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, physiologic, and biochemical changes, but also psychological adaptation. 1 Under these circumstances, women may experience multiple psychosomatic symptoms (e.g., fatigue, nausea, vomiting, and anxiety), 2–4 and these symptoms not only affect pregnant women, but also have a potential negative impact on the offspring. For example, negative emotions could over-activate the hypothalamic–pituitary–adrenergic axis in pregnant women, leading to preterm delivery and low birth weight. 5 Consequently, it is necessary to attend to psychosomatic symptoms in pregnant women.

Hormonal and anatomical changes influence the duration and severity of symptoms, varying across different stages of pregnancy, and are particularly prominent during early and late pregnancy. 6,7 During early pregnancy, i.e., less than 13 weeks of pregnancy, women commonly experience nausea and vomiting to various degrees, which may lead to electrolyte imbalance, and impaired fetal development in severe cases. 8 Pregnant women are more likely to experience sharp emotional changes (e.g., unpleasant emotions triggered by transition between roles) and raise concerns about fetal growth and development. 9,10 In late pregnancy, i.e., more than
28 weeks, the functional load on the maternal organs gradually approaches its maximum, subsequently producing symptoms such as difficulty in breathing and sleep disorders.\(^{11}\) In addition, as the due date approaches, women become concerned about the outcomes of the delivery and the baby’s health.\(^{12}\) Faced with various problems, 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 emphasize early recognition and intervention.

Multiple symptoms of pregnancy commonly occur simultaneously and have complicated interactive relationships. For example, Andersson et al.\(^ {13}\) found that pregnant women with anxiety or depressive symptoms experienced more frequent nausea and vomiting. Considering the co-occurrence and interaction of symptoms, it may be feasible to manage the symptoms 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.\(^ {14}\) Current evidence has demonstrated that the treatments for one symptom may “cross over” the others within a cluster.\(^ {15}\) 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.\(^ {14}\)

At present, the majority of research on symptom clusters has focused on the areas of cancer and other chronic diseases. 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. 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, so as to diversify the research in this field.

## 2 Materials and Methods

This was a cross-sectional study conducted by consecutive sampling at the obstetrics clinics of two tertiary hospitals in Jinan City, Shandong Province, China. We recruited participants during their early and late pregnancy (<13 weeks and ≥28 weeks of pregnancy, respectively) from March 2019 to October 2019.

The sample size was determined using the formula, \(n = \frac{U^2 \times S^2}{d^2}\), 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 (\(\alpha = 0.05, S_1 = 7.239, S_2 = 7.362\) [where \(1\) indicates early pregnancy and \(2\) indicates late pregnancy]), it was necessary to include 202 and 209 people, respectively, at each stage of pregnancy. Besides, referring to the sample size requirements for network analysis model, there are at least three to five individuals per edge parameter. In the present study, the numbers of nodes of the network model in early and late pregnancy were, respectively, 12 and 11, as mentioned subsequently in the Results section, and the edge parameters were respectively 66 (12 \times 11/2) and 55 (11 \times 10/2), which required a minimum sample size of 198 and 165, correspondingly. We finally enrolled 249 and 308 people in each stage of pregnancy, which was sufficient for exploratory data-driven analyses.

Pregnant women aged 20 years or older were eligible to participate if they had no severe physical or mental impairments, were able to understand and complete the questionnaires, and were willing to participate. Women who had threatened abortion, intended to undergo surgical abortion, or those with fetal intrauterine growth restriction were excluded. All participants were informed about the purpose and procedure of the present 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.

Information on sociodemographic and clinical characteristics was collected from a questionnaire designed by the researchers, which included age, self-reported body mass index (calculated as weight in kilograms divided by the square of height in meters), education, employment status, having children (yes/no), abortion history, pregnancy complications, and gestational stages.

The Memorial Symptom Assessment Scale (MSAS) was developed by Portenoy et al.\(^ {16}\) to measure multidimensional information on a wide range of common symptoms over the past 7 days. The MSAS contains 32 entries, with the first 24 evaluating frequency, severity, and distress, while the remaining eight symptoms assess only severity and distress (as they are unlikely to change in frequency over the course of a week). Each symptom is rated on a four-point scale for frequency and severity, and on a five-point scale 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 “weight gain” commonly occurs during pregnancy according to clinical experience, we added the symptom “weight gain” to the investigation. The scale is currently widely used, 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.

All analyses were conducted using SPSS (version 25; IBM) and R statistical software (version 4.0.2). None of the variables violated normality (skewness >3 and kurtosis >10). Statistical description methods were presented using means and standard deviations (SDs)
for continuous variables and frequencies with percentages for categorical variables. Independent Student t test and \( \chi^2 \) test were performed to compare the differences in sociodemographic information and symptom scores at different stages of pregnancy.

The optimal number of symptom clusters was investigated in all three steps: Spearman correlation analysis, partial correlation networks, and hierarchical cluster analysis. First, 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 existed after controlling for other symptoms. We used the graphical least absolute shrinkage and selection operator to lower the probability of spurious edges and obtain a parsimonious network. Finally, hierarchical cluster analysis was used to cluster the symptoms, and the similarity between different clusters was assessed using Wald method with the Euclidean distance; a dendrogram was drawn up to provide visualization of the results of cluster analysis.

3 | RESULTS

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 ± 2.71 SD, and 308 were in late pregnancy, with an average gestational week of 34.07 ± 3.26 SD. The sociodemographic characteristics and differences in the different stages of the participants are shown in Table 1.

| Variables | Early pregnancy (n = 249) | Late pregnancy (n = 308) | \( t/\chi^2 \) | P value |
|-----------|--------------------------|--------------------------|----------------|---------|
| Age, year | 29.80 ± 3.93             | 30.08 ± 4.23             | 0.805          | 0.421   |
| BMI       | 21.66 ± 2.91             | 26.53 ± 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 |                          |                          | 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)                |                |         |

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

\(^a\)Data are represented as mean ± standard deviation or number (percentage).
lack of energy with difficulty in concentrating (0.591) and feeling drowsy (0.542), and for vomiting and lack of appetite (0.522) (Table S1), whereas 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) (Table S2).

Association networks based on partial correlation matrices in early pregnancy (Table S3) and late pregnancy (Table S4) were conducted to present description of the relationships among the symptoms, and hierarchical cluster analyses were performed in different stages, as illustrated by the dendrograms. Taking the above three methods into consideration, we finally described four symptom clusters in early pregnancy (Figure 3): pregnancy

FIGURE 1 Prevalence, intensity, and distress of symptoms in early pregnancy (n = 249). BLO, feeling bloated; CFT, change in food tastes; CON, constipation; COU, cough; CS, changes in skin; DC, difficulty concentrating; DIA, diarrhea; DIZ, dizziness; DLM, "I don't look like myself"; DM, dry mouth; DR, feeling drowsy; DS, difficulty sleeping; DSW, difficulty swallowing; HL, hair loss; IRR, feeling irritable; ITC, Itching; LA, lack of appetite; LEN, lack of energy; MS, mouth sores; NAU, nausea; NER, feeling nervous; NU, numbing/tingling in hands/feet; PA, pain; SAD, feeling sad; SBR, shortness of breath; SP, problems with sexual interest or activity; SW, sweats; SWE, swelling of arms or legs; UP, problems with urination; VO, vomiting; WG, weight gain; WL, weight loss; WOR, worrying.

FIGURE 2 Prevalence, intensity, and distress of symptoms in late pregnancy (n = 308). BLO, feeling bloated; CFT, change in food tastes; CON, constipation; COU, cough; CS, changes in skin; DC, difficulty concentrating; DIA, diarrhea; DIZ, Dizziness; DLM, "I don't look like myself"; DM, dry mouth; DR, feeling drowsy; DS, difficulty sleeping; DSW, difficulty swallowing; HL, hair loss; IRR, feeling irritable; ITC, Itching; LA, lack of appetite; LEN, lack of energy; MS, mouth sores; NAU, nausea; NER, feeling nervous; NU, numbing/tingling in hands/feet; PA, pain; SAD, feeling sad; SBR, shortness of breath; SP, problems with sexual interest or activity; SW, sweats; SWE, swelling of arms or legs; UP, problems with urination; VO, vomiting; WG, weight gain; WL, weight loss; WOR, worrying.
TABLE 2  Symptom scores and differences in different stages of pregnancy (n = 557).a

| Symptoms                                          | Early pregnancy (n = 249) | Late pregnancy (n = 308) | t    | P value |
|---------------------------------------------------|--------------------------|--------------------------|------|---------|
| 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   |
| Diarrhea                                          | 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 do not 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   |

aData are represented as mean ± standard deviation unless otherwise stated.

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 in late pregnancy, as shown in Figure 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.

4 | 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.
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 previous studies, indicating that these symptoms are commonly experienced during early pregnancy. This may be related to an increase in the levels of human chorionic gonadotropin, a decrease in gastric acid secretion, and prolonged gastric emptying time, which occur during early pregnancy. 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, lack of energy was a common symptom experienced in both stages, which is similar to the findings of Beebe et al. In addition, consistent with previous studies, weight gain and difficulty in falling asleep were common during late pregnancy. Pregnant women tend to gain weight due to local changes (e.g., fetal 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). In addition, as the pregnancy progresses, the uterus enlarges and gradually presses upward on the diaphragm, causing mechanical changes in the respiratory system, thereby increasing susceptibility to difficulty in breathing and affecting sleep patterns. Difficulty in falling asleep may be related to fetal movement and specific types of pain commonly experienced during late pregnancy (e.g., leg cramps, lumbopelvic pain or pressure,
and restless legs syndrome). Moreover, during the gestational period, women’s basal metabolic rate increases, 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 pregnant women. 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 underlying mechanism might be 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. The second symptom cluster 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 are prevalent among pregnant women. Fatigue during the gestational period is associated with the occurrence of emotional problems, which might aggravate fatigue in turn, resulting in a vicious circle. The third symptom cluster included problems with sexual interest or activity and change in food tastes. No other studies have replicated the symptom clusters, so we were not able to account for the association between the two symptoms. We had expected that the change in food taste might be related to the pregnancy reaction symptom cluster; however, this was not the case. Finally, the fourth cluster consisted of dry mouth and feeling bloated, which may be the result of gastrointestinal disorders induced by the alteration of hormones.

The first cluster determined during late pregnancy was the mood-fatigue symptom cluster, 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. 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 to adjust psychologically and physically until the birth. The second symptom cluster included difficulty in sleeping and feeling bloated. This gathering phenomenon might be attributed to a shared biologic mechanism underlying these symptoms. Specifically, in late pregnancy, due to the fluctuations in estrogen 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 difficulty in falling asleep. We also identified another symptom cluster consisting of dry mouth and sweating. One assumption was that the two symptoms are due to increased basal metabolic rate. Besides, two independent symptoms, pain and weight gain, were also observed. As these two symptoms were not incorporated into a specific cluster, this may, to some extent, account for their prominence and independence in late pregnancy, without being greatly associated with symptoms in other clusters, which needs to be explored in future investigations.

There are some limitations to the present study. First, the participants were enrolled from only two tertiary hospitals, and the representativeness and generalization of the results are somewhat restricted. Second, the available data were self-reported rather than being clinical diagnoses, which might have some bias. Future studies could consider personal interviews with clinical data capture to assess the studied symptoms. Third, there might be volunteer bias impacting our outcomes, which would be further evidenced in future research by using one-on-one interviews with clinical specialists. Fourth, the cross-sectional design limits the possibility of confirming changes in symptom evolution over time and associations between certain symptoms and adverse obstetric outcomes in pregnant women. Future studies could employ a longitudinal study design for further investigation. 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.

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; hence, symptom clusters might potentially be more powerful in shaping a pregnant woman’s functional status and quality of life. Awareness of existence of symptom clusters 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 biologic mechanisms of each symptom cluster’s effects to diversify our current understanding of this emerging field.

In conclusion, pregnant women experience multiple somatic symptoms during pregnancy, and the manifestation of symptoms varies at different gestational stages. The present study has provided new insights into the symptom clusters of pregnant women, 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. The 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.

**AUTHOR CONTRIBUTIONS**

Yunxue Zhang participated in participant recruitment and interpretation of data and prepared the draft manuscript. Xiaofang Xu participated in the study design and recruitment of participants and prepared the draft manuscript. Zhihu Xie, Yuanyuan Li, Di Zhao, and Gaorong Lv joined the study design and provided critical revisions for this manuscript. Ping Li designed the study, coordinated the data collection and analyses, and contributed to critical revisions for this manuscript. All authors approved the final version.
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CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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