Hidden high rate of preeclampsia in twin compared to singleton pregnancies

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Preeclampsia in twins

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ABSTRACT

Objective: To examine the gestational age at delivery with and without preeclampsia (PE) in dichorionic (DC) and monochorionic (MC) twin pregnancies and determine the relative risk for total and preterm-PE compared to singleton pregnancies.

Methods: This was a screening study for PE in twin pregnancies undergoing first-trimester combined screening for aneuploidy and subsequently delivering two phenotypically normal live or stillborn babies at ≥24 weeks' gestation. The distribution of gestational age at delivery of DC and MC twins was determined and this was compared to singleton pregnancies from the same population. The relative risk for total and preterm-PE in twins compared to singleton pregnancies was determined. Kaplan Meier estimates of the cumulative incidence of PE in twin and singleton pregnancies assuming no other cause for delivery were determined and hazard ratios for twins relative to singletons were obtained from a Cox proportional hazards regression model.

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Results: The rate of PE in singletons was 2.3% (2,162 of 93,297), in DC twin pregnancies it was 8.1% (145 of 1,789) and in MC twins it was 6.0% (26 of 430); compared to singletons, the relative risk of total PE was 3.5 for DC twins and 2.6 for MC twins. Delivery at <37 weeks' gestation occurred in 5.5% of singletons, 46.5% of DC twins and 91.4% of MC twins. The rate of preterm-PE was 0.6%, 5.5%, 5.8% for singletons, DC twins and MC twins, respectively; compared to singletons, the relative risk of preterm-PE was 8.7 for DC twins and 9.1 for MC twins. In the Cox proportional hazards model the hazard ratios for DC and MC twin pregnancies relative to singleton pregnancies were 14 and 23, respectively.

Conclusions: The relative risk for preterm-PE in DC and MC twins is similar and they are both substantially higher than in singleton pregnancies. In ongoing pregnancies the relative risk of PE in the subsequent few days is much higher in twin than singleton pregnancies and they therefore merit a higher intensity of monitoring.

Key words: First trimester screening, Preeclampsia, Twin pregnancy, Pyramid of pregnancy care.

Introduction

In singleton pregnancies the rate of preeclampsia (PE) is 2-3%; in 25-30% of cases of PE delivery occurs at <37 weeks' gestation (preterm-PE) and in 70-75% delivery is at term.[1] In twin pregnancies, the rate of PE is higher than in singletons. In 10 studies reporting on between 256 and 9,998 twin pregnancies the overall rate of PE was 9.5% (2,069 of 21,817).[2-11] Consequently, the relative risk of PE for twin compared to singleton pregnancies is about 3. Six studies examined the rate of PE in twins in relation to chorionicity; in five it was similar in dichorionic (DC) and monochorionic (MC) twins,[3-5,7,9] but in one the rate was twice as high in DC than MC twins.[6]

Twins are delivered at an earlier gestational age than singletons and consequently comparison of the overall rates of PE between twin and singleton pregnancies may underestimate the relative risk of preterm-PE in twins. The incidence of adverse fetal and maternal short-term and long-term consequences of PE is higher in preterm-PE than in term-PE.[12-16]

The objective of this study is to examine the gestational age at delivery with and without PE in DC and MC twin pregnancies and determine the relative risk for total and preterm-PE compared to singleton pregnancies.

Methods

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK. In this visit, at 11^{+0} –13^{+6} weeks' gestation, we record maternal characteristics and medical history and perform combined screening for aneuploidies.[17] Gestational age was determined by the measurement of fetal crown-rump length[18] of the larger twin. Chorionicity was determined by examining the inter-twin membrane at its junction with the placenta.[19] Women were screened between January 2006 and December 2015 and gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study on screening for PE were twin pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities, those ending in termination, miscarriage or fetal death before 24 weeks and those with an interval of more than three days between death of one fetus and live birth of the second twin. For comparison of data from twin pregnancies we obtained results form 93,297 singleton pregnancies that were examined in the same hospitals as the twins and were included in a previous publication.[1]

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to determine if the condition was PE as defined by the International Society for the Study of Hypertension in Pregnancy.[20] The systolic

blood pressure should be ≥140 mm Hg and/or the diastolic blood pressure should be ≥90 mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. There should also be proteinuria of ≥300 mg in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

Statistical analyses

The distribution of gestational age at delivery of DC and MC twins was determined and this was compared to singleton pregnancies. The risks of all PE and PE at <37 weeks' gestation in twin pregnancies relative to those in singleton pregnancies were compared. Since the rate of preterm birth in twin pregnancies is higher than in singletons, we also compared the risk of PE at <37 weeks in twins with singletons in those pregnancies that were still ongoing at 35 weeks' gestation. Kaplan Meier estimates of the cumulative incidence of PE in twin and singleton pregnancies assuming no other cause for delivery were determined and hazard ratios for twins relative to singletons were obtained from a Cox proportional hazards regression model. The statistical software package R was used for data analyses.[21] The R package survival [22] was used for the Cox regression.

Results

During the study period, we examined 2,554 twin pregnancies but excluded 335 (13.1%) cases because they had a major fetal defect (n=28), the pregnancy resulted in termination (n=61) or miscarriage (n=156) or there was no follow up (n=90); the study population included 1,789 DC and 430 MC twin pregnancies. The maternal and pregnancy characteristics of the twin and singleton pregnancies included in the study are shown in Table 1. In all DC twins, compared to singletons, there was a higher median maternal age and weight, lower incidence of smokers, higher incidence of nulliparous women and higher incidence of assisted conception. In all MC twins, compared to singletons, there was a higher incidence of conception by IVF. In DC twins that developed PE, compared to singletons that developed PE, there was a higher median maternal age, lower incidence of women of Afro-Caribbean racial origin, and much higher incidence of conception by IVF. The median gestational age at delivery was 40.0 weeks for singletons, 37.0 for DC twins and 35.4 for MC twins (Figure 1).

The risk of PE was 2.3% (2,162 of 93,297) in singletons, 8.1% (145 of 1,789) in DC twins and 6.0% (26 of 430) in MC twins; compared to singletons, the relative risk of total PE was 3.50 (95% CI 2.97-4.11) for DC twins and 2.61 (95% CI 1.79-3.77) for MC twins (Figure 2). Delivery at <37 weeks' gestation occurred in 5.5% of singletons, 46.5% of DC twins and 91.4% of MC twins. The risk of PE at <37 weeks was 0.6% (597 of 93,297) for singletons, 5.5% (99 of 1,789) for DC twins and 5.8% (25 of 430) for MC twins; compared to singletons, the relative risk of PE at <37 weeks was 8.65 (95% CI 7.02-10.63) for DC twins and 9.09 (95% CI 6.15-13.30) for MC twins (Figure 2).

At 35^{+0} weeks' gestation there were 91,196, 1,373 and 243 ongoing singleton, DC and MC pregnancies, respectively; PE with delivery at <37 weeks occurred in 249 (0.27%) of the

singletons, 53 (3.86%) of the DC twins and 13 (5.35%) of MC twins. Compared to singletons, the relative risk of PE at <37 weeks in these pregnancies that were ongoing at 35^{+0} weeks was 14.14 (95% CI 10.56-18.93) for DC twins and 19.59 (95% CI 11.38-33.73) for MC twins (Figure 2).

Kaplan Meier estimates of the cumulative incidence of PE in singletons and twins, assuming no other cause for delivery, are shown in Figure 3. In the Cox proportional hazards model the hazard ratios for DC and MC twin pregnancies relative to singleton pregnancies were 14.0 (95% CI: 9.5 - 20.6) and 23.3 (95% CI: 11.2 - 47.6), respectively.

Discussion

The finding of this study that in twin pregnancies, compared to singleton pregnancies, the overall rate of PE is about 3-times higher is consistent with the results of previous studies [2-11] We also found that the rate of PE for DC and MC twins is similar and this is also compatible with the results of previous studies.[3-5,7,9]

A new finding of the study is that in twin pregnancies the rate of preterm-PE, between 24^{+0} and 36^{+6} weeks' gestation, is 9-times higher than in singleton pregnancies. Indeed, if we consider the risk for preterm-PE in the subgroup of pregnancies that are ongoing at 35 weeks' gestation the relative risk is 14 for DC twins and 20 for MC twins and these rates were very similar to the hazard ratios of 14 for DC and 23 for MC twin pregnancies relative to singleton pregnancies. This hidden high risk of PE in twins relative to singletons is well illustrated in the Kaplan Meier estimates of the cumulative incidence of PE assuming no other cause for delivery.

The underestimate of the relative risk of PE in twins, by comparison with singletons, when reporting the total rate of PE from 24 to 43 weeks' gestation is the mere consequence of the lower gestational age at delivery in twin than singleton pregnancies. In our study the median gestational age at delivery was 40 weeks for singletons, 37 weeks for DC twins and 35 weeks for MC twins and delivery at <37 weeks' gestation occurred in 6% of singletons, 47% of DC twins and 91% of MC twins. These rates are similar to those reported for all births in the USA in 2014 where the rate of delivery at <37 weeks was 8% for singletons and 59% for twins.[23] Since a much higher proportion of twin compared to singleton pregnancies deliver before a given gestational age, in the ongoing pregnancies the relative risk of PE in the subsequent few days is much higher than the value of 3 implied from considering the overall rate of PE; the true relative risk is about 14 for DC twins and more than 20 for MC twins.

We have previously proposed the adoption of a survival-time model for the gestational age at delivery with PE.[1,24] This approach assumes that if the pregnancy was to continue indefinitely all women would develop PE and whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE. It is therefore likely that if the pregnancy in twins was as long as in singletons the overall rate of PE in twins would be considerably higher than the observed rate.

The incidence of adverse fetal and maternal consequences of PE is higher in preterm-PE than in term-PE.[12-16] Clinicians managing twin pregnancies should be aware that the rate of preterm-PE, relative to that in singleton pregnancies, is substantially higher than that implied by the overall rate of PE. Clinicians should also be aware that during the third trimester in ongoing pregnancies the relative risk of PE in the subsequent few days is much higher in

twin than singleton pregnancies and they therefore merit a higher intensity of monitoring for PE. Future studies will lead to the development of an algorithm for screening for PE that, as in singleton pregnancies, would adopt a survival-time model for the gestational age at delivery with PE.[1]

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Table 1. Maternal and pregnancy characteristics in the screening population.

Variable	Singleton pregnancies		Dichorionic twin pregnancies		Monochorionic twin pregnancies	
	All (n=93,297)	PE (n=2,162)	All (n=1,789)	PE (n=145)	All (n=430)	PE (n=26)
Maternal age in years	31.0 (26.4-35.0)	31.1 (26.4-35.6)	33.2 (29.1-36.5)*	34.0 (30.3-37.3)*	31.5 (27.0-35.8)	31.0 (28.0-36.6)
Maternal weight in kg	66.5 (59.0-77.0)	72.65 (63-86.5)	69.0 (60.5-79.0)*	72.0 (63.1-84.0)	65.3 (58.7-77.0)	71.9 (60.0-84.0)
Maternal height in cm	164 (160-169)	163 (159-168)	165 (161-170)	165 (160-168)	164 (160-168)	163 (159-169)
Gestational age in weeks	12.7 (12.3-13.1)	12.7 (12.3-13.1)	12.9 (12.5-13.3)	12.8 (12.4-13.2)	12.8 (12.5-13.3)	13.0 (12.5-13.5)
Racial origin						
Caucasian	70,380 (75.4)	1,273 (58.9)	1,390 (77.7)	104 (71.7)*	320 (74.4)	20 (76.9)
Afro-Caribbean	15,211 (16.3)	716 (33.1)	287 (16.0)	33 (22.8)*	66 (15.3)	4 (15.4)
South Asian	3761 (4)	97 (4.5)	57 (3.2)	4 (2.8)	23 (5.3)	2 (7.7)
East Asian	1,790 (1.9)	31 (1.4)	22 (1.2)	3 (2.1)	11 (2.6)	0
Mixed	2,155 (2.3)	45 (2.1)	33 (1.8)	1 (0.7)	10 (2.3)	0
Medical history						
Chronic hypertension	1,203 (1.3)	245 (11.3)	27 (1.5)	13 (9.0)	3 (0.7)	0
Diabetes mellitus	799 (0.9)	46 (2.1)	18 (1.0)	4 (2.8)	5 (1.2)	0
SLE/APS	148 (0.2)	12 (0.6)	4 (0.2)	1 (0.7)	0	0
Cigarette smokers	10,087 (10.8)	166 (7.7)	160 (8.9)*	8 (5.5)	43 (10.0)	0
Family history of PE	4,047 (4.3)	175 (8.1)	77 (4.3)	7 (4.8)	20 (4.7)	2 (7.7)
Parity						
Nulliparous	44,145 (47.3)	1,319 (61.0)	968 (54.1)*	101 (69.7)	216 (50.2)	13 (50.0)
Parous: previous PE	3,143 (3.4)	300 (13.9)	52 (2.9)	11 (7.6)	16 (3.7)	1 (3.8)
Parous: no previous PE	46,009 (49.3)	543 (25.1)	769 (43.0)*	33 (22.8)	198 (46.0)	12 (46.0)
Pregnancy interval in years	3.0 (2.0-5.0)	4.1 (2.5-7.1)	3.1 (2.0-5.3)	4.1 (3.0-7.2)	3.0 (1.7-4.9)	3.4 (2.1-4.6)
Gestation of last birth in weeks	40 (39-40)	39 (37-40)	40 (39-40)	40 (38-40)	40 (39-40)	40 (38-41)
Conception						
Spontaneous	90,275 (96.8)	2,048 (94.7)	1,162 (65.0)*	90 (62.1)*	385 (89.5)*	24 (92.3)
Ovulation induction	1,281 (1.4)	32 (1.5)	52 (2.9)*	5 (3.4)	3 (0.7)	0
In-vitro fertilization	1,741 (1.9)	82 (3.8)	575 (32.1)*	50 (34.5)*	42 (9.8)*	2 (7.7)

Variables given as median (interquartile range) or n (%); SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; PE = preeclampsia

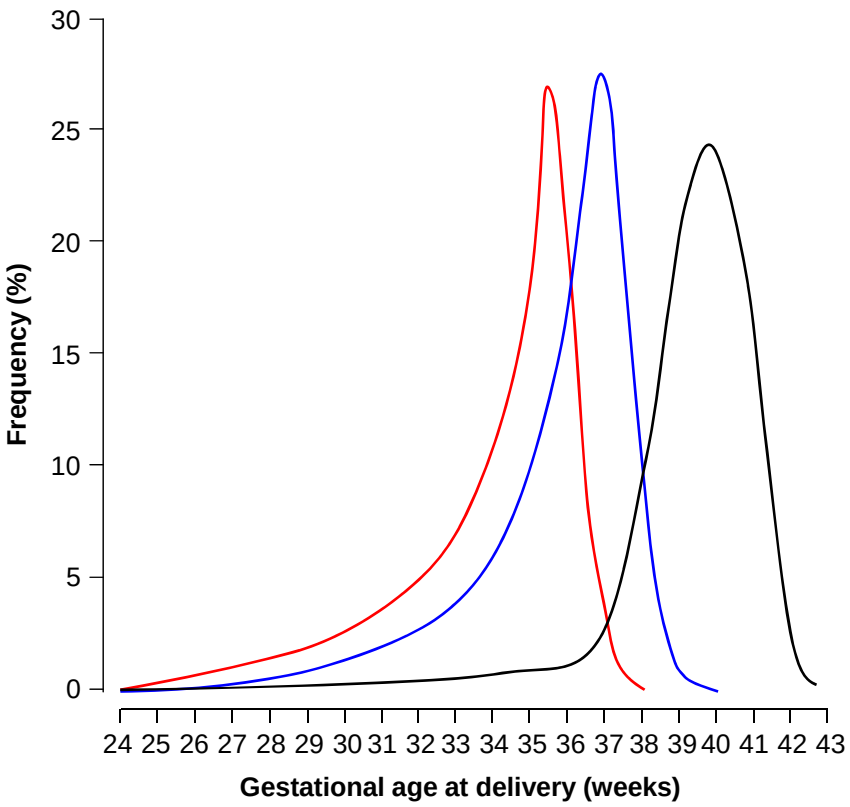
***** significant differences in the comparison of all dichorionic (DC) and monochorionic (MC twins against all singletons and between DC and MC twins with PE against singletons with PE. *Post hoc* Bonferroni correction was used for multiple comparisons and significance was defined by $p < 0.025$

Figure legends

Figure 1. Frequency (left) and cumulative frequency (right) of gestational age at delivery in singletons (black line), DC twins (blue lines) and MC twins (red lines).

Figure 2. Relative risks, with 95% confidence intervals, of total PE and PE at <37 weeks, at 12 and 35 weeks' gestation in DC twins (blue line) and MC twins (red line) compared to singletons.

Figure 3. Kaplan Meier estimates of the cumulative incidence of PE in singletons (black line), DC twins (blue lines) and MC twins (red lines) assuming no other cause for delivery.



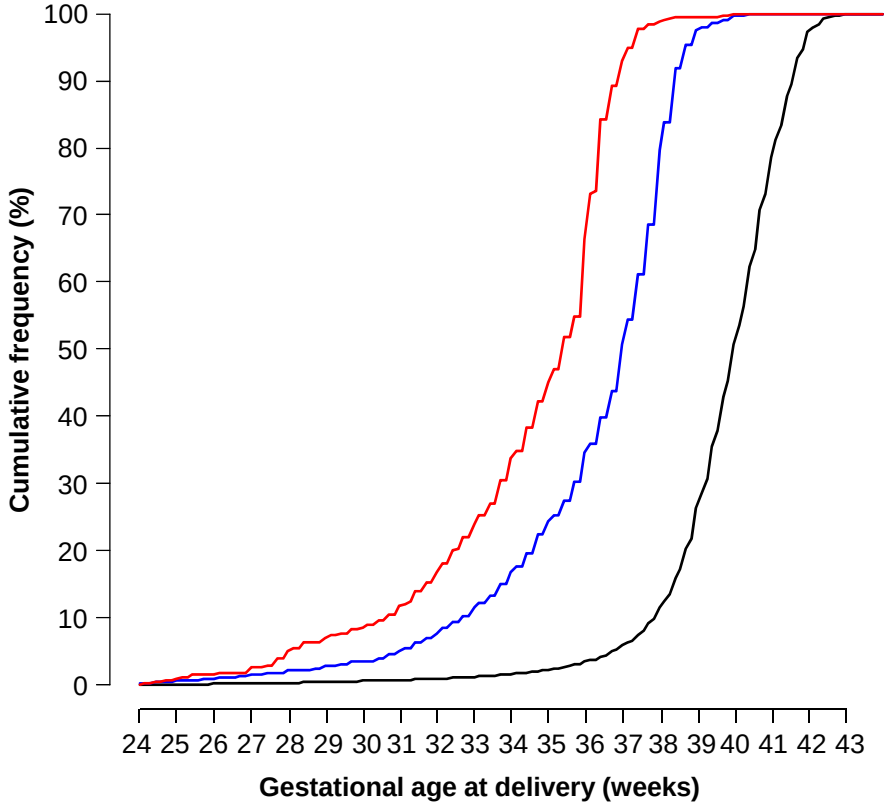


Figure 1

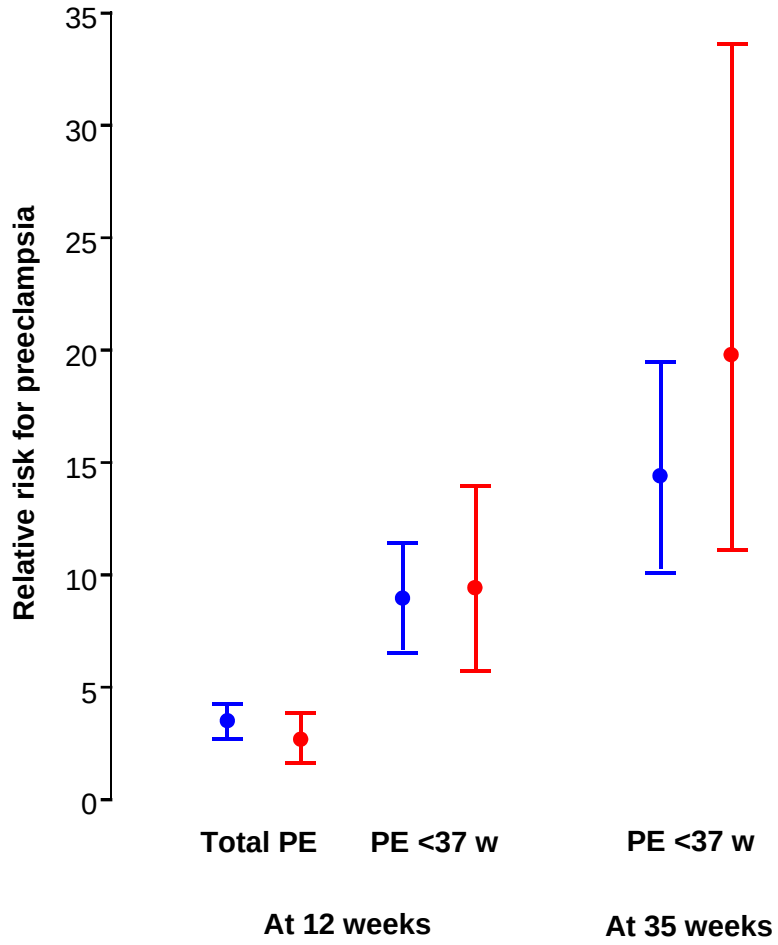


Figure 2

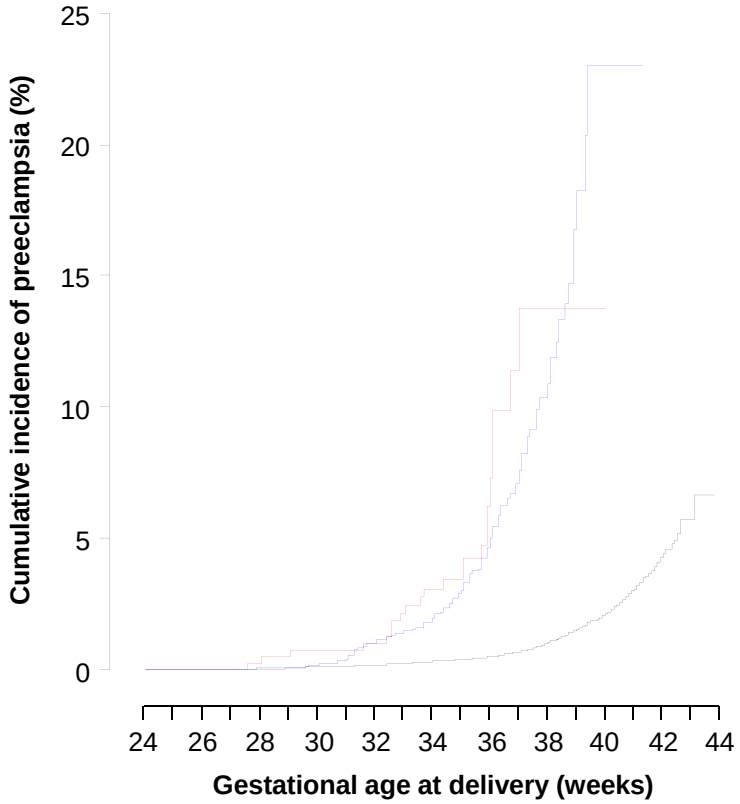


Figure 3