

# Identifying Symptom Clusters Among Pregnant Women During Early and Late Pregnancy

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## Research Article

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# Abstract

## Objectives

Symptom assessment and management among women in early and late pregnancy remains concerned, in consideration of multiple co-occurring symptoms; however, evaluation of multidimensional nature of symptom experience (e.g., frequency, severity and distress) and relevant symptom cluster among them is insufficient. To shed light on this understudied field, our study investigated the status of multiple psychosomatic symptoms among women and identified symptom clusters in different gestational stages.

## Methods

A convenience sample of 557 pregnant women were recruited at two tertiary hospitals in Shandong, China. They were asked to complete the Memorial Symptom Assessment Scale, and sociodemographic and clinical information. Spearman correlation analysis, partial correlation networks, and hierarchical cluster analysis were carried out to identify optimal number of symptom clusters.

## Results

Top five scores for symptoms in early pregnancy were nausea, lack of appetite, feeling drowsy, lack of energy, and vomiting; and weight gain, difficulty sleeping, sweating, lack of energy, and dry mouth scored highly in late pregnancy. Four clusters (pregnancy reaction symptom cluster, mood-fatigue symptom cluster, change in libido and food taste symptom cluster, and dry mouth-bloating symptom cluster) were identified in early pregnancy, and three clusters (mood-fatigue symptom cluster, sleep-bloating symptom cluster, and fluid deficiency symptom cluster) were determined in late pregnancy.

## Conclusion

Women experience multiple psychosomatic symptoms during pregnancy, and the manifestation of symptoms varies in different stages. Our study has provided new insights into symptom clusters of pregnant women. These results might potentially support the development of assessment and management of multiple co-occurring symptoms in this population.

## Introduction

Pregnancy is a common condition that has a considerable impact on a woman's life. During this period, a woman has to confront not only anatomical, physiological, and biochemical changes, but also psychological adaptation (e.g., reorientation and identification of personal, family, and social roles)(Kaur & Miller, 2017, Yu et al., 2020). Under these circumstances, women may experience multiple psychological

and physical symptoms such as fatigue, nausea, vomiting, anxiety, depression, and sleep disturbances (Daly et al., 2018, Ertmann, Nicolaisdottir, Kragstrup, Siersma, & Lutterodt, 2020, O'Connor, Poudevigne, Johnson, de Araujo, & Ward-Ritacco, 2018, Shawahna & Taha, 2017, Stray-Pedersen et al., 2018). Substantial literature has illustrated that psychosomatic symptoms during pregnancy not only affect pregnant women, but also have a potential negative impact on the offspring. For example, sleep disorders in pregnant women increase risk of gestational diabetes (Wang et al., 2017), and negative emotions such as anxiety and depression during pregnancy could over-activate the hypothalamic-pituitary-adrenergic axis in pregnant women, leading to preterm delivery and low birth weight (Liou, Wang, & Cheng, 2016, Nylén, O'Hara, & Engeldinger, 2013). In addition, daytime lethargy during pregnancy might be a risk factor for internalised psychiatric problems, symptoms of attention deficit hyperactivity disorder, and poorer executive functioning in the offspring (Lahti-Pulkkinen et al., 2019). Consequently, it is necessary to attend to psychosomatic symptoms in women during pregnancy.

Actually, as the hormonal and anatomical changes, along with the development of the foetus, influence the duration and severity of symptoms (e.g., frequent urination, constipation, fatigue, insomnia, and back pain), varying across different stages of pregnancy, and the occurrence of these symptoms is particularly prominent during early and late pregnancy (Beebe, Gay, Richoux, & Lee, 2017, Nazik & Eryilmaz, 2014). During early pregnancy, i.e., gestational age of less than 13 weeks, women commonly experience nausea and vomiting, and the majority suffer from pregnancy reactions to various degrees, which may lead to dehydration, electrolyte disbalance, and impaired foetal development in severe cases (Einarson, Piwko, & Koren, 2013, Viljoen, Visser, Koen, & Musekiwa, 2014). In addition, pregnant women are more likely to experience sharp emotional changes (e.g., the surprise and expectations of newborns' arrival or unpleasant emotions triggered due to transition between roles) and raise concerns about the foetal growth and development as well (Bergbom, Modh, Lundgren, & Lindwall, 2017, Taubman-Ben-Ari, Chasson, Horowitz, Azuri, & Davidi, 2021). In regard to late pregnancy, i.e., gestational age of more than 28 weeks, the functional load on the organs of women gradually approaches its maximum, consequently increasing the burden on the maternal body, and subsequently developing symptoms such as difficulty in breathing and sleep disorders (Kaur & Miller, 2017, Mindell, Cook, & Nikolovski, 2015). In addition, as the due date approaches, women start getting concerned about the outcomes of the delivery and the baby's health (Bisetegn, Mihretie, & Mucche, 2016), and some are even placed under pressure coming from family's acceptance of the newborn's gender (Zhou et al., 2020). Faced with various problems related to pregnancy, mothers-to-be are more prone to suffer from health impairment. Therefore, there is an urgent need to pay attention to the psychosomatic symptoms of women during early and late pregnancy and to emphasise on early recognition and intervention.

It is noteworthy that multiple symptoms of pregnancy may commonly occur simultaneously and have complicated interactive relationships. For example, Andersson found that pregnant women with anxiety or depressive symptoms experienced more frequent nausea and vomiting (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2004), while Lardon and Ertmann reported that pregnancy-related lumbopelvic pain could be accompanied by impaired sleep quality (Ertmann et al., 2020, Lardon, St-Laurent, Babineau, Descarreaux, & Ruchat, 2018). Considering the co-occurrence and interaction of

symptoms, it may be feasible to manage the symptoms of pregnancy by grouping them, allowing the identification of symptom clusters. Symptom clusters, by definition, are two or more symptoms that interrelate and occur together, and the association between symptoms of one symptom cluster is usually stronger than symptoms of distinct symptom clusters and/or independent symptoms (Barsevick, 2016, Miaskowski et al., 2017). Current evidence has demonstrated that the treatments for one symptom may 'cross-over' the others within a cluster (Kwekkeboom et al., 2012). This complex interrelationship may potentially offer the possibility of targeting a single intervention to diminish the adverse effects of multiple co-occurring symptoms on individual outcomes, which has important practical implications for symptom management (Miaskowski et al., 2017). At present, the majority of research on symptom clusters has focused on the areas of cancer (e.g., breast, lung, and head and neck cancers) (Dong, Butow, Costa, Lovell, & Agar, 2014, Russell et al., 2019, So et al., 2021, Xiao et al., 2013) and other chronic diseases (e.g., chronic obstructive pulmonary disease and heart failure) (DeVon et al., 2017, Jenkins, Athilingam, & Jenkins, 2019, Zhu, Zhao, & Hu, 2019). For instance, a survey conducted by Coomans et al. on 4,307 newly diagnosed glioma patients observed four symptom clusters: a motor cluster (motor dysfunction and weakness of the legs), a fatigue cluster (fatigue and drowsiness), a pain cluster (pain and headache), and a gastrointestinal/seizures/bladder control cluster (nausea and vomiting, diarrhoea, seizures, and bladder control) (Coomans et al., 2019). Given the distinctiveness of pregnancy and the concurrence and interaction of symptoms, it is reasonable to deduce that specific symptom clusters may also exist in pregnant women. However, existing studies on symptom clusters in pregnant women are insufficient, warranting further investigation.

To sum up, consideration is required for the assessment and management of multiple, co-occurring symptoms during early and late pregnancy, to improve outcomes in pregnant women. And strategies to promote the development of symptom science through symptom cluster research could potentially contribute to a relevant body of empirical knowledge, enabling innovative interventions for symptom management in this population. Therefore, the objectives of this research were to understand the occurrence of multiple symptoms in pregnant women during early and late pregnancy, and to identify symptom clusters in different stages, so as to diversify the research in this field.

## Methods

### Study Population

This was a cross-sectional study conducted by convenience sampling at the obstetrics clinic of two tertiary hospitals in Jinan City, Shandong Province, China, and the study strictly followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. We recruited participants during their early and late pregnancy (gestational age <13 weeks and >28 weeks, respectively) from March 2019 to October 2019.

$$n = \frac{U_{1-\alpha/2}^2 S^2}{d^2}$$

The sample size was determined using the formula,  $n = \frac{U_{1-\alpha/2}^2 S^2}{d^2}$ , and was estimated on the basis of a pilot study. In this formula,  $S$  represents standard deviation and  $d$  represents allowable tolerance, which is generally chosen as 1 based on clinical experience. According to the values of these variables ( $\alpha = 0.05$ ,  $S_1 = 7.239$ ,  $S_2 = 7.362$  [<sub>1</sub>early pregnancy, <sub>2</sub>late pregnancy]), it was necessary to include 202, 209 people in each stage of pregnancy. Assuming a non-response rate of 10%, the final total sample size required was of at least 457 participants.

Pregnant women aged 20 years or above were eligible to participate if they had no other severe physical or mental impairments, were able to understand and complete the questionnaires, and were willing to participate. Those who had threatened abortion, intended to undergo surgical abortion, or those with foetal intrauterine growth retardation were excluded. All participants were informed about the purpose and procedure of the study in detail, were assured of data confidentiality, and could withdraw at any time without disclosing the reason. After obtaining informed consent, the questionnaires were filled out anonymously, and one-on-one guidance was provided if participants had any queries about the questionnaires.

This study was approved by the Research Ethics Committee of the authors' affiliations.

## Measures

### *Sociodemographic and Clinical Variables*

Information on sociodemographic and clinical characteristics was collected from a questionnaire designed by the researchers, which included age, self-reported body mass index (BMI), education (below college/college and above), employment status (employed/not employed), having children (yes/no), abortion history (yes/no), pregnancy complications (yes/no), and gestational stages.

### *Symptoms Experience During Different Stages of Pregnancy*

The Memorial Symptom Assessment Scale (MSAS) was developed by Portenoy and his colleagues to measure multidimensional information on a wide range of common symptoms over the past seven days (Portenoy et al., 1994). The MSAS contains 32 entries, with the first 24 evaluating frequency, severity, and distress, while the remaining eight symptoms assess only severity and distress (for that they are unlikely to change in frequency over the course of a week), such as weight loss and change in food tastes. Each symptom is rated on a 4-point scale ranging from 1 to 4 for frequency and severity, and on a 5-point scale ranging from 0 to 4 for distress. The score for each symptom is determined by the average of the scores on frequency, severity, and distress, or if appropriate, the scores on severity and distress scales only. Besides, taking into account that the original scale had the symptom of 'weight loss', while 'weight gain' commonly occurs during pregnancy according to clinical experience, we added the symptom 'weight gain' in the investigation. The scale is currently widely used in patients with cancer, chronic

obstructive pulmonary disease, and heart failure, and has been shown to have good reliability in pregnant women. The Cronbach's  $\alpha$  of the MSAS in the present study was 0.963.

## Statistical analysis

All analyses were conducted using SPSS (version 25) and R statistical software (version 4.0.2). Statistical description methods were presented using means (M) and standard deviations (SDs) for continuous variables and frequencies with percentages for categorical variables. Independent Student's *t*-test and the Chi-squared test were performed to compare the differences in sociodemographic information and symptom scores at different stages of pregnancy.

The optimal number of symptom clusters were carried out in all three steps: Spearman correlation analysis, partial correlation networks, and hierarchical cluster analysis (HAC). Firstly, Spearman correlation analyses were performed to determine the interrelationships between the symptoms. Second, associations between symptoms were represented in a Gaussian graphical model based on the partial correlation matrix, which was applied to examine whether the associations between symptoms yet existed after controlling for other symptoms. We used the graphical least absolute shrinkage and selection operator to lower the probability of spurious edges and get a parsimonious network. Finally, hierarchical cluster analysis (HCA) was utilised to cluster the symptoms, and the similarity between different clusters was assessed using Wald's method with the Euclidean distance, and a dendrogram was drawn up to provide visualisation of the results of cluster analysis.

# Results

## Characteristics of the Study Population

A total of 557 pregnant women were investigated, of which 249 were in the early pregnancy stage, with an average gestational week of 9.00 (SD=2.71), and 308 were in the late pregnancy stage, with an average gestational week of 34.07 (SD=3.26). The sociodemographic characteristics and differences in the different stages of the participants are shown in Table 1. The mean age of pregnant women in early and late pregnancy was  $29.80 \pm 3.93$  and  $30.08 \pm 4.23$  years, respectively, and the average BMI was  $21.66 \pm 2.91$  kg/m<sup>2</sup> and  $26.53 \pm 3.34$  kg/m<sup>2</sup>, respectively. Most of the women had a college degree or above and were all predominantly employed. The majority of women were childless, had no history of abortion, and had no complications during pregnancy. The results of independent Student's *t*-test or the Chi-squared test showed that there were differences in BMI, employment status, abortion history, and pregnancy complications among women in different stages of pregnancy. Specifically, women in early pregnancy were more likely to be employed (81.9% vs. 72.7%,  $P = 0.010$ ) and to have a history of abortion (43.4% vs. 32.1%,  $P = 0.006$ ), while those in late pregnancy had higher BMI ( $t = 18.093$ ,  $P < 0.001$ ) and higher pregnancy-related complications (23.7% vs. 6.8%,  $P < 0.001$ ).

## Prevalence, Intensity, and Distress of Symptoms

Fig. 1 shows the results of symptom experience in early pregnancy, and the prevalence, intensity, and distress of symptoms in late pregnancy are reported in Fig. 2. In terms of prevalence, the five most common symptoms experienced during early pregnancy were nausea (84.3%), drowsiness (81.5%), lack of energy (79.5%), lack of appetite (73.1%), and difficulty in concentrating (66.3%). During late pregnancy, weight gain (79.2%), lack of energy (70.8%), drowsiness (66.6%), sweating (63.3%), and difficulty in sleeping (63.0%) were more commonly reported. Regarding the intensity of symptoms, the most severe symptoms reported during early pregnancy were nausea, lack of appetite, drowsiness, lack of energy, and vomiting, while those reported during late pregnancy were weight gain, difficulty in sleeping, lack of energy, sweating, and dry mouth. In addition, the most distressful symptoms experienced by women during early pregnancy were nausea, loss of appetite, drowsiness, lack of energy, and vomiting, while weight gain, difficulty in sleeping, sweating, lack of energy, and dry mouth were highly distressing for women in late pregnancy.

### **Symptom Scores**

We evaluated and ranked the scores for symptoms (the average of the scores on frequency, severity, and distress) in different stages of pregnancy and found that the first five symptoms during early pregnancy were nausea, lack of appetite, drowsiness, lack of energy, and vomiting. In late pregnancy, weight gain, difficulty in sleeping, sweating, lack of energy, and dry mouth scored highly among the 33 symptoms. The majority of scores for symptoms differed in these two periods, apart from those for pain, cough, feeling nervous, dry mouth, problems with urination, diarrhoea, feeling sad, worrying, problems with sexual interest or activity, dizziness, and mouth sores (Table 2).

### **Symptom Clusters**

In order to ensure the clinical implications of the investigation and have a manageable number of symptoms for cluster analysis, symptom clusters were identified by selecting >50% occurrence. Therefore, 12 symptoms (difficulty in concentrating, lack of energy, feeling nervous, dry mouth, nausea, feeling drowsy, feeling bloated, vomiting, problems with sexual interest or activity, lack of appetite, feeling irritable, and change in food tastes) were eventually incorporated in early pregnancy, and 11 symptoms (difficulty in concentrating, pain, lack of energy, feeling nervous, dry mouth, feeling drowsy, difficulty in sleeping, feeling bloated, sweating, feeling irritable, and weight gain) were included in late pregnancy.

The results of the Spearman correlations between the symptoms above in different stages were presented, with the strongest correlations found in early pregnancy between nausea with vomiting (0.730) and lack of appetite (0.626), lack of energy with difficulty in concentrating (0.591) and feeling drowsy (0.542), and for vomiting and lack of appetite (0.522) (Supplementary Table 1), while in late pregnancy, the highest correlations were reported between feeling nervous and feeling irritable (0.594), difficulty in concentrating with lack of energy (0.560) and feeling irritable (0.544), and lack of energy with feeling drowsy (0.553) and feeling irritable (0.525) (Supplementary Table 2).

Association networks based on partial correlation matrixes in early pregnancy (Supplementary Table 3) and late pregnancy (Supplementary Table 4) were conducted to present description of the relationships among the symptoms, and HCAs were performed to identify symptom clusters in different stages, as illustrated by the dendrograms, in accordance with the similarities between them.

Taking the above three methods into consideration, we finally figured out four symptom clusters among the 12 symptoms in early pregnancy (Fig. 3): pregnancy reaction symptom cluster (nausea, vomiting, and lack of appetite), mood-fatigue symptom cluster (feeling nervous, feeling irritable, lack of energy, difficulty in concentrating, and feeling drowsy), change in libido and food taste symptom cluster (problems with sexual interest or activity and change in food tastes), and dry mouth-bloating symptom cluster (dry mouth and feel bloated). Three symptom clusters and two single symptoms were identified for the 11 symptoms integrated in late pregnancy, as shown in Fig. 4. The three symptom clusters were mood-fatigue symptom cluster (feeling nervous, feeling irritable, lack of energy, difficulty in concentrating, and feeling drowsy), sleep-bloating symptom cluster (difficulty in sleeping and feeling bloated), and fluid deficiency symptom cluster (dry mouth and sweating), while pain and weight gain were recognized as independent symptoms.

## Discussion

By employing the MSAS to assess the status of multiple psychosomatic symptoms among women at different gestational stages, we investigated the multidimensional nature of symptoms (e.g., frequency, severity, and distress) and identified four symptom clusters in early pregnancy, along with three symptom clusters and two independent symptoms in late pregnancy. These results provide further evidence for studies in related fields.

In this study, the symptoms with higher symptom scores, frequency, severity, and distress in early pregnancy were nausea, lack of appetite, drowsiness, lack of energy, and vomiting. This result is consistent with those of previous studies, indicating that these symptoms are commonly experienced during early pregnancy (Bai et al., 2016; Chan et al., 2010; Mindell et al., 2015; Wang Lei et al., 2013). This may be related to an increase in the levels of human chorionic gonadotropin (HCG), a decrease in gastric acid secretion, and prolonged gastric emptying time that occurs during early pregnancy (Committee on Practice, 2018). Whereas the symptoms with higher symptom scores, frequency, severity, and distress in late pregnancy were weight gain, difficulty in sleeping, sweating, lack of energy, and dry mouth. Among them, the lack of energy was a common symptom experienced in both the stages, with an incidence of 70.8–79.5%, which is similar to the findings of Beebe et al. (Beebe et al., 2017). This may be due to disruption of sleep and insufficient sleep duration during pregnancy (Mindell et al., 2015). In addition, consistent with previous studies, weight gain and difficulty in falling asleep were common symptoms experienced by women during late pregnancy (Beebe et al., 2017). Pregnant women tend to gain weight due to local changes (e.g., foetal growth and development, uterine enlargement, and the formation of placenta and amniotic fluid) and metabolic changes (e.g., water retention, fat deposition, and protein storage) (Sally, dos Anjos, & Wahrlich, 2013; Torgersen & Curran, 2006). In addition, as the pregnancy

progresses, the uterus enlarges and gradually presses upward on the diaphragm, causing mechanical changes in the respiratory system (i.e., increase in the tidal volume, decrease in the functional reserve capacity and residual volume), thereby increasing susceptibility to difficulty in breathing and affecting sleep patterns (Nazik & Eryilmaz, 2014; Torgersen & Curran, 2006). Difficulty in falling asleep may be related to foetal movement and specific types of pain commonly experienced during late pregnancy (e.g., leg cramps, lumbopelvic pain or pressure, and restless legs syndrome) (Mindell et al., 2015; Nazik & Eryilmaz, 2014). Moreover, during the gestational period, women's basal metabolic rate (BMR) increases (Lof et al., 2005; Sally et al., 2013), which accounts for dry mouth and sweating in late pregnancy.

To the best of our knowledge, this study is the first to identify symptom clusters in a population of pregnant women. Eventually, four symptom clusters (pregnancy reaction symptom cluster, mood-fatigue symptom cluster, change in libido and food taste symptom cluster, and dry mouth-bloating symptom cluster) were identified in early pregnancy, and three symptom clusters (mood-fatigue symptom cluster, sleep-bloating symptom cluster, and fluid deficiency symptom cluster) and two independent symptoms (pain and weight gain) were identified in late pregnancy.

In early pregnancy, nausea, vomiting, and lack of appetite formed a cluster called the pregnancy reaction symptom cluster. These three symptoms are typically noted during early pregnancy, and the exact underlying mechanism remains unclear. The prevailing opinion is that it is related to the elevation of progesterone during pregnancy, i.e., progesterone can inhibit the smooth muscles of both the pylorus and the small intestine, resulting in reduced contractility of the gastrointestinal tract and decreased intestinal motility (Body & Christie, 2016). The second symptom cluster identified was comprised of feeling nervous, feeling irritable, lack of energy, difficulty in concentrating, and feeling drowsy, and was named the mood-fatigue symptom cluster. Previous studies have indicated that fatigue, anhedonia, and emotional problems, including anxiety and distress are prevalent among pregnant women (Beebe et al., 2017; Verbeek, Arjadi, Vendrik, Burger, & Berger, 2015). Fatigue during the gestational period is associated with the occurrence of emotional problems (van de Loo et al., 2018), which might aggravate fatigue in turn (Giallo, Gartland, Woolhouse, & Brown, 2016; Jiansheng et al., 2019), consequently resulting in a vicious cycle. The third symptom cluster included problems with sexual interest or activity and change in food tastes. By far, there are no other studies that have replicated the symptom clusters, and therefore, we not yet been able to account for the association between the two symptoms in the third cluster. We had expected that the change in food taste might be related to the cluster consisting of nausea, vomiting, and lack of appetite; however, this was simply not the case. Finally, the fourth and last cluster consisted of dry mouth and feeling bloated, which may be the result of gastrointestinal disorders induced by the alteration of hormones (Keller, Frederking, & Layer, 2008).

The first cluster determined during late pregnancy was the mood-fatigue symptom cluster, which included symptoms such as feeling nervous, feeling irritable, lack of energy, difficulty in concentrating, and feeling drowsy, which was also one of the clusters detected in early pregnancy. This indicated that the mood-fatigue cluster persisted during the two periods and that there was an interaction among these

symptoms, despite the fact that we could not figure out the causality of them. This finding implies the need to pay special attention to these interrelated symptoms related to mood and fatigue in symptom management during both early and late pregnancy, which would help pregnant women and their families adjust psychologically and physically till the birth of the offspring. The second symptom cluster identified included symptoms such as difficulty in sleeping and feeling bloated. This gathering phenomenon might be attributed to a shared biological mechanism underlying these symptoms. Specifically, in late pregnancy, due to the fluctuations in oestrogen and progesterone and the mechanical effects of uterine enlargement, the transit rate of the small intestine and colon decreases, which results in symptoms of abdominal distension. Simultaneously, owing to the combined effects of these factors, pregnant women often have multiple types of sleeping disorders, such as difficulty in falling asleep and frequent night awakenings (Keller et al., 2008; Nazik & Eryilmaz, 2014). We also identified another symptom cluster consisting of dry mouth and sweating. One might assume that the two symptoms are due to increased BMR observed in late pregnancy (Lof et al., 2005; Sally et al., 2013), despite there being no clear reasoning for the coexistence of these symptoms in a cluster. Besides, two independent symptoms, pain and weight gain, were also observed during late pregnancy. As these two symptoms were not incorporated into a certain cluster, this may, to some extent, account for their prominence and independence in late pregnancy, without sharing some common causes or being greatly associated with symptoms in other clusters (they were more weakly connected with other symptoms with respect to correlations and location of the network matrix), which needs to be explored in future investigations.

There are some limitations to our study. Firstly, the subjects of this study were enrolled from only two tertiary hospitals, and the representability and generalisation of the results are somewhat restricted. Secondly, the available data were self-reported by pregnant women, which may have resulted in recall bias. Thirdly, the instrument adopted for evaluating symptom experience was not specifically designed for pregnant women; therefore, several specific types of pain commonly experienced in late pregnancy, such as leg cramps, lumbopelvic pain or pressure, and restless legs syndrome were not described exactly. Future investigations should adopt a more comprehensive and specific tool to assess the studied symptoms. Additionally, to ensure clinical implications and have a manageable number of symptoms for cluster analysis, the clusters were identified by symptoms with a prevalence over 50%; however, it was challenging beyond this to reach consensus on what remaining symptoms should be contained within. Moreover, there is still some debate about the minimum number of symptoms within a symptom cluster, and the more prevalent ones are the two symptoms proposed by Kim et al. (Kim, McGuire, Tulman, & Barsevick, 2005). These were also selected in the present study, which might have had an impact on our results. Furthermore, we used three commonly used approaches (i.e., correlation analysis, partial correlation analysis, and HCA) to determine the symptom clusters, which have been applied to head and neck cancer patients with endotracheal tubes and newly diagnosed glioma patients (Coomans et al., 2019; Li et al., 2020). Nonetheless, the identified symptom clusters may differ when other methods (e.g., factor analysis) are utilised. It remains controversial as to which analytical method is optimal.

Despite the limitations mentioned above, our research has significant implications for further clinical practice. The effects of symptom clusters on individuals may be distinct from, or even greater than, the

cumulative effects of a single symptom within a cluster; thus, symptom clusters might potentially be more powerful in shaping a pregnant woman's functional status and quality of life. A more in-depth understanding of how these symptoms coexist during the progression of pregnancy could facilitate the design of comprehensive and appropriate healthcare programs to manage symptoms for multiple potential conditions. Future studies are warranted to explore the underlying biological mechanisms of each symptom cluster to diversify our current understanding of this emerging field.

## **Conclusion And Implications**

Pregnant women experience multiple psychosomatic symptoms during pregnancy, and the manifestation of symptoms varies at different gestational stages. Our study has provided new insights into the symptom clusters of pregnant women by analysing a variety of common symptoms among them, with four clusters identified in early pregnancy, along with three clusters and two independent symptoms in late pregnancy. In particular, the mood-fatigue cluster was a persistent and stable symptom cluster in both phases. Notably, awareness of existence of symptom clusters during the progression of pregnancy would enable clinical staff to promptly identify some potentially neglected symptoms and facilitate the design of comprehensive and appropriate healthcare programs to manage symptoms for multiple potential conditions. Future research is required to estimate the mechanisms underlying the association of symptom clusters with the perspective of justifying targeted symptom management.

## **Declarations**

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### **Ethical approval**

This study was approved by the institutional review board of the School of Nursing and Rehabilitation, Shandong University (2017-R020).

### **Consent to participate**

Informed consent was obtained from all individual participants included in the study.

### **Author contribution**

Yunxue Zhang participated in participants' recruitment and interpretation of data and prepared the draft manuscript. Xiaofang Xu participated in the study design and participants' recruitment and prepared the

draft manuscript. Zihui Xie provided critical revisions for this manuscript. Yuanyuan Li provided critical revisions for this manuscript. Di Zhao provided critical revisions for this manuscript. Gaorong Lv provided critical revisions for this manuscript. Ping Li joined the study design, coordinated the data collection and analyses, and contributed to critical revisions for this manuscript. All authors approved the final version.

## Conflicts of Interest

No conflicts of interest to disclose.

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## Tables

**Table 1 Sociodemographic characteristics and differences in different stages of pregnancy women (N =557)**

Variables	Early pregnancy (n = 249)	Late pregnancy (n = 308)	t/ $\chi^2$	P
	N (%)	N (%)		
Age (mean $\pm$ SD)	29.80 $\pm$ 3.93	30.08 $\pm$ 4.23	0.805	0.421
BMI (mean $\pm$ SD)	21.66 $\pm$ 2.91	26.53 $\pm$ 3.34	18.093	0.001
Education			0.091	0.763
below College	46 18.5	60 19.5		
College and above	203 81.5	248 80.5		
Employment or not			6.549	0.010
No	45 18.1	84 27.3		
Yes	204 81.9	224 72.7		
having children			2.739	0.098
No	150 60.2	164 53.2		
Yes	99 39.8	144 46.8		
abortion history			7.437	0.006
No	141 56.6	209 67.9		
Yes	108 43.4	99 32.1		
pregnancy complications			28.939	0.001
No	232 93.2	235 76.3		
Yes	17 6.8	73 23.7		

**Table 2 Symptom scores and differences in different stages of pregnancy women (N=557)**

Symptoms	Early pregnancy (n = 249)	Late pregnancy (n = 308)	<i>t</i>	<i>P</i>
	M ± SD	M ± SD		
Difficulty concentrating	0.89±0.81	0.66±0.72	3.573	0.001
Pain	0.64±0.76	0.75±0.79	1.630	0.104
Lack of energy	1.34±0.95	0.94±0.77	5.347	0.001
Cough	0.32±0.64	0.33±0.60	0.110	0.913
Feeling nervous	0.76±0.81	0.68±0.75	1.159	0.247
Dry mouth	0.96±0.90	0.92±0.87	0.589	0.556
Nausea	1.67±1.11	0.53±0.82	13.575	0.001
Feeling drowsy	1.41±0.95	0.90±0.78	6.790	0.001
Numbness/tingling in hands/feet	0.26±0.54	0.61±0.81	6.149	0.001
Difficulty sleeping	0.67±0.89	0.98±0.96	3.935	0.001
Feeling bloated	0.93±0.99	0.72±0.88	2.603	0.010
Problems with urination	0.15±0.47	0.15±0.44	0.021	0.983
Vomiting	1.16±1.20	0.30±0.72	10.021	0.001
Shortness of breath	0.48±0.76	0.67±0.84	2.734	0.006
Diarrhoea	0.34±0.60	0.28±0.63	1.106	0.269
Feeling sad	0.52±0.75	0.43±0.67	1.489	0.137
Sweats	0.60±0.79	0.96±0.94	4.984	0.001
Worrying	0.67±0.86	0.61±0.75	0.981	0.372
Problems with sexual interest or activity	0.86±1.00	0.79±0.94	0.804	0.422
Itching	0.34±0.64	0.54±0.79	3.323	0.001
Lack of appetite	1.45±1.19	0.60±0.81	9.595	0.001
Dizziness	0.57±0.79	0.48±0.68	1.479	0.140

Difficulty swallowing	0.29±0.65	0.09±0.33	4.507	0.001
Feeling irritable	0.92±0.92	0.76±0.84	2.180	0.031
Mouth sores	0.15±0.42	0.15±0.41	0.185	0.853
Change in food tastes	0.85±1.04	0.33±0.63	6.912	0.001
Weight gain	0.45±0.70	1.14±0.86	10.501	0.001
Weight loss	0.37±0.70	0.16±0.49	3.920	0.001
Constipation	0.53±0.86	0.68±0.90	1.998	0.046
Swelling of arms or legs	0.09±0.36	0.64±0.84	10.367	0.001
'I don't look like myself'	0.29±0.70	0.43±0.72	2.312	0.021
Changes in skin	0.42±0.76	0.62±0.78	2.908	0.004
Hair loss	0.38±0.79	0.21±0.50	2.997	0.003

## Figures

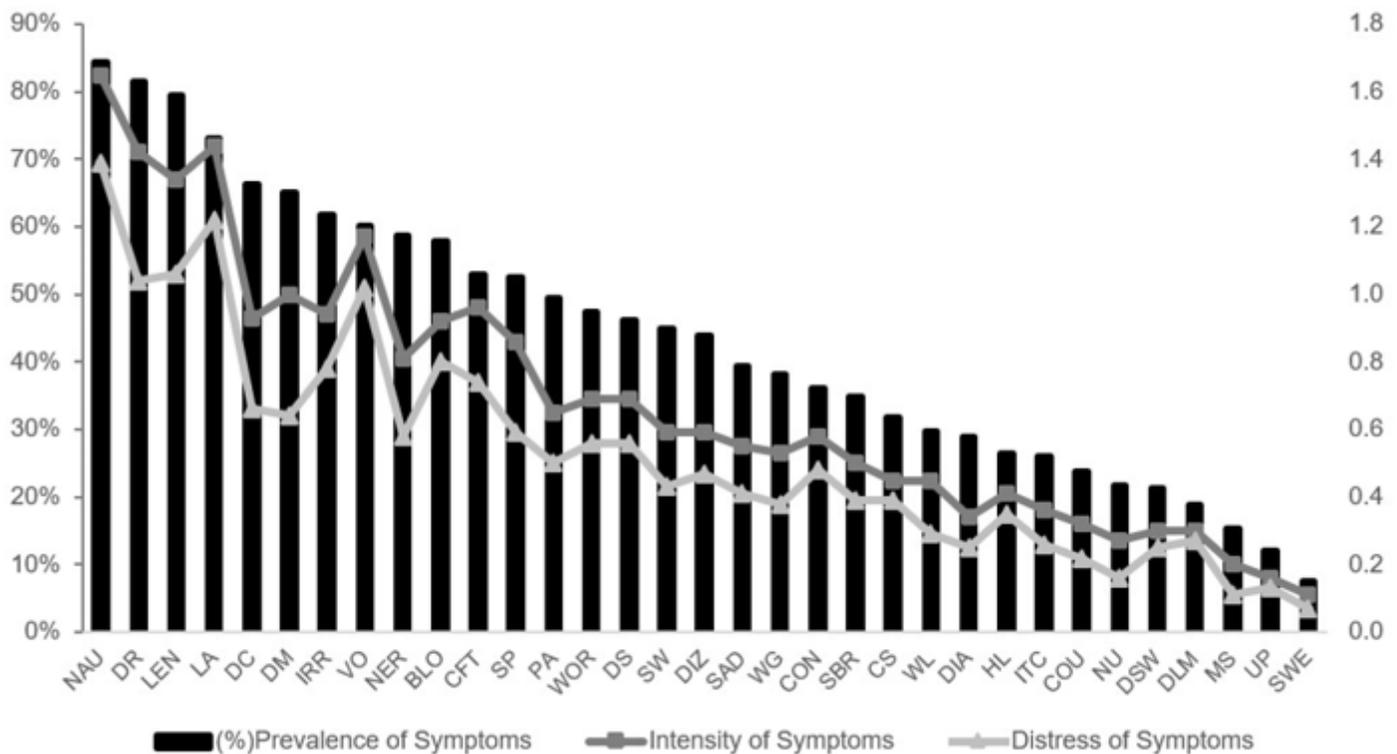
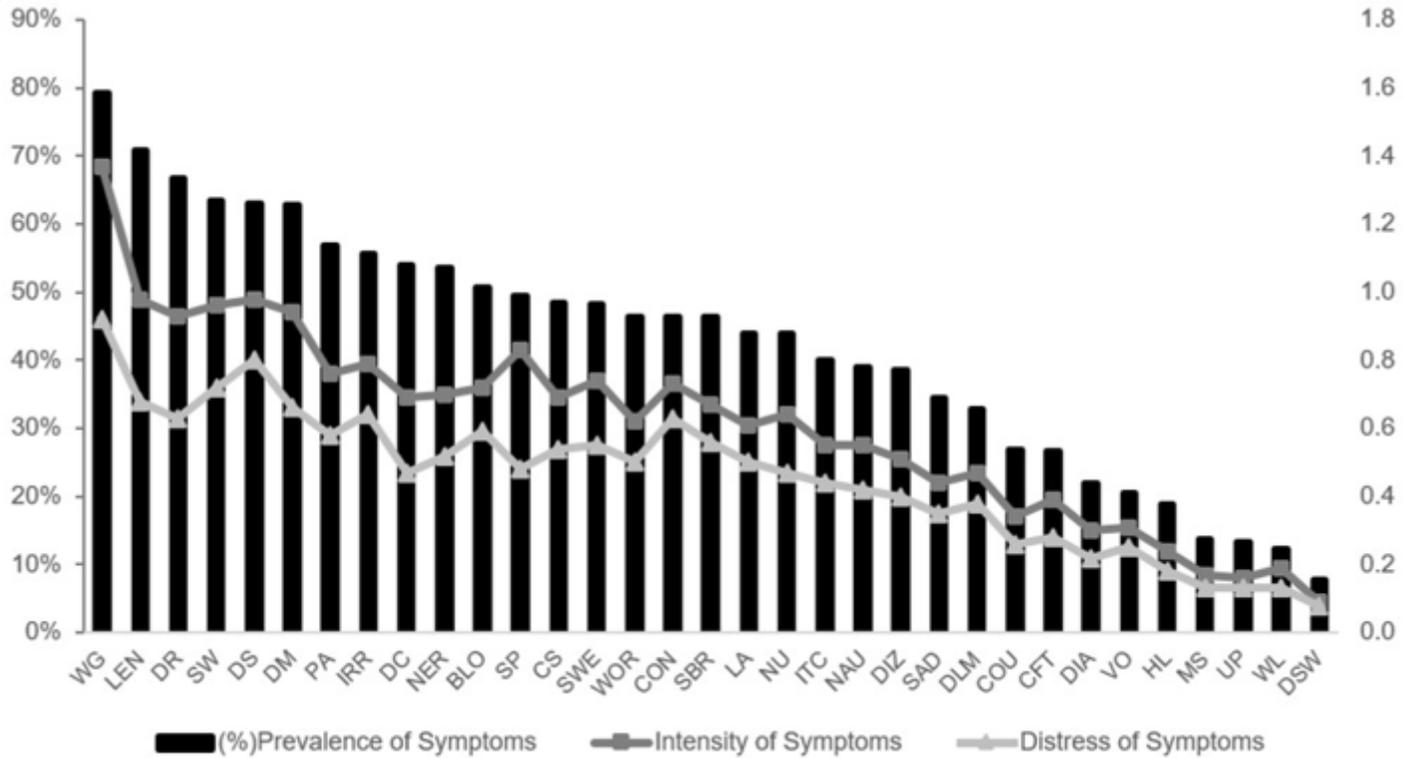


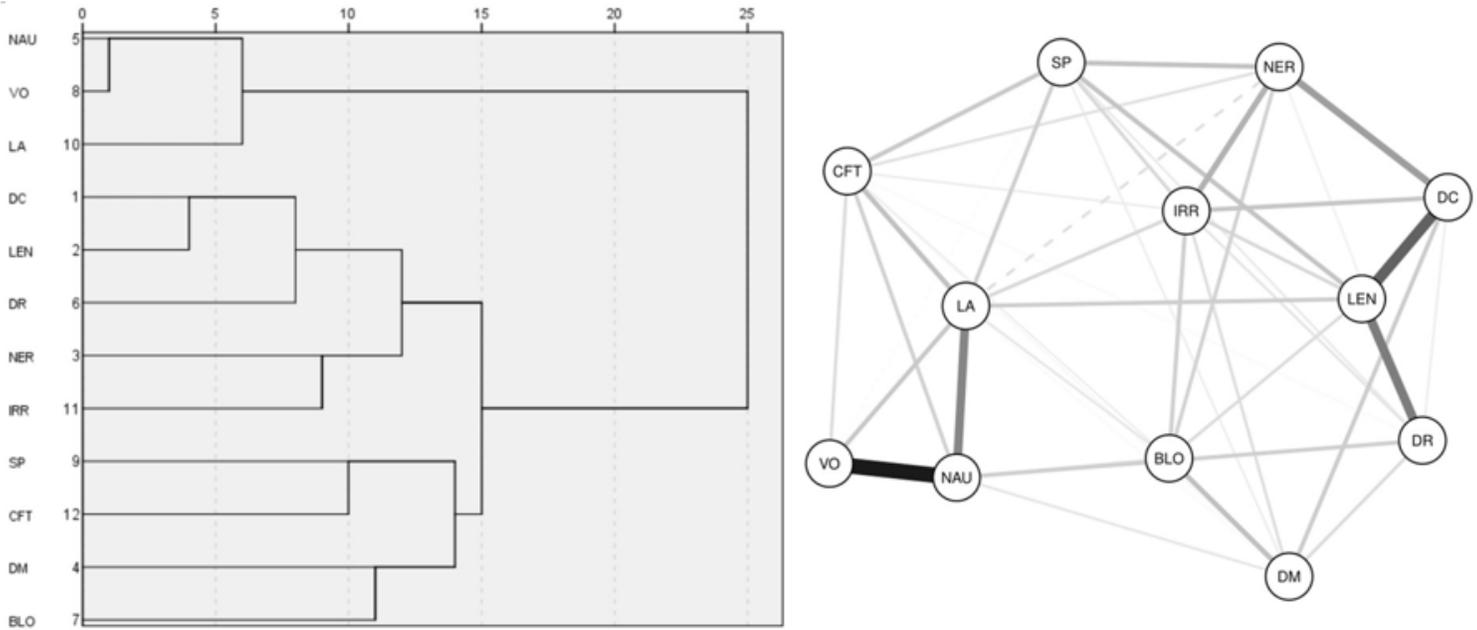
Figure 1

Prevalence, intensity and distress of symptoms in early pregnancy (n = 249) NAU, Nausea, DR, Feeling drowsy, LEN, Lack of energy, LA, Lack of appetite, DC, Difficulty concentrating, DM, Dry mouth, IRR, Feeling irritable, VO, Vomiting, NER, Feeling nervous, BLO, Feeling bloated, CFT, Change in food tastes, SP, Problems with sexual interest or activity, PA, Pain, WOR, Worrying, DS, Difficulty sleeping, SW, Sweats, DIZ, Dizziness, SAD, Feeling sad, WG, Weight gain, CON, Constipation, SBR, Shortness of breath, CS, Changes in skin, WL, Weight loss, DIA, Diarrhoea, HL, Hair loss, ITC, Itching, COU, Cough, NU, Numbness/tingling in hands/feet, DSW, Difficulty swallowing, DLM, 'I don't look like myself', MS, Mouth sores, UP, Problems with urination, SWE, Swelling of arms or legs.



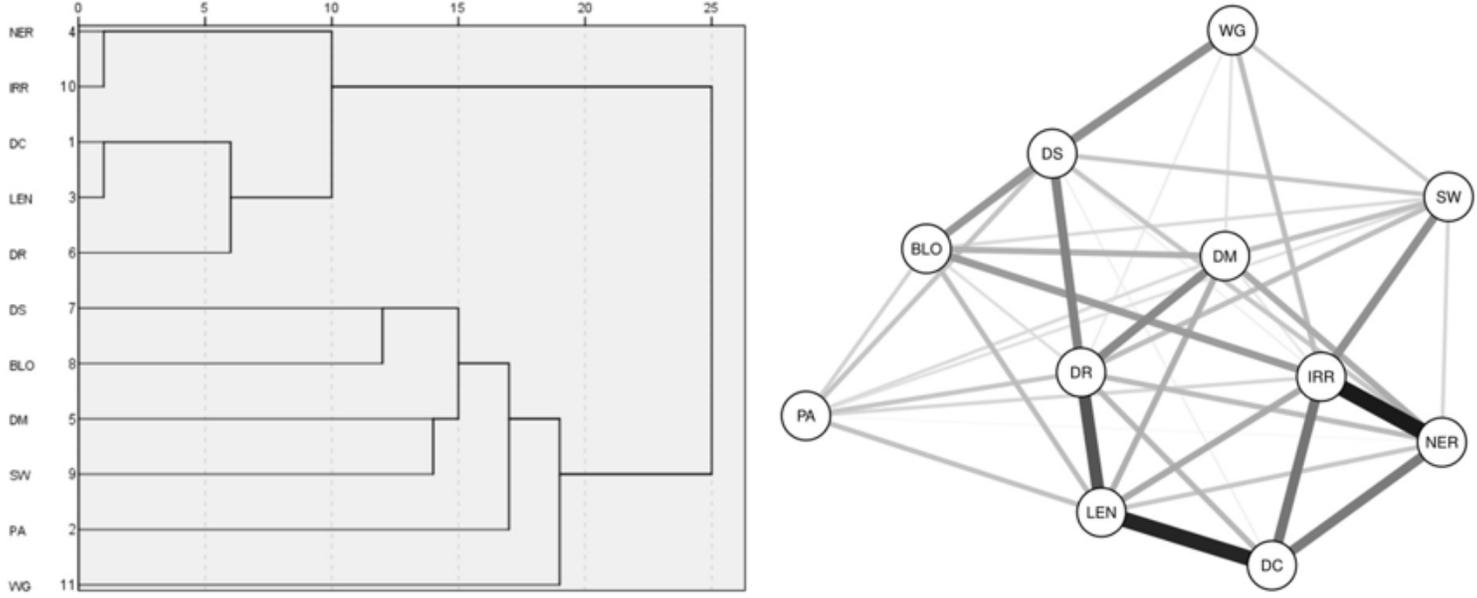
**Figure 2**

Prevalence, intensity and distress of symptoms in late pregnancy (n = 308) WG, Weight gain, LEN, Lack of energy, DR, Feeling drowsy, SW, Sweats, DS, Difficulty sleeping, DM, Dry mouth, PA, Pain, IRR, Feeling irritable, DC, Difficulty concentrating, NER, Feeling nervous, BLO, Feeling bloated, SP, Problems with sexual interest or activity, CS, Changes in skin, SWE, Swelling of arms or legs, WOR, Worrying, CON, Constipation, SBR, Shortness of breath, LA, Lack of appetite, NU, Numbness/tingling in hands/feet, ITC, Itching, NAU, Nausea, DIZ, Dizziness, SAD, Feeling sad, DLM, 'I don't look like myself', COU, Cough, CFT, Change in food tastes, DIA, Diarrhoea, VO, Vomiting, HL, Hair loss, MS, Mouth sores, UP, Problems with urination, WL, Weight loss, DSW, Difficulty swallowing.



**Figure 3**

Symptom clusters in early pregnancy (n = 249) Thicker and darker lines suggest stronger partial correlations. Solid lines represent positive partial correlations, dotted lines indicate negative partial correlations. NAU, Nausea, VO, Vomiting, LA, Lack of appetite, DC, Difficulty concentrating, LEN, Lack of energy, DR, Feeling drowsy, NER, Feeling nervous, IRR, Feeling irritable, SP, Problems with sexual interest or activity, CFT, Change in food tastes. DM, Dry mouth, BLO, Feeling bloated.



**Figure 4**

Symptom clusters in late pregnancy (n = 308) Thicker and darker lines suggest stronger partial correlations. Solid lines represent positive partial correlations, there were no negative partial correlations. NER, Feeling nervous, IRR, Feeling irritable, DC, Difficulty concentrating, LEN, Lack of energy, DR, Feeling

drowsy, DS, Difficulty sleeping, BLO, Feeling bloated, DM, Dry mouth, SW, Sweats,PA, Pain, WG, Weight gain.

## Supplementary Files

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