The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

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To cite this article: E. C. de Graaff, L. A. Wijs, S. Leemaqz & G. A. Dekker (2016): Risk factors for stillbirth in a socio-economically disadvantaged urban Australian population, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.3109/14767058.2016.1163678

To link to this article: http://dx.doi.org/10.3109/14767058.2016.1163678

Accepted author version posted online: 09 Mar 2016.
Published online: 29 Mar 2016.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, Early Online: 1–6
 DOI: 10.3109/14767058.2016.1163678

Taylor & Francis
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ORIGINAL ARTICLE

Risk factors for stillbirth in a socio-economically disadvantaged urban Australian population

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Abstract

Introduction: Several risk factors for stillbirth have been extensively investigated. Some risk factors are more common in socio-economically disadvantaged regions. The aim of this study was to identify risk factors for stillbirth in the Northern suburbs of Adelaide, one of the most socio-economically disadvantaged urban areas in Australia.
Material and methods: A retrospective case control study (two controls per case) of all women with a singleton pregnancy resulting in a stillbirth during the decade 2002–2012.
Results: One hundred and thirty stillbirths were registered over these 10 years. Using univariate analysis, the following risk factors were identified: obesity $\geq$40 body mass index (BMI) (OR 4.75), non-Caucasian ethnicity (odds ratio [OR] 2.737), pre-existing diabetes ($p<0.000$), polycystic ovary syndrome (PCOS) (OR 5.250), in vitro fertilisation (IVF) (OR 4.000), booking systolic blood pressure (SBP) $\geq$ 140 (OR 5.000) and booking diastolic blood pressure (DBP) $\geq$ 80 (OR 3.111). Many of these factors have complex interrelationships. Multivariate analysis identified the following independent risk factors: BMI $\geq$40 (OR 3.940), ethnic minorities (mainly indigenous Australians) (OR 2.255) and social issues (OR 3.079). PCOS had an independent effect to some extent, but this was clearly confounded by BMI.
Conclusion: These Australian data confirm the presence of several potentially modifiable risk factors for stillbirth, within this socio-economically disadvantaged region. Modifying these risk factors, in particular obesity, is a big challenge not only for maternity and primary care providers, but for overall society.

Keywords

Australia, risk factor, stillbirth

History

Received 18 December 2015
Revised 1 March 2016
Accepted 6 March 2016
Published online 28 March 2016

Introduction

It is often not recognised that stillbirth is 10 times more frequent than SIDS in most developed countries [1]. The WHO defines stillbirth as foetal death during pregnancy, but the exact gestational age at which foetal death is considered to be a stillbirth versus a late miscarriage differs amongst countries [2]. In Australia, foetal death after 20 weeks is regarded as stillbirth.

Recent series identified obesity, advanced maternal age and a high-risk lifestyle as major risk factors for stillbirth [3–5]. Some of these risk factors are associated with poverty, making certain disadvantaged regions potential high-risk environments [6].

The current study was conducted in the Northern suburbs of Metropolitan Adelaide, known as one of the poorest urban Australian regions, with a high prevalence of smoking, drug use, gambling problems, domestic violence, unemployment, depression and poor (quality) nutrition.

The aim of this study was to identify risk factors for overall stillbirth in this socio-economically disadvantaged region, since it provides a more or less unique opportunity to study a primarily Caucasian population with good access to free health care [7].

Materials and methods

This retrospective case control study was conducted in the Department of Obstetrics and Gynaecology of the Lyell McEwin Hospital, being the only tertiary maternity service in the Northern suburbs of Adelaide (University of Adelaide). For this study all stillbirths between 2002 and 2012 were included. All cases included in this analysis ($N=130$) were women with a singleton stillbirth during this decade, reported to the South Australian Health Pregnancy Outcome Unit.

One hundred and seventy seven cases were reported to the Pregnancy Outcome Unit as being stillborn. Stillbirths due to terminations of pregnancy because of chromosomal/congenital anomalies ($N=47$) were excluded from this study.

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The remaining 130 stillbirths were subjected to a systematic detailed analysis of the medical records.

Two controls were selected per case. Cases and controls were matched on parity and controls were identified as the first woman giving birth before and after the index case. Cases with parity >3 were matched to a control with a parity of ≥ 3.

Booking data extracted from medical records of cases and controls included: ethnicity, body mass index (BMI), maternal age at booking, smoking, alcohol use, drug use, social and emotional status, ANRQ (Antenatal Risk Questionnaire) and EPDS (Edinburgh Postnatal Depression Scale) scores, medical history, medication, method of conception, gravidity, parity, parity with current partner, any previous lower segment caesarean section (LSCS), compliance with antenatal care, booking blood pressure and highest blood pressure during pregnancy. Outcome of pregnancy was classified as live birth versus stillbirth, with information on pregnancy complications; gestational diabetes mellitus (GDM), pregnancy induced hypertensive disorders (PIHD: gestational hypertension and preeclampsia), gestational age at birth, birth weight and sex. Customised centiles (ethnicity, maternal height and weight) were used to identify SGA infants (birthweight <10th customised centile).

The following laboratory data were collected: results of first trimester screening (PAPP-A, hCG, NT), 28 weeks Glucose Challenge Test and/or Tolerance Test and the presence of Group B Streptococcus [GBS] (positive vaginal swab culture in the third trimester).

Definitions used in this study:

Stillbirth: Foetal death occurring at ≥ 20 weeks or a birth weight of ≥ 400 grams, if gestational age could not be confirmed.

ANRQ (Antenatal Risk Questionnaire) and EPDS (Edinburgh Postnatal Depression Scale) scores: an ANQR score ≥ 40 to identify a state of major anxiety and EPDS score ≥ 12 for minor depression and ≥ 18 for major depression.

Social issues: Three categories were used to score social factors: (1) no suggestion of any social problems, (2) minor social problems (e.g. suboptimal social support, financial issues or housing problems, notable relationship issues) and (3) major social problems (e.g. being isolated without any support, major financial issues and housing problems, and domestic violence). Patients with social problems associated with psychiatric disorders were identified under psychiatric issues.

Pregnancy compliance: Three categories were used, to assess the degree of compliance: (1) not compliant (e.g. missing most appointments, not being able to contact the patient and no antenatal care), (2) some compliance (e.g. missing some appointments but completed major screening tests) and (3) fully compliant for those patients coming to all antenatal appointments.

Gestational Diabetes (GDM): All patients had an Oral Glucose Challenge Test (OGCT) at 28 week's gestation. Patients with abnormal OGCT ($\geq$7.8 mmol/L) had a further Oral Glucose Tolerance Test (OGTT) (cut-off ≥ 5.5 mmol/L [fasting] and $\geq$8.0 mmol/L [120 min]).

Patients at high risk on type II diabetes had an OGTT shortly after their booking visit.

Statistics

Univariate analysis was performed on 44 variables to test their association with stillbirth and late stillbirth. Kruskal–Wallis tests were used to compare distributions of continuous variables, and Mantel–Haenszel (MH) tests were performed for categorical variables across each matched pairs. The MH odds ratios were calculated along with the 95% confidence intervals.

Independent risk factors were identified using conditional logistic regression on all relevant univariate risk factors ($p<0.1$). Variables with $>20\%$ missing values or with multicolinearity were omitted to minimise variable inflation and model overfitting. R version 3.1.0 was used to perform the analyses. Variables are considered significant at 5% significance level (i.e. p values <0.05).

Results

During the years 2002–2012, 26 387 children were born in the Lyell McEwin hospital in Adelaide, Australia. One hundred and seventy seven births were ascribed as stillbirths, which include 0.7% of all births. In this study, 0.5% of all births are included as true stillbirths of structurally normal foetuses in singleton pregnancies.

The main demographics and the results of the univariate risk analysis are presented in Tables 1, 2 and 3. The studied population had a normally distributed age, with a mean of 27.48 for the controls and 27.98 for the cases.

BMI: BMI as continuous variable did not show significant differences, even though the majority of the population studied was overweight or obese. However, using BMI categories, higher BMI categories were significantly associated with a higher risk for stillbirth. The distribution of BMI is shown in Figure 1. The effect of BMI on stillbirth was particularly striking in morbidly obese women (BMI ≥ 40) with an odds ratio (OR) of 2.855 (95% confidence internal [CI] 1.030–8.137).

Ethnicity: A significant difference was found when all Caucasian women (74.6%) were compared with all ethnic minorities combined, mainly consisting of indigenous Australian women (odds ratio 2.737; 95% CI 1.171–6.394).

Substance abuse: No significant difference could be found for all smoking versus no smoking (see Table 2) and for smoking <10 versus ≥ 10 cigarettes per day at booking. Alcohol and drug use showed no difference when comparing stillbirths to controls.

A significant difference (OR of 2.118, 95% CI 1.077–4.162) between no social issues versus minor and major social issues combined, was found. A high EPDS score was also identified as an almost significant risk factor in univariate analysis. The ANQR score showed no effect at all.

Medical disorders: Diabetes ($p<0.000$) and polycystic ovary syndrome (PCOS) (OR 5.250, 95% CI 1.646–16.741) were significantly more common in the stillbirth group. Also in vitro fertilisation (IVF) pregnancy was a risk factor in univariate analysis (OR 4.000, 95% CI 1.000–15.994). As for the antenatal tests, GDM during current pregnancy showed a close to significant association (p 0.0578), whereas first trimester screening results did not. The importance of increased blood pressure is demonstrated in the significant

Table 1. Main demographics of cases and controls.

Variable	Category	Control ($n = 260$) Mean ± SEMN (%)	Stillbirth ($n = 130$) Mean ± SEM N (%)	p
Ethnicity				0.0579
	Caucasian	223 (85.8%)	97 (74.6%)	Ref*
	African	4 (1.5%)	2 (1.5%)	0.2207
	Indian/Pakistani	2 (0.8%)	3 (2.3%)	0.2743
	Other Asian	20 (7.7%)	14 (10.8%)	0.2507
	Other†	11 (4.2%)	14 (10.8%)	**0.0164**
Age		27.48 ± 0.36	27.98 ± 0.51	0.3918
Height		163.25 ± 0.42	162.05 ± 0.62	0.1643
Weight		71.65 ± 1.20	73.50 ± 1.94	0.6622
BMI		26.82 ± 0.41	27.98 ± 0.67	0.2390
Folate multivitamins intake		168 (64.6%)	79 (64.8%)	0.9362
Psychiatric disorders		67 (25.8%)	43 (33.3%)	0.1228
Psychiatric medication		7 (2.7%)	7 (5.6%)	0.1698
Other medication		49 (18.8%)	20 (16.4%)	0.5563
Asthma		59 (22.7%)	30 (23.1%)	0.9317
Chronic HBP		3 (1.2%)	5 (3.8%)	0.0801
Pre-gestational DM				**0.0000**
	No	258 (99.2%)	114 (89.1%)	Ref*
	Diet	1 (0.4%)	4 (3.1%)	**0.0269**
	Metformin	0 (0.0%)	5 (3.9%)	**0.0030**
	Insulin	1 (0.4%)	5 (3.9%)	**0.0016**
DVT/PE		1 (0.4%)	1 (0.8%)	0.6171
PCOS		5 (1.9%)	11 (8.5%)	**0.0019**
Hypothyroidism		7 (2.7%)	2 (1.5%)	0.4795
UTI		17 (6.5%)	7 (5.4%)	0.6583
Other diseases		14 (5.4%)	7 (5.4%)	1.0000
Total gravidity		2.61 ± 0.10	2.87 ± 0.17	0.3517
Gravidity with current partner		2.17 ± 0.09	2.38 ± 0.17	0.7465
Booking SBP		110.94 ± 0.68	112.69 ± 1.26	0.3605
Booking DBP		65.34 ± 0.50	66.00 ± 0.87	0.8305

Bold indicates that values are significant.

BMI, body mass index; chronic HBP, chronic high blood pressure; DM, diabetes mellitus; DVT/PE, history of venous thromboembolism and/or pulmonary embolism; PCOS, polycystic ovary syndrome; UTI, urinary tract infection; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Ref = reference category for variable.

†Other = mainly Aboriginal patients (but also including Maori, South American Hispanic, etc.).

Table 2. Life-style characteristics of all cases and controls.

Variable	Category	Control ($n = 260$) Mean ± SEM N (%)	Stillbirth ($n = 130$) Mean ± SEM N (%)	p
Smoker		70 (27.0%)	35 (27.1%)	1.000
	Cigarettes/day	3.00 ± 0.38	3.43 ± 0.59	0.8557
Alcohol use		16 (6.2%)	9 (7.2%)	0.8254
Drug use		14 (5.4%)	12 (9.7%)	0.1489
Social issues				0.0682
	No issues	215 (87.8%)	91 (79.8%)	Ref*
	Minor issues	23 (9.4%)	21 (18.4%)	0.0257
	Major issues	7 (2.9%)	2 (1.8%)	0.5994
	ANQR score	17.16 ± 0.94	18.18 ± 1.36	0.6179
EPDS score		5.56 ± 0.41	6.79 ± 0.58	0.0587

*Ref = Reference category for variable.

higher rate of systolic hypertension (systolic blood pressure [SBP] ≥ 140) (OR 5.000, 95% CI 0.970–25.771) and diastolic hypertension diastolic blood pressure (DBP) (≥ 90) (OR 3.111, 95% CI 1.338–7.232) at booking.

Multivariate analysis identified the following independent risk factors: BMI >40 (OR 3.940, 95% CI 1.046–14.838), indigenous ethnicity (OR 2.255, 95% CI 1.024–4.970) and poor (minor and major issues combined) social status (OR 3.079, 95% CI 1.269–7.467). PCOS was a risk factor – but not significant when BMI was entered as the first variable in the multivariate analysis (Table 4).

Discussion

In this socio-economically disadvantaged region BMI was found to be the strongest risk factor for stillbirth, in line with previous studies [8,9]. A recent major USA study clearly demonstrated the risk of stillbirth associated with obesity.

Table 3. Obstetric characteristics and pregnancy outcomes of cases and controls.

Variable	Category	Control ($n = 260$) Mean ± SEM N (%)	Stillbirth ($n = 130$) Mean ± SEM N (%)	p
HBP previous pregnancy		27 (10.4%)	16 (12.3%)	0.5320
Mode of delivery	Previous LSCS	34 (13.1%)	23 (17.7%)	0.1980
Spontaneous pregnancy				0.1022
	Spontaneous	252 (96.9%)	118 (92.9%)	Ref*
	Ovulation induction	5 (1.9%)	3 (2.4%)	0.8026
	IVF	3 (1.2%)	6 (4.7%)	***0.0339***
PAPP-A		1.11 ± 0.06	1.07 ± 0.09	0.1816
hCG		1.20 ± 0.06	1.52 ± 0.43	0.6251
NT		1.47 ± 0.03	1.45 ± 0.07	0.1940
W28 Glucose challenge		6.06 ± 0.09	6.22 ± 0.22	0.7317
W28 GTT fasting		4.54 ± 0.12	4.79 ± 0.28	0.5194
W28 GTT 120′		7.10 ± 0.32	7.60 ± 0.72	0.9060
GDM		16 (6.9%)	8 (11.6%)	0.0578
GBS		27 (13.9%)	18 (18.0%)	0.3903
Preeclampsia				0.5533
	No	232 (89.2%)	119 (92.2%)	Ref*
	Yes	14 (5.4%)	4 (3.1%)	0.2667
	GIH	14 (5.4%)	6 (4.7%)	0.6860
Compliant				0.6021
	Not compliant	4 (1.6%)	4 (3.4%)	Ref*
	Little compliant	13 (5.1%)	6 (5.2%)	0.4147
	Compliant	238 (93.3%)	106 (91.4%)	0.3853
Foetal sex	Male	145 (55.8%)	61 (47.7%)	Ref*
	Female	115 (44.2%)	67 (52.3%)	0.1067
Gestation		38.90 ± 0.11	30.68 ± 0.66	***0.0000***
Birth weight		3313.70 ± 33.79	1738.47 ± 112.31	***0.0000***
Birth length		49.34 ± 0.15	40.59 ± 1.00	***0.0000***
Customised centile		46.44 ± 1.80	25.16 ± 2.64	***0.0000***

LSCS, lower segment caesarean section; IVF, in vitro fertilisation; First trimester screening, PAPP-A, hCG and NT; W28 GTT, 28 weeks glucose tolerance test; GDM, gestational diabetes mellitus; GBS, positive culture for group B streptococcus in lower vaginal swab.

*Ref = Variable category used as reference.

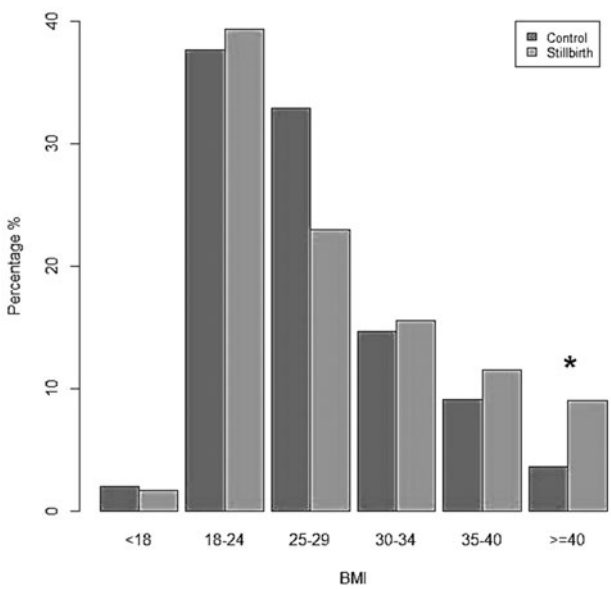

Figure 1. Distribution of BMI in categories of stillbirths and controls.

This risk increased steeply in the close to term and post-term period [10]. Post term, the curve in this USA study shows a sharp increase in risk in women with a BMI ≥ 40. Our study only shows an effect of BMI on stillbirth in morbidly obese (BMI ≥ 40) women, supporting these North American findings. In this South Australian study both cases and controls show a pattern of being overweight, although cases represent a larger percentage of BMI ≥ 30, whereas controls represent a larger percentage of BMI 25–30 (see Figure 1).

It should be noted that only two stillbirths in obese women could have potentially been avoided if labour would have been induced before term (e.g. 39–40 weeks). Within these ten years, 674 women with a BMI ≥ 40 would have been induced close to term to prevent these two stillbirths (NNT = 337). This number appears to be quite high, it is however noteworthy that most countries stopped vaginal breech deliveries; while for babies in breech position, the risk for major complications/death is about 1/400. As such, induction of labour <40 weeks in women with a BMI ≥ 40 could possibly represent a reasonable option, considering a NNT of 337 to prevent one term stillbirth [11]. The possible use of biomarkers (e.g. PlGF levels) and/or ultrasound (cerebroplacental ratio) in this setting represents an exciting area for further research.

Systolic and diastolic blood pressure showed significant outcomes in the univariate analysis, whereas no effect is seen in the multivariate analysis. This can be explained by the overlap between high blood pressure and increased BMI. No significant correlation was found between pre-eclampsia and stillbirth. Although preeclampsia is a well-known risk factor for adverse pregnancy outcome [12], modern management has led to early recognition and timely birth of the baby via induction of labour or LSCS [13].

Table 4. Multivariate analysis of cases and controls.

		OR	Lower 95% CI	Upper 95% CI
BMI 1	<30 versus ≥30–34	1.25	0.58	2.72
BMI 2	<30 versus 35–39	1.46	0.62	3.42
BMI 3	<30 versus ≥40	3.94	1.05	14.84
PCOS		5.36	0.80	35.92
Ethnicity	Cauc versus non-cauc	2.26	1.02	4.97
GDM		1.23	0.24	6.23
Social issues		3.08	1.27	7.47
Method of conception 1	Spontaneous versus ovulation induction	2.00	0.12	33.49
Method of conception 2	Spontaneous versus IVF	7.27	0.69	76.85
SBP ≥ 140 mmHg		3.12	0.20	48.63
DBP ≥ 90 mmHg		1.55	0.47	5.08
Height		0.97	0.92	1.01

BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure.

In this study, PCOS was identified as a significant risk factor for stillbirth. While Boomsma et al. reported PCOS as risk for perinatal death, data on stillbirth are not provided [14]. PCOS patients often present with fertility problems. It is therefore not surprising that a higher rate of nonspontaneous conception was also identified as a risk factor within the univariate analysis, with in particular a significant difference between spontaneous and IVF pregnancies [15]. Also PCOS and glucose intolerance have a well-known association, which could explain why diabetes is a significant risk factor for stillbirth in the univariate analysis, is dropped out of the multivariate analysis. Despite the small number of cases with diabetes in our population, a strong association was found in terms of stillbirths, which makes diabetes an important risk factor; a finding in line with prior studies [16,17]. Also for gestational diabetes a close to significant effect was found in the univariate analysis, in line with previous research [18]. This, once more, emphasises the importance of managing pre-pregnancy weight, and also pregnancy weight gain.

For the variable ethnicity the univariate analysis showed an effect between Caucasian cases and the ''minor ethnicities'' as a group, which in this study mainly consisted of indigenous Australians. r. The high risk for indigenous pregnant women has been well recognised. Most of their risks appear to be associated with poverty and poor living conditions [19].

Risk factors typically associated with stillbirth include low social status, smoking, obesity and drug use. In this study, both univariate and multivariate analysis on social issues were significant. Smoking did not show a significant effect on stillbirth. Information on cigarette use was obtained during the antenatal booking appointment. Because of the retrospective study design these findings could not be verified. However, in the prospective SCOPE study (Lyell McEwin Hospital was the site for the Australian arm of SCOPE) 3196 patients nulliparous pregnant women were included, of which 17 had a stillbirth; only two were smokers. Kennare et al. stated drug use, especially multi drug use, as an important risk factor for stillbirth. Although, it was recognised that adverse social factors had a strong interaction with drug use in the Kennare et al. study [20]. In the univariate analysis of this study, drug use was not found to be a significant risk factor.

Other known risk factors for stillbirth are male foetal sex [21] and previous LSCS [22]. Within this study population, these were not identified as risk factors. A change of paternity, a known risk factor for developing preeclampsia and SGA [23], was not a risk factor for stillbirth.

A limitation of this study is its retrospective design, as such all data had to be extracted from the medical records. Additionally, the same risk analysis was done for late term stillbirth (>28 weeks), however the sample size becomes extremely reduced. Therefore, the results were not published.

The aim of this study was to identify independent and hopefully modifiable risk factors for stillbirth in a high-risk population like the Northern suburbs of Adelaide. Independent risk factors for stillbirth included BMI, indigenous ethnicity and poor social status. In particular, BMI stands out as the major potentially modifiable risk factor for stillbirth. Although it is still not possible to predict stillbirth, a better understanding of combinations of risk factors in pregnant women in socio-economically disadvantaged areas may help to reduce future stillbirths [24,25].

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