Women' S Preferences for Prenatal Diagnostic Tests in China

Women' s Preferences for Prenatal Diagnostic Tests in China

by

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Overview of the thesis papers

Prenatal tests can be used for early diagnosis of fetal problems and prevention of abnormal birth in high-risk pregnancies. Several types of diagnostic tests are available, among which some are more accurate than others. However, in rare situations, these tests result in miscarriage, even when the baby is healthy. Moreover, there is little information about women's preferences toward different attributes of those tests.

Discrete Choice Experiment (DCE) is a preference elicitation technique that can be used to quantify the trade-offs that individuals are willing to make among different attributes of a product or service (e.g. diagnostic test). Using DCE, we can estimate the relative impact of treatment attributes on patients' choices. This study will extend our current understanding of patients' preferences for benefits, risks, and cost of prenatal diagnostic tests. This study offers a systematic method to incorporate woman' opinions in the choice of prenatal diagnostic tests and therefore, can be a useful tool in patient-centered outcome research. The results of this study can inform decisions about evaluation of current and new prenatal diagnostic tests.

With the guide of my mentors, I have undertaken two studies towards creating a deeper understanding of the women's preference for prenatal diagnostic tests. The two studies investigate the important factors related to patients' preferences and their willingness-to-pay for various prenatal screening tests. The first paper addresses women's preference for prenatal diagnostic tests using a DCE. The second paper aims to understand variation in women's preferences for prenatal diagnostic tests by using a latent class analysis of choice data.

Abstract/Summary of Paper 1

Background: Prenatal tests can be used for the early diagnosis of fetal problems and can prevent abnormal birth in high-risk pregnancies. Several types of diagnostic tests are available, and some are more accurate than others. Using a Discrete Choice Experiment (DCE), we elicited women's preferences and relative importance that they assign to various attributes of prenatal diagnostic tests.

Methods: A sequence sample of individuals who visited the clinic for prenatal consultation at The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China between 18 January 2018 and 2 April 2018 consented to this study. We designed a choice questionnaire containing 12 choice questions where each question presented two hypothetical test profiles (Test A vs. Test B) and no test option. Profiles were described using 5 key attributes: test procedure, wait time, detection rate, miscarriage rate, and test cost. We collected data on choices that the women made between different test profiles and analyzed the data using conditional logistic regression to estimate the impact of each attribute level on choices that were made.

Results: A total of 92 women were enrolled in this study. The mean age in our sample was 31.9 years (SD: 5.2), and the mean gestational week was 14.0 (SD: 5.5) weeks. Almost one-third of the respondents (n = 31; 34%) reported they had a fetal abnormality during a previous pregnancy such as a genetic abnormality or spontaneous abortion. All other attributes being equal, the odds of choosing a non-invasive test procedure over an invasive one was 2.53 (95%CI 2.42–2.64). The patients also had a positive preference for higher levels of detection sensitivity. The odds of choosing a test with 96% detection rate was 1.085 (95%CI 0.995 - 1.182) compared to a test with 94% detection rate. This odds ratio was 1.453 (95%CI 1.336 - 1.580) 1.913 (95%CI 1.758 - 2.082) for a test with 98% and 100% detection rate, respectively. The odds of choosing a test with 3 weeks wait time was 0.972 (95%CI 0.909 - 1.039) compared to a test with 1 week wait time. As expected, women had a negative preference weight for increase in miscarriage rate. The odds of choosing a test with 4% miscarriage rate was 0.825 (95%CI 0.772 - 0.881), and the odd of choosing a test with 5% miscarriage rate was 0.677 (95%CI 0.633 - 0.724) compared to a test with 3% miscarriage rate. Women also had a negative preference weight for increase in the test cost. The odds of choosing a test that cost RMB$8000 was 0.773 (95%CI 0.699 - 0.854) compared to a test with no cost. Overall, participants had strong preference for the non-invasive test and were willing to pay up to RMB$28,810 (approximately US$4,610) for a non-invasive test rather than taking an invasive test that had similar attributes otherwise. Women were willing to pay RMB$6,061(US$970) to reduce the miscarriage rate by 1% and up to RMB$3,356 (US$537) to increase the detection rate by 1%. The subjects were less sensitive to the waiting time, and they were willing to pay up to RMB$443 (US$71) for a 1-week reduction in wait time.

Conclusion:
The implementation of NIPT for routine antenatal care in China depends on multiple factors such as test procedure, accuracy, risk of miscarriage, and costs. The women have a strong preference for non-invasive tests that ensures safety of fetus. Women are also concerned about the invasiveness the test procedure when making decisions about prenatal testing. This indicates the need for effective pre-test counseling to ensure that women understand the testing process. This could lead to better decisions that accommodate patient preferences and values and better outcomes. Future studies will be conducted in larger and more representative populations. Larger and more representative sample is needed to ensure accuracy of our current findings and to provide better power for measuring preference heterogeneity among women.

Keywords*: Prenatal tests; Choice Behavior; Discrete Choice Experiment*

Abstract/Summary of Paper 2

Background: Prenatal diagnostic tests can be used to prevent abnormal delivery in high-risk pregnancies including cases of Down syndrome. Women whose babies are at an increased risk of gene abnormalities have traditionally been offered invasive prenatal tests such as chorionic villus sampling or amniocentesis. These are the gold standard methods for confirming the diagnosis with high accuracy. Here, we extended our previous analysis to explore the underlying heterogeneity in preferences of women when choosing among prenatal diagnostic tests.

Methods: A discrete choice experiment (DCE) was used to elicit patients' preferences for different attributes of prenatal diagnostic tests. The sample was recruited from a group of women with relatively high-risk pregnancies who visited an outpatient clinic for prenatal consultation in China between January 18, 2018, and April 2, 2018. We then conducted latent class analysis (LCA) in the choice data to identify individuals with similarities in their preferences.

Results: The mean age of the women was 31.9 years (SD: 5.2), and the gestational age was 14.0 weeks (SD: 5.5). Of these women, 34% had an abnormal fetus from a previous pregnancy, 4% had a family history, and 14% knew someone among their family or friends with a history of fetal abnormality. LCA identified three classes of respondents with distinct preference patterns for attributes of the test. The preference weights for test attributes are presented in Figure 2 for the three classes: 35 (37.3%), 16 (17.4%), and 41 (45.3%) of the women fell into class 1, class 2, and class 3, respectively. Women in Class 1 put a large importance on the test procedure. Women in Class 2 had larger importance weights for the test cost, and class 3 a larger importance weight for detection rate and miscarriage rate. The importance estimated for turnaround time varied and was relatively unimportant across all three classes. We found that a significantly larger proportion of women in Class 3 had fetal abnormalities in their previous pregnancy.

Conclusion: In conclusion, we identified classes of women who had different preferences for diagnostic test attributes. Some of these differences in preferences could be partially explained based on a prior history of having an abnormal baby. Our results might influence clinicians' perception about the aspects of diagnostic tests that are important for patients. Knowledge about these aspects can improve the discussions with patients during the consultation.

***Keywords**: Prenatal tests; choice behavior; Latent class analysis*

Paper 1

Eliciting Women' s Preference for Prenatal Diagnostic Tests:

A Discrete Choice Experiment

Paper 1 Eliciting Women' s Preferences for Prenatal Diagnostic Tests: A Discrete Choice Experiment

Background

Prenatal diagnostic tests can be used for early diagnosis of fetal problems and prevention of abnormal birth in high-risk pregnancies, such as Down syndrome. Several types of diagnostic tests are currently used for this purpose that varies regarding diagnostic performance, invasiveness, and cost. Chorionic villus sampling that involves obtaining a sample from the placenta and amniocentesis test that requires sampling of amniotic fluid by using a hollow needle inserted into the uterus are examples of invasive diagnostic tests that often provide an accurate diagnosis of potential developmental abnormalities in a fetus. Non-invasive prenatal diagnosis tests (NIPT) that usually rely on a simple blood test from the mother are generally safe and less costly but are associated with higher false negative rates. The research found that the costs the similar as current Downs screening at the cost of £500 per NIPT in the United Kingdom and NIPT have a better T21 detection and reduce euploid fetal loss with a lower total healthcare cost in the United States (1, 2). Women at high risk of having babies with genetic abnormalities, usually are offered invasive prenatal diagnosis, to ensure higher detection rates. However, in approximately 1-3% of cases, invasive diagnostic tests might result in miscarriage, even when the baby is healthy (3, 4). Recent years, noninvasive tests which are based on the technology to investigate the Cell-free fetal DNA inside a maternal blood sample, become one of the major alternatives of invasive tests and also available in China and the accuracy of NIPT was reported with a >99% in both sensitivity and specificity (5-7).

However, in the past decade, it is not included in the universal coverage, patient have to pay for themselves, and the services are mainly provided by the private laboratories.

Use of NIPT has been introduced for a self-payment option in a national health screening programme for pregnancy in some jurisdictions in China(8). However, there is still a debate about the optimal choices, consider the trade-offs that need to be made among different attributes of various diagnostic tests, including detection rate, the risk of miscarriage, invasiveness, and cost.(9, 10) Understanding women's preferences for different attributes of diagnostic tests can help physicians to enhance the process for shared decision making for the choice of best diagnostic strategy in high-risk pregnancies.

Discrete Choice Experiment (DCE) is a preference elicitation technique that has been used widely in transportation, environmental science, marketing and more recently in healthcare to quantify the trade-offs that individuals are willing to make among different attributes of a product or service. In recent years, DCE has been widely used in health-care research to understand the patients' preferences for medications and health services (11). Using DCE, we aim to estimate the relative impact of attributes of diagnostic tests on patients' choices when deciding among different pre-natal diagnostic tests. This study will extend our current knowledge about patients' preferences for benefits, risks, and cost of prenatal diagnostic tests.

Materials and Methods

Study population

This study was a cross-sectional survey that involved completion of a questionnaire consisting of 13 questions. The study was conducted at a university hospital in South China (The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China). We recruited our sample from women with relatively high-risk pregnancy who visited the outpatient clinic for prenatal consultation between 18 January 2018 and 2 April 2018. Our inclusion criteria were being at least 18-years-old, attending the first visit for prenatal diagnostic consultation, and ability to comply with the protocol procedures (including availability for follow-up visits). We excluded women with obstetrics related medical history or those who had previously received a prenatal diagnostic consultation.

Study Design and Procedure

The study design and analysis followed current guidelines for conducting DCEs in a healthcare setting (12-15). The DCE methodology is grounded in multi-attribute utility theory in economics. The technique is based on the assumption that any commodity (e.g., prenatal diagnosis test) can be characterized by several key attributes and their levels (e.g., test procedure, detection rate, test cost). Therefore, individuals choose among their options (e.g., different diagnostic tests) by comparing those attributes and levels.

In this study, we presented a questionnaire to the study participants that described a vignette following with 13 questions. The vignette described a hypothetical situation in which the participants are at increased risk of having an abnormal baby (genetic-related) and need to decide among different diagnostic tests available to them. The 13 questions presented to patients comprised of 1 demographic question and 12 choices question. Table 2 shows a sample choice question. Each choice question included three choice options: diagnostic test A, diagnostic test 2, and No test option. We used five attributed to characterize hypothetical tests: test procedure, wait time for test results, detection rate, the risk of miscarriage, and test cost (Table 1). In each choice question, participants were asked to choose one of the three options that they perceived to be better by comparing their attributes. The next 11 choice questions followed a similar format, but test profiles varied as we changed the attribute levels in each question each time and asked participants to make their choices based on the new test profiles. Using this approach, we can understand the impact of test attributes on choices that are made.

The test profiles presented in choice questions were created by generating permutations of attribute levels. There are total 360 combinations we could generate based on the level of each attribute. We then created a fractional factorial design using Sawtooth that met balance and orthogonality properties (14). Balance (i.e., each attribute level appears equally often within an attribute) and orthogonality (i.e., each pair of levels appears equally often across all pairs of attributes) ensures minimizing the bias and improves the precision of estimated preferences. We generated 100 versions of the questionnaire and assigned each respondent to a version in a random manner to facilitate achieving balance and orthogonality. Three of 12 choice questions presented fixed scenarios that did not vary across This include three fixed (question 1, 6 and 12) and nine random choice questions. This is a web-based questionnaire and facilitated direct data entry into our secure server. This questionnaire was performed using the Choice Based Conjoint application of Sawtooth Lighthouse Studio (SSI Web version 9.4.0; Sawtooth Software Inc;).

Statistical Analysis

The data collected in DCE allows quantifying the correlation between the choices made and attribute levels of various test profiles. For this purpose, a conditional logit regression model was used to analyze the DCE data(16) where the choices were used as dependent variable and attribute level of tests as covariates. The levels for the test procedure, time to wait for results, detection rate, miscarriage, and test cost were effects coded. The conditional logistic model provided statistical inferences about respondents' preference weights for each of the attributes and levels included in the questionnaire. The coefficients sign (positive or negative) indicates the direction of the women' preference for a given attribute level in the conditional logit regression model. To understand the trade-offs that the participants were willing to make between attributes (Test procedure, Time to wait for results, Detection rate, Miscarriage), we calculated the marginal rate of substitution between cost and each attribute and attributed importance. The attribute importance (ranking information) was incorporated into the Mixed Logit. We explored incorporating the ranking information by estimate the covariate explaining marginal utilities and a contraction of the marginal utility towards zero where the degree of contraction. Sawtooth Lighthouse Studio (SSI Web version 9.4.0; Sawtooth Software Inc;)was used to perform statistical analysis.

Table 1. Attributes and levels

Attributes	Levels of attributes (regression coding)	
Test procedure	L1	Invasive: requires collecting samples from amniotic fluid or placenta
	L2	Non-invasive: only requires a sample of mother's blood
Time to wait for results	L1	1 week
	L2	2 weeks
	L3	3 weeks
Detection rate	L1	94%
	L2	96%
	L3	98%
	L4	100%
Miscarriage	L1	3%
	L2	4%
	L3	5%
Test cost	L1	RMB$0
	L2	RMB$2000
	L3	RMB$4000
	L4	RMB$6000
	L5	RMB$8000

Table 2. A Sample Discrete Choice Experiment Choice Question

<u>Question</u>

If Prenatal test A, B, or neither were your only options, which one would you choose?

Attributes	Test A	Test B	Neither
Test procedure	Invasive: requires collecting samples from amniotic fluid or placenta	Non-invasive: only requires sample of mother's blood	No test, no cost, and 3% risk of miscarriage.
Time to wait for results	3 weeks	1 weeks	
Detection rate	94%	100%	
Miscarriage	5%	3%	
Test cost	RMB$2000	RMB$4000	
	☐	☐	☐

Ethical Consideration

Ethics approval has been gained from The Institutional Review Board (IRB) of The First Affiliated Hospital of Sun Yat-sen University, China and was reviewed and approved by the Brigham and Women's Hospital Institutional Review Board. Qualified research staff has been trained on ethics and data protection issues before recruitment.

Results

A total of 92 women who visited the clinic for prenatal diagnostic consultation and provided complete responses to all questions were included in the analysis. Initially, 136 women were approached during their visit to the clinic. Of those, 19 women (11.6%) declined to participate in the study and 25 (18.4%) did not complete all choice questions and were excluded for analysis.

The mean age in our sample was 31.9 (SD: 5.2) years and the mean gestational week was 14.0 (SD: 5.5) weeks. Almost one-third of respondents (n = 31; 34%) reported that they had a fetus abnormality during a previous pregnancy, such as a genetic abnormality or spontaneous abortion. Four (4%) of the respondents reported a family history of fetus abnormality and 13 (14%) knew of friends or relatives with a history of fetus abnormality. The demographic information of the participants is summarized in Table 3.

Table 3. Demographics and Characteristics of Patients in this Study

Variable	N=92
Age, mean (SD) years	31.9 (5.2)
Gestational week, mean (SD) weeks	14.0 (5.5)
Abnormality of a fetus of previous pregnancy (%)	31 (34%)
Family history (%)	4 (4%)
Abnormality of fetus history of friends or relatives (%)	13 (14%)

Among the 92 respondents, 65 (70.7%) chose the non-invasive procedure choice for question 1 (choosing between non-invasive, invasive, and neither). The details of these options are: (1) Non-invasive, only requires a sample of the mother's blood, 2-week results wait time, 98% detection rate, 3% miscarriage rate, and RMB$4000; (2) Invasive, requires collecting samples from amniotic fluid or placenta, 3-week results wait time, 98% detection rate, 5% miscarriage rate, and RMB$6000; and (3) No test, no cost, and 3% risk of miscarriage. These three choices represented the current practice, and 14 (15.2%) of the participants selected No test (Table 4). Six respondents (6.5%) chose the 'No test' option for all 12 questions, regardless of the attribute levels of the presented tests. Among the remaining respondents, 23 (25%) failed to choose the dominant treatment option in at least one fixed choice question (fixed choice questions 2 and 3).

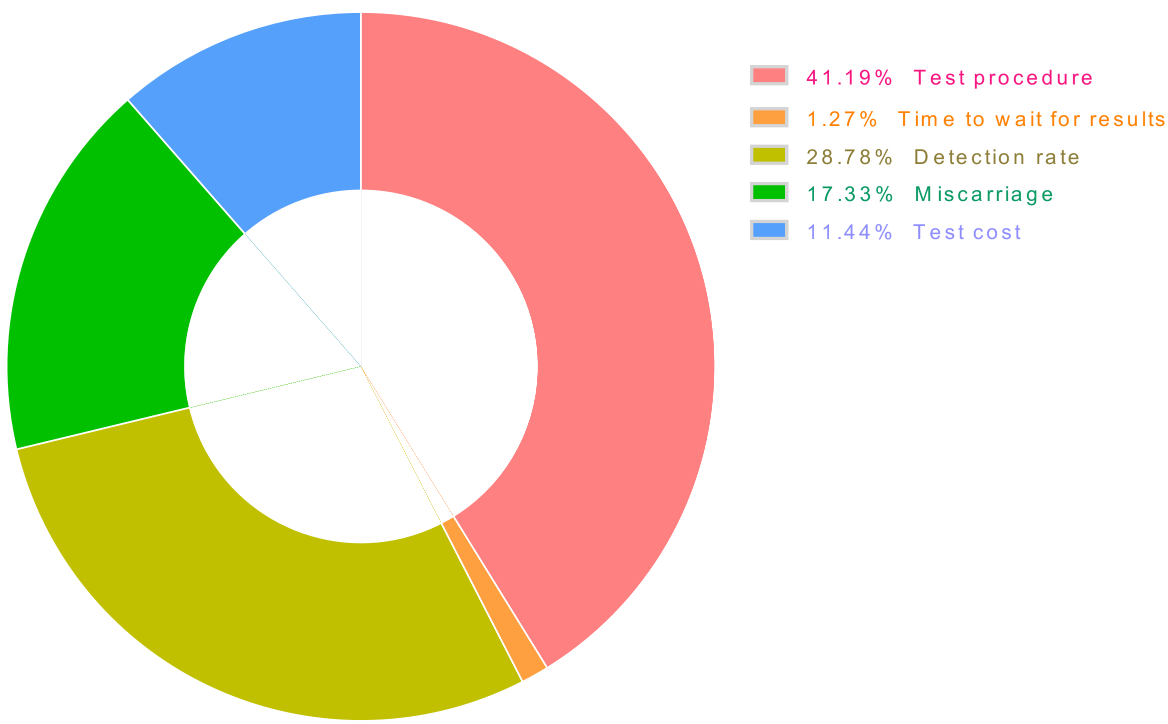
Table 4. Response of fixed questions (n=92)

Response	Fixed Question 1	Fixed Question 2	Fixed Question 3
	Current clinical practice	Test B Dominant	Test A Dominant
Test A	65 (70.65)	8 (8.70)	73 (79.35)
Test B	13 (14.13)	73 (79.35)	8 (8.70)
No test	14 (15.22)	11 (11.96)	11 (11.96)

Importance of attributes

Overall, the respondents in our experiment considered the test procedure as the most important attribute, followed by detection rate, miscarriage rate, and test cost, respectively. Wait time for the results was considered the least important aspect of the test (Figure 1).

Figure 1. Importance of attributes



Conditional logit model

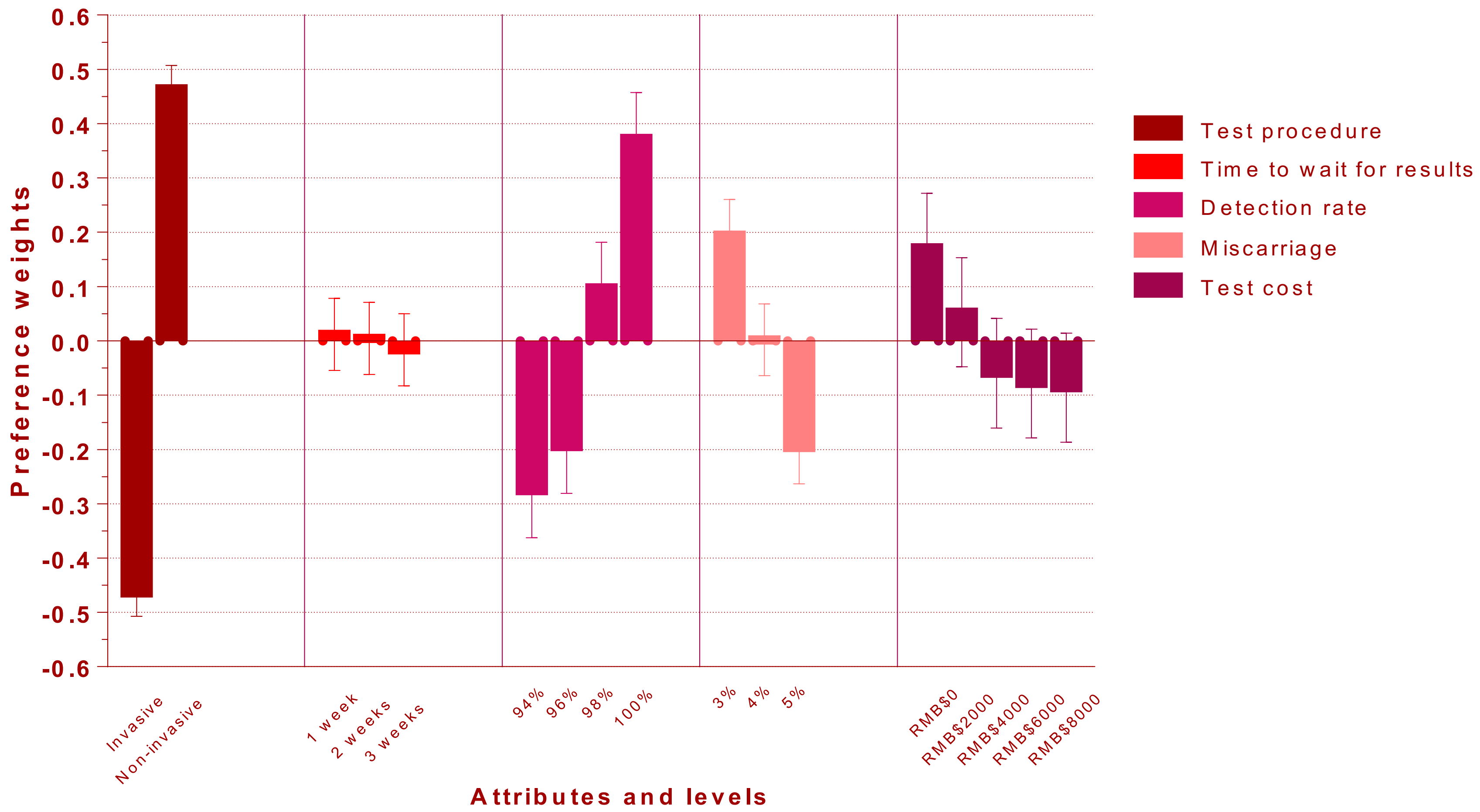
The results of the conditional logit model are presented in Table 5, which includes estimated average preference weights, standard error, and p-values for all attribute levels. The estimated odds ratios and their confidence intervals are also reported in Table 5. Figure 2 provides a visual presentation of the estimated preference weights in our study sample (n = 92). The estimated preference weight for the non-invasive procedure was 0.928 (P-value < 0.0001). All other attributes being equal, the odds of choosing a non-invasive test procedure over an invasive one was 2.53 (95%CI 2.42–2.64). The patients also had a positive preference weight for higher levels of detection. While using a 94% detection rate as a reference group, the odds of choosing 96% was 1.085 (95%CI 0.995–1.182), 98% was 1.453 (95%CI 1.336–1.580), and 100% was 1.913 (95%CI 1.758–2.082). The negative preference weights increase for a 1-week waiting time. The odds for choosing 2-week and 3-week wait times were 0.992 (95%CI 0.929–1.061) and 0.972 (95%CI 0.909–1.039) respectively. Patients had a large negative preference related to miscarriage complication increase. The odds of opting for an additional 1% risk of miscarriage was 0.825 (95%CI 0.772–0.881) and for an additional 2% risk was 0.677 (95%CI 0.633–0.724). There is negative preference related to a cost increase. The odds of choosing RMB$2000 was 0.888 (95%CI 0.803–0.982), RMB$4000 was 0.794 (95%CI 0.717–0.878), RMB$6000 was 0.779 (95%CI 0.704– 0.861), and RMB$8000 was 0.773 (95%CI 0.699–0.854).

The coefficients signs of the test procedure and detection rate suggest that women prefer a non-invasive test with higher detection rate. The negative coefficient for time to wait for results > 2 weeks, the risk of miscarriage > 4%, and test cost > RMB $2000 indicate a preference for an earlier test, lower miscarriage rate, and lower test cost.

Table 5. Estimated Relative Preference Weights

	Estimated preference weights				Odd ratio	
Attribute	Level	Coefficient	Standard Error	P value	Odd ratio	95% CI
Test procedure	Invasive: requires collecting samples from amniotic fluid or placenta	-0.464	0.043	<0.001	Reference	
	Non-invasive: only requires sample of mother's blood	0.464	0.043	<0.001	2.531	(2.424 - 2.642)
Time to wait for results	1 week	0.012	0.066	0.856	Reference	
	2 weeks	0.004	0.066	0.946	0.992	(0.929 - 1.061)
	3 weeks	-0.017	0.066	0.804	0.972	(0.909 - 1.039)
Detection rate	94%	-0.276	0.087	0.002	Reference	
	96%	-0.195	0.086	0.026	1.085	(0.995 - 1.182)
	98%	0.098	0.084	0.246	1.453	(1.336 - 1.580)
	100%	0.373	0.085	0.004	1.913	(1.758 - 2.082)
Miscarriage	3%	0.194	0.066	0.978	Reference	
	4%	0.002	0.066	0.004	0.825	(0.772 - 0.881)
	5%	-0.196	0.067	<0.001	0.677	(0.633 - 0.724)
Test cost	RMB$0	0.172	0.100	0.091	Reference	
	RMB$2000	0.053	0.101	0.601	0.888	(0.803 - 0.982)
	RMB$4000	-0.060	0.101	0.558	0.794	(0.717 - 0.878)
	RMB$6000	-0.079	0.100	0.436	0.779	(0.704 - 0.861)
	RMB$8000	-0.086	0.100	0.392	0.773	(0.699 - 0.854)
Log likelihood			-757			
Log likelihood of model without predictors			-910			
Akaike Info Criterion (AIC)			1539			
Bayesian Information Criterion (BIC)			1600			

Figure 2. The visual presentation of estimated preference weights in the full sample



Willingness to pay

Participants had a strong preference for a non-invasive test and were willing to pay up to RMB$28,810 (approximately US$4,610) for a non-invasive test. Also, women were willing to pay RMB$6,061(US$970) to reduce the miscarriage rate 1 % and up to RMB$3,356(US$537) to increase 1% of the detection rate of the test. Women were less sensitive to the wait time for the result, and they were willing to pay RMB$443 (US$71) for a 1-week reduction in wait time. (Table 6)

Table.6 Willingness to pay

Attribute	Willingness to pay	
	RMB ($)	USD ($)
Test procedure (non-invasive)	28810	4610
Time to wait for results (per 1-week reduction)	443	71
Detection rate (per 1% increase)	3356	537
Miscarriage (per 1% reduction)	6061	970
Test cost	Reference	

$1 RMB = $0.16 USD

Discussion

The choice of prenatal diagnosis is an important clinical decision for women with high-risk pregnancy. Factors such as the robustness of the test, the test cost, and the preferences of women need to be considered in the design and implementation of national screening programs. Therefore, understanding the trade-offs that women are willing to make among different attributes of tests can provide useful information to physicians and decision makers. Using a discrete choice experiment, we elicited relative preferences regarding different attributes of prenatal diagnostic testing. We found that when making decisions regarding prenatal testing, women have significant preference for non-invasiveness and high detection rate of the tests. On average, however, women are not sensitive to the wait time for receiving the results as compared with other attributes.

Although the risk of miscarriage was not the most important concern among our participants, it had a significant impact on choices. When compared to other DCE studies regarding Down's syndrome screening, women in our study place relatively less emphasis on test safety (i.e., miscarriage rate). This finding also differs from research from the United States in which women thought the most important feature of NIPT would be the safety of the fetus. One possibility to account for these differences is that women in our cohort have a relatively higher history of abnormality of the fetus in a previous pregnancy (34% of the participants). Our participants are also more concerned about the accuracy of the test than the miscarriage complication, meaning that for our study participants having a baby without genetic disease was more important than a procedure complication such as miscarriage. These findings might have resulted from family planning policy (two-child policy) that influences families' decisions and choices in China. Our results show that the invasiveness of test procedure was the most influential attribute for women when they chose prenatal tests.

Six respondents (6.5%) chose no test in all 12 choice questions, regardless of the probabilities presented in the question. This indicates that patients require greater guidance in their decision making. Apart from the women preference we found in the study, we suggest that physicians' training and communication skills on consultation are likely to be vital for the successful introduction of NIPT as the physicians could provide precise information based on the women preference. Because the women are most concerned about the test procedure and safety (extra miscarriages rate), more detailed information of the tests should be provided to the woman about the available testing options and the tests relative advantages and disadvantages.

There a are some DCEs studies published and examine preferences for screening and diagnostic tests, looking at attributes such as miscarriage risk (17-22).

Our study offers a systematic method to incorporate woman' opinions in a choice of prenatal diagnostic tests, which we believe can become a useful tool in patient-centered outcome research. We hope to integrate these results in the harm-benefit analysis of prenatal diagnostic tests for high-risk patients. We believe that the results of this study can inform decisions about safety evaluation of current and new prenatal diagnostic tests. We also believe that these results can help improve the quality of conversations about prenatal diagnostic tests between physicians and women with a high-risk pregnancy.

An important advantage of using DCE is that it allows quantifying individuals' preferences for multiple attributes, as well as the trade-offs that they are willing to make among those attributes. In this study, we collected useful information about women's preferences for prenatal diagnostic testing by recruiting from a major hospital of Guangzhou city. Several issues, however, may limit the generalizability of our findings. Most pregnant women who took part in this study were living in the city, and our sample is not representative of the whole population of women in a similar situation in China. Preferences of women living in rural areas could be different and need to be explored in the future studies using larger and more representative samples. Our study had a small sample size. Our estimated preference weights were robust with acceptable confidence intervals. However, conducting further subgroup analysis could be challenging given the sample size. For the McFadden's conditional logit, also known as multinomial logit (9, 20-22), we used in this paper; the strength includes this focuses on average preference, a parsimonious estimator with a unique solution, requires relatively small sample size. However, the limitations of this methodology are the assumption of homogeneity in preference. A further study on latent class analysis is needed to understand the different class preference. Only five attributes were considered for characterizing prenatal diagnostic tests. However, in the real-life situation, other factors may affect choices about prenatal tests, such as limitation of the test (such as cannot perform Chorionic villus sampling excess 13 gestation weeks), false positives access to tests and physician consultation. Qualitative approaches that provide an in-depth understanding of the women's thought process and preferences regarding NIPT could complement and enhance our results using quantitative DCE approach.

Conclusions

Guidelines for the implementation of NIPT need to consider women's preference to ensure patients' need and proprieties are met as much as possible. The implementation of NIPT for routine antenatal care in China will depend on multiple factors, such as test procedure, accuracy, miscarriage risks, and costs.

Women's strong preference for non-invasive tests demonstrates that consideration for the safety of the fetus and the access to the test. Apart from this, women also concern the surgery pain (test procedure) when making decisions regarding prenatal testing. This indicates the need for effective pretest counseling and to ensure women's better understanding of the testing process. This could lead to better-informed decisions that accommodate patient preference and values as well. Future studies conducted in larger and more representative samples are needed to enforce our current findings and to facilitate measuring potential preference heterogeneity among women.

Disclosure

The authors declare no conflict of interest.

Sources of Funding

No funding was used for the conduct of this study.

Paper 2

Understanding variation in women's preferences for prenatal diagnostic tests: A latent class analysis of choice data.

Paper 2 Understanding variation in women's preferences for prenatal diagnostic tests: A latent class analysis of choice data.

Background

Prenatal diagnostic tests can be used to prevent abnormal delivery in high-risk pregnancies, including cases of Down syndrome. Women whose babies are found to be at an increased risk of gene abnormality have traditionally been offered invasive prenatal diagnosis such as chorionic villus sampling or amniocentesis, which has long been the gold standard method for affirming the end result with high accuracy. Non-invasive prenatal testing (NIPT) using cell-free DNA (cfDNA) from maternal blood has become an attractive alternative option for prenatal tests in the recent years. NIPT has >99% sensitivity and specificity, but they are often more expensive and not listed as the first-line tests in the national guidelines in the past two decades. It is crucial to provide women with accurate information about the benefit-risk profile of different testing methods such as miscarriage rate, detection rate, and cost. Understanding women's preferences for prenatal diagnostic tests is also essential for physicians to ensure successful prenatal consultation.

Discrete choice experiment (DCE) is a useful method to for eliciting preferences and has been commonly used in healthcare's setting in the recent years. Our previous study using DCE showed that overall, women in our sample put a higher emphasis on invasiveness of testing procedure and detection rate when choosing among different tests. However, our results reflected average preferences of participants, and we did not explore the potential differences that might exist among women. The conditional logit used in our previous study assumed preference homogeneity among the study population. In reality, however, we expect to see differences in preferences across women, that reflect variation in their values, personal experience, or characteristics among other factors.

In this study, we extended our analysis to explore underlying heterogeneity in references of women when choosing among prenatal diagnostic tests using a latent class analysis (LCA). In the context of DCE, LCA is a useful method to identify sub-groups of respondents with more similar preferences.

Materials and Methods

Study design and population

The study design and analysis followed current guidelines for conducting DCEs in a healthcare setting (12-15). This study used a cross-sectional survey that involved the completion of a questionnaire consisting of 13 questions. The sample was recruited from a group of women with relatively high-risk pregnancy who visited an outpatient clinic for prenatal consultation in China between January 18, 2018, and April 2, 2018. Patients were approached by clinical fellows at clinic's waiting room, and those who consented to participate were asked to complete the questionnaire. The study was conducted at the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. All participants were at least 18 years old, and we excluded those who had a previous prenatal diagnostic consultation for the current pregnancy.

Study Procedure

A DCE was used to elicit patients' preferences for different attributes of prenatal diagnostic tests. The DCE methodology is grounded in multi-attribute utility theory in economics and is a technique to measure individuals' valuation of different aspects of their potential options. This theory is based on the assumption that any commodity (such as prenatal diagnosis tests) can be characterized by several key attributes and their levels (such as test procedure, detection rate, and test cost) and that individuals choose among their available options by comparing those attributes and levels.

In this study, the vignette in the questionnaire described a hypothetical situation in which participants want to choose among different diagnostic tests. The questionnaire then included 1 demographic question followed by 12 choice questions. In each choice question, they could choose among three options (Test A, Test B, or No test) by comparing their attributes. Each item was characterized using five attributes: test procedure, the wait time for test results, detection rate, the risk of miscarriage, and test cost (Table 1). The options varied in terms of the value of these 5 attributes. Table 2 shows a sample DCE choice question.

Statistical Analysis

We coded the choice data. All levels of five attributes were effects coded (test procedure, time to wait for results, detection rate, miscarriage risk, and test cost). A conditional logit regression model was used to analyze the DCE data (16). We then conducted LCA to identify classes of individuals with similarities in their preferences (23-25). LCA is a semiparametric approach that explores the correlation structure of the choice data and identifies classes that are more homogenous in terms of variance structure. Using this approach, we could identify distinct classes of women in our sample in terms of their preference pattern. Therefore, LCA can help to understand underlying heterogeneities among women's preferences.

The data collected in DCE allows quantifying the correlation between the choices made and attribute levels of various test profiles. For this purpose, a conditional logit regression model was used to analyze the DCE data (16) where the choices were used as dependent variable and attribute level of tests as covariates. The levels for the test procedure, time to wait for results, detection rate, miscarriage, and test cost were effects coded. The conditional logistic model provided statistical inferences about respondents' preference weights for each of the attributes and levels included in the questionnaire. The coefficients sign (positive or negative) indicates the direction of the women' preference for a given attribute level in the conditional logit regression model. In order to understand the trade-offs that the participants were willing to make between attributes (Test procedure, Time to wait for results, Detection rate, Miscarriage), we calculated the marginal rate of substitution between cost and each attribute and attributed importance.

Exploring preference heterogeneities using an LCA involves repeating the analysis for a various pre-specified number of classes (2 to 5 classes). The optimum number of classes was determined by comparing the model fit based on Akaike information criteria (AIC) and Bayesian information criteria (BIC). We also considered the resulted class sizes to ensure obtaining classes with a meaningful number of members in them.

The attribute importance (ranking information) was incorporated into the Mixed Logit. We explored incorporating the attribute importance of different class by estimate the covariate explaining marginal utilities and a contraction of the marginal utility towards zero where the degree of contraction. Willingness to pay was calculated by a spreadsheet of the Microsoft Excel (Microsoft, Redmond, WA). Sawtooth Lighthouse Studio (SSI Web version 9.4.0; Sawtooth Software Inc;)was used to perform statistical analysis.

Ethical Consideration

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University, China, as well as by the Brigham and Women's Hospital Institutional Review Board. Research staff involved in this study which recruited participants at the clinic were trained on ethics and data protection issues before study launch. All participants were allowed to withdraw at any point during the survey without any impact on the usual care that they received at the clinic.

Table 1. Attributes and levels

Attributes	Levels of attributes (regression coding)	
Test procedure	L1	Invasive: requires collecting samples from amniotic fluid or placenta
	L2	Non-invasive: only requires a sample of mother's blood
Time to wait for results	L1	1 week
	L2	2 weeks
	L3	3 weeks
Detection rate	L1	94%
	L2	96%
	L3	98%
	L4	100%
Miscarriage	L1	3%
	L2	4%
	L3	5%
Test cost	L1	RMB$0
	L2	RMB$2000
	L3	RMB$4000
	L4	RMB$6000
	L5	RMB$8000

Table 2. A Sample Discrete Choice Experiment Choice Question

<u>Question</u>

If Prenatal test A, B, or neither were your only options, which one would you choose?

Attributes	Test A	Test B	Neither
Test procedure	Invasive: requires collecting samples from amniotic fluid or placenta	Non-invasive: only requires sample of mother's blood	No test, no cost, and 3% risk of miscarriage.
Time to wait for results	3 weeks	1 weeks	
Detection rate	94%	100%	
Miscarriage	5%	3%	
Test cost	RMB$2000	RMB$4000	
	☐	☐	☐

Results

Table 3 showed the baseline characteristics of patients in this study. The mean age of the women was 31.9 (SD: 5.2), and the gestational age was 14.0 (SD: 5.5). Among these women, 34% have an abnormality of a fetus of previous pregnancy, 4% of them have a family history, and 14% knew someone among their family or friends with a history of abnormality of the fetus. The AIC and BIC were minimized for LCA models with 3 classes, suggesting three segments of participants were identifying in the data. The preference weights for test attributes are presented in Figure 2 for the three classes: 35 (37.3%), 16 (17.4%), and 41 (45.3%) women fell into class 1, class, 2 and class 3, respectively. Class 1 had more substantial attribute importance toward test procedures. Class 2 was more sensitive to the test cost, and class 3 had more massive attribute importance for a higher detection rate and more considerable attribute importance for a lower risk of miscarriage. The preference for the time to wait for the results varied and were relatively unimportant among the three groups. For class 3, there was a significant difference in the rate of fetus abnormalities from a previous pregnancy among the three classes.

Table 3 Baseline Characteristics of Patients in this Study

	N=92
Age, mean (SD)	31.9 (5.2)
Gestational week, mean (SD)	14.0 (5.5)
Abnormality of a fetus of previous pregnancy	31 (34%)
Family history	4 (4%)
Knew someone among their family or friends with a history of abnormality of the fetus	13 (14%)

Figure 1. Importance of attributes by classes

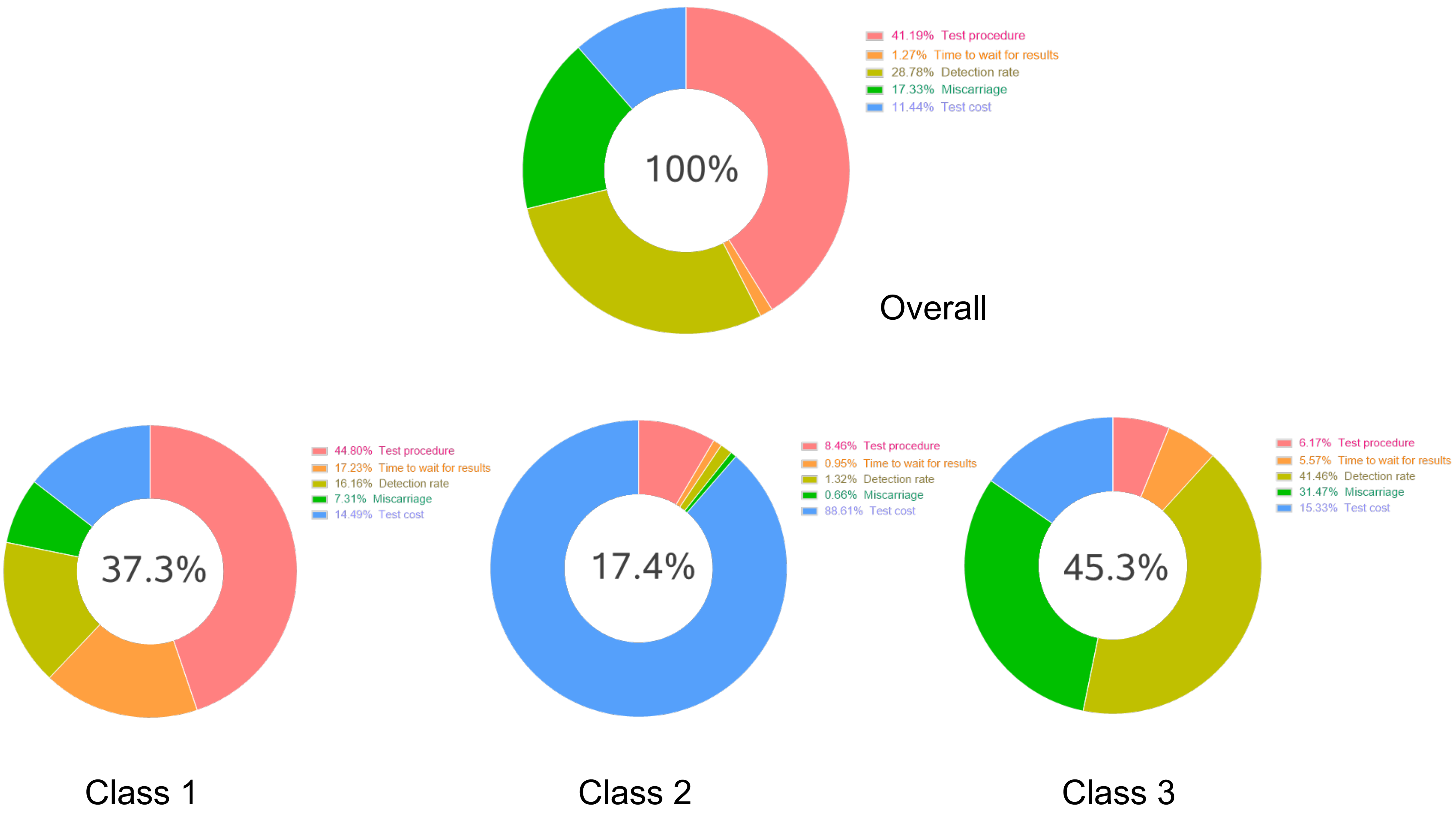


Table 4 Estimated Relative Preference Weights

Attribute		Class 1 n=35 (37.3%)			Class 2 n=16 (17.4%)			Class 3 n=41(45.3%)		
		Coefficient	SE	P value	Coefficient	SE	P value	Coefficient	SE	P value
Test procedure	Invasive	**-2.599**	**0.390**	**<0.001**	**-1.711**	**0.508**	**0.004**	0.064	0.056	0.257
	Non-invasive	**2.599**	**0.390**	**<0.001**	**1.711**	**0.508**	**0.004**	-0.064	0.056	0.257
Time to wait for results	1 week	**-1.305**	**0.422**	**0.004**	0.197	0.310	0.534	0.035	0.090	0.701
	2 weeks	0.693	0.348	0.055	-0.187	0.326	0.574	0.041	0.092	0.658
	3 weeks	0.612	0.324	0.067	-0.010	0.307	0.975	-0.076	0.092	0.413
Detection rate	94%	-0.469	0.365	0.208	-0.085	0.385	0.829	**-0.433**	**0.121**	**<0.001**
	96%	-0.559	0.396	0.167	-0.127	0.431	0.772	-0.216	0.118	0.074
	98%	-0.287	0.351	0.418	-0.161	0.383	0.680	0.215	0.117	0.073
	100%	**1.315**	**0.461**	**0.007**	0.373	0.366	0.323	**0.434**	**0.118**	**<0.001**
Miscarriage	3%	0.220	0.294	0.460	0.124	0.305	0.689	**0.366**	**0.092**	**<0.001**
	4%	0.314	0.268	0.249	0.018	0.316	0.955	-0.074	0.090	0.415
	5%	-0.534	0.312	0.095	-0.142	0.333	0.676	**-0.292**	**0.092**	**0.003**
Test cost	RMB$0	**1.025**	**0.480**	**0.040**	7.816	649.738	0.991	0.131	0.142	0.361
	RMB$2000	-0.518	0.490	0.298	6.910	649.738	0.992	0.142	0.140	0.318
	RMB$4000	0.030	0.427	0.945	7.084	649.738	0.991	-0.179	0.139	0.207
	RMB$6000	0.119	0.390	0.761	-28.019	2598.950	0.992	0.000	0.142	0.999
	RMB$8000	-0.657	0.441	0.145	6.209	649.738	0.992	-0.094	0.141	0.510

Willingness to pay

For Class 1, the willingness to pay estimates confirmed women's strong preference for a non-invasive test, as they were willing to pay RMB$24727 (US$3956) to avoid an invasive test. Women were willing to pay RMB$1794 (US$287) to reduce the miscarriage rate by 1% and RMB$1415 (US$226) to increase the detection rate of the test by (1%). The women in class 1 were more sensitive to waiting time for the result than those in the other two classes; we found that women were willing to pay RMB$4561 (US$730) for a reduction in waiting time of one week.

Women in Class 2, had a strong preference for a non-invasive test and were willing to pay up to RMB$17034 (US$2725) to avoid an invasive test, assuming everything else being equal. However, they were only willing to pay RMB$663 (US$106) to reduce the miscarriage rate by 1% and RMB$379 (US$) to increase the detection rate of the test by 1%. Members of this class also were not sensitive to waiting time for the result as compared to other two classes and were willing to pay up to RMB$515 (US$82) for a reduction in waiting time of one week.

Women in Class 3, had smallest importance score for non-invasiveness of the test and were wiliness to pay up to RMB$4589 (US$743) for that. In contrast, they were willing to pay RMB$11708 (US$1873) to reduce the miscarriage rate by 1% and RMB$5142 (US$823) to increase the detection rate of the test by 1%. This is 6 times and 15 times larger than WTP estimates for class 1 and class 2, respectively in the concern of miscarriage. Similarly, the women were more sensitive to the waiting time for the result than the other two classes; Women in class 3 were willing to pay RMB$1967 (US$315) for a reduction in waiting time of one week (Table 5).

Table 6 showed the demographics and characteristics of patients in this study among classes, the mean age of the women is 33.5 (SD: 5.9), 32.1 (SD: 4.9) and 30.5 (SD:4.4), respectively in class 1, class 2 and class 3. There is no is statistically significant in the mean age of the women, family history and abnormality of fetus history of Friends of relatives among three groups. In contrast, Class 1 with highest mean gestational age 16.1 (SD: 6.8) and the mean gestational age are 12.1 (SD: 1.9) and 13.3 (SD: 4.9), respectively in class 2 and class 3. There is statistically significant among three groups with the gestational age (P = 0.043). For the abnormality of a fetus of previous pregnancy, Class 2 with the higher proportion in Class 1 (37%) and Class 3 (41%) while class 2 only 6%. There is statistically significant among three groups with the gestational age (P = 0.035).

Table 5 Willingness to pay

Attribute	Willingness to pay							
	Overall N=92 (100%)		Class 1 n=35 (37.3%)		Class 2 n=16 (17.4%)		Class 3 n=41(45.3%)	
	RMB ($)	USD ($)	RMB ($)	USD ($)	RMB ($)	USD ($)	RMB ($)	USD ($)
Test procedure (non-invasive)	28810	4610	24727	3956	17034	2725	4589	743
Time to wait for results (per 1-week reduction)	443	71	4561	730	515	82	1967	315
Detection rate (per 1% increase)	3356	537	1415	226	379	61	5142	823
Miscarriage (per 1% reduction)	6061	970	1794	287	663	106	11708	1873
Test cost	Reference		Reference		Reference		Reference	

$1 RMB = $0.16 USD

Figure 2. visual presentation of estimated preference weights

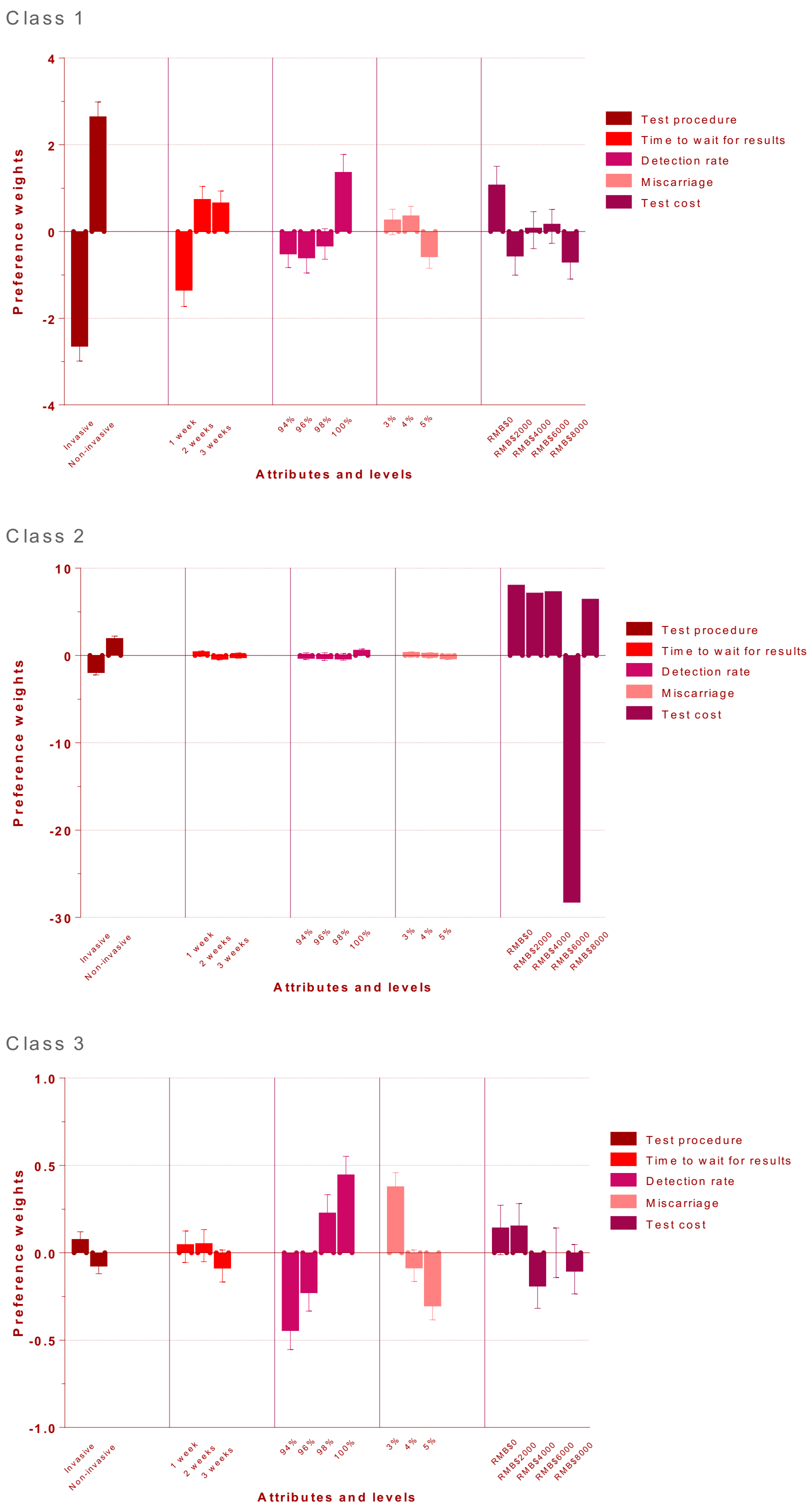


Table 6 Demographics and characteristics of patients in this study

	Class 1 n=35 (37.3%)	Class 2 n=16 (17.4%)	Class 3 n=41 (45.3%)	*p value*
Age, mean (SD)	33.5 (5.9)	32.1 (4.9)	30.5 (4.4)	0.052
Gestational week, mean (SD)	16.1 (6.8)	12.1 (1.9)	13.3 (4.9)	**0.043***
Abnormality of fetus of previous pregnancy	13 (37%)	1 (6%)	17 (41%)	**0.035***
Family history	1 (3%)	0 (0%)	3 (7%)	0.41
Abnormality of fetus history of Friends of relatives	4 (11%)	2 (13%)	7 (17%)	0.76

Discussion

In our study, the LCA revealed three classes of women who had different preference pattern for various test attributes.

Most patients want more information than is usually given, and many would like to increase their level of involvement in the decision-making process. Many women, however, are not aware of the inherent uncertainty in outcomes and the variation in performance and risks of different diagnostic testing options. Guidelines for the choice of prenatal tests should consider women's preference and fulfill both patients' needs and values as well as public health aspect of those choices. Therefore, there are difficult but inevitable choices that need to be made in clinical practice on a daily basis in by physicians for women with high risk pregnancies. Additional knowledge about patient preferences and their priorities and concerns can help physicians in a shared decision-making process. This information might help physicians focus on the factors that are important for patients and can influence their choice when deciding a prenatal diagnostic test.

The LCA has an advantage in exploring the association between preferences (class membership) and background characteristics. In our study, we found that having a history of the abnormal baby was associated with greater sensitivity of women with regards to the accuracy and the risk of miscarriage. In contrast, those without a history of the abnormal baby appeared to be more sensitive to the test cost.

Our results suggest that clinicians might want to focus on particular patient's needs to improve quality of consultation process. Clinicians can use this information to provide more targeted consultations and concentrate on the risks and benefits aspects of the test that might influence patient's decision. This will ideally result in better choices since it incorporates patient's concerns and preferences and the evidence on available diagnostic options in the decision-making process.

Our study has several limitations. We recruited women from a major hospital in Guangzhou city. However, this may have limited representativeness of our sample and therefore, the generalizability of our findings to all women in China. Other limitations of our study were the small sample size and self-reported exposures. Larger sample size would help to obtain more robust findings in the LCA analysis. Some inconsistencies in the order of estimated preferences that we have observed in our data might be caused by small sizes of classes, especially in class 2. We only included five attributes to characterize prenatal diagnostic tests. This was to avoid the complexity of choice questions and reduce the burden of questionnaires for the respondents. However, we acknowledge that choices regarding prenatal tests might be affected by other factors such as false positive rates and availability of diagnostic tests among others.

In the future, an in-depth exploration of the processes that leads to decisions about prenatal diagnostic tests using qualitative methods can be conducted to inform selection of attributes and for framing of the choice questions.

Conclusion

In conclusion, we identified classes of women who had different preferences for the diagnostic test attributes. Some of these differences in preferences could be partially explained based on the history of having an abnormal baby in the past. Our results might influence clinicians' perception of the aspects of diagnostic tests that need to be discussed with patients during the consultation.

Disclosure

The authors declare no conflict of interest.

Sources of Funding

No funding was used for the conduct of this study.

Summary of Paper 1 and Paper 2 conclusions

Guidelines for the implementation of NIPT need to consider women's preference to ensure patients' need and proprieties are met as much as possible. The implementation of NIPT for routine antenatal care in China will depend on multiple factors, such as test procedure, accuracy, miscarriage risks, and costs.

Women's strong preference for non-invasive tests demonstrates that consideration for the safety of the fetus and the access to the test. Apart from this, women also concern the surgery pain (test procedure) when making decisions regarding prenatal testing. This indicates the need for effective pretest counseling and to ensure women's better understanding of the testing process. This could lead to better-informed decisions that accommodate patient preference and values as well. Future studies conducted in larger and more representative samples are needed to enforce our current findings and to facilitate measuring potential preference heterogeneity among women.

We identified classes of women who had different preferences for the diagnostic test attributes. Some of these differences in preferences could be partially explained based on the history of having an abnormal baby in the past. Our results might influence clinicians' perception of the aspects of diagnostic tests that need to be discussed with patients during the consultation. Incorporating patient preferences can support more informed and patient-centered decision making. This could potentially improve the quality of care delivered and increase the patient satisfaction. Including family or caregivers in decisions may also help the process.

Discussion and perspectives

In this study, we elicited preferences for prenatal diagnostic tests among women who visited the prenatal clinic of a major hospital of Guangzhou City in China.

In the first study, we estimated average preference weight for different test attributes in the whole sample of 92 women. For this purpose, we used McFadden's conditional logit, also known as multinomial logit (11, 16, 26, 27) to analyze the choice data. Strengths of this approach included the focus on average preferences in the overall sample, a parsimonious estimator with a unique solution, and relatively small sample size required. However, the limitations of this methodology were the assumption of homogeneity in preference. LCA is a semiparametric approach that explores the correlation structure of the choice data and identifies classes that are more homogenous in terms of variance structure. Using this approach, we could identify distinct classes of women in our sample in terms of their preference pattern. Therefore, LCA can help to understand underlying heterogeneities among women's preferences.

Several issues might have limited the generalizability of our findings. Most pregnant women who took part in this study were living in an urban setting. A limitation of this study is that the sample is not representative of the whole population of women in similar health state in China. We would expect some differences between urban and rural women. For example, willingness to pay for a different aspect of tests might be profoundly influenced by income and social status of participants. Other limitations of our study were the small sample size and the use of self-reported exposures. Finally, we only used five attributes to describe prenatal tests. In reality, women and physicians might consider other factors in their decisions and choices among diagnostic tests. Larger sample size would help to obtain more robust findings in the LCA analysis

We have planned future work to address the following four areas: (i) increasing the sample size; (ii) Patient follow-up to obtain their clinical data and their actual test choice, and therefore, to compare their stated preferences (SP) with their revealed preferences

(RP); (iii) conduct the same survey in the community of healthcare professional to understand how their preferences are compared to women; (iv) conduct the same survey in a larger and more diverse population; and (v) to supplement our results with a qualitative study that provided an in-depth understanding of the thought process of pregnant women regarding choice of diagnostic tests.

Appendix

List of appendix files

1. Consent form

Consent form

Dear Study Participant,

Every day, patients like you decide between different prenatal tests. These choices can be difficult, because each test might have different benefits and risks. We are conducting a study to understand women's preferences for prenatal tests. I am writing to ask you to participate in this study.

If you participate, you will complete a 10-minute online survey.

○ **I WANT to participate in this study.**

○ **I DO NOT want to participate in this study.**

We understand that participation in this survey may cause anxiety for some patients. Your participation is voluntary. You can choose to skip a question or withdraw from the study at any time, and this will not affect the medical care that you receive in any way. If you have any questions, please feel free to contact Dr. Ming, Email: mingwj@mail.sysu.edu.cn / wai-kit_ming@hms.harvard.edu, phone: (86) 14715485116 (China) / (857) 930 8584 (US). Your rights to privacy are protected by both federal and state laws (both in the US and China), which ensure that any responses you provide will be kept confidential. If you would like to speak to someone not involved in this research, contact the Hospital IRB (86) 20-8775576 (China). Thank you for your support of this study.

Regards,

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Research Fellow, Harvard Medical School, United States

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