Prenatal diagnosis of 2193 pregnant women with invasive indications for chromosomal abnormalities in southern China: a retrospective study

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Research

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Abstract

Background: Although a variety of non-invasive techniques are used for prenatal genetic screening and diagnosis, our knowledge remains limited regarding the relationship between high-risk prenatal indications and fetal chromosomal abnormalities.

Methods: We retrospectively investigated the prenatal genetic screening and karyotype analysis results of pregnant women who had undergone invasive prenatal testing in Prenatal Diagnosis Department of Meizhou People's Hospital during Jan. 1, 2015 to Dec. 31, 2019. We analyzed the frequencies of chromosome abnormalities in women with high-risk indications.

Results: A total of 2,193 pregnant women who had underwent invasive prenatal testing were included in our analysis. Chromosomal abnormalities occurred in 10.3% of these women, and rate increased with maternal age ($P < 0.001$). The frequencies of chromosome abnormalities varied for women with different high-risk indications, which was 10.3% (226/2193) for abnormal ultrasound results, 3.3% (31/938) for positive serum screening test results, 61.4% (78/127) for positive NIPT results, 9.3% (13/140) for AMA and 11.1% (10/90) for obstetric/family history. Follow up data showed that 380 pregnant women opted for termination the pregnancy, including 211 (55.5%) due to karyotype abnormalities and 169 (45.5%) due to abnormal ultrasonic outcomes.

Conclusion: Our data suggested that the prenatal screening methods have high false positive rates. NIPT is the most accurate non-invasive prenatal screening. Apart from karyotype abnormality, abnormal ultrasound results alone accounted for a big part of pregnancy termination.

Introduction

Invasive procedures which mainly include chorionic villus sampling (CVS) and amniocentesis are currently recommended for prenatal diagnosis of fetal chromosomal abnormalities (1). However, according to guidelines, CVS are performed after 10 weeks of gestation and amniocentesis are performed approximately 16 weeks of gestation (2, 3). Meanwhile, karyotype analysis takes about 10 days, a period which produces great psychological stress on pregnant women.

Nowadays, a variety of non-invasive technologies, such as ultrasound, serum screening test and non-invasive prenatal genetic testing (NIPT) are used in prenatal genetic screening and diagnosis(4). Ultrasound screening is recognized as a safe and convenient non-invasive procedure to detect fetal anomalies, i.e. heart abnormality, bone abnormality, brain abnormality, multi-system malformations (5). Previous studies suggested that fetal increased nuchal translucency (NT) values and nasal bone growth were closely associated with the occurrence of Down's syndrome (DS, trisomy 21) (6). Ultrasound examination combined with maternal serological of double-marker, namely free beta human chorionic gonadotropin (free β-hCG) and pregnancy-associated plasma protein A (PAPP-A), or triple-marker, namely free β-hCG, alpha fetoprotein (AFP) and unconjugated estriol (uE3) is commonly used to determine the risk of fetal aneuploidy of chromosome 21 and 18 (7).

Non-invasive prenatal test (NIPT), which analyzes the fetal genetic traits in maternal blood samples using DNA sequencing technique, is considered as a safe and accurate method for fetal aneuploidies detection, and becomes increasingly accepted in clinical practice (8). However, clinical guidelines also state that NIPT is a screening method rather than diagnostic (9). But for elderly pregnant women who have no intention of invasive procedure, NIPT would be recommended as a proper alternate. With the two-child policy full implemented from 2016 in China, the number of pregnant women with advanced maternal age (AMA) has risen sharply (10). AMA is considered as an important risk factor for fetal chromosomal abnormalities (11).

Meizhou city, located in southern China, is known as the capital of Hakkas in the world, with unique culture, diet habits and physiological characteristics (12). Due to underdeveloped economic stature and traffic difficulty, the population in this area remains stable and suffered badly from various diseases, such as thalassemia, cancers and infectious diseases. The two-child policy sharply increases the number of pregnant women in the recent years, especially women with AMA, and thus highlights the importance of prenatal diagnosis.

Although many studies have focused on evaluating the efficiency and accuracy of prenatal screening techniques, our knowledge remains limited regarding the relationship between high-risk prenatal indications and fetal chromosomal abnormalities. The present study investigated the frequencies of fetal chromosomal abnormalities in Hakka pregnant women with high-risk indications. We aimed to determine the relationship between high-risk indications and chromosomal abnormalities. The findings would provide useful information for pregnant women with high-risk indications.

Materials And Methods

Patients

This retrospective study included 2,321 pregnant women who had undergone invasive prenatal testing at Prenatal Diagnosis Department of Meizhou People's Hospital, Guangdong Province at a period of January 1th, 2015 to December 31th, 2019. The study was approved by the Ethics Committee of Meizhou People's Hospital (No. MPH-HEC 2015-A-22). Informed consent was obtained by phone from all participants. 128 women were excluded either without consent or without karyotype results. Follow-up data on pregnancy outcomes and fetal health were collected by phone from all pregnant women.

Invasive prenatal tests were performed by either amniocentesis or CVS. Invasive prenatal testing was conducted for the following indications: abnormal ultrasound, positive serum screening result, positive NIPT outcome, AMA (age ³ 35 years), and obstetric/family history (record of fetus or child with aneuploidy, or parental carriers of chromosomal balance translocations or inversions). Abnormal ultrasound results included increased NT, heart abnormality, choroid plexus cyst, neck lymphatic hydrocele, bone abnormality, brain abnormality, increased NF, kidney abnormality, and multiple abnormality. Positive serum screening was defined as risk value ≥ 1/270 for DS or ≥1/350 for ES. Positive NIPT outcome was defined as absolute value of z-score ≥ 3.

Cytogenetic analysis

Chorionic villus samples or amniotic fluid were collected from pregnant women by professional gynecologist. Fetus cells derived from chorionic villus samples or amniotic fluid were cultured in Amniotic Cell Medium (Dahui Bio, Guangzhou, China) for 8 to 13 days at 37 ℃ with 5% CO_2. Three hours before the endpoint of culture, cells were treated with colcemid solution. Karyotype analysis was performed following GTG banding (13). A Zeiss Axio Imager Z2 system (Zeiss, Wetzlar, Germany) was used to capture microscopic images of metaphase cells for karyotype analysis. For each sample, at least 20 GTG-banded metaphases were counted and at least five metaphases were analyzed. Karyotypes were classified according to the International System for Human Cytogenetic Nomenclature 2013 (13).

Prenatal serological analysis

At 11 to 13^{+6} weeks of gestation, risk calculation for first-trimester combined screening (FTS) was performed using maternal age, fetal NT thickness, and maternal serum levels of free β-hCG and PAPP-A. At 15 to 20^{+6} weeks of gestation, risk calculation for second-trimester triple screening was performed using maternal age and maternal serum levels of AFP, free β-hCG, and uE3. Gestational week was determined by crown-rump length or biparietal diameter. Ultrasound testing and blood collection of pregnant women for FTS were performed on the same day. The levels of FTS serum markers were determined by Cobas e601 analyzer (Roche, Basel, Switzerland). The multiples of the median were derived from marker levels and NT thickness and used to calculate the risk of chromosomal abnormalities according to gestational age. Maternal weight, maternal age, and history of smoking were also considered in calculating Down syndrome risk on pregnancy. A risk cut-off value ≥ 1/270 was recognized as positive for trisomy 21 (Down's syndrome, DS) and a risk rate ≥1/350 was considered positive for trisomy 18 (Edwards syndrome, ES).

NIPT analysis

5-10 ml of maternal peripheral blood was collected and placed in EDTA-containing tubes (BD Biosciences, Franklin Lakes, NJ, USA). The blood sample was centrifuged at 1600 × g for 10 minutes at 4 ℃ to separated plasma from the peripheral blood cells. Followed by carefully transferred the plasma into a polypropylene tube and centrifuged at 16,000 × g for 10 minutes at 4 ℃ to deposit the remaining cells. Briefly, cell-free DNA was extracted from 600 μL plasma using a nucleic acid extraction kit (CapitalBio Genomics, Beijing, China) according to the manufacturer's protocol. DNA was used for library construction and semiconductor sequencing, using a fetal aneuploidies (trisomies 21, 18, and 13) detection kit following the manufacturer's instructions (CapitalBio Genomics). An absolute value of z-score ≥3 in target chromosome were considered positive (14).

Statistical analysis

Data were analyzed using chi-squared test in SPSS 20.0 software (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

A total of 2,193 women who received an invasive test for prenatal diagnosis in Meizhou People's Hospital at a period of 2015 - 2019 were included for analysis in our study. The average age of all pregnant women was 29.9 ± 5.9 years (range 16 to 47 years). Participants had either of the following high-risk indications, including abnormal ultrasound, positive serology, positive NIPT, AMA and obstetric/family history.

Totally, 226 participants (10.3%) were diagnosed as chromosomal abnormalities, and the frequency of abnormality went up as maternal age increased ($P < 0.001$, Table 1). Among 898 pregnant women who were ultrasound abnormal, 94 (10.5%) were found to be karyotype abnormal. There were 938 participants that had positive serum screening results, and abnormal karyotypes were found in 31 (3.3%) pregnant women. As for 127 women who showed positive NIPT outcomes, 78 (61.4%) of them were confirmed to be karyotype abnormal. Among 140 participants of AMA, 13 (9.3%) had abnormal chromosome karyotypes. In addition, 10 out of 90 (11.1%) participants who had a record of obstetric/family history were diagnosed as chromosome abnormality (Figure 1).

The most frequent associated indication among 226 abnormal cases was abnormal ultrasonic finding (94/226; 41.6%), followed by a positive NIPT outcome (78/226; 34.5%), a positive serological result (31/226; 13.7%), women of AMA (13/226; 5.8%) and obstetric/family history (10/226; 4.4%). Figure 2 showed the distribution of chromosomal abnormalities in the study subject. The majority of abnormalities are trisomy 21, which took up near half of the cases (108/226; 47.8%); followed by trisomy 18, which contributed to 30% of the cases. The sex chromosomal abnormalities constituted 35% of the cases, including monosomy X (19%) and Klinefelter syndrome (16%). Follow-up data showed that 211 (55.5%) pregnant women terminated pregnancy due to karyotype abnormalities, while 169 (44.5%) pregnant women who terminated the pregnancy because of abnormal ultrasonic outcomes.

Next, we analyzed the ultrasonic abnormal findings of the 94 chromosomal abnormalities. Increased NT (40/94; 42.6%) was the most common ultrasonic indication, followed by heart abnormality (15/94; 16.0%), bone abnormality (12/94; 12.8%), multiple abnormality (12/94, 12.8%) and other abnormalities (Table 2).

Our data indicated that the true positive rate for NIPT was 61.4% (78/127), and false positive rate was 38.6% (49/127). However, the accuracy of NIPT for different types of chromosomal abnormalities remained largely diverse. As shown in Table 3, NIPT was exclusively effective in diagnosing abnormality in trisomy 21 with the true positive rate of 83.6%. NIPT was also helpful in diagnosing abnormality in trisomy 18 and sex chromosome, with the true positive rate of 60.0% and 56.3%, respectively. As for abnormalities occurring in other sites, this method showed absent of accuracy.

Of 938 participants who had positive serum screening test, abnormal fetal karyotype was confirmed in 31 (3.3%) of them. As shown in Table 4, the positive serum screening test results were classified into four groups. The true positive rate of karyotype abnormality was 10% if pregnant women have both DS ≥

1/270 and ES ≥ 1/350, while it dropped to 2.8% if only DS ≥ 1/270 or 7% if only ES ≥ 1/350. In addition, none of the 60 pregnant women with 1/270 > DS ≥ 1/500 or 1/350 > ES ≥ 1/500 was further confirmed to be karyotype abnormal.

Discussion

The present study investigated the chromosomal abnormalities in pregnant women with different high-risk prenatal indications, and comprehensively characterized the relationship between high-risk prenatal indications and fetal chromosomal abnormalities in southern China.

It is well known that several different techniques are used for prenatal screening and diagnosis. Ultrasonography has been recognized as a safe and essential method for pregnancy imaging, although it does not detect genetic defects. Ultrasonography can detect abnormalities and even minor structural changes in fetus, which are related to chromosomal abnormalities (15). The 2013 ISUOG practice guidelines stated that fetal NT thickness can predict chromosomal abnormalities in the first trimester of pregnancy (16), and a wide range of other abnormalities have been reported in associations with increased NT (17). Our findings suggested that increased NT (42.6%) was the most frequent indication.

NIPT was applied to clinical practice since 2011, and became increasingly widely used in prenatal screen of trisomy 21 and other (18). NIPT is considered an unparalleled screening test for fetal aneuploidy because of its high accuracy. In the present study, 61.4% cases with positive NIPT results were confirmed to be fetal karyotype abnormal. Notably, NIPT performed well in detecting trisomy 21 with a true positive rate of 83.6%, which was similar to that reported by Rulin et al (19). However, NIPT was less effective in detecting trisomy 18 and even less for other chromosome abnormalities. The American Academy of Medical Genetics and Genomics suggested in 2016 that NIPT be used as only a screening test rather a diagnostic technology in aneuploidy (9). The serum screening is a conventional method to determine the risk of fetal aneuploidy. However, the true positive rate for serum screening testing was poor in our data. Recent study found that serum screening combined with ultrasonography could improve the detection rate of fetal chromosomal aneuploidy (20).

As for pregnant women with high-risk indications by prenatal screen procedures, prenatal diagnosis should be implemented. The frequencies of chromosome abnormalities varied for women with different high-risk indications, which was 10.5% for abnormal ultrasound results, 3.3% for positive serum screening test results, 61.4% for positive NIPT results, 9.3% for AMA and 11.1% for obstetric/family history. These data suggested that positive NIPT result was the worst risk indictor of chromosomal abnormalities. However, NIPT by no mean can replace invasive diagnostic techniques in clinical practice. Besides, follow up data showed that 169 (45.5%) women terminated pregnancy based on ultrasonic outcomes, which highlighted the importance of ultrasonography in prenatal screen. Previous studies exploring the effect of maternal age on self-generating abortion found that AMA was a crucial factor related to fetal chromosome aneuploidy (21, 22). Consistently, we confirmed AMA as an important risk factor of chromosome abnormalities.

There are some limitations in our study that need to be clarified. First, retrospective study design is a limitation of the present study. Second, the option for NIPT was low in our study. It is because the hospital started NIPT test from 2018 and the test far outspend other screening tests.

Conclusion

We observed a relatively high frequency of chromosomal abnormalities in prenatal samples from Hakka pregnant women. Our data suggested that the prenatal screening methods have high false positive rates. NIPT is the most accurate non-invasive prenatal screening. Apart from karyotype abnormality, abnormal ultrasound results account for a big part of pregnant termination.

Abbreviations

AMA: advanced maternal age; NT: nuchal translucency; free β-hCG: free beta human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein A; uE3: unconjugated estriol; CVS: chorionic villus sampling; NIPT: noninvasive prenatal testing; FTS: first-trimester combined screening

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Meizhou People's Hospital (No. MPH-HEC 2015-A-22). Informed consent was obtained by phone from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are included within the article.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

ZZ conceived and designed the experiments; XG contributed to the data collection and the manuscript draft. SL, HW, RW and XG helped to collect clinical data, conducted the clinical performances and researches; XG analyzed the data and wrote the paper.

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Not applicable.

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Tables

Table 1 Fetal chromosomal abnormality indications and maternal age

	Cases, n	<25, n (%)	25-29, n (%)	30-34, n (%)	≥35, n (%)
Abnormal ultrasound	94	16 (10.1)	36 (12.3)	20 (7.0)	22 (10.9)
Positive serology	31	6 (2.8)	4 (1.0)	11 (5.9)	10 (9.2)
Positive NIPT	78	5 (35.7)	14 (48.3)	18 (62.1)	41 (74.5)
Obstetric/family history	10	0 (0)	5 (11.4)	2 (10.0)	3 (21.4)
AMA	13	0 (0)	0 (0)	0 (0)	13 (9.3)
Total*	226	27 (6.7)	59 (7.8)	52 (10.0)	88 (17.0)

NIPT: positive non-invasive prenatal testing; AMA: advanced maternal age, age ≥35; *Chromosome abnormalities showed an increased trend with maternal age (P<0.001).

Table 2 Fetal positive karyotype analysis of ultrasonic indications

	Positive karyotype	T21	T18	T13	45,X	XXN	Other chromosome abnormal
NT≥2.5 mm	40 (42.6)	15	4	1	8	4	8
Choroid plexus cyst	1 (1.1)	0	0	0	0	0	1
Neck lymphatic hydrocele	2 (2.1)	0	0	0	2	0	0
Heart abnormality	15 (16.0)	3	3	2	2	0	5
Bone abnormality	12 (12.8)	7	2	1	1	0	1
Brain abnormality	5 (5.3)	0	2	1	0	1	1
NF≥6.0 mm	4 (4.3)	3	0	0	0	1	0
Kidney abnormality	3 (3.2)	0	0	0	0	1	2
Multiple abnormality	12 (12.8)	1	4	1	3	1	2
Total	94 (10.5)	29	15	6	16	8	20

Data are presented as n (%) or n. NT: nuchal translucency; NF: nuchal fold thickness; Multiple abnormality: fetus presented more than two abnormalities; T21: trisomy 21; T18: trisomy 18; T13: trisomy 13; 45,X: monosomy X; XXN: 47,XXY, 47,XYY, 47,XYY and 69,XXX; Other chromosome abnormal: translocation, deletions, inversion, duplication, unbalanced rearrangement, trisomy 9, trisomy 10 and trisomy 22.

Table 3 Fetal positive karyotype analysis of NIPT (n=127)

Fetal karyotype	True positive, n (%)	False positive, n (%)
Trisomy 21	51 (83.6)	10 (16.4)
Trisomy 18	6 (60.0)	4 (40.0)
Trisomy 13	1 (11.1)	8 (88.9)
Sex chromosome abnormal	18 (56.3)	14 (43.8)
Other chromosome abnormal	2 (13.3)	13 (86.7)
Total	78 (61.4)	49 (38.6)

NIPT: positive non-invasive prenatal testing.

Table 4 Fetal positive karyotype analysis of serum screening (n=938)

	True positive, n (%)	False positive, n (%)
DS ≥ 1/270 & ES ≥ 1/350	3 (10.0)	27 (90.0)
DS ≥ 1/270	21 (2.8)	728 (97.2)
ES ≥ 1/350	7 (7.0)	93 (93.0)
1/270 > DS ≥ 1/500 or 1/350 > ES ≥ 1/500	0 (0.0)	60 (100.0)
Total	31 (3.3)	907 (96.7)

DS: Down's syndrome; ES: Edwards syndrome.

Figures

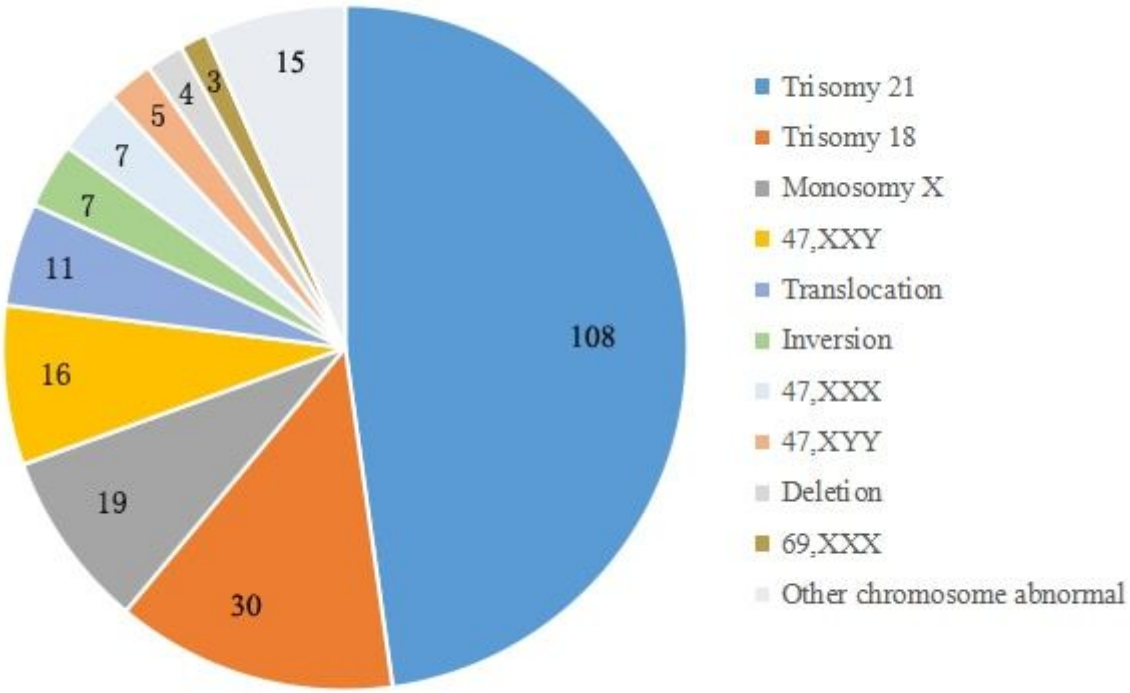

Figure 1

Distribution of different chromosomal abnormalities. Other chromosome abnormal: duplication, unbalanced rearrangement, trisomy 9, trisomy 10 and trisomy 22

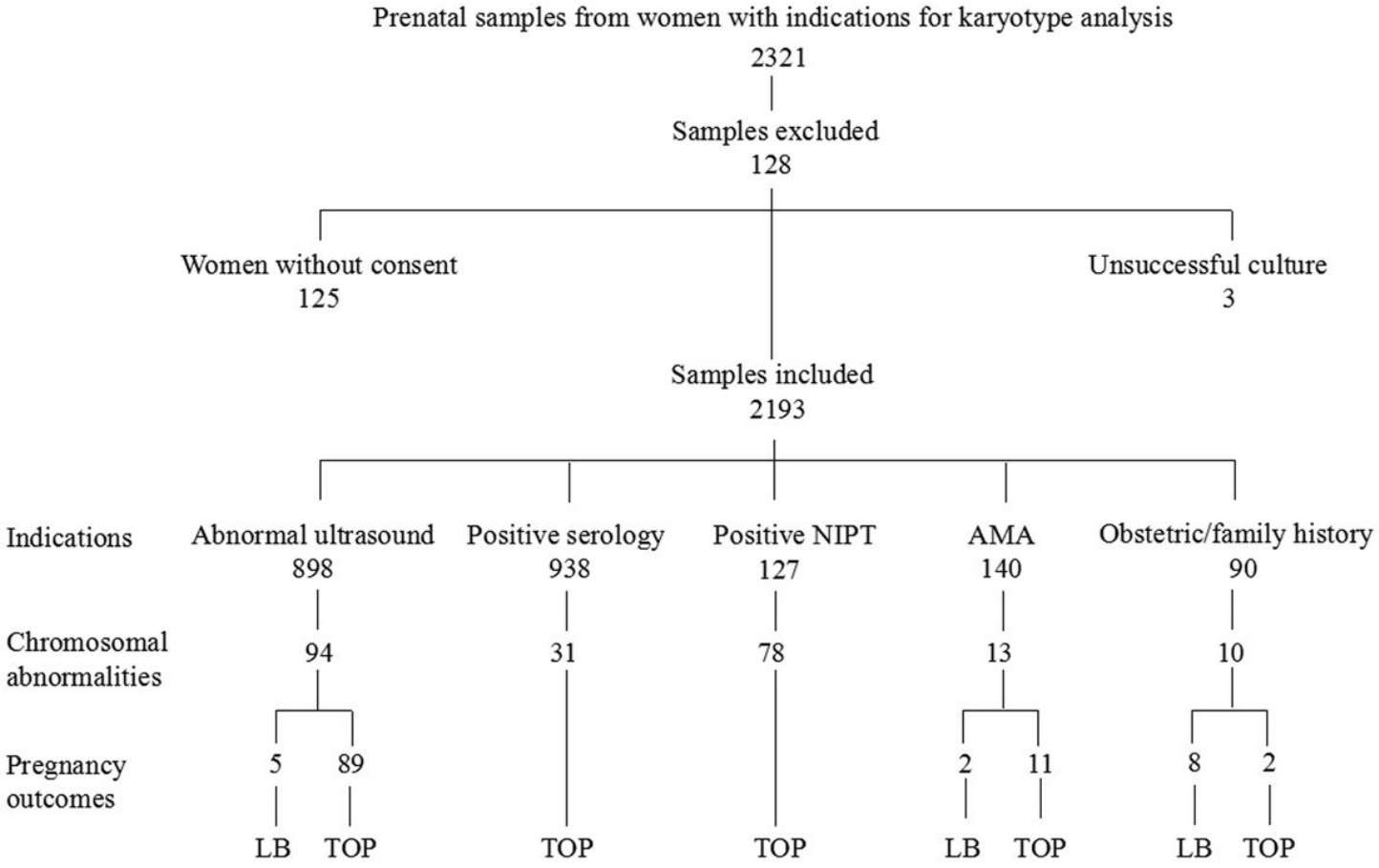

Figure 2

Pregnant women with invasive indications and outcomes of prenatal diagnosis. LB: liveborn; TOP: termination of pregnancy.