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Substantial decrease in preeclampsia prevalence and risk over two decades: A population-based study of 1,153,227 deliveries in Norway

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ABSTRACT

Objectives: Analyze secular trends of preeclampsia in Norway based on risk factors.
Study design: Population-based cohort study of 1,153,227 women using data from Medical Birth Registry of Norway from 1999 to 2018. Aggregated data from Norwegian Prescription Database from 2004 to 2018 were used. Main exposure variable was time period. Descriptive statistics identified the prevalence of preeclampsia, labor induction and aspirin use. Multiple logistic regression analysis was performed to estimate the risk of preeclampsia during the time periods.
Main outcome measures: Preeclampsia.
Results: Overall preeclampsia prevalence decreased from 4.3% in 1999–2002 to 2.7% in 2015–2018. A reduction was observed in all subgroups of women with known risk factors (age, nulliparity, diabetes, chronic hypertension, assisted reproduction, twin pregnancy). Adjusted risk of preeclampsia was reduced by 44% from 1999-2002 to 2015–2018 (aOR = 0.56, 95%CI 0.54, 0.58), while the net prevalence of gestational hypertension remained stable over the study period. Labor induction increased 104%. Aspirin prescriptions increased among fertile women in the general Norwegian population.
Conclusions: Preeclampsia prevalence and risk were reduced regardless of risk factors and despite an increased proportion of high-risk parturients (advanced age, lower parity, use of assisted reproduction). A corresponding increase in aspirin prescriptions among fertile women and an overall increase in labor inductions were also observed, suggesting that clinical interventions may partly explain the observed reduction in preeclampsia prevalence. Lower average blood pressure and improved health in the population may also explain some of the reduction.

1. Introduction

Preeclampsia is a complex medical syndrome affecting 3–5% of pregnancies worldwide [1]. The etiology of preeclampsia is likely due to spiral artery pathology, placenta malperfusion and syncytiotrophoblast stress of other causes [2–5]. A two-stage paradigm describes how placenta syncytiotrophoblast stress and underlying maternal factors increase susceptibility to the generalized maternal vascular inflammatory response that causes endothelial dysfunction and clinical disease. [4]. Perinatal adverse effects of preeclampsia can cause long-term health consequences for both mother and child [6–8].

Previous studies have reported associations between several biologic risk factors and preeclampsia, such as extremes of maternal age, nulliparity, pre-gestational and gestational diabetes mellitus, chronic hypertension [9], prior history of preeclampsia [10], autoimmune disease [11], assisted reproductive technology (ART) [12], multiple gestation [13] and obesity [14]. We also have evidence for the association between socioeconomic factors and preeclampsia, such as maternal country of birth and education [15], while smoking has shown to be protective [16].

Interventions to reduce the risk of preeclampsia have also been studied. Prophylactic low-dose aspirin reduces the risk of pre-term

Abbreviations: aOR, adjusted odds ratio; ART, assisted reproductive technology; ATC, Anatomic Therapeutic Chemical; BMI, Body Mass Index; CHTN, chronic hypertension; CI, confidence interval; GH, gestational hypertension; MBRN, Medical Birth Registry of Norway; OR, odds ratio; PE, preeclampsia/eclampsia.

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preeclampsia (before 37 weeks of gestation) in high-risk women based on maternal factors, biophysical findings, and placental and maternal biomarkers [17].

Although many studies have focused on preeclampsia risk factors, studies on temporal trends [18] of hypertensive disorders of pregnancy are scarce. The demographics of delivering women has changed, and updated reports of preeclampsia prevalence are needed. The aim of this study was to analyze secular trends of preeclampsia in Norway from 1999 through 2018 based on risk factors, and reflect on how the increasing trend of clinical interventions, such as labor induction and aspirin use may have altered the prevalence of the disease over time.

2. Methods

This study is part of the larger PURPLE Study, which investigates adverse pregnancy outcomes in Norway from 1967 to 2018 using data from the Medical Birth Registry of Norway (MBRN). The study was approved by The Regional committee for Medical and Health Research Ethics in South-Eastern Norway (#2015/681) and the Institutional Personal Data Officer at Oslo University Hospital. Patient consent was not required for the use of de-identified and anonymized registry data.

Our study population included all women who delivered a singleton or twin pregnancy in Norway between 1999 and 2018 at gestational age ≥22 and <45 weeks (n = 1,153,227 women). The main exposure variable was time period of delivery, using 4-year increments.

Obstetric history, past medical history and other current maternal morbidity are routinely recorded in the standardized ambulatory prenatal record used throughout Norway. Mandatory notification to the MBRN occurs immediately after delivery by automatic transfer of information from the electronic hospital charts of both mother and baby. Gestational age at birth was based on fetal biometry performed at 17–20 weeks of gestation (98% of the study population), or on the first day of the last menstrual period in the rare instances when ultrasound-dating was not available (2%).

The main outcome variable was preeclampsia. Women with eclampsia were merged into the preeclampsia group for the analysis. Preeclampsia was defined as repeatedly confirmed de novo blood pressure elevation ≥140/90 mmHg after 20 weeks gestational age accompanied by proteinuria. Proteinuria was defined as $\geq 1^{+}$ on urine dipstick with a minimum of two measurements, or by urine protein ≥0.3 g/24 h or total protein/creatinine ratio >0.3. Eclampsia was defined as peripartum generalized seizures occurring up to seven days postpartum associated with preeclampsia or gestational hypertension.

Risk factors for hypertensive disorders of pregnancy were assessed as possible confounders to the main exposure variable. Maternal age at delivery was categorized into six groups (<20, 20–24, 25–29, 30–34, 35–39 and ≥40 years). Parity was categorized as 0, 1 and ≥2. Maternal country of birth was assigned as Norway or other. First-trimester smoking was categorized into four groups (no smoking, sometimes, daily, missing information). Maternal diabetes was classified into three categories: Type 1, type 2 and gestational diabetes based on national screening criteria in use at the time of the pregnancy. Chronic hypertension was defined as a binary variable and excluded hypertension as a complication of pregnancy, delivery or postpartum. Pre-pregnancy Body Mass Index (BMI) was categorized using World Health Organization classifications. Twin gestation and ART were dichotomized to yes/no variables.

Labor induction and aspirin use were studied as possible explanations for changes in preeclampsia prevalence over time. Induction of labor was dichotomized as yes/no. Population-based data on aspirin use among women age 20–39 years were taken from the Norwegian Prescription Database, using the Anatomic Therapeutic Chemical (ATC) code B01A C06 for acetylsalicylic acid 75 mg, the dose recommended in Norway during the study period for preeclampsia prevention in high-risk women. Only aggregate data was available, reported as use per 1000 women.

IBM SPSS Statistics for Windows version 27.0.0.0 was used for the analysis. We used descriptive statistics to determine the prevalence of preeclampsia and gestational hypertension, according to maternal characteristics, gestational age at delivery and use of labor induction. Logistic regression analysis was performed to estimate the crude odds ratios (OR) with 95% confidence intervals (CIs) of preeclampsia. Using multivariable logistic regression analysis, we assessed the independent association of time periods in 4-year increments to preeclampsia, with women delivering in 1999–2002 as the reference group. Adjustments were made for maternal age, parity, twin gestation, ART, country of birth, diabetes, chronic hypertension and 1st-trimester smoking.

3. Results

3.1. Main findings

Characteristics of the study population are reported in Table 1. Overall, the proportion of women with risk factors for preeclampsia increased during the study. Giving birth at advanced age (≥35 years) increased over the study period from 14.5% in 1999–2002 to 20.4% in 2014–2018 (Table 1). The proportion of nulliparous women increased, and women with higher parity decreased. Use of assisted reproduction increased, while 1st-trimester smoking decreased by 80% between the first and last time periods. Labor induction more than doubled in the study population from 1999 to 2002 (10.9%) to 2015–2018 (22.2%) (Table 1).

Of the 1,153,227 deliveries in the study population, 3.4% (n = 39,165) were affected by preeclampsia and 1.7% (n = 19,937) were affected by gestational hypertension (Table 2). The prevalence of preeclampsia was highest in the first time period in 1999–2002 (4.3%, CI 4.23, 4.44) with decreasing prevalence across successive time periods to 2.7% (CI 2.62, 2.75) in 2015–2018. Gestational hypertension prevalence had a transient increase from 1.5% (CI 1.42, 1.52) in 1999–2002 to 2.0% (CI 1.90, 2.01) in 2007–2010, and then progressively decreased to 1.6% (CI 1.55, 1.65) in 2015–2018.

Table 3 reports prevalence of preeclampsia by maternal and pregnancy characteristics and risk factors. Preeclampsia prevalence consistently decreased in all subgroups and time periods. Table 4 reports crude (OR) and adjusted odds ratios (aORs) for preeclampsia in all five time periods. After adjustment for risk factors for preeclampsia (maternal age, parity, twin pregnancy, ART, maternal country of birth, diabetes, chronic hypertension and smoking), a 44% decrease in the risk of preeclampsia (aOR = 0.56, 95%CI 0.54, 0.58) was observed in 2015–2018 compared to years 1999–2002. This adjustment only slightly changed the OR from the univariate analysis (OR = 0.61, 95%CI 0.59, 0.63), suggesting that these risk factors did not explain the reduction in preeclampsia prevalence.

Fig. 1 juxtaposes the prevalence of hypertensive diseases of pregnancy (total, preeclampsia and gestational hypertension) with risk for preeclampsia over the same time periods to illustrate the temporal decreasing trend.

3.2. Maternal age

Preeclampsia prevalence reduced in all maternal age groups. Among women ≥35 years old, preeclampsia decreased 30% from 4.2% at the start to 2.9% at the end of the study period (Table 1 and 3).

3.3. Parity

Preeclampsia prevalence declined 38% in nulliparous women (6.4% in 1999–2002 versus 4.0% in 2015–2018) (Table 3). There was a 43% decrease in preeclampsia among primiparous women (3.0 % in 1999–2002 versus 1.7% in 2015–2018) and a 37% decrease in multiparous women (2.7% in 1999–2002 versus 1.7% in 2015–2018).

Table 1
Characteristics of study population, per time period (n = 1,153,227 deliveries).

	1999–2002n = 226 117 % (n)	2003–2006 n = 225 205 % (n)	2007–2010 n = 238 502 % (n)	2011–2014n = 235 687 % (n)	2015–2018 n = 227 716 % (n)
Age, years					
<20	2.6 (5776)	2.1 (4792)	2.3 (5555)	1.6 (3741)	1.0 (2299)
20–24	15.4 (34 792)	14.2 (31 953)	14.7 (35 119)	13.9 (32 759)	10.9 (24 883)
25–29	35.0 (79 228)	31.9 (71 733)	31.0 (73 933)	31.7 (74 807)	32.7 (74 562)
30–34	32.4 (73 368)	34.6 (77 832)	32.7 (77 884)	33.1 (78 121)	35.0 (79 620)
35–39	12.5 (28 374)	14.8 (33 400)	16.3 (38 832)	16.2 (38 243)	16.7 (38 025)
≥ 40	2.0 (4579)	2.4 (5495)	3.0 (7179)	3.4 (8016)	3.7 (8327)
Parity					
0	40.2 (90 853)	41.2 (92 869)	42.5 (101 304)	42.3 (99 649)	42.4 (96 551)
1	35.6 (80 498)	35.7 (80 408)	35.4 (84 519)	36.6 (86 287)	37.1 (84 590)
≥ 2	24.2 (54 766)	23.1 (51 928)	22.1 (52 679)	21.1 (49 751)	20.5 (46 575)
Twin gestation	1.8 (4103)	1.8 (4130)	1.7 (4069)	1.6 (3833)	1.6 (3586)
Assisted reproduction	1.6 (3603)	2.2 (4955)	2.8 (6625)	3.1 (7362)	4.0 (9222)
Diabetes					
Type 1	0.4 (949)	0.5 (1068)	0.5 (1120)	0.5 (1090)	0.4 (981)
Type 2	0.2 (432)	0.3 (705)	0.4 (929)	0.3 (824)	0.4 (806)
Gestational	0.8 (1774)	0.9 (2044)	1.4 (3437)	2.8 (6614)	4.9 (11 236)
Chronic hypertension	0.7 (1483)	0.5 (1016)	0.6 (1388)	0.6 (1345)	0.5 (1189)
Country of birth					
Norway	83.4 (188 692)	81.4 (183 379)	78.2 (186 419)	73.1 (172 375)	69.8 (158 954)
Other	16.6 (37 425)	18.6 (41 826)	21.8 (52 083)	26.9 (63 312)	30.2 (68 762)
Smoking, 1st trimester					
No	64.7 (146 208)	67.3 (151 572)	72.7 (173 341)	78.3 (184 569)	87.2 (198 671)
Sometimes	2.2 (4900)	1.7 (3797)	1.4 (3440)	1.1 (2702)	0.7 (1688)
Daily	18.1 (40 990)	12.8 (28 726)	9.5 (22 584)	6.5 (15 244)	3.3 (7433)
Missing	15.0 (34 019)	18.3 (41 110)	16.4 (39 137)	14.1 (33 172)	8.7 (19 924)
Labor induction	10.9 (24.693)	13.6 (30 594)	16.3 (38 828)	20.0 (47 064)	22.2 (50 649)

Table 2
Prevalence of hypertensive disorders in pregnancy in the study population, per time period (n = 1 152 227 deliveries).

	1999–2002% (n)CI[a]	**2003–2006% (n)CI**	**2007–2010% (n)CI**	**2011–2014% (n)CI**	**2015–2018% (n)CI**
Preeclampsia	4.3 (9755)CI 4.23–4.44	3.8 (8561)CI 3.72–3.89	3.4 (8121)CI 3.33–3.47	2.8 (6613)CI 2.74–2.87	2.7 (6115)CI 2.62–2.75
Gestational hypertension	1.5 (3327)CI 1.42–1.52	1.8 (4128)CI 1.78–1.89	2.0 (4665)CI 1.90–2.01	1.8 (4169)CI 1.71–1.82	1.6 (3648)CI 1.55–1.65
Preeclampsia and gestational hypertension	5.8 (13 082)CI 5.69–5.88	5.6 (12 689)CI 5.53–5.72	5.4 (12 786)CI 5.27–5.45	4.6 (10 782)CI 4.45–4.66	4.3 (9763)CI 4.20–4.37

[a] CI: 95% confidence interval

3.4. Gestational age

Decreased prevalence of preeclampsia in both term and preterm deliveries over time was observed, with the highest prevalence in time period 1999–2002 (<34 weeks: 21.1%, 34–36 weeks: 14.8%, 37–44 weeks: 3.5%) and the lowest prevalence in time period 2015–2018 (<34 weeks: 17.7%, 34–36 weeks: 11.6%, 37–44 weeks: 2.1%) (Table 3).

3.5. Assisted reproduction and multiple gestation

The prevalence of preeclampsia decreased by approximately one-third among women with pregnancies resulting from assisted reproduction (7.9% versus 5.2%) (Table 3). There was a similar reduction in preeclampsia prevalence among women with twin gestations (13.6% versus 9.1%) and women with singleton pregnancies (4.1% versus 2.6%) over the study period. Twin gestations comprised less than two percent of the study population. A sensitivity analysis that excluded twin gestations (data not shown) from the logistic regression analysis found no change in the adjusted odds ratio describing a 44% reduction of preeclampsia risk from the start to the end of the study. Thus, twin gestations did not confound the observed decreasing risk of preeclampsia over the study period.

3.6. Maternal chronic diseases

Pre-gestational diabetes (type 1 and 2 diabetes) remained low and stable during the study period (Table 1). Preeclampsia prevalence among women with type 1 or type 2 diabetes was reduced from the first to the last time period by 35% and 45%, respectively (Table 3). Gestational diabetes increased from 0.7% at the study start to 4.9% at the study end (Table 1), but in these women, the prevalence of preeclampsia was significantly reduced (52%) over time. The prevalence of chronic hypertension was low during all study periods (<1%), and preeclampsia among women with chronic hypertension decreased 31% throughout the study period, from 21.4% in 1999–2002 to 14.8% in 2015–2018.

3.7. Socioeconomic risk factors

The proportion of foreign-born women giving birth in Norway almost doubled during the study period (16.5% in 1999–2002 versus 30.2% in 2015–2018) (Table 1). The prevalence of preeclampsia decreased among both Norwegian-born and immigrant women, by 36% and 39%, respectively (Table 3). There was a decreasing trend of preeclampsia prevalence among both smokers and non-smokers during the study period, as well as among women with missing data for smoking.

Table 3
Prevalence of preeclampsia (%) in the subgroups of women in time periods (n = 1 152 227 deliveries).

	1999–2002	2003–2006	2007–2010	2011–2014	2015–2018
Age, years					
<20	5.2 (302)	5.2 (250)	4.9 (270)	5.2 (194)	4.5 (103)
20–24	5.0 (1740)	4.5 (1446)	3.9 (1379	3.5 (1149)	3.3 (818)
25–29	4.4 (3458)	3.8 (2736)	3.3 (2472)	2.7 (2013)	2.7 (2007)
30–34	3.9 (2868)	3.4 (2623)	3.1 (2383)	2.4 (1860)	2.3 (1828)
35–39	4.1 (1163)	3.8 (1254)	3.4 (1332)	2.7 (1050)	2.7 (1021)
≥ 40	4.9 (224)	4.6 (252)	4.0 (285)	4.3 (347)	4.1 (338)
Parity					
0	6.4 (5820)	5.5 (5147)	4.8 (4892)	4.1 (4116)	4.0 (3855)
1	3.0 (2437)	2.7 (2135)	2.4 (2053)	1.9 (1603)	1.7 (1471)
≥ 2	2.7 (1498)	2.5 (1279)	2.2 (1176)	1.8 (894)	1.7 (789)
Gestational age, weeks					
≤34	21.1 (963)	21.1 (914)	19.4 (854)	19.2 (756)	17.7 (633)
34–36	14.8 (1490)	14.0 (1395)	12.5 (1276)	11.1 (1037)	11.6 (1053)
37–44	3.5 (7302)	3.0 (6252)	2.7 (5991)	2.2 (4820)	2.1 (4429)
Singleton gestation	4.1 (9197)	3.6 (8049)	3.3 (7682)	2.7 (6208)	2.6 (5788)
Twin gestation	13.6 (558)	12.4 (512)	10.8 (439)	10.6 (405)	9.1 (327)
Assisted reproduction	7.9 (285)	7.4 (366)	6.5 (430)	4.9 (361)	5.2 (483)
Diabetes					
Type 1	19.1 (181)	14.0 (150)	14.3 (160)	13.0 (142)	12.4 (122)
Type 2	11.1 (48)	7.5 (53)	10.4 (97)	7.3 (60)	6.1 (49)
Gestational	9.9 (175)	8.9 (181)	7.0 (240)	5.3 (352)	4.8 (542)
Chronic hypertension	21.4 (318)	21.8 (221)	20.7 (287)	17.1 (230)	14.8 (176)
Country of birth					
Norway	4.5 (8409)	4.0 (7269)	3.6 (6699)	3.0 (5156)	2.9 (4591)
Other	3.6 (1346)	3.1 (1292)	2.7 (1422)	2.3 (1457)	2.2 (1524)
Smoking, 1st trimester					
No	4.5 (6591)	3.9 (5881)	3.6 (6196)	2.9 (5373)	2.7 (5437)
Sometimes	3.7 (181)	3.4 (130)	2.8 (95)	3.0 (81)	2.2 (37)
Daily	3.5 (1427)	3.3 (953)	3.0 (671)	2.5 (379)	2.1 (154)
Missing	4.6 (1556)	3.9 (1597)	3.0 (1159)	2.4 (780)	2.4 (487)

Table 4
Risk of preeclampsia in time periods, crude and adjusted odds ratios (n = 1 152 227 deliveries).

	CrudeOR (95%CI)[a]	Adjusted[b]OR (95%CI)
Time period		
1999–2002	Ref	Ref
2003–2006	0.88 (0.85–0.90)	0.86 (0.83–0.89)
2007–2010	0.78 (0.76–0.81)	0.74 (0.72–0.77)
2011–2014	0.64 (0.62–0.66)	0.60 (0.58–0.62)
2015–2018	0.61 (0.59–0.63)	0.56 (0.54–0.58)

[a] OR (95%CI): Odds ratio (95% confidence interval)
[b] Adjusted for maternal age, parity, twin gestation, assisted reproduction, maternal country of birth, diabetes, chronic hypertension, 1st-trimester smoking

3.8. Aspirin

Aggregated data from the Norwegian Prescription Database showed an increase in aspirin prescriptions among women younger than 40 years old from 2004 to 2018 (Fig. 2). In 15–19 year-old women, a 146% increase in aspirin prescriptions from 2004 (0.35 per 1000 women) to 2018 (0.86 per 1000 women) was observed. Aspirin prescriptions increased by 65%, 80%, 70% and 29% among women 20–24, 25–29, 30–34, and 35–39 years old, respectively.

4. Discussion

4.1. Principal findings

In the present study with a 20-year population-based data of 1,153,227 women, preeclampsia prevalence decreased 37% between the first and last four-year time increments. This trend was observed despite an increasing proportion of high-risk parturients. Advanced maternal age and assisted reproduction, both risk factors for preeclampsia, increased during the study period. Conversely, 1st-trimester smoking, which is inversely associated with preeclampsia, decreased. After adjustment for known risk factors associated with preeclampsia, preeclampsia risk was reduced by 44% during the study period, indicating that the observed population changes could not explain the decreasing risk of preeclampsia.

A previous Norwegian study using MBRN data showed an increase in preeclampsia prevalence from 1967 to 1999 and a decreasing trend from 2000 to 2010 [19]. The latter is in line with our findings of a further decreasing preeclampsia prevalence. A novel finding in our study is that we observed that the reduction in preeclampsia prevalence occurred in all subgroups of women with known risk factors, despite that the proportion of high-risk women increased over time. Globally, preeclampsia prevalence increased during our study period [20]. In low and middle-income countries, preeclampsia rates are reported to be higher than in high-income countries such as Norway [21]. Preeclampsia prevalence in non-European countries with high socioeconomic indices and comprehensive national healthcare systems observe conflicting results. Our findings differ from a Canadian study that observed a doubling of preeclampsia prevalence from 1989 to 2012 [22]. In line with our findings, however, an Australian study found a decreasing prevalence of preeclampsia between 2000 and 2008 [23].

Changes in clinical routines such as increased use of labor induction regardless of indication could partially explain the reduction of preeclampsia prevalence in late gestation, but not in the earlier gestations where induction of labor is rarely used. Labor induction for pregnancies >41 weeks gestational age has been shown to reduce the risk of adverse perinatal outcomes, including preeclampsia [24,25], and has become standard care in the past decade [26]. Norway has not implemented elective labor induction at 39 weeks in low-risk nulliparous women, despite studies showing decreased risk of Cesarean delivery [27], maternal morbidity and perinatal mortality [28] compared to expectant management. We observed that the temporal increase in labor induction corresponded with a temporal decreased prevalence of preeclampsia.

We analyzed gestational hypertension in our study population and observed a minimal net positive change in prevalence during the total study period. The transient increase in gestational hypertension

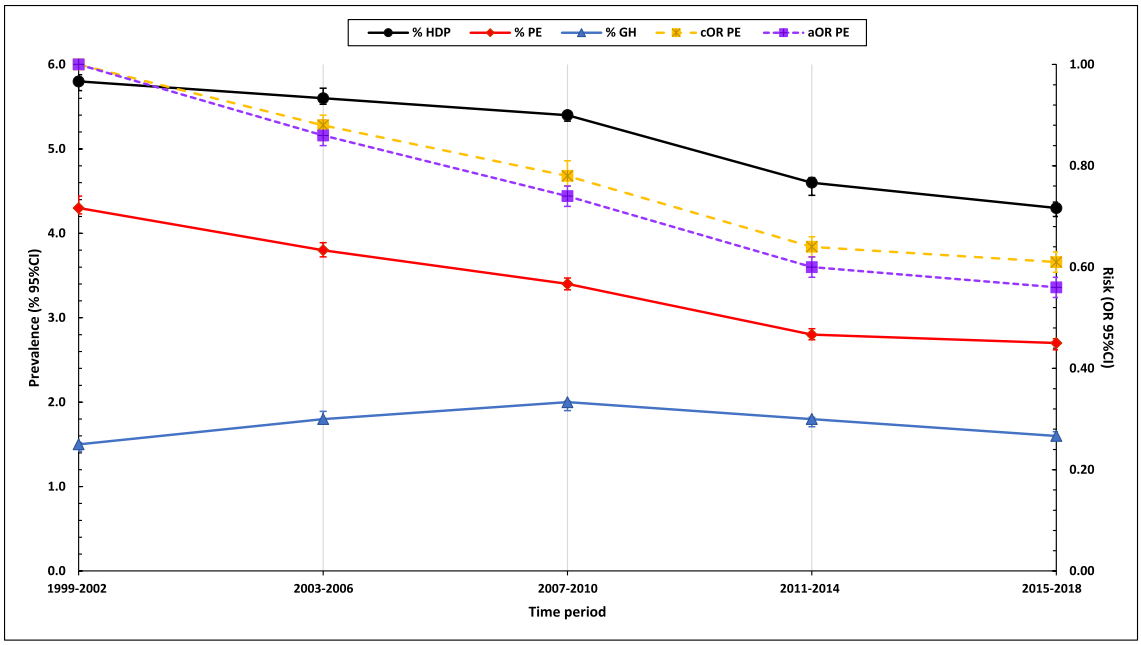

Fig. 1. Title: Prevalence of hypertensive disorders of pregnancy (total, preeclampsia, gestational hypertension) and risk of preeclampsia, per time period (n = 1 152 227 deliveries). %: percent, OR: odds ratio, 95% CI: 95% confidence interval, cOR: crude odds ratio, aOR: adjusted odds ratio (adjusted for maternal age, parity, twin gestation, assisted reproduction, maternal country of birth, diabetes, chronic hypertension, 1st-trimester smoking), HDP: hypertensive disorders of pregnancy (preeclampsia and gestational hypertension), PE: preeclampsia. GH: gestational hypertension.

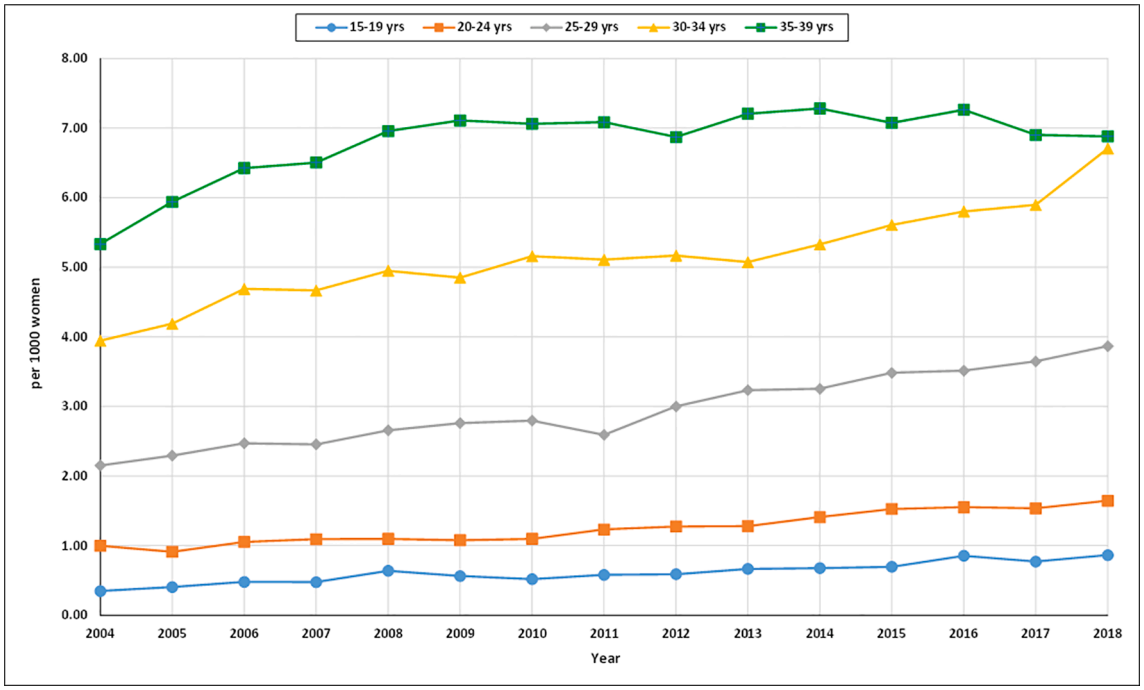

Fig. 2. Title: Aspirin prescriptions among women in Norway by age group. yrs: years old.

paralleling the reduced preeclampsia prevalence seen in the early years of the study, could indicate that the hypertensive disorder of pregnancy phenotype shifted from the more severe form (preeclampsia) to the clinically less severe form (gestational hypertension). However, gestational hypertension prevalence at the end of the study was similar to the study start (net increase of 6.7%), whereas preeclampsia prevalence continued to fall. This suggests a more profound effect across the hypertensive disorder group, where less women were affected, and with a less severe phenotype.

Similar to current NICE guidelines [29], Norwegian national guidelines since 2014 [30] have recommended prenatal low-dose aspirin starting at the end of the first trimester for preeclampsia prevention in high-risk pregnancies. As far back as 1998 [31], aspirin was mentioned in the Norwegian guidelines for preeclampsia prevention in parous women with a previous history of preeclampsia. It is thus likely that aspirin has been used in high-risk pregnancies before the 2014 recommendation, but at an unknown frequency.

Aspirin 75 mg-dose is only available by prescription in Norway. Low-

dose aspirin is used for prevention of cardiovascular diseases in high-risk populations [32], but women of reproductive age rarely take aspirin for this indication [33]. Aspirin used for pain, fever and rheumatologic illnesses are usually prescribed at higher doses. We interpret the increased prescriptions of 75 mg aspirin daily to women <40 years old in Norway from 2004 to 2018 is likely due to increased preeclampsia aspirin prevention, although specific indications for aspirin use were not available.

Decreased preeclampsia prevalence in the preterm groups may be associated with increased aspirin prescriptions in women of reproductive age in the study period. However, the Norwegian recommendations have targeted parous women with previous obstetric complications, and thus probably cannot explain the 38% reduction of preeclampsia prevalence among the nulliparous women in our study. Although the specific pathophysiologic effects of aspirin in preventing especially early-onset preeclampsia remain unknown, a recent paper suggests that efficient aspirin prophylaxis delays the metabolic clock of gestation in high-risk women [34].

Mean systolic and diastolic blood pressures have decreased among women in Norway in all age groups over the past decades, despite a greater prevalence of overweight/obesity and diabetes in the population [35,36]. The cause of this trend is unknown, but an association between health, wellbeing, and socioeconomic status in Norway has been reported [37]. It has been speculated that general health improvement over time, such as dietary changes including reduced use of salt, may explain this trend [36]. General improvement in health behavior with more focus on diet, physical activity and smoking cessation may also have had an overall positive effect on maternal health during our study period. A general improvement in health resulting in fewer hypertensive complications may represent an unmeasurable confounder in our study.

4.2. Strengths and limitations

The strength of this study is its large population-based dataset of 1,153,227 deliveries, including information on the main risk factors for preeclampsia. MBRN data are considered suitable for research [38] with validated variables [39]. For the multivariate regression analysis, we included biologic and socioeconomic exposure variables previously known to be associated with hypertensive disorders of pregnancy [9,13,15]. The risk of information bias is low, as all deliveries in Norway are registered in the MBRN with standardized recording of pregnancy and birth outcomes. MBRN still uses a classic definition of preeclampsia, which is an added strength of this large patient-based epidemiological study, as the classification of hypertensive disorders of pregnancy did not change over the study period. Updated definitions of preeclampsia that include signs of preeclampsia-associated organ dysfunction in the absence of proteinuria [14,40] were not applicable in this study, as these data were not available. Since such expanded preeclampsia definition likely increases the preeclampsia rate and reduces the rate of gestational hypertension [41,42], preeclampsia prevalence in our study may be underreported. Women with new-onset preeclampsia without proteinuria were registered as gestational hypertension in the MBRN. This may have resulted in non-differential misclassification [43] of the outcome variables for hypertensive disorders of pregnancy, resulting in a slight underestimation of the reported odds ratios.

Sixty-five percent of deliveries lacked BMI data, since the MBRN only started collecting data on pre-pregnancy height and weight in 2006. As such, BMI was not included in the analyses in our study, although it is a known risk factor for both early and late-onset preeclampsia [44].

4.3. Clinical implications

To interpret our findings in a clinical context, we investigated the temporal trends of aspirin prescriptions and labor induction during the study period. During our study, there was a parallel increase in aspirin prescriptions among women <40 years old and an increase in labor induction. Both interventions – aspirin and labor induction – may improve maternal and fetal health, but the optimal risk/benefit balance and targeted patient groups for preventing preeclampsia with these interventions merit further research. We suggest that future studies on elective labor induction should also investigate temporal changes in preeclampsia prevalence.

4.4. Conclusion

During the 20-year study period, we observed a decreasing trend in preeclampsia prevalence and risk regardless of gestational age group at delivery, parity, maternal age, maternal chronic disease, and socioeconomic indices. The observed demographic changes would expectedly have increased the overall prevalence of preeclampsia; delivering women were older, had lower parity, and higher rates of assisted reproduction and gestational diabetes. Other preeclampsia risk factors such as pre-gestational diabetes, chronic hypertension and twin gestation remained relatively stable during the study period.

In conclusion, we found that measurable epidemiological changes could not account for the reduced preeclampsia risk in the present study. Changes in clinical routines may partly explain the reduction of preeclampsia prevalence, namely aspirin use for parous women and labor induction in term pregnancies. General health improvements on a population level may also have affected the results of this study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] E. Abalos, C. Cuesta, A.L. Grosso, D. Chou, L. Say, Global and regional estimates of preeclampsia and eclampsia: a systematic review, Eur. J. Obstet. Gynecol. Reprod. Biol. 170 (1) (2013) 1–7, https://doi.org/10.1016/j.ejogrb.2013.05.005.
[2] T.Y. Khong, E.E. Mooney, I. Ariel, N.C.M. Balmus, T.K. Boyd, M.-A. Brundler, H. Derricott, M.J. Evans, O.M. Faye-Petersen, J.E. Gillan, A.E.P. Heazell, D. S. Heller, S.M. Jacques, S. Keating, P. Kelehan, A. Maes, E.M. McKay, T.K. Morgan, P.G.J. Nikkels, W.T. Parks, R.W. Redline, I. Scheimberg, M.H. Schoots, N.J. Sebire, A. Timmer, G. Turowski, J.P. van der Voorn, I. van Lijnschoten, S.J. Gordijn, Sampling and definitions of placental lesions: amsterdam placental workshop group consensus statement, Arch. Pathol. Lab Med. 140 (7) (2016) 698–713, https://doi.org/10.5858/arpa.2015-0225-CC.
[3] C.W.G. Redman, A.C. Staff, J.M. Roberts, Syncytiotrophoblast stress in preeclampsia: the convergence point for multiple pathways, Am. J. Obstet. Gynecol. (2020), https://doi.org/10.1016/j.ajog.2020.09.047.
[4] A.C. Staff, The two-stage placental model of preeclampsia: An update, J. Reprod. Immunol. 134–135 (2019) 1–10, https://doi.org/10.1016/j.jri.2019.07.004.
[5] C.W.G. Redman, A.C. Staff, biomarkers, syncytiotrophoblast stress, and placental capacity, Am. J. Obstet. Gynecol. 213 (4) (2015) S9.e1–S9.e4, https://doi.org/10.1016/j.ajog.2015.08.003.
[6] B.W.J. Mol, C.T. Roberts, S. Thangaratinam, L.A. Magee, C.J.M. de Groot, G. J. Hofmeyr, Pre-eclampsia, Lancet 387 (10022) (2016) 999–1011, https://doi.org/10.1016/S0140-6736(15)00070-7.
[7] L.C. Chappell, C.A. Cluver, J. Kingdom, S. Tong, Pre-eclampsia, Lancet 398 (10297) (2021) 341–354, https://doi.org/10.1016/S0140-6736(20)32335-7.
[8] A.C. Staff, C.W.G. Redman, D. Williams, P. Leeson, K. Moe, B. Thilaganathan, P. Magnus, E.A.P. Steegers, E.Z. Tsigas, R.B. Ness, L. Myatt, L. Poston, J.M. Roberts, Pregnancy and long-term maternal cardiovascular health: progress through harmonization of research cohorts and biobanks, Hypertension 67 (2) (2016) 251–260, https://doi.org/10.1161/HYPERTENSIONAHA.115.06357.
[9] K.B. Sole, A.C. Staff, K. Laine, Maternal diseases and risk of hypertensive disorders of pregnancy across gestational age groups, Pregnancy Hyperten. 25 (2021) 25–33, https://doi.org/10.1016/j.preghy.2021.05.004.

[10] C. Ebbing, S. Rasmussen, R. Skjaerven, L.M. Irgens, Risk factors for recurrence of hypertensive disorders of pregnancy, a population-based cohort study, Acta Obstet. Gynecol. Scand. 96 (2) (2017) 243–250, https://doi.org/10.1111/aogs.13066.
[11] Y. Dong, F. Yuan, Z. Dai, Z. Wang, Y. Zhu, B. Wang, Preeclampsia in systemic lupus erythematosus pregnancy: a systematic review and meta-analysis, Clin. Rheumatol. 39 (2) (2020) 319–325, https://doi.org/10.1007/s10067-019-04823-8.
[12] S.H. Petersen, C. Bergh, M. Gissler, B.O. Asvold, L.B. Romundstad, A. Tiitinen, et al., Time trends in placenta-mediated pregnancy complications after assisted reproductive technology in the Nordic countries, Am. J. Obstet. Gynecol. (2020) e1–e19, https://doi.org/10.1016/j.ajog.2020.02.030.
[13] K. Laine, G. Murzakanova, K.B. Sole, A.D. Pay, S. Heradstveit, S. Räisänen, Prevalence and risk of pre-eclampsia and gestational hypertension in twin pregnancies: a population-based register study, BMJ Open 9 (7) (2019) e029908, https://doi.org/10.1136/bmjopen-2019-029908.
[14] M.A. Brown, L.A. Magee, L.C. Kenny, S.A. Karumanchi, F.P. McCarthy, S. Saito, et al., The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice, Pregnancy Hypertens. 13 (2018) 291–310, https://doi.org/10.1016/j.preghy.2018.05.004.
[15] K.B. Sole, A.C. Staff, K. Laine, The association of maternal country of birth and education with hypertensive disorders of pregnancy: A population-based study of 960 516 deliveries in Norway, Acta Obstet. Gynecol. Scand. 97 (10) (2018) 1237–1247, https://doi.org/10.1111/aogs.13393.
[16] L. England, J. Zhang, Smoking and risk of preeclampsia: a systematic review, Front Biosci. 12 (2007) 2471–2483, https://doi.org/10.2741/2248.
[17] D.L. Rolnik, D. Wright, L.C. Poon, N. O'Gorman, A. Syngelaki, C. de Paco Matallana, R. Akolekar, S. Cicero, D. Janga, M. Singh, F.S. Molina, N. Persico, J. C. Jani, W. Plasencia, G. Papaioannou, K. Tenenbaum-Gavish, H. Meiri, S. Gizurarson, K. Maclagan, K.H. Nicolaides, Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, N. Engl. J. Med. 377 (7) (2017) 613–622, https://doi.org/10.1056/NEJMoa1704559.
[18] C.L. Roberts, J.B. Ford, C.S. Algert, S. Antonsen, J. Chalmers, S. Cnattingius, M. Gokhale, M. Kotelchuck, K.K. Melve, A. Langridge, C. Morris, J.M. Morris, N. Nassar, J.E. Norman, J. Norrie, H.T. Sorensen, R. Walker, C.J. Weir, Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study, BMJ Open 1 (1) (2011) e000101, https://doi.org/10.1136/bmjopen-2011-000101.
[19] K. Klungsøyr, N.H. Morken, L. Irgens, S.E. Vollset, R. Skjærven, Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival, Paediatr. Perinat. Epidemiol. 26 (3) (2012) 190–198, https://doi.org/10.1111/j.1365-3016.2012.01260.x.
[20] W. Wang, X. Xie, T. Yuan, Y. Wang, F. Zhao, Z. Zhou, et al., Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study, BMC Pregnancy Childbirth 21 (1) (2021) 364, https://doi.org/10.1186/s12884-021-03809-2.
[21] L. Ghulmiyyah, B. Sibai, Maternal mortality from preeclampsia/eclampsia, Semin. Perinatol. 36 (1) (2012) 56–59, https://doi.org/10.1053/j.semperi.2011.09.011.
[22] N. Auger, Z.-C. Luo, A.M. Nuyt, J.S. Kaufman, A.I. Naimi, R.W. Platt, W.D. Fraser, Secular trends in preeclampsia incidence and outcomes in a large canada database: a longitudinal study over 24 years, Can. J. Cardiol. 32 (8) (2016) 987.e15–987.e23, https://doi.org/10.1016/j.cjca.2015.12.011.
[23] C. Thornton, H. Dahlen, A. Korda, A. Hennessy, The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000–2008, Am. J. Obstet. Gynecol. 208 (6) (2013) 476.e1–476.e5, https://doi.org/10.1016/j.ajog.2013.02.042.
[24] Wennerholm UB, Saltvedt S, Wessberg A, Alkmark M, Bergh C, Wendel SB, et al. Induction of labour at 41 weeks versus expectant management and induction of labour at 42 weeks (SWEdish Post-term Induction Study, SWEPIS): multicentre, open label, randomised, superiority trial. BMJ. 2019;367:l6131. https://doi.org/10.1136/bmj.l6131.
[25] M.K. Campbell, T. Østbye, L.M. Irgens, Post-term birth: risk factors and outcomes in a 10-year cohort of Norwegian births, Obstet. Gynecol. 89 (4) (1997) 543–548, https://doi.org/10.1016/s0029-7844(97)00049-5.
[26] Heimstad R, Augensen K, Grønberg M, Nakling J, Strindsklev S. Overtidig svangerskap 2010, Norsk gynekologisk forening Veileder i fødselshjelp (2008). [updated August 30, 2010. Available from: https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/arkiv-utgatte-veiledere/].
[27] W.A. Grobman, M.M. Rice, U.M. Reddy, A.T.N. Tita, R.M. Silver, G. Mallett, K. Hill, E.A. Thom, Y.Y. El-Sayed, A. Perez-Delboy, D.J. Rouse, G.R. Saade, K.A. Boggess, S. P. Chauhan, J.D. Iams, E.K. Chien, B.M. Casey, R.S. Gibbs, S.K. Srinivas, G. K. Swamy, H.N. Simhan, G.A. Macones, Labor induction versus expectant management in low-risk nulliparous women, N. Engl. J. Med. 379 (6) (2018) 513–523, https://doi.org/10.1056/NEJMoa1800566.
[28] W.A. Grobman, A.B. Caughey, Elective induction of labor at 39 weeks compared with expectant management: a meta-analysis of cohort studies, Am. J. Obstet. Gynecol. 221 (4) (2019) 304–310, https://doi.org/10.1016/j.ajog.2019.02.046.
[29] Hypertension in pregnancy: diagnosis and management: NICE guidelines; 2019 [updated June 25, 2019. Available from: https://www.nice.org.uk/guidance/ng133/chapter/Recommendations.
[30] Staff A, Andersgaard AB, Henriksen T, Langesæter E, Magnussen E, Michelsen TM, et al. Hypertensive svangerskapskomplikasjoner og eklampsi. Norsk gynekologisk forening Veileder i fødselshjelp (2014). [Available from: https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/arkiv-utgatte-veiledere/veileder-i-fodselshjelp-2014/28.-hypertensive-svangerskapskomplikasjoner-og-eklampsi-pasientinformasjon-2016/].
[31] Øian P, Henriksen T, Sviggum O. Hypertensive svangerskapskomplikasjoner. Norsk gynekologisk forening Veileder i fødselshjelp (1998). [Available from: https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/arkiv-utgatte-veiledere/].
[32] Collaborative overview of randomised trials of antiplatelet therapy–I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. 1994;308 (6921):81-106.
[33] P.M. Ridker, N.R. Cook, I.-M. Lee, D. Gordon, J.M. Gaziano, J.E. Manson, C. H. Hennekens, J.E. Buring, A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women, N. Engl. J. Med. 352 (13) (2005) 1293–1304, https://doi.org/10.1056/NEJMoa050613.
[34] X. Li, A. Milosavljevic, S.H. Elsea, C.C. Wang, F. Scaglia, A. Syngelaki, K. H. Nicolaides, L.C. Poon, Effective aspirin treatment of women at risk for preeclampsia delays the metabolic clock of gestation, Hypertension 78 (5) (2021) 1398–1410, https://doi.org/10.1161/HYPERTENSIONAHA.121.17448.
[35] I. Njølstad, E.B. Mathiesen, H. Schirmer, D.S. Thelle, The Tromso study 1974–2016: 40 years of cardiovascular research, Scand. Cardiovasc. J. 50 (5–6) (2016) 276–281, https://doi.org/10.1080/14017431.2016.1239837.
[36] J. Holmen, T.L. Holmen, A. Tverdal, O.L. Holmen, E.R. Sund, K. Midthjell, Blood pressure changes during 22-year of follow-up in large general population - the HUNT study, Norway, BMC Cardiovasc Disord. 16 (2016) 94, https://doi.org/10.1186/s12872-016-0257-8.
[37] J.A. Olsen, M.H. Lindberg, A.N. Lamu, Health and wellbeing in Norway: Population norms and the social gradient, Soc. Sci. Med. 259 (2020) 113155, https://doi.org/10.1016/j.socscimed.2020.113155.
[38] J. Langhoff-Roos, L. Krebs, K. Klungsøyr, R.I. Bjarnadottir, K. Källén, A.-M. Tapper, M. Jakobsson, P.E. Børdahl, P.G. Lindqvist, K. Gottvall, L.B. Colmorn, M. Gissler, The Nordic medical birth registers–a potential goldmine for clinical research, Acta Obstet. Gynecol. Scand. 93 (2) (2014) 132–137, https://doi.org/10.1111/aogs.12302.
[39] L.C.V. Thomsen, K. Klungsøyr, L.T. Roten, C. Tappert, E. Araya, G. Baerheim, K. Tollaksen, M.H. Fenstad, F. Macsali, R. Austgulen, L. Bjørge, Validity of the diagnosis of pre-eclampsia in the Medical Birth Registry of Norway, Acta Obstet. Gynecol. Scand. 92 (8) (2013) 943–950, https://doi.org/10.1111/aogs.12159.
[40] A.L. Tranquilli, G. Dekker, L. Magee, J. Roberts, B.M. Sibai, W. Steyn, G.G. Zeeman, M.A. Brown, The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP, Pregnancy Hypertens. 4 (2) (2014) 97–104, https://doi.org/10.1016/j.preghy.2014.02.001.
[41] N. Khan, W. Andrade, H. De Castro, A. Wright, D. Wright, K.H. Nicolaides, Impact of new definitions of pre-eclampsia on incidence and performance of first-trimester screening, Ultrasound Obstet. Gynecol. 55 (1) (2020) 50–57, https://doi.org/10.1002/uog.21867.
[42] A. Tochio, S. Obata, Y. Saigusa, R. Shindo, E. Miyagi, S. Aoki, Does pre-eclampsia without proteinuria lead to different pregnancy outcomes than pre-eclampsia with proteinuria? J. Obstet. Gynaecol. Res. 45 (8) (2019) 1576–1583, https://doi.org/10.1111/jog.14017.
[43] L. Gordis, Epidemiology, 4th. edition, Saunders, Elsevier, Philadelphia, 2009.
[44] M.J. Bicocca, H. Mendez-Figueroa, S.P. Chauhan, B.M. Sibai, Maternal obesity and the risk of early-onset and late-onset hypertensive disorders of pregnancy, Obstet. Gynecol. 136 (1) (2020) 118–127, https://doi.org/10.1097/AOG.0000000000003901.