Exploring the influence of advanced maternal age on adverse perinatal outcome in Southern Anhui province, China

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Abstract
Background : Elderly parturient women may face many pregnancy risks, which have serious consequences for perinatal and maternal. The objective of this study is to explore the association between advanced maternal age and adverse perinatal outcomes.

Methods : In this study, we used retrospective study to randomly selected 977 puerpera ( aged 35 years and older) as the research group and 977 puerpera (aged 20 to 34 years older) as the control group from Yijishan Hospital for the years 2017-2018. Univariate analysis was used to test the association between gestational age and adverse perinatal outcomes. Multiple logistic regression analysis was performed to examine the factors associated with adverse perinatal outcome. A nomogram was conducted to explore the risk probability between risk factors and adverse perinatal outcome.

Results : the AMA group (23.2%)exhibited a higher incidence of adverse perinatal outcome than the Non-AMA group(17.8%). Multiple logistic regression analysis showed among those who experienced multiple pregnancy, premature, hypertension, diabetes were more likely to induce adverse perinatal outcome. In this study, the risk of adverse perinatal outcome occurred in women aged 35 to 45 years with multiple pregnancy and preterm birth all was 42%-48%. The risk of adverse perinatal outcome in women aged 35 to 45 years with other variables respectively were 18%-19% (diabetes), 16%-18% (hypertension).The risk of adverse perinatal outcomes among women with AMA combined with these variables were higher than the counterpart.

Conclusions : AMA is the risk factor for adverse perinatal outcome among pregnancy women and the probability that these risk factors combined with age produced poor perinatal outcome were also found. Active intervention measures focusing on the complications and treatment in AMA should be taken to ensure the health of mother and baby.

Background
An increasing trend in the prevalence of pregnant women with advanced maternal age (AMA) has been witnessed worldwide since the 1980s\(^1\). In the United States, the proportion of pregnancies in advanced maternal age had raised nearly eight-fold between 1970 and 2006. Moreover, the percent
of childbirth decreased by 35% among women aged 20 to 24 years and increased by nearly 30% among women aged 35–39 years between 1980 and 2013\(^2\). Similarly, in Europe also increasing trend of delay in the average childbearing age had been observed from 29.3 years in 2003 to 29.8 years in 2009 and the proportion of pregnant women over 35 years of age had increased by 10.6% in 15 years from 1990 to 2004\(^3\). In China, the National Bureau of Statistic of China reported that the proportion of China’s fertile women (aged 35 to 49) in the total population was 11.82% at the end of 2016\(^4\). Furthermore, with the implementation of the universal two-child policy, the birth rate has been continually increasing, and the proportion of pregnant women with AMA has also been increasing significantly\(^5\). This state on fertility of AMA was bound to be several serious challenges to the individuals, the family, and also to the society, including higher health care burdens on social insurance and public services. Therefore, AMA represents an important concern that deserves immediate attention.

The International Federation of Gynecology and Obstetrics defined advanced maternal age as the age of the first parturient at no less than 35 years or the age of the multipara greater than or equal to 40 years at the time of delivery\(^6\). Studies have shown that aging is an important factor affecting fertility and pregnancy outcomes\(^7\)\(^8\)\(^9\)\(^{Prysak, 1995 \#12;}^{M.Jolly, 2000 \#11;}^{Carolan, 2013 \#10;}^{Carolan, 2013 \#10;}^{M.Jolly, 2000 \#11;}^{M.Jolly, 2000 \#11;}^{Carolan, 2013 \#10;}^{M.Jolly, 2000 \#11;}^{Qiujun, 2014 \#8}\). With an advancing maternal age, the fertility of women declines progressively, particularly after the age of 32, and advanced maternal age has also been associated with a decline in ovarian oocyte reserve and quality with increasing number of ovulatory cycles, poor oocyte quality is associated with an increased risk for aneuploidy and chromosomal anomalies in the fetus\(^{10,11}\)\(^{Maomei, 2015 \#9;}^{Qiujun, 2014 \#8;}^{Zheng, 2016 \#1}\). Evidently, advanced maternal age leads to various adverse pregnancy outcomes, including for perinatal babies.

To our best knowledge, there are a lot of studies exploring the association of AMA with many pregnancy outcomes\(^{12,13}\)\(^{14}\). Those studies shown that pregnant women with AMA were at
increased risk of adverse pregnancy outcomes compared with non-AMA, including difficult labor, postpartum fever, postpartum anemia and maternal death and severe maternal outcome\cite{15,16}. Furthermore, some other studies proved that AMA could induce some serious pregnancy complications, such as pregnancy hypertension, gestational diabetes, placenta previa, placental abruption\cite{11,17}. However, the majority of these studies predominantly focused on the association of AMA with many pregnancy outcomes and pregnancy complications. There is a paucity of studies on the association between advanced maternal age and adverse perinatal outcome in China, but there is also lack of the research to test the risk degree of advanced maternal age and adverse perinatal outcome. Therefore, to remedy this situation, the present study analyzed the adverse perinatal outcomes of pregnant women in southern Anhui province, and explored the influence of advanced age pregnancy on perinatal outcomes. To do so, we have following specific objectives. First we will identify the prevalence of the adverse perinatal outcomes among pregnant women with AMA. Second, we will compare the perinatal outcome across different groups of the participants. Finally, we will use logistic regression model and nomogram plot to explore the association between pregnancy age and perinatal outcomes among the pregnancy women in southern Anhui province China. This study will provide evidences for the maternal and child health promotion in China.

Methods

Subjects

In this study, retrospective study was used to randomly select subjects who hospitalized during January 2017 to January 2018 according to Hospitalization Numbers. This study was conducted in Yijishan Hospital, which is the biggested hospital in Southern Anhui province, China\cite{18}. In this study, the inclusion criteria of research subjects were shown as: 1) aged 20 and above; 2) women giving birth for the first time under 40 years old; 3) more than 28 weeks of gestational age; 4) data on pregnancy outcomes are complete, Exclusion criteria: patients with severe complications during pregnancy, autoimmune diseases, heart disease, chronic diseases before pregnancy and familial genetic diseases were excluded. Finally, total of 1954 pregnancy women (average age is 32.92±5.32; the gestational age is 37.1±3.1) were selected, including 977 puerperas aged 35 years and above (as AMA group),
977 puerperas aged between 20 and 34 years (as Non-AMA group). A total of 1019 neonates were born to the mother of AMA group (with an average maternal age of 37 years, ranging from 35 to 45 years), 1,024 babies were born in the Non-AMA group (the average age of 29 years, ranging from 20 to 34 years). Among them, the AMA group was the research group and the non-AMA group was the control group.

**Data collection**

We used retrospective study to collected the data from Medical record management system for the years 2017–2018 of Yijishan Hospital in Anhui province, China. To ensure data quality, collected data were carefully checked by quality supervisors.

**Measures**

**Pregnancy outcomes and complications**

Pregnancy outcomes (low birth weight infant, macrosomia, perinatal death and fetal anomaly) and pregnancy complications (diabetes, hypertension, preterm birth, scarred uterus, fibroid, placenta previa, cord around neck, postpartum hemorrhage, oligoamnios / polyhydramnios, malposition and abnormal labor) in pregnant women are diagnosed and measured by doctors and nurses.

**Adverse perinatal outcome**

For adverse perinatal outcome, we assessed four variables including low birth weight infant, macrosomia, perinatal death (fetal death, stillbirth, neonatal death), and fetal anomaly. If the mother gave birth to a newborn with at least one of these outcomes, then was considered to exhibit an adverse perinatal outcome.

**Nomogram**

Its basic principle is established on the basis of the regression model, by calculating the contribution of the factors affecting the results variables, giving the influence score of each factors, then adding up the scores to get the total score. Finally, the function conversion relationship between the total score and the probability of the outcome event is presented. Thus, the predicted value of the individual outcome event can be calculated.

**Statistical analysis**
All statistical analyses were performed using SPSS 22.0 and R3.5.1. Firstly, the Chi-square test and T-test were performed to determine the association between gestational age and adverse perinatal outcomes. Secondly, univariate analysis by use correlation test to evaluate the correlation between adverse perinatal outcome and pregnancy complications. Thirdly, two multivariate logistic regression models were performed to determine the association of adverse perinatal outcome and some variables selected through the univariate analysis. Finally, the identified factors associated with adverse perinatal outcome were included in nomogram. The reported CIs were calculated at the 95% level and statistical significance was set at the 5% level.

Results
See from table1 the AMA group exhibited a higher incidence of low birth weight infant, macrosomia, perinatal death, fetal anomaly and adverse outcome than the Non-AMA group. However, macrosomia and adverse perinatal outcome were statistically significantly associated with AMA ($p<0.05$). There were no significant differences were observed in other factors. As represented in Table2, there were statistical significant correlation between cesarean, diabetes, multiple pregnancy, hypertension, malposition, preterm birth and adverse perinatal outcome ($p<0.05$). Other factors were not significantly associated with adverse perinatal outcome.

We employed two multivariate logistic regression models to examine the associations between some variables and adverse perinatal outcome. Model 1(including variables except age) showed that the variables of preterm birth ($p < 0.05$), diabetes ($p < 0.05$), hypertension ($p < 0.05$), multiple pregnancy ($p < 0.05$) were significantly associated with adverse perinatal outcome. When we included the variable of age (See Model 2), these variables still had significant association with adverse perinatal outcome, while the value of OR were mediated by age (See the Table 2).

A nomogram plot was used to joint diagnosis or prediction of adverse perinatal outcome progression by multiple indicators among the pregancy women. The variables that showed statistically significant association to adverse perinatal outcome were included in the nomogram. Figure 3 illustrated the probability of risk association between the various risk factors and adverse perinatal outcome. In this study, the risk of developing adverse perinatal outcome among women aged 35 to 45 years with
multiple births, preterm birth was 42%-48% higher than among women aged 20–34 (36%-41%). The risk of developing adverse perinatal outcomes in AMA were 18%-19% for diabetics (higher than 14%-17% among non-AMA) and 16%-18% for hypertension (higher than 12.5%-15% among women aged 20–34). The risk of adverse perinatal outcome was significantly higher when several complications were recorded at the time of delivery, for instance, the risk of adverse perinatal outcomes was no less than 85 percent among women of AMA with multiple pregnancy and preterm birth.

**Discussion**

The present study showed a significantly higher prevalence of adverse perinatal outcome among pregnant women who gave birth at age over 35 (23.2%) compared with the women aged 20–35 years (17.8%). Studies at home and abroad have reached similar conclusions[19,20]. Consistent with previous studies, the present study also indicated that advanced gestational age had a significant influence on macrosomia. A clinical study of 320 women showed that both multipara and parturient women with AMA are risk factors for the delivery of macrosomia[21]. Studies contributed to that delayed childbearing leads to the risk of developing obesity when pregnant women enter middle age due to excessive nutritional requirement during pregnancy, which leads to macrosomia[19] [22] [13] {Khalil A, 2013 #20; Zheng, 2016 #1; Gilbert, 1999 #47}. Therefore, the need for weight monitoring and blood glucose control during pregnancy must be strengthened. Moreover, women who gave birth at advanced age significantly experience perinatal mortality, which is attributed to the elderly parturient women's uterine fertility decline, dystocia, abortion and pregnancy predisposed to a variety of complications, including, gestational hypertension, diabetes and fetal distress[23]. Consequently, the pregnancy monitoring of pregnant women with AMA becomes crucial. However, low birth weight and fetal anomaly were not found to be statistically significant with the age in this study. This may be related to the AMA paying more attention to nutrition and the continuous improvement of prenatal screening and prenatal diagnosis. Apparently, we found that pregnancy at an advanced age combined with hypertension, diabetes, preterm delivery, and multiple pregnancy were the significant risk factors for adverse perinatal
outcome. And present study also indicated that the risk of poor perinatal outcome among women with AMA combined with diabetes was higher than the counterpart. Studies at home and abroad have also indicated that women with AMA are more likely to develop diabetes than non-AMA pregnant women [24] and those with diabetes may become even worse pregnancy outcomes[25,26]. A large number of studies have confirmed that the failure to strengthen the control of blood glucose during pregnancy would increase the risk of maternal and infant complications[13,14], including concurrent infection, macrosomia, dystocia, premature birth, malformation, neonatal respiratory distress syndrome, and even fetal death in utero[27,28]. Similarly, with the advanced maternal age, the risk for pregnancy-related complication of hypertension is considerably increased and is more prominent in women with AMA[29] [30] [31]. Moreover, pregnant women with AMA and hypertension may substantially experience the risk of low birth weight, fetal growth and development restriction, neonatal death and neonatal congenital malformation[20,32] [33]. Accumulating studies have shown that pregnancy with a complication of hypertension may be one of the major causes of uterine fetal death[33]. Our findings also indicated that women with AMA (aged35–45) complicated with gestational diabetes and hypertension would significantly increase the risk of developing adverse perinatal outcome compared to AMA with one disease, others studies also confirmed this fact[25,34]. The present study also revealed that AMA with multiple pregnancy and preterm birth had 42%-48% chance occurred adverse perinatal outcome, which was higher than non-AMA group. A study on twin pregnancy over a 20-year period reported that twin pregnancy was more susceptible to experience asphyxia, perinatal death, low birth weight, and premature birth, and premature rupture of membranes than single pregnancies[35]. Furthermore, women with AMA exhibited severe complications and higher risk, which contributed to a greater risk of adverse perinatal outcomes in twin pregnancy[36,37]. While premature delivery can lead to severe consequences including neonatal pneumonia, immature development of various organs and systems, extremely low birth weight, and neonatal and perinatal morbidity and mortality[38]. Therefore, the need to reinforce health of twin pregnancy and premature infants
through improvement of the quality of obstetric care and attention to the pregnant woman with AMA to modify the perinatal outcomes related with a twin pregnancy and premature infants.

Using logistics regression analysis and nomogram, this study revealed a significant influence of pregnancy age and various risk factors on adverse perinatal outcome. Furthermore, all risk factors combined with advanced age significantly increased the risk of adverse perinatal outcomes. Thus, these findings imply the policy makers to develop interventions for early detection of the complications and timely treatment (through medical genetic counseling, prenatal screening and prenatal diagnosis, and neonatal disease screening), particularly for those belong to high-risk groups (advanced maternal age), for a long-term risk management and critical care to substantially decrease the prevalence of adverse perinatal outcomes among women with AMA in China.

Several limitations of the study are also worth mentioning. First, the data and analyses were derived based on retrospective study, which tend to produce some bias, including selected bias. This will inevitably affect the accuracy of the research results. Second, the subjects in this study did not include the age group of over 45. This will limit the conclusions of this study as a generalization to very advanced age group of over 45 years. Despite these limitations, our study has notable strengths. Our estimations were based on large sample size, from a single medical center, thereby decreasing the likelihood of incorrect data interpretation.

Conclusions

In summary, the results of the present study revealed AMA is the risk factors for adverse perinatal outcome among pregnancy women and the probability that risk factors when combined with advanced maternal age, contributed substantially to poor perinatal outcome. These findings implied for a need to develop preventative strategies for early detection of the complications and timely treatment, particularly for those belonging to high-risk groups (advanced maternal age), for a long-term risk management and critical care. Thus, a comprehensive and systematic assessment of all potential complications among pregnant women with advanced age is needed to significantly decrease the prevalence of adverse perinatal outcome among pregnant women with AMA in China.

Abbreviations
Declarations

Ethics approval and consent to participate

This study was exempted from ethical review by the regional ethics committee of Yi Jishan hospital (Wuhu, China), and all patients were discharged without informed consent and informed consent was not obtained because of all patients had been discharged.

Ethics review application

The subject of this study is “Analysis of Pregnancy Outcomes in advanced maternal age with Perinatal Births”. The data content is mainly medical records of inpatients, and does not include blood, tissues, specimens, etc., and special applications are not subject to ethical review.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Dandan Ge conceived the idea. Dandan Ge, Xia Yong, Si Mingshu participated in the statistical analysis and interpretation of the results. Dandan Ge drafted the manuscript. All authors read and approved the final manuscript.

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Tables
Table 1 Comparison of perinatal outcomes between AMA group and Non-AMA group
| Group         | Weight x±s, g | Low birth weight infant | Macrosomia     | Perinatal death | Fetal anomaly |
|---------------|---------------|-------------------------|----------------|-----------------|---------------|
| AMA group     | 3202±551.6    | 11011.3%                | 11011.3%       | 6(0.6%)         | 101.0%        |
| Non-AMA group | 3174±556.5    | 949.6%                  | 75(7.7%)       | 10.1%           | 40.4%         |
| \( t/ c^2 \) value | 295.6          | 1.401                   | 10.57          | 3.975           | 2.59          |
| \( P \)         | 0.412         | 0.237                   | 0.007          | 0.046           | 0.108         |

a: APO is Adverse Perinatal outcome

b:AMA is advanced maternal age

Table 2 Correlations among the complication of pregnancy, pregnant syndrome and Adverse Perinatal outcome

| Group                  | APO               | Non-APO            | \( R^2 \) |
|------------------------|-------------------|--------------------|-----------|
| Scarred uterus         | 14518.5%          | 63781.5%           | -0.040    |
| Caesarean              | 24219.1%          | 102380.9%          | -0.047    |
| Fibroid                | 2922.7%           | 9977.3%            | 0.013     |
| Diabetes               | 3727.2%           | 9972.8%            | 0.045     |
| Multiple pregnancy     | 5157.3%           | 3842.7%            | 0.199     |
| Placenta previa        | 1823.7%           | 5876.3%            | 0.016     |
| Cord around neck       | 2726.2%           | 7673.8%            | 0.033     |
| Postpartum hemorrhage  | 314.3%            | 1885.7%            | -0.016    |
| Oligoamnios / polyhydramnios | 1514.3% | 9085.7% | -0.037 |
| Hypertension           | 10831.2%          | 23868.8%           | 0.123     |
| Test-tube baby         | 28(23.9%)         | 89(76.1%)          | 0.021     |
| Malposition            | 23.4%             | 5796.6%            | 0.199     |
| Abnormal labor         | 1013.9%           | 6286.1%            | -0.032    |
| Preterm birth          | 19152%            | 17648%             | 0.375     |
Table 3 Multivariate logistic regression models for factors associated with adverse perinatal outcome among the pregnancy women

| Observations                | Model1 |           |           | Model |
|-----------------------------|--------|-----------|-----------|-------|
|                             | OR     | 95% CI    | P         | OR    | 95% CI |
| Caesarean (yes vs. no)      | 0.870  | 0.68      | 1.12      | 0.280 | 0.897  |
| Preterm birth (yes vs. no)  | 7.432  | 5.71      | 9.67      | 0.000 | 7.820  |
| Diabetes (yes vs. no)       | 1.231  | 0.79      | 1.93      | 0.013 | 1.244  |
| Hypertension (yes vs. no)   | 2.371  | 1.77      | 3.17      | 0.000 | 2.551  |
| Malposition (yes vs. no)    | 0.157  | 0.04      | 0.68      | 0.365 | 0.151  |
| Mutiple pregnancy (yes vs. no) | 7.584 | 4.71      | 12.21     | 0.000 | 7.623  |
| Age                         | -      | -         | -         | 1.387 | 1.05   |
Figure 1

The risk probability between the factors and adverse perinatal outcome