Risk factors

Maternal drug use
Gestational hypertension
Gestational diabetes mellitus

Key words:

Available online April 1, 2022
Accepted in revised form March 2, 2022

How Risky Are Risk Factors? An Analysis of Prenatal Risk Factors in Patients Participating in the Congenital Upper Limb Differences Registry

Tyler Schaeffer, BA, Maria F. Canizares, MD, MPH, Lindley B. Wall, MD, MSc, Deborah Bohn, MD, Suzanne Steinman, MD, Julie Samora, MD, PhD, Mary Claire Manske, MD, Douglas T. Hutchinson, MD, Apurva S. Shah, MD, MBA, Andrea S. Bauer, MD; on behalf of the CoULD Study Group

Purpose: Risk factors for congenital upper limb differences (CoULDs) are often studied at the general population level. The CoULD registry provides a unique opportunity to study prenatal risk factors within a large patient sample.

Methods: All patients enrolled between June 2014 and March 2020 in the prospective CoULD registry, a national multicenter database of patients diagnosed with a CoULD, were included in the analysis. We analyzed self-reported, prenatal risk factors, including maternal smoking, alcohol use, recreational drug use, prescription drug use, gestational diabetes mellitus (GDM), and gestational hypertension. The outcome measures included comorbid medical conditions, proximal involvement of limb difference, bilateral involvement, and additional orthopedic conditions. Multivariable logistic regression was used to analyze the effect of the risk factors, controlling for sex and the presence of a named syndrome.

Results: In total, 2,410 patients were analyzed, of whom 72% (1,734) did not have a self-reported risk factor. Among the 29% (676) who did have at least 1 risk factor, prenatal maternal prescription drug use was the most frequent (376/2,410; 16%). Maternal prescription drug use was associated with increased odds of patient medical comorbidities (odds ratio [OR] = 1.52, P = .04), additional orthopedic conditions (OR = 1.58, P = .04), and gestational diabetes mellitus (GDM) and gestational hypertension (OR = 1.42, P <.001) and additional orthopedic conditions (OR = 1.25, P = .03). Gestational diabetes mellitus was associated with increased odds of comorbid medical conditions (OR = 1.51, P = .02), additional orthopedic conditions (OR = 1.52, P = .04), and proximal involvement (OR = 1.53, P = .04). Overall, reporting 1 or more risk factors increased the odds of patient comorbid medical conditions (OR = 1.42, P <.001) and additional orthopedic conditions (OR = 1.25, P = .03).

Conclusions: Most caregivers (72%) did not report a risk factor during enrollment. However, reporting a risk factor was associated with patient medical and orthopedic comorbidities. Of note, GDM alone significantly increased the odds of both these outcome measures along with proximal limb differences. These findings highlight the ill-defined etiologies of CoULDs but suggest that prenatal risk factors, especially GDM, are associated with a higher degree of morbidity.

Type of study/level of evidence: Prognostic III.

Original Research

How Risky Are Risk Factors? An Analysis of Prenatal Risk Factors in Patients Participating in the Congenital Upper Limb Differences Registry

Tyler Schaeffer, BA, * Maria F. Canizares, MD, MPH, * Lindley B. Wall, MD, MSc, † Deborah Bohn, MD, ‡ Suzanne Steinman, MD, § Julie Samora, MD, PhD, ¶ Mary Claire Manske, MD, * Douglas T. Hutchinson, MD, ** Apurva S. Shah, MD, MBA, †† Andrea S. Bauer, MD *; on behalf of the CoULD Study Group

© 2022, THE AUTHORS. Published by Elsevier Inc. on behalf of The American Society for Surgery of the Hand. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**Declaration of interests**: No benefits in any form have been received or will be received by the authors related directly or indirectly to the subject of this article.

**Corresponding author**: Andrea S. Bauer, MD, Boston Children’s Hospital, 300 Longwood Avenue, Hunnewell 2, Boston, MA 02115. E-mail address: andrea.bauer@childrens.harvard.edu (A.S. Bauer).

Establishing the epidemiologic profile of congenital upper extremity differences is important for health resource planning and alerting the scientific community about new potential teratogens. The exact source of many congenital limb differences is unclear and
likely multifactorial, with a minority of non-Mendelian cases associated with discrete exposures, although there are certain teratogens, such as thalidomide and misoprostol, that are well-known to cause serious limb anomalies.2-7

Many prior studies have sought to connect certain exposures with an increased risk of limb differences. A systematic review of literature published between 1959 and 2010 indicated that maternal smoking is a risk factor for musculoskeletal anomalies, including congenital limb differences.8 Maternal environmental exposure to heavy metals, endocrine disruptors, and the maternal use of pharmaceutical drugs, such as certain epilepsy medications, have also been established as suspected limb teratogens.9,10 Animal and observational studies have shown that vasoactive recreational drugs, eg, cocaine, are associated with an increased risk of a variety of congenital anomalies, including limb differences.11,12 Although definitively associated with other congenital malformations and neonatal disease, the association of maternal alcohol use with congenital limb differences is more equivocal.13,14

The health of the mother during pregnancy may also be associated with congenital malformations. Pre-existing maternal diabetes mellitus is a known risk factor for congenital limb differences related to caudal regression and other major birth anomalies, and glycemic control has been shown to reduce teratogenic impact.15-17 On the other hand, the extent of teratogenicity due to gestational diabetes mellitus (GDM) is debated in the literature, with several studies finding that GDM does not increase the risk of limb differences.15,18,19 The data on the effects of various hypertensive states (eg, eclampsia) on the risk of congenital limb differences have also been mixed.20-22

The body of research on congenital limb differences described above has evaluated risk factors as they pertain to the general population. In contrast, the present study was designed to evaluate how potential risk factors manifest in a subpopulation of patients with an upper limb difference. Specifically, our goal was to understand how self-reported risk factors are distributed within a sample of patients from a national multicenter registry of congenital upper limb differences (CoULDS). In addition, we aimed to analyze the potential associations between the presence of self-reported maternal risk factors and patient outcomes, including associated conditions and the severity of limb differences. The study hypothesis was that most subjects with CoULDS would not present with any self-reported maternal risk factors.

Materials and Methods

Design and data source

This cross-sectional, observational study used patient information collected by the CoULD registry, an ongoing multicenter, prospective, cohort registry involving 9 pediatric tertiary care centers across the United States.23 The database contains information regarding the epidemiology, clinical characteristics, function, and health status of children with CoULDS. Patients under 18 years of age are eligible to enroll in the CoULD registry if a diagnosis of a congenital upper extremity difference has been established and no surgical treatment has been previously performed. Demographic information, including prenatal history, as well as clinical and radiographic data are collected at initial enrollment. Patient diagnoses are categorized according to the Oberg-Manske-Tonkin (OMT) classification system.24 Although the OMT system is a continuously updated classification system, the current CoULD registry uses the version of the OMT system that was adopted by the International Federation of Societies for Surgery of the Hand in 2014. Subjects who do not consent to prospective data collection or those who do not speak English can optionally consent to the 1-time data collection of OMT diagnosis and basic demographic information that excludes prenatal history. The study data are collected and managed using the Research Electronic Data Capture tool.25 The parents of the children are asked whether they consent to study participation, and the child assents when appropriate. Institutional review board approval was obtained for the CoULD registry protocol at each participating institution, and additional approval was obtained for the current study. The CoULD registry is supported by institutional funds at each participating center; no outside funding was received for the registry or for this investigation.

Study participants

Between June 2014 and March 2020, 3,134 patients were enrolled in the CoULD registry. Of them, 344 were excluded from
Patient Characteristics (N = 2,410)

| Characteristics                          | Frequency | (%)  |
|------------------------------------------|-----------|------|
| Age at enrollment (y; median [IQR]; n = 1,972) | 1.4       | (0.40–5.60) |
| Sex (% male)                             | 1,139     | (55%) |
| Race (% White)                           | 1,811     | (75%) |
| Hispanic (% n = 2,383)                   | 306       | (13%) |
| Number of risk factors                   |           |      |
| 0                                        | 1,734     | (72%) |
| 1                                        | 507       | (21%) |
| >1                                       | 169       | (7%)  |
| Risk factors                             |           |      |
| Smoking                                  | 130       | (5%)  |
| Prescription drug use                    | 376       | (16%) |
| Recreational drug use                    | 38        | (2%)  |
| Alcohol use                              | 16        | (1%)  |
| Gestational diabetes                     | 156       | (6%)  |
| Gestational hypertension                 | 167       | (7%)  |

IQR, interquartile range.

* The number in parentheses represents the number of cases with available data for the given characteristic.

**Table 1**

this study because they did not opt for the longitudinal arm of the study. The CoULD registry only collected basic demographic information from these patients. There were 2,790 patients with recorded data on risk factors; however, only patients with malformations, determined based on the OMT classification system (as opposed to deformations and dysplasias), were included in the analysis, leaving 2,410 patients (Fig.). The median age was 1.4 years (interquartile range, 0.4–5.6 years) at the time of enrollment. There were 1,319 (55%) boys, and the patients were predominantly White (75%) and non-Hispanic (87%). In addition to the upper limb differences, determined based on the OMT classification system (as opposed to deformations and dysplasias), were included in the analysis, leaving 2,410 patients (Fig.). The median age was 1.4 years (interquartile range, 0.4–5.6 years) at the time of enrollment. There were 1,319 (55%) boys, and the patients were predominantly White (75%) and non-Hispanic (87%). In addition to the upper limb difference, 27% of the patients presented with an additional orthopedic condition. Medical comorbidities were summarized using frequency and percentage. The multivariable logistic regression analysis was used to determine whether there was an association between each prenatal risk factor and the prevalence of syndromes. The reported P values for these models were adjusted based on the Benjamini-Hochberg false discovery rate method. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for significant factors. Presented P values less than .05 were considered statistically significant.

Study outcomes

Prenatal information, including self-reported maternal risk factors, was collected at enrollment for all patients who consented in the longitudinal arm of the CoULD registry. These risk factors included maternal smoking, prescription drug use, recreational drug use, alcohol use, GDM, gestational hypertension, and other maternal medical conditions during pregnancy. “Other maternal medical conditions” defines a broad category of maternal diseases that complicate pregnancy, regardless of gestational timing, and hence, were not analyzed as a part of the current study. The positive reporting of a risk factor was used to determine the distribution and prevalence of risk factors within the CoULD registry.

All the risk factors recorded in the CoULD registry were self-reported to study staff by guardians of the patients when they joined the study. Any named syndromes as well as additional orthopedic and medical conditions were self-reported by the patients and their family at the time of enrollment. This information was verified and updated via an annual review of the patients’ electronic medical records. In addition, the study participants were asked to specify which, if any, prescription drugs, recreational drugs, or other risk factors were present during pregnancy. Prescription drugs were categorized according to the World Health Organization’s Anatomical Therapeutic Chemical Classification system. The drug use frequency data are provided in Appendix 1 (available on the Journal’s website at www.jhsph.org). The maternal medical conditions during pregnancy were categorized based on the standards of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems. Only maternal GDM and maternal gestational hypertension were analyzed further.

Using other data collected from the registry at the time of enrollment, we selected outcome measures that were related to the severity of presentation at the time of enrollment. Specifically, we compared subjects with additional orthopedic conditions, 1 or more organ systems affected by medical comorbidities, bilateral involvement, or proximal involvement with those who presented without these conditions. Orthopedic conditions were defined as musculoskeletal conditions present in the spine, hip, and lower extremities, including foot conditions. Medical comorbidities were defined as nonorthopedic pathologies in the cardiovascular, gastrointestinal, neurologic, respiratory, renal, hematologic, and genitourinary systems as well as other conditions that were not grouped in these systems. We excluded allergic conditions, such as eczema, allergic rhinitis, and food allergies, because these were considered “mild” for the analysis. Proximal involvement was defined as any diagnosis based on the OMT classification system specified in “Malformation: Failure of Axis Formation/Differentiation—Entire Upper Limb.” Demographic characteristics (sex, race, and ethnicity) and family history were covariates in the analysis. The prevalence of a named syndrome or association was also considered a covariate and controlled for in the analysis.

Statistical methods

The demographic and risk factor summary statistics were summarized for the cohort. Continuous variables were summarized using median and interquartile range, and categorical variables were summarized using frequency and percentage. The multivariable logistic regression analysis was used to determine whether there was an association between each prenatal risk factor and the likelihood of each outcome, with controlling for sex and the presence of syndromes. The reported P values for these models were adjusted based on the Benjamini-Hochberg false discovery rate method. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for significant factors. Presented P values less than .05 were considered statistically significant.

Results

Twenty-eight percent (676/2,410) of the patients had at least 1 recorded prenatal risk factor, with prenatal prescription drug use being most frequent (376/2,410; 16%), followed by prenatal gestational hypertension (167/2,410; 7%) (Table 1). Having a recorded “prenatal risk factor” refers to a study participant reporting 1 or more of the 6 potential risk factors described above: maternal smoking, prescription drug use, recreational drug use, alcohol use, GDM, and gestational hypertension.

Medical comorbidities

Thirty-one percent of the subjects (746/2,381) had at least 1 medical comorbidity affecting 1 or more organ systems (Table 2). The multivariable analysis showed that a patient whose mother used prescription drugs had 1.4-times higher odds (OR = 1.43; 95% CI = 1.11–1.84; P = .02) of having a medical comorbidity compared with a patient whose mother did not use prescription drugs (Table 2). Reported GDM increased the odds (OR = 1.58; 95% CI = 1.10–2.26; P = .04) of a patient having a medical comorbidity by 58% compared with no reported GDM (Table 2). The multivariable analysis showed that a patient with at least 1 prenatal risk factor had 1.4-times higher odds (OR = 1.42; 95% CI = 1.16–1.75; P < .001)
of having a medical comorbidity compared with a patient who did not have any prenatal risk factors.

**Bilateral involvement**

Fifty-seven percent of the subjects (1,365/2,393) had bilateral involvement (Table 2). We found no associations between any of the risk factors and bilateral involvement. Similarly, we did not find any significant associations between having at least 1 prenatal risk factor and proximal involvement.

**Proximal involvement**

Eighteen percent of the subjects (434/2,410) had proximal involvement (Table 2). The multivariable analysis showed that a patient whose mother had GDM had 1.5-times higher chances (OR = 1.51; 95% CI = 1.04–2.23; P = .03) of having an additional orthopedic condition compared with a patient whose mother did not have GDM (Table 2). Furthermore, a patient with at least 1 prenatal risk factor had 1.3-times higher chances (OR = 1.25; 95% CI = 1.02–1.53; P = .03) of having an additional orthopedic condition compared with a patient who did not have any prenatal risk factors.

**Discussion**

The etiology of CoULDs is still not well understood. This study of 2,410 patients from the CoULD registry attempted to shed light on the risk factors for CoULDs. A majority of the analyzed patients did not have an identified risk factor for an upper limb difference, and the overall risk profile of the mothers of the patients in this study was not substantially different from that of the general population.26–31 However, maternal prescription drug use and GDM significantly increased the odds of a patient presenting with at least 1 comorbid medical condition, additional orthopedic conditions, and proximal limb involvement.

These findings are supported by several prior studies. Prenatal prescription drug use has been previously associated with an increased risk of pediatric disease, such as the connection between
gastroesophageal reflux therapies and childhood asthma.\textsuperscript{29} Gestational diabetes mellitus has also previously been shown to increase the odds of medical morbidity for neonates, which is consistent with our findings.\textsuperscript{33,34} The prevalence of GDM and gestational hypertension has been estimated to be around 5.6\% and 3\%, respectively.\textsuperscript{28,31} We found a 6\% prevalence rate of GDM, similar to the expected prevalence. However, the mothers in this study had a 7\% prevalence rate of gestational hypertension, which is more than twice the expected prevalence. Others have postulated an association between gestational hypertension and CoULDs, but the current study did not find that gestational hypertension increased the odds of proximal limb involvement or other orthopedic or medical conditions.\textsuperscript{32} Further research is needed to understand this potential association, and care should be taken to not infer causality because gestational hypertension is, by definition, a condition diagnosed after 20 weeks of pregnancy—long after limb development is complete.\textsuperscript{35}

The presence of GDM significantly increased the odds of proximal involvement as well as other medical and orthopedic comorbidities in the children. Gestational diabetes mellitus impacts fetal and neonatal development, but it has not been specifically characterized as an upper limb teratogen.\textsuperscript{18} A possible explanation for GDM’s association in this study is that GDM generates vascular and placental changes that can exacerbate pre-existing teratogenic processes.\textsuperscript{36} As in gestational hypertension, GDM is typically diagnosed by testing between 24 and 28 weeks, after major limb and organ development has occurred.\textsuperscript{37} On the other hand, GDM can occur in patients with undiagnosed pre-existing type 2 diabetes because its diagnosis includes all diabetes first observed during pregnancy.\textsuperscript{38} Therefore, it is possible that the association between GDM and proximal involvement in this study was confounded. Gestational diabetes mellitus is strongly linked to other metabolic conditions and risks, such as obesity, which is known to alter fetal development and maternal-fetal blood flow.\textsuperscript{39,40} More research will be needed to understand the potential explanations and make more granular distinctions.

The lack of an association between maternal alcohol use, smoking, or recreational drug use during pregnancy and more severe presentation appears to contradict previously described findings. All 3 factors have been associated with adverse medical events in neonates and fetuses, and there is evidence that smoking and vasoactive recreational drug use may have specific limb teratogenicity.\textsuperscript{8,12} This discrepancy may reflect biases inherent to the method of data collection used in the study. Although verification using medical records was attempted, this study did use self-reporting as the method of data collection for the risk factors. Self-reporting is particularly subject to social desirability and recall biases—both of which might have underestimated the true frequency of the risk factors and outcomes in our patient population.\textsuperscript{41} For example, the reported rates of maternal prescription drug use, smoking, and alcohol consumption were lower in our cohort than in recent population-level studies.\textsuperscript{29,42,43} In addition, 16\% of the patients in the registry had mothers who reported taking prescription medication during pregnancy, but most studies have estimated the rate of maternal prescription drug use to be much higher in the United States—with 1 national study of 30,000 women revealing that 70\% used a prescription medication at some point during pregnancy.\textsuperscript{44} Because of the equivocal nature of the data in this case, it is of great importance that the results of this study are not interpreted to downplay the risk of substance use of any kind in the prenatal period.

An additional limitation is that this study was performed in a sample of patients from the United States who were participants in the CoULD registry, and thus, the study findings are only generalizable to the population of patients treated at these tertiary institutions. Because all data in the registry come from these centers, the descriptive profiles in the present study are potentially subject to a referral bias.\textsuperscript{44} The ratios of the demographic and clinical features of the total population of patients with a CoULD in the United States may differ from those derived from the subset of patients who seek treatment at registry facilities.

The overall risk profile of the mothers in the CoULD study was not very different from that of the general population. Families should be reassured that maternal behavior and health is not the sole causative etiology of their child’s condition. However, surgeons should be aware that both the presence of maternal prescription drug use and GDM increase the odds of patients with a CoULD having additional medical and orthopedic conditions. For this reason, a thorough examination of these patients is warranted.

Our study found that 72\% of the 2,410 analyzed patients from the CoULD registry did not report any risk factors. Therefore, environmental factors affecting the etiology of CoULD remain poorly understood. The source of CoULDs, in general, is likely multifactorial, and surgeons should continue to counsel their patients that there is no evidence that mitigating the risk would prevent the formation of a limb difference. Although GDM, in particular, significantly increased the odds of the patients having a comorbid medical condition, proximal involvement, and an additional orthopedic condition, it is not generally diagnosed until long after the critical period of fetal limb development. Surgeons should be aware of the potential increased risk of undiagnosed conditions in patients with CoULDs who have a history of maternal GDM. To guide clinical practice, further research on the association between specific risk factors and patient outcomes is needed. The CoULD registry represents an excellent opportunity for continuing investigations into the prenatal risk of CoULDs.

Acknowledgments

For the present study, the CoULD Study Group consists of Donald S. Bae, MD, Boston Children’s Hospital, Boston, Massachusetts; Charles A. Goldfarb, MD, Washington University School of Medicine Department of Orthopedic Surgery, St. Louis Children’s Hospital, and Shriners Hospitals for Children – St. Louis, St. Louis, Missouri; and Danielle L. Cook, MA, Boston Children’s Hospital, Boston, Massachusetts.

References

1. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaa Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg. 2011;36(6):1058–1065.
2. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects–Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008;57(1):1–5.
3. McGuirk CK, Westgate MN, Holmes LB. Limb deficiencies in newborn infants. Pediatrics. 2001;108(4):e64.
4. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140–156.
5. Olney RS, Khoury MJ, AlO CJ, et al. Increased risk for transverse digital deficiency after chorioic villus sampling: results of the United States multistate case-control study, 1986-1992. Teratology. 1995;51(1):20–29.
6. Firth H. Chorion villus sampling and limb deficiency - cause or coincidence? Prenatal Diagnosis. 1997;17(13):1313–1330.
7. Gonzalez CH, Marques-Dias MJ, Kim CA, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. Lancet. 1998;351(9106):1624–1627.
8. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Hum Reprod Update. 2011;17(5):589–604.
9. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016;11(11):CD010224.
10. Alexander PG, Clark K, Tuan RS. Prenatal exposure to environmental factors and congenital limb defects. Birth Defects Res C Embryo Today. 2016;108(3):243–273.
11. Huestis MA, Choo RE. Drug abuse’s smallest victims: in utero drug exposure. Forensic Sci Int. 2002;128(1–2):20–30.
12. David AL, Holloway A, Thomasson L, et al. A case-control study of maternal periconceptional and pregnancy recreational drug use and fetal malformation using hair analysis. PLoS One. 2014;9(10):e111038.
13. Caspers Conway KM, Romitti PA, Holmes L, Olney RS, Richardson SD. National Birth Defects Prevention Study. Maternal periconceptional alcohol consumption and congenital limb deficiencies. Birth Defects Res A Clin Mol Teratol. 2014;100(11):863–876.
14. Dejong K, Olyaei A, Lo JO. Alcohol use in pregnancy. Clin Obstet Gynecol. 2019;62(1):142–155.
15. Aberg A, Westbom L, Källén B. Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes. Early Hum Dev. 2001;61(2):83–93.
16. Balducci S, Sacchetti M, Haxhi J, et al. Physical exercise as therapy for type II diabetes mellitus. Diabetes Metab Res Rev. 2014;32(3):13–23.
17. Gabbay-Benziv R, Reece EA, Wang F, Yang P. Birth defects in pregestational diabetes: defect range, glycemic threshold and pathogenesis. World J Diabetes. 2015;6(3):481–488.
18. Mills J. Malformations in infants of diabetic mothers. Birth Defects Res A Clin Mol Teratol. 2010;88(10):769–778.
19. Yang CR, Dye TD, Li D. Effects of pre-gestational diabetes mellitus and gestational diabetes mellitus on macrosomia and birth defects in Upstate New York. Diabetes Res Clin Pract. 2019;155(1):107811.
20. Bánhidy F, Szilasi M, Czerzel AE. Association of pre-eclampsia with or without superimposed chronic hypertension in pregnant women with the risk of congenital abnormalities in their offspring: a population-based case-control study. Eur J Obstet Gynecol Reprod Biol. 2012;163(1):17–21.
21. Bateman BT, Huybrechts KF, Fischer MA, et al. Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study. Am J Obstet Gynecol. 2015;212(3):337.e1–317.e14.
22. Bellizzi S, Ali MM, Abalos E, et al. Are hypertensive disorders in pregnancy associated with congenital malformations in offspring? Evidence from the WHO multicountry cross sectional survey on maternal and newborn health. BMC Pregnancy Childbirth. 2016;16(1):1–10.
23. Bae DS, Canizares MF, Miller PE, Waters PM, Goldfarb CA. Functional impact of congenital hand differences: early results from the congenital upper limb differences (CoULD) Registry. J Hand Surg Am. 2018;43(4):321–330.
24. Ezaki M, Baek GH, Horii E, Hovius S. IFSSH scientific committee on congenital conditions. J Hand Surg Eur. 2014;39(6):676–678.
25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–381.
26. World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC classification index with DDDs, 2020. World Health Organization; 2019. Accessed March 22, 2022. https://www.who.int/atc-ddd-toolkit/atc-classification
27. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization; 1992. Accessed March 22, 2022. https://escholarship.org/uc/item/0n26f37t
28. Dickens LT, Thomas CC. Updates in gestational diabetes prevalence, treatment, and health policy. Curr Diab Rep. 2019;19(6):1–11.
29. Drake P, Driscoll AK, Mathews TJ. Cigarette smoking during pregnancy: United States, 2016. NCHS Data Brief. 2018;(305):1–8.
30. Forray A. Substance use during pregnancy. F1000Res. 2016;5:F1000.
31. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):391–403.
32. Källén B, Finnström O, Nygren KG, Otterblad Olausson P. Maternal drug use during pregnancy and asthma risk among children. Pediatr Allergy Immunol. 2013;24(1):28–32.
33. Azad MB, Moyer BL, Guilleminette L, et al. Diabetes in pregnancy and lung health in offspring: developmental origins of respiratory disease. Paediatr Respir Rev. 2017;21:19–28.
34. Boksleg A, van Weissenbruch M, Mol BW, de Groot CJ. Preeclampsia: short and long-term consequences for mother and neonate. Early Hum Dev. 2016;102:47–50.
35. Mamaro A, Carrara S, Cavalieri A, et al. Hypertensive disorders of pregnancy. J Prenat Med. 2009;3(1):1–5.
36. Nguyen-Ngo C, Jayabal N, Salomon C, Lappas M. Molecular pathways disrupted by gestational diabetes mellitus. J Mol Endocrinol. 2019;63(3):R51–R72.
37. Rani PR, Begum J. Screening and diagnosis of gestational diabetes mellitus, where do we stand. J Clin Diagn Res. 2016;10(4):QE91–QE94.
38. Virjee S, Robinson S, Johnston DG. Screening for diabetes in pregnancy. J R Soc Med. 2001;94(10):502–509.
39. Howell KR, Powell TL. Effects of maternal obesity on placental function and fetal development. Reproduction. 2017;153(3):R97–R108.
40. Battarbee AN, Venkatesh KK, Aliaga S, Boggess KA. The association of pregestational and gestational diabetes with severe neonatal morbidity and mortality. J Perinatol. 2020;40(2):232–239.
41. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. J Multidiscip Healthc. 2016;9:211–217.
42. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1–51.e8.
43. Popova S, Lange S, Probst C, Parunashvili N, Rehm J. Prevalence of alcohol consumption during pregnancy and fetal alcohol spectrum disorders among the general and Aboriginal populations in Canada and the United States. Eur J Med Genet. 2017;60(1):32–48.
44. Melton LJ. Selection bias in the referral of patients and the natural history of surgical conditions. Mayo Clin Proc. 1985;60(12):880–885.