

Maternal and fetal risk factors for stillbirth: population based study

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Contexte anglais

- Problème de santé publique au RU
- mortalité « inévitable »
- Intérêt pour le RCIU
- Prédiction difficile des morts-nés

objectifs

- Etudier le lien entre plusieurs facteurs d'exposition (démographiques, sociaux et médicaux) et la mortalité.
- Evaluer la contribution respective de ces facteurs au taux de mortalité d'une région Anglaise.

méthode

Design / lieu

- cohorte rétrospective
- Exhaustive
- 19 maternités des West Midlands (Ang)

population

- Registre informatique des épisodes obstétricaux (NHSnet ; WMPI)
- Inclusion des naissances : juin 2009 - mai 2011
- Exclusions
 - Anomalies congénitales
 - Grossesses multiples

Variables explicatives

- Caractéristiques maternelles et fœtales (87 items)
- Age gestationnel
 - Datation écho (96.5 %)
 - ou DDR (3.5 %)
- RCIU : Pds de naissance < 10eme percentile
- Suivi des RCIU en anténatal : non-standardisé

Données de mortalité

- Registre (NHS – WMPI)
- Définition des morts-nés :
 - Naissance > 24 SA
 - Aucun signe de vie à la naissance
 - Déduction de 48h sur l'âge gestationnel

Analyses statistiques

- Régression de Poisson
 - bivariée
 - multivariée
 - Méthode stepwise (forward-backward)
 - Vérification du modèle
- Fractions de risque attribuable (RA)
- Stata v11

résultats

descriptifs

- 105 476 naissances
- 13 258 exclues (anomalie congénitale, grossesse multiple)
- 92 218 naissances incluses
 - 91829 NN en vie
 - 389 morts-nés
- Taux de mortinatalité = 4.2 / 1000
- 841 (0.9 %) de grossesses répétées

Analyses bivariées

Table 1| Univariate analysis of risk factors associated with stillbirths compared with live births

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Total	92 218 (100)	389 (100)	4.2	—
General maternal characteristics				
Age (years):	n=92 208	n=389		
<20	6456 (7.0)	33 (8.5)	5.1	1.3 (0.9 to 1.9)
20-24	20 834 (22.6)	99 (25.5)	4.8	1.2 (0.9 to 1.6)
25-30	27 110 (29.4)	107 (27.5)	3.9	Reference
30-34	23 110 (25.1)	79 (20.3)	3.4	0.9 (0.6 to 1.2)
≥35	14 698 (15.9)	71 (18.3)	4.8	1.2 (0.9 to 1.6)
Parity:	n=91 160	n=377		
0	38 653 (42.4)	192 (50.9)	5.0	1.9 (1.4 to 2.4)
1	29 791 (32.7)	79 (21.0)	2.7	Reference
2	13 421 (14.7)	56 (14.9)	4.2	1.6 (1.1 to 2.2)
≥3	9295 (10.2)	50 (13.3)	5.4	2.0 (1.4 to 2.9)
Body mass index:	n=90 350	n=389		
<18.5	3109 (3.4)	12 (3.1)	3.9	1.0 (0.5 to 1.8)
18.5-24.9	43 898 (48.6)	173 (44.5)	3.9	Reference
25-29.9	25 156 (27.8)	101 (26.0)	4.0	1.0 (0.8 to 1.3)
30-34.9	11 427 (12.6)	61 (15.7)	5.3	1.4 (1.0 to 1.8)
≥35	6760 (7.5)	42 (10.8)	6.2	1.6 (1.1 to 2.2)

Table 1 (continued)

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Maternal ethnic origin:	n=87 911	n=334		
European:				
UK	60 130 (67.9)	192 (57.5)	3.2	Reference
Non-UK	4254 (4.8)	17 (5.1)	4.0	1.3 (0.8 to 2.1)
African*	2986 (3.2)	22 (5.7)	7.4	2.3 (1.5 to 3.6)
African-Caribbean*	1796 (2.0)	12 (3.1)	6.7	2.1 (1.2 to 3.7)
Bangladeshi*	1674 (1.8)	7 (1.8)	4.2	1.3 (0.6 to 2.8)
Indian:				
UK	2282 (2.6)	9 (2.7)	3.9	1.2 (0.6 to 2.4)
Non-UK	2189 (2.5)	14 (4.2)	6.4	2.0 (1.2 to 3.4)
Pakistani:				
UK	3412 (3.9)	14 (4.2)	4.1	1.3 (0.7 to 2.2)
Non-UK	4378 (4.9)	30 (9.0)	6.9	2.1 (1.5 to 3.1)
Other:				
UK	1535 (1.7)	6 (1.8)	3.9	1.2 (0.5 to 2.8)
Non-UK	3275 (3.7)	11 (3.3)	3.4	1.1 (0.6 to 1.9)
Place of birth:	n=88 559	n=334		
UK	69 878 (78.9)	236 (70.7)	3.4	Reference
Other	18 681 (21.1)	98 (29.3)	5.2	1.6 (1.3 to 2.1)

Table 1 (continued)

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Social factors				
Mother not employed:	n=86 969	n=330		
No	50 905 (58.5)	176 (53.3)	3.5	Reference
Yes	36 064 (41.5)	154 (46.7)	4.3	1.2 (1.0 to 1.5)
Partner not employed:	n=81 624	n=310		
No	63 212 (77.4)	230 (74.2)	3.6	Reference
Yes	11 950 (14.6)	58 (18.7)	4.9	1.3 (1.0 to 1.8)
No partner	6462 (7.9)	22 (7.1)	3.4	0.9 (0.6 to 1.4)
Baby's father blood relation:	n=81 627	n=298		
No	76 084 (93.2)	273 (91.6)	3.6	Reference
Yes	5543 (6.8)	25 (8.4)	4.5	1.3 (0.8 to 1.9)
Index of multiple deprivation (fifths):	n=92 218	n=389		
1-3 (least deprived)	34 863 (37.8)	115 (29.6)	3.3	Reference
4	19 230 (20.9)	69 (17.7)	3.6	1.1 (0.8 to 1.5)
5 (most deprived)	38 125 (41.3)	205 (52.7)	5.4	1.6 (1.3 to 2.0)

Table 1 (continued)

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Maternal history				
Mental health problems:	n=89 985	n=340		
No	79 553 (88.4)	285 (83.8)	3.6	Reference
Yes	10 432 (11.6)	55 (16.2)	5.3	1.5 (1.1 to 2.0)
Pre-existing hypertension:	n=90 965	n=342		
No	88 528 (97.3)	329 (96.2)	3.7	Reference
Yes	2437 (2.7)	13 (3.8)	5.3	1.4 (0.8 to 2.5)
Pre-existing diabetes:	n=90 965	n=342		
No	90 238 (99.2)	332 (97.1)	3.7	Reference
Yes	727 (0.8)	10 (2.9)	13.8	3.7 (2.0 to 6.9)
Cardiac disease:	n=90 965	n=342		
No	89 051 (97.9)	331 (96.8)	3.7	Reference
Yes	1914 (2.1)	11 (3.2)	5.7	1.5 (0.8 to 2.8)
Previous stillbirth para ≥ 1 (n=53 565):	n=52 475	n=184		
No	51 482 (98.1)	173 (94.0)	3.4	Reference
Yes	993 (1.9)	11 (6.0)	11.1	3.3 (1.8 to 6.0)

Table 1 (continued)

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Pregnancy related factors				
Smoking in pregnancy:	n=85 337	n=333		
Non-smoker	52 473 (61.5)	166 (49.8)	3.2	Reference
Smoker	17 834 (20.9)	104 (31.2)	5.8	1.8 (1.4 to 2.3)
Passive smoker	15 030 (17.6)	63 (18.9)	4.2	1.3 (1.0 to 1.8)
Alcohol consumption:	n=88 569	n=329		
No	81 288 (91.8)	305 (92.7)	3.8	Reference
Yes	7281 (8.2)	24 (7.3)	3.3	0.9 (0.6 to 1.3)
Antenatal folic acid:	n=88 173	n=326		
Yes	74 526 (84.5)	262 (80.4)	3.5	Reference
No	13 647 (15.5)	64 (19.6)	4.7	1.3 (1.0 to 1.8)
Late booking (≥13 weeks):	n=89 886	n=338		
No	74 644 (83.0)	269 (79.6)	3.6	Reference
Yes	15 242 (17.0)	69 (20.4)	4.5	1.3 (1.0 to 1.6)

Table 1 (continued)

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Complications in pregnancy				
Gestational diabetes:	n=91 010	n=339		
No	88 134 (96.8)	326 (96.2)	3.7	Reference
Yes	2876 (3.2)	13 (3.8)	4.5	1.2 (0.7 to 2.1)
Pregnancy induced hypertension:	n=91 010	n=339		
No	86 640 (95.2)	322 (95.0)	3.7	Reference
Yes	4370 (4.8)	17 (5.0)	3.9	1.0 (0.6 to 1.7)
Pre-eclampsia:	n=91 010	n=339		
No	89 936 (98.8)	326 (96.6)	3.6	Reference
Yes	1072 (1.2)	11 (3.2)	10.3	2.8 (1.5 to 5.1)
Antepartum haemorrhage:	n=91 010	n=339		
No	83 902 (92.2)	277 (81.7)	3.3	Reference
Yes	7108 (7.8)	62 (18.3)	8.7	2.6 (2.0 to 3.5)

Table 1 (continued)

Risk factors	No (%) of all births	No (%) of stillbirths	Rate/1000 births	Relative risk (95% CI)
Fetal/neonatal characteristics				
Sex:	n=92 136	n=383		
Boy	47 308 (51.3)	209 (54.6)	4.4	Reference
Girl	44 828 (48.7)	174 (45.4)	3.9	0.9 (0.7 to 1.1)
Gestational age at delivery	n=92 218	n=389		
Median (interquartile range) days	280 (272-286)	240 (198-271)		
Birth weight (g):	n=91 858	n=389		
Mean (SD)	3343.3 (569.1)	1931.6 (1146.2)		
Gestation related optimal weight centile:	n=88 053	n= 380		
Median (interquartile range)	41.5 (19.5-67.5)	9.7 (0.6-37.3)		
≤10	69 840 (75.7)	168 (43.2)	16.7	6.8 (5.6 to 8.4)
10-90	11 697 (12.7)	195 (50.1)	2.4	Reference
>90	6516 (7.1)	17 (4.4)	2.6	1.1 (0.7 to 1.8)
Fetal growth restriction†:	n=88 053	n=380		
No	76 356 (86.7)	185 (48.7)	2.4	Reference
Yes				
Detected antenatally	3601 (4.1)	35 (9.2)	9.7	4.0 (2.8 to 5.7)
Not detected antenatally	8096 (9.2)	160 (42.1)	19.8	8.0 (6.5 to 9.9)

*Place of birth combined if either subgroup <1000 women.

†Birth weight <10th gestation related optimal weight centile.

Table 2| Smoking and fetal growth restriction (birth weight <10th gestation related optimal weight centile)

Variables	Proportion of total (%)	Stillbirth rate/1000 births
All	100.0	4.2
Smokers:	18.7	5.8
Fetal growth restriction	4.3	13.0
No fetal growth restriction	13.7	3.7
Non-smokers:	81.3	3.8
Fetal growth restriction	8.3	18.3
No fetal growth restriction	68.7	2.1

Analyse multivariée

- 25 021 naissances (103 morts-nés) exclues
- Tx de mortalité = 4.1 / 1000 (semblable)
- Analyses de sensibilité
 - Facteurs exclus
 - Variable maternité
 - Grossesses répétées
- Intéractions entre les variables : NS...
- ...Sf pour tabac / RCIU

Table 3| Multivariable analysis of significant (P<0.1) risk factors in table 1

Variables	Adjusted relative risk (95% CI)	P value	Prevalence (%)	Population attributable risk (%)
Parity:				
0	1.8 (1.3 to 2.5)	<0.01	43.4	21.3
≥3	1.6 (1.0 to 2.5)	0.05	9.4	4.6
Ethnic origin, place of birth:				
African*	2.4 (1.2 to 4.6)	0.01	3.0	2.9
African-Caribbean*	2.3 (1.3 to 4.1)	0.01	2.0	2.2
Indian*	2.1 (1.3 to 3.5)	<0.01	5.2	3.9
Pakistani, non-UK	3.0 (1.9 to 4.8)	<0.01	4.6	6.4
Body mass index:				
30-34.9	1.4 (1.0 to 2.0)	0.07	12.5	4.5
≥35	1.6 (1.1 to 2.4)	0.03	7.3	4.2
Mental health history	1.4 (1.0 to 1.9)	0.06	11.7	4.7
Pre-existing diabetes	3.9 (1.7 to 8.9)	<0.01	0.7	2.0
Antepartum haemorrhage	3.4 (2.6 to 4.5)	<0.01	8.1	15.5
Maternal smoking, no fetal growth restriction†				
Active smoker	2.5 (1.7 to 3.6)	<0.01	14.9	9.4
Passive smoker	1.3 (0.8 to 2.0)	0.28	15.7	—
Maternal smoking, fetal growth restriction†:				
Active smoker	5.7 (3.6 to 8.9)	<0.01	4.6	6.1
Passive smoker	10.0 (6.6 to 15.8)	<0.01	2.1	9.1
Fetal growth restriction†, non-smoker	7.8 (5.6 to 10.9)	<0.01	6.5	22.2

Reference group: para 1, UK born, non-smoking European mother; body mass index 18.5-24.9.

*UK and non-UK groups combined because of small numbers.

†Birth weight <10th gestation related optimal weight centile.

Table 4| Gestational age at delivery and risk of stillbirths in pregnancies with fetal growth restriction*, with and without antenatal detection

Variables	Prevalence (%)	Median (interquartile range) gestational age at delivery (days)	Adjusted relative risk† (95% CI)	P value	Population attributable risk (%)
No fetal growth restriction	86.8	280 (273-286)	Reference		
Fetal growth restriction:					
Detected antenatally	4.0	270 (261-279)	3.4 (2.2 to 5.2)	<0.01	6.2
Not detected antenatally	9.2	280 (273-287)	6.5 (4.9 to 8.4)	<0.01	32.0

*Adjusted for ethnicity, parity, body mass index, pre-eclampsia, antepartum haemorrhage, history of mental health problems, and smoking.

†Birth weight <10th gestation related optimal weight centile.

Table 5| Fetal growth restriction and other pathological factors before and after 34 weeks of gestation

Variables	Adjusted relative risk* (95% CI)	P value	Prevalence (%)	Population attributable risk (%)
24-33 weeks				
Pre-eclampsia	0.3 (0.1 to 0.6)	<0.01	10.5	-13.2
Fetal growth restriction†	4.0 (2.9 to 5.6)	<0.01	14.3	49.5
≥34 weeks				
Body mass index:				
30-34	1.9 (1.3 to 3.0)	<0.01	12.0	9.9
≥35	1.8 (1.1 to 3.0)	0.02	7.3	5.1
Mental health history	1.7 (1.0 to 2.7)	0.04	11.3	7.6
Late booking	1.6 (1.1 to 2.3)	0.01	16.6	9.1
Antepartum haemorrhage	3.1 (2.0 to 4.7)	<0.01	7.5	13.0
Smoker, no fetal growth restriction†	1.7 (1.1 to 2.7)	0.02	14.1	7.3
Smoker, fetal growth restriction†	2.5 (1.3 to 5.1)	0.01	4.3	2.5
Fetal growth restriction†, non-smoker	5.1 (3.4 to 7.6)	<0.01	8.0	22.7

*Adjusted for ethnicity, maternal age, parity, and body mass index.

†Birth weight <10th gestation related optimal weight centile.

discussion

FDR précoces

- Parité
 - Nulliparité (concordant avec la littérature)
 - Relation en « U » ??
- Origine ethnique
- obésité, Diabète, ATCD psychiatriques
- Hémorragie anténatale

tabac

- Dans la littérature : RR = 1,36 (1,8 dans l'étude)
- Intéraction tabagisme / RCIU
- programmes d'aides pour l'arrêt du tabac +++
- Tx de mortalité le + haut
 - non-fumeuses + RCIU
- Tabgisme passif

FDR modifiables

- RCIU (RA = 37,4 %)
- Tabagisme actif sans RCIU (RA 9,4%)
- BMI >30 (RA 8,7%)

implications

- Risque accru associé aux RCIU non-dépistés
 - Concordant avec la littérature
 - Seulement 31% dépistés
 - → importance d'une approche standardisée de qualité pour le dépistage des RCIU en routine
- Intérêt des programmes d'éducation
 - Efficacité pas claire

conclusion

- FDR principaux de mortalité
 - RCIU
 - Tabac
 - Obésité
- Intérêt du dépistage précoce des RCIU
 - Pour réduire le risque de mortalité
 - indicateur de qualité

Forces

- Cohorte prospective
- Effectif ++
- Registres
- Modèle multivarié justifié
- Quantification des RA
- Peu de perdus de vues et de données manquantes
- Bonne surveillance des biais de classement

limites

- Représentativité
- Calcul de RA pour des association NS
- Beaucoup de tests
- Biais potentiels
 - confusion : nbre de refus d'autopsie?
 - mesure : dépistage des RCIU

Causalité du RCIU ?

- Concordance avec la littérature
- Plausibilité bio
- Force de l'association (RR de 5,7 à 10)
- Cohérence chronologique

- Mais...
- Relation dose-effet?
- Reproductibilité?

Exemple schématisé de la méthode « backward stepwise » pour l'analyse multivariée

