THE APPLICATION AND FACTORS INFLUENCING THE IMPLEMENTATION OF NON-INVASIVE PRENATAL TESTING (NIPT) WORLDWIDE: A REVIEW

DAMIYA AHMAD UZHIR, BSc
DEPARTMENT OF BIOMEDICAL SCIENCE, KULLIYYAH OF ALLIED HEALTH SCIENCES, INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA, JALAN SULTAN AHMAD SHAH, BANDAR INDERA MAHKOTA CAMPUS, KUANTAN 25200, PAHANG DARUL MAKMUR.
mialong1207@gmail.com

SITI AESAH @ NAZNIN MUHAMMAD, MMed
DEPARTMENT OF PATHOLOGY, KULLIYYAH OF MEDICINE, INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA, JALAN SULTAN AHMAD SHAH, BANDAR INDERA MAHKOTA CAMPUS, KUANTAN 25200, PAHANG DARUL MAKMUR.
naznin@iium.edu.my

NORAFIZA ZAINUDDIN, PhD (CORRESPONDING AUTHOR)
DEPARTMENT OF BIOMEDICAL SCIENCE, KULLIYYAH OF ALLIED HEALTH SCIENCES, INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA, JALAN SULTAN AHMAD SHAH, BANDAR INDERA MAHKOTA CAMPUS, KUANTAN 25200, PAHANG DARUL MAKMUR.
znorafiza@iium.edu.my

ABSTRACT

The purpose of this paper is to review the current scientific evidence on the application of non-invasive prenatal testing (NIPT) besides Trisomy 21, 13 and 18 and factors influencing the implementation of NIPT worldwide from the perspective of pregnant women and other service users. Three databases were searched for related articles using chosen keywords. The PRISMA guidelines were used for the purpose of conducting this review. The assessment of the quality of the articles was done using the Crowe Critical Appraisal Tool (CCAT) version 4.1. Nine articles were accepted as meeting the inclusion criterion and were reviewed. Six applications of NIPT besides Trisomy 21, 13 and 18 were identified: 1) a rare de novo 18p terminal deletion with inverted duplication, 2) skeletal dysplasia, 3) foetal achondroplasia, 4) microdeletion abnormalities of foetal chromosome 15, 5) detection of various foetal sex chromosome abnormalities (SCAs) (Turner syndrome, Triple X syndrome, Klinefelter syndrome and XYY syndrome) and 6) Duchenne and Becker muscular dystrophies. This review identified six factors that influenced the implementation of NIPT: 1) the test detection rate or accuracy, 2) early access to conduct test, 3) cost-effectiveness of implementing NIPT (for the detection of Down Syndrome), 4) availability of informed consent process (preference of service users), 5) education level of service users and 6) a measure of reassurance to service users. To conclude, this review had collated data on the utilization of NIPT in the screening of various chromosomal and genetic disorders and was able to delineate factors influencing the clinical implementation of NIPT from the perspective of health professionals and pregnant women. The findings are expected to contribute towards future implementation of NIPT worldwide.

KEYWORDS: Non-invasive prenatal testing, non-invasive prenatal screening, NIPT, pregnant women, obstetric professionals and implementation factors

INTRODUCTION

Prenatal testing is offered to pregnant women in order to determine if the foetus has a possibility of being born with a genetic abnormality. The two main prenatal diagnostic methods, the amniocentesis and chorionic villus sampling (CVS) are considered as invasive procedures. Amniocentesis refers to the transabdominal aspiration of amniotic fluid from the uterine cavity (Ghi et al. 2016). A volume of 15 mL to 30 mL of amniotic fluid is aspirated for further laboratory testing. This procedure is performed at 15 weeks period of gestation (Cruz-Lemini et al., 2014). As for the CVS, it refers to the procedure of withdrawing trophoblastic cells from the placenta (Ghi et al., 2016) and it is performed from 11 gestational weeks (Alfirevic, Navaratnam & Mujezinovic, 2017). According to Tabor & Alfirevic (2010), miscarriage related to amniocentesis is estimated to be around 1.0% while the overall risk of miscarriages from CVS is 1 to 2% (Akolekar, Beta, Picciarelli, Ogilvie & D'Antonio, 2015).

Non-invasive prenatal testing (NIPT) was introduced into clinical practice in 2011 (Allyse et al., 2015). It is based on the analysis of cell free foetal DNA (cffDNA) that is acquired from maternal circulation. NIPT may be a substitute alternative to conventional screening for chromosomal numerical disorders namely Down syndrome (Trisomy 21), Patau syndrome (Trisomy 13), and Edwards syndrome (Trisomy 18) (Gregg et al., 2016). It can be carried out at any point during pregnancy beginning from 10 weeks of gestation. As a result, the use of NIPT has expanded globally and are made accessible in many developed countries (Allyse et al., 2015).

Every foetus has a small risk of being born with a chromosomal or genetic condition. Hence, prenatal screening for some of the chromosomal and genetic disorders is offered to pregnant women in order to provide additional information about her unborn child. Presently, the available methods for this specific diagnosis is only by an invasive test (amniocentesis or CVS). As all diagnostic tests carry a small risk of abortion, screening programmes in the recent years aim to minimize the requirement for invasive testing, while still being able to provide a high chance of detecting chromosomal abnormalities in the foetus (Tara, Lotfalizadeh & Moeindarbari, 2016).

As a result, prenatal testing is inclined towards non-invasive methods with the aim of lessening the risk of spontaneous abortion. Special progress in the testing methods for foetal genetic abnormalities, specifically aneuploidies, was triggered by the rapid development of current high-throughput molecular technologies with the detection of cffDNA. These tests are known as NIPT or non-invasive prenatal screening. Due to their many advantages, the implementation of NIPT in clinical setting is currently progressing. Nevertheless, the above-mentioned invasive sampling procedures is still significant in the diagnosis to confirm NIPT-positive findings (Pös, Budiš & Szemes, 2019).

Currently, NIPT is commonly used for the detection of Down syndrome (Trisomy 21), Patau syndrome (Trisomy 13), and Edwards syndrome (Trisomy 18). However, current evidence has demonstrated the possible use of this procedure in detecting other different types of genetic disorders. This may help in making NIPT as a substitute and a more prominent screening procedure for other genetic disorders. As NIPT is being introduced globally, knowledge related to factors influencing the implementation of NIPT from the perspective of pregnant women and other service users may contribute to global development in this pertinent area.

METHODOLOGY

Systematic review process

The review methodology follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff and Altman (2009). There are four main components in the PRISMA guidelines which include identification of the sources of the journal articles, screening of the article based on title, eligibility based on the inclusion criteria and screening to identify studies for further analysis.

Search strategy

Three online databases were used to obtain peer reviewed articles namely Science Direct, Scopus, and PubMed. Additional sources were also obtained from manual searches through reference list of obtained articles. The search strategy used in this study to obtain as many relevant studies pertaining to the topic is based on chosen keywords. Individual key search terms were entered for each database combining them with the Boolean operators as relevant. The combination of keywords used were "non-invasive prenatal testing", "non-invasive prenatal screening", "NIPT", "pregnant women", "obstetric professionals" and "implementation factors".

Inclusion criteria

Studies were selected if they targeted the use of NIPT to detect genetic diseases of foetus in pregnant women or discussed factors influencing the implementation of NIPT. To be included, studies have to be peer reviewed articles published in English starting from January 2009 until November 2019. Studies were excluded if they are letters, editorials, meetings and abstracts.

Methods of the review

The titles and abstracts were screened to identify articles potentially meeting the inclusion and exclusion criteria. For those articles, full text versions were retrieved and screened to determine whether they met the inclusion criteria and answered the research question. Screening process was repeated three times to increase the reliability of the search results.

Collating, summarizing, and reporting results

An evidence table was used to collect data of relevant study information for articles meeting inclusion and exclusion criteria. Information such as the author's name, type of study design, participants, publication year and summarized results were presented in Table 1.

Quality assessment of studies

The identified studies were assessed for meeting eligibility criteria using the Crowe Critical Appraisal Tool (CCAT) version 4.1 which is a general critical appraisal tool for all identified quantitative studies. It has reported validity and reliability data better than that of informal appraisal tools. The CCAT can be used for both quantitative and qualitative studies.

RESULTS

The article selection process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1). The searches identified 1292 articles. Following the elimination of duplicate articles, 625 articles were identified. A total number of 211 articles were screened using its title and abstract. One hundred and seventy-three articles were excluded due to non-relevance to our aims of research and the keywords did not match with the intended ones. The abstracts of 38 articles were subsequently evaluated. At this stage, twenty-nine articles were excluded as they were not primary studies that explore the applications and factors influencing the implementation of NIPT worldwide. Thirteen of the 29 articles were published in non-English language, while eleven of the articles were editorials and five were letters. These 29 articles were also excluded because it was not published during the year 2009-2019 which is part of the inclusion criteria. As a result, nine articles were finally included in this systematic review. The whole review process is depicted in Figure 1. The studies were mostly carried out in different regions of China such as Beijing (Dan et al., 2016; Zhu et al., 2019), Nanning (Yin et al., 2019) and Chengdu (Deng et al., 2019), while other countries include United Kingdom (Parks et al., 2016), Spain (Bayón et al., 2019), the United States (Farrell, Agatisa & Nutter, 2014), France

(Vivanti et al., 2018) and Canada (Birko et al., 2019). The characteristics of included studies were collated in Table 1. In all, there were nine quantitative studies as summarised below.

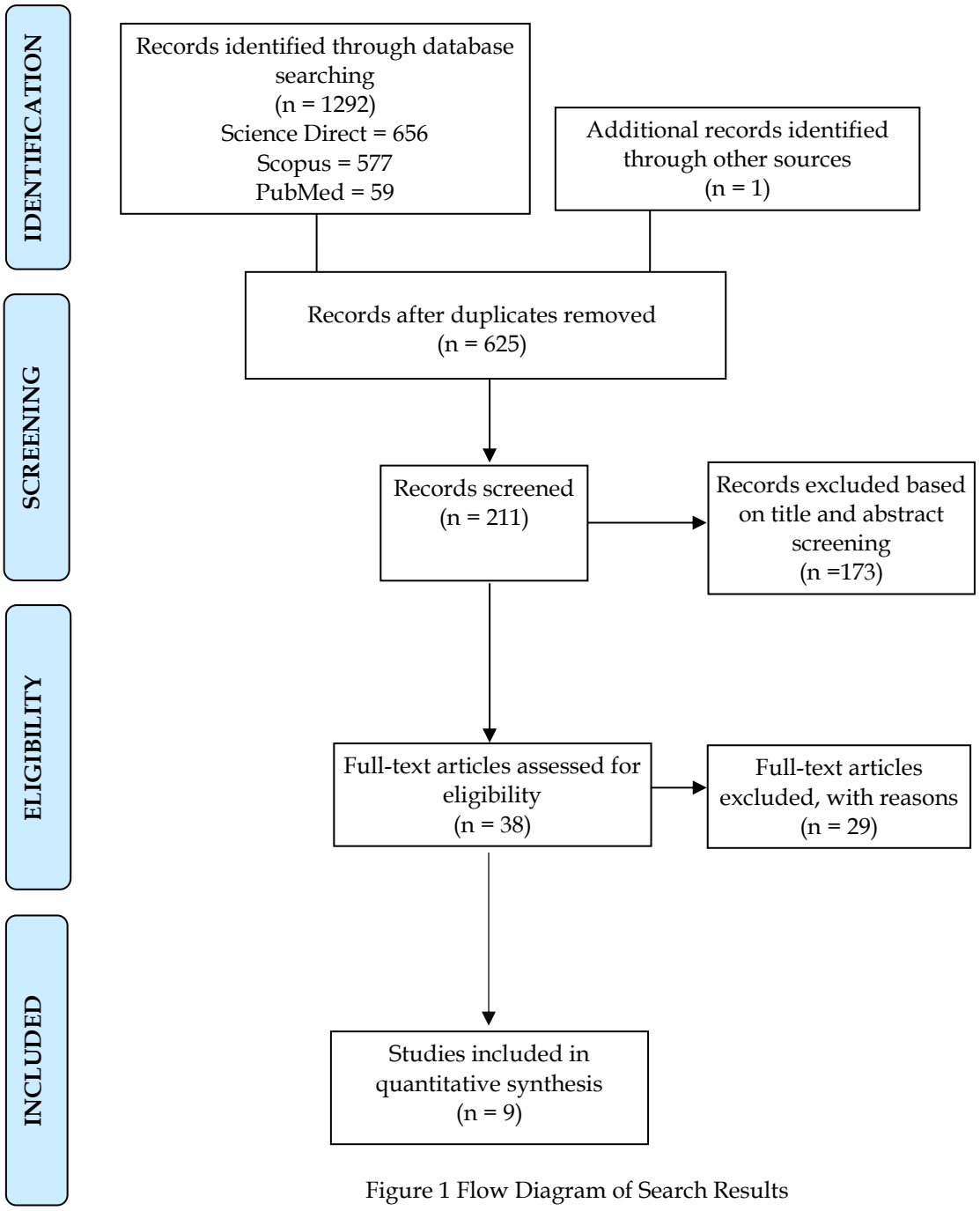

Figure 1 Flow Diagram of Search Results

Table 1 Characteristics of Included Studies

Study No.	Author and year	Title of Study	Journal	Country	Study population	No. of participants	Study Design	Method	Genetic Disorders	Factors
1	Zhu et al., (2019)	Detection of a rare de novo 18p terminal deletion with inverted duplication in a Chinese pregnant woman	Molecular Genetics & Genomic Medicine	Beijing, China	Pregnant woman	1	Case Study	Quantitative	18p terminal deletion	
2	Dan et al., (2016)	Non-Invasive Prenatal Diagnosis of Lethal Skeletal Dysplasia by Targeted Capture Sequencing of Maternal Plasma	PLOS ONE	Beijing, China	Pregnant women, male participants (woman's husband)	3	Case control study	Quantitative	Lethal Skeletal Dysplasia	
3	Vivanti et al., (2018)	Optimal non-invasive diagnosis of fetal achondroplasia combining ultrasonography with circulating cell-free fetal DNA analysis	Ultrasound in Obstetrics & Gynecology	France	High risk pregnant women	86	Prospective multicenter study	Quantitative	Fetal achondroplasia	
4	Yin et al., (2019)	Noninvasive prenatal testing detects microdeletion abnormalities of fetal chromosome 15	Journal of Clinical Laboratory Analysis	Nanning, China	Pregnant woman	1	Case Study	Quantitative	Microdeletion abnormalities of fetal chromosome 15	
5	Deng et al., (2019)	Clinical application of non-invasive prenatal screening for sex chromosome aneuploidies in 50,301 pregnancies: initial experience in a Chinese hospital	Scientific Reports	Chengdu, China	Pregnant women	50,301	Retrospective observational study	Quantitative	Fetal sex chromosome aneuploidies	

6	Parks et al., (2016)	Non-invasive prenatal diagnosis of Duchenne and Becker muscular dystrophies by relative haplotype dosage	Prenatal Diagnosis	Birmingham, United Kingdom	Healthy pregnant women and pregnant DMD carriers	7 pregnant women, 2 pregnant DMD carriers	Retrospective observational study	Quantitative	Duchenne and Becker muscular dystrophies
7	Bayón, Orruño, Portillo & Asua, (2019)	The consequences of implementing non-invasive prenatal testing with cell-free foetal DNA for the detection of Down syndrome in the Spanish National Health Service: a cost-effectiveness analysis	Cost Effectiveness and Resource Allocation	Spain	Pregnant women	Estimated 100,000	Analytical short-term decision model	Quantitative	Cost-effectiveness analysis of NIPT
8	Farrell et al., (2014)	What Women Want: Lead Considerations for Current and Future Applications of Non-invasive Prenatal Testing in Prenatal Care	Birth	Ohio, United States	Pregnant women	334	Cross-sectional study	Quantitative	- Detection rate - Early access to conduct test - Informed Consent - Education level of service users
9	Birko et al., (2019)	The value of non-invasive prenatal testing: preferences of Canadian pregnant women, their partners, and health professionals regarding NIPT use and access	BMC Pregnancy and Childbirth	Canada	Pregnant women, partners of pregnant women and healthcare professionals	1,461	Cross-sectional survey	Quantitative	- Detection rate - Early access to conduct test -Measure of reassurance

Description of included studies

From the studies, six chromosomal and genetic disorders have been identified that were screened by NIPT and there were six factors that influenced the implementation of NIPT. The six applications of NIPT included screening of a rare *de novo* 18p terminal deletion with inverted duplication, skeletal dysplasia, foetal achondroplasia, microdeletion abnormalities of foetal chromosome 15, detection of various foetal sex chromosome abnormalities (Turner syndrome, Triple X syndrome, Klinefelter syndrome and XYY syndrome) and Duchenne and Becker muscular dystrophies (DMD/BMD).

In addition, the six factors influencing the implementation of NIPT were the test detection rate (accuracy), early access to conduct test, cost-effectiveness of implementing NIPT (for the detection of Down Syndrome), availability of informed consent process (preference of service users), education level of service users and a measure of reassurance to service users.

Quality of the included studies

The quality assessment of the included nine quantitative studies are shown in Table 2. All the studies sufficiently described their objective, defined the outcomes, reported results and had conclusions which supported their results. The total score for Zhu et al., (2019), Dan et al. (2016), Vivanti et al., (2018), Yin et al., (2019), Deng et al., (2019), Parks et al., (2016), Bayón et al., (2019), Farrell et al., (2014) and Birko et al., (2019) are 83%, 85%, 93%, 80%, 83%, 88%, 90%, 85% and 83% respectively.

DISCUSSION

This systematic review has provided an insight into the applications of NIPT and the factors influencing the implementation of NIPT. Of 625 papers, nine studies were identified to be relevant with the two topics that the authors tried to gather which were the applications of NIPT and the factors influencing the implementation of NIPT. Six applications of NIPT and six factors influencing the implementation of NIPT were successfully identified. The six applications included the detection of a rare de novo 18p terminal deletion with inverted duplication, skeletal dysplasia, foetal achondroplasia, microdeletion abnormalities of foetal chromosome 15, detection of various foetal sex chromosome abnormalities (Turner syndrome, Triple X syndrome, Klinefelter syndrome and XYY syndrome) and Duchenne and Becker muscular dystrophies. In addition to that, the six factors which have emerged from this synthesis of primary studies that influenced the implementation of NIPT were 1) the test detection rate (accuracy), 2) early access to conduct test, 3) cost-effectiveness of implementing non-invasive prenatal testing (NIPT) (for the detection of Down Syndrome), 4) availability of informed consent process (preference of service users), 5) education level of service users and 6) a measure of reassurance to service users.

The deletion and inverted duplication of the short arm of chromosome 18 is known to be a very rare type of chromosome abnormality detected by NIPT. In this particular case, the genes involved, such as LPIN2, SMCHD1, and TGIF1, are known to be linked to genetic diseases, and the loss of these genes may cause clinical manifestations related to intellectual disability, delayed speech and language impairment (Zhu et al., 2019). In the detection of skeletal dysplasia using NIPT, there were three cases found according to study 2, including type 1 of thanatophoric dysplasia, osteogenesis imperfecta type 2 and achondroplasia (Dan et al., 2016). The detection of 5 Mb microdeletion abnormalities of foetal chromosome 15 was also successful using NIPT technology which was consistent with a study that found NIPT can detect microdeletion and microduplication greater than 300Kb in foetal genomes (Yin et al., 2019). NIPT seemed to more accurately predict SCAs of triple X and XYY syndrome, but performed poorly as a predictor of foetal monosomy X. This is possibly due to the contributing maternal factors, including abnormal chromosome chimerism in pregnant women, copy number variation and even maternal neoplastic conditions (Deng et al., 2019). Non-invasive prenatal diagnosis of Duchenne and Becker muscular dystrophies by relative haplotype dosage is known to be a newly developed method which is used in testing patients at risk with a foetal fraction of higher than 4% (Parks et al., 2016).

Table 2 Checklist for Quality Assessment of Quantitative Studies

No.	Item	Study No. 1	Study No. 2	Study No. 3	Study No. 4	Study No. 5	Study No. 6	Study No. 7	Study No. 8	Study No. 9
1.	Preliminaries - Title (aims and design) - Abstract (key information, balanced, informative) - Text (sufficient detail, clear writing/ table/ diagram/ figure)	5	5	5	5	4	5	5	5	4
2.	Introduction - Background - Objective	4	4	4	3	4	4	5	4	3
3.	Design	4	3	4	5	3	4	4	4	4
4.	Sampling	5	4	5	5	5	5	4	4	5
5.	Data collection	4	4	5	4	5	5	4	5	4
6.	Ethical matters	4	4	4	2	2	3	5	4	5

Table 2 Continued

No.	Item	Study No. 1	Study No. 2	Study No. 3	Study No. 4	Study No. 5	Study No. 6	Study No. 7	Study No. 8	Study No. 9
7.	Results	3	5	5	4	5	5	4	4	4
8.	Discussion	4	5	4	5	5	4	5	4	4
9.	**Total (%)**	**83**	**85**	**90**	**83**	**83**	**88**	**90**	**85**	**83**

Note. Adapted from Crowe, M. (2013). CCAT form v1.4

Based on the respondent of the surveys in included studies, having early access to the prenatal testing and knowing the high detection rate of NIPT itself have made service users more determined in having a better option for prenatal testing. Besides that, despite the non-invasive aspects of NIPT, service users stated the need for a formal informed consent process must take place before undergoing NIPT. In study 8, it also showed how education level is essential as these pregnant women prioritized on equipping themselves with information about NIPT beforehand (Farrell et al., 2014). By analysing the cost-effectiveness study in the detection of Down Syndrome (DS) using NIPT, NIPT as contingent testing (screening test) resulted in fewer miscarriages, in comparison to invasive procedures and a slight decrease in detecting cases of DS in comparison to current screening methods. Yet, it is still considered a better alternative (Bayón, Orruño, Portillo & Asua, 2019).

Based on study 9, in choosing NIPT, it also can provide a measure of reassurance over amniocentesis as the service users may question why would they risk miscarriage by choosing amniocentesis if they just want to know the condition of their foetus "for knowing's sake" only. Besides that, in a way, knowing what to expect is also a sense of comfort for the pregnant women to be prepared, even if the result may be positive (Birko et al., 2019).

The quality of all included studies using the Crowe Critical Appraisal Tool (CCAT) version 4.1 are 80% and higher which seems of high standard quality. Hence, this review validates the wide use of NIPT to determine and detect the risk of multiple genetic abnormalities beyond Down syndrome (Trisomy 21), Patau syndrome (Trisomy 13), and Edwards syndrome (Trisomy 18). Furthermore, the identification of factors influencing the implementation of NIPT will be able to encourage the vast application of NIPT by healthcare providers and pregnant women globally.

Strength and limitation of studies

The strength of this review includes obtaining related articles from three databases with peer reviewed journals which ensures the quality of the articles. This review also provides a current and up to date knowledge as it only includes studies since January 2009 to December 2019. However, few of the included studies were case studies which focuses on individual case. The limitation of this tool is that it is dependent on the appraiser's scoring, which in this case only one appraiser is involved. There may be a temptation to overlook the performance in the individual categories and only focused on the total scoring. This review also included studies published in English only, which could exclude some relevant literature. In addition, most studies reviewed focused on Western countries while from that of Asia, studies reviewed were only from China which may or may not be reflective of other parts of the world.

CONCLUSION

The review identified six additional applications of NIPT besides Trisomy 21, 13 and 18 in the detection of foetal genetic abnormalities and also manages to identify six factors that influenced the implementation of NIPT. This review provides current scientific evidence of the additional chromosomal and genetic disorders screened by NIPT and delineates factors influencing the clinical implementation of NIPT from the perspective of health professionals and service users. It is hoped that through this study, contributions can be made towards the future implementation of NIPT on various genetic disorders globally.

ACKNOWLEDGEMENT

The authors would like to thank the lecturers at the Department of Biomedical Science, Kulliyyah of Allied Health Sciences, IIUM for the feedback on search strategy. The authors however bear full responsibility on the paper.

REFERENCES

Akolekar, R., Beta, J., Picciarelli, G., Ogilvie, C., & D'Antonio, F. (2015). Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound In Obstetrics & Gynecology*, *45*(1), 16-26. doi: 10.1002/uog.14636

Alfirevic, Z., Navaratnam, K., & Mujezinovic, F. (2017). Amniocentesis and chorionic villus sampling for prenatal diagnosis. *Cochrane Database Of Systematic Reviews*. doi: 10.1002/14651858.cd003252.pub2

Allyse, M., Minear, M., Rote, M., Hung, A., Chandrasekharan, S., Berson, E., & Sridhar, S. (2015). Non-invasive prenatal testing: a review of international implementation and challenges. *International Journal Of Women's Health*, 113. doi: 10.2147/ijwh.s67124

Bayón, J., Orruño, E., Portillo, M., & Asua, J. (2019). The consequences of implementing non-invasive prenatal testing with cell-free foetal DNA for the detection of Down syndrome in the Spanish National Health Service: a cost-effectiveness analysis. *Cost Effectiveness And Resource Allocation*, *17*(1). doi: 10.1186/s12962-019-0173-8

Birko, S., Ravitsky, V., Dupras, C., Le Clerc-Blain, J., Lemoine, M., & Affdal, A. et al. (2019). The value of non-invasive prenatal testing: preferences of Canadian pregnant women, their partners, and health professionals regarding NIPT use and access. *BMC Pregnancy And Childbirth*, *19*(1). doi: 10.1186/s12884-018-2153-y

Cruz-Lemini, M., Parra-Saavedra, M., Borobio, V., Bennasar, M., Goncé, A., Martínez, J., & Borrell, A. (2014). How to perform an amniocentesis. *Ultrasound In Obstetrics & Gynecology*, *44*(6), 727-731. doi: 10.1002/uog.14680

Dan, S., Yuan, Y., Wang, Y., Chen, C., Gao, C., & Yu, S. et al. (2016). Non-Invasive Prenatal Diagnosis of Lethal Skeletal Dysplasia by Targeted Capture Sequencing of Maternal Plasma. *PLOS ONE*, *11*(7), e0159355. doi: 10.1371/journal.pone.0159355

Deng, C., Zhu, Q., Liu, S., Liu, J., Bai, T., & Jing, X. et al. (2019). Clinical application of noninvasive prenatal screening for sex chromosome aneuploidies in 50,301 pregnancies: initial experience in a Chinese hospital. *Scientific Reports*, *9*(1). doi: 10.1038/s41598-019-44018-4

Farrell, R., Agatisa, P., & Nutter, B. (2014). What Women Want: Lead Considerations for Current and Future Applications of Noninvasive Prenatal Testing in Prenatal Care. *Birth*, *41*(3), 276-282. doi: 10.1111/birt.12113

Ghi, T., Sotiriadis, A., Calda, P., Da Silva Costa, F., Raine-Fenning, N., Alfirevic, Z., & McGillivray, G. (2016). ISUOG Practice Guidelines: invasive procedures for prenatal diagnosis. *Ultrasound In Obstetrics & Gynecology*, *48*(2), 256-268. doi: 10.1002/uog.15945

Gregg, A. R., Skotko, B. G., Benkendorf, J. L., Monaghan, K. G., Bajaj, K., Best, R. G., … Watson, M. S. (2016). Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genetics in Medicine*, *18*(10), 1056–1065. doi: 10.1038/gim.2016.97

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Plos Medicine*, *6*(7), e1000097. doi: 10.1371/journal.pmed.1000097

Parks, M., Court, S., Cleary, S., Clokie, S., Hewitt, J., & Williams, D. et al. (2016). Non-invasive prenatal diagnosis of Duchenne and Becker muscular dystrophies by relative haplotype dosage. *Prenatal Diagnosis*, *36*(4), 312-320. doi: 10.1002/pd.4781

Pös, O., Budiš, J., & Szemes, T. (2019). Recent trends in prenatal genetic screening and testing. *F1000research*, *8*, 764. doi: 10.12688/f1000research.16837.1

Tabor, A., & Alfirevic, Z. (2010). Update on Procedure-Related Risks for Prenatal Diagnosis Techniques. *Fetal Diagnosis And Therapy*, *27*(1), 1-7. doi: 10.1159/000271995

Tara, F., Lotfalizadeh, M., & Moeindarbari, S. (2016). The effect of diagnostic amniocentesis and its complications on early spontaneous abortion. *Electronic Physician*, *8*(8), 2787-2792. doi: 10.19082/2787

Vivanti, A., Costa, J., Rosefort, A., Kleinfinger, P., Lohmann, L., Cordier, A., & Benachi, A. (2018). Optimal non-invasive diagnosis of fetal achondroplasia combining ultrasonography with circulating cell-free fetal DNA analysis. *Ultrasound In Obstetrics & Gynecology*, *53*(1), 87-94. doi: 10.1002/uog.19018

Yin, L., Tang, Y., Lu, Q., Shi, M., Pan, A., & Chen, D. (2019). Noninvasive prenatal testing detects microdeletion abnormalities of fetal chromosome 15. *Journal Of Clinical Laboratory Analysis*, *33*(6). doi: 10.1002/jcla.22911

Zhu, J., Qi, H., Cao, S., Cai, L., Wen, X., & Tang, G. et al. (2019). Detection of a rare de novo 18p terminal deletion with inverted duplication in a Chinese pregnant woman. *Molecular Genetics & Genomic Medicine*, *7*(9). doi: 10.1002/mgg3.868