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Original article

Modification of non-invasive prenatal screening of Down syndrome: New approach using data mining analysis

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Abstract

Background: The introduction of next generation sequencing (NGS) in recent decade to determine fetal aneuploidies through cell free fetal DNA (cffDNA) in maternal circulation has caused new challenges for conventional prenatal first and trimester screening. Limiting the conventional screening tests to the most powerful criteria would be an appropriate strategy in reducing the time around and cost of traditional tests before non-invasive NGS method.

Methods: In this study, the most important factors affecting the risk of Down syndrome was found using statistical and data mining analysis of pregnant women undergoing conventional prenatal screening.

Results: First trimester proteinuria, previous history of Down syndrome, consanguinity, nuchal translucency (NT) and inhibin-A were the most significant factors identified to be associated with the risk of Down syndrome.

Conclusion: Incorporating those critical factors into new screening software could be valuable in advance of cffDNA testing as a perfect accurate non-invasive prenatal screening.

Keywords: Data Mining, Down syndrome, Prenatal screening, Risk factor

Introduction

Down syndrome (DS) is the most common cause of human mental retardation and live birth chromosomal abnormalities. Major health problems including significant heart risk factors, Alzheimer's disease, leukemia, and relatively short life span of DS patients are among convincing reasons to screen DS during early pregnancy (1, 2). The current approach recommended by American Congress of Obstetricians and Gynecologists (ACOG) for prenatal diagnosis (PND) of DS is primarily based on the selection of high-risk pregnancies using a combination of non-invasive first and second trimester assessment. High risk pregnant women can then undergo invasive procedures including Chorionic villus sampling (CVS) and amniocentesis to isolate fetal cells for karyotype analysis. Although the recent trials on the use of Cell-free fetal DNA (cffDNA) after the nine weeks of pregnancy have shed promising lights on non-invasive screening of DS, traditional screening programs are still the most commonly used methods to identify affected pregnancies. It was recommended that due to high false positive results of cffDNA testing, it should not be considered as the initial prenatal screening test (3). However, the sensitivity and specificity of the current cffDNA tests mostly based on next generation sequencing (NGS) is not 100%, and positive cases still require definite diagnosis through invasive tests (4). Traditional screening tests could be

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used for the identification of the most important risk factors, which may be more beneficial than conventional screening tests before cffDNA analysis. The first trimester screening includes the measurement of two biochemical markers, β-subunit of hCG gonadotropin β-hCG) and Pregnancy-associated plasma protein-A (PAPP-A) in maternal serum and an ultrasound marker known as nuchal translucency (NT). The second trimester screening comprises the detection of the serum levels of three biochemical markers in triple test including β-hCG, α-fetoprotein (AFP), and unconjugated estriol (uE3 or free estriol). The triple test is enhanced to quad test when Inhibin-A, as a marker, is added to the screening test. The maximum detection rate of combined first and second trimester screening is 96%, and the false positive rate is 5-10% (5). The detection rate of either the first or second trimester screening is solely 75-85% with the false positive rate of 3-5%. It is believed that maternal age and biochemical markers are the most essential parts of criteria to be considered. In most medical laboratories, especially those specializing prenatal screening, other risk factors are usually considered in forms filled by mothers. They usually report a number of gravidity and likely abortions, education and job, weight, weeks of pregnancy along with history of mongolism and other genetic disorders, drug, medical and familial problems, infertility, high blood pressure, proteinuria and gestational diabetes, in vitro fertilization (IVF), and other assisted reproductive technologies. However, except for biochemical markers and maternal age, none of other mentioned factors are considered in the final calculation of risk. Most software programs introduced for prenatal screening programs, especially version 5 of SsdwLab prenatal screening, have the ability to incorporate more than 10 markers with known Gaussian distribution and correlation coefficients (http://www.sbpsoftware.com/SsdwLab-5.html).

Determining the risk of DS may be modified with different medical, drug, and even demographic features of the mother. It was reported that pre-gestational diabetes may increase the chance of chromosomal nondisjunction and aneuploidies due to the presence of autoantibodies (6). On the other hand, the level of maternal biochemical serum markers has shown to be changed with the status of in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) induced and twin pregnancies, smoking, nulliparity against multiparity and ethnicity (7-9). To obtain the most flawless risk in order to minimize the demand for doing invasive procedures, final result should be adjusted for the mentioned factor so as to be as accurate as possible. Many relevant studies need to be performed to clearly define the role of those and other factors in determining the final risk of DS, 13 and 18.

Data mining, known as knowledge discovery of data, has many applications in engineering, marketing, and medicine, which can help find the most important, extrapolative data in the shortest time possible (10).

Herein, we aimed to assess the correlation between some of the major maternal demographic and medical parameters and the risk of fetal DS through specific data mining and statistical analyses. Final results can help us identify the most relevant and possibly effective risk factors of DS, which can be inserted in screening software for analysis. Confounding factors can also increase the rate of positive and negative results, which could be defined as soon as possible.

Materials & Methods

Patient selection

Pregnant women referring to do the second trimester screening, between 15-22 weeks of pregnancy (2012-2014), were randomly enrolled in the study. All the participants had their first trimester screening ultrasound including nuchal translucency (NT: fluid-filled region in the posterior of fetal neck) measurement. Maternal serum level of four biochemical markers including AFP, uE3, β-hCG and Inhibin-A were measured and were then represented as of multiple of the median (MoM) of normal pregnancies with similar age.

Statistical and data mining analysis

Test of normalization was performed on all obtained data by drawing histogram and the observed normalized patterns ($p<0.05$). Parametric tests were performed to analyze the difference of string variables between two normal and DS pregnancies. Chi square test was also used to seek the significantly different nominal and ordinal variables between both studied groups.

Both SPSS and data mining analysis were performed in two steps. Pilot study was done on 100 normal and 20 DS samples. In the second step of analysis, all obtained data, including 991 normal and 71 DS samples,

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underwent SPSS analysis, whereas 191 normal and 63 DS samples were selected to be analyzed through data mining.

Since the response variable, status of disease, is a binary variable, "generalized linear model" (GLM) was used to analyze the data to find the relation between status of disease and other parameters. GLM is a generalization of linear regression that includes both linear and logistic regression as special cases (11).

Typically, the GLM includes three elements:

- A probability distribution from the exponential family such as the Gaussian (normal), binomial, Poisson, families of distributions.
- A linear function of regression.
- A link function which transforms the expectation of the response variable to the linear predictor.

In case of binary response variable, the family of distribution is binomial and link function is Logic function.

In order to apply the method on the data, cv.glmnet (function from glmnet R-package) was used which fitted the GLM via penalized maximum likelihood. The regularization path was computed for the lasso or elastic net penalty at a grid of values for the regularization parameter lambda (for more information please see the reference (12).

In cv.glmnet (.) function, there is an elastic net mixing parameter, which controls the speed of convergence. In the first experiment, the examination of the relationship between disease and Inhibin-A, AFP, NT, and β-hCG, is set to be 0.5, and in the second experiment, the examination of the relationship between disease status and whole variables in the experiment is set to be 1.

Also, please note that cv.glmnet (.) function performs k-fold cross-validation (CV) for glmnet. The CV is a validation technique used to assess how a trained model by training samples can be generalized to an unseen data set, testing samples. In k-fold CV, the original data set is randomly partitioned into equal sized subsamples. In each step, one of the folds is retained as the validation data for testing the model, and the remaining k − 1-fold is used to train the model. The final estimation is the average of results obtained from each fold assessment. It is worth noting that 5-fold CV was used in both experiments.

Compliance with Ethical Standards

All the participants filled the consent forms according to 1964 Declaration of Helsinki and its later amendments or comparable ethical standards of the local Ethical Committee of Tehran University of medical sciences (Ethics code: 92-02-30-21577).

Results

SPSS analysis

Pilot SPSS analysis indicated a significant association between risk of DS and proteinuria, consanguineous marriage, NT measurement, Inhibin-A, maternal diabetes mellitus ($p<0.05$). SPSS analysis on selected samples has revealed that there was a significant association between DS pregnancy and positive previous history of DS, consanguineous marriage and proteinuria ($p<0.05$). Amongst quantitative variables, Inhibin-A, NT measurement, and the age were meaningfully associated with affected pregnancies by DS ($p<0.05$) (Table 1).

According to SPSS analysis of all obtained data, among quad biochemical markers, there was a meaningful association between DS and uE3 ($p=0.03$) and Inhibin-A ($p=0.02$). Among demographic characteristics, there was a significant association between the medium level of activity and risk of DS ($p<0.001$). In addition, the association of DS and diploma level of education was strong, while the risk was shown to be minimal for Master of Science (MSc) degree ($p<0.001$). Positive history of DS in any relatives of parents and the NT measurement were in strong association with the risk of DS ($p<0.001$).

Table 1: Mean of the analyzed parameters in the selected samples using SPSS analysis.

Prenatal factor	Normal Mean±SD	Down Syndrome Mean±SD	p-value
Gestational age	15±2.0	15±2.0	0.200
Age	28.8±5.4	29.8±5.2	0.600
α-fetoprotein	34.3±24.7	29.9±15.6	0.900
β-hCG*	47.5±39.3	61.7±334.6	0.400
uE3**	2.6±11.0	1.8±0.9	0.030
NT***	1.5±0.7	3.7±0.3	<0.001
Inhibin A	281.6±180.3	333.8±235.3	0.001

*β-hCG: Human Chorionic Gonadotropin (hCG), β-Subunit;
** uE3: free estriol; ***NT: Nuchal translucency

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Consanguineous parents also had statistically higher risk of having fetus affected by DS (p=0.02). In assessment of the effect of drug history during pregnancy, the consumption of any drugs during pregnancy has increased the risk of DS. To determine which type of drug has the most effect on the risk of DS, all the used drugs were classified into four major groups including: antibiotics, anti-inflammatory drugs, hormonal medications. A meaningful correlation was found between hormonal drugs and the risk of DS (p=0.01).

In an attempt to find an association between string variables and the maternal serum level of four biochemical markers, there was a significant correlation between AFP and β-hCG concentrations and gestational age (p=0.01). The number of gravidities was in meaningful correlation with serum β-hCG (p=0.01) and uE3 levels (p=0.05). It was also found that Inhibin-A concentration has a significant correlation with NT measurements (p=0.01).

The second part of statistical analysis was focused on the assessment of the effect of studied factors on the accuracy of the performed quad test. Positive drug history was significantly associated with higher rate of false positive results (p<0.001). Maternal weight and proteinuria were demonstrated to have significant effect on taking false positive and negative results, respectively. Although it was not meaningful, abnormal NT measurement was negatively correlated with the possibility of false positive rate.

Data mining analysis

Pilot data mining of 100 normal and 20 trisomy samples demonstrated considerable significant effect of Inhibin-A, NT, gestational age, age, gravidity number, proteinuria, weight, and education on the risk of DS.

In the second step of analysis, the assessment of 191 normal and 63 DS samples replicated the initial results for factors including Inhibin-A, NT and proteinuria. In contrast, with increasing one unit per each of mentioned factors in addition to consanguineous marriage, age and gestational age, no change was found in the calculated risk of DS (calculated risk=0).

As the data set is imbalanced, "down-sampling" technique was used and the working data set included normal samples as well as samples with DS.

Then, the data set was divided into 65% training and 35% testing samples and logistic regression model was adjusted using cv.glmnet (.) function. The best to fit the model was 0.059938.

The characteristics of the fitted model have been provided by presenting the coefficients as well as odd ratios (Table 2). Odd ratios are defined as the ratio of the probability of DS and the probability of being normal. The odd ratios for variables are calculated as well. One unit increasing in Inhibin A causes 0.16% growth in DS, and one unit increasing in NT causes 51% growth in DS.

After training the model, it was tested using the data set of samples that the model had never seen. The obtained accuracy on testing data was %76.7. The corresponding procedure was shown to find the best which generates the minimum misclassification error.

Table 2: Examination of relationship between DS and four parameters

Variable	Coefficients	Odds ratio
Intercept	2.4-	NA
Inhibin A	0.0	1.0
α-fetoprotein	0.0	1.0
NT*	0.4	1.5
β-hCG**	0	1.0

*NT: Nuchal translucency;
**β-hCG: Human Chorionic Gonadotropin (hCG

The name of variables and corresponding coefficients as well as odd ratios have been described (Table 3). According to this information, a unit increasing in gestational age and age in case the other parameters are constant can respectively cause 6.5% and 5.1% growth in risk of DS. About Inhibin A and NT this growth is 0.2% and 67.8%, respectively, while the other parameters are constant.

Having no proteinuria and history of DS can cause 44.7% (100*(1-0.5535)) and 84. 6% (100*(1-15.4)) decline in risk of DS, respectively. Also, being non-consanguineous can cause decrease risk of DS up to 5.3%. The model was also tested using unseen data, and 78.9% accuracy achieved.

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Table 3: Examination of relationship between disease status and four parameters

Variable	Coefficient	Odd ratio
(Intercept)	-2.9	NA
Gestational Age	0.1	1.1
Age	0.1	1.1
Gravidity	0	1
α-fetoprotein	0	1
β-hCG*	0	1
uE3**	0	1
Inhibin-A	0.0	1.0
Nuchal translucency	0.5	1.7
Abortion's number	0	1
weight	0	1
No high blood pressure	0	1
Negative proteinuria	-0.6	0.6
Twin Pregnancy	0	1
Negative history of DS***	-1.9	0.2
IVF	0	1
Diabetes mellitus	0	1
Smoking	0	1
Infertility	0	1
Familial history	0	1
Medical history	0	1
All grades of education	0	1
All grades of job	0	1
Non-consanguinity	-0.1	0.9
Drug usage	0	1

*β-hCG: Human Chorionic Gonadotropin (hCG),
** uE3: free estriol;*** DS: Down Syndrome

Discussion

Herein, using Data mining analysis and SPSS evaluation, proteinuria, positive history of DS, NT, Inhibin-A and consanguinity are the major risk factors of DS found in our sample population.

Either excretion of protein in urine more than 300 mg/day or ≥ 2+ on a dipstick is diagnosed as proteinuria (13). In the Data mining analysis, it was found that negative history of proteinuria was associated with 44.7% decrease in risk of DS. This was confirmed in the pilot SPSS analysis in addition to the significant effect of proteinuria on false negative results. It was previously determined that maternal proteinuria was associated with higher AFP level of serum owing to pathologic increase in vascular permeability of placental vessels (14, 15). Higher level of AFP can confound the true result of prenatal screening and lead to generating either false positive or negative score of screening. The false effect of maternal age has been demonstrated in various studies on getting untrue prenatal screening result which was further approved here through data mining and SPSS analysis (16-18). Although it might be due to the bias toward more screening trend in higher maternal age, it has been incorporated in prenatal screening as one of the main elements of analysis (17, 19). Positive drug history was found to be associated with false positive result with significant trend toward human chorionic gonadotropin (HCG) injection. It is obvious that using HCG injection as infertility treatment choice used to induce ovulation can falsely increase the amount of β-hCG and then confound the screening results since the level of β-hCG is increased in pregnancies associated with DS. To our knowledge, no one of the currently used algorithms of prenatal screenings consider drug history, especially HCG derivative compounds.

Amongst biochemical markers, routinely used in prenatal screening, inhibin A in both data mining and SPSS analysis and uE3 in only SPSS analysis was found to be significantly associated with risk of DS. Although in combination of different markers adding Inhibin-A had not significantly increased the rate of DS detection, to the best of our knowledge this is the first study which separately analyzed each of biochemical markers as well as Inhibin-A with DS (20, 21). On the other hand, the price of cffDNA analysis and even combined screening is still expensive for many low-income families around the world. The selection of the most powerful criteria not only alleviates the overall cost of prenatal screening but also reduces the time around for doing both first and second trimester biochemical screening.

Although it is clear that positive familial history of DS increases the risk of DS associated pregnancy, having the previous affected child is calculated to increase the risk of recurrence up to 1% regardless of maternal age. However, in the case of parental chromosome translocation, the risk may increase to 2-3% except of 21q:21q translocation which always leads

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to an affected baby. Herein, using mathematical and statistical analysis, it was demonstrated that the positive family history enhanced the risk of DS up to over than 80%.

Consanguinity was another factor whose significant effect on the risk of DS was determined in both SPSS and Data Mining assessments. Consanguinity duplicates the risk of autosomal recessive genetic disorders and is usually more prevalent in low socioeconomic and low education level families. The correlation between consanguinity and the risk of DS also has been demonstrated in various populations and studies (22-24). Recently, the rate of consanguineous marriage has been increased in particular among religious countries as well as Iran due to some cultural good points of marriage among relatives including maintaining the integrity of family and more successful marriage.

The NT was another factor which was in significant association with risk of DS in both SPSS and Data Mining analysis. It was shown that including NT in prenatal screening decreased the false positive rate, but it had no meaningful effect on the detection rate (25). However, it was shown that measuring the NT at weeks 12 of gestation may increase the detection rate of affected pregnancies (8). In the present study, it was found that NT not only significantly increased the risk of DS but also it was associated with lower false positive rate. Of note, the average of gestational weeks in which the screening sonography was performed was around 12 weeks and it may highlight the right time of NT measurement that should be considered.

SPSS analysis, not Data Mining, demonstrated meaningful correlation between DS and level of education. It was previously shown that women who had not completed their education in high school level significantly tend to have an affected fetus with DS consistent with our finding (26, 27). How environmental factors as well as low socioeconomic and education level can affect the risk of meiotic non-disjunction specifically maternal one remained elusive. Limited access of lower education level mothers to useful information such as preventive dietary approaches and poor information about the healthy life style may be the possible rationales behind higher risk of DS in low education women. Moreover, most of the low education women live in poor income families which may deteriorate their access to healthy diet and medical consultation, diabetes mellitus diagnosis and prevention. Further studies are required to determine the detailed elements of low education and socioeconomic status affecting the risk of meiotic non-disjunction and risk of DS.

In the present study, in neither statistical nor data mining analysis, no significant association was found between pregnancy with IVF and risk of trisomy 21 beside false negative nor positive results. This is contrary to the previous report which indicated a higher prevalence of false positive screening tests among IVF pregnancies due to affecting the level of AFP and PAPP-A (28).

Owing to the emergence of non-invasive cell free fetal DNA analysis through maternal circulation, restricting screening markers to more significant items may improve detection rate in regions where in this technology is still unavailable. It is worth noting that in most of the countries around the world, especially in developing and underdeveloped population, even traditional screening is hardly done for low risk patients, while the birth rate of DS is significantly higher in them. On the one hand, achieving perfect positive and negative predictive values of cffDNA testing could not exclude the critical roles of ultrasound in detection of structural abnormalities with known or unknown genetic defect as well as anencephaly. On the other hand, enhancing the traditional screening tests considering the most important factors not only could alleviate the cost of test but also decrease the false positive results in following cffDNA test (29). Designing a new algorithm using found significant factor as our ongoing project could create a cost-effective prenatal screening before cffDNA testing to enhance its final results.

Conclusion

Herein, we primarily signify the importance of the detection of early proteinuria and NT measurement in risk of trisomy 21 through statistical and mathematic analysis deserving to be validated on larger sample sizes. These findings can improve prenatal screening tests results to alleviate the need for doing invasive tests as much as possible.

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Conflicts of Interest

There is no conflict of interest among authors.

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