University of Bristol - Explore Bristol Research
General rights

Association of common maternal infections with birth outcomes: a multinational cohort study

Jian-Rong He [1,2], Gabriella Tikellis [3], Ora Paltiel [4], Mark Klebanoff [5], Per Magnus [6], Kate Northstone [7], Jean Golding [8], Mary H. Ward [9], Martha S. Linet [10], Sjurdur F Olsen [11], Gary S. Phillips [12], Stanley Lemeshow [13], Xiu Qiu [1], Jane E Hirst [2,14*], Terence Dwyer [2,15,16*]

[1] Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China;

[2] Nuffield Department of Women's and Reproductive Health, University of Oxford, UK;

[3] Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Melbourne, Australia;

[4] Braun School of Public Health, Hadassah-Hebrew University Medical Center, Jerusalem, Israel;

[5] Center for Perinatal Research, The Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, USA.

[6] Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway;

[7] Faculty of Health Sciences, University of Bristol, Bristol, UK.

[8] Centre for Academic Child Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.

[9] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD

[10] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA.

[11] Centre for Fetal Programming, Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

[12] Consultant retired from the Center for Biostatistics, Department of Biomedical Informatics, Ohio State University, Columbus, Ohio, USA;

[13] Division of Biostatistics, College of Public Health, Ohio State University, Columbus, Ohio, USA;

[14] George Institute for Global Health, London, UK.

[15] Clinical Sciences Theme, Heart Group, Murdoch Children's Research Institute, Melbourne, Australia.

[16] Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia.

Correspondence to: Dr Jian-Rong He, Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China; jianrong.he@bigcs.org; phone: +86 20 38367159

* Joint senior authors

Acknowledgement

Abstract

Purpose: It is unclear whether common maternal infections during pregnancy are risk factors for adverse birth outcomes. We assessed the association between self-reported infections during pregnancy with preterm birth and small-for-gestational-age (SGA) in an international cohort consortium.

Methods: Data on 120,507 pregnant women were obtained from six population-based birth cohorts in Australia, Denmark, Israel, Norway, the UK and the USA. Self-reported common infections during pregnancy included influenza-like illness, common cold, any respiratory tract infection, vaginal thrush, vaginal infections, cystitis, urinary tract infection, and the symptoms fever and diarrhoea. Birth outcomes included preterm birth, low birth weight and SGA. Associations between maternal infections and birth outcomes were first assessed using Poisson regression in each cohort and then pooled using random-effect meta-analysis. Risk ratios (RR) and 95% confidence intervals (CI) were calculated, adjusted for potential confounders.

Results: Vaginal infections (pooled RR, 1.10; 95% CI, 1.02-1.20) and urinary tract infections (pooled RR, 1.17; 95% CI, 1.09-1.26) during pregnancy were associated with higher risk of preterm birth. Similar associations with low birth weight were also observed for these two infections. Fever during pregnancy was associated with higher risk of SGA (pooled RR, 1.07; 95% CI, 1.02-1.12). No other significant associations were observed between maternal infections/symptoms and birth outcomes.

Conclusion: ~~Whilst v~~Vaginal infections~~,~~ and urinary infections ~~and fever~~ during pregnancy were associated with a small increased risk of preterm birth and~~,~~ low birth weight, whereas fever was associated with ~~or~~ SGA~~, other common infections do not appear to increase these risks~~. These findings require confirmation in future studies with laboratory-confirmed infection diagnosis.

Keywords: Maternal infection; cohort study; preterm birth; fetal growth

Background

Infections are common among pregnant women. Nearly half of pregnant women experience some type of infection during their pregnancy [1]. Due to physiological changes such as altered immune tolerance for the fetus, urinary stasis, and respiratory volume reduction, pregnant women have a higher risk of severe infection-related consequences compared to the general population [2]. Severe maternal infections (e.g. pregnancy-related sepsis) are responsible for one in ten of maternal deaths worldwide [3]. Infections are responsible for up to a quarter of stillbirths in high-income settings and up to half of those in low-/middle-income countries [4, 5].

Fortunately, most infections during pregnancy are self-limited or improve with appropriate antimicrobial therapy. Whilst the mother may make a full recovery, exposure of the developing fetus to systematic or localised inflammatory responses and oxidative stress is hypothesised to affect growth and/or gestational duration [6]. However, evidence supporting this hypothesis is conflicting. Whilst an association between urinary tract infections and bacterial vaginosis during pregnancy with preterm birth (PTB) has been demonstrated [7], this has not been shown consistently in low-risk populations [8]. Few studies have evaluated the effects of non-urogenital infections, such as influenza or upper respiratory tract infections on adverse birth outcomes [9, 10].

Both infections and adverse birth outcomes are related to sociodemographic factors. Insufficient control of these factors in the analysis could lead to biased associations between maternal infections and birth outcomes. This may partly explain the discrepancies in results of previous studies with different sociodemographic patterns. Combining evidence from different settings, with appropriate assessment and adjustment of sociodemographic factors and other sources of potential heterogeneity, may help to more accurately quantify associations between maternal infections and birth outcomes.

In the present study, we aimed to investigate the associations between self-

reported common maternal infections (i.e., influenza-like illness, common cold, any respiratory tract infection, vaginal thrush, vaginal infections, cystitis, urinary tract infection, fever and diarrhoea) and preterm birth, low birth weight and small for gestational age at birth (SGA) in six international birth cohorts with a rich set of harmonized covariate data.

Methods

Data source

Data were obtained from six birth cohorts, including the Avon Longitudinal Study of Parents and Children (ALSPAC, UK; n=14,049; recruitment years, 1991-1992) [11], the Collaborative Perinatal Project (CPP, USA; n=53,738; 1959-1965) [12], the Danish National Birth Cohort (DNBC, Denmark; n=94,690; 1996–2002) [13], the Jerusalem Perinatal Study (JPS, Israel; n=90,079; 1964-1976) [14], the Norwegian Mother, Father and Child Cohort Study (MoBa, Norway; n=111,399; 1999-2008) [15], and the Tasmanian Infant Health Study (TIHS, Australia; n=10,624; 1988-1995) [16]. These six cohorts are participating members of the International Childhood Cancer Cohort Consortium (I4C) [17], the source of data for the present study.

Data on all children in ALSPAC, CPP, JPS and TIHS were included in I4C. Due to data sharing restrictions, available data from the other two cohorts (DNBC and MoBa) only included a random 10% sample of the cohort and all childhood cancer cases. In addition, JPS only collected maternal infection data in two subsets with no overlap in the population: the antenatal interview (n=11,467) and the postnatal interview (n=16,912) subcohorts [14]. We only included these two subsets rather than the full JPS cohort. We further excluded women who delivered non-singleton babies (n=6,642) or babies with trisomy 21 (n=138), resulting in a total sample of 120,507 pregnant women in the current analysis (Supplementary Fig. 1). De-identified data were transferred from the participating cohorts to the I4C International Data Coordinating Centre located at the Murdoch Children's Research Institute (Melbourne, Australia), where they were stored on a secure, password-protected server. This study and data use were approved by the I4C Steering

Committee and the Ethics Committees from the participating cohorts (supplementary materials).

Maternal infections during pregnancy

Data on infections during pregnancy were collected using different approaches across the six cohorts: self-reported questionnaires (ALSPAC, JPS, MoBa, TIHS), self-reports from telephone interviews (DNBC), and a combination of medical record review and self-reported interviews (CPP). We only included infections with a reported prevalence above 5% and data available in at least two cohorts: influenza-like illness, common cold, any respiratory tract infection, vaginal infections and their primary type—vaginal thrush, urinary tract infection and its primary type—cystitis and two infection-associated symptoms (fever and diarrhoea). We categorised exposure to the specific infection at any time during pregnancy as a binary outcome (yes/no). Details about the data collection, harmonisation and prevalence of the infection variables in the six cohorts have been reported in our previous publications [18] and are also shown in Supplementary Tables 1-3. In the pooled dataset, common cold and diarrhoea have the highest prevalence (>30%), followed by vaginal infections, vaginal thrush, fever and respiratory infection (20%-25%) (Supplementary Table 3). Prevalence of influenza-like illness and urinary tract infection (including cystitis) was slightly under 15%.

Birth outcomes

Preterm birth was defined as gestational age at birth less than 37 weeks of gestation. Gestational age (continuous variable in weeks) was determined based on the date of the last menstrual period or ultrasound scan. Low birth weight was defined as <2500 grams. SGA was defined as a birth weight <10th sex- and gestational-age-specific percentiles, according to the INTERGROWTH-21st birth weight standards.[19] Data on birth weight were extracted from medical records or birth registries. In the I4C dataset, data on gestational age at birth in ALSPAC, CPP, MoBa and TIHS are recorded as completed weeks of gestation. We thus added 3 days to the recorded

gestational age to reduce the misclassification of SGA for these four cohorts [20].

Covariates

Maternal characteristics include age at childbirth (<25, 25-34, ≥35 years) and educational level (≥12 or <12 years or the equivalent), smoking during pregnancy (yes/no), pre-pregnancy BMI (continuous), parity (primipara or multipara), any diabetes (before or during pregnancy; yes or no). Child sex was also included as a known predictor of birth outcomes. Data on these variables were mainly collected via self-reported questionnaires, interviews or birth records. BMI was calculated from self-reported height and weight [weight (kg)/height (m^2)] before pregnancy or in early weeks of pregnancy. These characteristics are generally considered to be related to birth outcomes. We also found that these factors, except fetal sex, were associated with infections during pregnancy (Supplementary Table 4). Therefore, these factors (except fetal sex) were considered to be potential confounders and thus included for adjustment in the association analysis between maternal infections and birth outcomes. Diabetes in TIHS and pre-pregnancy BMI in the JPS antenatal subset were not adjusted as these data were unavailable.

Statistical analysis

Supplementary Table 5 shows the percentage of missing values for each variable. We used Multiple Imputation by Chained Equations to generate 30 imputation datasets. To account for the clustering of children and the heterogeneity, the imputations were separately performed within each cohort. Continuous variables were imputed using truncated linear regression, whereas binary variables were imputed using logistic regression. All covariates, infection variables, birth variables (i.e. birth weight, gestational age at birth) and were included in the imputation models. Cancer variables were also included in the imputation models as cancer cases were overrepresented in DNBC and MoBa given the sampling strategy.

We performed a two-stage individual participant data meta-analysis to

examine the association of maternal infections/symptoms with birth outcomes. In the first stage, Poisson regression with robust error variance was used to examine the association of maternal infections with birth outcomes separately in each cohort. Risk ratios (RR) and corresponding 95% confidence intervals (CI) were calculated. Models were constructed for each infection separately. A regression coefficient was first estimated in each imputation dataset and then pooled using Rubin's rules over 30 imputation datasets [21]. In the second stage, cohort-specific RRs were combined using random-effect meta-analysis (DerSimonian and Laird method). I^2 was used to measure the heterogeneity across cohorts.

Several sensitivity analyses were performed. First, seasonality of both infections (e.g. respiratory tract infections, urinary tract infection) and birth outcomes have been observed. Associations between the two might be biased by seasonal factors. To address this, conception seasons were additionally included in the regression models. Second, for the analysis of low birth weight and SGA, women who delivered preterm were excluded as they might have a shorter exposure window. Third, for the analysis of preterm birth, we excluded caesarean section deliveries because they might not reflect spontaneous birth timing. Fourth, we excluded TIHS and JPS antenatal subset from the association analysis because adjustment for diabetes (TIHS) or pre-pregnancy BMI (JPS antenatal subset) was not available in these two cohorts.

All analyses were completed using STATA version 14 (StataCorp, College Station, TX, USA). P-values less than 0.05 were considered "statistically significant".

Results
Population characteristics
Overall, 9% of pregnant women were 35 years of age or older, 22% were overweight or obese before pregnancy, 34% smoked during pregnancy, 1% had diabetes during pregnancy, and 8% delivered via caesarean section

(Table 1). The overall incidence of preterm birth was 9.9%, of low birth weight 7.4% and of SGA 11.2%. Women who were younger than 25 years, had lower education, lower pre-pregnancy BMI, and were more likely to smoke during pregnancy than older mothers. Women younger than 25 were more likely to deliver preterm, low-birth weight or SGA babies compared with women at 25 years or older (Table 1). Maternal diabetes was associated with an increased risk of preterm birth but reduced risk of SGA. Babies born to primiparous women had a higher risk of low birth weight or SGA. Boys had a higher risk of preterm birth, while girls had increased risk of low birth weight or SGA.

Association with preterm birth
Urinary tract infection (pooled RR, 1.17; 95% CI, 1.09-1.26) and vaginal infections (pooled RR, 1.10; 95% CI, 1.02-1.20) during pregnancy were associated with higher risk of preterm birth (Fig. 1). Cohort-specific associations for urinary tract infection and vaginal infections are shown in Supplementary Fig. 2 and Fig. 3. Vaginal thrush (RR, 1.11; 95% CI, 0.97-1.26), and cystitis (RR, 1.12; 95% CI, 0.92-1.36) were also associated with a higher risk but did not reach statistical significance. Other infections were not associated with an increased risk of preterm birth. Heterogeneity across cohorts was low except for fever and diarrhoeas.
After adjusting for conception season, vaginal infections and urinary tract infection remained significantly associated with an increased risk of preterm birth (Supplementary Table 6). The confidence interval for the RR of vaginal infections became slightly wider after excluding caesarean section births (Supplementary Table 7). The association for urinary tract infection remained similar to the primary analysis after excluding caesarean section births (Supplementary Table 7) or excluding TIHS cohort (Supplementary Table 8).

Association with low birth weight
The pattern of associations evident between maternal infections and low birth weight was similar to that for preterm birth. Urinary tract infection (pooled RR, 1.14; 95% CI, 1.08-1.21) and vaginal infections (pooled RR, 1.06; 95% CI, 1.00-1.12) during pregnancy were associated with a significant increased risk

of delivering a baby with low birth weight (Fig. 2, Supplementary Fig. 4 and Fig. 5). The RR for cystitis was similar to that of urinary tract infection, but was less precise (pooled RR, 1.13; 95% CI, 0.87-1.47). Heterogeneity across cohorts was generally low except for diarrhoea.

Adjusting for conception season (Supplementary Table 6) and excluding births via caesarean section (Supplementary Table 7) or TIHS cohort (Supplementary Table 8) yielded similar results. We further excluded preterm births and found that vaginal infections were borderline significantly whereas urinary tract infection was still significantly associated with higher risk of term low birth weight (Supplementary Table 9), suggesting that the associations for low birth weight were not driven by preterm birth. Results without adjustment for any confounders were similar to those with adjustment (Supplementary Table 10).

Association with SGA

Fever during pregnancy (pooled RR, 1.07; 95% CI, 1.02-1.12) was associated with a higher risk of SGA (Fig. 3 and Supplementary Fig. 6). Respiratory infection (pooled RR, 1.09; 95% CI, 0.99-1.19), common cold (pooled RR, 1.10; 95% CI, 0.98-1.23) and urinary tract infection (pooled RR, 1.08; 95% CI, 0.99-1.17) were statistically marginally associated with increased SGA risk. Heterogeneity across cohorts was low except for vaginal infections.

In the sensitivity analysis adjusting for conception season (Supplementary Table 6) and excluding births via caesarean section (Supplementary Table 7), results were similar to the primary analysis. However, excluding the TIHS cohort enhanced the association for urinary tract infection and SGA (pooled RR, 1.14; 95% CI, 1.08-1.20; Supplementary Table 8). Also, after excluding preterm births, respiratory infection (pooled RR, 1.11; 95% CI, 1.01-1.22) and urinary tract infection (pooled RR, 1.10; 95% CI, 1.00-1.19) were statistically significantly associated with SGA risk (Supplementary Table 9).

Discussion

Summary of findings

In this pooled analysis of six international birth cohorts, we found that certain

types of common infections during pregnancy were associated with a modestly increased risk of preterm birth, low birth weight and SGA. To our knowledge, this is the first large-scale study to analyse associations of a broad spectrum of infections during pregnancy and birth outcomes with adjustment for many potential confounders, based on data from multiple countries.

Comparison with previous studies and implications

Urinary tract infection is one of the most common complications during pregnancy and has received substantial clinical attention in relation to birth outcomes [22]. We found urinary tract infection during pregnancy was associated with an increased risk of preterm birth. This finding is in line with those from previous studies since the 1970s [23, 24]. However, results from more recent studies were inconsistent. For example, a prospective cohort study of 4,918 low-risk pregnant women in Netherlands reported that symptomatic lower urinary tract infection [25], but not asymptomatic bacteriuria [26], during pregnancy was associated with increased risk of preterm birth. In contrast, a retrospective cohort study of 8807 pregnant women in Denmark reported that bacteriuria during pregnancy was associated with preterm delivery [27]. On the other hand, a nationwide population-based study of Chinese 42,742 pregnant women with diagnosed UTIs versus 42,742 controls did not observe a statistically significant association [28]. The discrepancies between studies may be attributed to the heterogeneity in populations or differences in the definitions/ measurement methods used to assess infections (e.g., urine culture, medical records or self-report). A recent review summarized the evidence on effectiveness of treatment against urinary tract infection during pregnancy and concluded that there is low-to-moderate-quality evidence that treating urinary tract infection could reduce the risk of preterm birth and low birth weight [29]. Therefore, more evidence is needed concerning the relationship between urinary tract infection during pregnancy and preterm birth in contemporary settings.

Vaginal infection (mainly vaginal thrush) during pregnancy was also

associated with an increased risk of preterm birth in our study. Supporting our results, a systematic review of two randomized trials found that the treatment of asymptomatic vaginal candidiasis in pregnancy reduced the rates of preterm birth [30]. However, most previous observational epidemiologic studies have found no association between vaginal thrush and preterm birth [31, 32], although a few studies have reported positive findings [33]. A recent systematic review and meta-analysis of 35 studies on 49,161 pregnant women reported a summary OR of 1.01 (95% CI 0.84–1.21) for the association of vulvovaginal yeast infections during pregnancy with preterm birth, but only three of the studies adjusted for potential confounding [34]. However, it should be noted that our data on infections are based on maternal self-report and pregnant women may mis-report other vaginal infections such as bacterial vaginosis and trichomoniasis (which has been associated with preterm birth [35]) as vaginal thrush. Therefore, further studies with laboratory-confirmed types of vaginal infections are needed to validate our findings.

Several studies have reported positive associations between urinary tract infection and SGA [24, 36], which is in line with our finding. However, two large retrospective cohort studies (85,484 and 141,035 women respectively) reported null results for diagnosed urinary tract infection or genitourinary infection and SGA [28, 37]. In addition, our study shows that respiratory infection was borderline associated with SGA risk. A previous population-based cohort study of 132,588 singleton deliveries also showed that pregnant women hospitalised for respiratory illness were more likely to deliver SGA or low birth weight babies [38]. A more recent retrospective cohort study of 1,430,669 women from four high-income countries reported that hospitalisation due to acute respiratory infection during pregnancy was related to increased risk of low birth weight but not SGA [39]. Furthermore, we found maternal fever during pregnancy was associated with increased SGA risk, which is consistent with a recent small case-control study [40]. Theoretically, fever could lead to dehydration and reduce uterine blood flow and hence compromise fetal growth.

The mechanisms by which urinary tract infections and vaginal infections during pregnancy impact fetal growth are likely multifactorial. Localized infections may induce an inflammatory response in the mother, resulting in the release of pro-inflammatory cytokines and other mediators that could negatively affect fetal growth [6]. Maternal infections can also interfere with placental function, potentially compromising the exchange of nutrients and oxygen between the mother and the fetus. Further studies are needed to elucidate the specific mechanisms through which maternal infections influence fetal growth.

Strengths and weaknesses

Our study has several strengths. First, data were collected from six different geographic settings over a period of about 50 years. Relatively low heterogeneity for most analysed associations across settings suggest reliability of the results. Second, data were collected prospectively, which could reduce recall bias. Third, compared with previous studies which mainly focused on a single maternal characteristic or infection, our study assessed a relatively wide spectrum of infections as well as maternal characteristics, the latter enabling statistical adjustment for confounding. Lastly, the large sample size allows us to detect moderate effects.

Limitations should be acknowledged. The current analysis did not take into account the timing of exposure. This could introduce a bias, as pregnant women with longer gestation periods would have more time to be diagnosed with an infection. This bias may make the infection appear protective against preterm birth, as it is associated with longer pregnancies. As a result, our findings on preterm birth might underestimate any adverse effect of the infection. However, the results for low birth weight and SGA are less likely to be affected by this bias, as our sensitivity analysis on term births yielded similar results to the primary analysis. Also, our analysis did not differ spontaneous and iatrogenic preterm births which may have different aetiology and development mechanisms. Given the self-reported nature of the data,

misclassification of maternal infection is possible. However, because the data were collected prospectively, this misclassification is likely non-differential between those with and without the outcomes and tends to underestimate the effect of the infection. We were unable to investigate the effects of infection due to different pathogen types (virus vs bacterium) on birth outcomes as data are unavailable. Data harmonisation across cohorts was difficult for some infection variables (e.g., influenza) as the definitions were different. Restricting the analysis to livebirths may create collider bias because both maternal characteristics (e.g., diabetes, smoking) and infections could affect fetal survival. However, this bias should be small as we only focused on common infections which do not affect fetal survival substantially. Stillbirth was not considered as an outcome in the present study because the I4C consortium only includes livebirths given its primary objective to examine associations with childhood cancer.[17] Although we have adjusted for many potential confounders in the model, residual confounding cannot be excluded, given the observational nature of the study. Finally, there are many exposure and outcome variables in this analysis, and we did not adjust for multiplicity.

Conclusions

This multinational cohort study adds evidence that self-reported vaginal infections and, urinary infections and fever during pregnancy were associated with a small increased risk of preterm birth and, low birth weight, whereas fever was associated with higher risk of or SGA. Future studies with laboratory-confirmed diagnosis, powered to explore the effects of exposure at different gestational age windows, would be useful to confirm our findings.

Declarations

Competing Interests

Funding

Ethics approval

This study and data use were approved by the I4C Steering Committee and the Ethics Committees from the participating cohorts.

Data and materials availability

The data underlying this article were provided by the original cohorts in I4C by permission. Please contact Prof Terence Dwyer regarding data access to I4C data (terence.dwyer@wrh.ox.ac.uk).

Authors' Contributions

Jian-Rong He conceived the study, formulated the clinical question and finalise the protocol, accessed the data, did the statistical analyses and wrote the report. Jane E Hirst and Terrence Dwyer conceived the study, formulated the clinical question, reviewed and revised the manuscript. All authors critically reviewed the report, interpreted the data and revised the manuscript. Jian-Rong He and Terrence Dwyer is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript.

References

1. Werenberg Dreier J, Nybo Andersen AM, Hvolby A, Garne E, Kragh Andersen P, Berg-Beckhoff G. Fever and infections in pregnancy and risk of attention deficit/hyperactivity disorder in the offspring. J Child Psychol Psychiatry. 2016;57(4):540-8. https://doi.org/10.1111/jcpp.12480.

2. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211-8. https://doi.org/10.1056/NEJMra1213566.

3. WHO Global Maternal Sepsis Study (GLOSS) Research Group. Frequency and management of maternal infection in health facilities in 52 countries (GLOSS): a 1-week inception cohort study. Lancet Glob Health. 2020;8(5):e661-e71. https://doi.org/10.1016/S2214-109X(20)30109-1.

4. Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. Lancet. 2010;375(9724):1482-90. https://doi.org/10.1016/S0140-6736(09)61712-8.

5. McClure EM, Dudley DJ, Reddy UM, Goldenberg RL. Infectious causes of stillbirth: a clinical perspective. Clin Obstet Gynecol. 2010;53(3):635-45. https://doi.org/10.1097/GRF.0b013e3181eb6620.

6. Adams Waldorf KM, McAdams RM. Influence of infection during pregnancy on fetal development. Reproduction. 2013;146(5):R151-62. https://doi.org/10.1530/REP-13-0232.

7. Pararas MV, Skevaki CL, Kafetzis DA. Preterm birth due to maternal infection: Causative pathogens and modes of prevention. Eur J Clin Microbiol Infect Dis. 2006;25(9):562-9. https://doi.org/10.1007/s10096-006-0190-3.

8. Morken NH, Gunnes N, Magnus P, Jacobsson B. Risk of spontaneous preterm delivery in a low-risk population: the impact of maternal febrile episodes, urinary tract infection, pneumonia and ear-nose-throat infections. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):310-4. https://doi.org/10.1016/j.ejogrb.2011.08.006.

9. Fell DB, Savitz DA, Kramer MS, Gessner BD, Katz MA, Knight M, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG. 2017;124(1):48-59. https://doi.org/10.1111/1471-0528.14143.

10. Harris J, Sheiner E. Does an upper respiratory tract infection during pregnancy affect perinatal outcomes? A literature review. Curr Infect Dis Rep. 2013;15(2):143-7. https://doi.org/10.1007/s11908-013-0320-x.

11. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2013;42(1):111-27. https://doi.org/10.1093/ije/dys064.

12. Klebanoff MA. The Collaborative Perinatal Project: a 50-year retrospective. Paediatr Perinat Epidemiol. 2009;23(1):2-8. https://doi.org/10.1111/j.1365-3016.2008.00984.x.

13. Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, et al. The Danish National Birth Cohort--its background, structure and aim. Scand J Public Health. 2001;29(4):300-7. https://doi.org/10.1177/14034948010290040201.

14. Harlap S, Davies AM, Deutsch L, Calderon-Margalit R, Manor O, Paltiel O, et al. The Jerusalem Perinatal Study cohort, 1964-2005: methods and a review of the main results. Paediatr Perinat Epidemiol. 2007;21(3):256-73. https://doi.org/10.1111/j.1365-3016.2007.00799.x.

15. Magnus P, Birke C, Vejrup K, Haugan A, Alsaker E, Daltveit AK, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol. 2016;45(2):382-8. https://doi.org/10.1093/ije/dyw029.

16. Dwyer T, Ponsonby AL, Newman NM, Gibbons LE. Prospective cohort study of prone sleeping position and sudden infant death syndrome. Lancet. 1991;337(8752):1244-7. https://doi.org/10.1016/0140-6736(91)92917-q.

17. Tikellis G, Dwyer T, Paltiel O, Phillips GS, Lemeshow S, Golding J, et al. The International Childhood Cancer Cohort Consortium (I4C): A research platform of prospective cohorts for studying the aetiology of childhood cancers. Paediatr Perinat Epidemiol. 2018;32(6):568-83. https://doi.org/10.1111/ppe.12519.

18. He JR, Hirst JE, Tikellis G, Phillips GS, Ramakrishnan R, Paltiel O, et al. Common maternal infections during pregnancy and childhood leukaemia in the offspring: findings from six international birth cohorts. Int J Epidemiol. 2022;51(3):769-77. https://doi.org/10.1093/ije/dyab199.

19. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68. https://doi.org/10.1016/S0140-6736(14)60932-6.

20. Hirst JE, Knight HE, Ohuma EO, Dwyer T, Hennig BD, Papageorghiou AT, et al. Social gradient of birthweight in England assessed using the INTERGROWTH-21(st) gestational age-specific standard. Arch Dis Child Fetal Neonatal Ed. 2019;104(5):F486-F92. https://doi.org/10.1136/archdischild-2018-315295.

21. Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons; 2004.

22. Urinary Tract Infections in Pregnant Individuals. Obstet Gynecol.

2023;142(2):435-45. https://doi.org/10.1097/AOG.0000000000005269.

23. Naeye RL. Causes of the excessive rates of perinatal mortality and prematurity in pregnancies complicated by maternal urinary-tract infections. N Engl J Med. 1979;300(15):819-23. https://doi.org/10.1056/NEJM197904123001503.

24. McGrady GA, Daling JR, Peterson DR. Maternal urinary tract infection and adverse fetal outcomes. Am J Epidemiol. 1985;121(3):377-81. https://doi.org/10.1093/oxfordjournals.aje.a114009.

25. Werter DE, Schneeberger C, Mol BWJ, de Groot CJM, Pajkrt E, Geerlings SE, et al. The Risk of Preterm Birth in Low Risk Pregnant Women with Urinary Tract Infections. Am J Perinatol. 2023;40(14):1558-66. https://doi.org/10.1055/s-0041-1739289.

26. Werter DE, Kazemier BM, Schneeberger C, Mol BWJ, de Groot CJM, Geerlings SE, et al. Risk Indicators for Urinary Tract Infections in Low Risk Pregnancy and the Subsequent Risk of Preterm Birth. Antibiotics (Basel). 2021;10(9). https://doi.org/10.3390/antibiotics10091055.

27. Greve VH, Greve T, Helmig RB. Bacteriuria in Pregnancy in a Danish Contemporary Cohort of Women. Infect Dis Obstet Gynecol. 2020;2020:8398537. https://doi.org/10.1155/2020/8398537.

28. Chen YK, Chen SF, Li HC, Lin HC. No increased risk of adverse pregnancy outcomes in women with urinary tract infections: a nationwide population-based study. Acta Obstet Gynecol Scand. 2010;89(7):882-8. https://doi.org/10.3109/00016349.2010.486826.

29. Ansaldi Y, Martinez de Tejada Weber B. Urinary tract infections in pregnancy. Clin Microbiol Infect. 2023;29(10):1249-53. https://doi.org/10.1016/j.cmi.2022.08.015.

30. Roberts CL, Algert CS, Rickard KL, Morris JM. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. Syst Rev. 2015;4:31. https://doi.org/10.1186/s13643-015-0018-2.

31. Blomberg L, Backman K, Kirjavainen PV, Karvonen AM, Harju M, Keski-Nisula L. Vulvovaginal yeast infections, gestational diabetes and pregnancy outcome. BMC Pregnancy Childbirth. 2023;23(1):70. https://doi.org/10.1186/s12884-023-05391-1.

32. Xu J, Sobel JD. Candida Vulvovaginitis in Pregnancy. Curr Infect Dis Rep. 2004;6(6):445-9. https://doi.org/10.1007/s11908-004-0063-9.

33. Donders GG, Van Calsteren K, Bellen G, Reybrouck R, Van den Bosch T, Riphagen I, et al. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. BJOG. 2009;116(10):1315-24. https://doi.org/10.1111/j.1471-0528.2009.02237.x.

34. Gigi RMS, Buitrago-Garcia D, Taghavi K, Dunaiski CM, van de Wijgert J, Peters RPH, et al. Vulvovaginal yeast infections during pregnancy and perinatal outcomes: systematic review and meta-analysis. BMC Womens Health. 2023;23(1):116. https://doi.org/10.1186/s12905-023-02258-7.

35. Mashburn J. Etiology, diagnosis, and management of vaginitis. Journal of midwifery & women's health. 2006;51(6):423-30.

36. Mazor-Dray E, Levy A, Schlaeffer F, Sheiner E. Maternal urinary tract infection: is it independently associated with adverse pregnancy outcome? J Matern Fetal Neonatal Med. 2009;22(2):124-8. https://doi.org/10.1080/14767050802488246.

37. Mann JR, McDermott S, Gregg A, Gill TJ. Maternal genitourinary infection and small for gestational age. Am J Perinatol. 2009;26(9):667-72. https://doi.org/10.1055/s-0029-1220792.

38. McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. Am J Obstet Gynecol. 2011;204(6 Suppl 1):S54-7. https://doi.org/10.1016/j.ajog.2011.04.031.

39. Regan AK, Feldman BS, Azziz-Baumgartner E, Naleway AL, Williams J, Wyant BE, et al. An international cohort study of birth outcomes associated with hospitalized acute respiratory infection during pregnancy. J Infect. 2020;81(1):48-56. https://doi.org/10.1016/j.jinf.2020.03.057.

40. Natarajan V, Singh P, Vigneshwar NKV, Anthony ML, Rao S, Chacham S, et al. Maternal and Placental Risk Factors for Small Gestational Age and Fetal Malnutrition. Curr Pediatr Rev. 2023;19(2):187-96. https://doi.org/10.2174/1573396318666220705154424.

Figure legends

Fig. 1 Association between maternal infections during pregnancy and preterm birth.

RR, risk ratio; CI, confidence interval; Phet, P for heterogeneity. RRs were adjusted for maternal age, educational level, smoking during pregnancy, parity, any diabetes and pre-pregnancy body mass index. I^2 represents the magnitude of heterogeneity across, ranging from 0 to 100%.

Fig. 2 Association between maternal infections during pregnancy and low birth weight.

LBW, low birth weight; RR, risk ratio; CI, confidence interval; Phet, P for heterogeneity. RRs were adjusted for maternal age, educational level, smoking during pregnancy, parity, any diabetes and pre-pregnancy body mass index. I^2 represents the magnitude of heterogeneity across, ranging from 0 to 100%.

Fig. 3 Association between maternal infections during pregnancy and small-for-gestational-age.

SGA, small-for-gestational-age; RR, risk ratio; CI, confidence interval; Phet, P for heterogeneity. RRs were adjusted for maternal age, educational level, smoking during pregnancy, parity, any diabetes and pre-pregnancy body mass index. I^2 represents the magnitude of heterogeneity across, ranging from 0 to 100%.