Knowledge, attitude and practices of obstetricians and gynecologists on non-invasive prenatal testing with cell free fetal DNA in a private tertiary hospital*

By Kristel Danica P. Panes, MD and Gumersinda Cruz-Javier, MD, FPOGS
Department of Obstetrics and Gynecology, The Medical City

ABSTRACT

There are a number of novel prenatal cytoogenetic analysis tests for obstetricians and gynecologists on detecting aneuploidies. In the recent years, screening of pregnant patients with non-invasive prenatal testing (NIPT) is one. As the spread of genomic medicine and preventive obstetrics continue, it is prudent for obstetricians and gynecologists to accept and optimize new screening modalities, whenever available.

Chromosomal abnormalities are common. Worldwide, one out of 150 live births may involve chromosomal abnormalities. The American College of Obstetrics and Gynecologists (ACOG) and American College of Medical Genetics recommend invasive and non – invasive prenatal testing (NIPT)[3]. The invasive testing, however, carries risk for procedure – related miscarriage. [4]This favors NIPT which avoids the risk. The current state of NIPT in the Philippines, is it was only in January 2018, were a NIPT workshop was conducted by the Society of Maternal Fetal Medicine.[6]

First, due to the minimal studies on personalized and precision medicine on prenatal testing, hence the strong move to conduct this study. In an extensive literature search review in Herdin, a local database and archives of Philippine Obstetrics and Gynecology, none specified researches on non – invasive prenatal testing.

Second, in our country alone, there is no provision for national prenatal tests. In our institution, it was already introduced but with no uptake yet. Because of this gap, scantiness and non - uptake on NIPT locally, hence the conduct of this study. The study aimed to investigate on the obstetricians and gynecologists (OB-GYNs) knowledge, attitude towards and practices (KAP) about NIPT. Majority of the OBGYNs were knowledgeable, had positive attitude and were practicing NIPT. Strikingly, a fourth of the respondents were not comfortable in explaining NIPT. The researcher recommends that there is a need to conduct this study on a larger scale cross - sectional survey and multiple studies due to the paucity of data.

Keywords: Non-invasive prenatal testing (NIPT), Cell free fetal DNA(CffDNA); Screening; Prenatal diagnosis

INTRODUCTION

Background

There are a number of novel prenatal cytoogenetic analysis tests and various recommendations for obstetricians and gynecologists on detecting aneuploidies. In the recent years, screening of pregnant patients with non – invasive prenatal testing is one. As the spread of genomic medicine and preventive obstetrics continue, it is prudent for obstetricians and gynecologists to accept and optimize new screening modalities such as this, whenever available.

Chromosomal abnormalities are common. Worldwide, one out of 150 live births may involve chromosomal abnormality.[1] In the Philippines, the top three chromosomal diagnosis were autosomal and sex chromosome abnormalities.[2] NIPT analyzes cell-free fetal DNA (cffDNA) in maternal blood. Fetal DNA can detected event at a minimum amount of 10 microliter lf maternal plasma and serum, and greater in nucleated blood cells in whole blood. The approach of using cell free fetal DNA instead of fetal cells is easier, less laborious and less time consuming in working with fetal DNA from the maternal circulation, this are new avenues for NIPT. Since then, there are various reports on cell free DNA for fetal aneuploidies such as Trisomy 21, Trisomy 18 and Trisomy 13 and sex chromosme anomalies detection.[4] The American College of Obstetrics and Gynecologists (ACOG) and American

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College of Medical Genetics recommend invasive and non-invasive prenatal testing (NIPT)[3]. The invasive testing, however, carries risk for procedure-related miscarriage. 4This favors NIPT which avoids the risk.[5]

The current state of NIPT in the Philippines, is it was only in January 2018, were a NIPT workshop was conducted by the Philippine Society of Maternal Fetal Medicine.[6]

First, due to the minimal studies on personalized and precision medicine on prenatal testing and or obstetrics, in general, hence the strong move to conduct this study. In an extensive literature search review in Herdin, a local database and archives of Philippine Obstetrics and Gynecology, none specified researches on Non – invasive prenatal testing.

Second, in our country alone, there is no provision for national prenatal tests. In our institution, it was already introduced but with no uptake yet. Because of this gap, scantiness and non-uptake on NIPT locally, hence the conduct of this study.

OBJECTIVES

General Objectives

The study aimed to investigate on the obstetrician and gynaecologists' (OB-GYNs) knowledge, attitude and practices (KAP) about NIPT.

Specific Objectives

The specific objectives were to:

a. determine the demographic profile based on: gender, age, civil status, years since graduation from residency, subspecialty and area of practice;
b. determine the knowledge base on NIPT,
c. determine the attitude towards NIPT and
d. determine if the obstetricians and gynaecologists are utilizing NIPT.

MATERIALS AND METHODS

Population and Sample

Study Population

The population for this study were OB-GYNs in a private tertiary hospital. There was a total of 153 consultant OB-GYNs as of May 2019. The population in the study included: the junior and senior consultants, who are presently employed by the institution as a regular or visiting consultant.

Inclusion and Exclusion criteria

The consultants who were on leave and unable to return the questionnaires, were deemed not eligible to be participants of this study. Informed consent was secured prior to conduct of the study. Using Slovin's formula, the researcher included to survey, with the following formula, where n = N / (1 + Ne^2) people, with margin of error of 0.05, where n = no. of samples, N = total population and e = error margin / margin of error. Thus, 153 / (1 + 153* 0.05 * 0.05) = 114 of 153 consultant OB-GYNs were an adequate and appropriate population.

METHODS

The study was conducted at two tertiary hospitals (pre-testing and actual conduct of study). The research protocol and the questionnaire were approved by the Institutional Review Board (IRB) of the two institutions. The survey was adapted from 2 previously constructed questionnaires (composed of 5-point Likert scale and multiple choices) used in studies of (Verweij, 2014; Tamminga et al., 2015; Van Schendel et al. 2015, 2016 and Davis, 2013). The questionnaire was further subjected for content validity (including face validity) and field content expert review. The three panel of experts were composed of one (1) Maternal and Fetal Medicine Specialist, one (1) OB GYN and Health Statistician/ Researcher. The COSMIN checklist (Consensus-Based Standards For The Selection Of Health Status Measurement Instruments) was adapted from Mokkink Et Al and utilized as tool for validation (Table 1).[8] There was 100% inter-rater agreement. The questionnaire was revised and modified based on the comments of the panel of three (3) experts. The validated questionnaire was further subjected for reliability testing (pilot-tested) among 15 OB-GYNs. Eligible subjects' data were held with utmost confidentiality. Questionnaires were accomplished with either by responses done via vis-avis, electronic mails or by postage. An electronic data collection procedure was initially done and repeated after 3 weeks which ensured greater yield.

Analysis

The data collected from the survey were divided into 2 sections: 1.) Demographics which included gender, age, civil status, years since graduation from residency, subspecialty and area of practice and 2.) Included items/ questions on assessment of knowledge, attitudes and practices domains of NIPT. The instrument was taken from the studies of (Verweij, 2014; Tamminga et al., 2015; van Schendel et al. 2015, 2016 and Davis, 2013) was re-designed along to be a 5-point Likert Scale and multiple choices.[12] Descriptive analysis was used to determine the profile the OB-GYNs and evaluation of the knowledge, attitude and practices of the OB-GYNs. Cronbach's Alpha based on the items was 0.7. Frequency count, percentage and sum of score were utilized. All statistical analysis were done through Microsoft Excel and

Table 1. Demographics of OB - GYNs

	Frequency	Percent (%)
GENDER		
Male	8	8.51
Female	86	91.49
STATUS		
No Data	3	3.19
Married	69	73.40
Single	20	21.28
Widow	2	
Separated	0	0
Others	0	0
AGE		
No Data	15	15.19
41-48	16	17.02
49-56	22	23.40
58-65	25	26.60
66 and above	16	17.02
YEARS INTERVAL SINCE RESIDENCY		
0-5	16	17.02
6-12	4	4.26
13-19	20	21.28
20-26	24	25.53
27-34	13	13.83
35-40	8	8.51
41-46	6	6.38
above 46	2	2.13
No data	1	1.06
BOARDED IN ANY OBSTETRICS AND GYNECOLOGY		
No	16	17.02
Yes	30	31.91
SUBSPECIALTY		
None	33	35.11
Ultrasound Gynecologic	34	36.17
Endoscopy Gynecologic	2	2.13
Oncology	3	3.19
Urogynecology	3	3.19
Maternal and Fetal Medicine	9	9.57
Reproductive Medicine	2	2.13
Infectious Disease	1	1.06
Others	1	1.06
AREA OF PRACTICE		
No Data	10	10.64
Obstetrics and Gynecology	84	89.36
Obstetrics	0	0
Gynecology	0	0
SPECIFIC AREA OF PRACTICE		
None	36	38.30
Ultrasound and Gynecologic	25	26.60
Endoscopy	3	3.19
Reproductive Medicine	7	7.45
Maternal and Fetal Medicine	11	11.70
Maternal Fetal Medicine and Ultrasound	6	6.38
Reproductive Medicine and Gynecologic Endoscopy	6	6.38

Statistical Package for Social Sciences (SPSS). A total of ninety-four (94) questionnaires had responses and twenty (20) OB - GYNs were non-responders. The overall response rate was 61. 43%.

RESULTS

In total, there were ninety four (94) OB-GYNs who responded in the study.The overwhelming majority were female (91.49%). The vast majority of of the participants were married (73.40%). Most of the survey respondents were from 58-65 years old (26.60%), closely followed by 49-56 years old (23.40%). The greatest number of OB - GYNs were 20-26 years (25.53%) in practice since graduation from residency. A large number of the respondents had training and are practicing as sonologists (34%, 26.60%). A vast majority of the OB-GYNs were practicing both obstetrics and gynecology.

Knowledge domain

Nearly half of the respondents scored 22, wherein highest possible score is 25 points (48.94%), closely followed by individuals who scored ranging form 19-21 (29.79%). The remaining respondents scored within the range 11-18 (21.28%). The vast majority of the respondents (71.28%) accurately identified NIPT as a screening test. Over half of the respondents (57.46%), think that NIPT will eventually be the standard of care for evaluation of chromosome aneuploidy.

Attitude domain

Over half of the respondents scored 35 (55.32%), wherein highest possible score is 40 points for the attitude items. Most of the respondents (26.60%) are uncomfortable in explaining NIPT.

Practice domain

A large number of the respondents (70.21%) are offering NIPT. 25.53% of the respondents identified correctly who are at risk for Trisomy 21 or Down Syndrome. The following are the top identified factors influence their decision to not use NIPT: (1) Not enough published data regarding detection rates, effectiveness, etc, (2) Lack of interest from their patients), (3) No published position papers or practice guidelines from their professional society(ies) about this testing and (4) Cost and/or lack of insurance coverage for the respondents' patients. Forty - five (45%) of the respondents offer NIPT 90-100% of the time to at risk individuals. Large number of study participants (86.17%) ordered NIPT for high risk patients, while 57% of the respondents, ordered it for low risk patients. A vast majority (80.85%) intended to incorporate NIPT in their practice.

Table 2. Knowledge, Attitude and Practices of Obstetricians and Gynecologists on Non – invasive Prenatal Testing in a Private Tertiary Hospital

Knowledge Base Of The Obstetricians And Gynecologists On NIPT		
Score Knowledge	**Frequency**	**Percentage**
No Data	7	7.45
2-5	0	0.00
6-7	2	2.13
8-10	0	0.00
11-13	2	2.13
14-16	3	3.19
17-18	6	6.38
19-21	28	29.79
22 above	46	48.94
Total	94	100.00
Attitude Of The Obstetricians And Gynecologists On NIPT		
Score Knowledge	**Frequency**	**Percentage**
No Data	4	4.26
4-8	1	1.06
9-12	2	2.13
13-16	1	1.06
17-21	0	0.00
22-25	2	2.13
26-29	12	12.77
30-34	20	21.28
35 above	52	55.32
Total	94	100.00
Practices Of The Obstetricians And Gynecologists On NIPT		
Score Practice Comfort in explaining NIPT	**Frequency**	**Percentage**
No Data	7	7.45
Uncomfortable	25	26.60
Somewhat	12	12.77
Neutral	14	14.89
Comfortale	21	22.34
Very comfortable	16	15.95
Total	94	100.00
Order NIPT		
No data	5	5.32
Yes	66	70.21
No	20	21.28
Refer to MFM or Genetics counselor	3	3.19
Factors Influence Your Decision To Not Use NIPT		
Score Practice	**Frequency**	**Percentage**
Not enough published data regarding detection rates, effectivenes, etc.	5	5.32
Lack of interest from patients	81	86.17
My colleagues and/or institution are not supportive of this test and/or are not using it	2	2.13
No published position papers or practice guidelines from my professional society(ies) about this testing	4	4.26
Cost and/or lack of insurance coverage for patients	2	1.12
(blank)	0	0.00
Grand Total	94	98.94

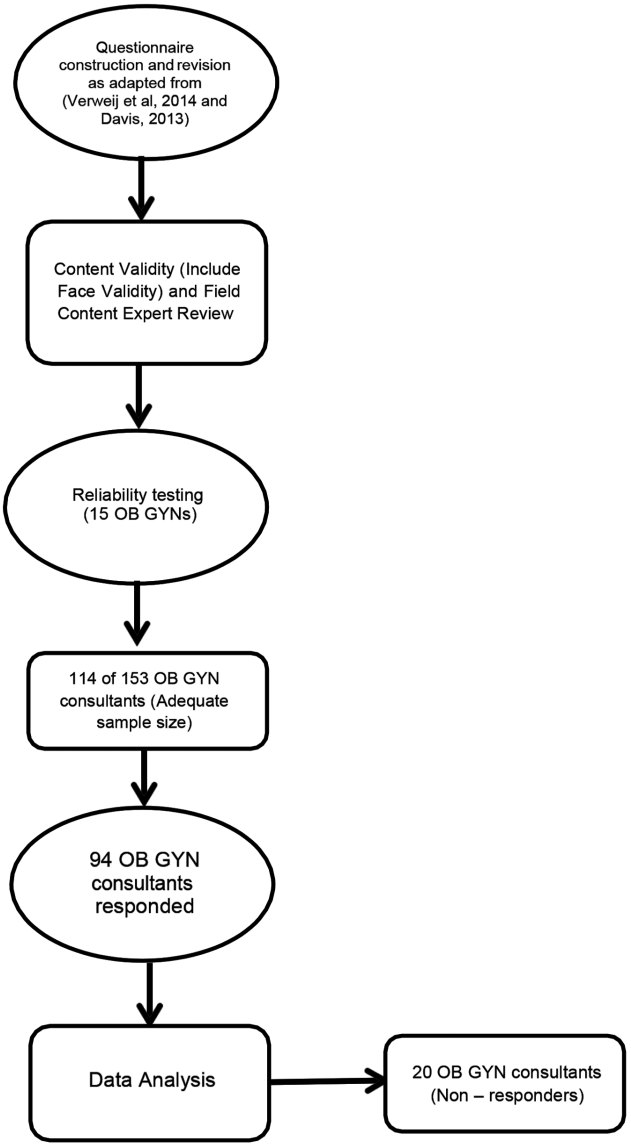

Figure 1. Diagrammatic Workflow of Methods

NIPT analyzes cell-free fetal DNA (cffDNA) in maternal blood. Fetal DNA can detected event at a minimum amount of 10 microliter lf maternal plasma and serum, and greater in nucleated blood cells in whole blood. The approach of using cell free fetal DNA instead of fetal cells is easier, less laborious and less time consuming in working with fetal DNA from the maternal circulation, this are new avenues for NIPT. Since then, there are various reports on cell free DNA for fetal aneuploidies such as Trisomy 21, Trisomy 18 and Trisomy 13 and sex chromosme anomalies. The following are the indications for NIPT: 1.) Maternal age >/= 35 years old at delivery, ultrasound findings with increased risk for aneuploidy, personal or family history of previous pregnancy with trisomy, positive test for aneuploidy and parental balanced translocation.[4] Although safe for pregnant patient, current prenatal screening tests for aneuploidy have poor accuracy with false negative rates between 12 and 23 percent and false positive rate between 1.9% and 5.2%. NIPT using cell free fetal DNA can significantly increase the detection rate among those with trisomy and address to decrease the false positive results.[4] In the United States of America, it is currently recommended to high - risk pregnancies and should be available for all. Several professional organizations (National Society of Genetic Counselors Position Statement, 2012 and The ACOG Diagnostic Practice Guidelines, 2016) recommend that all women should be offered prenatal screening options during pregnancy.[9] However, in the study of Allyse Et Al (2016), stipulates that little is known about NIPT among counselors.[10]

Knowledge

Overall, nearly half of the respondents had 22 points (48.94%), wherein highest score is 25 points, hence were highly knowledgeable about NIPT.

In the studies done by Morrow, K (2016) and Chan Et al (2018), they support the result of this study which showed that the counselors were knowledgeable about NIPT. In the study of Chan Et al (2018), it stipulated that the respondents, composed mostly of obstetrical providers possessied high level knowledge on NIPT.[7] The studies of Brewer et al further supports the result of this study which showed obstetricians had adequate understanding as well regarding NIPT.[11] Furthermore, the study of Martin Et al (2018) strengthened that the results of the study which showed generally strong knowledge among counsellors on NIPT.[11]

Attitude

Overall, more than half of the respondents had 35 points (55.32%)6wherein highest score is 40 points, hence, respondents had a positive attitude about NIPT.

In a study done by Soo Hyun Kim Et al (2018), most of the physicians had positive attitude toward clinical application of NIPT. The same result was distinguished in this study, showed positive attitude also.[13] The findings of the study on Introduction Of Non-Invasive Prenatal Testing As A First-Tier Aneuploidy Screening Test: A Survey Among Dutch Midwives About Their Role As Counsellors, showed the same results with this study which positive attitude towards prenatal screening.[11] Respondents (65.96%) in the study reported that introduction of this technology (NIPT) correctly identified that it will reduce the number of invasive procedures performed. NIPT which avoids the risk of invasiveness and carries the said advantage over the other.[4] Contrary to published data, a fourth of the respondents in this study showed that they were uncomfortable in explaining NIPT. As with the study done by Swaney (2016), most physicians feel

poorly prepared to use genomic advances into practice and are overwhelmed by the amount of information, they are expected to master, could be a possible reason for the level of uncomfort.[16] In the same study, it stated that the respondents demonstrated a high level of accuracy regarding NIPT, supporting the results of the study.

Practices

In the study of Allyse et al (2015), genetic counselors were comfortable in explaining them to their patients (99%), same was observed in the study.[9] The study of Sayres (2011) looked into the utility of NIPT, Obstetricians considered utilization of NIPT.[15] Genetic counselors were queried if they are offering NIPT, 95% of the respondents indicated that they offer NIPT to high-risk patients.[9] Overall, majority of the respondents are utilizing NIPT, offering it 90 -100% of the time. The factor that possibly limits the use of NIPT is the availability of NIPT in our institution and its fairly recent introduction by the PSMFM. When queried on the influence whether to use or not to use NIPT, a large portion, are open in using NIPT especially to high-risk patients. The following were identified as negative factors that influence OB-GYNs decision to not use NIPT: 1) Not enough published data regarding detection rates, effectiveness, etc, (2) Lack of interest from the patients), (3) No published position papers or practice guidelines from there professional society(ies) about this testing and (4) Cost and/or lack of insurance coverage for the respondents' patients.

CONCLUSION

Based on the findings, this research is a reasonable representation (with 61.4% response rate) of the local utilization of NIPT. Majority of the OBGYNs were knowledgeable, had positive attitude and are utilizing NIPT. Striking to note, a fourth of the respondents are not comfortable in explaining NIPT.

LIMITATION

The questionnaires were sent to all OB-GYNs, there were only 94 consultants who returned the questionnaires. Twenty (20) participants were non-responders. Blank data on the questionnaires were overlooked upon return. As with all questionnaire-based studies, response bias is a probability.

RECOMMENDATIONS

The researcher recommends that there is a need to conduct this study on a larger scale cross sectional survey (national level) and multiple studies.

Future steps of the research

The results of the study hopefully be platform for development of subsequent national prenatal screening program. This research can be reproduced on a multi-national level. The goal for this research was eventual multi – center patient education, ordering of tests by most of OB-GYNs and proficiency during explanation to patients.

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