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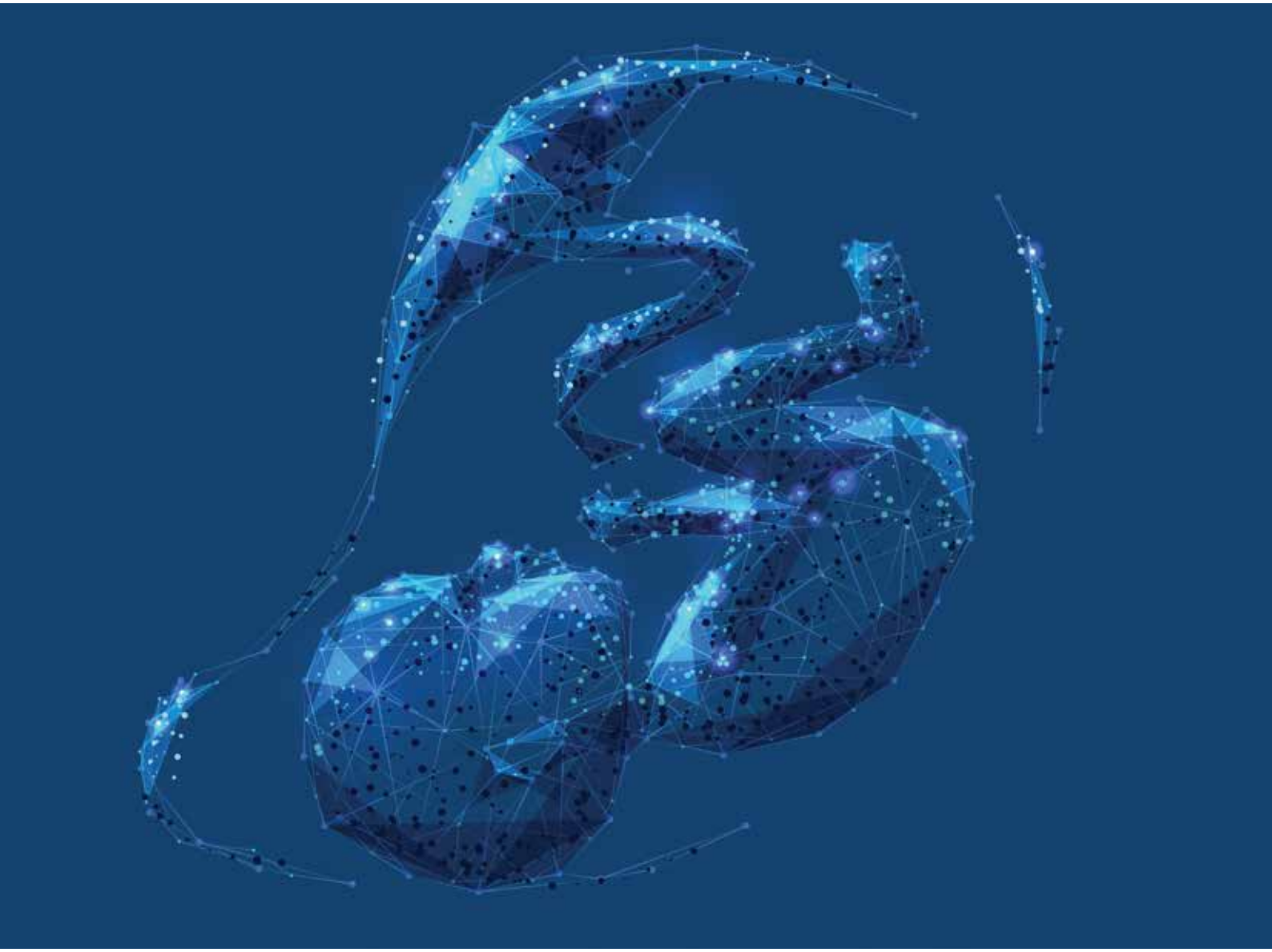

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CONTENTS

LETTER FROM THE EDITOR

Dear Colleagues,

The Hellenic Society of Ultrasound in Obstetrics & Gynecology has the pleasure to announce the publication of its new, open access, digital, scientific journal ***Obstetric and Gynecological Imaging*** **(OGI).**

OGI is focusing on all imaging methods in **Obstetrics and Gynecology (Ultrasound, MRI, Radiology),** while covering topics in **prenatal diagnosis, high-risk pregnancy, assisted reproduction** and **gynecological oncology.**

The scientific journal publishes original research papers, original research papers, systematic reviews, guidelines; instructional case reports and introduces a special innovative type of article that involves evidence-based answers. Following the latest publishing trends of relevant scientific community, the journal has an autonomous electronic article submission platform (www.ogijournal.com), a twitter account (in which each article is published in the form of twittable abstract) and a YouTube channel (in which the authors can present a three-minute summary of their article in English or Greek).

The Editorial Board consists of recognized and renowned specialists in the fields of Obstetrics & Gynecology, Neonatology, Pediatric Cardiology and Radiology and looks forward to the submission of your articles for the production of scientific knowledge related to the promotion of research and our specialty.

The scientific journal **Obstetric and Gynecological Imaging (OGI)** is published quarterly and is sent electronically to the members of the Hellenic Society of Ultrasound in Obstetrics and Gynecology and to gynecologists - obstetricians of related scientific associations, exceeding 1000 recipients.

Looking forward to a fruitful scientific cooperation, we thank you and we remain at your disposal.

Best regards

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ORIGINAL ARTICLE

Reproducibility of the first trimester uterine artery Doppler indices: comparing the transabdominal and the transvaginal approach

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ABSTRACT

Purpose: to assess the reproducibility of the uterine Doppler pulsatility index (UA-PI) in the first trimester using the transabdominal (TA) and the transvaginal (TV) approach.

Materials and Methods: prospective study in singleton pregnancies presenting at 11-13 weeks for routine assessment. The UA-PI was measured independently by two experienced sonographers transabdominally and transvaginally according to the ISUOG guidelines. The two techniques were evaluated with the computation of the intra-class correlation coefficients (ICC) for random effects models and the limits of agreement (LOA).

Results: 221 pregnancies were examined. Mean Ut-PI was 1.63 by TA and 1.66 by TV ultrasound scan. No significant paired differences were found between TA and TV measurements ($p>0.05$) and ICC were over 0.8 in all comparisons ($p<0.001$) among the two techniques.
The intra-observer ICC ranged from 0.87 to 0.96 and the inter-observerICC ranged from 0.82 to 0.91. ICC for intra and inter-observer variability was not influenced by maternal BMI for TA nor TV measurements. LOA between operators ranged between -0.7 and 0.7.

Conclusion: UA-PI shows moderate to good intra and inter-observer variability which is not influenced by the technique or the maternal characteristics. No significant difference was observed between the TA and TV, indicating that both techniques can be used for screening purposes.

KEY WORDS Uterine Doppler, first trimester, pre-eclampsia, screening

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Reproducibility of the first trimester uterine artery Doppler indices:
comparing the transabdominal and the transvaginal approach, p. 26-32
VOLUME 1 | ISSUE 1 | 2021
OGI

Introduction

Doppler studies of the uterine vessels in the late first trimester of the pregnancy can identify women at high risk for complications related to the malfunction of the feto-placental circulation whereas the sensitivity is increased for the early onset, severe disease [1]. As a result uterine artery mean pulsatility index (UA-PI) is one of the parameters commonly used in combined models predicting maternal pre-eclampsia (PET) and fetal microsomia in conjunction with other factors such as maternal weight, race, blood pressure and biochemical indices [2-7]. Although the applicability of the proposed models in populations different from the ones they have been derived from is under scrutiny, the existing literature shows that the addition of uterine artery Doppler enhances the predictive accuracy of the models [8].

Evidence is emerging that early administration of aspirin reduces the incidence of severe disease in women identified to be at high risk according to the first trimester screening for pre-eclampsia [9-11]. In consequence it is likely that in the near future first trimester uterine dopplers will be incorporated into the routine 11-13 weeks' scan. Recently FIGO advocated first trimester screening and administration of aspirin in high risk pregnancies in order to reduce the maternal mortality due to PET particularly in low income countries [12].

Given the role of the uterine artery (UA) dopplers in the prediction models it becomes important to assess the feasibility and the reproducibility of the measurement. Guidelines have been proposed to standardize the technique of UA Doppler studies at 11-13 weeks and to ensure conformity [13,14]. Few recent studies abiding to the suggested technique have explored UA-PI reproducibility at 11-13 weeks [15-17]. Our aim was to study and compare the transabdominal and the transvaginal approach of measuring first trimester UA Dopplers.

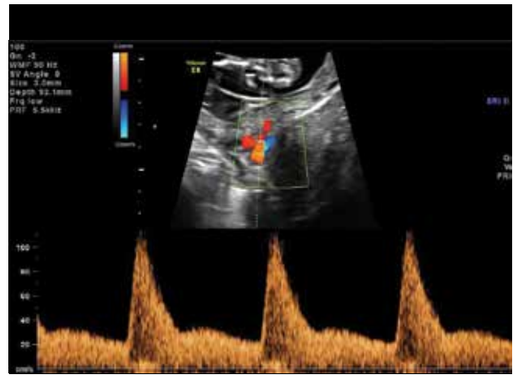

Figure 1a. *Transabdominal view of the uterine artery at 12 weeks of gestation.*

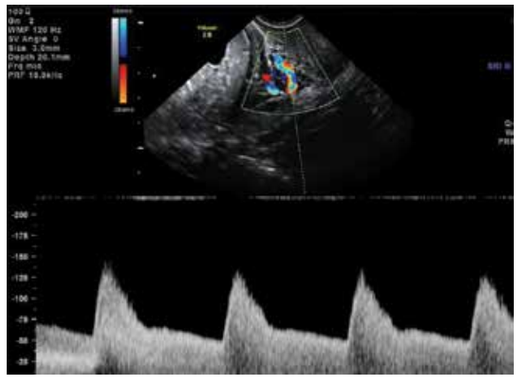

Figure 1b. *Transvaginal view of the uterine artery at 12 weeks of gestation.*

Methods

Prospective observational study conducted between 2018 and 2020. Women presenting for routine first trimester screening at 11-13 weeks of gestation were offered the option of participating in the study and consent was obtained.

As per protocol transabdominal measurement of the UA Doppler indices as well as transvaginal measurement of the cervical length is offered in all pregnant women examined at 11-13 weeks. The ones that decided to participate in the study had transabdominal (TA) as well as transvaginal (TV) measurements of the UA Doppler indices by two experienced operators (AS and AP). The abdominal UA Doppler examination was performed according to the ISUOG guidelines [14]. Briefly the uterine cervix was identified and the transducer was moved gently to the side in order to visualise the uterine artery by Colour Flow (recognised by the aliasing due to the high velocity flow, Figure 1a). Care was taken to maintain an insonation angle less than 30°. At least three consecutive cycles were obtained, the pulsatility index was measured and recorded and the process was repeated for the other side. Similarly for the transvaginal approach the internal cervical os was identified and the probe moved slightly to the side until the uterine vessel was seen using Colour Flow at the level of the internal

Table 1.Intraclass correlation coefficient (ICC) and paired differences among transabdominal (TA) and transvaginal (TV) measurements. A=operator A, B=operator B, RT=right side, LT=left side, 1=first measurement, 2=second measurement

	TA		TV					
A	**Mean**	**SD**	**Mean**	**SD**	**P Paired t-test**	**ICC**	**95% CI**	**P**
RT1	1.61	0.57	1.64	0.55	0.367	0.82	0.77 - 0.86	<0.001
LT1	1.69	0.62	1.74	0.61	0.174	0.80	0.73 - 0.84	<0.001
RT2	1.65	0.61	1.63	0.56	0.655	0.83	0.78 - 0.87	<0.001
LT2	1.71	0.60	1.68	0.54	0.376	0.83	0.77 - 0.87	<0.001
B								
RT1	1.57	0.53	1.60	0.53	0.308	0.80	0.74 - 0.85	<0.001
LT1	1.64	0.59	1.68	0.52	0.158	0.86	0.82 - 0.89	<0.001
RT2	1.55	0.48	1.57	0.53	0.390	0.82	0.77 - 0.86	<0.001
LT2	1.66	0.60	1.66	0.55	0.984	0.86	0.82 - 0.89	<0.001
Both operators								
RT1	1.59	0.55	1.62	0.54	0.173	0.82	0.77 - 0.84	<0.001
LT1	1.67	0.60	1.71	0.57	0.054	0.83	0.79 - 0.86	<0.001
RT2	1.60	0.55	1.60	0.54	0.815	0.83	0.79 - 0.86	<0.001
LT2	1.68	0.60	1.67	0.54	0.524	0.84	0.81 - 0.87	<0.001

Table2. Intra-observercorrelation coefficient (ICC) for transabdominal (TA) and transvaginal (TV) measurements for operator A =A and operator B=B, RT=right side, LT=left side, 1=first measurement, 2=second measurement.

	ICC	95% CI	P
A			
TA: RT1 - RT2	0.91	0.88 - 0.93	<0.001
TA: LT1 - LT2	0.89	0.86 - 0.92	<0.001
TV: RT1 - RT2	0.93	0.91 - 0.95	<0.001
TV: LT1 - LT2	0.90	0.87 - 0.92	<0.001
B			
TA: RT1 - RT2	0.87	0.83 - 0.90	<0.001
TA: LT1 - LT2	0.92	0.89 - 0.94	<0.001
TV: RT1 - RT2	0.96	0.95 - 0.97	<0.001
TV: LT1 - LT2	0.93	0.91 - 0.95	<0.001

Table 3. Inter-observer correlation coefficient (ICC) for transabdominal (TA) and transvaginal (TV) measurements between operator A =A and operator B=B, RT=right side, LT=left side.

	ICC	95% CI	P
RT			
TA: A vs B operator	0.82	0.77 - 0.86	<0.001
TV: A vs B operator	0.91	0.88 - 0.93	<0.001
LT			
TA: A vs B operator	0.87	0.84 - 0.90	<0.001
TV: A vs B operator	0.82	0.77 - 0.86	<0.001

Reproducibility of the first trimester uterine artery Doppler indices: comparing the transabdominal and the transvaginal approach, p. 26-32
VOLUME 1 | ISSUE 1 | 2021
OGI

Table 4. 95% confidence intervals of the limits of agreement (LOA) between operators for uterine pulsatility index measurements of the uterine arteriesat 11 to 13 weeks. 1=first measurement, 1=second measurement, RT=right uterine artery, LT=left uterine artery.

	ICC
RT	
TA: A vs B operator	-0.69-0.68
TV: A vs B operator	-0.47-0.51
LT	
TA: A vs B operator	-0.72-0.69
TV: A vs B operator	-0.59-0.63

Table 5.95% confidence intervals of thelimits of agreement (LOA) between the transvaginal and transabdominal technique of measuring uterine artery pulsatility index. 1=first measurement, 1=second measurement, RT=right uterine artery, LT=left uterine artery.

	LOA
RT 1	-0.89 to 0.84
RT 2	-1.35 to 1.45
LT 1	-0.85 to 0.84
LT 2	-0.83 to 0.85

os (Figure 1b). The uterine vessel was recognised by the features described previously. Women were asked not to void before the abdominal ultrasound scan whereas the transvaginal scan was performed with an empty bladder.

The first operator completed and stored his/hers measurements and subsequently the second operator entered the room and repeated the same process without being aware of the previous results. The UA-PI was measured after the examination in the stored images by manual tracing. A GE Voluson E8 machine was used for the study.

In two cases abdominal measurements could not be obtained because of maternal adiposity and these subjects were excluded from the analysis.

Statistical analysis

Quantitative variables are expressed as mean values (SD). Intra and inter-observer variability of the UA-PI were evaluated with the computation of the intra-class correlation coefficients (ICC) for random effects models and the Bland-Altman 95% confidence intervals (CI) for limits of agreement (LOA) [18-20]. It has been generally accepted that ICC equal or lower to 0.40 indicate poor to fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement and over 0.80 excellent agreement [19]. Paired t-tests were used to investigate differences in mean values among the two measurements techniques (TA and TV). Left and right uterine vessels are analysed separately. Agreement between the two measurements techniques was further assessed by Bland-Altman 95% confidence intervals (CI) for limits of agreement (LOA). The 95% CI for LOA indicates that 95% of the differences fall between these two limits.

All p values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 22.0).

Results

The study group consisted of 221 singleton pregnancies at 11 to 13 gestational weeks. There were 125 (56.5%) nulliparous women, median weight and height were 64 kgr and 163 cm respectively and median CRL was 62mm. Mean UA-PI was 1.63 for the TA and 1.66 for the TV route. The mean values for TA and TV measurements along with paired comparison between the TA and TV are presented in Table 1. No significant paired differences were found between TA and TV measurements ($p>0.05$) and ICC were over 0.8 in all comparisons ($p<0.001$), indicating good agreement among the two techniques. Intra-observer ICC between the first and second measurements of each operatorranged from 0.89 to 0.91 for operator A and from 0.87 to 0.96 for operator B (Table 2). The ICC for inter-observer agreement ranged from 0.82 to 0.91(Table 3). ICC for intra and inter-observer variability was not influenced by maternal BMI for TA nor TV measurements. LOA between operators are presented in Table 4 and LOA between techniques are presented in Table 5.

Discussion

The study examined a large sample of singleton preg-

nancies at 11-13 weeks recruited from the routine obstetric population presenting for the 11-13 weeks' scan. The measurements were performed by experienced operators who followed the ISUOG and FMF guidelines and were blind to each other's results. We chose to assess each PI separately rather than use the mean of the right and left measurements which could overestimate the reproducibility of the method. We found that UA-PI measurements have good reproducibility (ICC between 0.87 and 0.96 for intra and between 0.82 and 0.91 for inter-observer agreement). The transvaginal route seems to perform better although the difference was not significant. It is important to note that TA measurement was not possible in two obese subjects not included in the study. We have observed no significant difference in paired measurements acquired by TA or TV scan.

Until recently these results would be considered to indicate good to excellent agreement as they mean that more than 80% of the difference between Ut-PI measured by different operators is a 'true difference' whereas the remaining 20% can be attributed to physiological variation or error of the method. In the last decade the TRUST study suggested, somehow arbitrarily, stricter criteria for defining good reproducibility in obstetric Doppler measurements which would be difficult to be met by any fetal/maternal Doppler measurement and could discredit their use in clinical practice [21,22]. The new criteria on interpreting ICC (requiring ICC>95% for clinical use) have been criticized mainly for the failure to take into account the physiological variation of blood flow patterns [23, 24]. The authors acknowledge that LOA may be a better tool for assessing repeatability in Doppler measurements [23]. Indeed In our study LOA showed good agreement between operators with a range of -0.7 to 0.7.

Our results are consistent with the ones reported by-Marchi et al on 101 singleton pregnancies [17]. They observed very similar ICC for the TA and TV approach regarding intra-observer agreement whereas the inter-observer ICC of our study was comparable to the one achieved by the more experienced operators. Almost identical results are also reported by Ferreira et al on 97 first trimester pregnancies [16]. It is of interest that the two largest, recent studies as well as ours give very close estimates as to the reproducibility of the Ut-PI measurements with ICC between operators at about 0.8 at least and LOA between -0.8 and 0.8. The results are virtually identical for the experienced operators and indeed the Marchi study demonstrated that the only factor affecting reproducibility was the experience of the operator.

We did not find a significant difference in the mean Ut-PI between the TAS and the TVS approach. The issue was approached by three previous studies and the results are controversial [16,17,25]. The possible explanation for higher TAS Ut-PI found by two previous studies is that the TVS approach measures closer to the systemic circulation. Obviously it would not be possible to interrogate the uterine by TAS and TVS at exactly the same spot, but in our view both approaches target the uterine vessels at about the same level, provided that strict criteria are observed.

A possible disadvantage of our study is the extensive experience of the operators which may make the results not applicable to different settings. It is therefore reassuring that similar results were obtained by well-trained sonographers in a non-academic setting [17].

The uterine artery Doppler studies have at least moderate to good reproducibility, although the criteria to judge this are a matter of debate. Perhaps the real clinical issue however is how reproducible is the risk result that the patient is provided with and this is an interesting question for research. ■

Reproducibility of the first trimester uterine artery Doppler indices:
comparing the transabdominal and the transvaginal approach, p. 26-32
VOLUME 1 | ISSUE 1 | 2021
OGI

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ORIGINAL ARTICLE

Perinatal outcome of fetuses with high (>4.0 MoMs) first-trimester free beta-hCG levels

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ABSTRACT

Objective: To analyze the perinatal outcome of fetuses with high first-trimester free beta human chorionic gonadotrophin (b-hCG) levels and compare it with controls.

Method: Prospectively collected data from 113 fetuses with free b-hCG levels >4.0 MoMs and 3176 controls were analyzed to compare the rates of chromosomal abnormalities, structural defects, preeclampsia, hypertension, abruption, miscarriage, low birthweight, intrauterine or neonatal death, gestational diabetes and NICU admissions. Odds ratios with 95% confidence intervals (CIs) were calculated.

Results: Fetuses with free b-hCG levels >4.0 MoMs had a 8.8% (95% CI 4.8-15.3) rate of chromosomal abnormalities, mostly Down syndrome. The prevalence of preeclampsia in this group was 3.8% (95% CI 1.5-9.5), significantly higher (OR 3.1, 95% CI 1.1-8.9) compared to controls. There were no significant differences in any of the other outcomes. There were no cases of intrauterine or neonatal death.

Conclusion: The main concern in fetuses with high first-trimester free b-hCG levels is increased risk for chromosomal abnormalities. Fetuses with a normal karyotype may be at increased risk for preeclampsia.

KEY WORDS Chorionic gonadotrophine, growth, preeclampsia, PAPP-A

Introduction

The levels of maternal serum free beta chorionic gonadotrophin (free beta-hCG) and pregnancy associated plasma protein –A (PAPP-A) have been measured for over a decade in the context of first-trimester screening for chromosomal abnormalities, and specific level

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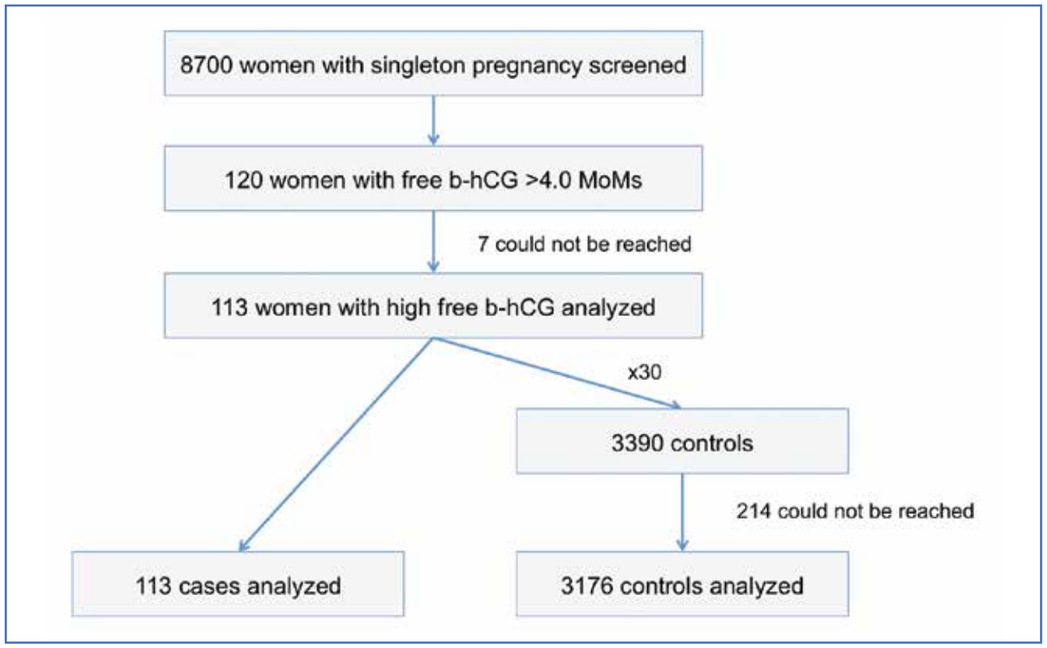

Figure 1. *Flow chart of participant selection*

patterns have been recognized for different conditions. Thus, compared with normal foetuses, those with trisomy 21 tend to have higher levels of free beta hCG (median: 1.95 MoMs) and lower levels of PAPP-A (median: 0.437 MoMs) [1], those with trisomies 18 and 13 tend to have lower levels of both hormones (median free beta hCG: 0.2 and 0.5 MoMs, respectively; median PAPP-A: 0.2 and 0.3 MoMs, respectively [2], and foetuses with triploidy tend to have significantly increased levels of free beta hCG (median 4.59 MoMs) and significantly low levels of PAPP-A (median 0.12 MoMs) [3].

Furthermore, as both proteins are produced by the trophoblast and their secretion may be altered in placenta-related obstetric complications, their levels have been studied as predictors for conditions such as preeclampsia (normal free beta hCG, low [median 0.844 MoMs] PAPP-A) [4], fetal growth restriction (normal free beta hCG, low [median 0.813 MoMs] PAPP-A) [4], small for gestational age (SGA) foetuses (normal free beta hCG, low [median 0.76 MoMs] PAPP-A) [5] and fetal death (low levels increase the risk) [6].

Approximately 1% of women will have free beta hCG levels ≥3.914 MoMs. Total beta hCG levels >4.0 MoMs have been associated with high risk for spontaneous miscarriage, small-for-gestational-age infants, pregnancy-associated hypertensive disorder, and preterm delivery in the second trimester [7], and 5 out of 6 fetuses with extremely high (>15 MoMs) hCG levels had pregnancy complications in a small series from Israel [8].

The aim of this study was to record the perinatal outcome of pregnancies with increased (>4.0 MoMs) first-trimester levels of free beta hCG and compare it with the outcome of pregnancies with lower (≤4.0 MoMs) free beta hCG levels.

Methods

This is a study of prospectively collected data from singleton pregnancies, drawn from a population attending routine first-trimester screening for aneuploidies in two prenatal diagnostic centers in Greece within three years. The study was approved by the corresponding Ethics Committees and consent was obtained from all participants.

All fetuses were scanned between 11+0 – 13+6 weeks by two Fetal Medicine Foundation (FMF) –accredited operators (ME and AS) according to the FMF protocol

Table 1. Descriptive data for cases with free b-hCG levels >4.0 MoMs (N=113) and controls (N=3176)

	Cases (≥4.0 MoMs)	Controls (<4.0 MoMs)	p-value
Median free bhCG MoMs	4.96	0.98	0.0001
Median PAPP-A MoMs	1.13	0.98	0.01
Median risk for trisomy 21	1:1478	1:9558	0.0001
Mean CRL (mm) (SD)	61.6 (7.0)	60.8 (6.8)	0.015
Mean NT (SD)	1.7 (0.4)	1.7 (0.4)	0.06
Mean gestational age at birth (wks) (SD)	38.5 (2.0)	39.0 (1.5)	0.06
Mean birth weight (gr) (SD)	3136 (626)	3230 (458)	0.094
Mean maternal age (yrs) (SD)	33.3 (5.2)	31.7 (4.2)	0.0001
Mean maternal BMI (SD)	23.8 (4.6)	24.4 (6.8)	0.546
Fetal sex (%male/female)	42.3/56.7	52.3/47.7	0.0001

(www.fetalmedicine.com). All scans were performed transabdominally, using either a GE E6 Expert or a GE E8 Expert ultrasound machine (wide band convex volume probe, 2.0-8.0 MHz, GE Medical Systems Kretztechnik, GmbH & Co., OHG, Austria). The data were entered into a specialized fetal database software (Astraia Obstetrics, Astraia Software GmBH, Munich, Germany).

Maternal serum free beta hCG and PAPP-A were measured using either a Brahms Kryptor (Kryptor system, Brahms AG, Berlin, Germany) or a Roche Elecsys (Roche Diagnostics Ltd., Switzerland) analyzer. The measured concentrations of the two hormone were converted to MoMs corrected for fetal crown–rump length (CRL), maternal weight, smoking status, racial origin, parity and method of conception according to the FMF software as described before [9].

Recorded outcome measures included pregnancy outcome (live birth, termination, miscarriage, intrauterine death / stillbirth, perinatal death), fetal karyotype, presence of major fetal structural abnormalities, preeclampsia, fetal growth restriction (defined as birth weight ≤5th centile for our screening population), cholestasis, placental abruption, gestational diabetes mellitus and admission to the neonatal intensive care unit (NICU).

In order to identify infants with birth weight below the fifth centile of our population, we first constructed normal ranges were constructed for birth weight, separately for boys and girls, as described according to Royston and Wright [10]. The birth weight for boys was described by the equation:

$Log_{10}BW= -0.342952 +0.174748*GA -0.001943*GA^2$ (SD=0.049678).

The corresponding equation for girls was:

$Log_{10}BW= -0.898371 +0.203513*GA -0.002327*GA^2$ (SD= 0.258046 -0.005390*GA)

For each woman with free beta hCG levels ≥4.0 MoMs, the next thirty women in the database with levels <4.0 MoMs were used as controls. Women were contacted by phone at least 4 months after their expected delivery date. When a woman could not be reached after two attempts, she was replaced by the next in list. Comparisons between the two groups were made using the chi-square (χ^2) or Fisher test, and the odds ratios with their respective confidence intervals (CIs) were calculated (IBM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp).

Results

The flowchart of participants is illustrated in Figure 1. One hundred and twenty women with a singleton pregnancy had free b-hCG levels ≥4.0 MoMs at 11^{+0} – 13^{+6} weeks (1.4%) . Seven of them were lost to follow-up and therefore the analysis included 113 women with free bhCG levels ≥4.0 MoMs and 3176 controls. The descriptive data for the two groups are shown in Table 1. The proportion of female foetuses was higher in cases

Table 2. Outcomes of cases with free b-hCG levels >4.0 MoMs (N=113) and controls (N=3176)

	Cases n/N (%)	Controls n/N (%)	OR (95% CI)
Live birth	103/113 (91.2)	3077/3176 (96.9)	0.3 (0.2-0.7)
Miscarriage	0	25/3176 (0.8)	N/A
Termination of pregnancy	10*/113 (8.8)	56*/3176 (1.8)	5.4 (2.7-10.9)
Intrauterine death	0	14/3176 (0.4)	N/A
Neonatal death	0	4 (0.1)	N/A
Preeclampsia	4/104 (3.8)	39/3095 (1.3)	3.1 (1.1-8.9)
Gestational hypertension	1/103 (1.0)	13/3096 (0.4)	2.3 (0.3-17.9)
Gestational diabetes mellitus	1/103 (1.0)	34/3095 (1.1)	0.9 (0.1-6.5)
Placental abruption	0	5/3095 (0.2)	N/A
Birth weight <5th centile	6/101 (5.9)	174/3011 (5.8)	1.0 (0.4-2.4)

with free b-hCG levels >4.0 MoMs (56.7%) than controls (47.7%) (p<0.001).

The distribution of outcomes in the two groups is shown in Table 2. Fetuses with free b-hCG levels >4.0 MoMs had significantly higher odds for termination of pregnancy because of chromosomal or structural abnormalities (OR 5.4, 95% CI 2.7-10.9). The rate of chromosomal abnormalities was 8.8% (95% CI 4.8-15.3); one fetus had triploidy (12.360 MoMs), eight had trisomy 21 (4.422-7.111 MoMs) and one had Turner syndrome (4.049 MoMs). The estimated risk for trisomy 21 for the eight affected cases ranged form 1:2 to 1:59 at the combined first-trimester screening. The risk for preeclampsia was also increased in cases with free b-hCG levels >4.0 MoMs (OR 3.1, 95% CI 1.1-8.9), while no significant difference was found in the other outcomes studied. All four cases with preeclampsia in the high b-hCG group were found in women with levels >5.0 MoMs (4/51 or 8%).

Discussion

In this case-control study, we found that free b-hCG levels >4.0 MoMs were associated with approximately 9% for chromosomal abnormalities, mostly Down syndrome, and 4% risk for preeclampsia. The risk for other placenta-related complications, including fetal growth restriction, was not found to significantly differ between the two groups.

Free beta-hCG levels >4.0 MoMs approximately correspond to the highest 1% of the measurements[9]; 1.3% of our population were found to have such levels. Since Down syndrome is characterized by high free b-hCG levels, women with such levels are commonly given the option for invasive prenatal diagnosis. Indeed, 25% of these fetuses had risk for Down syndrome >1:250, 20% had risk >1:100 and 7% actually had trisomy 21. We further analyzed the outcome of these fetuses in order to optimize counseling for this selected population.

We found that women with free b-hCG levels >4.0 MoMs had three times higher risk for preeclampsia compared to controls. Notably, all our cases with high free-hCG and preeclampsia had normal PAPP-A levels, ranging from 0.854 to 1.912.Maternal serum b-hCG concentrations have been tried as predictors for preeclampsia in the settings of both first- and second-trimester screening. The results are conflicting, as both lower [11], unchanged [12] or higher [13] free b-hCG levels have been reported in women who subsequently developed preeclampsia as opposed to controls, whereas free b-hCG was not found to be a significant factor in multivariable prediction models [14, 15]. In a recent study, *total* hCG levels ≥90th centile in nulliparous or≥ 95th centile in multiparous) were associated with a more than threefold risk for early-onset severe preeclampsia [16].

Second-trimester b-hCG levels >4 MoMs have been associated with a non-significant trend towards increased risk for low birth weight and hypertensive disease of pregnancy [17]. There is a theoretical basis for both reduced and increased b-hCG levels in preeclampsia. Women developing preeclampsia were found to have increased (and correlated) hydrogen peroxide and hCG levels, indicating that hCG may be a marker of oxidative stress [18]; moreover, a study in cultured trophoblastic cells showed that b-hCG secretion in response to hydrogen peroxide stimulation follows a bimodal pattern, with low stimulation enhancing and high stimulation suppressing cytotrophoblastic hCG secretion [19]. The dual pattern has also been reported for the soluble LH/hCG receptor (sLHCGR); most of the pregnancies developing preeclampsia exhibit very low levels, probably indicating early placental failure, whereas a significant proportion of such pregnancies have very high sLHCGR levels, probably associated with reduced hCG bioactivity and abnormal endothelial and immune response [20]. The dual pattern may, at least partly, explain the lack of significance of free b-hCG in regression models, where it is used as a continuous variable. Notably, none of the women with free b-hCG <0.3 MoMs (which roughly corresponds to the first centile in our population) and 0.7% of those with levels <0.4 MoMs (5th centile in our population) developed preeclampsia. Two out of the four preeclampsia cases in women with free b-hCG levels >4.0 MoMs resulted in delivery before 34 weeks, however much greater numbers of cases with increased free b-hCG are needed in order to draw firm conclusions.

Sharony et al. analysed the outcome of pregnancies with extremely high (>15 MoMs) free b-hCG levels, which had a frequency of about 1:8000 in their population. In 5 out of their 6 cases, an obstetric complication (intrauterine death, prematurity, failure to thrive) developed, without any apparent diagnosis responsible for that, except from one case with hydatidiform mole with a coexisting normal fetus [8]. Notably, the case with the highest free b-hCG level (12.360 MoMs) in our series was also a triploid fetus, and the patient developed preeclampsia at 17 weeks secondary to the development of theca lutein cysts.

Apart from chromosomal abnormalities and an association with preeclampsia, we did not detect an association of high free b-hCG levels with (or a trend towards) other obstetric or fetal complications. Similarly, in their prospective study, Brameld et al. concluded that high (>4.1 MoMs) levels of free b-hCG have limited use as predictors for adverse pregnancy outcomes [21]. Still, the rarity of certain events (e.g perinatal death) would require a much larger pool of cases, and therefore a 100-fold larger screening population, in order for potential associations to reach significance.

Conclusion

The data from our series indicate that, after excluding chromosomal abnormalities, a moderately increased risk for preeclampsia may be a concern in women with increased free b-hCG levels. Larger datasets are needed in order to substantiate this effect and determine whether these women would benefit from modified pregnancy management. ■

Conflict of interest: None

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REVIEW ARTICLE

Neurofibromatosis type-1 and pregnancy: a review

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ABSTRACT

Introduction: Neurofibromatosis type-1 (NF1) is an autosomal dominant tumor predisposition genetic disease, with diverse expression that can affect almost any organ system. Pregnancy among patients with NF1 is remarkably stated as at high risk of complications. **Purpose:** To present a short and comprehensive review of the literature concerning the relation between pregnancy and NF1. **Materials and Methods:** Articles identification through electronic databases was performed by using key terms: pregnancy, neurofibromatosis, neurofibromatosis type-1. **Pregnancy issues:** Most of the relevant citations are edited to announce case reports or studies based on few patients' samples. Since, authors in the past frequently delivered conflicting results, new retrospective studies, based on larger patient groups and matched with control groups, showed up over the last decade, to support that pregnancy in patients with NF1 is actually at high risk of complications. **Conclusions:** Pregnancy in women with NF1 seems to be notably at higher risk of complications, especially hypertension/preeclampsia, IUGR, stillbirth, preterm labor, cesarean section and maternal tumor growth tendency aggravation. Despite, most authors strongly recommend close monitoring of these patients during pregnancy, a normal outcome seems to be more probable to occur.

KEY WORDS Neurofibromatosis, neurofibromatosis type-1, NF1, pregnancy

Introduction

Neurofibromatosis type-1 (NF1), also known as Von Recklinghausen's disease, is a relatively common multisystem genetic autosomal dominant disorder, caused by mutation of the homonymous gene (NF1) located on chromosome 17 [1,2]. Mutations of the NF1 gene creates a syndrome characterized mainly by the development of multiple neurofibromas, café-au-lait spots (Fig. 1), Lisch nodules (iris hamartomas), freckling of the axillar or inguinal regions and optic gliomas [2]. The worldwide birth incidence of the disorder is 1:2500 – 1:3500, regardless of ethnicity or race, with over two million cases globally

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[3,4]. Half of the patients have a new NF-1 gene mutation while the other half have inherited the disorder [5-7].

Pregnancy, due to hormonal changes associated, might cause an increase in the size of already existing neurofibromas and appearance of new ones [8,9]. The majority of women with NF1 have healthy pregnancies, but need careful monitoring as early diagnosis and treatment results in better outcome [10,11]. The reported incidence of NF1 in pregnancy varies from 1:5000 to 1:18500 [12]. Fetal complications in women affected include spontaneous miscarriage, preterm delivery, intrauterine growth retardation and stillbirth, while maternal complications include, mostly, hypertensive and cerebrovascular disease [13,14].

Neurofibromatosis type 1 (NF1) is one of the most frequent dominantly inherited tumor predisposition genetic disorder, caused by mutation of the NF1 gene on chromosome 17q [1]. The NF-1 gene is responsible for the production of a large protein, called Neurofibromin, which acts as a tumor suppressor protein due to its function as negative regulator of Ras cellular pathways [15]. This tumor-suppressor protein is widely expressed throughout the body including the brain, kidney and blood vessels [16,17]. A myriad of possible mutations of the NF1 gene leads to abnormal growth and division in multiple body systems. For instance, loss of heterozygosity (LOH) in the melanocyte lineage results in cafe au lait macules (CALMs), hyperpigmented patches of skin present in nearly all patients, and LOH in the Schwann celllineage leads to the development of neurofibromas [2,3,18-21]. NF1 syndrome has markedly variable clinical expression, characterized by the development of multiple neurofibromas, café-au-lait spots, Lisch nodules (iris hamartomas), freckling of the axillar or inguinal regions, bone deformities, learning disabilities, attention deficit/hyperactivity disorder, gradual hearing loss, ringing in the ears, poor balance, headaches [10]. The classic NF1-associated tumours include malignant peripheral nerve sheath tumours (MPNSTs), optic pathway gliomas, rhabdomyosarcomas, neuroblastomas, juvenile myelomonocytic leukaemias, gastrointestinal stromal tumour (GIST), phaeochromocytomas and breast cancer [22,23]. Phenotypic expression of the NF1 gene mutation is extremely heterogeneous, therefore molecular diagnosis cannot predict clinical gravity of the disease [1].

The aim of this review is to evaluate the available evidence on how pregnancy can be affected by Neurofibromatosis type 1 disorder and contrarily in what way this genetic disease can be aggravated by a pregnancy hormone condition.

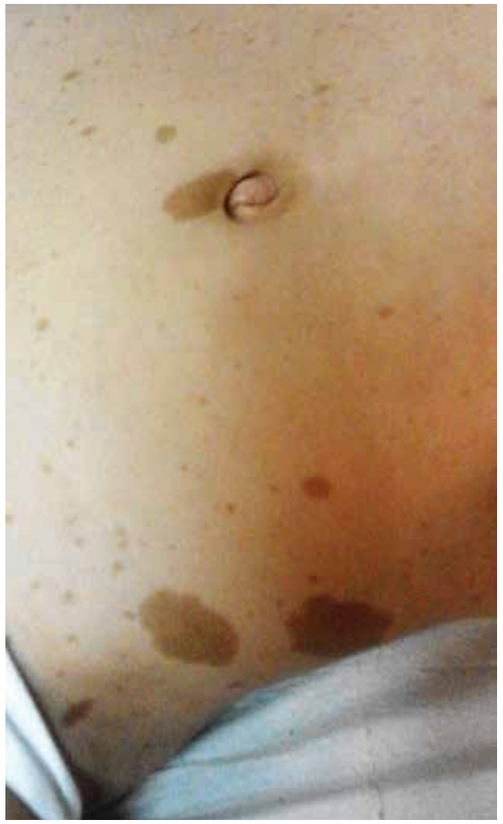

Fig 1. *Freckling and cafe au lait spots*

Pregnancy Issues

In the past, the majority of the articles available on the outcome of pregnancy in patients affected by neurofibromatosis type 1 was made of case reports. That fact created an impression of a high rate of maternal and fetal complications as well as disease worsening at the point that, some authors have recommended termination of pregnancies and sterilization of women with NF1 [24]. Lately, retrospective studies of patient groups, made of women with NF1 during pregnancy and matched with control groups, have given a clearer picture of the relation between pregnancy and NF1 disease.

Pregnant women affected by NF1 is believed by many

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Swapp & Main, 1973[25]	outcome of 24pregnancies in 10 NF pts	10 wo, 24 pregnancies	Café-au-lait spots; axillary freckling; nodular skin lesions (neurofibromas)	Hypertension (5 already hypertensive at 1st visit/to the end of their pregnancies all wo shown significant rise of mean BP; both pigmented & nodular lesions increased in size & number during pregnancy in all pts, in 7 of them there was considerable regression of nodular lesions following delivery	Not reported
Jarvis & Crompton, 1978[26]	outcome of 27 pregnancies in 10 NF pts	10 wo, 27 pregnancies	Histologically proven NF	Hypertension (2/27)	Spont abortion 4/27; therapeutic abortion 1/27; stillbirth 1/27
Weissman et al, 1993[12]	the experience with 34 pregnancies in 9 NF pts	9 wo, 34 pregnancies	Café-au-lait spots; multiple neurofibromas all over the body	None	Spont abortions of 1st trimester ; stillbirths 8.7%; IUGR 13%; high rate of CS 26%
Hadi, 1995[27]	outcome of 14 pregnancies in 8 NF pts	8 wo, 14 pregnancies	Café-au-lait spots; cutaneous neurofibroma; mental deficiency; seizures; ganglia neuroma; glioblastoma of the brain; scoliosis; oral tumor	Hypertension; maternal &fetal death due to intracranial hemorrhage after recurrence of a glioblastoma of the basal ganglia previously resected	Spont abortions 7.1%; therapeutic abortions 42.8%; IUGR 1 fetus; stillbirth 1 fetus; preterm labor 28,6%; live birth infants 50%
Dugoff & Sujansky, 1996[11]	Retrospective study of 247 pregnancies in 105 wo with NF1	105 wo, 247 pregnancies	Pts already diagnosed with NF1	-64/105 (60%) wo noted growth of new neurofibromas & 55/105 (52%) wo noted enlargement of existing neurofibromas during pregnancy; pregnancy induced hypertension (2%); preeclampsia (4%); HELLP (0,6%)	Preterm delivery 6%; IUGR 4%; PPROM 2%; PROM 3%; placental abruption 0,6%; placenta accreta 0,6%; postpartum hemorrhage 3%; CS 36%
Segal et al, 1999[28]	Study of 13 pregnancies in 8 wo with NF1 in 3 yrs, matched with a control group (1:5)	8 wo, 13 pregnancies	Pts already diagnosed with NF1	Hypertension (12,5% vs. 4,6%)	Preterm delivery 30,8% vs.. 6,1%; IUGR 46,2% vs. 8,9%; stillbirth 23% vs. 1,5%; CS 38,5% vs. 7,7%; lower fetal weight 2379±940 vs. 3186±517
Isikoglu et al, 2002[29]	a pregnant wo with a plexiform neurofibroma &its progress during & after pregnancy	1 case	Café-au-lait spots; multiple fibromas all over the body; axillary freckles; lisch nodules in R iris	Plexiform neurofibroma of R thigh which became smaller 10 mo after delivery (diameter of thigh from 105cm during pregnancy to 68cm). The pt claimed that the mass grew in all her past pregnancies, & shrunk somewhat after each delivery	Vacuum extraction for prolonged second stage

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Posma et al, 2003[30]	the development of malignant schwannoma during pregnancy in a pt with NF1	1 case	Typical neuro-cutaneous signs: multiple neurofibromas; café-au-lait spots; a 3-cm mass near the aortic arch (interpreted as a benign neurofibroma)	Thoracic pain; a 5-cm mass in the upper mediastinum (a large infiltrating mass in the foramina of the 3rd & 4th thoracic vertebrae without infiltration of the spinal cord); a malignant nerve sheath tumour grade III (not radically resected); photon radiotherapy; tumour-free for 3 yrs; 2nd pregnancy after ovulation induction; a short episode of sudden-onset thoracic & abdominal pain (subsided spontaneously) - in the postpartum period, severe abdominal pain recurred & became progressive (recurrent malignant schwannoma); the pt passed away 3 mo after delivery	Termination of the 1st pregnancy at 20 wks of gestation; delivery of the 2nd child at 40 wks of gestation
Kosec & Márton, 2006[31]	two cases of NF 1; previously known & detected during pregnancy respectively	2 cases	Café-au-lait spots; multiple fibromas all over the body; ophthalmologic lesions	Optic glioma	IUGR; preterm delivery by CS (1st case); termination of the pregnancy at 20 wks of gestation (2nd case)
Nelson et al, 2010[32]	a pregnant wo with NF1 who presented respiratory symptoms at 11-12 wks due to a mediastinal sarcoma mass arisen by a neurofibroma	1 case	Pt already diagnosed with NF1	Newly diagnosed (11-12 wks) mediastinal neurofibroma with transformation to malignant peripheral nerve sheath tumor, confirmed after surgical excision; at 23 wks the pt developed acute respiratory symptoms as a recurrence of the sarcoma; the pt died as no therapeutic options where possible.	Due to extremely preterm pregnancy (23 wks) the family requested no obstetric interventions; pregnancy with no complications at the time of maternal death
Islam, 2012[33]	A wo with NF1 &her pregnancy outcome	1 case	Café-au-lait spots; extensive cutaneous neurofibromas; multiple pelvic lesions (MRI); lesions within the spinal canal &foramina of all lower thoracic & lumbar vertebrae (MRI)	Aggravation of skin lesions	Labor induction at 40 wks due to aggravation of skin lesions with no problems

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Terry et al, 2013[13]	To investigate whether vascular & other complications are more common in pregnant wo with NF1	1553 cases (identified among 19 million pregnancy-related admissions between 1988-2009)	Café-au-lait spots; multiple fibromas all over the body	Gestational hypertension; preeclampsia ; cerebrovascular disease	IUGR; preterm labor by CS
Cecchi et al, 2013[34]	a pregnant wo with NF1 &undiagnosed pheochromocytoma who died suddenly during CS due to acute hypotension	1 case	Café-au-lait spots; multiple fibromas	Cardiomyopathy by combination of PHEO &NF1 that presents with fatal acute severe hypotension, pulmonary edema & tachyarrhythmia following general anesthesia; maternal death	CS as a result of previous CS for breech presentation
Harshini et al, 2014[35]	The pregnancy outcome of a wo with NF1	1 case	Neurofibromas all over the body ; café-au-lait spots all over the body	none	none
Ramos-Zúñiga & Saldaña-Koppel, 2015[36]	a progressive gradual increase in size &cystic transformation of a cervical neurofibroma during pregnancy, resected after delivery	1 case	Neurofibromas all over the body; café-au-lait spots all over the body	Cervical neurofibroma increasing in size: dysphagia, dysphonia, postural pain	none
Jain et al, 2015[37]	increased rate of complications associated with pregnancy of 2 NF pts; diagnostic evaluation, management &dilemmas	2 cases	Pallor; icterus; multiple big & small fibromas all over the body; numerous large & small neurofibromas all over the body with a big plexiform mass hanging out from R eye	Generalized tonic-clonic seizure on 4th postop day due to a meningioma; cholelithiasis	Placenta previa grade III; severe oligohydramnios (AFI 3cm); preterm delivery by CS
Xiong et al, 2015[38]	a pt with multiple neurofibromas beginning in the 3rd mo of her 1st pregnancy leading to diagnosis of NF1.		Dozens of new papules & nodules, progressively increasing in size &number; 3-10mm dark brown hyperpigmented papules & soft nodules located primarily on the back, chest, abdomen, arms; numerous 1-2mm hyperpigmented freckles onthe trunk, face, &axillae; more than 6 café-au-laitmacules larger than 1.5cm on the trunk; a dark brown hyperpigmented plaque on her R thigh (plexiform neurofibroma); mild scoliosis		
Dahiya et al, 2016[39]	a case of NF in pregnancy, with transmission to the baby	1 case	Skin lesions all over the body	Vaginal bleeding	Placenta previa; delivery by CS; NF lesions on the newborn on the 3rd day of delivery

Study	Study purpose	Sample Size	Maternal manifestations	Maternal Complications	Fetal Complications
Remon-Ruiz et al, 2017[40]	A pregnant wo with NF1 who developed hypertensive crises during 2nd trim (16 wks) that led to diagnosis of pheochromocytoma	1 case	Diagnosed with NF-1 during childhood	Mild hyperthyroidism in the 1st trimester; uncontrolled hypertensive crises (up to 170/105 mmHg) in 2nd trimester along with facial pallor, shaking hands &headache	History of 2 previous pregnancies: the 1st pregnancy ended in stillbirth at 31 wks due to placental abruption, the 2nd gave birth to a healthy 2500g female at 38 wks; Placental abruption with emergency CS at 35 wks at 3rd pregnancy; Adrenalectomy was performed at 23 wks
Leppävirta et al, 2017[41]	Retrospective register-based total population study in Finland, data comparison of pts with a confirmed diagnosis of NF1 with matched controls to examine pregnancies and deliveries;	176 NF1 wo with delivery between 1987-2013; 375 deliveries including 9 twin pregnancies (matched with 2.261 non-NF1 wo with delivery between 1987-2013)	Pts with a confirmed diagnosis of NF1 through register-based research	Increased risk for: hypertension; preeclampsia, maternal care for disproportion	Increased risk for: poor fetal growth; placental abruption; oligohydramnios; decreased gestational age at delivery, more significantly when mother &fetus were both affected by NF1; CS
Kalmantis et al, 2018[42]	A wo with NF-1 &her pregnancy outcome	1 case	Neurofibromas all over the body (cutaneous &subcutaneous); café-au-lait spots all over the body; demyelination lesions of the brain & arteriovenous malformation of subarachnoid space of the cervical spine diagnosed 2 months prior to pregnancy	Neurofibromas &café-au-lait spots increased in number &size according to the pt	Placenta previa; delivery by CS at 36 wks due to spontaneous onset of labor
Well et al, 2020[43]	to quantify growth of cutaneous & plexiform neurofibromas in NF1 pts during pregnancy, &to assess the onset of NF1 related symptoms	13 cases compared with 13 non-pregnant NF1 wo	Plexiform neurofibromas; cutaneous neurofibromas	No significant difference between groups; malignant transformation of PNF was not observed.	Not reported

CS: cesarean section; mo: month; NF: neurofibromatosis; pt: patient; spont: spontaneous; wo: woman/women

authors to have an increased risk of complications. Although information on pregnant women with NF1 is limited, the literature reports possible maternal disease aggravation as well as fetal/obstetric complications.

A short review of the literature is presented in Table 1.

Maternal complications reported, include increase of tumor burden, as a rise in number and size of tumors such as neurofibromas, café au lait spots, optic gliomas and malignant transformation of tumors [25,31,44,45]. Hypertensive complications, like gestational hypertension and preeclampsia as well as cerebrovascular complications are also of significant importance [11-14]. Cardiovascular disease of earlier onset and increased cardiac mortality seems to be the result of an incompletely understood effect of NF1 on the vascular system [46-48]. NF1 predisposes to pheochromocytoma and renal artery stenosis, both of which cause secondary hypertension of early onset [13]. A broad range of cerebrovascular abnormalities is also associated with NF1 including cerebral aneurysms [49] moyamoya syndrome [50] and ectatic or stenotic cerebral vessels [51] which may lead to stroke or cerebral hemorrhage predisposition. In the other hand fetal complications consist of spontaneous abortions of first trimester, stillbirth, intrauterine growth restriction, preterm labor by cesarean delivery, placenta previa, oligohydramnios [11,13,28,37,39,41]. All of these complications may be associated, at least in part, with the NF1-associated vasculopathy which is likely to determine a spectrum of disorders affecting trophoblast invasion and placental vascularity, thus causing abnormal placentation and resulting vasculopathy affecting the fetus [52-53]. Fetal distress, neurofibromatosis lesions on the newborn, malpresentations and cephalopelvic disproportion due to undiagnosed pelvic neurofibromas and pelvic bony contractures, as well as severe preeclampsia, abruptio placentae, pheochromocytoma, neurofibroma on spinal cord and elective repeat is reported to increase the rate of cesarean section in women affected by NF1 [11-13,41].

a. Effect of pregnancy on NF1

In most studies, an important percentage of patients, usually more than 50%, affected by NF1, during pregnancy, have reported an increase in terms of number and size of preexisting neurofibromas [11,54]. This growth tendency of neurofibromas, is suggested by in vitro studies, to be mediated mainly by estrogen, progesterone and androgens along with epidermal growth factor, fibroblast growth factor and transforming growth factor alfa [8,9]. Subsequently to delivery, often patients who mentioned aggravation of the disease while pregnant, referred regression but no case of complete regression has been reported [29,54].

Since 1906 Brickner has described nodular lesions, that appear during pregnancy and gradually disappear after delivery [55]. Later Sharpe & Young (1937) and Moritz & Snider (1962) stated that pregnancy may provide a growth stimulus on neurofibromatosis skin lesions and that way promote diagnosis of the disease if it hasn't been established until then [44,45]. Swapp and Main on 1973 released an interesting study of 10 NF patients and their 24 pregnancies [25]. In five out of ten patients, the lesions of neurofibromatosis appeared for the first time during pregnancy. In the others the lesions increased in size and number. The lesions regressed considerably after delivery in seven of ten patients. Furthermore, they stated that hypertension during these pregnancies is more than a chance association possibly due to Neurofibromatosis vasculopathy. All ten patients to the end of their pregnancies have shown significant rise of mean blood pressure, while five of them were already hypertensive at first visit. Several case reports and studies of more patients have followed, to support that pregnancy might worsen NF1 disease tumor lesions or stimulate the rise of new ones or even provoke malignant transformation and emergence of pheochromocytoma. Recently Well et al. (2020) published a retrospective study that investigated the effect of pregnancy on tumor burden in 13 patients with NF1, matched with 13 non-pregnant patients as control group [43]. In this study, although some NF1 patients experienced a subjective increase of NF1-related clinical symptoms and tumor growth during pregnancy, growth of plexiform and cutaneous neurofibromas in pregnant patients, with MRI observation, was not significantly different compared to non-pregnant patients. Furthermore, no patient developed new plexiform neurofibroma (PNF) and no PNF underwent malignant transformation, which was expected given the small investigated patient group. The only noteworthy difference between the two groups was a significant growth of four singular neurofibromas during pregnancy compared to significant growth of only one neurofibroma in the control group. This might indicate that singular neurofibromas can actually be affected by pregnancy, which is in

accordance with previously described heterogeneous responses of tumor growth to hormone exposure in vitro [17,19,22] and case reports that presented significant growth of singular neurofibromas like Isikoglu et al. and Ramos-Zúñiga et al. [29,36].

b. Effect of NF1 on pregnancy

Maternal, fetal and obstetric complications have always been in the center of interest in pregnant women affected by neurofibromatosis. Many authors in the past have reported cases of women with NF1 that presented complications in one or more pregnancies. Subsequently most of the studies on larger patient samples as well as retrospective register-based analysis have confirmed that pregnancy complications are significantly increased among women with NF1.

Initially the results between some studies with more patients were contradictory. Hadi in 1995 reported, as a result of a study focused on 14 pregnancies of 8 women with NF1, a rate of live births as low as 50% [27]. This result attracted interest as previous similar studies like Jarvis and Crompton (1978) [26] and Weissman et al. (1993) [12] had published live birth rates that exceeded 90% (95.5% and 91.3% respectively). Also, Jarvis and Crompton [26] did not observe higher rates incidence of obstetrical complications in NF patients compared to the general population. Later, Dugoff & Sujansky (1996) [11] announced the results of a study based on questionnaire and medical records review of a total of 247 pregnancies of 105 women affected by NF1. In their study, although the rate of live birth was 74% and the rate of cesarean deliveries was increased, no increased risk for pregnancy complications was reported. A few years later Segal et al. (1999) [28] showed up with the evaluation on outcomes of 13 pregnancies on 8 patients with NF1, matched 1 to 5 with a control group. Interestingly, it has been documented a significant increase of the risk of all major obstetric complications, mentioned before to relate with pregnancy in NF1. More precisely hypertension incidence in the study group was 12.5% versus 4.6% in the control group, preterm delivery 30.8% vs. 6.1%, IUGR 46.2% vs. 8.9%, Stillbirth 23% vs. 1.5% and cesarean section 38.5% vs. 7.7% respectively. Additionally, it has been registered a lower fetal weight at delivery in women with NF1 (2379±940g vs. 3186±517g). To make things clearer new retrospective studies on larger patient sample have followed. In 2013 Terry et al. [13] conducted a population-based retrospective study including data from 1553 cases of pregnant patients with NF1 in USA which demonstrated significantly higher rate of gestational hypertension, preeclampsia, intrauterine growth restriction, cerebrovascular disease, preterm labor and cesarean delivery. Recently Leppävirta et al. (2017) [41] with their retrospective total Finnish population study, confirmed once more that in women with NF1, the risk for cesarean delivery and pregnancy complications, including hypertension, preeclampsia, poor fetal growth, placental abruption, maternal care for disproportion, and oligohydramnios, was significantly increased. In addition, it has been showed for the first time that the NF1 syndrome of the fetus might shorten even more pregnancy duration.

Conclusion

Summarizing, the latest literature agrees that pregnancy in patients with NF1 should be considered as at increased risk for obstetric complications. These patients need to be at close antenatal monitoring at tertiary centers for signs of hypertension/preeclampsia and intrauterine growth restriction that are considered to be responsible for stillbirths, preterm labor and higher rates of cesarean sections. Furthermore, close observation for signs of disease aggravation by clinicians, expert on neurofibromatosis, is also needed in order to guarantee the best possible outcome. ■

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CASE REPORT

Prenatal Diagnosis of Atretic Parietal Cephalocele

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ABSTRACT

Introduction: Cephalocele is the herniation of intracranial structures such as arachnoid, glial and central nervous system rests through a fetal skull defect. Although the estimated incidence of cephaloceles is 0.8-4 per 10.000 live births, this number may be underestimated due to stillbirths and elective pregnancy terminations.

Case Presentation: We present the case of a 34-year-old primigravida with an uneventful medical and family history, who attended our unit for the second trimester fetal ultrasound examination. The ultrasound scan showed a singleton live fetus with a gestational age of 23 weeks and normal growth parameters for the gestational age of the pregnancy. The sonographic evaluation of the fetal head revealed a posterior protruding sac-like structure, which appeared to originate from the right lambdoid suture. The mass measured 22.6 x 27 x 16 mm and did not appear to include brain tissue. MRI revealed the apparent elevation of the straight venous sinus, a pathognomonic feature of congenital atretic parietal cephaloceles.

Conclusion: Careful evaluation of the fetal head during the second trimester ultrasound is essential for the timely and accurate diagnosis of atretic cephaloceles. MRI is helpful to differentiate sculp lesions such as sinus pericranii, lipomas, teratomas, sarcomas and cephaloceles. Early prenatal detection of cephaloceles allows more time for delivery planning and parental counselling.

KEY WORDS Cephalocele; atretic parietal cephalocele; meningioma; congenital brain lesions; central nervous system abnormalities

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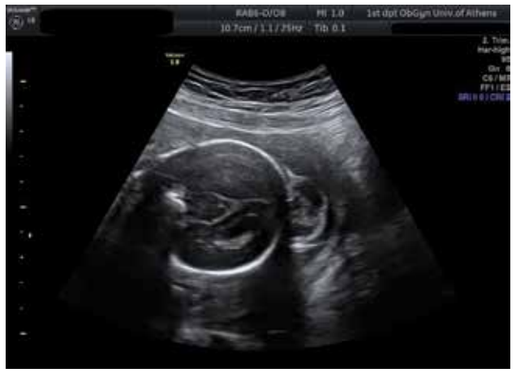

Figure 1

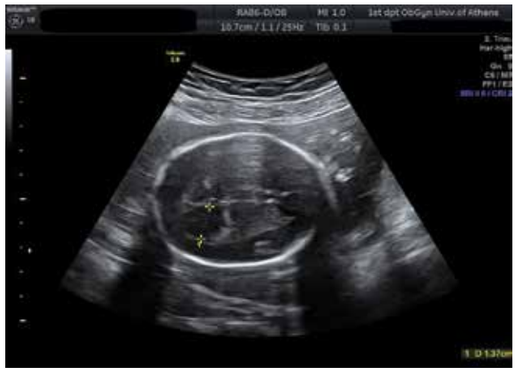

Figure 2

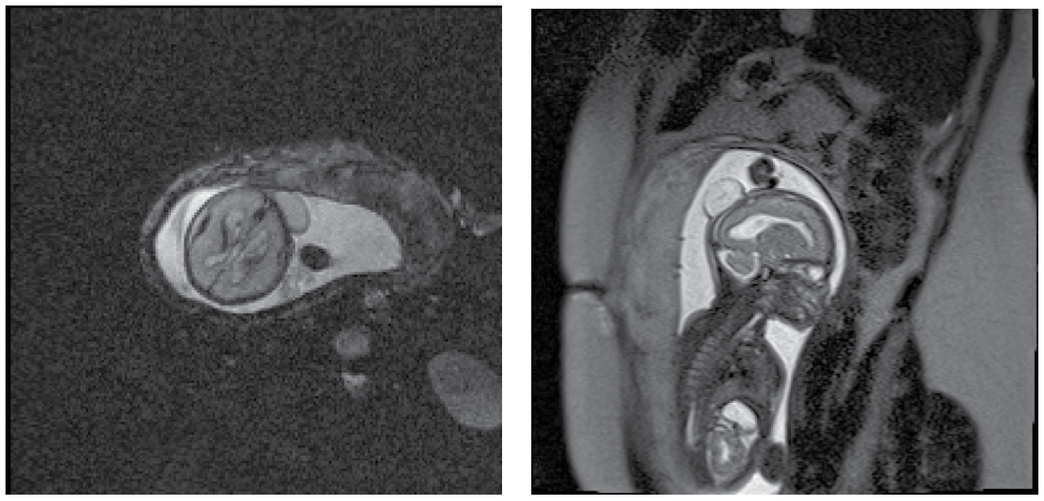

Figure 3

Introduction

Cephalocele is the herniation of intracranial structures through a fetal skull defect (1). The protruding mass consists of meningeal and vestigial tissues such as arachnoid, glial and central nervous system rests. When the lesion includes brain tissue the lesion is classified as encephalocele (1). Cephaloceles are categorized in Type I which consist mostly of arachnoid tissue and anomalous blood vessels and type II which have ectopic foci of neural and/or glial elements (2). Further classification separates cephaloceles in primary which are present at birth and secondary which are a result of surgery or trauma.

The incidence of cephaloceles is estimated at 0.8 - 4:10,000 live births (3). However, this number may be underestimated due to stillbirths and elective pregnancy termination. A female predisposition has also been reported in small case series (4). Atretic cephaloceles account for 4-17% of all cephaloceles and they occur more commonly near the lambdoid suture either parietally or occipitally. Parietal cephaloceles account for 37.5-50% (2,5).

Diagnosis of cephalocele is usually made postnatally, due to the detection of a scalp lesion or as part of congenital hydrocephalus evaluation. However, prenatal identification of cephaloceles has also been reported and it facilitates postnatal planning and treatment. We report the case of an atretic parietal cephalocele that was identified during a routine antenatal visit in the second trimester of pregnancy.

Case description

A 34-year-old pregnant woman presented to the Obstetrics Ultrasound Department of Alexandra Maternity Hospital in Athens, Greece during the second trimester of her pregnancy. The woman was Gravida 1 Para 0 (G1P0). The gestational age of the pregnancy was 23 weeks and 0 days. The woman's past medical history was uneventful.

During her pregnancy, she was subjected to prenatal testing including a first trimester scan. Ultrasound examination revealed one fetus with normal growth parameters and amniotic fluid index for the gestational age of the pregnancy. Biparietal Diameter was 56.5mm, Head Circumference 197.2mm, Abdominal Circumference 186.6mm, Femur Length 43.6mm and the estimated fetal weight was 617gr. The sonographic evaluation of the fetal head revealed a posterior protruding sac-like structure (Figure 1). The mass appeared to originate from the right lambdoid suture and measured 22.6 x 27 x 16 mm. The lesion did not appear to include brain tissue. However, a small vascular structure was detected within the protruding mass. Further evaluation of the fetal head revealed ventriculomegaly, as the posterior horns of the lateral ventricles measured 13.7mm and 12mm respectively (Figure 2). The anomaly scan did not reveal any other congenital malformations. Considering the position of the lesion, a fetal brain Magnetic Resonance Imaging (MRI) scan was suggested. The MRI scan showed an apparent elevation of the straight venous sinus, the sagittal venous sinus and the cerebellar tentorium. The bone defect measured 5mm laterally to the right lambdoid suture (Figure 3a and 3b). Development of the cerebral cortex appeared pathological, as suggested by the presence of cerebral grooves which do not correspond to the normal brain development for the gestational age of the fetus. The subarachnoid space was diminished, and a small impression of the fetal cranium was noted. The posterior horns of the lateral ventricles appeared enlarged at 10.4mm and 10mm respectively. The cerebellar tonsils and the cerebellar vermis appeared normal. The corpus callosum also appeared normal. After careful evaluation of the ultrasound and MRI characteristics of the lesion, the diagnosis of cephalocele was suggested.

Discussion

There are many theories regarding the cause of atretic cephaloceles. A viable theory suggests that the origin of the cephalocele can be attributed to the persistence of neural crest remnants, while others have proposed the persistence of a fetal neural bleb to be the aetiologic factor of cephaloceles (5–7).

Abnormal presentation of the straight sinus, which is positioned vertically, is a common find in parietal cephaloceles (7). The straight sinus is positioned vertically during fetal cranial development until the third month of gestation when cerebral hemisphere expansion results in a more horizontal orientation (6). The embryonic positioning of the straight sinus could be a result of a fibrous strand connecting the tectum to the membranous cranium resulting in the interruption of the normal fetal cranial development (6).

Differential diagnosis of atretic cephaloceles includes sinus pericranii, lipomas, teratomas, sarcomas and other sculp lesions. In the majority of cases, the presence of a vertical straight sinus is sufficient to differentiate atretic cephaloceles from other lesions. Sinus pericranni can be differentiated by its relationship with the underlying Dural venous sinus (8).

The presence of atretic cephaloceles has been associated with a variety of other congenital anomalies. Occipital atretic cephaloceles have been associated with Meckel-Gruber syndrome and Walker-Warburg syndrome (5,9). Atretic parietal cephaloceles have also been associated with Dandy Walker Syndrome, Holoprosencephaly, Chiari type II malformations and corpus callosal agenesis (2).

Determination of the prognosis of patients with atretic cephalocele remains challenging given the rarity of the condition and the lack or relevant studies. It is generally accepted that the prognosis of infants with atretic cephaloceles varies depending highly on the presence or absence of other central nervous system abnormalities (10). Good prognosis has been reported for patients with no other central nervous system abnormalities (10). In any case, early prenatal detection allows more time for parental counselling and delivery planning. ■

Conflict of interest

The authors declare that they have no conflict of interest.

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CASE REPORT

Prenatal diagnosis of complete transposition of the great arteries at 12 weeks of gestation in a fetus with normal nuchal translucency: a case report

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ABSTRACT

Introduction: Complete transposition of the great arteries (TGA) is a common cardiac malformation with atrioventricular concordance and ventriculoarterial discordance with and incidence of 20-30 per 100,000 cases. While prenatal diagnosis of TGA remains challenging, especially in the first trimester ultrasound scan, advances in ultrasound equipment and sonographer training have resulted in an increased detection rate (from 12.5% to 72.5%) in the last decades.

Case Presentation: We present the case of a 31-year-old Caucasian primigravida with no medical or family history of congenital anomalies, who attended our unit for the routine first trimester ultrasound examination. The initial scan revealed a singleton live fetus with a gestational age of 12 weeks and a normal nuchal translucency, nasal bone, flow pattern in the ductus venosus and no regurgitation in the tricuspid valve of the fetal heart. While the four-chamber view of the heart appeared normal, careful examination of the outflow tracts failed to show the crossing of the pulmonary artery with the aorta. The parallel course of the great arteries confirmed the diagnosis of complete transposition of the great arteries.

Conclusion: Examination of the two outlet echocardiographic views during the 11 - 13+6 ultrasound scan by obstetric sonographers allows for early detection of TGA. The presence of TGA warrants a thorough anomaly scan and genetic counselling as TGA is associated in 10% of the cases with other noncardiac malformations. Finally, antenatal detection of TGA results in better clinical status before surgery and improved postoperative outcome of the neonate.

KEY WORDS Transposition of the great arteries; TGA; X-sign; cardiac defect; parallel course

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Introduction

Dextro-transposition of the great arteries (d-TGA) characterized by situs solitus, atrioventricular concordance and ventriculoarterial discordance , is associated with early and severe neonatal central cyanosis, requiring urgent diagnosis and appropriate treatment [1]. It represents 5-7% of all congenital cardiac malformations, corresponding to an incidence of 20-30 per 100.000 cases and a 1.5:1 to 3.2:1 male preponderance [1-5]. In 10% of the cases d-TGA may be associated with other non-cardiac malformations [2], while the karyotype in most cases is normal [6]. Prenatal diagnosis of transposition of TGA remains a great challenge in fetal medicine, due to the difficulties associated with the evaluation and correct identification of great arteries and their origin [7-11]. The diagnosis of TGA during the first trimester of pregnancy is an even greater challenge. Studies regarding prenatal screening for congenital heart malformations show a sensitivity of identifying d-TGA around 3-17% [1,7,12]. This detection rate according to some studies has increased the last decades from 12.5% to 72.5% [13].The diagnosis of d-TGA is possible during the 11-13+6 weeks scan, but as expected detecting d-TGA at that time is more difficult than in the second trimester and most cases are missed [14]. The relationship between increased nuchal translucency (NT) and major cardiac defects has been established and an early fetal echocardiography in fetuses with increased NT is suggested [15-16]. However, the effectiveness of detailed examination of the fetal heart as a routine, in fetuses considered low-risk after the NT examination and first trimester sonographic markers – nasal bone (NB), ductus venosus (DV) and tricuspid regurgitation (TR) – remains unclear [17-19]. We present a case of TGA diagnosed at 12 weeks of gestation during the routine 11-13+6 weeks scan, in a patient with normal NT, and normal DV and TR.

Case description

A 31-year-oldCaucasian woman in her first pregnancy, with an unremarkable medical and family history for congenital malformations or genetic disorders, attended our unit for the routine 11-13+6 ultrasound examination, for screening of fetal chromosomal abnormalities. The examination in our unit is performed according to the guidelines of the fetal medicine foundation (FMF) with measurement of the NT and the other first trimester sonographic markers suggested by FMF for the screening of chromosomal defects (NB, DV, TR, facial angle - FA) in combination with maternal serum biochemistry (PAPP-A and freeβ-hCG). All examiners are accredited by the FMF for all the above examinations. In our unit as part of a multicenter study we perform an extended morpho-genetic ultrasound protocol during the 11-13+6 weeks scan for the detection of structural abnormalities. Ultrasound examinations are performed with a GE 730 PRO and PHILIPS HD 11 ultrasound machine with abdominal transducer. The initial ultrasound examination showed a singleton live pregnancy with a fetal heart rate (FHR) of 162 bpm and a crown rump length (CRL) of 53.6 mm, corresponding to gestational age (GA) of 12 weeks, which was in agreement with the GA calculated by the last menstrual period of the woman (LMP). Further ultrasound assessment of the fetus showed a normal NT for the GA (NT=1.9 mm), normal NB, normal flow pattern in the DV and no regurgitation in the tricuspid valve of the fetal heart. According to our protocol we proceeded to further assessment of the fetal anatomy. For the assessment of the fetal thorax the protocol of our study is as follows: transverse planes (transverse cardiac sweep): a. situs evaluation, b. area one quarter to one third of the chest and angle 45+/-15° from the antero-posterior midline (subjective appreciation, measured only if seemed abnormal), c. atrio-ventricular valve offsetting in four chambers view and tricuspid valve (TV) flow assessment using pulsed Doppler, d. aorta arising from the left ventricle and pulmonary trunk arising from the anteriorly placed right ventricle and crossing to the fetal left side over the ascending aorta, e. color-flow investigation of four-chamber view, outflows emergence - 'X' sign (the crossing of the main pulmonary artery with the aorta and being equal in size), and three vessel view - 'V' sign (the connection of the aortic arch and ductus arteriosus), f. ductus venosus (DV) flow assessment using pulsed Doppler.

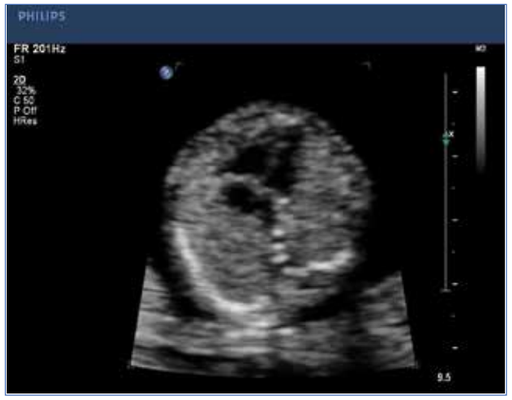

Figure 1. *Normal 4 chamber view of the fetal heart*

The examination revealed a normal four chamber view (Figure 1) and three vessel view of the fetal heart. However, careful examination of the outflow tracts failed to show the crossing of the pulmonary artery with the aorta (X-sign). The fetus was examined by a specialist in fetal echocardiography who confirmed the "parallel course" of the great arteries (Figure 2), raising the possibility of congenital heart disease affecting the origin of great arteries, including transposition of the great arteries. The pulmonary artery coming out from the left ventricle is depicted in Figure 3.

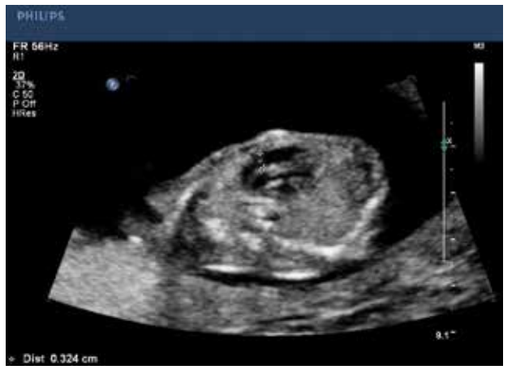

Figure 2. *The parallel course of the great arteries*

The fetus was reassessed at 14^{+4} weeks with an ultrasound examination which confirmed the diagnosis. The couple had extensive counseling by specialists in fetal medicine, fetal echocardiography, neonatal cardiology and pediatric cardiac surgery, from the tertiary neonatal unit that our unit is affiliated with. They were informed about the follow up they should have during pregnancy, the possibilities and the prognosis of the neonatal outcome. They also decided to proceed to examination of the fetal karyotype at 16 weeks of GA, in order to exclude particularly microdeletions of 22q11. The amniocentesis showed a normal male karyotype (46XY). However, the parents decided to proceed with termination of the pregnancy at 18 weeks of gestation, due to socio-economic reasons. The postmortem examination showed a complete transposition of great arteries without any other obvious cardiac or extracardiac abnormalities.

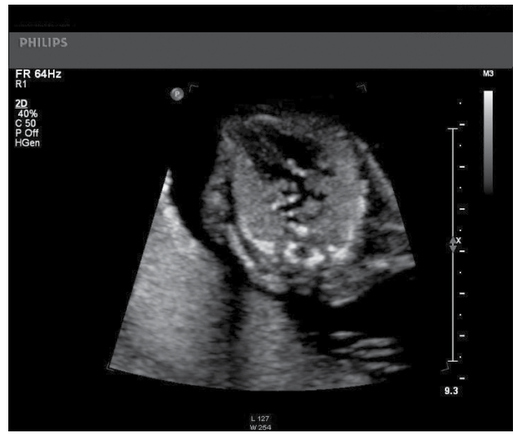

Figure 3. *The pulmonary artery coming out from the left ventricle*

Discussion

D-transposition of the great arteries is one of the most common cyanotic congenital heart defects in the neonatal period, representing 5-7% of all congenital heart diseases, corresponding to 20-30/100000 live births. In 10% of cases TGA is associated with other noncardiac malformations [2,20]. Antenatal diagnosis of TGA results in better clinical status before surgery and improved postoperative outcome, compared to those diagnosed postnatally [21]. Early management includes intravenous administration of prostaglandin E1 in order to maintain the patency of the arterial duct [22]. When prostaglandin infusion proves insufficient, balloon atrial septostomy (known as the Rashkind procedure) is performed to ensure proper oxygenation and to allow for more time before the corrective operation is performed [23]. The treatment of choice is the arterial switch operation which has shown survival rates of 88% at both 10 and 15 years of age [24].

The diagnosis of D-TGA was infrequently recognized by obstetric sonographers in the era of the four-chamber view [12, 25]. There is a rise in the detection rate from 20% with the increased number of routine antenatal scans and a policy of careful training for two outlet echocardiographic views [12, 25]. Regions of Paris achieved a detection rate of 72% between 1995 and 2000) [13].

Early detection of D-TGA allows for more time for genetic counselling and fetal karyotyping. Even though d-TGA is rarely associated with genetic syndromes, it has been sporadically associated with trisomy 8, trisomy 18, VACTREL syndrome, CHARGE syndrome, tuberous sclerosis, deletion of the long arm of chromosome 11 and the short arm of chromosome 18, Turner syndrome, Noonan syndrome, Williams syndrome and Marfan syndrome [26-32]. Early detection also facilitates planning of the delivery in a tertiary hospital with a neonatal intensive care unit and a pediatric cardiac surgery department, hence improving neonatal outcomes. However, antenatal detection of congenital heart defects has been also associated with an increased probability for termination of pregnancy decisions [33]. In any case, every abnormal early fetal echocardiogram should be followed by a re-evaluation scan by a fetal cardiology expert in mid-gestation to corroborate the initial diagnosis. ■

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CITATION

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CASE REPORT

Evaluating Ductus Venosus absence by three-dimensional ultrasonography

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ABSTRACT

Absence of ductus venosus in the fetus is a rare finding. Prognosis in these cases is determined by the extent of portal system development. Three dimensional ultrasound images visually reconstruct the complex course of fetal vessels, which with two dimensional ultrasound in most cases is unattainable, establishing proper diagnosis and enabling appropriate counseling.

KEY WORDS ductus venosus absence, 3D ultrasonography, Abernethy malformation, portosystemic shunt

The absence of ductus venosus (DV) in the fetus is a rare finding (0,04%), that is increasingly being recognized in the detailed first trimester ultrasound examination [1]. In these cases, there is an increased risk for portal system malformations and abnormal portosystemic shunts, diverting portal blood to the inferior vena cava (IVC). An extrahepatic shunt that may connect to variable sites of the systemic circulation is named Abernethy malformation, and can be readily visible in fetal ultrasound examination [2]. Prognosis is mainly determined by the extent of portal system development.

This is the three-dimensional (3D) Doppler ultrasound image (GE Voluson E10) at gestational age 24+6 weeks, showing the normally developed portal system and the discontinuation of the normal sequence of the umbilical vein (UV) due to absence of DV (Figure 1). An aberrant vessel (AV) emerges from the UV just below the umbilicus, and coursing above the bladder and between the umbilical arteries (UAs), anastomoses with the IVC. Color depicts opposite direction of blood flow in the AV than in the UAs. Thus, this case was diagnosed as an Abernethy malformation Type 2, since there is a normal portal system and the AV functions as a shunt, diverting umbilical blood directly to the IVC. Fetal karyotype was normal. The fetus was delivered vaginally at term, weighing 2.800 g. Transient hyperbilirubinemia was observed during the neonatal period, and the infant is reported as asymptomatic at four months of age.

The pathophysiological significance of DV absence in the fetal state of circulation is not yet fully understood. Establishment of connection between umbilical and systemic circulation is critical for the viability of the early embryo. This connection is formed in the fetal liver through the portal circulation and the hepatic veins, and through the DV which physiologically bypasses the liver. The liver then becomes the 'metabolic brain' of the fetus by regulating the amount of umbilical blood that passes through the liver parenchyma or bypasses it via the DV directly to the infracardiac portion of the IVC. The effect on fetal wellbeing due to replacement of the DV by an abnormal extrahepatic shunt is not clear. The prognosis for postnatal life though, is primarily determined by the possibly coexisting portal system abnormalities and not by the size or type of fetal shunt. If the portal vein is absent, as in Abernethy malformation type 1, there is an increased risk for hepatic failure requiring transplantation as well as hepatic malignancies later in life [3].

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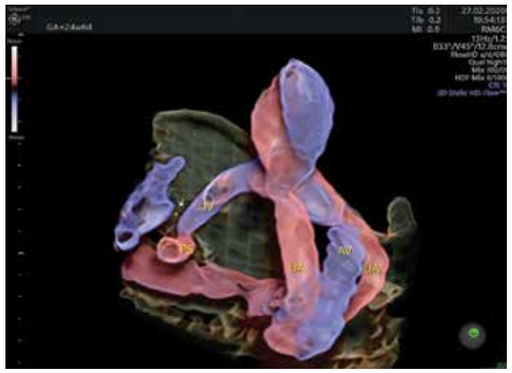

Figure 1: *Three-dimensional (3D) Doppler ultrasound image of ductus venosus (DV) absence at 24+6 weeks. The DV is absent (arrow *) and umbilical blood flow is diverted to the inferior vena cava by an aberrant vessel (AV). UV: umbilical vein, UA: umbilical artery, PS: portal system.*

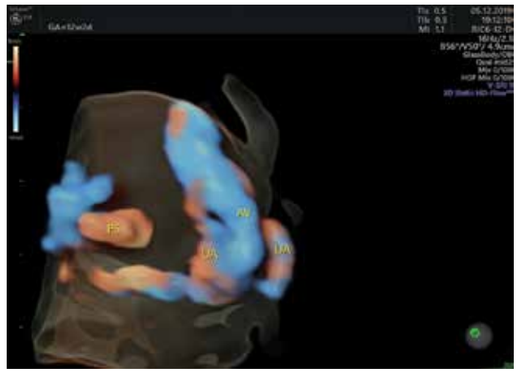

Figure 2: *Three-dimensional (3D) Doppler ultrasound image of ductus venosus (DV) absence at 12+2 weeks. Umbilical blood flow is diverted to the inferior vena cava by an aberrant vessel (AV). UA: umbilical artery, PS: portal system.*

Consequently, visualizing the integrity of the fetal portal system is very important for prenatal counseling, and it is ultrasonographically more challenging than identifying the usually large bore aberrant vessel. It is of note that most of the above described vascular configurations were identifiable at gestational age 12+2, but they were not considered adequate for definite diagnosis (Figure 2). Optimization of volume acquisition and rendering settings could possibly have resulted in even more informative 3D images in the first trimester.

Three-dimensional ultrasound images visually reconstruct the complex course of fetal vessels, which with 2D in most cases is unattainable, establishing proper diagnosis and enabling appropriate counseling. ■

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ORIGINAL ARTICLE

Sonographic predicting factors of latency interval in pregnancies complicated by preterm premature rupture of membranes

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ABSTRACT

Objectives: Preterm prelabor rupture of membranes (PPROM) is associated with significant perinatal morbidity and mortality. To date, the latency period to delivery cannot be reliably predicted. The aim of this study was to identify potential sonographic predictors of the interval until delivery in cases with PPROM.

Methods: This was a retrospective cohort study of all singleton pregnancies with PPROM between 24^{+0} and 33^{+6} gestational weeks that were admitted in the 3rd Academic Department of Obstetrics and Gynecology Department of the Aristotle University of Thessaloniki between January 2016 and December 2019. Sonographic parameters including the cervical length (CL) and the deepest vertical pool (DVP) of amniotic fluid, as well as the pregnancy outcomes were examined.

Results: In total, 50 women fulfilled the inclusion criteria and were included in the study. The multivariate analysis (multiple linear regression) revealed that only the CL made a unique contribution (p=0.001, beta=0.542) to the latency interval. Moreover, in the subgroup multivariate analyses (binary logistic regression), only the CL correlated significantly with a latency interval greater than 2 days (p=0.008, OR=1.142, 95% CI=1.036-1.262) or latency>7 days (p=0.034, OR=1.076, 95% CI=1.005-1.125).

Conclusions: The CL may be an independent predictor for the latency interval in pregnancies with PPROM between 24 and 34 gestational weeks. Further research is needed on potential sonographic and other biomarkers for the effective prediction of imminent delivery.

KEY WORDS preterm prelabor rupture of membranes, cervical length, ultrasound, amniotic fluid, prediction

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Introduction

Preterm (<37 weeks) prelabor rupture of membranes (PPROM) complicates about 2% of pregnancies and 40% of these cases result in prematurity, thus, contributing to the associated neonatal morbidity and mortality [1-4]. In cases with PPROM after 24 weeks of gestation, all the major guidelines recommend expectant management, at least until 34 weeks [5]. Moreover, antenatal corticosteroids when administered between 24 and 34 weeks improve perinatal outcome, especially when delivery occurs within 2 to 7 days [6]. Furthermore, the administration of magnesium sulfate before 32 weeks of gestation improves neonatal outcome, when given up to 24 hours before delivery [6].

In most countries, women with PPROM are managed as inpatients, however, there are countries that may allow outpatient surveillance in selected cases; a significant proportion of women will deliver within 48 hours or within 7 days from the rupture, however many will remain undelivered, some for more than 2 weeks [7]. Predictive factors of the neonatal outcome in cases with PPROM include gestational age, severe oligohydramnios and cesarean delivery [8]. Therefore, the accurate prediction of the onset of labor in cases with PPROM would be clinically useful for timely administration of antenatal corticosteroids and magnesium sulfate and also for the triage of women that may be safely managed expectantly as outpatients.

It has been shown that ultrasound may be useful in the prediction of the interval between membrane rupture and labor onset, by the measurement of cervical length and presence of funneling and also the amniotic fluid volume at presentation [9], however existing evidence is not definite. Thus, the aim of this study was to investigate sonographic predictive factors for the latency interval in pregnant women with PPROM.

Materials and Methods

Study design, setting and participants

This was a retrospective cohort study including patients with singleton viable pregnancies complicated by PPROM between 24^{+0} and 33^{+6} gestational weeks, that were admitted in the high-risk pregnancy unit of the 3rd Obstetrics and Gynecology Department of the Aristotle University of Thessaloniki, between January 2016 and December 2019. Women with multiple pregnancies, history of cervical surgery and those with missing fetal ultrasound biometry

Table 1. General characteristics of the study population (n=50)

Maternal characteristics		Median	Range	IQR
Age		33.7	15-41.1	6.8
BMI		23	18.6-41	6.78
Weight gain (kg)		9	0-29	7
Latency (days)		5.5	0-29	10.5
			N	%
Smoking	no		27	54
	yes		23	46
GDM	no		46	92
	yes		4	8
Multiparous	no		27	54
	yes		23	46
Last delivery mode (multiparous)	CS		7	30.4
	VD		16	69.6
Fetal and US characteristics		**Median**	**Range**	**IQR**
Days from US to Delivery		3	0-16	3.25
GA at birth		32	24-34	4.75
		Mean	**SD**	
Estimated fetal weight (g)		1646	514	
EFW-centile		35.8	21.6	
Birthweight (g)		1746	523	
Birthweight centile		49.3	28.8	
Cervical length		22.78	11.98	
Deepest pocket		2.1	1.2	
		Number	**Percentage (%)**	
Cephalic presentation	yes	36	72	
	no	14	28	
Gender	male	29	58	
	female	21	42	
Funneling	yes	10	20	
	no	40	80	

BMI: body mass index, US: ultrasound, GDM: gestational diabetes mellitus, EFW: estimated fetal weight

GA: gestational age, SD: standard deviation,

Table 2. Univariate analysis between latency period and each factor

Spearman's correlation	MA	BMI	DP	Cervical length	Weight gain	EFW	BW	GA birth
P values	0.858	0.691	0.892	**<0.001**	0.237	0.04	0.17	0.193
rho	-0.026	-0.058	0.02	**0.626**	-0.17	-0.291	-0.197	-0.187
Mann-Whitney	**Smoking**	**GDM**	**Parity**	**Abnormality**	**Funneling**	**Gender**	**Previous delivery mode**	
P values	0.742	0.21	0.464	0.116	**0.019**	0.497	0.298	

BMI: body mass index, GDM: gestational diabetes mellitus, EFW: estimated fetal weight
GA: gestational age, MA: maternal age DP: deepest pocket

and incomplete outcome data were excluded from the study. The gestational age was determined by first trimester ultrasound (crown-rump length) or by head circumference measurement during the second trimester if there was no first trimester ultrasound available.

According to the local protocol, all women were routinely hospitalized until delivery. In cases where spontaneous delivery did not occur, either induction of labor or cesarean delivery were performed at 34 gestational weeks and the mode of delivery was decided based on standard obstetric indications. The diagnosis of PPROM was made based on clinical history and physical examination. Their management included administration of corticosteroids for fetal lung maturation, antibiotic treatment for 7 days (ceftriaxone, clarithromycin and metronidazole), weekly growth scans and daily non-stress tests after 28 weeks of gestation. All sonographic examinations were performed with an S8 Voluson GE ultrasound, by obstetricians certified in obstetric ultrasonography. Patients' demographic data, somatometric and medical history including maternal age and weight, weight gain, body mass index (BMI), smoking, parity and diagnosis of gestational diabetes mellitus were collected. Sonographic measurements [estimated fetal weight (EFW), presentation, placental position, cervical length (CL), cervical funneling, deepest vertical pool - DVP] were routinely prospectively collected and recorded in an electronic database (Astraia). The cervical length was measured transvaginally, as previously described [10]. The perinatal outcome parameters, including date, indication and mode of delivery, birthweight and neonatal complications were also routinely recorded in the same database.

Statistical analysis

Except for descriptive data (parametric: mean ± SD, non-parametric: median, range, IQR), a normality test was used for selecting parametric and non-parametric variables and their respective analysis. Latency was the dependent variable and was examined both as continuous and binary (latency > 2 days and latency > 7 days). Initially, the association between maternal data, ultrasound parameters, pregnancy outcome and latency was examined separately for each independent variable with parametric and non-parametric tests (Spearman's correlation, t-test, Mann-Whitney test, Chi-square test). Following that, multivariate analysis was performed, including all previously important factors. In all tests the statistical significance was set at 0.05. Finally, women were divided according to gestational age at PPROM, group A: 24^{+0} - 27^{+6} weeks (N= 15) and group B: 28^{+0} - 33^{+6} weeks (N=35). Subgroup analysis included both comparisons between the groups and investigation of the independent variables of latency. The IBM Statistical package for Social sciences (SPSS), version 25.0 was used for statistical analyses.

Results

Overall, 50 women fulfilled the inclusion criteria and were included in the study. The participants' demographic data are presented in Table 1. Of note, no cases of clinically and laboratory confirmed chorioamnionitis were detected in our sample.

The association of each independent variable with the latency period was examined separately for each variable. Among all variables, CL showed a significant positive correlation with the latency interval (p<0.001, rho=0.626) while EFW (p=0.040, rho= -0.291) showed a significant negative correlation. The absence of funneling also correlated to an increased latency period (absence, Median-MD=8.5 days R=0-29 IQR=12.5 vs presence, MD=3 days R=0-11 IQR=5, p=0.019, Mann-Whitney) (Table 2). The multivariate analysis (multiple linear regression) that included all previous significant factors revealed that only CL makes a unique contribution (p=0.001, beta=0.542) and this model explained 29.9% of the variance of latency (p<0.001).

A subgroup analysis with latency period as a categorical variable was also performed. In particular, participants were separated according to latency period: group A≤2 days and group B >2days and group C≤7 days and group D>7 days. Regarding latency >2 days, cephalic presentation was correlated with latency period >2 days (p=0.030, Chi-square test) and also, there was statistically significant difference in CL between women with latency ≤2 days and >2 days (group A: Mn= 10.25, SD=8.79 vs group B: Mn=25.1. SD=11.04, p=0.001, t-test). Multivariate analysis (binary logistic regression), including the previous factors, revealed that only CL correlated significantly with the presence of latency>2 days (p=0.008, OR=1.143, 95% CI=1.036-1.262). Multivariate analysis for CL=15mm as a cut-off revealed that only CL>15mm correlated independently with latency>2 days (p=0.014, OR=10.165, CI=1.595-64.766) (Table 3).

Table 3. Multivariate analysis between latency period and each factor.

Variables /p values	Cephalic presentation	CL	CL>15	EFW	Funneling	model	
Latency	--	**P<0.001 beta=0.542**	--	P=0.193 beta= -0.16	P=0.987 beta=0.002	**P<0.001, Adjusted R^2= 0.299**	Multiple Linear Regression
Latency<2d	P=0.067 OR=5.963	**p=0.008 OR=1.143**	--	--	--	**p<0.001**	Binary logistic regression
Latency<2d	P=0.062 OR=5.497	--	**P=0.014 OR=10.165**	--	--	**p=0.002**	
Latency<7d	--	**P=0.034 OR=1.076**	--	P=0.081 OR=0.999	P=0.343 OR=0.306	**P=0.002**	
Latency<7d	--	--	**P=0.025 OR=6.011**	**P=0.036 OR=0.999**	P=0.193 OR=0.204	**P=0.005**	

For latency>7 days, there was statistically significant difference in CL (group C: Mn= 18.07, SD=10.84 vs group D: Mn=28.77, SD=10.81, p=0.001, t-test) and EFW (group C: Mn= 1777 SD=544 vs group D: Mn=1479 SD=430, p=0.041, t-test) between the two groups. Presence of funneling also correlated with latency ≤7days (p=0.016, Chi-square test). Multivariate analysis (binary logistic regression) including the previous factors revealed that only CL was correlated significantly with the presence of latency>7 days (p=0.034, OR=1.076, 95% CI=1.005-1.125). Multivariate analysis (binary logistic regression-hierarchical) for CL=15mm as a cut-off revealed that both CL>15mm (p=0.025, OR=6.011) and EFW (p=0.036, OR=0.999) correlated independently with latency>7 days (Table 3).

Finally, subgroup analysis according to gestational age at PPROM was performed. Patients with PPROM at <28w delivered significantly lower birthweight neonates, (p<0.001, group A:1144±316 gr vs group B:2004±353 gr) and had lower sonographic EFW (p:0.001, group A:1069±244 gr vs group B:1893±383 gr) compared to those with PPROM at later gestational age. However, there were no other differences in measurements between the groups. Furthermore, in group A, a moderate association between CL and latency was identified (p=0.019, r=0.595) and there was significant difference in latency interval (p=0.021) between nullip-

arous (Mn:7.75±6.73 d) and multiparous (Mn:17±6.83 d) women. Multivariate analysis (multiple linear regression) including both parity and CL in the model, explained 48.7% of variance (ANOVA R^2=0.487, p=0.018) without revealing any single independent variable (Parity Beta=0.408, p=0.102, CL Beta=0.415, p=0.096). No other factors correlated significantly with latency in univariate analysis. Regarding patients with PPROM at <28w (group B), only CL correlated strongly and positively with latency (p<0.001, rho:0,644).

Discussion

This study has shown that: 1) in cases with PPROM between 24 and 34 weeks, the measurement of CL may predict the latency interval, 2) a short CL may be an independent predictor for early delivery in such cases and 3) there is a moderate positive linear correlation between CL and latency interval.

This study is clinically relevant as there is uncertainty on the best approach in cases with PPROM, regarding the timely use of antenatal corticosteroids and magnesium sulfate, as well as the option and the appropriate antibiotic scheme. To date, few studies have addressed this issue.

The value of CL in the second trimester of pregnancy on the prediction of preterm delivery is well established [11]. In addition, we found that CL in PPROM may be an accurate predictor for the latency interval until delivery. Our results are consistent with those from the study by Lee et al., who conducted a retrospective analysis in 121 cases of PPROM and found that the combination of CL and DVP may accurately predict the latency interval with a reported sensitivity of 82.2% and specificity of 75.9% [12].

We also found that cervical funneling was correlated with the latency interval in the univariate analysis, but no such correlation was identified in the multivariate model. Evidence from a prospective study on PPROM concluded that the use of transvaginal ultrasonography for CL measurement in those cases may predict an early delivery but cannot predict the risk of chorioamnionitis or neonatal sepsis [13]. The same study mentioned that funnelling was present in cases with short CL, but it was not identified as an independent predictor for the latency interval.

With regard to DVP, we found that it is not an accurate predictor for early delivery in cases of PPROM. This may be related to the small sample size of our study and is in contrast with previously published data. Thus, in the study by Melamed et al., gestational age on admission (Hazard ratio - HR = 1.29; 95% CI = 1.22-1.37), oligohydroamnios (HR = 1.49; 95% CI = 1.18-1.87), cervical dilation >1 cm (HR = 0.65; 95% CI = 0.52-0.83), fetal growth restriction (HR = 2.94; 95% CI = 1.24-6.94) and nulliparity (HR = 1.28; 95% CI = 1.12-1.63) were associated with shorter latency interval until delivery [9]. As already mentioned, the residual amniotic fluid may play a crucial role in the neonatal outcomes, as it has a direct impact on survival rates and increases the risk of developing respiratory distress syndrome [14].

Regarding antibiotics, following the publication of the study of Lee et al. we routinely adopted the antibiotic scheme of ceftriaxone, clarithromycin and metronidazole for 7 days [15]. This scheme was implemented universally during the study period, so by following this policy we minimized the risk of bias. A Cochrane review concluded that for cases with PPROM the use of antibiotics was associated with a statistically significant reduction in chorioamnionitis (Relative Risk – RR= 0.66; 95% CI= 0.46-0.96) and a reduction in the delivery rate within 48 hours (RR= 0.71; 95% CI= 0.58-0.87) and 7 days of randomisation (RR= 0.79; 95% CI= 0.71-0.89) [16]. Moreover, the incidence of neonatal infections was reduced (RR= 0.67, 95% CI= 0.52-0.85) [16].

This study has certain limitations. First, the retrospective study design may preclude some causal associations, however all relevant data are routinely prospectively collected. Second, some self-reported data may be associated with recall bias, mostly regarding the medical and obstetric history, however this is a standard limitation even in prospective studies. Third, our findings were based on a sample of pregnant women in a single center; however, the latter covers a population of more than 2 million people in northern Greece. Finally, history of preterm birth could be considered a plausible source of bias. However, only one patient reported previous preterm birth.

To conclude, we found that the CL at the time of diagnosis of PPROM may be an accurate predictor for cases complicated by PPROM. With regard to the available international campaigns for the prevention and elimination of the incidence of preterm delivery, more biomarkers are needed for high-risk pregnancies. Moreover, the healthcare policy planners need to establish recommendations on the proper surveillance of pregnancies complicated with PPROM and thus minimize the adverse outcomes of prematurity. ■

Sonographic predicting factors of latency interval in pregnancies complicated by preterm premature rupture of membranes, p. 60-65
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Conflict of interest

The authors declare no conflict of interest.

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• **Blinded manuscript:** Blinded title page including only the title of the manuscript with no affiliation.

• **Abstract:** An abstract presenting the most important results and conclusions is required for all papers except for Letters to the Editor. For Original Articles the abstract needs to be structured as follows: Purpose, Material and Methods, Results, Conclusions. For Reviews and Pictorial Essays, a 1-paragraph unstructured abstract is required.

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• **Text structure:** the text of the Original Articles needs to be organised as follows: Introduction, Material and Methods, Results and Discussion. Review Articles and Pictorial Essays require Introduction and Discussion sections only.

• **Fonts:** The suggested font is doublespaced Arial (11 pt) or Times New Roman (12 pt). The text should display page and line numbers throughout its length.

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• **Acknowledgements, sponsorships and grants:** Acknowledgements need to be placed at the end of the manuscript before 'References' section. Any grant received or sponsorship from pharmaceutical companies, biomedical device manufacturers or other corporations whose products or services have been used needs to be included in the Conflicts of Interest Form and also mentioned in acknowledgements section.

• **Measurement Units:** All measurements should be mentioned in international units (SI). The full stop should be used as a decimal (i.e. 3.5 cm). Spaces should be added around the plus/minus symbol (i.e. 13.6 ± 1.2). There should not be any spaces around range indicators (i.e. 15-20) or equality/inequality symbols (i.e. r=0.37, p<0.005).

8. Figures and Tables

All figures and tables need to be cited in text consecutively in the order in which they appear in text into brackets and in Arabic numbers: i.e. (Fig. 1) and (Table 1). Figure parts need to be identified with lower case letters, i.e (Fig. 1a).

Figures need to be of high quality. Vector graphics, scanned line drawings and line drawings need to be in bitmap format and should have a minimum resolution of 1,200 dpi. Halftones (photographs, drawings or paintings) need to be in TIFF or JPEG format, up to 174 mm wide and up to 234 mm high and in minimum resolution of 300 dpi.

A figure caption and a table caption need to be added in the figure and table section respectively for each figure and table. Explanatory signs (arrows, asterisks etc) should be used when imaging findings are not obvious. These should be white, black or in shades of grey and proportionate in size compared to the size of the image. Please refrain from using coloured signs. Tables should appear at the end of the main document, numbered in Arabic numerals, each on a different page. Each table should have a title describing its content.

Abbreviations appearing in the table need to be explained in a footnote. All table columns must have a subhead that describes the type of data included in the column.

9. References

The accuracy of references is the responsibility of the authors. The EB suggests to the authors to be accurate regarding citations and check meticulously the correct primary source.

References need to be cited in the text in the order in which they appear. The numbering needs to be in Arabic numbers and placed in the respective areas of text into square brackets i.e [1].

References that have not been published at the point of submission need to cited with the respective DOI (digital object identifier) number given for on-line first articles.

All authors (surnames and initials of first name) should be listed when they are three or fewer. If authors are more than three, the first three authors should be listed, then 'et al.' needs to follow the name of the third author.

When a book chapter is cited, the authors and title of the chapter, editors, book title, edition, city and country, publisher, year and specific chapter pages should be mentioned.

For Online Document, the following should be mentioned: authors (if any), title of page, name of institution or owner of Web site; URL; dates of publication, update, and access.

Reference examples:

Journal article:

Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2018;52(2):186-195.

or

Mazer Zumaeta A, Wright A, Syngelaki A, Maritsa VA, Bardani E, Nicolaides KH. Screening for trisomies at 11-13 weeks' gestation: use of PAPP-A, PlGF or both [published online ahead of print, 2020 Jul 4]. *Ultrasound Obstet Gynecol*. 2020;10.1002/uog.22140. doi:10.1002/uog.22140.

Book chapters:

Allen G, Wilson D. Current role for Ultrasonography. In: Karantanas A (ed). Sports Injuries in children and adolecents (Medical Radiology, Diagnostic Imaging). Springer, Berlin Heidelberg New York 2011, pp 83-97.

Online document:

National Institute for Health and Care Excellence. Twin and triplet pregnancy. NICE guideline [NG137] Published date: 04 September 2019. Available via . Accessed July 20, 2020.

10. Review of manuscripts

Revised manuscripts should be resubmitted according to the Editor's letter. For accepted manuscripts, authors need to make proof corrections within 72 hours upon pdf supplied, check the integrity of the text, accept any grammar or spelling changes and check if all the Tables and Figures are included and properly numbered. Once the publication is online, no further changes can be made. Further changes can only be published in form of Erratum.

11. Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines:

- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- The submission file is in OpenOffice, Microsoft Word, RTF, or WordPerfect document file format.
- Where available, URLs for the references have been provided. The text is double spaced; uses Arial (11 pts) or t Times New Roman (12 pts) font; employs italics, rather than underlining (except with URL addresses). All illustrations and figures should be submitted separately as additional files.
- Tables should appear at the end of the main document.
- The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.
- If submitting to a peer-reviewed section of the journal, the instructions in Ensuring a Blind Review have been followed.
- All authors have sufficiently participated and read the submitted material and fully agree to its content.

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Authors of accepted papers are invited to prepare a short (up to 5 slides, up to 3 minutes) presentation in English, narrated either in English or in Greek, which will be uploaded in the YouTube channel of the journal. The content of these presentations should strictly adhere to the content of the accepted article and should not contain any graphical details (including logos of institutions etc) that could be regarded as advertisement.

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