



Trends in the use for labor analgesia in twin pregnancies: A nationwide register-based analysis in Finland

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ABSTRACT

Objectives: The aim of this study is to calculate the trends in the use of labor analgesia in vaginal twin pregnancies at or after 37⁺⁰ weeks of gestation and evaluate the use of different labor analgesia in vaginal twin deliveries when compared to vaginal singleton pregnancies.

Study design: Data from the National Medical Birth Register during the years 2004–2018 was used to evaluate the usage of labor analgesia in vaginal twin deliveries at or after 37⁺⁰ weeks of gestation when compared to a comparison group consisting of singleton deliveries at or after 37⁺⁰ weeks of gestation. These results are presented as adjusted risk ratios (aORs) with 95% confidence intervals (Cis). The model was adjusted by maternal age and gestational diabetes, year of the pregnancy, and labor induction.

Results: A total of 3060 twin deliveries and 669 718 singleton deliveries (comparison group) were included in our study. The use of spinal analgesia in vaginal twin deliveries has shown a steadily growing trend increasing from 7.8% (95% Ci 4.8, 12.0) in 2004–24.8% (95% Ci 16.0, 33.0) in 2018. When compared to singleton deliveries, there was increased use of epidural analgesia (57.3% vs 46.1%, aOR 1.41; 95% Ci 1.31, 1.51), but lower use of spinal analgesia (12.3% vs 16.7%, aOR 0.66; 95% Ci 0.59, 0.73), another medical (7.9% vs 12.5%, aOR 0.55; 95% Ci 0.48, 0.63), and nonmedical analgesia (21.8% vs 30.2%, aOR 0.69, 95% Ci 0.63, 0.76) observed among women with twin pregnancies.

Conclusions: The main finding of this study was that women with twin pregnancies had a higher rate of epidural analgesia than women with singleton pregnancies. The results of this study should be acknowledged by midwives, obstetricians, and anesthesiologists to provide optimal pain relief for mothers with twin pregnancies and encourage researchers to further research on this topic.

Introduction

Twin deliveries constitute 2–3% of all deliveries [1]. In Finland, perinatal mortality and early neonatal mortality in twins have continuously decreased during the years 1987–2014, decreasing from 45 per 1000 neonates for the first twin and 54 per 1000 neonates for the second twin in 1987–6.5 per 1000 neonates for the first twin and 11.9 per 1000 neonates for second twin in 2014 [2]. However, especially the delivery of second twin is still facing more complications, and research on minimizing these challenges is warranted [2]. However, the information on the use of labor analgesia in twin pregnancies is currently lacking.

Previous literature has only focused on the effects of epidural analgesia on maternal and fetal outcomes in twin pregnancies. In these studies, epidural analgesia was found to be the optimal option in terms of delivery mode and health of the twins, as it shortened the mean time of labor and made possible the performance of all necessary instrumental and obstetrical maneuvers, without additional anesthesia or adverse effects on the second twin [3–5]. However, a study published in 2019 found that epidural analgesia in twin pregnancies prolongs the second stage of labor in both twins [6]. In 2021, a study assessed the effects of epidural analgesia on the mode of delivery for the second twin and found that the risk for CS was reduced [7]. However, despite these

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findings, there are currently no reports on the use of different labor analgesia in twin pregnancies.

Based on our hypothesis, the need for pain relief might be increased due to more challenging labor. Women with twin pregnancies may have an increased need for labor analgesia due to a higher incidence of uterine hyperstimulation, increased pressure on the uterus and birth canal, increased risk of complications, and higher likelihood of medical interventions, resulting in more challenging and possibly more painful labor [8,9]. Thus, the aim of this study is to calculate the trends in the use of labor analgesia in vaginal twin pregnancies at or after 37⁺⁰ weeks of gestation and evaluate the use for different labor analgesia in these vaginal twin deliveries, when compared to vaginal singleton pregnancies.

Materials and methods

In this nationwide retrospective register-based cohort study, data from the National Medical Birth Register (MBR) was used to evaluate the usage of labor analgesia in twin pregnancies when compared to singleton deliveries. The MBR is maintained by the Finnish Institute for Health and Welfare. The study encompassed the timeframe from January 1st, 2004 to December 31st, 2018.

The MBR encompasses data regarding pregnancies, delivery metrics, and perinatal results for all births with a birthweight of ≥ 500 g or a gestational age of $\geq 22^{+0}$ weeks. The MBR boasts extensive coverage and exceptional data quality, with a nearly 100% current coverage rate [10]. We included all spontaneous and assisted (vaginal breech, forceps, or vacuum delivery) vaginal deliveries occurring after 37⁺⁰ weeks of gestation in our study. Elective or urgent CS as a mode of delivery ($n = 129\ 353$), deliveries occurring before 37⁺⁰ weeks of gestation ($n = 40, 015$), triplets or more ($n = 144$), and out-of-hospital deliveries ($n = 2301$) were excluded from the labor analgesia analysis. Twin pregnancies with CS as a mode of delivery for both twins were excluded, but pregnancies with vaginal delivery for the first twin and CS for the second twin were included. Only vaginal deliveries at or after 37⁺⁰ weeks of gestation were included, as the rate of preterm deliveries and cesarean section (CS) is higher among twin pregnancies, and these have markable effects on the use of pain reliefs. A total of 672 778 pregnancies were included in this study. Forming of the study groups is shown as a flowchart in Fig. 1.

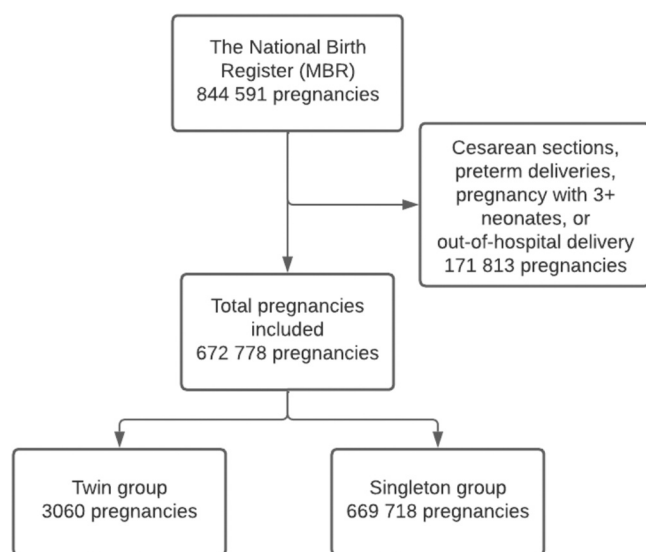


Fig. 1. Flowchart of the study groups. Full-term twin pregnancies, with at least the first neonate born vaginally at or after 37⁺⁰ weeks of gestation, were compared to the comparison group consisting of singleton vaginal deliveries at or after 37⁺⁰ weeks of gestation.

Statistics

The primary focus of our study was the utilization of labor analgesia. We categorized the analgesia methods into various groups, including neuraxial analgesia (epidural, spinal, and combined), pudendal, paracervical, nitrous oxide, other medical options (including opiates), other non-medical alternatives (such as bath, aqua bubbles, and TENS), and the absence of analgesia. These categories were analyzed as dichotomous variables (yes or no), as the register lacks more detailed information, such as specific dosage used. The register only gathers information on intrapartum analgesia used during vaginal delivery, thus, the medical analgesia used during CS is not included. One patient may have had none or many of these analgesias during the labor. In addition, the annual trends in the use of labor analgesia in twin pregnancies were analyzed for the most common pain reliefs (epidural, spinal, paracervical, pudendal, and nitrous oxide). These results are presented as annual proportions of all vaginal twin deliveries. Continuous variables were reported as mean with standard deviation. Categorized variables were presented as absolute numbers and percentages with 95% confidence intervals (Cis). The Cis for proportions were calculated using Poisson regression. To analyze the odds for different labor analgesia, when confounding factors were considered, adjusted odds ratios (aORs) with 95% Cis were calculated. The model was adjusted by maternal age, maternal gestational diabetes, year of the pregnancy, and labor induction. We performed adjustments by selecting variables for a multivariable model based on directed acyclic graphs (DAGs) constructed using the online software DAGitty (dagitty.net), which is freely available [11]. The utilization of the DAG approach aids in the selection of covariates to be incorporated into conventional statistical methods, thereby minimizing the potential bias in the resulting estimate [12]. The variables incorporated into the DAGs were selected by considering established risk factors and hypothesized causal pathways [13–17]. DAGitty automatically provides suggested sets of adjustment variables that may impact the primary outcome. (Supplementary Table 1). The findings of this study are presented in accordance with the STROBE guidelines [18]. The statistical analysis was conducted utilizing R version 4.0.3.w.

Ethics

The ethical review process for retrospective studies utilizing routinely collected healthcare data was waived by the Ethical Committee of Tampere University Hospital, based on the regulations outlined in the law of medical research 488/1999 and the law of patient rights 785/1992. Each patient in the MBR is assigned a pseudonymized identification number, which was generated by the Finnish data authority Findata. The authors of the study did not have access to the pseudonymization key. In adherence to Finnish regulations (The law of secondary use of routinely collected healthcare data 552/2019), obtaining informed written consent was not required as the study design was retrospective and did not involve direct patient contact. The study protocol underwent evaluation by Findata, and permission for data access was granted accordingly.

Results

A total of 3060 twin deliveries at or after 37⁺⁰ weeks of gestation with at least the first neonate born vaginally were included in this study. The comparison group consisted of a total of 669 718 singleton vaginal deliveries at or after 37⁺⁰ weeks of gestation. Women with twin pregnancies were older than those in the comparison group (mean 30.8 years vs 29.6 years). A higher proportion of women with twin pregnancies had been diagnosed with gestational diabetes, than those who were in the comparison group (13.5%; 95% Ci 12.2, 14.8 vs 11.9%; 95% Ci 11.8, 12.0). A notably higher proportion of twin pregnancies had labor induction (66.2%; 95% Ci 63.3, 69.1 vs 20.5%, 95% Ci 20.4, 20.7).

Background information on the study groups is shown in Table 1.

The higher proportion for vaginal breech deliveries (3.7%, 95% Ci 3.0, 4.4 vs 0.6%, 95% Ci), and vacuum or forceps deliveries (19.2%, 95% Ci 17.7, 20.8 vs 10.3%, 95% Ci 10.3, 10.4) was observed among twin pregnancies when compared to comparison group consisting of singleton pregnancies. Only 2.5% (95% Ci 2.0, 3.2) of vaginal twin deliveries for the first twin ended up as a CS for the second twin. (Table 2).

There was increased use of epidural analgesia (57.3% vs 46.1%, aOR 1.41; 95% Ci 1.31, 1.51) observed among women with twin pregnancies at or after 37⁺⁰ weeks of gestation when compared to the comparison group consisting of singleton pregnancies at or after 37⁺⁰ weeks of gestation. However, the use of spinal (12.3% vs 16.7%, aOR 0.66; 95% Ci 0.59, 0.73), another medical (7.9% vs 12.5%, aOR 0.55; 95% Ci 0.48, 0.63), and nonmedical analgesia (21.8% vs 30.2%, aOR 0.69, 95% Ci 0.63, 0.76) was lower among women with twin pregnancies, when compared to the comparison group. Both groups had low proportions of women who delivered completely without analgesia (0.0% and 0.2%). (Table 3).

During the years 2004–2018, the use of epidural, nitrous oxide, and paracervical in vaginal twin pregnancies has remained stable in Finland, except for the year 2006, when the use of nitrous oxide (33%) and epidural analgesia (36%) decreased markedly. However, the proportion of spinal analgesia has shown a steadily growing trend during the years 2004–2018, increasing from 7.8% (95% Ci 4.8, 12.0) in 2004–24.8% (95% Ci 16.0, 33.0) in 2018. (Fig. 2 and supplementary Table 1).

Table 1

Background information on study cohorts. Twin pregnancies, with at least the first neonate born vaginally at or after 37⁺⁰ weeks of gestation, were compared to the comparison group consisting of singleton pregnancies at or after 37⁺⁰ weeks of gestation. The proportions are presented with 95% confidence intervals (Cis).

	Twin pregnancy		Comparison group	
	n	% (95% Ci)	n	% (95% Ci)
Total number of patients	3060		669 718	
Age (mean; sd)	30.8 (4.9)		29.6 (5.3)	
Nulliparous	969	31.7 (29.7, 33.7)	263,018	39.3 (39.1, 39.4)
Maternal smoking status				
smoker	402	13.1 (11.9, 14.5)	96,446	14.4 (14.3, 14.5)
Unknown	60	2.0 (1.5, 2.5)	17,601	2.6 (2.6, 2.7)
Maternal BMI* (mean; sd)	24.4 (4.7)		24.2 (4.7)	
BMI missing	146	4.8 (4.0, 5.6)	28,130	4.2 (4.2, 4.3)
Diagnosed gestational diabetes	412	13.5 (12.2, 14.8)	79,674	11.9 (11.8, 12.0)
Labor induction	2025	66.2 (63.3, 69.1)	137,553	20.5 (20.4, 20.7)
Obstetric complications				
tear of perineum	19	0.6 (0.4, 1.0)	6981	10.4 (10.2, 10.7)
episiotomy	894	29.2 (27.3, 31.2)	164,972	24.6 (24.5, 24.8)

** Mode of delivery for the first newborn in twin pregnancies

* BMI = Pre-pregnancy body mass index (kg/m²)

Table 2

Mode of delivery for both twins in the twin group, and mode of delivery in the comparison group. The proportions are presented with 95% confidence intervals (Cis). CS = Cesarean section.

	Twin pregnancy		Comparison group	
	n	% (95% Ci)	n	% (95% Ci)
Total number of patients	3060		669 718	
Mode of delivery for the first twin				
spontaneous	2360	77.1 (74.0, 80.3)	596,055	89.0 (88.8, 89.2)
vaginal breech delivery	113	3.7 (3.0, 4.4)	4289	0.6 (0.6, 0.7)
vacuum or forceps	587	19.2 (17.7, 20.8)	69,374	10.3 (10.3, 10.4)
Mode of delivery for the second twin				
spontaneous	1831	59.8 (57.1, 62.6)	-	-
vaginal breech delivery	585	19.1 (17.6, 20.7)	-	-
vacuum or forceps	566	18.5 (17.0, 20.1)	-	-
urgent or emergency CS	78	2.5 (2.0, 3.2)	-	-

Discussion

The main finding of this study was that women with twin pregnancies had higher use of epidural analgesia than women with singleton pregnancies. However, the use of other analgesia, especially spinal, other medical, and nonmedical analgesia was lower. In addition, the use of spinal analgesia showed an evenly increasing trend in vaginal twin pregnancies during our study period.

The use for epidural analgesia was notably higher among twin pregnancies, where at least the first neonate was born vaginally when compared to singleton pregnancies. This is also supported by the findings in previous literature [3–5]. These studies concluded that epidural analgesia was the best choice for the mode of delivery and the health of twins, as it reduced the average duration of labor and allowed for all required instrumental and obstetric procedures to be performed, without the need for supplementary anesthesia or any negative effects on the second twin [3–5]. However, compared to our study, the study sample was relatively small, and these studies were published in 1977, meaning that the use of labor analgesia may have undergone additional changes and advancements since then, including the development of new techniques and drugs, increased focus on personalized pain management, and improved safety measures [3–5]. There are also few recently published studies on this topic. In 2019, a study revealed that the use of epidural analgesia during twin pregnancies can extend the second stage of labor for both twins, while in 2021, another study examined the impact of epidural analgesia on the delivery mode for the second twin and demonstrated a lower risk of cesarean section [6,7]. However, in our study the exact reason for the increased proportion of epidural analgesia in twin pregnancies remains unknown due to the register-based study design. Confounding factors, such as higher maternal age and body mass index, gestational diabetes, and a higher proportion of instrumental vaginal deliveries (possibly requiring more pain relief in advance) among women with twin pregnancies might partly explain the higher proportion [13], but the aORs still showed markedly increased odds for epidural analgesia among women with twin

Table 3

Use of labor analgesia among both study cohorts. Twin pregnancies, with at least the first neonate born vaginally at or after 37⁺⁰ weeks of gestation, were compared to the comparison group consisting of singleton vaginal pregnancies at or after 37⁺⁰ weeks of gestation. Values are numbers (proportion). The results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (Cis).

	Twin pregnancy		Comparison group		aOR* (95% Ci)
	n	% (95% Ci)	n	% (95% Ci)	
Total number of patients	3060		669 718		
Labor analgesia					
epidural	1753	57.3 (54.6, 60.0)	308,845	46.1 (46.0, 46.3)	1.41 (1.31, 1.51)
spinal	376	12.3 (11.1, 13.6)	111,791	16.7 (16.6, 16.8)	0.66 (0.59, 0.73)
combined spinal-epidural	56	1.8 (1.4, 2.4)	12,116	1.8 (1.8, 1.8)	0.90 (0.68, 1.16)
paracervical block	494	16.1 (14.8, 17.6)	117,199	17.5 (17.4, 17.6)	0.90 (0.81, 0.99)
pudendal block	276	9.0 (8.0, 10.1)	57,154	8.5 (8.5, 8.6)	1.09 (0.96, 1.24)
nitrous oxide	1647	53.8 (51.3, 56.5)	377,046	56.3 (56.1, 56.5)	0.87 (0.81, 0.94)
other medical analgesia	243	7.9 (7.0, 9.0)	83,872	12.5 (12.4, 12.6)	0.55 (0.48, 0.63)
non-medical analgesia	668	21.8 (20.2, 23.6)	201,934	30.2 (30.0, 30.3)	0.69 (0.63, 0.76)
no analgesia	0	-	1688	0.2 (0.2, 0.3)	-

* Adjusted by maternal age, maternal gestational diabetes, year of the pregnancy, and labor induction.

pregnancies. However, according to a recent study in Finland, women with gestational diabetes, to which women with twins are at higher risk [14], had no higher proportion for labor analgesia [15].

There is no literature on the rate or effects of other medical analgesia, such as spinal, pudendal, paracervical, or nitrous oxide. Interestingly, the use of spinal, other medical, and nonmedical analgesia was lower among women with twin pregnancies. The exact reason for this remains unknown but may be due to the higher use of epidural analgesia used among twin deliveries. In addition, the proportion of the use of spinal analgesia showed an evenly increasing trend during the years 2004–2018 in Finland. However, this is most likely explained by the fact that the use of spinal analgesia has also had an increasing trend in singleton deliveries in Finland [13]. Interestingly, the use of epidural analgesia and nitrous oxide temporarily decreased strongly in 2006, but the reason for this remains unknown. This could possibly be due to changes in patient preferences, incorrect registration, or changes in clinical guidelines, but the exact reason for this is unknown. The results of this study can be useful for healthcare providers when counseling women with twin pregnancies on their pain management options during labor. Women who are aware of the higher rates of epidural analgesia use in twin pregnancies may feel more confident and reassured that effective pain relief will be available to them during labor. This, in turn, may lead to higher levels of satisfaction with their overall childbirth experience.

The primary advantage of this study lies in its comprehensive nationwide register coverage, which encompasses nearly all deliveries in Finland [10]. Furthermore, the register demonstrates high levels of validity and precision, adding to the strength of the study [10]. The primary constraint of this study is the absence of data regarding attempted analgesia methods, as the register only captures successful instances of analgesia. Another limitation stems from the lack of information on analgesic doses, leaving potential distinctions between the two groups unexplored. Additionally, the register solely collects data on intrapartum analgesia, and thus, postpartum analgesia was not analyzed. Furthermore, since the data originates from a nationwide register, regional variations within Finland are not accounted for.

Conclusion

Women with twin pregnancies had a higher use of epidural analgesia, than women with singleton pregnancies. However, the use of other analgesia, especially spinal, other medical, and nonmedical analgesia was lower. During our study period, the proportions for spinal analgesia had an evenly increasing trend in twin pregnancies with at least the first neonate born vaginally. The results of this study should be

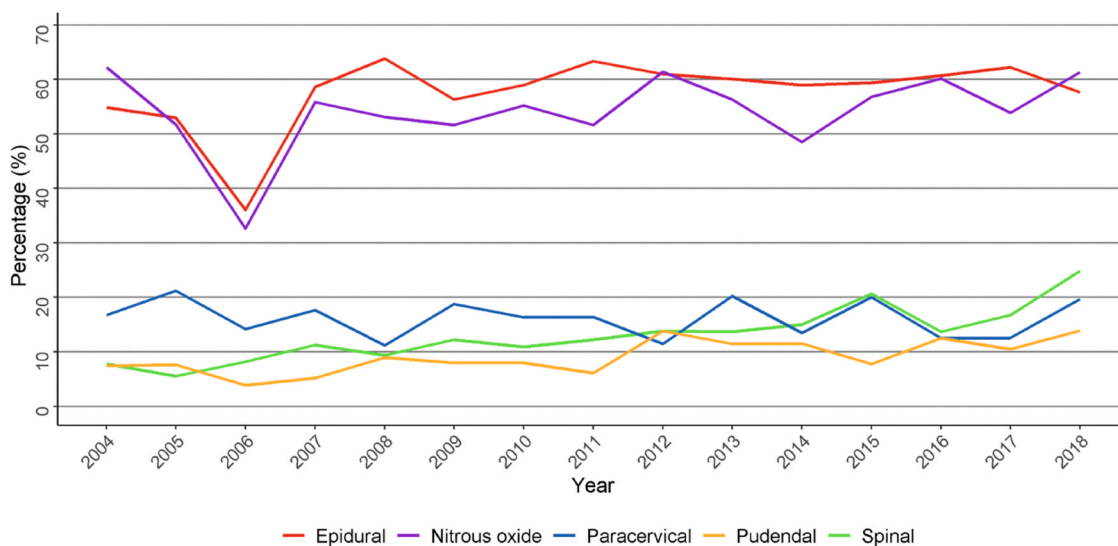


Fig. 2. Annual trends (proportion) in the use of labor analgesia for the most common types of pain reliefs (epidural, nitrous oxide, paracervical, spinal, pudendal) in twin pregnancies with at least first neonate born vaginally during the years 2004–2018 in Finland.

acknowledged by midwives, obstetricians, and anesthesiologists to provide optimal pain relief for mothers with twin pregnancies and encourage researchers to further research on this topic.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.eurox.2023.100232](https://doi.org/10.1016/j.eurox.2023.100232).

References

- [1] Trends in twin and triplet births: 1980–97 - PubMed. Accessed February 6, 2023. (<https://pubmed.ncbi.nlm.nih.gov/11968567/>).
- [2] Rissanen ARS, Jernman RM, Gissler M, Nupponen IK, Nuutila ME. Perinatal outcomes in Finnish twins: a retrospective study. *BMC Pregnancy Childbirth* 2019; 20(1):2. <https://doi.org/10.1186/s12884-019-2670-3>.
- [3] Weekes AR, Cheridjian VE, Mwanje DK. Lumbar epidural analgesia in labour in twin pregnancy. *Br Med J* 1977;2(6089):730–2. <https://doi.org/10.1136/bmj.2.6089.730>.
- [4] Jaschevatzky OE, Shalit A, Levy Y, Grünstein S. Epidural analgesia during labour in twin pregnancy. *Br J Obstet Gynaecol* 1977;84(5):327–31. <https://doi.org/10.1111/j.1471-0528.1977.tb12592.x>.
- [5] Gullestad S, Sagen N. Epidural block in twin labour and delivery. *Acta Anaesthesiol Scand* 1977;21(6):504–8. <https://doi.org/10.1111/j.1399-6576.1977.tb01252.x>.
- [6] Aleksandrovich BK, Munevich SE, Alekseevna GT, Vladimirovna BM, Sharma K, Gupta S. Impact of labor epidural analgesia on maternal and neonatal outcomes with trial of labor in previous caesarean delivery: a prospective, controlled, longitudinal study. *J Obstet Anaesth Crit Care* 2020;10(2):123. https://doi.org/10.4103/joacc.JOACC_45_20.
- [7] Farghali MM, Ibrahim AS, Farrag WS. Effect of labor epidural analgesia on delivery of second twin: a prospective observational study. *Ginekol Poloznictwo* 2021;16(3):1–6.
- [8] Lopian M, Kashani-Ligumsky L, Cohen R, et al. Induction of labor in twins—double trouble. *J Clin Med* 2023;12(5):2041. <https://doi.org/10.3390/jcm12052041>.
- [9] Gill P, Lende MN, Van Hook JW. *Twin Births*. StatPearls. StatPearls Publishing; 2023. Accessed May 3, (<http://www.ncbi.nlm.nih.gov/books/NBK493200/>).
- [10] Gissler M, Shelley J. Quality of data on subsequent events in a routine Medical Birth Register. *Med Inf Internet Med* 2002;27(1):33–8. (<http://www.dagitty.net/development/dags.html>).
- [11] Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Method* 2008;8(1):70. <https://doi.org/10.1186/1471-2288-8-70>.
- [13] Kuitunen I, Kekki M, Ponkilainen V, Huttunen T. Labour analgesia in obese and morbidly obese parturients: a nationwide register analysis in Finland from 2004 to 2018. *Anaesthesia* 2022;77(3):351–3. <https://doi.org/10.1111/anae.15652>.
- [14] Vaajala M, Liukkonen R, Ponkilainen V, Kekki M, Mattila VM, Kuitunen I. Higher odds of gestational diabetes among women with multiple pregnancies: a nationwide register-based cohort study in Finland. *Acta Diabetol* 2023;60(1):127–30. <https://doi.org/10.1007/s00592-022-01984-y>.
- [15] Kuitunen I, Vähä-Tuisku S, Huttunen T. Gestational diabetes mellitus and labor analgesia: nationwide register-based analysis in Finland. *Acta Diabetol Publ Online* 2022. <https://doi.org/10.1007/s00592-022-01944-6>.
- [16] Labor induction in twin pregnancies: Does the perinatal outcome differ according to chorionicity? - PubMed. Accessed April 25, 2023. (<https://pubmed.ncbi.nlm.nih.gov/34599679/>).
- [17] Warner LL, Arendt KW, Theiler RN, Sharpe EE. Analgesic considerations for induction of labor. *Best Pr Res Clin Obstet Gynaecol* 2021;77:76–89. <https://doi.org/10.1016/j.bpobgyn.2021.09.004>.
- [18] Elm E, von, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61(4):344–9. <https://doi.org/10.1016/j.jclinepi.2007.11.008>.