The Association between Season and Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-Analysis

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Abstract

Background: There is increasing and inconsistent evidence of a relationship between hypertensive disorders of pregnancy (HDP) and season of delivery or conception.

Methods: Four databases, the Cochrane Library, PubMed, EMBASE and Web of Science, were searched until September 29th, 2021. Two authors extracted data independently. A random effects model and the Mantel-Haenszel method were used to calculate pooled ORs and 95% CIs.

Results: Twenty articles were included in the systematic review, and 11 articles were included in the meta-analysis. The quantitative analysis of the association between delivery season and HDP showed that the odds of HDP was higher in women who deliver in winter than in those who delivered in summer (OR=1.18, 95% CI 1.02-1.38, $p < 0.001$) and all other seasons (OR = 1.17, 95% CI 1.03-1.34, $p < 0.001$). In the qualitative analysis of the association between conception season and HDP, 4 of 7 studies suggested that women who conceived in summer had a higher risk of HDP than those who conceived in other seasons.

Conclusions: Based on the evidence to date, we found weakly positive relationships between HDP and summer conception and winter delivery.

Background

Hypertensive disorders of pregnancy (HDP) is a common obstetric disease, occurring in 5%-10% of all pregnancies and accounting for 10%-16% of total pregnancy-related deaths; it is the leading cause of maternal death (1, 2). HDP not only has short-term impacts during pregnancy but also long-term impacts on the health of mothers and their offspring, potentially causing maternal coronary heart disease, stroke and hypertension in offspring (3–5). At present, the precise etiology of HDP is unclear and is considered to be the result of the interaction between genes and the environment. However, a number of risk factors have been demonstrated, such as older age, low maternal educational status and multiple pregnancies (6, 7).

Seasonal changes affect the occurrence and development of many diseases, such as cardiovascular diseases and autoimmune diseases (8, 9). Similarly, seasonal changes also increased the risk of maternal and neonatal mortality and the incidence of delivery complications (10). HDP deserves our attention because some studies have reported that HDP is associated with season, but the findings have been inconsistent. Some researchers reported that the prevalence rates of gestational hypertension and preeclampsia were higher in women who delivered in winter and conceived in summer (7, 11). However, some studies found no association with season (6) or found an opposite result (12).

It is important to synthesize such findings to determine which season or month of delivery or conception is related to HDP to facilitate HDP management and interventions targeting high-risk groups.

Methods

The Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (13) and Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) (14) guidelines were followed for this systematic review and meta-analysis. This study did not require ethical approval or patient consent.

Search strategy

Four databases, the Cochrane Library, PubMed, EMBASE and Web of Science, were searched until September 29th, 2021 by two independent authors (LL and XW). Medical Subject Headings (MeSH) terms combined with free text were used to identify studies on associations between seasons and HDP. The detailed search terms of PubMed can be found in Table 1 and appropriate adjustments were made in other databases. Furthermore, we manually searched the citations of the included articles to prevent omission. After retrieval, we used the Endnote X9 library (Clarivate Analytics, Philadelphia, PA, USA) to check for duplicates and manage references.

Table 1
Search strategy for PubMed.

Outcome: Hypertensive Disorders of Pregnancy		
#1	MeSH terms	"hypertension, pregnancy induced"[MeSH Terms] OR "pre eclampsia"[MeSH Terms] OR "Eclampsia"[MeSH Terms]
#2	Title/Abstract	"hypertension pregnancy induced" OR "pregnancy induced hypertension" OR "gestational hypertension" OR "hypertension gestational" OR "transient hypertension pregnancy" OR "pregnancy transient hypertension" OR "pregnancy hypertension" OR "hypertension in pregnancy" OR "pre eclampsia" OR "Preeclampsia" OR "pregnancy toxemias" OR "pregnancy toxemia" OR "edema proteinuria hypertension gestosis"
#3	#1 OR #2	
Exposure: season		
#4	MeSH terms	"seasons"[MeSH Terms] OR "climate"[MeSH Terms] OR "meteorology"[MeSH Terms] OR "weather"[MeSH Terms] OR "temperature"[MeSH Terms]
#5	Title/Abstract	"season*" OR "summer" OR "spring" OR "autumn" OR "winter" OR "climat*" OR "meteorology*" OR "weather*" OR "temperatur*" OR "Cold" OR "frigidity" OR "Hot" OR "Heat"
#6	#4 OR #5	
#7	#3 AND #6	

Selection criteria

Inclusion criteria

- 1) The exposure of interest was season or month.
- 2) The investigation outcome was HDP.
- 3) The study design was a case-control, cohort or cross-sectional design.
- 4) Odds ratios (ORs) and 95% confidence intervals (95% CIs) or relevant data that could be computed were provided

Exclusion criteria

- 1) Studies on season or month of admission.
- 2) Studies for which the full text could not be downloaded.
- 3) Studies that were not published in English.

Data extraction and quality assessment

We designed a data extraction table during the full-text review stage. Two authors (LL and XW) extracted the data independently. The information recorded included first author, published year, study region, research type, sample size, study period, exposure definition, and outcome definition. We also recorded adjusted ORs and 95% CIs or crude ORs and 95% CIs from the original data if provided. If necessary, authors were contacted for additional details or figure data.

Based on the UK's official weather service definition, March is regarded as the beginning of spring, and spring, summer, autumn and winter are defined in three-months increments (15). When the study country or region was in the Southern Hemisphere, we adjusted the seasons accordingly. We used Google maps to estimate the average latitudes of countries and regions (16).

If a disagreement arose, we consulted a third author (RZ) or discussed until consensus was reached. Only studies that had sufficient data for calculation were included in the meta-analysis.

Study quality was evaluated by two author (LL and XW) with the Newcastle-Ottawa quality assessment scale (NOS) (17), which includes three categories and eight items, with a total score of nine. A NOS score of seven or higher indicated high quality.

Statistical analysis

Stata/SE 15.1 (StataCorp, College Station, TX, USA) was used for the quantitative analysis. In studying the relationship between season of delivery and preeclampsia, summer was chosen as the reference month because most previous studies suggested that the prevalence associated with summer delivery was low (7, 18-21). Similarly, winter was chosen as the reference season in the analysis of conception season (22-26).

A random effects model and the Mantel-Haenszel method were used to calculate pooled ORs and 95% CIs. ORs were displayed using a forest plot. Heterogeneity was estimated by the Cochrane Q statistic ($p < 0.1$ indicates the existence of heterogeneity) and inconsistency index (I^2) (low: 25-50%; moderate: 50-75%; high: 75-100%). To explore the source of heterogeneity, subgroup analyses and sensitivity analyses were performed. Subgroup analyses were performed according to sample size, latitude, income group and whether multiple pregnancies were included. In addition, we used a stepwise elimination method to perform the sensitivity analysis and verify the robustness of the results. Begg's funnel plot and Egger's test were used to check for the risk of publication bias.

Results

Study selection

Figure 1 shows the literature selection process in detail. A total of 2759 studies were retrieved for further screening based on the established selection criteria. After removing duplicates, the titles and abstracts of 2140 studies were screened, and 2007 unqualified studies were excluded. Finally, we screened the full texts of the remaining and excluded 113 unqualified studies. Consequently, 20 studies were included in the systematic review (6, 7, 11, 12, 18-33), and 11 studies with sufficient quantitative data were included in the meta-analysis (6, 7, 18-21, 27-31).

Study characteristics and quality assessment

Table 2 shows the detailed descriptions and quality assessments of all the studies included in the review. Studies were carried out in 7 countries, all from the Northern Hemisphere, with different latitudes. All disease-related data was extracted from medical records. Fourteen studies reported the relationship between delivery season or month and HDP (6, 7, 11, 18-21, 26-32), while seven studies reported the relationship between conception season or month and HDP (12, 22-26, 33). The outcome definition was not completely uniform. Some studies focused on comprehensive HDP, while other studies focused on only severe preeclampsia. Using the quality assessment guidelines (17), seventeen studies were considered to be high quality (score of 7 or more). Three articles scored six points because they lacked ample control of confounding factors, such as singleton pregnancy or maternal-related disease history.

Table 2
Characteristics of the included studies.

Author	Publication year	Study region	Study design	Period	Total/case (n)	Exposure definition	Outcome definition	Latitude	Income group	NOS
Rohr Thomsen et al.	2020	Denmark	cohort	1989-2010	50665/4285	Month of conception	HDP	Middle	High	8
Farzaneh et al.	2019	Sistan and Baluchestan, Iran	nested case-control	2017	540/270	Season of delivery	Preeclampsia	Low	Middle	7
Shayan et al.	2019	Hamadan, Iran	case-control	2005-2015	1458/729	Season of conception	Preeclampsia	Middle	Middle	6
Weinberg et al.	2017	Norway	cohort	1999-2009	356662/13959	Month of conception	Preeclampsia and eclampsia	High	High	8
Li et al.	2016	Hunan, China	cohort	2010-2011	6223/449	Season of delivery	Preeclampsia	Middle	Middle	7
Ali et al.	2015	Sudan	case-control	2008-2010	306/153	Month of delivery	HDP	Low	Low	7
Tran et al.	2015	Paris, France	cohort	2008-2011	63633/526	Season of conception	Severe preeclampsia	Middle	High	8
Morikawa et al.	2014	Japan	cohort	2005-2009	301501/13848	Month of delivery	HDP	Middle	High	8
Luo et al.	2013	Sichuan, China	case-control	2007-2010	1300/650	Season of delivery	Preeclampsia	Middle	Middle	7
Wellington et al.	2012	Texas, USA	cohort	2001	31207/12481	Season of delivery	Preeclampsia and eclampsia	Middle	High	7
Rylander et al.	2011	Sweden	cohort	1990-1994	482659/182	Season of delivery	Eclampsia	High	High	8
Bullock et al.	2011	Oklahoma, USA	cohort	2005-2007	3050/176	Month of delivery	Preeclampsia	Middle	High	6
Tam et al.	2008	Hong Kong, China	cohort	1995-2002	15402/245	Season of conception	Preeclampsia and eclampsia	Low	Middle	8
Soroori et al.	2007	Gilan, Iran	cross-sectional	1999-2001	12142/397	Season of delivery	Preeclampsia	Middle	Middle	7
Rudra et al.	2005	Washington, USA	cross-sectional	1987-2001	83228/6680	Month of conception	Preeclampsia	Middle	High	7
Phillips et al.	2004	Vermont, USA	case-control	1995-2003	7904/142	Season of conception and delivery	Preeclampsia	Middle	High	7
Magnus et al.	2001	Norway	cohort	1967-1998	1869388/51801	Month of delivery	Preeclampsia	High	High	7
Makhseed et al.	1999	Kuwait	case-control	1992-1994	26805/692	Month of delivery	Preeclampsia	Low	High	6
Ros et al.	1998	Sweden	cohort	1987-1993	10193/557	Season of delivery	Eclampsia	High	High	8
Jamelle et al.	1998	Pakistan	case-control	1996	18878/395	Month of delivery	Eclampsia	Low	Middle	6

Season of delivery and HDP

Fourteen articles assessed the relationship between delivery season and HDP (6, 7, 11, 18–21, 26–32), and eleven articles with sufficient data were included in the meta-analysis (6, 7, 18–21, 27–31). Because the heterogeneity between studies was high ($p < 0.1$, $I^2 > 25\%$), we used a random effects model to pool the ORs and 95% CIs.

With summer delivery as the reference, a significant association between HDP and winter delivery (OR = 1.18, 95% CI 1.02-1.38, $p < 0.001$) was found, but there was no association with spring delivery (OR = 1.09, 95% CI 0.97-1.22, $p = 0.066$) or fall delivery (OR = 1.01, 95% CI 0.92-1.11, $p = 0.189$) (Figure 2).

Subgroup analyses were carried out according to latitude, income group, sample size, and whether multiple pregnancies were excluded in the studies. The results of the associations of HDP with winter delivery and summer delivery were as follows. In the latitude subgroup analysis (Figure 3), the heterogeneity decreased slightly (high latitude: $I^2 = 42.6\%$, $p = 0.187$; middle latitude: $I^2 = 67.2\%$, $p = 0.016$; low latitude: $I^2 = 0.0\%$, $p = 0.931$), and a stronger association was observed in high-latitude countries (OR = 1.62, 95% CI 1.20-2.20) and middle-latitude countries (OR = 1.24, 95% CI 1.00-1.55). However, at low latitudes, the result was nonsignificant (OR = 0.90, 95% CI 0.76-1.05). When stratified by income group and excluding studies with a sample size $< 10,000$, the heterogeneity did not change considerably, and the correlation between HDP and winter delivery remained positive. In 2 studies excluding women with multiple pregnancies, the studies by Li (OR = 1.56, 95% CI 0.91-2.69) and Rylander (OR = 1.99, 95% CI 1.33-2.98) still showed significant associations between HDP and winter delivery (7, 21). The results of the subgroup analyses for spring and fall delivery versus summer delivery were nonsignificant.

The sensitivity analysis suggested that no single study altered the association (Figure 4). In the publication bias test, three Begg's funnel plots were symmetric, and Egger's test was nonpositive (winter $p = 0.175$; spring $p = 0.454$; fall $p = 0.623$) (Figure 5).

Based on the above results, we further compared winter delivery with delivery in other seasons. The result yielded a statistically significant result (OR = 1.17, 95% CI 1.03-1.34, $I^2 = 75.4\%$, $p < 0.001$) (Figure 6). Subgroup analysis did not significantly reduce the interstudy heterogeneity. The results of the sensitivity analysis were stable. Symmetrical Begg's funnel plots and Egger's test ($p = 0.155$) showed that there was no publication bias.

Two of the remaining three studies that were not included in the quantitative analysis revealed that the risk of HDP was highest when women delivered in the winter months (11, 32), which was consistent with our quantitative analysis. Morikawa reported that the relative risks of pregnancy-induced hypertension were 1.12 (95% CI 1.06–1.19) for delivery in January–February and 1.16 (95% CI 1.09–1.22) for delivery in March–April compared with delivery in July–August (11). Magnus reported that delivery in August was associated with the lowest risk of preeclampsia, while the risk was highest in the winter months (for December, adjusted OR = 1.26, 95% CI 1.20–1.31) (32). However, Phillips found that there were no significant differences in the rates of preeclampsia in women with winter and spring deliveries, but women with summer deliveries (OR = 0.63, 95% CI 0.39–0.99 vs. spring) and fall deliveries (OR = 0.60, 95% CI 0.37–0.98 vs. spring) had reduced odds of developing preeclampsia (26).

Season of conception and HDP

Seven studies assessed the relationship between conception season or month and HDP. Four studies supported that conception in summer increased the risk of developing HDP (22, 24–26).

Rohr Thomsen showed that women who conceived in August (OR = 1.35, 95% CI 1.11-1.64) had the highest risk of gestational hypertension, and those who conceived in June (OR = 1.17, 95% CI 0.94-1.45) had the highest risk of preeclampsia, which occurred in both the summer months (22). Tran found that conception in summer was associated with the highest risk of severe preeclampsia (OR = 1.53, 95% CI 1.27-1.85, vs. winter) (24). Tam (OR = 1.7, 95% CI 1.2–2.5, vs. autumn) and Phillips (OR = 1.7, 95% CI 1.1-2.8 vs. spring) revealed that conception in summer was associated with an increased risk of preeclampsia (25, 26).

However, the results of 3 studies were not consistent with the above conclusion. Rudra reported that conception in February (OR = 1.17, 95% CI 1.03-1.33 vs. January) and April (OR = 1.18, 95% CI 1.03-1.34 vs. January) through August (OR = 1.14, 95% CI 1.01-1.30 vs. January) were associated with significantly higher risks of preeclampsia (33). However, Shayan found that conception in autumn increased the odds of preeclampsia (OR = 1.13, 95% CI 0.73-1.76, vs. winter) and that conception in summer was associated with the lowest odds of preeclampsia (OR = 0.26, 95% CI 0.17-0.38, vs. winter) (12). Weinberg revealed that women who conceived in spring had a higher risk of HDP, while those that conceived in autumn had a lower risk (23).

Discussion

Main findings

This systematic review of 20 studies and meta-analysis of 11 studies explored the relationship between season and the development of hypertensive pregnancy disorders. The results showed increased odds of HDP in women who delivered in winter compared with those who delivered in summer (OR = 1.18, 95% CI 1.02-1.38, $p < 0.001$) and other seasons (OR = 1.17, 95% CI 1.03-1.34, $p < 0.001$). Furthermore, in the analysis of the relationships between HDP and seasons or months of conception, 4 of 7 studies reported that women who conceived in summer had a higher risk of HDP.

Some studies have suggested that HDP may be more strongly associated with conception time than with delivery time (26, 34). Although the stages of pregnancy in the included studies were different, we combined them by gestation period. For example, in the studies on delivery and conception

months, women who conceived in hot months generally delivered in cold months in the following year (11, 18, 22, 27, 32). Women who conceived in June and delivered in March had the highest risk of preeclampsia (22). The differences in these study results studies were possibly associated with premature delivery in women with HDP and the miscalculation of conception time. First, many studies have reported that women with HDP are prone to premature delivery (35-37), and low-dose aspirin could decrease the incidence of preterm birth, particularly if initiated before 16 weeks of gestation (36). Therefore, this could help explain the high incidence of HDP in women who conceived in summer and delivered in winter. Second, a lack of ultrasound examination to determine the date of conception or the presence of menstrual disorders may cause inaccurate estimates of the date of conception, resulting in less accurate conclusions about the relationship between HDP and month of conception (25, 33).

Based on our analysis, it was not possible to explain how season factors could affect the onset of HDP. According to basic research and epidemiological investigations, a number of possible mechanisms influenced by factors such as nutritional status, sunlight exposure, temperature, humidity, and infection, may explain the correlation. Here, we discuss some relevant factors. Among the different seasons, there is wide variation in the nutrients consumed by people, resulting in different risks of pregnancy-related diseases (38). Lowensohn reported that calcium supplementation may reduce the risk of HDP, especially in low-calcium populations (38). In addition, Mirzakhani reported that vitamin D levels above 30 ng/ml at the start of the trial and in late pregnancy were associated with a lower risk of preeclampsia (39). Vitamin D levels are not only affected by seasonal variations in nutrient intake but are also closely related to sunlight exposure. Vitamin D is produced naturally in the skin when skin is exposed to sunlight, which varies greatly among seasons (18, 21, 22). In a recent study by Horton-French, young adults had a 3 times higher risk of vitamin D deficiency in the winter than in the summer, which was consistent with our findings of a higher risk in women who delivered in winter (40). Additionally, variations in temperature and humidity have also been hypothesized. Xiong reported that in the early stages of pregnancy, cold temperatures reduced the risk, whereas hot temperatures increased the risk (34). Moreover, the incidence of preeclampsia was significantly higher during the dry season than during the rainy season (41, 42). As a possible explanation, Krininger reported that heat shock was found to compromise embryo implantation in an animal model (43). Water loss resulting in reduced plasma volume in warm months may increase the risk of developing preeclampsia (44), which may indirectly explain the increased risk of HDP in women who conceive in summer. Exposure to cold temperatures could lead to vasospasms and subsequent ischemia (45), which is a possible reason for the increased risk of HDP in winter (20). All of these factors that affect cardiovascular conditions may together increase blood pressure, promoting the formation of HDP. Finally, seasonal fluctuations in infection rates may result in variability in the seasonal occurrence of preeclampsia (46), which could cause a maternal systemic inflammatory response.

In this meta-analysis of studies on delivery season and conception season, the heterogeneity was high, possibly due to confounding factors such as sample size, latitude, income group, study design, and definitions of outcomes. To solve this problem, we performed subgroup analyses to find the source of the heterogeneity. The heterogeneity slightly decreased in only the latitude subgroup analysis. Although we failed to find the major source of heterogeneity, our sensitivity analysis indicated that our results were valid. In addition, because reference seasons or months were different and some original data could not be obtained, we failed to carry out a meta-analysis of studies on conception season and HDP. Therefore, more studies need to be analyzed to minimize heterogeneity and explore the relationship between conception season and HDP to obtain more accurate correlation results.

In summary, additional large-scale multicenter studies analyzing specific seasonal factors, such as temperature, humidity and pollution, are needed to thoroughly study the relationship between season or month and HDP. Furthermore, the identification of risk factors for the onset of HDP is important because it could greatly improve pregnancy and fetal outcomes.

Strengths and limitations

Accurate and robust statistical results were reported in this meta-analysis on the positive association between season and HDP. In addition, this is the first quantitative analysis of this topic.

However, this study has some limitations. First, we found heterogeneity in our meta-analysis. Many factors beyond our control, such as sample size, latitude, income group, study design, and definitions of outcomes, could all affect the degree of heterogeneity. Thus, additional high-quality studies are needed to reduce heterogeneity in the future. Second, in the study of the relationship between conception season and HDP, the reference season or month differed, and original data were not reported. This caused difficulty in performing a meta-analysis, resulting in insufficient reliability of the results. Third, we excluded non-English articles, which led to the exclusion of studies not published in English, potentially influencing the representativeness of our results.

Conclusion

Based on the evidence to date, we found weakly positive relationships between HDP and summer conception and winter delivery. Additional large-scale multicenter studies analyzing detailed seasonal factors, such as temperature, humidity and pollution, are needed to thoroughly study the relationship between season or month and HPD.

Abbreviations

HDP : Hypertensive disorders of pregnancy

MOOSE : The Meta-Analysis of Observational Studies in Epidemiology

PRISMA : Preferred Reporting Items for Systematic review and Meta-Analyses

MeSH : Medical Subject Headings

ORs :Odds ratios

95% CIs: 95% confidence intervals

NOS : the Newcastle-Ottawa quality assessment scale

Declarations

Availability of data and materials

Data will be available from the corresponding author upon reasonable request.

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Contributions

LL and XW performed experiments and analyzed the results. LL conceived the study and prepared the manuscript. ML modified the figure. YG, YY and RZ supervised the study. All authors contributed to the article and approved the submitted version.

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Ethics declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

PRISMA flow diagram of study process.

Figure 2

The forest plots show the association between HDP and delivery season. Spring (A), Autumn (B), Winter (C) compared with summer as reference.

Figure 3

Forest plot of subgroup analysis of HDP and winter delivery compared with summer on latitude.

Figure 4

Sensitivity analysis of HDP and winter delivery compared with summer.

Figure 5

Begg's funnel plot of HDP and winter delivery compared with summer.

Figure 6

The forest plots show the association between HDP and delivery season: winter delivery compared with other seasons.