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CLINICAL ARTICLE

Prenatal diagnostic testing among women referred for advanced maternal age in Beijing, 2001–2012

Jingmei Ma, Pan Hong, Jie Fu, Li Yu, Huixia Yang *

Department of Obstetrics and Gynecology, Cytogenetic Laboratory, Peking University First Hospital, Beijing, China

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ABSTRACT

Objective: To determine the proportion of women with advanced maternal age (AMA) undergoing amniocentesis and assess the recommended indication of 35 years or older in China. *Methods:* Data were retrospectively evaluated from 9641 patients who underwent diagnostic prenatal amniocentesis in Beijing, China, between January 2001 and December 2012. Maternal age, indication for testing, and karyotype data were collected. Patients referred for AMA were stratified in 2 ways: 35–37 years, 38–40 years, and 41 years or older; and indication of AMA alone or combined with other screening. Outcomes and safety performance were compared among the groups. *Results:* From 2001 to 2012, the annual rate of amniocentesis and the proportion of AMA-related indications increased ($P < 0.01$). Overall, 82 abnormalities were detected. In the AMA group, the spontaneous abortion rate was 0.5% (22/4748). The positive predictive value (PPV) of AMA alone was 0.5% for women aged 35–37 years. Only among women aged 41 years or older was the PPV of AMA alone better than that of AMA plus other indications (2.3% vs 1.5%, respectively). *Conclusion:* The PPV of 35 years or older did not offset the risk of spontaneous abortion. AMA alone should not be used as an indication for amniocentesis especially among women aged 35–40 years.

1. Introduction

Prenatal diagnosis for Down syndrome or other significant chromosomal abnormalities in a high-risk population via an invasive procedure (amniocentesis or chorionic villus sampling) [1] has gradually been implemented in countries worldwide including China. In recent decades, the indications for referral have been changing mainly from advanced maternal age (AMA) to high-risk women identified by screening. To avoid invasive procedures that can induce spontaneous abortion, many approaches to risk assessment, such as AMA and serum plus nuchal translucency screening, are providing the opportunity to identify those women whose fetuses are unlikely to be affected by a chromosomal disorder, and thereby reduce the number of unnecessary invasive procedures performed.

In 2007, the American College of Obstetricians and Gynecologists [2] recommended that a "maternal age of 35 years alone should no longer be used as a threshold to determine who is offered screening versus who is offered invasive testing," on the basis of advances in prenatal screening, such as maternal serum inhibin A measurements, nuchal translucency measurements, and use of second-trimester ultrasonography to identify abnormalities or markers associated with aneuploidy.

For low-income countries such as China or India with a huge population, and limited resources, AMA and mid-trimester screening have been the first choice for prenatal diagnosis for a long time. Regular medical care visits during pregnancy, including accurate nuchal translucency measurements, remain impractical. In this context, careful reconsideration and research on an accurate effective definition of AMA in a representative population are needed for overall prenatal healthcare. The medical and safety performance of the strategy should be carefully evaluated on the basis of patient data.

In China, the official guideline of the Ministry of Health of China, entitled "The technical standards of prenatal screening and diagnosis for fetal common chromosomal abnormalities and neural tube defects," was issued in December 2010 [3]. Similar to other low-income countries, China's most popular and available screening strategy remains AMA and second-trimester serum triple screening, and without satisfactory quality control for early nuchal translucency measurement, this strategy may remain nationwide for some time.

The national population-based register systems for screening, diagnosis, and follow-up period in China need improvement. As a result, the current recommendation was based on evidence from North America and European countries [4–6]. Furthermore, the definition of AMA is the same as that of the old ACOG committee [4]. In other countries such as France, by contrast, "AMA" is defined as 38 years and older [5], whereas The Netherlands uses "36 years" as a cutoff for prenatal diagnosis [6]. Meanwhile, the actual practice of prenatal diagnosis might

* Corresponding author at: Xianmen Street No. 1, Xicheng District, Peking University First Hospital, Beijing 100034, China. Tel.: +86 13601165721; fax: +86 1066518086.
E-mail address: yanghuixia@bjmu.edu.cn (H. Yang).

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differ considerably from the published guideline. Some women with AMA might choose prenatal diagnosis directly, whereas others might choose serum or ultrasound screening first, and undergo an invasive procedure only when necessary in order to avoid the risk of procedure-related spontaneous abortion. However, data from the Chinese population remain insufficient for both obstetricians and pregnant women, and defining a more appropriate and specific indication for invasive diagnosis in China is essential.

Although China's population is more than 1.3 billion, it is unevenly distributed. Beijing is the capital of China, with a growing population of nearly 20 million. Peking University First Hospital is 1 of 5 referral centers for prenatal diagnosis in Beijing, and carries out one-fifth of amniocentesis testing in total among patients referred from different grades of clinic.

The main aim of the present study was to analyze the medical and safety performance of amniocentesis carried out in a single cytogenetic laboratory of a hospital in order to assess the current Chinese guideline for the indication of AMA. The following issues were addressed: first, the trend in the proportion of AMA in prenatal diagnosis; second, the value of "AMA as 35 years old and older" as the only indication, and its medical performance and procedure-related risk of spontaneous abortion; and third, whether or not the current definition of AMA for amniocentesis indication is appropriative.

2. Materials and methods

The present study retrospectively assessed data from pregnant women who were referred to Peking University First Hospital, Beijing, China, for amniocentesis between January 1, 2001, and December 31, 2012. The study was approved by the ethics committee of Peking University First Hospital. Because it was a retrospective analysis of the clinical database with no intervention, informed consent from the women was not required.

After introduction of the maternal serum screening method in China in 1998, the laboratory began to provide the second-trimester serum screening in 2000. Since 2006, as 1 of the 5 authorized diagnostic centers in Beijing, the laboratory began to provide the services of prenatal screening and diagnosis to patients from more than 10 other hospitals (satellite centers that cover one-fifth of all pregnancies in Beijing). From 2011, the amniocentesis indications for prenatal cytogenetic diagnosis have strictly followed the Chinese guideline, which recommends that the amniocentesis should be offered to "all AMA women aged 35 years and older at the expected date of delivery" and "younger woman whose maternal serum screening test result is positive." Other indications include "abnormal fetal structure identified by ultrasound," "history of previous fetus with aneuploidy," "either parent of the fetus with chromosomal abnormality," and other investigations requested by the physicians involving "anxiety" or "need to identify a single-gene inheritance disease."

The laboratory database was used to evaluate and track the trend in the proportion of women with AMA as the diagnostic indication over the study period. Data recorded between January 1, 2011, and December 31, 2012, after implementation of the official guideline, were used to further analyze the trend in AMA as the only indication for amniocentesis.

For all women, conventional cytogenetic analysis of amniotic fluid cells was performed. Karyotype results were obtained for more than 99% of samples, of which over 80% were followed-up to identify any cases of misdiagnosis.

The indication for prenatal diagnosis was entered into the database from test requisition forms. For the analysis, the indications were stratified into the following groups: AMA alone, AMA plus serum or ultrasound screening; and AMA plus ultrasound abnormalities. Women with more than 1 reason for referral were classified according to the main clinical indication for the prenatal invasive procedure in the order: ultrasound abnormalities, followed by positive prenatal serum screening. In addition, to evaluate the best cut-off of maternal age at the expected date of delivery, the AMA population was stratified into the following 3 groups: 35 to less than 38 years; 38 to less than 41 years; and 41 years or older.

Chromosome abnormalities included aneuploidy, all cytogenetically unbalanced chromosome abnormalities (including autosomal and sex chromosomal abnormalities, mosaicism, and marker chromosome), and de novo cytogenetically balanced chromosome rearrangements. For the most common aneuploidies and other cytogenetically unbalanced abnormalities, different groups of AMA were used to compare the medical performance in terms of positive predictive value (PPV) and number of amniocenteses needed to diagnose 1 case of chromosome abnormality.

All analyses were conducted with SPSS version 13.0 (IBM, Armonk, NY, USA). Linear regression models were used to evaluate the trend in the proportion of AMA categories and AMA-related indications. Frequencies of outcomes were compared between the groups by χ^2 test. A P value of less than 0.05 was considered to be statistically significant.

3. Results

During the study period, data from 10 180 pregnancies were analyzed. In total, 539 cases were excluded from the analysis owing to unavailable karyotyping (n = 31), indication of molecular genetics history (n = 402), and family history of chromosome abnormalities (n = 206). As a result, data from 9641 pregnancies were assessed.

The annual rate of amniocentesis increased from 83 in 2001 to 2008 in 2012. To assess this pattern of growth, data from the "Beijing Public Health Information Center" [7] were used as a baseline. Among the 9641 tests carried out at Peking University First Hospital Cytogenetic Laboratory from 2001 to 2012, the number of those with an indication of AMA showed the same pattern of increase (Fig. 1).

To analyze further the trend in maternal age, the mean age of the women referred for AMA in each year was compared (Fig. 2). The results showed that the age of the AMA group has been increasing since 2003, and especially since 2010, from 36.4 to 38.0 years ($P < 0.01$). In terms of the indication for amniocentesis, the proportion of women referred for AMA reduced by half from 2001 to 2003 (from 67.5% to 34.4%), and then increased gradually and stayed at approximately 50% from 2005 until 2012.

Since implementation of the official guideline in 2011, among women in the AMA group, more than 80% of the indications were AMA alone, compared with AMA plus another indication such as serum screening or ultrasound abnormalities (Fig. 3).

Among the 4748 pregnancies among women with AMA, 82 (1.7%) abnormal karyotypes were detected. Forty-three of these abnormalities (52.4%) were trisomy 21, accounting for 0.9% of the AMA population. The other chromosomal abnormalities included trisomy 18, trisomy 13, 47,XXY, 47,XXX, 45,X, 45X/46,XY, and 46,X,i(Xp), in addition to mosaicism of 47,XN, +marker, 47,XN, +9.

Table 1 shows the performance of different AMA-related indications for Down syndrome and other chromosome abnormalities in terms of PPV and the number of amniocenteses needed to diagnose 1 case of chromosome abnormalities. For the indication of AMA alone, which accounted for most of the study group (nearly 80%), the PPV was 0.8% for Down syndrome and 1.5% for all abnormalities. When AMA was combined with other methods, the PPV for Down syndrome and all abnormalities increased by approximately 40% (1.1%) and 30% (2.0%), respectively, for screening; and by more than 6-fold (5.9% and 11.8%, respectively) for ultrasound. The number of amniocenteses needed to diagnose 1 case of Down syndrome was also significantly reduced from 129.5 to 17.0 for AMA combined with ultrasound.

Medical performance was also compared among different age groups (Table 2). For the youngest age group (≥35 to <38 years), the PPV and number of amniocenteses needed to diagnose 1 case of