Appendix 1. Description of Subset of Pregnancies With Date of Preeclampsia Diagnosis and Sensitivity Analysis

Since 1999, the Medical Birth Registry of Norway has categorized its information on hypertensive disorders in pregnancy in the following categories: “preeclampsia, mild”, “preeclampsia, severe”, “preeclampsia, before 34 weeks”, “HELLP syndrome”, “eclampsia”, “gestational hypertension (without proteinuria)” and “pre-existing hypertension.”[31] Data for the birth registry is gathered from the prenatal record, the hospital chart and from information gathered from the mother and health care professionals. We defined a preeclamptic pregnancy as a pregnancy with any of the 3 preeclampsia diagnoses (mild, severe or before 34 weeks), HELLP, or eclampsia. We excluded pregnancies with a preeclampsia diagnosis in the presence of “pre-existing hypertension.” 21,020 pregnancies met our criteria for preeclampsia.

The date of clinical diagnosis of preeclampsia is not recorded in the birth registry. This information may be found in the prenatal record, which contains clinical information from routine prenatal visits. The prenatal record may still not capture the diagnosis of all cases of preeclampsia. For example, if symptomatic preeclampsia arises acutely, the woman may be referred directly to hospital. Preeclampsia diagnosis would be recorded in the hospital chart but would not be evident in the prenatal records. Similarly, cases of preeclampsia that emerge in the hospital setting after labor has begun will not appear in prenatal records.

As a separate project, prenatal records and hospital discharge records had been reviewed for

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women participating in the Norwegian Mother and Child Cohort Study (MoBa). The purpose of this project was to validate preeclampsia as it is recorded in the birth registry. MoBa enrolled 107,000 early and ongoing pregnancies during 1999-2008. For the validation study, Norwegian investigators requested that the delivering hospitals in Norway provide prenatal clinic records and hospital discharge codes for all pregnancies in MoBa for which the birth registry had recorded a diagnosis of preeclampsia. In addition, records were requested for a random sample of 2000 MoBa pregnancies without preeclampsia.

Prenatal records were inspected for the earliest evidence of elevated blood pressure (systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg after 20 weeks gestation) and at least 1+ proteinuria at the same visit. Gestational age at the time of clinical diagnosis was based on the gestational age recorded by the midwife/ doctor at the time of the visit.

We used data from this validation subset to estimate a distribution of the time of preeclampsia diagnosis that we could apply to all cases of preeclampsia in our study. In order to take into account the time that preeclampsia might have been present before being recorded at a prenatal visit, we assumed that preeclampsia emerged half-way between the prenatal visit of diagnosis and the previous prenatal visit. Prenatal care is provided to all pregnant women in Norway and is widely used. Before week 30, median time between date of diagnosis and previous visit was 2 weeks; the median thereafter was 1 week. We made the further assumption that, once diagnosed, preeclampsia lasted until the end of pregnancy.

There were 3800 singleton pregnancies with preeclampsia recorded in the birth registry and

eligible for inclusion in this study. Two hospitals, representing 581 pregnancies (15%), declined participation in the validation study. Of the remaining 3219 pregnancies, adequate prenatal records were received for 3037 pregnancies (94%).

Among the 3037 pregnancies with adequate documentation, 1857 (61%) could be assigned a gestational age at diagnosis of preeclampsia. Of the remaining 1180 without an explicit date of diagnosis, 220 (19%) met full criteria for preeclampsia in the antenatal chart but had 4 or fewer visits abstracted for administrative purposes. We excluded these because the date of diagnosis (taking into account the timing since previous visit) could not be inferred with precision.

This exclusion left 960 cases without a time of diagnosis. 65% had evidence of either hypertension or proteinuria but not both; another 14% had evidence of both hypertension and proteinuria, but not at the same visit; and 21% of had no evidence of either hypertension or proteinuria in the prenatal record. While this 21% might include false-positive reports, they also would include women with abrupt appearance of symptoms that led them to be admitted directly to hospital, women whose preeclampsia emerged during labor, and women with milder forms of disease.

For the purposes of estimating time of diagnosis in the primary analysis, we excluded all 1180 pregnancies without a recorded diagnosis in the prenatal records, implicitly assuming that their pregnancy week of diagnosis had the same distribution as all other cases of preeclampsia. There is no reason to suppose that their diagnosis could have been even earlier than observed among the 1857 pregnancies with date of diagnosis. We did a sensitivity analysis in which we assumed the opposite: that preeclamptic pregnancies lacking a prenatal date of diagnosis

received a diagnosis of preeclampsia on the date of their delivery. This assumption is consistent with intrapartum emergence of preeclampsia which seems more plausible for many of these pregnancies. We present results of this sensitivity analysis below.

Before extrapolating from the 1857 women in the subset with a defined date of preeclampsia diagnosis to the whole population of 21,020 pregnancies with preeclampsia, we made two comparisons. First, we compared the 1857 pregnancies with date of preeclampsia diagnosis with the 1180 pregnancies with preeclampsia having no identified date of diagnosis; the two groups were virtually identical (Appendix 4). We then compared the 1857 pregnancies having a date of diagnosis with all 21,020 preeclamptic pregnancies in the birth registry (Table 2). Based on the similarity of those two groups, we concluded that the distribution of preeclampsia diagnosis based on the 1857 pregnancies reasonably characterized all cases of preeclampsia in the birth registry. We applied this distribution to the full sample of deliveries with preeclampsia.

Sensitivity analysis

The main analysis relied on the assumption that the distribution of preeclampsia diagnosis times in the 1857 pregnancies with evidence of preeclampsia in the prenatal record was representative of the distribution of diagnosis times among all pregnancies in the birth registry. In order to test this assumption we conducted a sensitivity analysis in which the date of diagnosis for the 1857 pregnancies in the main analysis remained the same. For those additional pregnancies (N=220) with clinical criteria in the prenatal record but with 4 or fewer visits abstracted, we assigned a diagnosis time at the gestational age when clinical criteria were first

met. For the remaining 960 pregnancies without evidence of preeclampsia in the prenatal record, the diagnosis of preeclampsia was assigned at the time of birth.

Sensitivity Analysis Results

The new assumptions in the sensitivity analysis shifted the overall distribution of preeclampsia diagnosis times later in gestation, with a median time of diagnosis of 37 weeks (10^{th} and 90^{th} percentile; 30.5 weeks and 40 weeks). This shift did not affect the risk of stillbirth in non-preeclamptic pregnancies, but it did increase the risk in preeclamptic pregnancies compared with the primary analysis. In the sensitivity analysis, the risk of fetal death was 19 per 1,000 at 26 weeks, 7 per 1,000 at 28 weeks, 4 per 1,000 at 30 weeks and almost 2 per 1,000 at 34 weeks (Appendix 5). These higher risks produced higher risk ratios at every week (Appendix 5), with the same pattern of steeply declining risk across gestation.

The assumptions of the sensitivity analysis allow us to consider the result if some cases of preeclampsia emerge fully only at the time of delivery. The fetuses in these pregnancies are presumably exposed to preeclampsia for a shorter time, but the risk among those exposed is greater. To the extent that preeclampsia in a portion of pregnancies emerged late in pregnancy without being recorded in the prenatal records, our main analysis provides a conservative estimate.

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Appendix 2. Statistical Methods

Estimation of the numbers of new preeclampsia cases by gestational week

Using medical records, we assigned a date of clinical diagnosis for 1857 cases of preeclampsia who met our strict criteria for diagnosis (see Appendix 1). Thus, we have data on the number of pregnancies with diagnosis of preeclampsia in each gestational week w (denoted n_w^*) from a total $N_0^* = 1857$ pregnancies that resulted in live births (the asterisks [*] convey that the data come from the sub-study within The Norwegian Mother and Child Cohort Study (MoBa sub-study). We estimated the gestational-week-specific probability of diagnosis as $\hat{p}_w^* = \frac{n_w^*}{N_0^*}$. We used these probabilities subsequently to estimate how many of the preeclamptic pregnancies from the entire cohort, a total of $N_0^+ = 21020$, experienced diagnosis in any given gestational week. The number of new cases of preeclampsia in gestational week w is denoted n_w. We estimated it using $\hat{n}_w = \hat{p}_w^* \, N_0^+$.

In a sensitivity analysis, we determined date of diagnosis using different criteria that included more pregnancies from the MoBa sub-study. The estimation of probabilities and numbers of new cases under these different criteria proceeded in the same manner.

Estimation of week-specific risk of stillbirth in pregnancies with and without preeclampsia

We estimated gestational-week-specific risks using life-table methods. We modified the standard procedures somewhat to accommodate the feature that presence/absence of preeclampsia is a characteristic of a pregnancy that changes over time. Consequently, our life

table deals with two sub-cohorts of pregnancies: one without preeclampsia and one with preeclampsia. A pregnancy switches sub-cohort membership upon diagnosis with preeclampsia. We assume that a pregnancy is at risk of stillbirth without preeclampsia in all gestational weeks before diagnosis, and is at risk of stillbirth with preeclampsia in the gestational week of diagnosis and all subsequent weeks until birth. First, we review the basic life table calculations for a single cohort (1) and then describe how we modified these calculations to accommodate preeclampsia diagnosis.

For a single cohort, the data at hand are: N_0, the total number of pregnancies in the cohort, the collection of l_w and s_w values (live births and stillbirths, respectively) for each week $w \in \{1,2,3,\cdots,g\}$. (Subscripts start at 1 here for convenience; we actually consider weeks 24 through 42.) We regard stillbirths as the event of interest ("death") and live births as censored observations ("withdrawn" or "lost to follow-up"). Two basic quantities needed in the life-table calculations are the number of pregnancies at risk entering week w, denoted E_w; and the effective number of pregnancies at risk during week w, denoted R_w.

E_w is computed recursively as the number of pregnancies entering the preceding week less the number that died and the number who were censored during the preceding week, that is,

$$E_w = E_{w-1} - l_{w-1} - s_{w-1} \text{ for } w \in \{1,2,3,\cdots,g\}$$

To make this equation apply to $w = 1$, one defines $l_0 = s_0 = 0$ and $E_0 = N_0$. The definition of R_w is motivated by an approximation: that censoring (live births) happens uniformly in time

throughout the week. Thus, to calculate the effective number of pregnancies at risk during week w, one discounts the number entering the week by half the number censored that week. That is,

$$R_w = E_w - \tfrac{1}{2} l_w.$$

The conditional probability that a stillbirth occurs during week w given that the pregnancy lasts past the beginning of week w (i.e., $\Pr(T \in [w, w+1) | T > w)$ where T is the gestational age at stillbirth) is denoted q_w. The classic life-table estimator of this gestational-week-specific conditional stillbirth probability is $\hat{q}_w = \frac{s_w}{R_w}$.

Now, return to the situation where each week n_w pregnancies experience the diagnosis of preeclampsia and, for the moment, assume that that number is part of the data just as the number of live births and stillbirths are. New cases of preeclampsia in any week are regarded as a "loss to follow-up" (censored) for the sub-cohort containing those without preeclampsia and regarded as an "accrual" to the sub-cohort containing those with preeclampsia.

Consider first the sub-cohort without preeclampsia. Apply the superscript "-" with the previously established notation to indicate "without preeclampsia". Incorporating the additional censoring of n_i pregnancies each week as they are diagnosed with preeclampsia, the general formulae above become specific to the sub-cohort without preeclampsia as:

$$E_w^- = E_{w-1}^- - n_{w-1} - l_{w-1}^- - s_{w-1}^- \text{ and}$$

$$R_w^- = E_w^- - \tfrac{1}{2}(l_w^- + n_w).$$

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To make the equation for E_w^- apply when $w = 1$, we define $l_0^- = s_0^- = 0$, $E_0^- = N_0$, and take n_0 as the number of pregnancies with preeclampsia immediately before week 1. Thus, $E_1^- = N_0 - n_0$, which represents the number in the entire cohort without preeclampsia at the beginning of week 1. These sub-cohort-specific quantities are used to estimate $\hat{q}_w^-$ via the formula given earlier.

Next consider the sub-cohort with preeclampsia. Apply the superscript "+" with the previously established notation to indicate "with preeclampsia". Pregnancies accrue into the sub-cohort with preeclampsia as gestational age advances. Our approximation regards the accruals as occurring uniformly during the week (mirroring their loss to the other sub-cohort). Consequently, the general formulae above become specific to the sub-cohort with preeclampsia as:

$$E_w^+ = E_{w-1}^+ + n_{w-1} - l_{w-1}^+ - s_{w-1}^+ \text{ and}$$

$$R_w^+ = E_w^+ + \tfrac{1}{2}n_w - \tfrac{1}{2}l_w^+.$$

Again, to make the equation for E_w^+ apply when $w = 1$, we define $l_0^+ = s_0^+ = 0$ and $E_0^+ = 0$ so that $E_1^+ = n_0$. These sub-cohort-specific quantities are used to estimate $\hat{q}_w^+$ as described above.

In our study, we observed l_w^-, l_w^+, s_w^- and s_w^+ for each gestational week of interest; we also observed N_0 and could partition it into N_0^+, the number of pregnancies in the cohort that experienced preeclampsia at some point before birth (though the week of diagnosis was unknown), and N_0^-, the number of pregnancies in the cohort that never experienced

preeclampsia. We did not, however, observe values of n_w for any week nor did we observe n_0; but instead we estimated those values using $\hat{n}_w = \hat{p}_w^* N_0^+$ as described above.

The full Life Table is presented in Table 1 in the article.

Numerical calculations and estimation of confidence limits

We carried out the calculations needed to populate the life table and to provide point estimates and confidence intervals for the associated probabilities (risks) and relative risks using a custom program written in GAUSS® (Aptech Systems Inc., Maple Valley, WA).

The program used the formulae described in preceding sections to estimate gestational-week-specific value of $\hat{q}_w$ separately for those with and without preeclampsia. We smoothed those week-specific estimates using running geometric means. We regarded each $q_w = \Pr(T \in [w, w+1) | T > w)$ as aligned to the beginning of week *w* and computed the smoothed estimate for $\hat{q}_w$, namely $\hat{q}_w^s$, as $exp([ln(\hat{q}_{w-1}) + ln(\hat{q}_w) + ln(\hat{q}_{w+1})]/3)$. These smoothed estimates were used in subsequent calculation of relative risks.

To calculate confidence intervals for any quantities interest, we used a resampling-based approach (bootstrapping). For each bootstrap sample, we generated resampled counts for all the variables that we observed, while fixing certain marginal totals, including the total number of births and the total number of preeclampsia births in the cohort. From the entire cohort, we observed week-specific counts for four variables: stillbirths and live births, separately for

pregnancies with and without preeclampsia. In addition, from a subsample of 1857 pregnancies, we observed week-specific counts of new preeclampsia cases. We regarded each such vector of week-specific counts as a multinomial observation with 19 categories (gestational weeks 24-42) except that the preeclampsia-diagnosis multinomial had a 20th category to accommodate the number of preeclampsia cases that occurred before week 24. To create a single bootstrap sample from the cohort, we randomly generated each vector independently from its own multinomial distribution whose total was fixed at the corresponding observed total and whose parameter vector was estimated from the corresponding observed counts. For stillbirths and live births, we estimated the parameter vector via maximum likelihood. Because the week-specific preeclampsia-diagnosis data were from a subset of the cohort, we added an extra resampling step to reflect that subsampling. We first drew a multinomial sample of the 1857 using the original parameter estimate to mimic the subsampling process and used it to estimate new week-specific diagnosis probabilities that varied slightly from the original estimates. Using these resample-based estimated probabilities, we then drew a second multinomial sample of 1857 to calculate estimated week-specific counts ($\hat{n}_w$) for the entire cohort as part of the life-table calculations.

With each resampled data set, we calculated week-specific values of $\hat{q}_w$ separately for those with and without preeclampsia and used them in turn to calculate smoothed estimates and any other risk quantities that depend on those week-specific smoothed estimates. We repeated the entire resampling process 10,000 times and used the resulting lists of bootstrap estimates to calculate 95% bootstrap percentile confidence limits (2) for any parameters of interest.

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Appendix 3: Relative risk of fetal death in the presence of preeclampsia in 226,954 nulliparous singleton pregnancies from Norway 1999-2008[a]

Week	Relative Risk[b]
25	74
26	73
27	47
28	42
29	26
30	30
31	19
32	22
33	14
34	7.3
35	4.2
36	1.8
37	1.8
38	1.7
39	1.4
40	1.5

a Estimates based on the distribution of preeclampsia diagnosis observed among 1219 nulliparous pregnancies in the validation subset.
b Estimates from a life table analysis using smoothed (3-week running geometric mean) week-specific risk of fetal death per 1,000 ongoing pregnancies. Reference is ongoing nulliparous pregnancies without preeclampsia.

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Appendix 4. Maternal and pregnancy characteristics of women in validation subset comparing women for whom date of diagnosis of preeclampsia was or was not determined

	Known Diagnosis Date N=1857		Unknown Diagnosis Date N=1180	
	N	%	N	%
Discharge ICD-10 Code[a]				
Any O14 Code	1243	67	649	55
O14 (Gest. HTN + sig.proteinuria)	8	0.4	5	0.4
O14.0 (Moderate PE)	675	36	322	27
O14.1 (Severe PE)	461	25	234	20
O14.2 (HELLP Syndrome)	83	4	89	8
O14.9 (Unspecified PE)	77	4	27	2
O15 (Eclampsia)	18	1	23	2
Maternal age (years) ≤24	274	15	191	16
25-34	1275	69	794	67
≥35	308	17	195	17
Parity 0	1219	66	702	59
1	413	22	310	26
≥2	225	12	168	14
Smoking at end of pregnancy				
No	1411	76	938	79
Yes	61	3	44	4
Missing	385	21	198	17
Gestational Age at delivery (week)				
<=26	10	1	7	1
27-30	50	3	38	3
31-34	133	7	87	7
35-36	213	11	119	10
37-38	487	26	254	22
39-40	685	37	463	39
41-42	279	15	212	18
Birth weight (g) <1000	27	1	19	2
1000-1999	138	7	87	7
2000-2999	504	27	281	24
3000-3999	930	50	587	50
≥4000	258	14	206	17

Abbreviations: HELLP hemolysis elevated liver enzymes and low platelets; HTN hypertension; PE preeclampsia

a Pregnancies can have multiple ICD-10 diagnosis codes

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Appendix 5. Results of Sensitivity Analysis in Estimation of Stillbirth Risk in Pregnancies With and Without Preeclampsia in 554,333 Singleton Births in Norway, 1999-2008

	Smoothed Stillbirth risk per 1,000 pregnancies			Risk Ratio		
	Preeclamptic pregnancies		Controls			
Week	Main Analysis[a]	Sensitivity Analysis[b]	Both[c]	Main Analysis	Sensitivity Analysis	Sensitivity 95% CI[d]
25	(10.7)	17.1	0.16	(69)	110	52 to 196
26	(11.6)	18.6	0.14	(86)	137	73 to 230
27	(6.5)	10.3	0.13	(49)	78	38 to 136
28	(4.6)	7.3	0.13	(36)	58	27 to 99
29	(2.6)	4.2	0.11	(23)	37	15 to 63
30	(3.1)	5.0	0.12	(27)	44	21 to 69
31	(2.7)	4.5	0.13	(22)	36	18 to 55
32	(2.5)	4.1	0.13	(19)	32	17 to 47
33	(1.8)	3.0	0.14	(13)	22	11 to 32
34	(1.1)	1.8	0.15	(7)	12	5.4 to 19
35	(0.8)	1.3	0.17	(4)	7	3.2 to 11
36	(0.8)	1.3	0.21	(4)	6	2.8 to 9.1
37	(0.9)	1.5	0.28	(3)	5	2.8 to 7.6
38	(1.1)	1.8	0.36	(3)	5	2.9 to 7.2
39	(1.0)	1.8	0.54	(2)	3	1.6 to 4.9
40	(1.6)	2.8	0.82	(2)	3	1.6 to 5.0

a Main analysis applied the distribution of time of preeclampsia diagnosis from 1857 pregnancies with observed diagnosis time to all pregnancies with registered preeclampsia 1999-2008 (21,020)

b Sensitivity analysis updated the distribution of time of preeclampsia diagnosis with an additional 1180 pregnancies with registered preeclampsia but unobserved diagnosis. The diagnosis was assumed to occur during the week of delivery.

c For pregnancies without preeclampsia the risk to 3 significant digits is equivalent for the main and sensitivity analysis.

d 95% bootstrap percentile confidence intervals based on 10,000 resamples of the diagnosis-time distribution from the sensitivity analysis, and both live and stillbirth distributions conditional on preeclampsia status

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