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ORIGINAL PAPER/OBSTETRICS

A novel prenatal index predicting the probability of neonatal intensive care in pregnants: amnion progesterone receptor to alfa fetoprotein rate

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ABSTRACT

Introduction: Amniocentesis (AC) is the most used interventional procedure for prenatal diagnosis. The study aims to evaluate the pregnancy outcomes undergoing AC and the potential of amnion progesterone receptor (aPR) to alfa fetoprotein (AFP) rate for predicting the probability of neonatal intensive care unit (NICU).

Material and methods: This prospective cross-sectional study population consisted of 85 pregnant women who underwent mid-trimester AC. All cases were screened by ultrasound before AC. Maternal venous and amniotic samples were obtained simultaneously to evaluate the serum progesterone (sPRG), aPR, and aAFP and analyzed with patient results.

Results: Unlike sPRG and aAFP, aPR showed a positive correlation with NICU and a negative correlation with parity. In linear regression, the aPR-AFP rate showed strong linearity with NICU and parity. In an aPR-AFP rate analysis, we saw a strong predictivity for NICU compared to the other three parameters. It presented 73.4% specificity and 79% sensitivity at 0.0075 cut-off (AUC: 0.78; p = 0.003; 95% CI: 0.608–0.914).
Conclusions: Evaluating the PR either alone or in a rational combination with AFP will provide physicians with valuable information about the advanced process of pregnancy and postpartum complications. The physicians might use the aPR-AFP rate to predict NICU potential for pregnancy and need further studies to make more vital predictions on postpartum complications.
Key words: amnion progesterone receptor; alfa fetoprotein; neonatal; intensive care

INTRODUCTION

Amniocentesis (AC) is the oldest known and most commonly used interventional procedure for prenatal diagnosis [1]. The primary purpose of prenatal diagnosis is to have information about the fetus's health at the earliest time. Since the fetus plays a crucial role in forming amniotic fluid (AF), AC is proper for evaluating fetal health and the prenatal diagnosis of hereditary diseases [2]. The most common indications for AC are advanced maternal age, high risk in maternal serum screening test, family history of neural tube defect, stillbirth, two or more spontaneous abortions, a family history of metabolic or molecular genetic disease, and fetal birth defect [3]. To date, AF was the first method for biochemical analysis. Studies are used for prenatal diagnosis of congenital disorders to determine fetal well-being and predict fetal maturity.

Progesterone (PRG) is an essential steroid sex hormone for required to maintain a healthy pregnancy. It helps physicians on detecting and understanding abnormalities of pregnancy period [4, 5]. The corpus luteum produces it in the first eight weeks of pregnancy, but the placenta plays this role from 8 to 12 weeks [6–8]. Progesterone prepares the tissue lining of the endometrium for stimulating glands in the early endometrium. It suppresses uterine contractions and protects pregnancy as well. It regulates the mother's immune response to prevent embryo rejection and improves uteroplacental circulation and luteal phase support. Fetal membranes and decidua are potential target tissues for PRG [6, 7, 9, 10]. Eventually, for delivery, PRG effectiveness on the myometrium must change for the myometrium to switch from silent to active. The tissue achieves this change with neither peripheral maternal blood nor myometrial PRG but with the shift in myometrial progesterone

receptor (PR). The interaction with PR primarily mediates the physiological effects of PRG [7, 9–12]. Progesterone receptors are in at least three functional isoforms in the tissues of the human reproductive system: PR-A, PR-B, and PR-C [9, 10, 12, 13]. These hormones pass through plasma membranes by simple diffusion in target cells, and the specific receptor in the nucleus binds [10]. There may be efficacy differences in PR isoforms. For example, PR-B was the dominant PR type in the decidua, while PR-C was efficient in the amnion [12].

Amniocentesis (AC) is the most used interventional procedure for prenatal diagnosis. The study aims to evaluate the pregnancy outcomes undergoing AC and the potential of amnion progesterone receptor (aPR) to alfa fetoprotein (AFP) rate for predicting the probability of neonatal intensive care unit (NICU).

MATERIAL AND METHODS

Study design

This research is a prospective cross-sectional clinical study performed in the University Hospital setting between August 2020 and February 2021. A total of 85 pregnant women with a singleton pregnancy who are willing to join the present research with their demographic/outpatient data joined the study. The Ethical Committee approved the current study (Date: 10.07.2020 — ID: E-20/311). All the participants gave written consent before contributing to the study.

Patient selection

The study population consisted of pregnant women who underwent mid-trimester AC between 16–20 gestations for different indications. All cases were screened by ultrasound for fetal anomalies before AC. As given in the flowchart (Fig. 1), we performed a power analysis for the participants. We recorded gestational age by the concordant menstrual period or via the earliest ultrasound if the last menstrual period was discordant or unsure. The indications for AC were; major fetal anomalies (Ventriculomegaly, Cleft lip/palate, Cardiac defects, Omphalocele, Cystic hygroma) (n = 10; 11.7%), high risk in NIPT (non-invasive prenatal testing)(n=4; 5%), ultrasound-determined soft signs (Second-Trimester Sonographic Markers Associated with Fetal Trisomy 21: Nuchal fold thickening, Single umbilical artery, Echogenic intracardiac focus, Renal pelvis dilation, Aberrant right subclavian artery, Echogenic bowel, Nasal bone absence or hypoplasia) (n = 30; 35.2%), maternal factors (maternal request, anxiety and advanced maternal age (if the mother > 35 years)(n = 9; 10.5%), abnormal biochemical marker results in the first or second-trimester aneuploidy screening test results, a

family background of chromosomal abnormalities such as; structural rearrangements in one of the parents or previous fetus or child with a de novo chromosomal anomalies (n = 30; 35.2%), abnormal ultrasound scan in the first or second trimester of the pregnancy (n = 3; 3.5%). We followed the patients and prospectively collected their data regarding pregnancy complications. Preexisting medical problems and demographics were collected elaborately for each patient. None of the patients were in the labor stage. The study excluded the followings: pregnancies who received hormonal medications, twin pregnancies, determined fetal aneuploidies incompatible with life, or fetal death following AC procedure.

Amniocentesis procedure

Each participant gave informed consent to the AC procedure, an approach under ultrasound guidance between 15 and 20 weeks. We performed a fetus scan before the amniocentesis to assess fetal condition. The puncture was done with a 22-gauge (9 cm) spinal-needle, apart from the fetus's body and free from the fetal cord. The first 1 ml of amniotic fluid was discarded, and another 25 mL of amniotic fluid was withdrawn for chromosome and PR assessment. Following the procedure, the color and clarity of the fluid are documented. The patients were discharged 20 minutes after the process was complete unless they encountered complications. All the women were informed to directly attend our gynecology and obstetrics ward if any complications occurred following the discharge. The same maternal and fetal unit specialist in our clinic performed all procedures in the study.

Blood collection and laboratory tests

Maternal venous blood specimens were obtained simultaneously as the AF to evaluate the serum progesterone (sPRG) levels. The collected samples were immediately processed and stored at –80ºC until thawed for assessment. Both serum and AF samples were not subjected to freeze-thaw cycles before evaluation. sPRG, amniotic AFP (aAFP) was measured using the competitive immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). Amniotic fluids were collected via the AC procedure from each patient. The samples were centrifuged at 2000 rpm for 12 min, and the supernatant was kept in -80C conditions until the analysis time. AF supernatant was evaluated for PR levels using ELISA kits (Bioassay Technology Human Progesterone Receptor ELISA Kit, Shangai, China). The amniotic PR (aPR) was assessed using the ELISA according to the manufacturer's instructions. Inter & intra-assay variability were < 8% and 14%, respectively.

Statistical analysis

The significance level of statistical hypothesis tests was < 0.05 for the current research. The SPSS version 22.0 (IBM Soft. Comp.,USA) statistical software conducted the statistical analysis. For normally distributed variables, results were expressed as mean and standard deviation. Categorical data were compared using chi-square analysis or Fisher's exact test. Two groups with continuous variables were compared with an unpaired t-test, and three groups were compared using a one-way analysis of variance followed by Tukey's multiple comparison test. Non-normally distributed data are presented as the median. Using Dunn's multiple comparison test, groups were compared using the Kruskal–Wallis with post-hoc analysis. Additionally, stepwise linear regression was performed to identify potential clinical preoperative confounders for the comparisons. A receiver operating characteristic (ROC) curve assessed the potential of amnion progesterone receptor to alfa fetoprotein rate (aPR-AFP) for predicting the probability of neonatal intensive care.

RESULTS

Demographics

As given in Table 1 with details, the participant's mean age was 32,6 ± 5 years (n = 85, range: 19–44). Thirty-nine of the deliveries were by cesarean section, 46 were delivered by standard delivery, and 45 of the babies were boys, while 40 were girls. Seven babies required neonatal intensive care.

Regression analysis

In the analysis of sPRG and aAFP, there was no correlation on factors such as post-pregnancy NICU, gravida, birth week, smoking, a/s indication, gender, mode of delivery, third-trimester complication, chromosomal anomaly, abortion, weight, parity ($p > 0.05$). Unlike sPRG and aAFP, aPR showed a positive correlation with NICU and a negative correlation with parity. This correlation was not strong. We observed linear regression analysis that the aPR-AFP rate showed strong linearity with NICU and pregnancy parity, as in Table 2.

ROC analysis

The ROC analysis we did for the predictability of NICU, given in Table 3 with details and Figure 2 with graphic, showed that sPRG (AUC: 0.42; $p = 0.341$) and aAFP (AUC: 0.41; $p = 0.283$) have no diagnostic efficiency in terms of predicting NICU. Unlike, aPR showed a

predictive potential for NICU with 74,1% specificity and 67,2% sensitivity at 59,7 cut-off values [AUC: 0.69; p = 0.044; 95% confidence interval (CI) 0.472–0.881]. In the aPR-AFP rate analysis, we saw a strong predictivity for NICU compared to the other three unique parameters. It presented 73,4% specificity and 79% sensitivity at 0,0075 cut-off value (AUC: 0.78; p = 0.003; 95% CI 0.608–0.914).

DISCUSSION

In the present analysis, we predicted that the study of the amniotic hormones in the early pregnancy period might be informative for the pregnancy and postpartum processes. Evaluating the PR in the AF alone or in rational combination with AFP will provide physicians with useful information about the advanced pregnancy and postpartum complications process.

Before the onset of labor, there is a substantial decrease in maternal PR, which is essential in decreasing the effects of PRG in the initiation of delivery in animals [14]. Unlike animals, this is different in the human fetus. According to the analysis of PRG values, maternal and AF concentrations do not show any change before the labor [15]. According to recent studies, if PRG support is given as an external supplement, it causes a decrease in the frequency of uterine contractions [16, 17]. For these reasons, new research has focused on mechanisms that may explain the effect of PRG more strongly, especially at the myometrium or decidua level. In this sense, the relationship between AF and PRG has become a focal point for us physicians to analyze the course of pregnancy and the possibility of complications after it.

Amniotic fluid, which is the habitat of the fetus, is a liquid substance of diagnostic importance not only in the nutrition of the fetal membranes but also in the homeostasis of pregnancy. During pregnancy, there are changes in electrolyte values in the AF of the pregnant, and hormones are produced by fetal trophoblastic cells and secreted into the maternal circulation [18]. In a study by Mazor et al. [19], maternal and serum PRG was correlated, though the study of Nagamani et al. [20] found that they did not find any correlation. Norwitz et al. [21] showed the in-vitro homeostasis role of PR in the fetalmembrane. So-Youhun et al. [22] reported uterine PR and its relationship to labour, and PR-A and B types were described by them. According to Leonhardt et al. [23], changes in PR can have a role in labor at term delivery. A shift in PR expression may mediate PRG withdrawal. In the present study, we would be able to obtain information about both the

pregnant and the baby in the later stages of pregnancy by measuring aPR and aAFP, unlike serum measurements. We analyzed total PR instead of sub-receptor analysis.

In our analysis, sPRG and aAFP showed no significant correlation with post-pregnancy NICU, gravida, birth week, smoking, gender, mode of delivery, third-trimester complication, chromosomal anomaly, abortion, weight, or parity. Unlike sPRG and aAFP, aPR showed a positive correlation with NICU and a negative correlation with pregnancy parity. In linear regression analysis, the aPR-AFP rate showed strong linearity with NICU and pregnancy parity. In the aPR-AFP rate analysis, we saw a strong predictivity for NICU compared to other parameters. It presented 73.4% specificity and 79% sensitivity; hence, physicians might use this novel index to predict NICU potential for pregnant women.

This prospective clinical research had some limitations. The major limitation is the inability to correlate amniotic hormone levels with maternal levels in these samples. Changing PR levels influences gestational length in humans, which is particularly important to research on regulating PR isoform expression. We measured total PR instead of all lower Progesterone receptors (PR-A, PR-B, and PR-C), which allowed us to reach a generalizable result over total PR rather than a specific PR effect. The efficacy and NICU specificity of the results may be increased in a study with all specific receptors. As a minor limitation, we analyzed samples of hormones at different times.

CONCLUSIONS

Amniotic hormones are essential to obtain information about both the pregnant and the baby in the later stages of pregnancy by measuring PR and AFP, unlike serum measurements. Evaluating the PR alone or in rational combination with AFP will provide physicians with useful information about the advanced pregnancy and postpartum complications process. The physicians might use the aPR-AFP rate to predict NICU potential for pregnancy and need further studies to make more vital predictions on postpartum complications. The data are preliminary and require further analysis.

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None.

Ethics statement

The Ethical Committee's approval of the study was obtained (Date: 10.07.2020 — ID: E-20/311). All procedures performed in those studies involving human participants were

following the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For studies using human participants, state whether written informed consent was obtained from participants to participate.

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None

Author's contributions

S.B.A.: study concept and design; S.A., T.A., and G.S.Y.: data acquisition, data analysis, and interpretation; S.B.A, T.E., and O.S.: manuscript preparation; T.A.: correspondence.

Data availability statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Conflict of interest

The authors declare no conflicts of interest.

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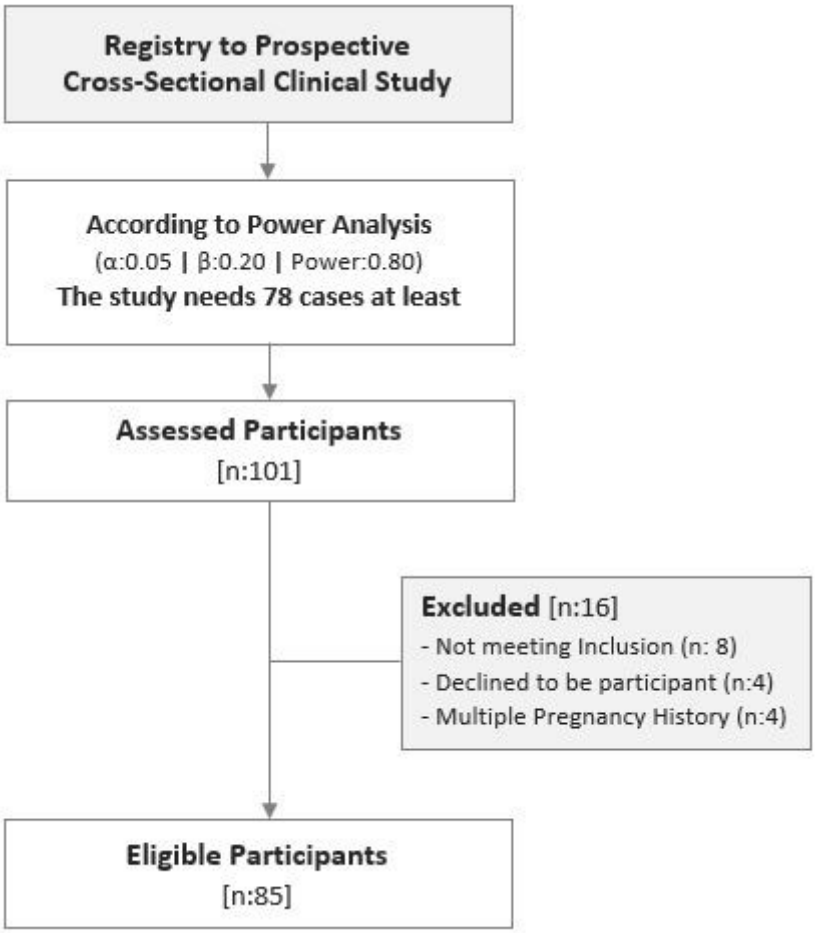

Figure 1. Flow chart for the selection and enrollment of the participants

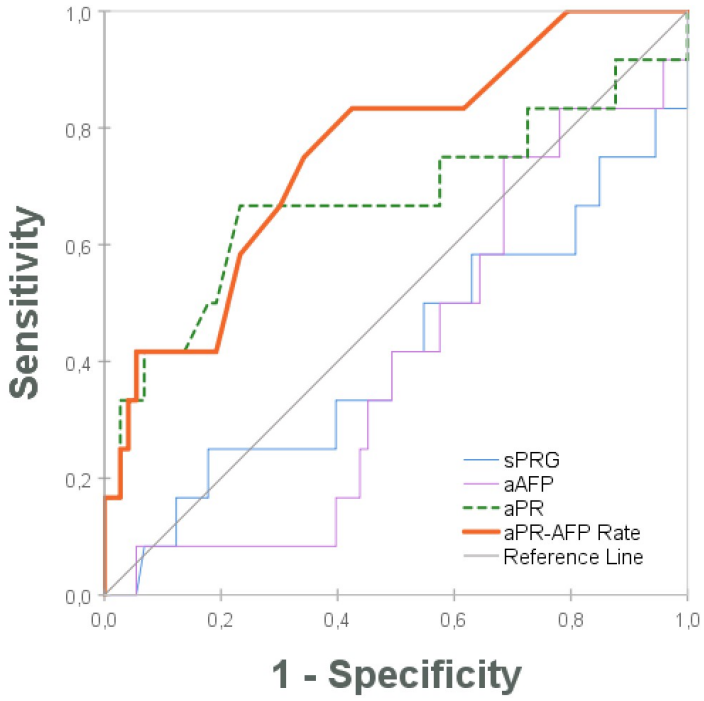

Figure 2. The receiver operating characteristic (ROC) curve of amniotic hormones for predicting neonatal intensive care unit (NICU); sPRG — serum progesterone; aAFP — amniotic alfa fetoprotein; aPR — amnion progesterone receptor; aPR-AFP — amnion progesterone to alfa fetoprotein

Table 1. Demographic and clinical features of the participants

Variables		Mean/frequency	Range/percent
Age [years]		32.6 ± 5.9	19–44
Maternal weigh [kg]		67.4 ± 13	41–103
Height [m]		159.9 ± 6.4	140–180
aPR [ng/mL]		69.8 ± 101	13–746
aAFP [ng/mL]		9470 ± 7402	474–43150
aPR-AFP rate		0.011 ± 0.0001	0.001–0.087
Birth weigh [g]		2770 ± 1110	125–4180
NICU period [days]		1.6 ± 7.7	0–64
Gender	Male	45	52.9%
	Female	40	47.1%
Delivery	Normal	46	54.1%
	Caesarean	39	45.9%
Cigarette	No	73	85.9%
	Yes	12	14.1%
Gravida	1	18	21.2%
	2	27	31.8%
	3	12	14.1%
	4	17	20.0%
	5	9	10.6%
	6	2	2.4%
Parity	0	24	28.2%
	1	28	32.9%
	2	21	24.7%
	3	10	11.8%
	4	2	2.4%
AC indication	MFA	10	11.8%
	NIPT	4	4.7%
	Soft Signs	29	34.1%
	Test Risk	36	42.4%
	Maternal	6	7.1%
Abortus	0	58	68.2%
	1	14	16.5%
	2	10	11.8%
	3	1	1.2%
	4	2	2.4%

aPR — amnion progesterone; aAFP — amnion alfa fetoprotein; aPR-AFP — amnion progesterone to alfa fetoprotein rate; NICU — neonatal intensive care unit; AC — amniocentesis; MFA — major fetal anomaies; NIPT — non-invasive phetal test

Table 2. Linear regression analysis of amnion progesterone receptor to alfa fetoprotein rate

Variables	Beta	T	p value	95% confidence interval	
				Lower	Upper
Constant	–	6.179	0.0001	0.008	0.017
NICU	0.445	4.592	0.0001	0.01	0.024
Pregnancy parity	–0.271	–2.798	0.006	–0.006	–0.001

Dependent variable: amnion progesterone receptor to alfa fetoprotein rate (aPR-AFP); **Predictors**: NICU, gravida, smoking, chromosomal anomaly, delivery (Caesarean or normal), gender, third-trimester complication, abortion, parity; NICU — eonatal intensive care unit

Table 3. The receiver operating characteristic (ROC) curve analysis for neonatal intensive care unit (NICU) possibility

Variables	Area	SE	p value	95% confidence interval	
				Lower	Upper
sPRG [µg/L]	0.42	0.09	0.341	0.219	0.608
aAFP [ng/mL]	0.41	0.08	0.283	0.243	0.562
aPR [ng/mL]	0.69	0.11	0.044	0.472	0.881
aPR-AFP	0.78	0.07	0.004	0.608	0.914

Variables: sPRG, aAFP, aPR, aPR-AFP; sPRG — serum progesterone; aAFP — amnion alfa fetoprotein; aPR — amnion progesterone; aPR-AFP — amnion progesterone to alfa fetoprotein rate