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**Invasive prenatal diagnostic testing recommendations are influenced by
maternal age, statistical misconception and perceived liability**

Running Head: Non-clinical influences on invasive prenatal screening recommendations

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ABSTRACT

Funding policy and a medico-legal climate are part of physicians' reality and might permeate clinical decisions. This study evaluates the influence of maternal age and government funding on obstetrician/gynecologist recommendation for invasive prenatal testing (i.e. amniocentesis) for Down syndrome (DS), and its association with the physician's assessment of the risk of liability for medical malpractice unless they recommend amniocentesis.

Israeli physicians (N=171) completed a questionnaire and provided amniocentesis recommendations for women at 18 weeks gestation with normal preliminary screening results, identical except aged 28 and 37.

Amniocentesis recommendations were reversed for the younger ('yes' regardless of testing results: 6.4%; 'no' regardless of testing results: 31.6%) versus older woman ('yes' regardless of testing results: 40.9%; 'no' regardless of testing results: 7.0%; $\chi^2=71.55$, $p<.01$). About half of the physicians endorsed different recommendations per scenario; of these, 65.6% recommended amniocentesis regardless of testing results for the 37-year-old woman. Physicians routinely performing amniocentesis and those advocating for amniocentesis for all women \geq age 35 were approximately twice as likely to vary their recommendations per scenario. Physicians who perceived risk of liability for malpractice as large were nearly one-and-a-half times more likely to vary recommendations.

The results indicate physicians' recommendations are influenced by maternal age, though age is already incorporated in prenatal DS risk evaluations. The physician's assessment of the risk that they will be sued unless they recommend amniocentesis may contribute to this spurious influence.

Keywords: decision making, prenatal testing, clinician recommendation, bias, maternal age, amniocentesis, defensive medicine, funding policy.

INTRODUCTION

Studies have shown that physicians incorporate background factors that may exert a subjective influence on clinical decision making, when deciding whether to administer amniocentesis testing (Asher et al. 2013; Jena et al. 2015; Srebnik et al. 2013). Here, we examined the effect of legal concerns on physicians' recommendations for invasive prenatal diagnostic testing for Down syndrome, beyond the effect of the clinical information, i.e. screening results. This is an example when a medico-legal climate, and the way the public interprets funding practices, may permeate recommendations.

Since 1993 the Israeli Ministry of Health has funded amniocentesis for all women of advanced maternal age ('AMA'), i.e., of 35 years of age or older. Likewise, it has funded amniocentesis for women younger than 35 years based on high risk ultrasound findings or relevant family history (Israel Ministry of Health 1992; Israel Ministry of Health 2007; Israel Ministry of Health 2011; Israel Ministry of Health 2013). This has led to a prevailing belief among Israeli women that age is a risk factor in and of itself and that AMA women must have amniocentesis (Grinshpun-Cohen et al. 2014; Grinshpun-Cohen et al. 2015). Indeed, a study among Israeli women with normal triple serum screening results found that 87.6% of AMA women had amniocentesis, while only 6.6% of younger women had the procedure (Grinshpun-Cohen et al. 2015). The reasoning often referred to age as necessitating amniocentesis.

This belief is not medically supported by the American College of Obstetricians and Gynecologists (ACOG) guidelines, which stated in 2007 that neither 35 years nor any specific age should be used as a threshold for invasive or non-invasive testing. Notably, the Israeli funding policy does not mandate amniocentesis for AMA women, but rather states that they are

eligible for funding, and that recommendations should be based on screening results (Israeli Ministry of Health n.d.).

The mismatch between beliefs and funding guidelines is not the only complicating factor. Complication is compounded for physicians by a medico-legal climate; evidence suggests that physicians' decisions are influenced by fear of being liable for malpractice (Shwayder 2010; Socol and Socol 2012). For example, a study on cesarean sections concluded that the liability environment influences the choice of delivery method in obstetrics and that fear of liability is a strong motivator in physicians' decision to offer testing (e.g., for cystic fibrosis) (Morgan et al. 2004; Pergament and Ilijic 2014; Stark et al. 2013). Indeed, to mitigate perceived liability, obstetricians and gynecologists may seek out laboratories that test for as many fetal genetic mutations as possible (Kaufman et al. 2008).

In order to examine whether physicians' recommendations about invasive prenatal diagnostic testing are influenced by legal concerns, an issue that is increasingly relevant, the present study compares recommendations made by Israeli physicians for a 28-year-old woman with those made for a 37-year-old woman in an otherwise identical hypothetical scenario.

METHODS

Participants

Prior to data collection, an exemption for ethical approval was obtained from the institutional review board committee of Shaare Zedek Medical Center as this is a non-interventional, observational study that does not involve direct contact with patients or patient identifying information. A link to an anonymous online questionnaire was emailed to the directors of the four regional branches of the Israeli Society for Obstetrics and Gynecology and to the chairs of

obstetrics and gynecology departments at Israeli hospitals asking that they distribute the link to all their staff members. Both in the email and on the first screen of the survey website, the study was presented as a 'position survey on maternal age and amniocentesis'.

Settings

The data were collected in 2011-2012. We state this, because non-invasive cell free fetal DNA prenatal testing (NIPT) (ACOG 2015; Buchanan et al.2014), which is increasingly becoming an acceptable alternative to amniocentesis, was not yet widely used, and therefore, its presence did not emerge in physician responses to the survey, nor could it have been included.

In Israel, most pregnant women visit public clinics fully covered by the national health insurance system. The follow up is conducted by a general OB/GYN every 4-6 weeks. Ultrasound examinations, including mid trimester anatomic scan, and second trimester 'triple test' are fully covered. In addition, the vast majority of the young Israeli population holds complementary health insurance, covering nuchal translucency and first trimester serum screening tests, (which became part of the national health insurance policy in 2012), and most costs of amniocentesis, as indicated. Therefore, monetary cost is usually not a significant personal issue. Either the OB/GYN the woman usually sees or another clinician performs the amniocentesis through a public or private service.

Procedures

Participants provided informed consent and were then presented with a clinical scenario as part of a larger study on views concerning invasive prenatal diagnostic testing (Srebnik et al. 2013). Here we report on data relevant to physicians' recommendations regarding the same scenario at two different maternal ages. The scenario described the case of a pregnant woman at 18 weeks gestation who came in to discuss results of biochemical and sonographic screening

results, pointing to low risk for Down syndrome (defined as 1:380 or lower by the Israeli Ministry of Health). The scenario stated that all risks and benefits of performing or avoiding amniocentesis were discussed with the patient. Participants received two versions of the scenario in random order, one referring to a 28-year-old pregnant woman and the other referring to a 37-year old pregnant woman. The versions were otherwise identical.

Participants were asked to read each woman's scenario and indicate their recommendation by selecting one of five options:

- (i) I would recommend performing amniocentesis.
- (ii) I would recommend performing amniocentesis if the risk according to screening results is high in my opinion.
- (iii) I would recommend avoiding amniocentesis.
- (iv) I would refuse to state my opinion.
- (v) None of the above reflects my opinion.

After choosing an option, participants responded to several demographic questions (age, gender, years of experience, whether they perform amniocentesis and place of work).

Next, participants were asked to rank their agreement with statements about amniocentesis.

Data Analysis

First, we measured the correlation between all variables in the dataset. Next, we created a variable categorizing physicians into those who gave different recommendations for the 28-year-old scenario and the 37-year-old scenario, and those that gave the same recommendation. For example, if the clinician recommended avoiding amniocentesis for the 28-year-old scenario but recommended amniocentesis regardless of testing results for the 37-year-old scenario, the clinician would be categorized as one whose recommendations differed. Then, we conducted a

binary logistic regression to examine the influence of demographic characteristics and attitudes towards amniocentesis on the physicians' recommendation in the two different age scenarios.

A sign test (Dixon and Mood 1946) was conducted for the physicians who varied their recommendations per scenario in order to examine if physicians' recommendations became more aggressive for the scenario of the AMA woman. To perform the sign test, we first removed the 21 physicians who responded with 'none of the above' for only one scenario, as to be able to scale the remaining responses ('no', 'depends on screening result', and 'yes') ordinally.

The study did not have any external funding source.

RESULTS

A total of 188 physicians completed the questionnaire. Seventeen participants were excluded due to refusal to state their recommendations regarding the described scenarios. The analysis was therefore based on 171 participants. Demographic characteristics are shown in Table I.

Figure 1 shows the proportion of physicians who endorsed each recommendation for the two scenarios (28-year-old, 37-year-old). Prevalence of recommendations favoring amniocentesis was only 6.4% for the 28-year-old woman, but 40.9% for the 37-year-old woman. Conversely, prevalence of recommendations to avoid amniocentesis was 31.6% for the 28-year-old woman, but only 7.0% for the 37-year-old woman. Of the 171 physicians included in the study, 81 had the same recommendation for both, while 90 varied their recommendations between the 28-year-old woman and the 37-year-old woman. As hypothesized, the sign test revealed that physicians were more likely to recommend more aggressive testing for the 37-year-old woman than the 28-year-old woman, $z = -8.066$, $p < 0.001$. (There were only 15 physicians who changed their recommendation from 'no' for the younger woman to 'yes' for the older

woman. A binomial test performed on the smaller number, 0, revealed that there was a 0.0031% chance of having 0 ‘successes’ out of 15.)

Table II shows the percentage of physicians’ responses to various statements regarding their attitudes toward amniocentesis. The table indicates that the majority of physicians agreed with the argument that failing to recommend amniocentesis for women over the age of 35 may result in liability in a medical malpractice lawsuit if a baby is born with Down syndrome (‘Highly agree’ and ‘Agree’: $n = 114$, 67.1%). In contrast, over half of the physicians (56.8%) disagreed with the argument that over the age of 35, the risk of missing the Down syndrome diagnosis in a fetus during preliminary screening is too high, and it is therefore justified to perform amniocentesis in all pregnancies (‘Completely disagree’ and ‘Disagree’; $n = 96$, 56.8%). Nearly half of the physicians disagreed with the argument that no referral for amniocentesis over the age of 35 years is interpreted by the patient as inappropriate and unprofessional medical procedure (‘Completely disagree’ and ‘Disagree’; $n = 79$, 46.5%).

The representation of the physicians’ recommendations at maternal age of 37 years relative to those at age 28 years allowed us to distinguish among physicians who endorsed the same recommendations and those that endorsed different recommendations at the two maternal ages (28 and 37; Figure 2). Overall, about half the physicians endorsed different recommendations ($n=90$ of 171, 52.6%). Of the physicians who endorsed different recommendations, the majority ($n = 59$, 65.6%) did not favor automatic amniocentesis for the younger woman but favored amniocentesis regardless of screening results in the older woman (Figure 2b), and only 21.1% of these said they would recommend amniocentesis based on the risk associated with the screening results, even though the experimental scenario stated that these results were normal.

The statement, “Over the age of 35, the risk of missing the DS diagnosis in a fetus is too high and therefore it is justified to perform amnio in all pregnancies” was found to be negatively correlated with recommending amniocentesis to the 37-year-old woman, -0.488 , $p < 0.001$. (The negative correlation is due to a decision to code the statements of greater agreement as higher values, whereas the recommendations for amnio were coded as 1 for ‘yes’, 2 for ‘depends’, 3 for ‘no’, etc.)

Next, backward stepwise binary logistic regression analysis was conducted to examine which predictors were associated with physicians' endorsement of different (vs. the same) recommendation depending upon the maternal age (28 and 37 years) of the woman in the scenario. Predictors included clinician demographic characteristics (i.e., years of experience, gender and whether they perform amniocentesis) as well as their attitudes toward amniocentesis. This analysis revealed that the more the clinician agreed with the statement that over age 35, the high risk of missing Down syndrome during preliminary screening justifies performing amniocentesis in all pregnancies, the more likely s/he was to make a different recommendation for a 37-year-old woman as compared to a 28-year-old woman (odds ratio OR: 1.92; 95% CI: 1.42–2.58). Likewise, degree of agreement with the statement that not recommending amniocentesis for women over the age of 35 would risk liability in a malpractice suit if a Down syndrome baby were born was associated with a higher likelihood of a different recommendation at maternal age 37 vs. 28 (OR: 1.47; 95% CI: 1.12–2.58). The variation in degree of agreement with these statements among physicians with either the same or differing recommendations per scenario is illustrated in Figure 3. Similarly, physicians with fewer years of experience (OR: 1.04; 95% CI: 1.00–1.08) and those who routinely perform amniocentesis (OR: 2.19; 95% CI: 1.03–4.63) were more likely to make a different recommendation for the 37-year-old woman.

Gender, age, place of work, and the agreement with the statement about patient interpretation of lack of amniocentesis recommendation were all non-significant predictors and were thus excluded from the final model. Figure 4 shows the ROC curves for the (A) original and (B) final models. Table III is the final regression table for our model.

DISCUSSION

Clinical judgment as a whole, but especially regarding procedures and invasive diagnostic testing, requires knowledge, skill, and responsibility. The clinical environment is increasingly complex, and a growing body of evidence shows that clinical decision making nowadays is also impacted by concerns over malpractice suits (ACOG 2013), which may lead to defensive medicine (Asher et al. 2013), and by funding policies and the way the public interprets them as informing what should be done, rather than what could be done, with health insurance funding (Shurtz et al. 2016). To our knowledge, the present study is the first to extend this line of investigation to examining whether physicians' recommendations for invasive prenatal diagnostic testing can be influenced by non-clinical factors such as maternal age, and legal concerns.

Our data show that physicians' decisions are swayed by the age of the expectant mother in the absence of clinical justification. That is, age is already accounted for as triple serum screening results are calculated as a function of the presence of biochemical markers, as well as maternal age. Therefore, there is no need to factor in age again to the mental calculation of risk. Thus, when the physicians in our study considered maternal age separately from the screening results, they were effectively placing additional weight on age alone and either placing lower weight on the screening results or dismissing them altogether (in the case of normal screening results). Indeed, a significant portion of respondents exhibited precisely this tendency, by

recommending amniocentesis to an AMA woman whose clinical profile was identical to that of a younger woman for whom they did not recommend invasive diagnostic testing.

There was a close split among the participants: 52.6% of the respondents made a different prenatal testing recommendation for the younger woman vs. the older one, while 47.4% retained the same recommendation. The most common difference was between recommending amniocentesis to a 28-year-old woman depending upon the screening result, but recommending amniocentesis to a 37-year-old without any dependence on previous screening results. The main measure that correlated with physicians' decision to recommend amniocentesis at 35 was their degree of agreement with the statement: "Over the age of 35, the risk of not diagnosing Down syndrome following preliminary screening of a fetus is too high, and therefore it is justified to perform amniocentesis in all pregnancies." However, clinical data show that the detection rate for women over 35 years of age during preliminary prenatal screening is higher compared to the detection rate for their younger counterparts (89.8% of DS pregnancies vs. 66.7% of DS pregnancies) (Simpson 2012). It might be that there is a prevailing belief among physicians that they are expected to prescribe amniocentesis at AMA due to government funding, and that this is being interpreted as having a medical basis.

As previously mentioned, the main measure that correlated with physicians' decision to recommend amniocentesis at 35 was their degree of agreement with the (untrue) statement: "Over the age of 35, the risk of not diagnosing Down syndrome following preliminary screening of a fetus is too high, and therefore it is justified to perform amniocentesis in all pregnancies." We attribute the increased weight these OB/GYNs placed on maternal age to two factors, the first being physicians' limited understanding of screening test statistics (Wegwarth et al. 2012). Research has shown that OB/GYNs have gaps in their ability to comprehend statistical concepts

(Anderson et al. 2014), and, perhaps surprisingly, genetic counselors often need further clarification from the testing laboratory about test results (McGovern et al. 2003). If this is true of genetic counselors with thorough genetics training, it is certainly reasonable to assume that OB/GYNs with minimal genetics training should feel less than confident in their knowledge and interpretation of results. The second factor for the association between age and risk is that in Israel where the study took place, public funding exists for amniocentesis after the age of 35. This, in and of itself, creates a climate associating this age as one in which amniocentesis is required, at least as perceived by patients (Grinshpun-Cohen et al. 2014; Grinshpun-Cohen et al. 2015). The two factors may compound. In the absence of thorough understanding of the screening test, physicians may make the leap from public funding guidelines to age-associated risk. This would result in the prevalent, yet false, belief that was present in our sample that the high risk of not diagnosing DS during preliminary screening at AMA justifies performing amniocentesis in all AMA pregnancies.

Option (ii), “I would recommend performing amniocentesis if the risk according to screening results is high in my opinion”, was designed to give physicians room to interpret the screening results as they see fit. It effectively created an ordinal scale of ‘no’, ‘depends’, and ‘yes’. The fact that so many physicians chose this option indicates that they take the threshold recommended by the Israeli Health Ministry with a grain of salt, factoring in other elements. Although, we cannot say exactly what those elements are. Figure 2 shows that more physicians varied their answers depending on age (90 physicians) than physicians who responded identically for both age scenarios (81 physicians). Furthermore, Figure 2B shows that a clear majority of the physicians who varied their recommendations ‘upgraded’ their recommendation to be more

aggressive when moving from the 28-year-old woman to the 37-year-old woman; that is, either from ‘depends on screening test’ to ‘yes’, ‘no’ to ‘yes’, or ‘no’ to ‘depends on screening test’.

Practice Implications

While we tested amniocentesis recommendations in Israel, the topic examined in this study is much broader, and spans other countries and other instances, where availability of funding is perceived as a directive to screen, test (Zhao et al. 2013), vaccinate (Hayashi et al. 2012), etc. In Israel, as in the UK, (National Health Service, UK 2014), amniocentesis is fully funded above the age of 35, which women take as an indication that the test is mandatory or at least highly recommended; AMA women who know that their screening results are normal choose nonetheless to undergo amniocentesis and cite their age as a determining factor (Grinshpun-Cohen et al. 2015). Therefore, for a clinician to recommend against the test to an AMA woman is a non-trivial and potentially controversial decision (Blumenthal-Barby and Krieger 2014; Croskerry 2015).

The second important factor influencing whether physicians made a different recommendation for a younger vs. older woman was concern over liability in potential litigation if they did not recommend amniocentesis. The physician’s assessment of the risk of a lawsuit unless they recommend amniocentesis has previously been demonstrated to play a role in physicians' decisions. Bishop and colleagues (Bishop et al. 2010) found that physicians consider malpractice fear as a problem impacting their practice. In the field of obstetrics, for example, it has been shown that litigation fear directly contributes to the rising prevalence of cesarean sections (Minkoff 2012; Rossignol et al. 2013).

Study Limitations

This study has several limitations, including a relatively modest sample size and number of predictor variables. Secondly, we were unable to ascertain the true representativeness of our sample. The survey was broadly distributed, potentially reaching all obstetrician/gynecologists and OB/GYN residents in Israel (1200; Shen et al. 2010), but was completed by only 14% of them (or 16% of the 1000 obstetrician/gynecologists, as residents were ultimately excluded from analysis). However, in the absence of data on how many failed to receive the email link to the survey, we cannot report a true response rate. Still, because confounding factors like age, gender and clinical settings (hospital versus community) did not affect the results, a selection bias for respondent answers appears to be unlikely. Further, our sampling rate is higher than the 7% of Israeli physicians sampled in a recent national survey (Asher et al. 2012) and comparable with those of other surveys of the membership of large medical associations (Raffi et al. 2012; Ghaderi et al. 2013). Thirdly, the study was conducted in Israel, and cultural factors may limit its generalizability. Still, Israel, like the US, endorses guidelines defining AMA as a possible indication for amniocentesis testing, and the guideline is therefore relevant to physicians' choices. A fourth limitation is that physicians were asked to provide recommendations based upon hypothetical scenarios rather than actual clinical scenarios. However, this aspect of the study design may also be considered a strength in that these decisions were inherently independent of patient preferences, which are influenced by a plethora of reasons (Lesser and Rabinowitz 2001). This provides unique insight into physicians' preferences, motivations, and potential concerns. Additionally, as this survey was circulated only among OB/GYN physicians and not genetic counselors, for example, there was no way to compare physician and genetic counselor attitudes towards amniocentesis. Finally, invasive prenatal testing may quickly be supplanted by newer, non-invasive techniques, which, when applied contingently, are also cost-

effective (Gyselaers et al. 2015). More specifically, another issue that this study does not address is the addition of NIPT as an important option to physicians' arsenal of non-invasive screening tests (Gyselaers et al. 2015). However, the issue of the influence of non-clinical factors on clinical decisions remains highly relevant. NIPT notwithstanding, the dilemma at the core of this study of noninvasive screening vs. invasive diagnostic testing has not been resolved. In fact, this dilemma has become even more complex, given the added options with overlapping but not identical benefits (Pergament & Ilijic 2014). NIPT offers genetic information through a simple blood test, while amniocentesis is an invasive procedure, which carries risk. However, the accuracy of NIPT is believed to be better in the high-risk population, compared to the general obstetric population. Therefore, the American College of Obstetricians & Gynecologists recommend that it not be used as the sole consideration in pregnancy management decisions (ACOG 2015).

Research Recommendations

Our results suggest that OB/GYN physicians' choices regarding prenatal diagnosis are influenced by the medico-legal climate and might demonstrate the practice of defensive medicine. The results demonstrate a higher prevalence of amniocentesis recommendations for an AMA woman, whereas a younger woman presenting with the same screening results would receive a different recommendation. While maternal age is an integral part of screening results for Down syndrome, a significant portion of doctors who would recommend avoiding an invasive prenatal diagnostic test at younger maternal age would recommend such testing at advanced maternal age, even when screening results are low. Fear of legal liability may contribute to this tendency, which indicates that the reasons for the different recommendations are not purely medical. This can be taken one step further by examining other funding and

reimbursement policies and their effect on physicians' recommendations, as well as on patients' reading of the situation. Such a line of work can inform the allocation of financial resources, and the way policies are designed and implemented to address the medico-legal challenges which physicians face. This may help address the recent call to optimize women's healthcare resources (Jennings 2014), including the decrease in unnecessary tests.

Additionally, prenatal genetic counseling may be provided by a geneticist (physician), a genetic counselor, or OB/GYN provider (Israel Ministry of Health 2017; Sagi and Uhlmann 2013). This study only investigated OB/GYN physicians' attitudes towards invasive procedures in Israel. However, the dilemmas presented to respondents here are commonly relevant to other professionals who provide prenatal genetic counseling. Future research can investigate how physicians from other medical specialties and how other clinicians within in the field of OB/GYN view invasive diagnostic tests and procedures.

ETHICAL STATEMENT

Talya Miron-Shatz, Sivan R. Rapaport, Naama Srebnik, Yaniv Hanoach, Jonina Rabinowitz, Glen M. Doniger, Linda Levi, Jonathan J. Rolison, and Avi Tsafirir declare that they have no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

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