and subsequent complications.[5] In contrast to the preference for oral anticoagulants in the non-pregnant population, parenteral low-molecular-weight heparin (LMWH) is generally recommended for pregnant people when anticoagulation is indicated,[2,4,6,7] as it does not cross the placenta and has a well established safety record based on its historical usage.[8] For oral anticoagulants, vitamin K antagonists (VKAs) are strongly advised against (with the exception of high-thrombotic-risk mechanical heart valves, for which VKAs remain an alternative to LMWH[9,10]) due to the risk of embryopathy and fetopathy. Direct oral anticoagulants (DOACs) are also contraindicated due to the absence of safety data and potential placental passage with reproductive toxicity observed in animal and human model studies.[11]

In the past decade, DOACs have replaced VKAs as the preferred anticoagulants for most indications in the non-pregnant population,[12] raising a concern about increasing unintended exposure to DOACs in early pregnancy.[13,14] Meanwhile, with the safety and efficacy of low-dose aspirin for preeclampsia prevention being established[15,16] and implemented in guidelines,[17–19] increasing use of antiplatelet drugs (ie, aspirin) during pregnancy is expected. It remains unknown at the population level how and whether these changes have reshaped antithrombotic therapy during pregnancy and risks of relevant clinical outcomes (eg, thromboembolism and bleeding, preeclampsia and low birthweight). Understanding these

Research in context

Evidence before this study

We searched PubMed for literature on epidemiology of antithrombotic therapy in the general pregnant population. The search was conducted on July 15, 2024, with search terms including antithrombotic agents and pregnancy. We did not apply limitations on language or publication time, but excluded animal studies. By screening the titles and abstracts of the 15 384 results, we found that no studies had comprehensively reported antithrombotic therapy and relevant maternal and perinatal outcomes in a large (ie, regional or nationwide) and unselected general pregnant population. A few studies examined changes in use of heparin for venous thromboembolism prophylaxis, or aspirin use for preeclampsia prevention after implementation of new guidelines, but reported inconsistent results.

Added value of this study

To our knowledge, this study is the first that thoroughly presents epidemiological information about antithrombotic therapy during pregnancy and various maternal and perinatal outcomes based on recent nationwide individual-level data. The findings show current practice of antithrombotic therapy during pregnancy in a high-income country, provide insights into relevant questions (including whether pregnant people might be increasingly exposed to direct oral anticoagulants), how guideline recommendations are translated into current practice, and whether the increasing use of low-dose aspirin for preeclampsia prevention might lead to a population-level reduction in adverse maternal and perinatal events. The statistics will also serve as a valuable benchmark for further improving maternal and perinatal health.

Implications of all the available evidence

Anticoagulant treatment is not uncommon in the general pregnant population, and both medical professionals and prevalent users of oral anticoagulants should raise awareness of the importance of periconceptional anticoagulant management. Since randomised controlled trials have confirmed the efficacy of low-dose aspirin for preeclampsia prevention, and in our study the same time period saw an increasing trend in aspirin use accompanied by decreasing trends in preeclampsia and eclampsia and low birthweight, it might be reasonable to infer that the increasing adoption of this treatment should eventually lead to a reduction in disease burden.

changes will show how well antithrombotic therapy was provided in real practice and what could be further improved. To fill in this knowledge gap, we aimed to comprehensively describe time trends in antithrombotic therapy during pregnancy and risks of relevant maternal and perinatal outcomes in the general pregnant population in the Netherlands from 2013 to 2019.

Methods

Study design and participants

This study was a nationwide cohort study that used data from the Dutch perinatal registry and several individually linked nationwide population registries in the Netherlands. In brief, all pregnant people in the Netherlands from Jan 1, 2013, to Dec 31, 2019, and their infants were grouped by the calendar year when a pregnancy started, after which antithrombotic therapy and clinical outcomes were compared by year to evaluate their time trends.

The Dutch perinatal registry (coordinated by Perined) provides both maternal and perinatal data. This registration is compulsory for all deliveries at or after 22 weeks' gestation in the Netherlands, but optional for deliveries before 22 weeks' gestation. The other nationwide data were provided by Statistics Netherlands (Centraal Bureau voor de Statistiek [CBS]), including outpatient medication prescriptions, in-hospital diagnoses, and mortality of Dutch residents. Only successfully linked data were used in the study, after further excluding records with potentially suboptimal data quality (ie, when there was inconsistency in different variables or data sources referring to the same information; appendix 2 pp 1–2).

See Online for appendix 2

By examining the Dutch perinatal registry, we identified all female individuals who had at least one delivery record in the registry with a start date of pregnancy (determined by subtracting the amenorrhea duration from the date of delivery) between Jan 1, 2013, and Dec 31, 2019. To exclude potential data error (ie, unlikely maternal age), we only included records with maternal age at the start of pregnancy between 16 years and 45 years. If the same individual had more than one record that met the above inclusion criteria, all records would be included for study. Since the observation period of study interest for each included pregnancy was only the gestation (ie, from the start date of pregnancy until the date of delivery), and there was never overlap between different pregnancies of the same individual, all maternal analyses in the study were performed only at the level of pregnancy. In addition to the maternal analyses, all infants from the investigated pregnancies were included for studying perinatal outcomes, and all perinatal analyses were performed at the level of the infant. Except for the outcome stillbirth, the investigations into all other perinatal outcomes were restricted to liveborn infants only, as the linked data from CBS were not available for the stillborn infants.

We complied with the Declaration of Helsinki, and the study was approved by the Scientific Committee of the Department of Clinical Epidemiology of the Leiden University Medical Center (number A198) with a waiver of participant consent due to the use of pre-existing, de-identified data only.

Procedures

We identified prescriptions of antithrombotic agents (ie, VKAs, heparin group, DOACs, or antiplatelet drugs) during pregnancy based on the 5-digit Anatomic-Therapeutic-Chemical (ATC) system of WHO (appendix 2 pp 4–6). Data on these medication groups were available, but without further specification to distinguish their subtypes. However, according to the publicly accessible summary statistics of medications (based on 7-digit ATC codes) prescribed to female individuals aged 15–44 years in the Netherlands between 2013 and 2020 (appendix 2 p 7), the prescribed heparin group almost entirely consisted of LMWH (99·1%, 174 411 of 175 986), and the prescribed antiplatelet drugs largely consisted of aspirin (ie, acetylsalicylic acid [57·9%, 81 461 of 140 617] and carbasalate calcium [21·2%, 29 808 of 140 617]), followed by clopidogrel (14·3%, 20 104 of 140 617). For this reason, we assumed the heparin group prescribed to our study population consisted of LMWH only, and the antiplatelet drugs were mainly aspirin.

Since information on the amount of each prescription (ie, the duration for which a prescribed medication can be used) was unavailable, several criteria were used to define the period of medication exposure. The strict criterion of medication exposure required that a medication had to be prescribed exactly within the period of interest (eg, the entire pregnancy; the first, second, or third trimester; or a specific gestational week). As sensitivity analyses, we relaxed the strict definition of medication exposure by assuming each prescription of a medication was prescribed for 7, 14, 30, 60, or 90 days (unless there was an earlier refill or a prescription of a competing medication, whereby VKAs, LMWH, and DOACs were considered as a competing medication of each other).

To quantify medication exposure during a period of interest (appendix 2 pp 61–64), with the strict criterion of medication exposure, we calculated the proportion of pregnancies with two or more prescriptions (or one or more, as a sensitivity analysis) of the medication within the period of interest. With the relaxed criteria, as long as the period of interest during pregnancy and the assumed medication exposure period partly overlapped, the pregnancy would be counted into the numerator to calculate the proportion of pregnancies exposed to the medication. In addition to such a dichotomous metric, we calculated how many days within the period of interest were exposed to the medication (ie, proportion of days covered [PDC] by the medication). We refer to the relaxed criteria of medication exposure as 7-day, 14-day, 30-day, 60-day, or 90-day PDC criteria.

Outcomes

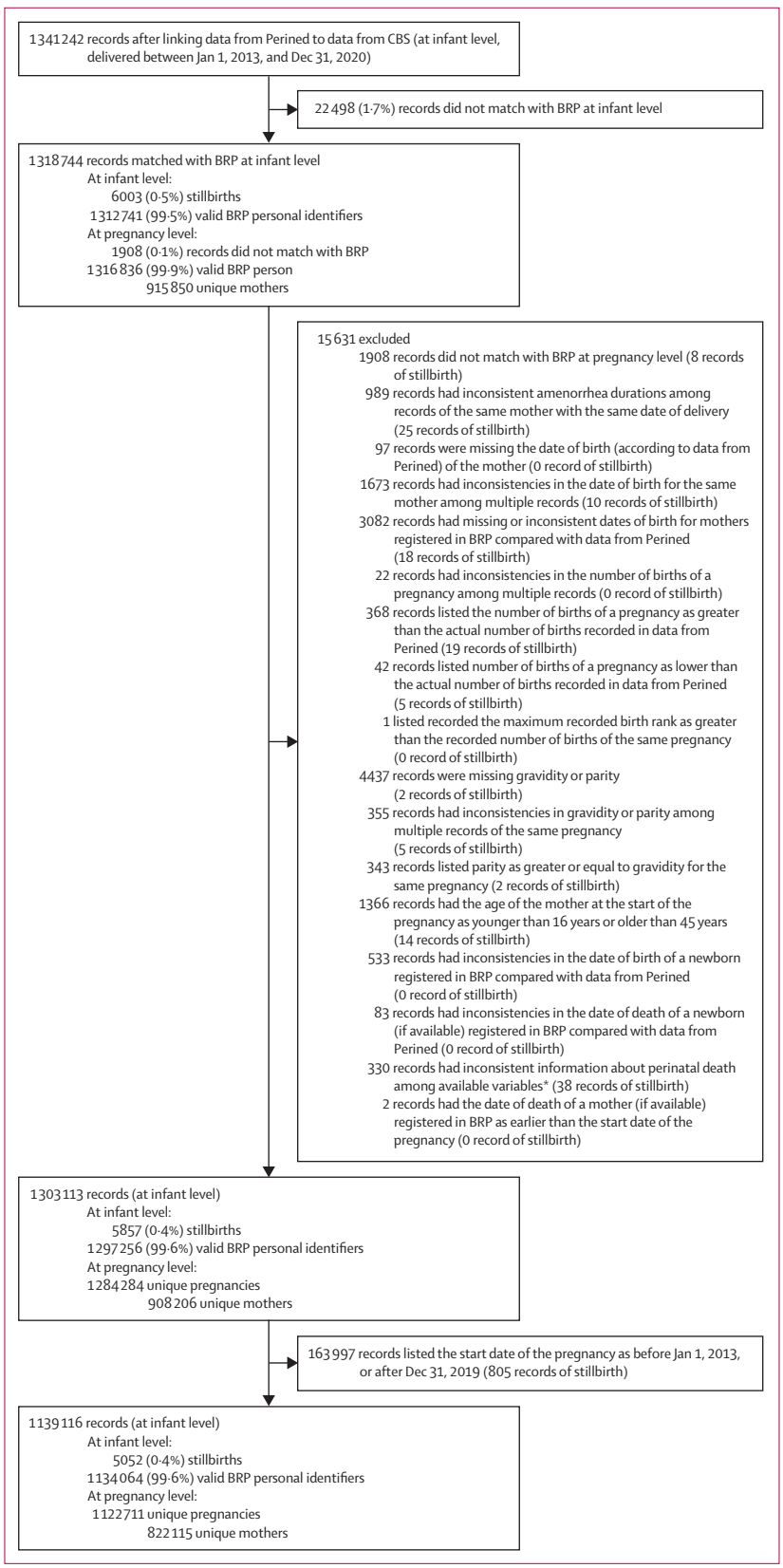
The included pregnant people were followed from the start date of pregnancy until the date of delivery, and the following maternal outcomes were separately studied: obstetric venous thromboembolism (VTE, mainly antepartum); ischemic stroke, transient ischemic attack (TIA), systemic arterial thromboembolism, or myocardial infarction; obstetric bleeding (mainly antepartum or intrapartum haemorrhage); preeclampsia or eclampsia; gestational diabetes; and all-cause mortality. All liveborn infants (regardless of gestational age) were followed from the date of delivery for 28 days or 1 year to determine the following perinatal outcomes: all-cause mortality (within the first 28 days and the first year); congenital malformations, deformations, and chromosomal abnormalities (diagnosed within the first year); and neonatal bleeding (within the first 28 days). These maternal and perinatal outcomes were identified using data from CBS on in-hospital diagnoses and primary cause of death during follow-up (appendix 2 p 6). For each outcome, only the first event during follow-up was counted. We assumed there was no loss to follow-up, since the nationwide data from CBS fully covered the follow-up periods, and we ignored possible emigration. Details about timing of the VTE or bleeding events and several planned sensitivity analyses are described in the appendix 2 (p 3).

Stillbirth (antepartum or intrapartum, among infants delivered at ≥24 or 28 weeks' gestation), neonatal intensive care unit (NICU) admission, birthweight below 2·5 kg, Hoftiezer chart birthweight percentile below 10%, and 5-min Apgar score of 3 or lower were also studied as perinatal outcomes, which were directly provided by the Dutch perinatal registry. Except for stillbirth, these outcomes were identified for liveborn infants only (regardless of gestational age), and those with missing values were excluded from analyses.

Statistical analysis

Summary statistics were presented as mean (SD), median (IQR), or n (%). Time trends in maternal characteristics and general information on the investigated pregnancies (appendix 2 p 3), and proportions of antithrombotic therapy during the entire pregnancy period or the first, second, or third trimester (using both the strict criterion and the PDC criteria of medication exposure) were described by presenting their summary statistics according to the calendar years of start of pregnancy (2013–19).

To provide more information about how antithrombotic therapy was prescribed during pregnancy, including insights into preconception anticoagulant management, we also described the distribution of antithrombotic therapy prescription by gestational week (by calculating the proportion of pregnancies with antithrombotic therapy prescription at various weeks' gestation); and the types of antithrombotic agent received during pregnancy according to the types received in the 6 months before the start of pregnancy (among the prevalent users). In addition, to provide information about potential indications for antithrombotic therapy, we presented maternal characteristics and



general information on the investigated pregnancies according to types of antithrombotic agent received during pregnancy. As the numbers of these individuals are relatively small, these analyses were presented for the entire study population only (instead of by calendar year).

Risks of maternal and perinatal outcomes were estimated after stratifying the pregnant people and their infants by calendar year of the start of pregnancy to show their time trends. Absolute risk of an outcome was evaluated by the cumulative incidence of the event, which was calculated by dividing number of events (during the defined follow-up periods) by number of pregnant people (or infants) at baseline, with the 95% CI being estimated by the Clopper-Pearson exact method. As a proxy for relative risk, odds ratios (ORs) of each outcome in pregnant people (or infants) in different calendar years (*vs* 2013) were estimated by logistic regression. To account for the inclusion of female individuals with multiple delivery records or infants from multiple births, the 95% CIs of the ORs were estimated by the clustered sandwich estimators (using the R package sandwich, version 3.1.0).

In addition to a crude model, several multivariable models were planned using logistical regression to account for potential differences in baseline characteristics of pregnant people or their infants in different calendar years. For the maternal outcomes, model 1 adjusted for age at start of pregnancy, immigration background, ethnicity, socioeconomic status, and degree of urbanity; model 2 adjusted for model 1, plus gravidity, parity, timing of first prenatal visit, and number of births; model 3 adjusted for model 2, plus two or more prescriptions of VKAs, LMWH, DOACs, and antiplatelet drugs in the 6 months before the start of the pregnancy. For the perinatal outcomes, model 1 adjusted for sex of the infant, number of births (during the pregnancy), type of delivery, and maternal covariates including age at start of pregnancy, immigration background, ethnicity, socioeconomic status, degree of urbanity, gravidity, and parity; model 2 adjusted for model 1, plus timing of first prenatal visit, maternal congenital abnormalities, and adverse (maternal) events during pregnancy (ie, the previously mentioned maternal outcomes, except for all-cause mortality); models 3–8 adjusted for the variables included in model 2, plus types and timing (ie, the first, second, and third trimester) of (maternal) antithrombotic therapy during pregnancy, based on the different criteria of medication exposure. These analyses allowed the calculation of adjusted ORs for these outcomes.

Figure 1: **Flow chart of data cleaning and inclusion of the study population**
There were several variables about perinatal death in data from both Perined and CBS, which could be inconsistent. The stillbirths presented here are only based on data from CBS before data cleaning (ie, the variable RINPERSOONS='D'). CBS=Statistics Netherlands (*Centraal Bureau voor de Statistiek*). BRP=Basic Registration of Persons (*Basisregistratie Personen*). *Details are provided in the appendix (pp 1–2).

	Overall	2013	2014	2015	2016	2017	2018	2019
Number of pregnancies	1 122 711	163 479	161 059	163 218	160 378	158 405	157 518	158 654
Number of (unique) pregnant people	822 115	163 401	160 983	163 133	160 297	158 324	157 430	158 562
Age at start of pregnancy (years)	30·5 (27·3–33·7)	30·2 (27·0–33·5)	30·3 (27·1–33·6)	30·3 (27·2–33·6)	30·5 (27·3–33·7)	30·5 (27·4–33·7)	30·6 (27·6–33·8)	30·8 (27·7–33·9)
Gravidity	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Parity	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)
Immigration background*								
Without immigration background	773 781 (68·9%)	116 255 (71·1%)	113 108 (70·2%)	113 329 (69·4%)	109 947 (68·6%)	107 919 (68·1%)	106 070 (67·3%)	107 153 (67·5%)
First-generation immigration background	213 034 (19·0%)	28 989 (17·7%)	29 294 (18·2%)	30 512 (18·7%)	30 753 (19·2%)	30 759 (19·4%)	31 655 (20·1%)	31 072 (19·6%)
Second-generation immigration background	135 896 (12·1%)	18 235 (11·2%)	18 657 (11·6%)	19 377 (11·9%)	19 678 (12·3%)	19 727 (12·5%)	19 793 (12·6%)	20 429 (12·9%)
Ethnicity*								
White	886 085 (78·9%)	133 373 (81·6%)	130 927 (81·3%)	131 039 (80·3%)	126 784 (79·1%)	122 959 (77·6%)	119 987 (76·2%)	121 016 (76·3%)
Other	218 561 (19·5%)	28 212 (17·3%)	28 480 (17·7%)	30 468 (18·7%)	31 473 (19·6%)	32 044 (20·2%)	33 665 (21·4%)	34 219 (21·6%)
North African	15 602 (1·4%)	2564 (1·6%)	2295 (1·4%)	2143 (1·3%)	2232 (1·4%)	2250 (1·4%)	2130 (1·4%)	1988 (1·3%)
Other African	29 696 (2·6%)	4180 (2·6%)	4192 (2·6%)	4301 (2·6%)	4340 (2·7%)	4326 (2·7%)	4201 (2·7%)	4156 (2·6%)
Turkish	4502 (0·4%)	<200	<200	305 (0·2%)	632 (0·4%)	1080 (0·7%)	1142 (0·7%)	1130 (0·7%)
Latin American	1938 (0·2%)	<10	<40	161 (0·1%)	307 (0·2%)	563 (0·4%)	446 (0·3%)	430 (0·3%)
Hindustani	13 954 (1·2%)	1965 (1·2%)	1910 (1·2%)	1971 (1·2%)	1958 (1·2%)	1960 (1·2%)	2043 (1·3%)	2147 (1·4%)
Other (Asian)	35 730 (3·2%)	4152 (2·5%)	4452 (2·8%)	5022 (3·1%)	5292 (3·3%)	5306 (3·3%)	5794 (3·7%)	5712 (3·6%)
Other (including mixed)	117 139 (10·4%)	15 246 (9·3%)	15 492 (9·6%)	16 565 (10·1%)	16 712 (10·4%)	16 559 (10·5%)	17 909 (11·4%)	18 656 (11·8%)
Missing or unknown	18 065 (1·6%)	1894 (1·2%)	1652 (1·0%)	1711 (1·0%)	2121 (1·3%)	3402 (2·1%)	3866 (2·5%)	3419 (2·2%)
Socioeconomic status†								
0–20%	209 254 (18·6%)	30 676 (18·8%)	29 995 (18·6%)	30 474 (18·7%)	29 787 (18·6%)	29 449 (18·6%)	29 296 (18·6%)	29 577 (18·6%)
20–40%	223 499 (19·9%)	32 470 (19·9%)	31 904 (19·8%)	32 551 (19·9%)	31 971 (19·9%)	31 676 (20·0%)	31 488 (20·0%)	31 439 (19·8%)
40–60%	225 695 (20·1%)	32 912 (20·1%)	32 509 (20·2%)	32 820 (20·1%)	32 336 (20·2%)	31 693 (20·0%)	31 586 (20·1%)	31 839 (20·1%)
60–80%	225 412 (20·1%)	32 713 (20·0%)	32 380 (20·1%)	32 900 (20·2%)	32 055 (20·0%)	31 833 (20·1%)	31 628 (20·1%)	31 903 (20·1%)
80–100%	234 415 (20·9%)	33 955 (20·8%)	33 670 (20·9%)	33 833 (20·7%)	33 667 (21·0%)	33 160 (20·9%)	32 892 (20·9%)	33 238 (20·9%)
Missing or unknown	4436 (0·4%)	753 (0·5%)	601 (0·4%)	640 (0·4%)	562 (0·4%)	594 (0·4%)	628 (0·4%)	658 (0·4%)
Degree of urbanity‡								
Very highly urban	287 538 (25·6%)	40 198 (24·6%)	41 138 (25·5%)	42 309 (25·9%)	41 799 (26·1%)	40 855 (25·8%)	40 576 (25·8%)	40 663 (25·6%)
Highly urban	284 341 (25·3%)	40 559 (24·8%)	41 736 (25·9%)	42 113 (25·8%)	40 771 (25·4%)	39 348 (24·8%)	39 905 (25·3%)	39 909 (25·2%)
Moderately urban	212 398 (18·9%)	31 271 (19·1%)	29 763 (18·5%)	30 385 (18·6%)	30 135 (18·8%)	30 085 (19·0%)	29 849 (18·9%)	30 910 (19·5%)
Few urban	194 336 (17·3%)	28 735 (17·6%)	27 394 (17·0%)	28 240 (17·3%)	27 685 (17·3%)	27 914 (17·6%)	27 264 (17·3%)	27 104 (17·1%)
Non-urban	130 379 (11·6%)	20 116 (12·3%)	18 414 (11·4%)	18 128 (11·1%)	18 212 (11·4%)	18 556 (11·7%)	18 361 (11·7%)	18 592 (11·7%)
Missing or unknown	13 719 (1·2%)	2600 (1·6%)	2614 (1·6%)	2043 (1·3%)	1776 (1·1%)	1647 (1·0%)	1563 (1·0%)	1476 (0·9%)

Data are n, n (%), or median (IQR). *Information of immigration background was collected from Statistics Netherlands; first-generation immigrants refer to people who were born abroad with at least one parent who was born abroad, second-generation immigrants refer to people who were born in the Netherlands with at least one parent who was born abroad. Information of self-reported ethnicity was directly obtained from the Dutch perinatal registry. †0% indicates low socioeconomic status, 100% indicates high socioeconomic status, calculated by the Social and Cultural Planning Office (Sociaal en Cultureel Planbureau). ‡Very highly urban, >2500 addresses per km^2; highly urban, 1500–2500 addresses per km^2; moderately urban, 1000–1500 addresses per km^2; few urban, 500–1000 addresses per km^2; non-urban, <500 addresses per km^2.

Table 1: **Maternal and perinatal characteristics of the investigated pregnancies per calendar year**

For all the previously mentioned analyses (except for the analyses of perinatal outcomes), a subgroup analysis was performed for female individuals with a first pregnancy (ie, gravidity of one and parity of zero). For the analyses of maternal and perinatal outcomes, an additional subgroup analysis was performed in pregnancies delivered at 37 weeks' gestation or later.

All statistical analyses were performed with SPSS Statistics (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY, IBM) and R (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 2013, and Dec 31, 2019, there were 1 122 711 pregnancies in 822 115 individuals, with a total of

	Overall (n=1 122 711)	2013 (n=163 479)	2014 (n=161 059)	2015 (n=163 218)	2016 (n=160 378)	2017 (n=158 405)	2018 (n=157 518)	2019 (n=158 654)
Anticoagulant (LMWH, VKA, or DOAC)								
≥2 prescriptions	1749 (0·2%)	252 (0·2%)	240 (0·1%)	259 (0·2%)	269 (0·2%)	239 (0·2%)	239 (0·2%)	251 (0·2%)
≥1 prescription of LMWH	1338 (76·5%)	195 (77·4%)	202 (84·2%)	208 (80·3%)	210 (78·1%)	188 (78·7%)	179 (74·9%)	156 (62·2%)
≥1 prescription	3983 (0·4%)	601 (0·4%)	554 (0·3%)	575 (0·4%)	578 (0·4%)	562 (0·4%)	564 (0·4%)	549 (0·3%)
≥1 prescription of LMWH	3403 (85·4%)	522 (86·9%)	482 (87·0%)	506 (88·0%)	506 (87·5%)	485 (86·3%)	478 (84·8%)	424 (77·2%)
Last prescribed anticoagulant								
None	1 118 728 (99·6%)	162 878 (99·6%)	160 505 (99·7%)	162 643 (99·6%)	159 800 (99·6%)	157 843 (99·6%)	156 954 (99·6%)	158 105 (99·7%)
VKA	582 (0·1%)	115 (0·1%)	97 (0·1%)	93 (0·1%)	89 (0·1%)	59 (0·0%)	56 (0·0%)	73 (0·0%)
LMWH	3199 (0·3%)	484 (0·3%)	450 (0·3%)	474 (0·3%)	479 (0·3%)	465 (0·3%)	449 (0·3%)	398 (0·3%)
DOAC	<200 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<40 (0·0%)	<60 (0·0%)	<80 (0·0%)
Multiple types	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)
Oral anticoagulant (VKA or DOAC)								
≥2 prescriptions	662 (0·1%)	101 (0·1%)	78 (0·0%)	89 (0·1%)	92 (0·1%)	80 (0·1%)	100 (0·1%)	122 (0·1%)
≥1 prescription	921 (0·1%)	137 (0·1%)	126 (0·1%)	122 (0·1%)	115 (0·1%)	115 (0·1%)	135 (0·1%)	171 (0·1%)
VKA								
≥2 prescriptions	508 (0·0%)	101 (0·1%)	75 (0·0%)	85 (0·1%)	84 (0·1%)	48 (0·0%)	54 (0·0%)	61 (0·0%)
≥1 prescription	709 (0·1%)	137 (0·1%)	120 (0·1%)	115 (0·1%)	107 (0·1%)	75 (0·0%)	70 (0·0%)	85 (0·1%)
LMWH								
≥2 prescriptions	1198 (0·1%)	168 (0·1%)	178 (0·1%)	189 (0·1%)	195 (0·1%)	171 (0·1%)	155 (0·1%)	142 (0·1%)
≥1 prescription	3403 (0·3%)	522 (0·3%)	482 (0·3%)	506 (0·3%)	506 (0·3%)	485 (0·3%)	478 (0·3%)	424 (0·3%)
DOAC								
≥2 prescriptions	156 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	32 (0·0%)	47 (0·0%)	61 (0·0%)
≥1 prescription	229 (0·0%)	<10 (0·0%)	<10 (0·0%)	<10 (0·0%)	11 (0·0%)	44 (0·0%)	70 (0·0%)	90 (0·1%)
Antiplatelet drug								
≥2 prescriptions	1264 (0·1%)	155 (0·1%)	149 (0·1%)	170 (0·1%)	197 (0·1%)	194 (0·1%)	197 (0·1%)	202 (0·1%)
≥1 prescription	2547 (0·2%)	326 (0·2%)	323 (0·2%)	335 (0·2%)	392 (0·2%)	353 (0·2%)	403 (0·3%)	415 (0·3%)
Timing of first prenatal visit (weeks)	7 (5–10)	7 (5–10)	7 (5–10)	7 (5–10)	7 (5–10)	7 (5–10)	7 (5–9)	6 (5–9)
0–4	163 965 (14·6%)	16 846 (10·3%)	19 258 (12·0%)	22 195 (13·6%)	23 299 (14·5%)	24 220 (15·3%)	26 874 (17·1%)	31 273 (19·7%)
5–8	562 448 (50·1%)	80 559 (49·3%)	80 292 (49·9%)	81 014 (49·6%)	79 674 (49·7%)	79 431 (50·1%)	79 902 (50·7%)	81 576 (51·4%)
9–12	181 494 (16·2%)	32 006 (19·6%)	28 389 (17·6%)	27 279 (16·7%)	26 337 (16·4%)	24 409 (15·4%)	22 445 (14·2%)	20 629 (13·0%)
>12	181 477 (16·2%)	25 025 (15·3%)	26 685 (16·6%)	27 069 (16·6%)	26 620 (16·6%)	27 080 (17·1%)	25 843 (16·4%)	23 155 (14·6%)
Missing or unknown	33 327 (3·0%)	9043 (5·5%)	6435 (4·0%)	5661 (3·5%)	4448 (2·8%)	3265 (2·1%)	2454 (1·6%)	2021 (1·3%)
Gestational age (weeks)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)	39 (38–40)
<28	5713 (0·5%)	775 (0·5%)	768 (0·5%)	774 (0·5%)	804 (0·5%)	797 (0·5%)	856 (0·5%)	939 (0·6%)
28–32	6848 (0·6%)	1040 (0·6%)	1057 (0·7%)	992 (0·6%)	989 (0·6%)	946 (0·6%)	914 (0·6%)	910 (0·6%)
32–37	56 611 (5·0%)	8699 (5·3%)	8363 (5·2%)	8255 (5·1%)	8064 (5·0%)	7764 (4·9%)	7776 (4·9%)	7690 (4·8%)
≥37	1 053 539 (93·8%)	152 965 (93·6%)	150 871 (93·7%)	153 197 (93·9%)	150 521 (93·9%)	148 898 (94·0%)	147 972 (93·9%)	149 115 (94·0%)
Number of births								
1	1 106 526 (98·6%)	161 071 (98·5%)	158 683 (98·5%)	160 872 (98·6%)	158 042 (98·5%)	156 204 (98·6%)	155 262 (98·6%)	156 392 (98·6%)
2	15 967 (1·4%)	2374 (1·5%)	2343 (1·5%)	2305 (1·4%)	2317 (1·4%)	2164 (1·4%)	2227 (1·4%)	2237 (1·4%)
>2	218 (0·0%)	34 (0·0%)	33 (0·0%)	41 (0·0%)	19 (0·0%)	37 (0·0%)	29 (0·0%)	25 (0·0%)

Data are n (%) or median (IQR). LMWH=low-molecular-weight heparin. VKA=vitamin K antagonist. DOAC=direct oral anticoagulant.

Table 2: **Characteristics of antithrombotic therapy within 6 months before start of pregnancy, per calendar year**

1 139 116 infants ([582 890 [51·2%] of 1 139 116 male, 556 226 [48·8%] of 1 139 116 female; figure 1). Summary statistics of the maternal and perinatal characteristics, including those of the first pregnancies, are presented in table 1 and the appendix 2 (pp 8–14). In the 6 months before the start of the pregnancy, 0·2% (1749 of 1 122 711) of individuals had been receiving two or more prescriptions of anticoagulants, of whom most (1338 [76·5%] of 1749) received one or more prescriptions of LMWH, and 0·1% (1264 of 1 122 711) received two or more prescriptions of antiplatelet drugs. These numbers remained constant over the years (table 2).

During pregnancy, 0·7% (8298 of 1122711) of individuals received two or more prescriptions of anticoagulants, of whom more than 99% received one or more prescriptions of LMWH. Only 177 pregnant people received two or more prescriptions of VKAs, and only 16 pregnant people received two or more prescriptions of DOACs (appendix 2 pp 15–16). The proportion of pregnant people receiving two or more prescriptions of LMWH slightly increased from 0·7% (1063 of 163479) in 2013 to 0·9% (1352 of 158654) in 2019 (figure 2A; appendix 2 p 15). Regarding antiplatelet drugs, 2·0% (21982 of 1122711) of individuals received two or more prescriptions during pregnancy, with an increase from 0·7% (1129 of 163479) in 2013 to 4·8% (7671 of 158654) in 2019 (figure 2A; appendix 2 p 16). The same time trends were observed when evaluated by the PDC criteria of medication exposure (appendix 2 pp 17–21). In individuals with a first pregnancy, both anticoagulants (1951 [0·5%] of 392011 received ≥2 anticoagulant prescriptions) and antiplatelet drugs (4001 [1·0%] of 392011 received ≥2 antiplatelet drug prescriptions) were less frequently prescribed than in individuals with a subsequent pregnancy, but the marked increase in antiplatelet drug prescriptions was similarly noted (from 0·2% [98 of 58325] in 2013 to 3·3% [1809 of 54996] in 2019; appendix 2 pp 22–23).

When stratifying by pregnancy trimester (figure 2), similar time trends are observed: the proportion of pregnant people receiving one or more prescription of LMWH slightly increased from 2013 to 2019, and the proportion of pregnant people receiving one or more prescription of antiplatelet drugs markedly increased in all the three trimesters.

The proportion of pregnancies with LMWH prescriptions started to increase at 5–8 weeks' gestation, which concurred with a noticeable drop in the proportions of pregnancies with VKA and DOAC prescriptions, whereas the proportion of pregnancies with antiplatelet drug prescriptions increased from week 5 and peaked at week 12 (appendix 2 p 65). Among the 582 pregnant people who most recently received VKAs in the 6 months before their pregnancy (appendix 2 p 24), only 15% (87 of 582) received two or more prescriptions of VKAs during pregnancy; among the previous DOAC users, almost all stopped receiving DOAC prescriptions during pregnancy (57 [29%] of 194 received one or more prescriptions, less than 10 received two or more prescriptions; appendix 2 p 24). Similar results were found when the medication exposure was evaluated by the PDC criteria and when restricting to the first pregnancy (appendix 2 pp 25–30, 66–71).

Maternal characteristics by antithrombotic therapy are presented in the appendix 2, both in total cohort who received an antithrombotic agent within 6 months before start of pregnancy or during pregnancy based on the strict criterion of medication exposure (pp 31–34) and in the subgroup of individuals on their first pregnancy exposed in the same way (pp 35–38). Among those who received VKAs during pregnancy, the most

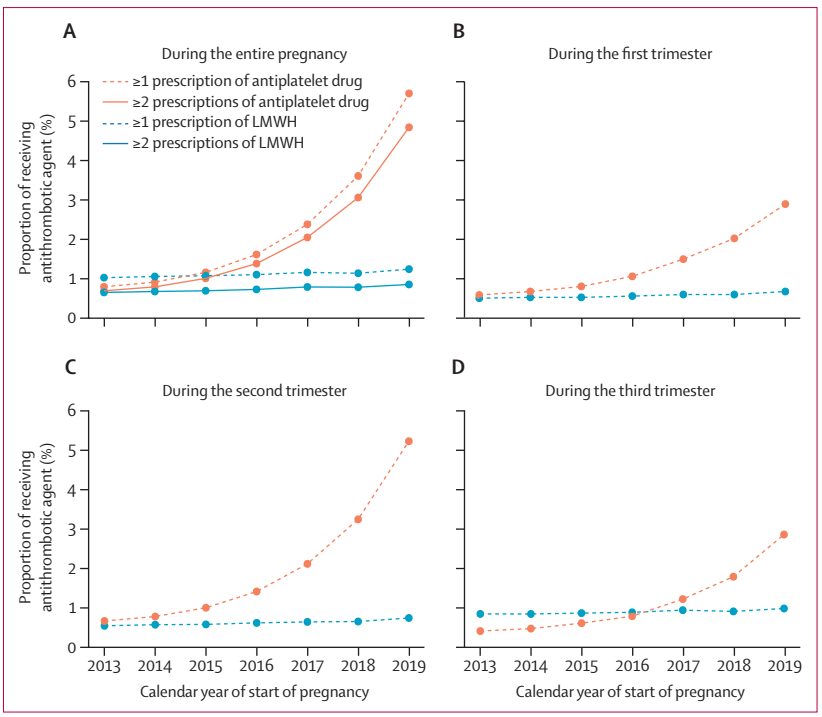


***Figure 2*: Time trends in proportions of pregnancies with antithrombotic therapy**
Based on the strict criterion of medication exposure during the entire pregnancy (A), the first trimester (week 1–12; B), the second trimester (week 13–26; C), and the third trimester (after week 27; D). Data on vitamin K antagonists and direct oral anticoagulants are not shown. LMWH=low-molecular-weight heparin.

prevalent comorbidities were a history of VTE (18 [10%] of 177), rheumatic mitral stenosis or mechanical heart valves (11 [6%] of 177), and other valvular heart diseases (10 [6%] of 177). For those who received LMWH during pregnancy, a history of VTE (551 [6·7%] of 8276), gestational hypertension (454 [5·5%] of 8276), coagulopathy (409 [4·9%] of 8276), obstetric bleeding (394 [4·8%] of 8276), and recurrent or previous spontaneous miscarriage (382 [4·6%] of 8276) were the most prevalent. Among those who received antiplatelet drugs during pregnancy, a history of gestational hypertension (4551 [20·7%] of 21982), obstetric bleeding (1151 [5·2%] of 21982), and gestational diabetes (719 [3·3%] of 21982) were the most prevalent.

From 2013 to 2019, the cumulative incidences of obstetric VTE, ischemic stroke, TIA, thromboembolism, myocardial infarction, and obstetric bleeding during pregnancy remained constant (figure 3). The time trends in VTE and bleeding risks were similar when further including general VTE and major bleeding into the definition of obstetric events (appendix 2 pp 39–40). Maternal all-cause mortality was rare and remained constant over the study period (appendix 2 p 40). However, the risk of preeclampsia and eclampsia increased from 1·70% (95% CI 1·63–1·76) in 2013 to a peak of 2·05% in 2017 (1·98–2·13; model 3-adjusted OR 1·24 [1·18–1·31] *vs* 2013, p<0·0001), after which it decreased to 1·83% (1·77–1·90) in 2019 (adjusted OR 1·11

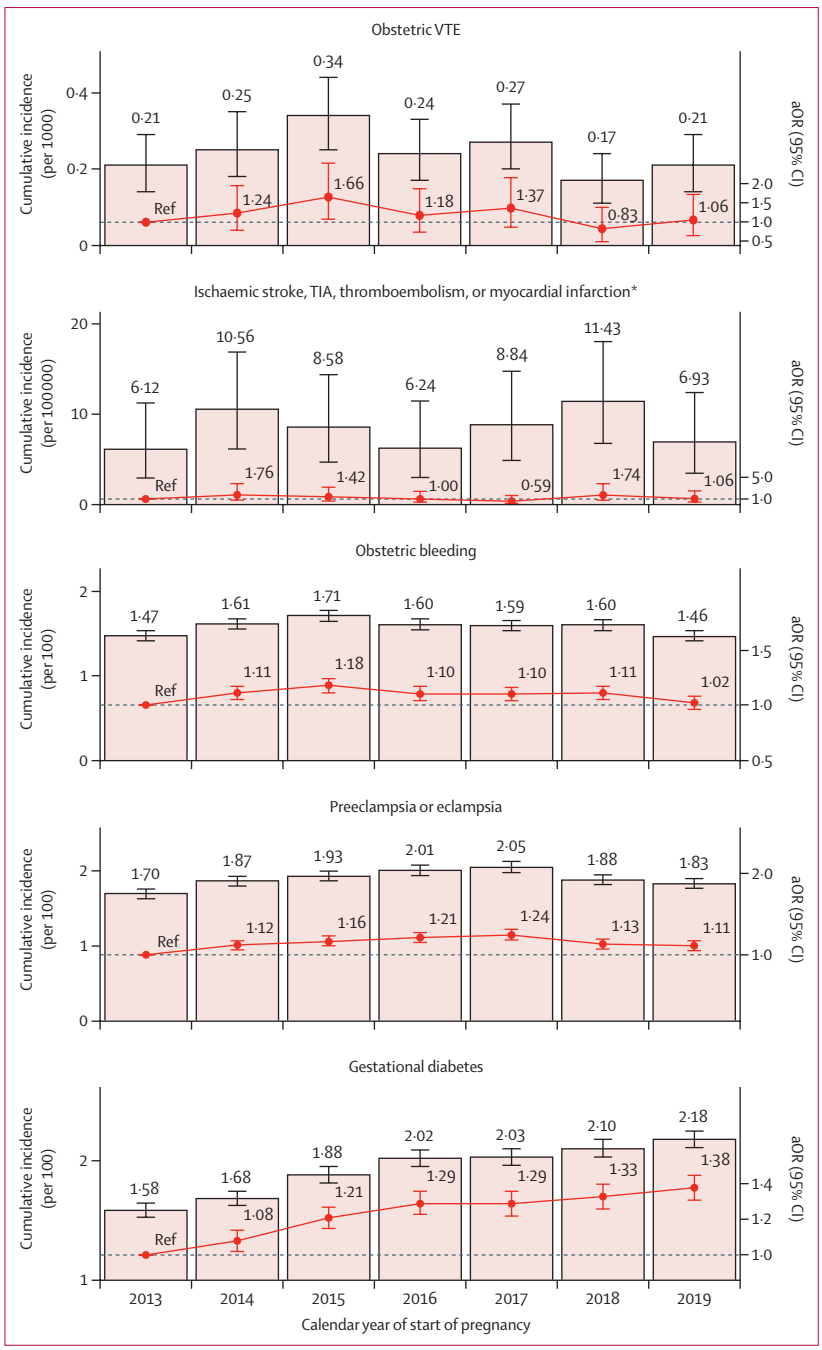


Figure 3: **Time trends in maternal outcomes during pregnancy**
The aOR was adjusted using model 3 (details about adjustment models are provided in the Methods section). aOR=adjusted odds ratio. TIA=transient ischemic attack. VTE=venous thromboembolism. *Due to a low event number (<10), the exact cumulative incidence of ischemic stroke, TIA, thromboembolism, and myocardial infarction of pregnant people in 2017 was masked by Statistics Netherlands to prevent potential disclosure of individual data. We imputed it as the mean of cumulative incidence in 2016 and 2018 when plotting the figure.

[1·05–1·17], *vs* 2013, p=0·0002; appendix 2 p 40). The risk of gestational diabetes steadily increased from 1·58% (1·52–1·64) in 2013 to 2·18% (2·11–2·25) in 2019, with an adjusted OR of 1·38 (1·31–1·45; p<0·0001; appendix 2 p 40). These trends were consistently observed when restricting to individuals with a first pregnancy, or to those who delivered at 37 weeks' gestation or later (appendix 2 pp 41–44).

Throughout the study period, improvement was observed in several perinatal outcomes, including neonatal mortality, congenital abnormalities, and low birthweight (figure 4). In detail, the risk of stillbirth (either ≥24 or ≥28 weeks) remained constant throughout the study period (appendix 2 pp 45–52). Among the liveborn infants, 28-day all-cause mortality decreased from 0·234% (95% CI 0·211–0·258) in 2013 to 0·160% (0·141–0·181) in 2019, with a model 2-adjusted OR of 0·67 (0·57–0·79; p<0·0001; appendix 2 p 45). There was also a significant decrease (2019 *vs* 2013) in risk of congenital abnormalities (0·88 [0·84–0·92]; p<0·0001; appendix 2 p 46), low birthweight (0·92 [0·90–0·94]; p<0·0001; similar results when based on birthweight <2·5 kg; appendix 2 p 48), NICU admission (0·93 [0·88–0·97]; p=0·0029; appendix 2 p 48), and low (≤3) 5-min Apgar score (0·84 [0·74–0·96]; p=0·010; appendix 2 p 48). However, the 28-day risk of neonatal bleeding remained unchanged (0·95 [0·73–1·24]; p=0·71; appendix 2 p 45). When restricting to liveborn infants delivered at 37 weeks' gestation or later, the decreasing trends in congenital abnormalities and low birthweight remained, but differences in the other neonatal outcomes were not statistically significant (appendix 2 pp 53–60).

Discussion

In this nationwide cohort study, we found that anticoagulant use during pregnancy in the Netherlands did not change over time (2013–19), with LMWH being preferred, and a switch from oral anticoagulants in early pregnancy, whereas antiplatelet drug prescriptions have increased since 2013. During the same time period, maternal thromboembolism and bleeding risks remained constant, whereas preeclampsia and eclampsia risk decreased after reaching a peak in 2017, and several neonatal outcomes (including low birthweight) improved.

Our study highlights that anticoagulant therapy during pregnancy is relatively common—about one in every 100 pregnant people—and therefore health-care providers are likely to encounter these individuals in daily practice. Although data to identify the exact indications for each anticoagulant prescription were unavailable in our study, female individuals who received anticoagulants during pregnancy more often had a history of VTE, VTE risk factors, or valvular heart diseases. We also found coagulopathy and recurrent or previous spontaneous miscarriage were relatively more prevalent in those receiving anticoagulant prescriptions than those who did not, suggesting that they could have been considered as indications for LMWH, albeit controversial. The ALIFE2 trial[20] showed that LMWH did not increase livebirth rates among individuals with recurrent pregnancy loss with inherited thrombophilia. For female individuals with persistent antiphospholipid antibodies and recurrent

pregnancy loss, the combination of heparin and aspirin might increase the chance of livebirths, but the supporting evidence is of very low certainty.[21] Considering the newly available evidence from the ALIFE2 trial,[20] future research is encouraged to keep monitoring how the time trend in anticoagulant therapy during pregnancy will evolve. It is not surprising to see that LMWH dominated anticoagulant therapy during pregnancy, as DOACs are considered contraindicated during pregnancy,[11] and the teratogenic effects of VKAs have been long established.[22] The rather complete switch from VKAs and DOACs to LMWH at 5–8 weeks' gestation we observed suggests that Dutch practice regarding anticoagulant use in pregnancy is in line with the guidelines, and awareness of this issue among individuals with preconceptional anticoagulant therapy is probably high. In line with the unchanged proportion of anticoagulant use, we found no difference in maternal risk of VTE or obstetric bleeding risk over the study period. Of note, the obstetric events we identified were mainly antepartum and intrapartum, and the time trends in postpartum events might differ. Before our study, evidence about time trends in arterial thromboembolism during pregnancy was scarce. A European registry study showed a decreasing trend in adverse pregnancy outcomes in those with cardiovascular disease, but the study mainly focused on maternal mortality and heart failure.[23]

Regarding antiplatelet drug use during pregnancy, it is not unexpected to observe the substantial increase in its use during our study period, since high-quality evidence on low-dose aspirin for preeclampsia prevention has been established,[5,15,16] and updated guidelines have been implemented in recent years.[17–19] We found the start of antiplatelet drug prescriptions peaked at the end of the first trimester, which is in line with the current guidelines,[18,19] and a recent online survey among Dutch gynaecologists and residents (ie, starting aspirin at 12 [IQR 10–12] weeks' gestation).[24] A major strength of our study is that we present time trends in various maternal and perinatal outcomes over a period when aspirin use during pregnancy surged. It is promising to see that the risks of preeclampsia and eclampsia as well as low birthweight decreased in the most recent years (2017 onwards). Although some previous studies did not observe a decreased preeclampsia burden after the implementation of guidelines that recommend low-dose aspirin,[25,26] our findings suggest a modest population-level improvement, whereby the magnitude of the benefit could be even larger when taking into account the persistent increase in maternal age and the risk of gestational diabetes—an important risk factor of preeclampsia.[27] However, our study design cannot determine whether the changes in clinical outcomes were caused by the increase in aspirin use, as other (unmeasured) changes over the same time period might also contribute to these time trends (eg, improvement in other perinatal care[28,29] and changes in other maternal risk factors such as overweight and obesity[30]). Nevertheless, given the established effectiveness of low-dose aspirin for preventing placenta-mediated pregnancy complications,[5,16] it is reasonable to speculate that the increase in antiplatelet drug prescriptions during pregnancy might at least partly explain the decrease in risk of preeclampsia and eclampsia and low birthweight, and hence our findings can be seen as a support for the current guidelines.[17,19] Regardless of

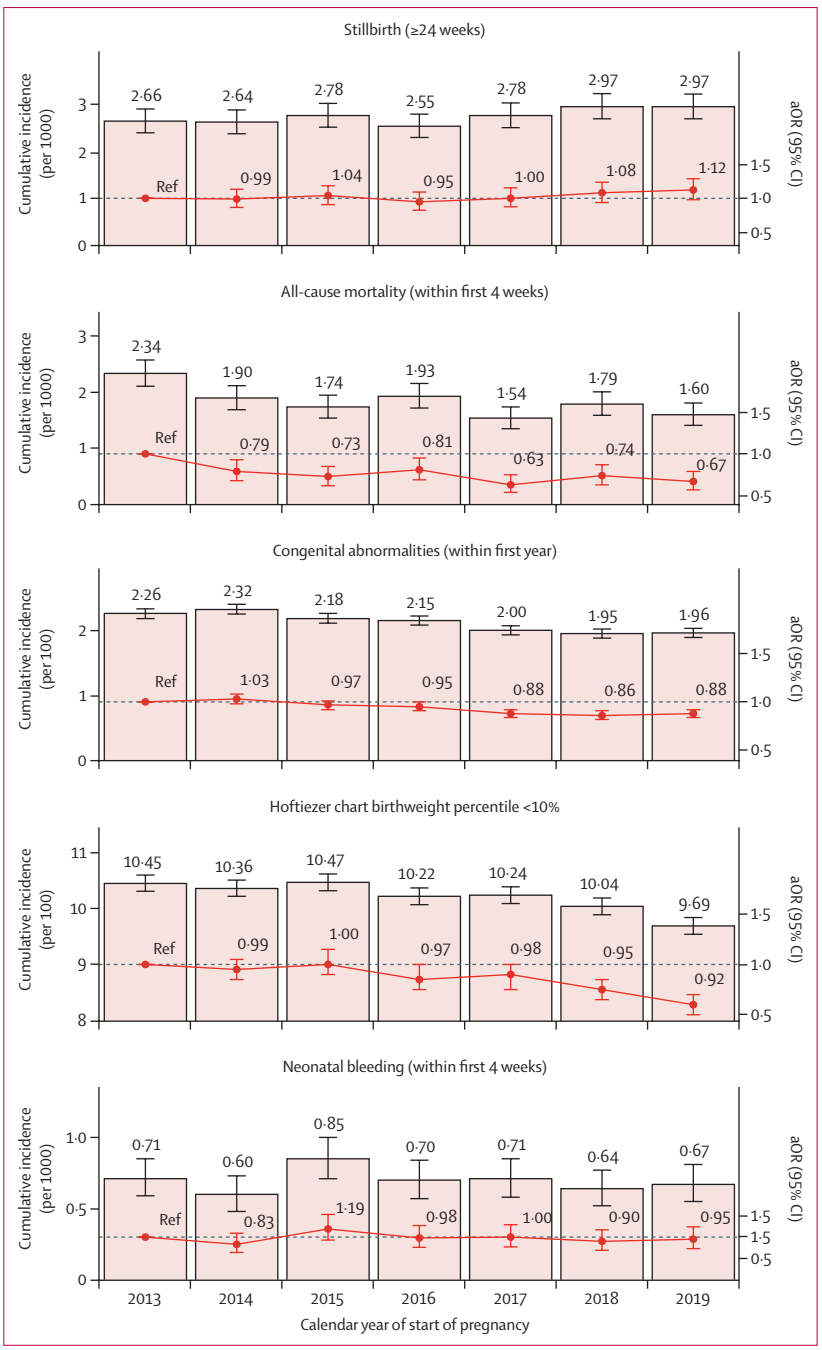


Figure 4: **Time trends in perinatal outcomes**
Except for the outcome of stillbirth (≥24 weeks), only liveborn infants were included for analyses. The aOR was adjusted using model 2 (details about adjustment models are provided in the Methods section). aOR=adjusted odds ratio. VTE=venous thromboembolism.

causality, our study indicated that at the population level, the burden of several maternal and perinatal outcomes was decreasing.

The following limitations should be noticed when interpreting our results. First, our data mainly covered pregnancies of Dutch residents with a gestational age of 22 weeks or more, and hence our findings cannot be directly applied to non-Dutch residents or pregnancies that did not continue until 22 weeks, which warrant additional research. Second, all variables in the study were identified by routinely collected data, and hence at risk of misclassification (where the reported absolute risk or prevalence was likely to be underestimated). Importantly, the accuracy of International Classification of Diseases codes for clinical outcomes has not yet been validated in our data. The various comorbidities were identified by diagnoses registered within hospitalisations before pregnancy, but they might not always require a hospitalisation. In addition, over-the-counter use of aspirin during pregnancy is possible in the Netherlands, although it is strongly recommended against, so the prevalence of aspirin use during pregnancy might have been slightly underestimated. However, it might be reasonable to assume the degree of misclassification is consistent over the years, and hence the time trends on the relative scale should not be influenced. Third, since details on the specific types of antithrombotic agents were not available, we assumed the heparin group prescribed during pregnancy exclusively concerned LMWH, and aspirin was the most commonly prescribed antiplatelet drug. Assumptions were also introduced when determining medication exposure due to lack of data on dose or amount of each medication prescription, or medication prescribed during hospitalisation. The consistent results from the various sensitivity analyses suggest that our findings should be considered robust, but further confirmations are needed if relevant data are available. Fourth, since we only examined antithrombotic therapy during pregnancy, we restricted the follow-up until dates of delivery to keep the time frames consistent. However, due to data limitations, when an obstetric event was diagnosed in a hospitalisation admitted before delivery but discharged later, we were unable to distinguish whether the event occurred before or after delivery. Fifth, the time trends we observed in the Dutch population might not be generalisable to a different population or health-care setting. Finally, as a reminder, our study is of a descriptive nature, and due to other unmeasured contemporaneous changes (ie, confounding factors), the findings cannot be causally interpreted.

Contributors

QC and LJJS contributed to the conceptualisation and design of the study and directly accessed and verified the underlying data reported in the manuscript. QC contributed to the literature search, data curation, data analysis, and data interpretation, and drafted the initial version of the manuscript. NvR, SCC, and LJJS contributed to the statistical analysis plan and data interpretation, and provided critical revisions for important intellectual content. LB, SM, and KWMB contributed to data interpretation and critical revisions for important intellectual content. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

The study used Dutch perinatal registry from Perined and non-public microdata from Statistics Netherlands. These data cannot be shared directly by the authors. Under certain conditions, these data are accessible for statistical and scientific research. For further information email info@perined.nl and microdata@cbs.nl.

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