Accept (06-Jul-2016)

Stillbirth and intrauterine fetal death: contemporary demographic features of > 1000 cases from an urban population

J. Man*†, J. C. Hutchinson*†, M. Ashworth*, A. Heazell‡, I. Jeffrey§ and N. J. Sebire*†

*Department of Histopathology, Camelia Botnar Laboratories, Great Ormond Street Hospital, London, UK; †University College London, Institute of Child Health, London, UK; ‡Department of Obstetrics and Gynaecology, St Mary's Hospital, Manchester, UK; §Department of Histopathology, St George's Hospital, London, UK

Correspondence to: Prof. N. J. Sebire, Department of Histopathology, Level 3 Camelia Botnar, Laboratories, Great Ormond Street Hospital, Great Ormond Street, London WC1N 3JH, UK (e-mail: Neil.sebire@gosh.nhs.uk)

KEYWORDS: ethnicity; intrauterine death; maternal age; miscarriage; obesity; stillbirth

+A: Abstract

Objectives Of 780 000 births annually in the UK, around 3300 are stillborn, a rate of around 4 per 1000 births. Traditional epidemiological associations are based on historic data. The aim of this study was to provide contemporary demographic findings in a large series of > 1000 deaths *in utero* in London and compare these with national datasets.

Methods From a dedicated database, including > 400 data fields per case, of fetal, infant and pediatric autopsies performed at Great Ormond Street Hospital and St George's Hospital, London, we extracted information on all intrauterine deaths, excluding terminations of pregnancy, from 2005 to 2013, inclusive. Data were analyzed according to the gestational age at which fetal death occurred (second-trimester intrauterine fetal death (IUFD), subdivided into early (< 20 weeks) and late (20–23 weeks) IUFD, and third-trimester stillbirth (≥ 24 weeks)) and compared with national datasets when available, through queries and statistical tests run using Microsoft Access, Excel, Graph Pad Prism and Stats Direct.

Results Data were available from 1064 individual postmortem reports examining intrauterine deaths delivered between 12 and 43 weeks' gestation, including 425 IUFDs (246 early and 179 late) and 639 stillbirths. Compared with the overall UK pregnant population, women in whom an intrauterine death occurred were significantly older and more obese. White mothers were significantly overrepresented in the stillbirth compared with the IUFD group compared with non-white mothers, whereas black mothers were significantly overrepresented in the IUFD group. Increased body mass index was associated with increased risk across all groups. Women who had uterine fibroids, those

who had a history of vaginal bleeding in early pregnancy and those who had undergone assisted conception were significantly more likely to have an IUFD than a stillbirth.

Conclusions Based on a large series of > 1000 autopsies in cases of intrauterine death, these data continue to highlight the increased risk for fetal loss associated with maternal demographic factors in contemporary clinical practice, particularly associations with increased maternal age and body mass index. Among women in whom an intrauterine death occurs, maternal ethnicity, mode of conception and gynecological history are associated with differing timing of fetal loss. Further research is required to understand the mechanisms involved in such maternal factors in order to develop preventative strategies.

+A: Introduction

There are an estimated 2.6 million stillbirths worldwide per annum[1]. In 2013, there were 780 000 births in the UK, of which 3300 were stillborn, a rate of around 4 per 1000 births[2,3]. Traditional epidemiological associations include factors such as nulliparity or grand multiparity, increased maternal body mass index, maternal diabetes mellitus (DM), history of antenatal vaginal bleeding and older maternal age[3,4], with women aged over 40 years having a significantly increased risk of stillbirth[2,5]. While these associations are important, the majority occur in women without recognized risk factors.

Progress towards a reduction in the global stillbirth burden is proving to be slower than anticipated[6]. Although some risk factors, such as maternal cigarette smoking[7], have been declining in prevalence in many western countries[8], increasing maternal obesity and a shift towards older maternal age are becoming increasingly

prevalent risk factors faced by clinicians and may be slowing the reduction in stillbirth rates[1,5,9].

The majority of data regarding demographic factors associated with deaths *in utero* relate to historical population-based datasets of stillbirths in the third trimester. The aim of this study was to present contemporary demographic findings from a large series of > 1000 intrauterine deaths in London which underwent autopsy investigation, and to examine these features in relation to the gestational age at which fetal death occurred, including deaths across both second and third trimesters, which are not captured by traditional registry-based approaches.

+A: Methods

This analysis was part of a larger study evaluating several aspects of postmortem investigation of IUFDs. Data were extracted from autopsy examination packs and reports according to predefined standard criteria and entered into a research Microsoft Access Autopsy Database (Microsoft Corp., Redmond, WA, USA), including over 400 datafields per case. All demographic information was as provided to the pathologist at the time of postmortem examination. The database was searched to identify all stillbirths, and early (< 20 weeks) and late (20–24 weeks) IUFDs from 2005 to 2013, inclusive. Cases were from Great Ormond Street Hospital and St George's Hospital, both in London. For all cases, objective, pre-defined criteria were used for consistency of classification. All autopsies had been performed according to standard protocols as suggested by the UK Royal College of Pathologists. Briefly, cases underwent clinical review, postmortem imaging if appropriate, external examination, prosection and internal examination, and ancillary investigations such as fetal histological examination

and microbiology/virology as appropriate. For the purposes of the current study, we searched the database to identify all intrauterine deaths (excluding terminations) from 2005 to 2013, inclusive. For all cases, objective, pre-defined criteria were used for consistency of classification.

Information relating to maternal demographic features and main cause of death was identified and study data were analyzed according to the gestational age at which fetal death occurred (second-trimester intrauterine fetal death (IUFD), subdivided into early IUFD (< 20 weeks) and late IUFD (20–23 weeks), and third-trimester stillbirth (≥ 24 weeks)). Data were compared with national datasets when available. Analysis was through queries and statistical tests run using Microsoft Access and Microsoft Excel (Microsoft Corp.), Graph Pad Prism and Stats Direct, with $P < 0.05$ regarded as statistically significant. Comparison of proportion testing and distribution comparisons using Mann Whitney U tests were performed as appropriate. The study was approved by the local research ethics committee.

+A: Results

Data were available from 1064 individual postmortem examinations following intrauterine death. Cases had been delivered between 12 and 43 weeks' gestation and included 425 IUFDs (246 early (< 20 weeks' gestation) and 179 late (20–23 weeks)) and 639 stillbirths (≥ 24 weeks). Overall, there were 298 (28%) intrapartum/fresh IUFDs, whilst the majority had undergone a period of retention following the death prior to delivery. Among the 639 stillbirths, 117 (18%) were intrapartum/fresh stillbirths, the remainder being retained stillbirths.

Overall, there was a non-significant peak in prevalence of intrauterine deaths in the summer months ($z = 0.06$, P=0.95; Figure 1). There was a small but significant excess of male fetal deaths, ($z = 4.47$, $P < 0.0001$ (569 (53%) *vs* 466 (44%)), consistent with the findings of a previous review[10], but there was no significant difference in the proportion of males to females between stillbirths and IUFDs ($z = 0.01$, $P = 0.9$).

The overall maternal age distribution is shown in Figure 2. There was no significant difference in maternal age distribution between the stillbirth and IUFD groups. However, compared with the overall UK population of 671 255 pregnant women in 2012–2013[11], women in whom an intrauterine death occurred were significantly older ($z = 3.14$, $P = 0.001$; Figure 3), although, when compared with national population data for 3220 women in whom stillbirth occurred, the maternal age of the study stillbirth population was not significantly different ($z = 0.98$, $P = 0.16$)[2]. These data demonstrate that, in terms of age, first, the study population is representative of the national stillbirth population; second, women in whom an intrauterine death occur are significantly older than the overall obstetric population; and third, that the risk of fetal loss in relation to increased maternal age is similar across the second and third trimesters and is not limited to third-trimester stillbirth.

Caucasians, versus non-white women, were significantly overrepresented in the stillbirth compared with the IUFD groups ($z = 4.14$, $P < 0.0001$), whereas black women were significantly overrepresented in the IUFD groups compared to stillbirths ($z = 3.94$, $P < 0.0001$; Figure 4). There were significantly more black mothers in the study population compared with in the general pregnant population according to the national HSCIC data of 671 255 births[11] ($z = 28.1$, $P < 0.0001$).

Maternal body mass index (BMI) was classified as follows: underweight, ≤ 18; normal, 18–24; overweight, 25–29; and obese, ≥ 30[12]. BMI data were available in only 261 cases at the time of autopsy; there were no significant differences in BMI between mothers in whom IUFD occurred and those in whom stillbirth occurred ($z = 0.67$, $P = 0.51$). However, compared with national data from the Health Survey for England[12], the overall study population was significantly more overweight ($z = 3.0$, $P = 0.003$) and obese ($z = 3.92$, $P < 0.0001$) than the general population of women of childbearing age (Figure 5). These data demonstrate that increased BMI is associated with increased risk of intrauterine death throughout the second and third trimesters, not just being associated with late third-trimester stillbirth.

One third (356/1064) of the mothers in our study population were primigravid, while 16% had experienced at least one previous pregnancy with no live births (i.e. miscarriages, stillbirths, terminations and ectopic pregnancies). Primigravidae were significantly more likely to have a stillbirth than an IUFD ($z = 4.38$, $P < 0.0001$). Two hundred and four (19%) women had significant gynecological history, features of which differed according to presentation group. Specifically, there were significantly more women with fibroids ($z = 3.74$, $P < 0.001$), women with a history of vaginal bleeding during pregnancy ($z = 3.55$, $P < 0.001$) and women who had conceived by assisted conception methods such as *in-vitro* fertilization (IVF) ($z = 3.81$, $P < 0.0001$) in the IUFD compared with the stillbirth group (Figure 6).

Information on maternal DM was available for 1008 (98%) women, of whom 26 (3%) had pre-existing DM and 37 (4%) had gestational DM. There were significantly more stillbirths, compared with IUFDs, in those with any form of DM ($z = 2.41$, $P = 0.02$). Furthermore, compared with national data, the study population had a greater

proportion of women with some form of DM ($z = 2.65$, $P = 0.008$). These data indicate that maternal DM is associated with increased risk of intrauterine death, mainly third-trimester stillbirth.

+A: Discussion

Our findings provide contemporary demographic characteristics of an urban population of women presenting with intrauterine death in the second or third trimester between 2005 and 2013; this population is representative of the overall UK stillbirth population. The data are based on 1064 autopsies following intrauterine death, the majority of which were antepartum with significant intrauterine retention following fetal demise. There was a small but significant excess of male fetuses. Compared with the unselected national population of births, the study population (overall and separately for stillbirths and for IUFDs) was significantly older, consistent with epidemiological data; the year 2011 saw the largest percentage increase in fertility in women 40 years and older since 2001 in England and Wales[3,5,13].

There were significantly more black women in the study population compared with the general UK pregnant population, in keeping with published data that the risk of intrauterine death is increased in mothers of African or Asian ethnicity[2,4,14,15]. In particular, black women were more likely to have an IUFD than a stillbirth. Women in the study population were significantly more overweight and obese compared with the general population of women of childbearing age, but with no significant difference in BMI in relation to timing of intrauterine death, this being associated with both IUFD and stillbirth[3,16].

Women in the study population who were primigravid were more likely to have a stillbirth than an IUFD, whereas women with a history of early pregnancy vaginal bleeding or uterine fibroids and those who had conceived by IVF were significantly more likely to have an IUFD. Compared with the national population, there were relatively more women with DM in the study group, particularly in those who had a stillbirth.

The current large dataset is unique, being derived from specialist centers rather than registry data, and includes both third-trimester stillbirths and second-trimester IUFDs, thus allowing novel insights. For example, Caucasian women had relatively more stillbirths, whilst black women had a relatively higher prevalence of IUFDs, which is likely related to the increased frequency of ascending genital tract infection in this group[17–19]. Furthermore, whilst increased maternal BMI has been reported to be associated with increased risk of stillbirth, in a dose-related manner[20,21], the present data suggest that the risk of maternal obesity applies to intrauterine death across the gestational range studied, rather than being limited to stillbirths. These findings raise questions relating to the possible mechanisms by which increased maternal BMI could lead to such fetal deaths, which are apparently acting throughout the second and third trimesters. Suggested mechanisms may include placental disease and chronic systemic inflammation, including release of proinflammatory cytokines, CRP and secondary metabolic effects[22–24].

The association of maternal gynecological history, such as a history of vaginal bleeding, with increased risk of second-trimester fetal loss is in keeping with previously published data[25–27], though determining a clear relationship between IVF and pregnancy loss remains difficult within the context of availability of different assisted reproductive

techniques and potential overlap with advancing maternal age and comorbid gynecological history. Some studies have demonstrated no increase in risk of fetal loss, for example for previously infertile women undergoing assisted conception, if other factors are accounted for.[28]

Despite the size of the current study and use of an unselected cohort of all intrauterine deaths undergoing autopsy examination, the study has limitations. The hospitals involved were tertiary referral centers for the investigation of perinatal death. As a result, cases analyzed within this autopsy database, whilst not being selected by the investigators, may have been preselected via the referral pathway from external hospitals; for example, the frequency of intrapartum or fresh stillbirths in the series was slightly greater than expected. However, since other features, such as the maternal age distribution, were not significantly different from the national stillbirth data, it is likely that, within this large dataset, such bias was negligible for the purposes of our study findings. Furthermore, full antenatal notes were not available to the investigators, and some data, such as BMI and maternal blood pressure, were not provided by the referring clinicians in every case, although they would have been available in the full medical notes.

In summary, the findings of this study provide current epidemiological data regarding women in whom intrauterine death occurred across the second and third trimesters. The data highlight the increased risk for intrauterine death associated with changing maternal demographics in contemporary clinical practice: namely, the ageing of the maternal population, increasing maternal BMI, and the trend towards delaying first pregnancy until later in life and conceiving with assisted conception techniques. These high-risk groups should be recognized, and, in order to develop strategically

appropriate interventions to reduce these deaths, future research must focus on understanding the mechanisms involved in association with such maternal factors rather than simply on identifying these associations.

+A: References

1. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, Flenady V, Frøen JF, Qureshi ZU, Calderwood C, Shiekh S, Jassir FB, You D, McClure EM, Mathai M, Cousens S. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; **387**: 587–603.

<OTHER>2. Manktelow BN, Smith LK, Evans TA, Hyman-Taylor P, Kurinczuk JJ, Field DJ, Smith PW, Mielewczyk F, Draper ES, on behalf of the MBRRACE-UK collaboration. *MBRRACE-UK perinatal mortality surveillance report. UK perinatal death for births from January to December 2013. Supplementary report. UK Trusts and Health Boards.* The Infant Mortality and Morbidity Studies Group, Department of Health Sciences, University of Leicester: Leicester, 2015.

3. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. *BMJ* 2013; **346**: f108.

4. Drysdale H, Ranasinha S, Kendall A, Knight M, Wallace EM. Ethnicity and the risk of late-pregnancy stillbirth. *Med J Aust* 2012; **197**: 278–281.

5. Kenny LC, Lavender T, McNamee R, O'Neill SM, Mills T, Khashan AS. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. *PLoS One* 2013; **8**: e56583.

6. Blencowe H, Cousens S, Jassir FB, Say L, Chou D, Mathers C, Hogan D, Shiekh S, Qureshi ZU, You D, Lawn JE, for The Lancet Stillbirth Epidemiology Investigator Group. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2016; **4**: e98–108.

7. Marufu TC, Ahankari A, Coleman T, Lewis S. Maternal smoking and the risk of still birth: systematic review and meta-analysis. *BMC Public Health* 2015; **15**: 239.

8. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, Coory M, Gordon A, Ellwood D, McIntyre H, Fretts RC, Ezzati M. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011; **377**: 1331–1340.

9. Johansson S, Villamor E, Altman M, Bonamy AK, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. *BMJ* 2014; **349**: g6572.

10. Mondal D, Galloway T, Bailey T, Mathews F. Elevated risk of stillbirth in males: systematic review and meta-analysis of more than 30 million births. *BMC Med* 2014; **12**: 220.

<EPATH>11. Hospital Episode Statistics Analysis, Health and Social Care Information Centre. NHS Maternity Statistics - England, 2012–13. http://www.hscic.gov.uk/article/2021/Website-Search?productid=13418&q=pregnancy&sort=Relevance&size=10&page=1&area=both#top [Accessed xxxxxxxxxxxxxxxxx].

<EPATH>12. Moody A. Chapter 10: Adult anthropometric measures, overweight and obesity. The Health and Social Care Information Centre. Health Survey for England, 2012. http://www.hscic.gov.uk/catalogue/PUB13218/HSE2012-Ch10-Adult-BMI.pdf. [Accessed xxxxxxxxxxxxxxxxx].

<EPATH>13. Office for National Statistics. Births and Deaths in England and Wales, 2011. Office for National Statistics, 2012.

http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/dcp171778_279934.pdf [Accessed 04/04/2016].

14. Penn N, Oteng-Ntim E, Doyle P. PPO.34 The role of ethnicity in determining the prevalence of stillbirth in an ethnically-diverse UK population. *Arch Dis Child Fetal Neonatal Ed* 2014; **99**: A161–A161.

15. Khalil A, Rezende J, Akolekar R, Syngelaki A, Nicolaides KH. Maternal racial origin and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol* 2013; **41**: 278–285.

16. The Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. *JAMA* 2011; **306**: 2469–2479.

17. Fassett MJ, Wing DA, Getahun D. Temporal trends in chorioamnionitis by maternal race/ethnicity and gestational age (1995–2010). *Int J Reprod Med* 2013; 2013: 906467.

18. Becroft DM, Thompson JM, Mitchell EA. Placental chorioamnionitis at term: epidemiology and follow-up in childhood. *Pediatr Dev Pathol* 2010; **13**: 282–290.

19. Holzman C, Lin X, Senagore P, Senagore P, Chung H. Histologic chorioamnionitis and preterm delivery. *Am J Epidemiol* 2007; **166**: 786–794.

20. Cnattingius S, Villamor E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. *Lancet* 2016; **387**: 558–565.

21. Bodnar LM, Parks WT, Perkins K, Pugh SJ, Platt RW, Feghali M, Florio K, Young O, Bernstein S, Simhan HN. Maternal prepregnancy obesity and cause-specific stillbirth. *Am J Clin Nutr* 2015; **102**: 858–864.

22. Schmatz M, Madan J, Marino T, Davis J. Maternal obesity: the interplay between inflammation, mother and fetus. *J Perinatol* 2010; **30**: 441–446.

23. Retnakaran R, Hanley AJ, Raif N, Connelly PW, Sermer M, Zinman B. C-reactive protein and gestational diabetes: the central role of maternal obesity. *J Clin Endocrinol Metab* 2003; **88**: 3507–3512.

24. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004; **15**: 2792–2800.

25. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *BMJ* 1997; **315**: 32–34.

26. Benson CB, Chow JS, Chang-Lee W, Hill JA, Doubilet PM. Outcome of pregnancies in women with uterine leiomyomas identified by sonography in the first trimester. *J Clin Ultrasound* 2001; **29**: 261–264.

27. Wang J, Norman R, Wilcox A. Incidence of spontaneous abortion among pregnancies produced by assisted reproductive technology. *Hum Reprod* 2004; **19**: 272–277.

28. Pezeshki K, Feldman J, Stein DE, Lobel SM, Grazi RV. Bleeding and spontaneous abortion after therapy for infertility. *Fertil Steril* 2000; **74**: 504–508.

+A: **ACKNOWLEDGMENTS**

N.J.S. is supported by an NIHR Senior Investigator award and is partially funded by the Great Ormond Street Hospital Children's Charity and the NIHR Biomedical Research Centre at Great Ormond Street Hospital. J.M. is funded by a grant from SANDS (Stillbirth and Neonatal Death Society) charity. A.E.P.H. is supported by an NIHR Clinician Scientist fellowship and is partially funded by Tommy's. The views expressed

are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.