Research Square

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Predictive value of aberrant right subclavian artery for fetal Chromosome aneuploidy in women of advanced maternal age

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Research article

Keywords: Ultrasonography, Fetus, Aberrant right subclavian artery, Chromosomal abnormalities, Advanced maternal age

Posted Date: November 19th, 2020

DOI: https://doi.org/10.21203/rs.2.15296/v2

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Version of Record: A version of this preprint was published on February 18th, 2021. See the published version at https://doi.org/10.1186/s12884-021-03626-7.

Abstract

Background: In entire population, aberrant right subclavian artery (ARSA) was in closely association with chromosomal abnormalities. The risk of fetal chromosomal abnormalities increased with the maternal age exponentially. This situation in advanced maternal age (AMA)group is uncertain. This study aimed to establish the incidence of ARSA in Chinese AMA and non-AMA women and to determine the frequency of aneuploidy among AMA and non-AMA women with ARSA.

Methods: The retrospective study included 13,690 singleton pregnancies which were divided into AMA and non-AMA groups. Integrated obstetric ultrasonic screening, biochemical screening, noninvasive prenatal screening and fetal karyotype analysis were analyzed.

Results: 1. The overall incidence of ARSA was 0.69 % with no difference in both age groups. 2. The incidence rate of chromosomal abnormalities in AMA group (37 / 2,860) was much higher than that in non-AMA group. The risk of chromosomal abnormalities significantly increased with both ARSA detected and additional ultrasound findings. 3. With combined ARSA detected in AMA ones, the lilelihood of the incidence of chromosomal abnormalities increased. 4. Additionally, a case with chimeric (45X / 46XX) was found with isolated ARSA in AMA pregnancy.

Conclusion: There is a high prevalence of chromosomal abnormalities in AMA fetuses. ARSA would increase the risk of chromosomal abnormalities in both age groups, especially combined ARSA. Moreover, when combined ARSA is found in AMA ones, it confers a high likelihood of chromosomal abnormalities.

Background

Advanced maternal age (AMA) is defined as a woman who conceiving and delivering at the age of 35 years or older [1-4]. According to data from Office for National Statistics, in 2013, 20% of births in England and Wales were to women aged 35 years or over and the average age of mothers has dramatically increased with years [1]. In China, the proportion of AMA pregnant women increased gradually from 10.1% in 2011 to 20.5% in 2016, and it would grow to new highs especially after “ Two-child Policy ” carried out [2].

As we known, maternal age was in close association with a range of pregnancy complications, such as preeclampsia, stillbirth and fetal anomalies [1-3]. The risk of fetal chromosomal abnormalities increased with the maternal age exponentially. For example, the overall incidence of Down's syndrome is one in every 800 births while it roughly climbs to 1.44 in every 100 births in AMA women [4].

Even so, according to Chen et al. [5], there is no need for AMA pregnant women to accept invasive prenatal diagnosis directly. But what if there are other associated fetal structural abnormalities in AMA women, like aberrant right subclavian artery (ARSA) ?

During pregnancy, ARSA may easily be detected by experienced / trained ultrasound operators during prenatal ultrasonography whatever the trimester of pregnancy [6]. The incidence rate of ARSA as an isolated abnormality in healthy populations is known to be about 1 % to 2 % [7]. Even so, Chaoui et al [8,9]. reported the prevalence of ARSA in fetuses with Down’s syndrome for the first time and recommended that an ARSA would

act as a new soft marker for trisomy 21 risk assessment. Prevalence of ARSA was 1.02% in euploid fetuses, whereas 23.6% in Down's syndrome fetuses [10]. Therefore, ARSA appears to be a fairly reliable ultrasound clue for fetal chromosomal abnormalities, especially congenital cardiac defects and aneuploid abnormality [6-10].

Most studies indicated that isolated ARSA had no much clinical significance, and there was no need to serve an invasive prenatal chromosomal testing [8-12]. In Italy, an invasive procedure was offered to all patients with intermediate risk and a retrotracheal ARSA [10]. In the study of Fehmi et al. [12], they suggested fetus with ARSA and aneuploidy relevant ultrasonic soft features, AMA and abnormal biochemical screening to undergo amniocentesis. They concluded that in fetuses with ARSA, karyotyping could be offered to detect Down's syndrome if any high risk factors present.

However, in most existing studies, the predictive value of from ARSA in AMA and non-AMA women was not compared. In AMA women, whether ARSA is an effective predictor for fetal chromosomal abnormalities? Is it necessary for those women to take an invasive routinely screened? Hence, the main purposes of this study were to: (1) determine the incidence of both isolated and nonisolated ARSA in AMA and non-AMA women in southern Fujian of China. (2) assess the association between fetal chromosomal abnormalities and ARSA with or without additional ultrasound findings in AMA pregnancy.

Methods

Study population and device

The retrospective study of 13,690 single pregnancies with complete data was recruited at Zhongshan hospital of Xiamen university and Maternity and Child Health Care Hospital of Xiamen University from September 2015 to January 2018. AMA is defined as a woman who conceiving and delivering at the age of 35 years of age or older [1]. The women were classified into two maternal age categories based on the age of their due dates: those younger than 35, known as the nonAMA group, and those equal to or older than 35, known as the AMA group.The approval from the Medical Ethics Committee of Xiamen university and written informed consent from the participants were collected. Prenatal ultrasonography screening was performed using a transabdominal high-resolution probe (C4-8-D probe and 9L-D high frequency probe; Voluson E8 / E10; GE Medical Systems, Zipf, Austria).

Study design

The information of all included pregnant women was retrieved from our computerized database. The complete materials incuded fetal ultrasonic prenatal screening(grade I, grade II, grade III and fetal echocardiography), biochemical screening, noninvasive prenatal testing (NIPT) and fetal karyotype analysis. All participants (whether ARSA or not) underwent routine ARSA screening and were followed up until birth by neonatal echocardiography. All ARSA fetuses and suspected cases should be diagnosed by two physicians (with prenatal diagnosis qualification and rich experience) and confirmed by at least one postnatal follow-up review. The relevant prenatal diagnostic information was classified and summarized including ultrasonography abnormity, soft markers, serum screening, noninvasive and invasive karyotype analysis, chromosomal microarray and so on. Prenatal consultation with noninvasive or invasive karyotype analysis

was recommended for all fetuses with ARSA. In pregnant women who did not undergo invasive karyotype analysis, noninvasive DNA testing, detailed prenatal testing, and neonatal follow-up revealed no significant aneuploidy or karyotype abnormalities that were considered normal. All aborted fetuses received autopsies with informed consent on time. The flow chart of this study was shown in **Figure 1**.

Method of ARSA detection

After routine examination, the fetal heart mode was turned on, and the local amplification function was adjusted to make the section clearly displayed. The angle of ARSA and incident sound wave was ensured less than 30. Axial view (the three vessel and trachea view), longitudinal view and coronal view were conventionally observed to screen ARSA [13]. When ARSA was displayed in two dimension mode, Doppler velocity was adjusted to (15 - 30) cm/s to verify the diagnosis. ARSA departed from the origin of the descending aorta, namely the junction of the aortic arch and ductal arch, walked between the trachea and the vertebra, and extended towards the right shoulder. Anatomical and ultrasonic diagram of fetal ARSA were shown in **Figure 2**.

Statistical analysis

Statistical analysis was completed using SPSS software, Version 20.0 (IBM Corporation, Somers, NY). A chi-square test and Fisher's exact test were utilized to compare the incidences of chromosomal abnormalities and ARSA between groups. The Mantel-Haenszel test was used to investigate a possible effect modification of age on the association between ARSA and chromosomal abnormalities. The the odds ratio (OR) was calculated and the Breslow - Day - Tarone test was used for the homogeneity. When contingency tables with structural zero, the homogeneity was tested by the logarithmic-transformation-based statistics. Likelihood ratios with 95% confidence intervals (CI) was calculated. $P < 0.05$ was considered statistically significant.

Results

Demographic data and general characteristics

During this period, a total of 13,690 singleton pregnancies (ranging from 16 weeks + 0 days to 38 weeks + 5 days) were recruited in the study, including 10,830 non-AMA women with the average age of (27.1 ± 4.15) year old and 2,860 AMA women with the average age of (38.3 ± 3.48) year old. Among these, ARSA was prenatally detected with the overall incidence of 0.69 % (95 / 13,690), including 63 cases (63 / 95, 66.32 %) with isolated ARSA. In non-AMA group, 70 of 10,830 fetuses were prenatally visualized with an ARSA, with the incidence of 0.65%. And in AMA group, 25 out of 2,860 fetuses were visualized with an ARSA, with the incidence of 0.87%. In our study, chromosomal abnormalities were detected with a rate of 0.75 % (102 / 13,690), including 0.63 % (65 / 10,380) in non-AMA group and 1.29 % (37 / 2,860) in AMA group. Demographic data and general characteristics were listed in **Table 1**.

Of the isolated ARSA fetuses, 63 (66.32 %) cases were born including 15 (60.00 %) cases in AMA group and 48 (68.57 %) cases in non-AMA group. Only one of the simple ARSA case in AMA group were detected with sex chromosome aneuploidies (SNP Array arr (1-22)x2,(X)x1-2), and no obvious abnormality was found in the rest during the clinical follow-up observation. The woman had no pregnancy high-risk factors and

complications with thecritical risk of Down's syndrome screen. Sex chromosome aneuploidies was firstly implied by Cell-free DNA detecting and verified by amniocentesis karyotype analysis. This case of isolated ARSA can only be a random coincidence, which was excluded in statistical analysis.

Of the 32 cases of ARSA with additional structural malformation, 28 cases had their pregnancies terminated and 11 cases of them had abnormal karyotype. There were 4 patients in AMA group and 7 patients in non-AMA group, including trisomy 13 syndrome, trisomy 18 syndrome and trisomy 21 syndrome. The other four normal karyotype fetuses were delivered smoothly, respectively associated with a choroid plexus cyst, unilateral renal agenesis, persistent left superior vena cava and pulmonary sequestration.

Incidence rate of chromosomal abnormalities

In the ARSA positive group, the incidence rate of chromosomal abnormalities was 20.00 % (5 / 25) in AMA group and 10.00 % (7 / 70) in non-AMA group. Furthermore, follow-up on fetus with combined ARSA and chromosomal abnormalities, we found 58.33 % (7 / 12) cases with trisomy 21 syndrome, 25.00 % (3 / 12) cases with trisomy 18 syndrome, 8.33 % (1 / 12) cases with trisomy 13 syndrome and 8.33 % (1 / 12) cases with chimeric Turner syndrome (45X / 46XX). Among these combined ARSA, the incidence of chromosomal abnormalities was 34.38 % (11 / 32) and the incidence of trisomy 21 syndrome was 21.88 % (7 / 32) including 30.00 % (3 / 10) in AMA group and 18.18 % (4 / 22) in non-AMA group respectively. More information was detailed in **Tables 2**.

The incidence rate of chromosomal abnormalities in AMA group was much higher when comparing to that in non-AMA group (= 13.79, df = 1, P 0.001, OR = 0.46, 95% CI : 0.31 - 0.69). While there was no difference in ARSA incidence rate between AMA and non-AMA group (= 1.39, df = 1, P = 0.24, OR = 1.36, 95% CI : 0.856 - 2.14), and so was that in isolated and combined ARSA (= 0.17, df = 1, P = 0.68, OR = 1.18, 95% CI : 0.66 - 2.12 and = 1.50, df = 1, P = 0.22, OR = 1.7, 95% CI : 0.82 – 3.65). The risk of chromosomal abnormalities significantly increased with ARSA detected (= 182.77, df = 1, P 0.001, OR = 21.70, 95% CI : 11.44 – 41.14). Among AMA and non-AMA ARSA positive cases, the incidence increased to 20.00 % (= 69.11, df = 1, P 0.001 , OR = 21.90, 95% CI : 7.74 – 61.96) and 10.00 % (= 104.35, df = 1, P 0.001, OR = 20.50, 95% CI : 9.008 – 46.66) respectively. The Odds Ratio for AMA and non-AMA was homogeneity (= 0.01, P =0.92). Thus, age was not a confounding factor in the association between ARSA and aneuploidy. The Mantel-Haenszel Common Odds Ratio estimated was 21.06, 95% CI : 11.05 – 40.15, P 0.001. Similarly, with additional ultrasonic findings, chromosomal abnormalities risk increased, simultaneously in AMA group and non-AMA group (Fisher’s exact test, all P 0.001).

The likelihood ratio and predictive value of ARSA for chromosomal abnormalities were gathered in Table 3. İn AMA group, the likelihood ratio of combined ARSA for chromosomal abnormalities was 246.00, which was higher than that in entire cohort and non-AMA group (respectively 69.76 and 97.82, all P 0.001).

Discussion

In this retrospective study, 13,690 singleton pregnancies were evaluated. We found that the incidence of an ARSA was 0.87% in Chinese AMA and 0.65% in non-AMA women. The incidence of chromosomal abnormalities was much higher in AMA group than that in non-AMA group. In ARSA positive, the incidence

climbed to 20 % in AMA group and 10 % in non-AMA group. However, age did not affect the incidence of ARSA, nor did it affect the incidence of aneuploidy in ARSA positive patients. The likelihood ratio of combined ARSA for chromosomal abnormalities was high in AMA group. Among aneuploidygroups, mostly detected was Down syndrome in both groups. Another chimeric Turner syndrome was found in an AMA woman with an isolated ARSA.

In most studies, the prevalence of a prenatal ARSA was studied in the entire population with a incidence rate ranging from 0.4 % to 1.5% [14,15]. Concordant with the previous studies, we found the incidence of ARSA in entire cohort was 0.69 %. And as a valuable complementarity, we confirmed there was no difference in the incidence of ARSA during AMA and non-AMA groups. On the timing of prenatal ultrasonic diagnosis of ARSA, Pico et al.[6] presented the mean gestational age for ARSA detecting was 19 weeks + 5 days, ranging from 11 weeks + 5 days to 34 weeks; SD = 4 days). In another study concerning the predictive value of ARSA for Down syndrome, authors successfully checked pregnant women at 16 weeks of gestation [12]. In our experience, ARSA can be detected as early as 12 weeks +4 days gestational age. However, due to the high omission diagnostic rate during the first trimester and the early mid-trimester, and in order to reduce the bias caused by the difference in technical level between examiners and ensure the accuracy, we set the threshold of 16 weeks of gestation for this study.

The association between ARSA fetuses and chromosomal abnormalities such as Down syndrome was described by some scholars [12,16,17]. Reported by Paladini et al. [15], ARSA should be considered among the three most powerful ultrasound indicators of Down syndrome in the second trimester resembling nasal bone abnormality and increased nuchal fold. As we found ARSA would increase the risk of chromosomal abnormalities, especially combined ARSA.

When it comes to isolated ARSA, a weak association between isolated ARSA and chromosomal abnormalities were reported by other scholars [14]. Recommended by Pico et al. [6], these fetus contained an isolated ARSA required a comprehensive evaluation instead of an invasive karyotype analysis considering isolated ARSA is a condition rarely associated with a chromosomal abnormality. In our study, only one AMA case with isolated ARSA showed to be chromosomal abnormality, which is Chimera (45X / 46XX). Turner syndrome is well known to be closely associated with cardiovascular malformations with the frequency of 23% to 45%. As reported by Lee et al. [18], an aberrant right subclavian artery was one of the most common major vessel abnormalities in the Turner syndrome patients (3 / 20 patients, 15 %). However, due to the small sample size, we do not have enough evidence to show that ARSA is related to Chimera (45X / 46XX). What's more, the clinical effect of NIPT in AMA pregnancy was discussed in a multicenter retrospective study [19]. Authors found the positive predictive value was approximately 41.30% for sex chromosome aneuploidy in AMA pregnancy. Most of the cases in this study did not undergo invasive karyotype analysis, we cannot exclude chimera from other fetuses with NIPT. Therefore, this case of isolated ARSA can only be a random coincidence, which was excluded in statistical analysis. Nevertheless, vigilance is still required when only isolated ARSA is found. An active prenatal counseling and a comprehensive prenatal assessment would be very conducive to further managing.

We found age did not affect the incidence of ARSA, nor did it affect the incidence of aneuploidy in ARSA positive patients. The Mantel-Haenszel Common Odds Ratio estimated was 21.06. That is, after removing the

confounding factors, in ARSA positive patients, the risk of aneuploidy was almost 20 times higher than in ARSA negative patients. The results of this study are supported by Chen et al. [5], there is no need for AMA ARSA pregnant women to accept invasive prenatal diagnosis directly. However, if AMA women with combined ARSA, the risk of aneuploidy is significantly increased.

When concerning combined ARSA, in virtue of prenatal detected the ARSA with other ultrasound signs, the risk for trisomy 21 increased by factor of 45 described by Fehmi et al. [12]. As in our study, the likelihood ratios of combined ARSA for chromosomal abnormalities in the entire population AMA and non-AMA group were as high as respectively 69.76, 246.00 and 97.82. The study performed by Svirsky et al.[16] was in support of our results. They claimed ARSA with additional ultrasound findings constitutes a strong predictor for aneuploidy.

There were also some limitations in our study. Firstly, a proportion of fetuses in non-AMA group did not undergo invasive karyotype analysis. The major aneuploidy abnormalities and karyotype abnormalities were excluded by the negative results of noninvasive DNA tests, detailed prenatal examinations and neonatal follow-up. In clinical practice, many people are reluctant to accept invasive karyotype analysis considering the possible risks of invasive operations. In theory, an isolated ARSA was not a sufficient indication for karyotype analysis [6]. Reported by Ranzini et al.[14], all fetuses with ARSA and genetic anomalies totally had additional ultrasound findings. Thus, in similar studies (respectively published in Fetal Diagn Ther and J Ultrasound Med) [6,7], the authors typically included fetuses have consistently classified fetuses with negative prenatal screening and postpartum follow-up as normal karyotypes. Therefore, we believe that the method adopted in this study is acceptable. Secondly, chromosomal microarray analysis was not analyzed in our current study. While it worth noting, quite a part of deformity might be neglected without chromosomal microarray analysis according to Maya et al. [17]. What's more, the incidence of ARSA in pregnancies over the age of 40 and its' predictive value for chromosome abnormality were not evaluated individually in our current study. That may probably have profound guiding significance in this group. We look forward to further discussion of these issues in future studies.

Conclusion

In conclusion, the incidence of an ARSA in Chinese AMA women resembled that in non-AMA women. ARSA would increase the risk of chromosomal abnormalities in both age groups. A high prevalence of chromosomal abnormalities in AMA fetuses was confirmed. Moreover, when combined ARSA is found in AMA ones, it confers a high likelihood of chromosomal abnormalities. In addition, it was worth further exploration in the incidence of ARSA in women over the age of 40 and its' predictive value for chromosome abnormality.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants in this study, and the study was approved by the Ethics Committee of the School of Medicine, Xiamen University.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors have no conflicts of interest.

Funding

This study was supported by grants from the Natural Science Foundation of Fujian Province (No. 2015D015 & No. 2015J01363) and Collaborative Innovation Center for Maternal and Infant Health Service Application Technology.

Authors' contributions

LP C: Writing - original draft, Perform experiment, Data curation.

YF L: Data statistics, Literature retrieval, Dcument review and Modification.

XH Z: Conceptualization, Conception and design of the study, Formal analysis.

JH Y: Experimental design, Project administration, Writing - review & editing.

JH C: Project development, Supervision.

JX X: Data management, Follow-up, Funding acquisition.

XK C: Analysis and interpretation of data.

XY C: Data collection, Figure editing.

GR L: Manuscript editing, Presentation.

All authors approved the final version of the manuscript.

Acknowledgements

We thank all department members for their support and cooperation.

Abbreviations

ARSA: Aberrant right subclavian artery;

AMA: Advanced maternal age;non-AMA, appropriate maternal age;

OR: Odds ratio;

CI: Confidence intervals;NIPT: Noninvasive prenatal testing.

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Tables

Table 1. Demographic data and general characteristics in our study

	AMA	non-AMA	Total
Case	2,860	10,830	13,690
Maternal age (y)	38.3±3.48	27.1±4.15	32.1±4.71
Gestinatal age (w)	24±2.11	26±3.75	25±3.43
Chromosomal abnormalities	1.29% (37/2,860)	0.60% (65/10,830)	0.75% (102/13,690)
ARSA positive	0.87% (25/2,860)	0.65% (70/10,830)	0.69% (95/13,690)
Isolated ARSA	60.00% (15/25)	68.57% (48/70)	66.32% (63/95)
Combined anomaly	35.13% (10/25)	31.43% (22/70)	33.68% (32/95)
Intracardiac malformation	12% (3/25)	7.14% (5/70)	8.42% (8/95)
Extracardiac malformation	12% (3/25)	11.43% (8/70)	11.58% (11/95)
Both	16% (4/25)	12.86% (9/70)	13.68% (13/95)
ARSA with Chromosomal abnormalities	20% (5/25)	10% (7/70)	12.63% (12/95)
ARSA negtive with Chromosomal abnormalities	1.13% (32/2835)	0.54% (58/10760)	0.66% (90/13595)

ARSA: Aberrant right subclavian artery; AMA: Advanced maternal age; non-AMA, appropriate maternal age.

Table 2. Follow-up on fetus with nonisolated ARSA and chromosomal abnormalities

Group	Maternal age (y)	Pregnant week	Additional anomalies (intracardiac or extracardiac)	Serum screening result	Cell-free DNA	Karyotype	Outcome
AMA							
NO.1	38	32	perimembranous ventricular septal defect; single umbilical artery; pyelectasis	positive	high risk	21-T	terminated
NO.2	42	26	unilateral cleft lip with alveolar cleft; single renal cyst	negative	high risk	21-T	terminated
NO.3	39	23	tetralogy of Fallot;	negative	high risk	21-T	terminated
NO.4	45	22	strawberry head; unilateral strephenopodia; fingers flexion and overlap; left ventricular dysplasia	positive	high risk	18-T	terminated
non-AMA							
NO.1	28	23	mild lateral ventricular dilatation; slight tricuspid regurgitation; eyes spacing widened	positive	high risk	21-T	terminated
NO.2	26	32	omphalocele; angle	negative	high	21-T	terminated

			of iliac ala increases		risk		
NO.3	28	12	increased nuchal translucency; hypoplastic nasal bone	positive	high risk	21-T	terminated
NO.4	27	26	persistent left superior vena cava; coronary sinus dilatation	positive	high risk	21-T	terminated
NO.5	26	24	perimembranous ventricular septal defect; micromandible; low-set ears; unilateral complete cleft palate (III)	positive	high risk	18-T	terminated
NO.6	30	28	increased nuchal fold; Dandy-Walker malformation; double outlet right ventricle	positive	high risk	18-T	terminated
NO.7	33	33	left ventricular hyperechoic plaques; polycystic renal dysplasia; semilobar holoprosencephaly; cyclopia; beak nose; intrauterine growth restriction	negative	high risk	13-T	terminated

Table 3. The independently predictive value of ARSA or nonisolated ARSA for chromosomal abnormalities

Group	Index	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value	Likelihood ratio
Entirecohort	ARSA	11.76% (6.23-19.65) %	99.39% (99.24-99.51) %	12.63% (6.70-21.03) %	99.34% (99.19-99.47) %	19.26
	Combined ARSA	10.78% (5.51-18.48) %	99.85% (99.76-99.90) %	34.38% (18.57-53.19) %	99.33% (99.18-99.46) %	69.76
AMA	ARSA	13.51% (4.54-28.77) %	99.29% (98.91-99.57) %	20.00% (6.83-40.70) %	98.87% (98.41-99.23) %	19.07
	Combined ARSA	10.81% (3.03-25.42) %	99.96% (99.90-99.98) %	40.00% (12.16-73.76) %	99.76% (99.66-99.83) %	246.00
non-AMA	ARSA	10.77% (4.44-20.94) %	99.41% (99.25-99.55) %	10.00% (4.12-19.52) %	99.46% (99.30-99.59) %	18.40
	Combined ARSA	10.77% (4.44-20.94) %	99.89% (99.82-99.94) %	31.82% (13.86-54.87) %	99.58% (99.45-99.68) %	97.82

ARSA: Aberrant right subclavian artery; AMA: Advanced maternal age; non-AMA, appropriate maternal age; OR: Odds ratio; CI: Confidence intervals

Figures

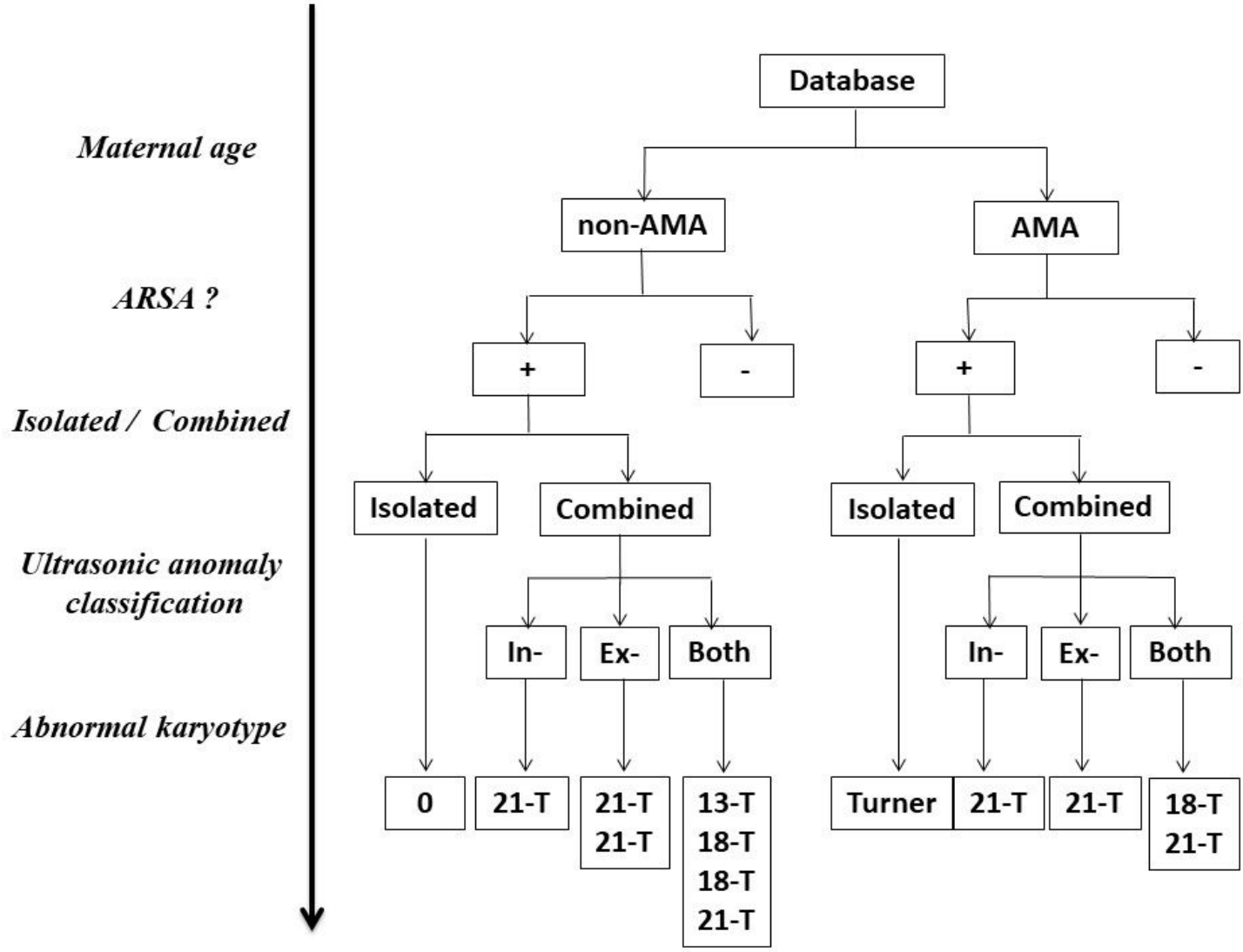

Figure 1

The flowchart of our study. AMA, advanced maternal age; non-AMA, appropriate maternal age; ARSA; aberrant right subclavian artery; In-, Intracardiac malformation; Ex-, Extracardiac malformation; Both, Intracardiac and extracardiac malformation.

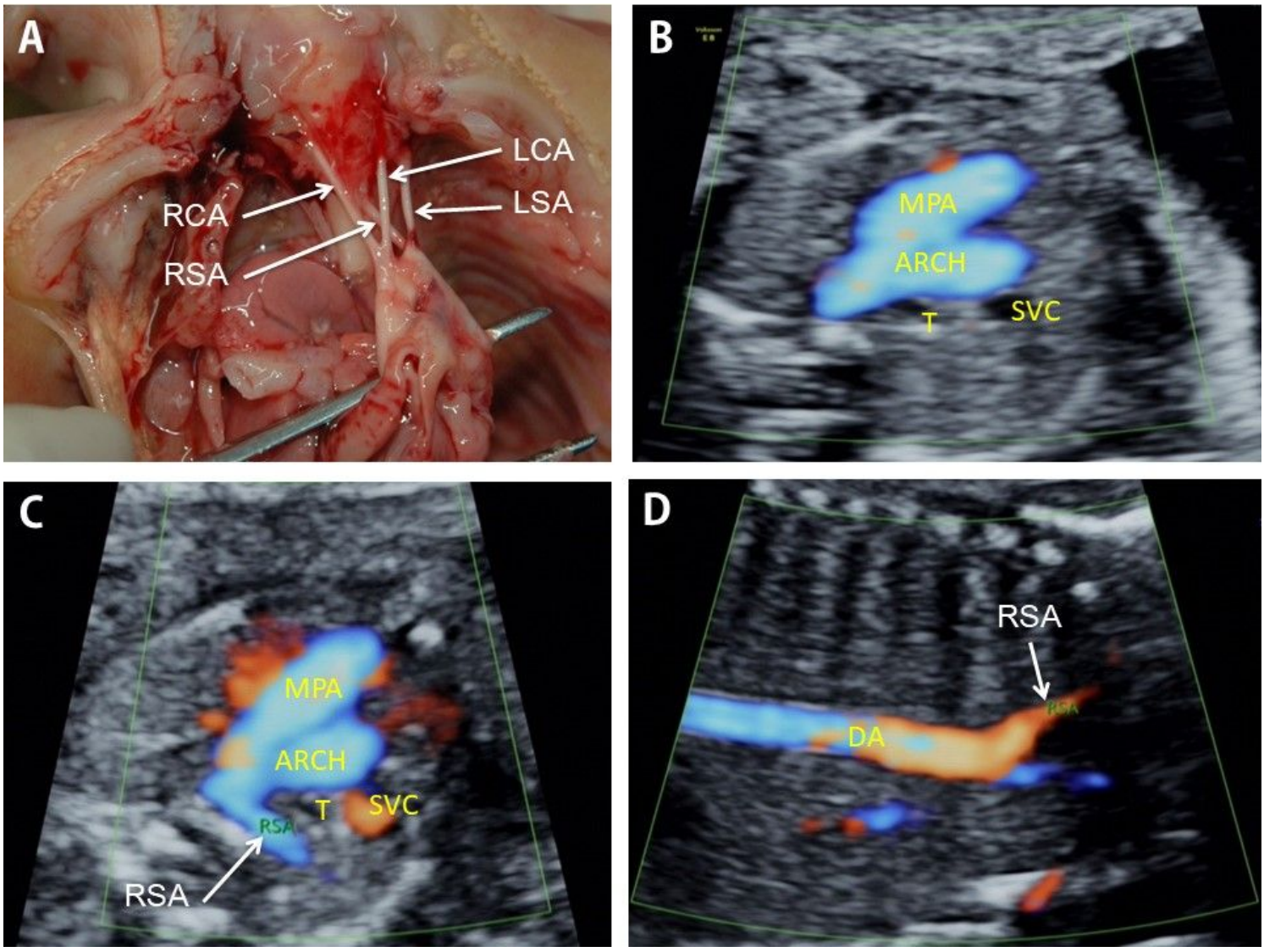

Figure 2

Inspection of fetal aberrant right subclavian artery (ARSA). a: Anatomical diagram of fetal ARSA. b: The three vessels and trachea view of nomal fetuses. c: Fetal ARSA in the three vessels and trachea view. d: Fetal ARSA in the coronal view. ARCH, aorta; DA, descending aorta; LCA, left carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery; RCA, right carotid artery; RSA, right subclavian artery; SVC, superior vena cava; T, trachea.