The Fetal Medicine Foundation

Differences in size of right and left choroid plexuses at 11-13 wks: an early sign of 'developmental' laterality?

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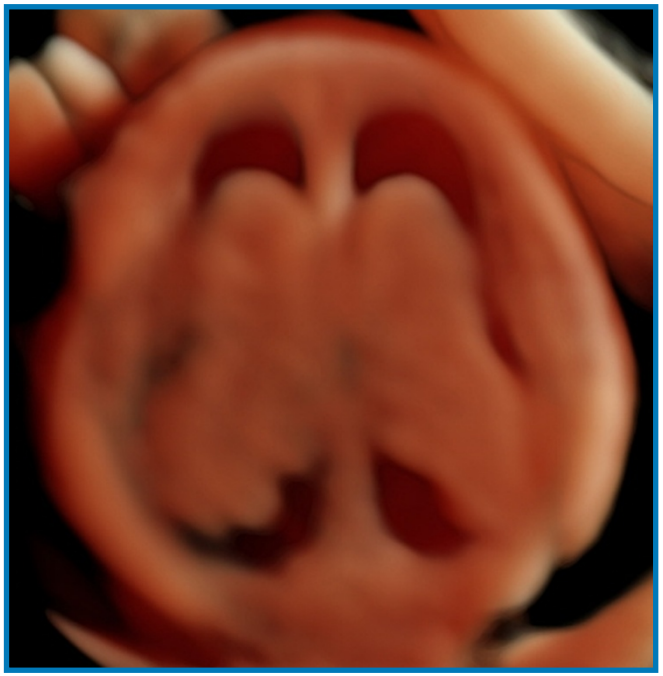

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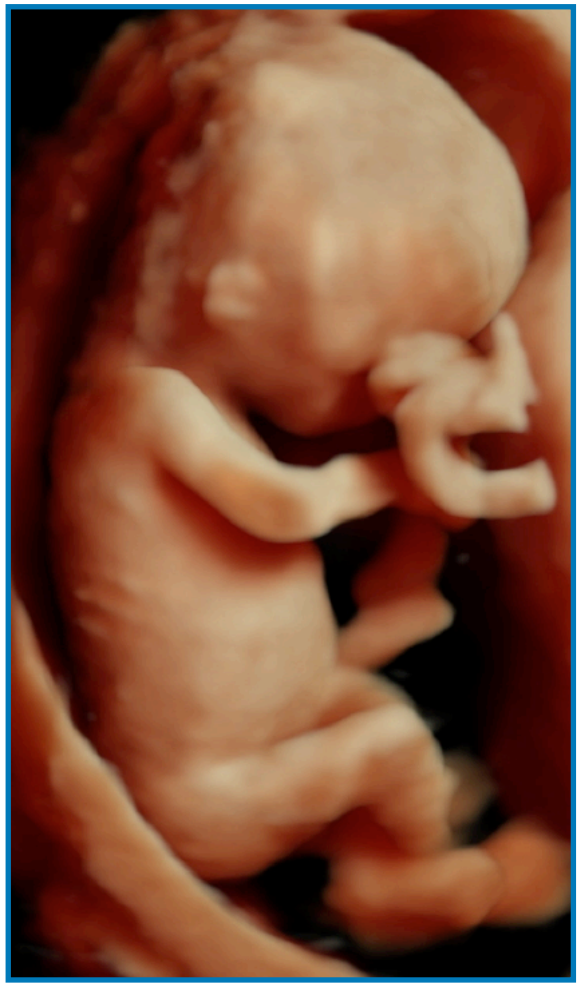
Choroid plexuses at 11-13 wks: an early sign of 'developmental' laterality?

Background

- Laws of symmetry (Bichat 1805)
- Human brain: structural asymmetry (Geshwind *et al* 1968)
- Human brain: functional laterality (Corballis 1991)
- Cerebral and behavioral asymmetries from 10 wks (Hepper *et al* 1991)
- 90% fetuses suck the right thumb (Hepper *et al* 2005)
- 2/3 fetuses present in the left fetal position, with the right side facing out in the third trimester (Taylor *et al* 1976)
- Critical role for the CP in developing CNS: large size in the FT creates shorter diffusional distances (Redzic *et al* 2005)
- Evidence for ventriculomegaly in Trisomy 18 (32.4%) and in Trisomy 13 (87.5%) (Loureiro *et al* 2012)



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Choroid plexuses at 11-13 wks: an early sign of 'developmental' laterality?

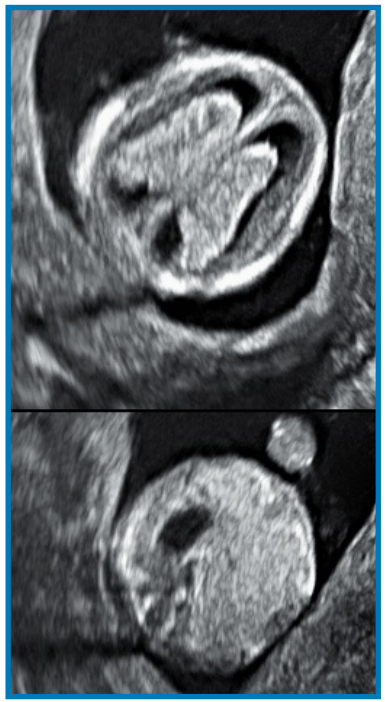
Objective

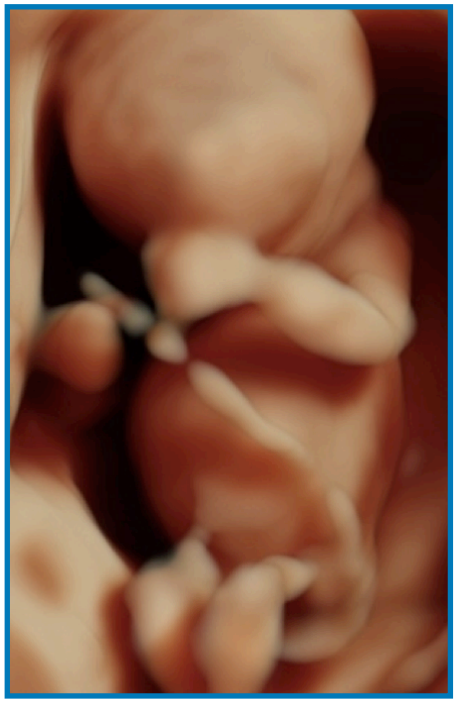
Compare the size of the right and left fetal choroid plexus at 11-13 wks

Methods

- Prospective study
- 114 normal fetuses at 11-13 wks

- Fetal situs established
- Plane of the butterfly obtained
- Length, area and circumference of each CP expressed as a function of BPD





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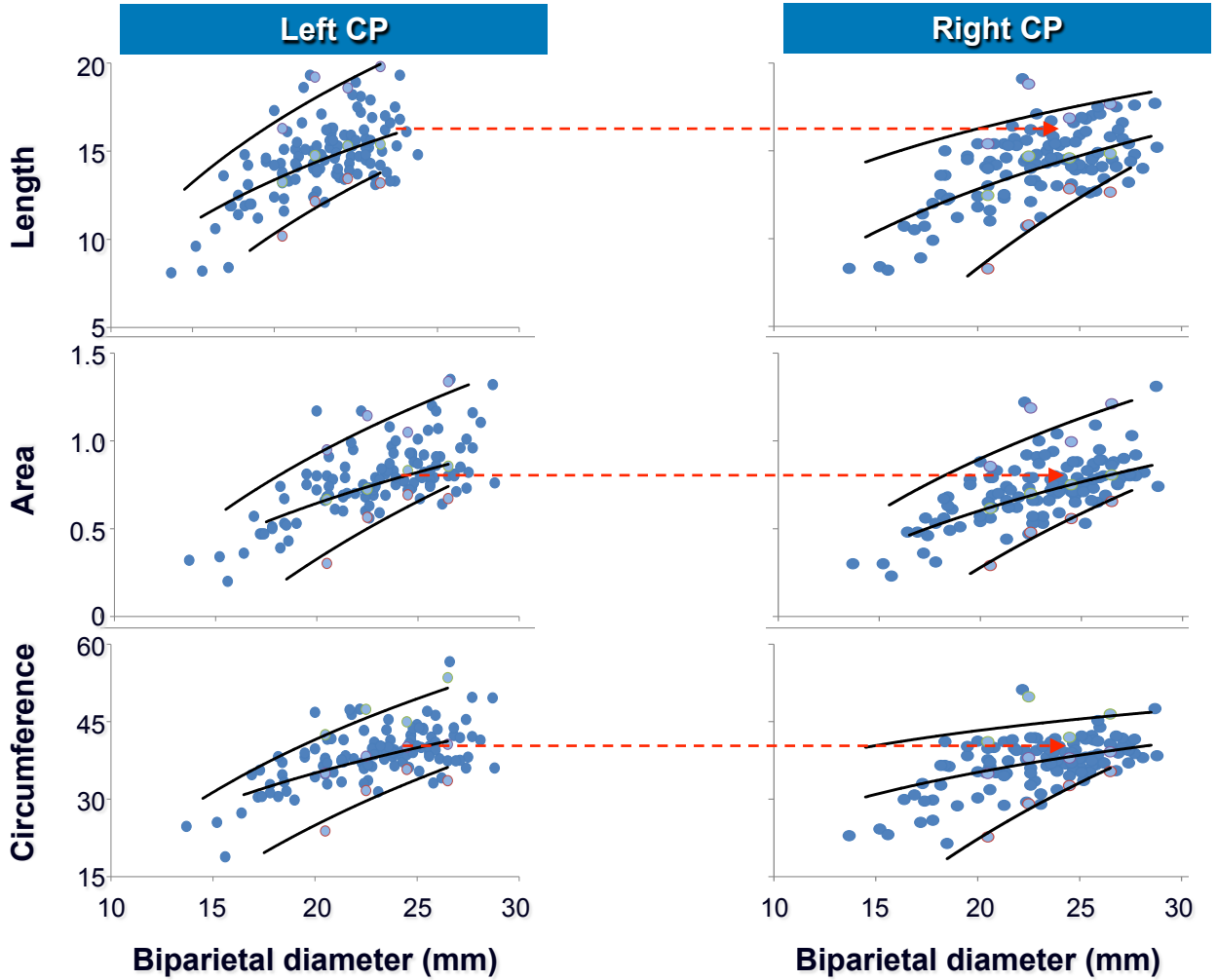
Choroid plexuses at 11-13 wks: an early sign of 'developmental' laterality?

Results



Left > Right
P < 0.0001

Paired t-test

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Choroid plexuses at 11-13 wks: an early sign of 'developmental' laterality?

Limitations

- Small study, single sonologist

Conclusions

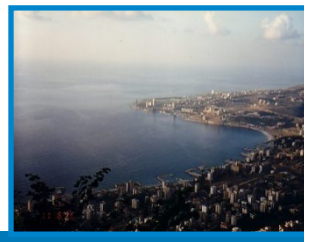
- First study comparing size of the two fetal CPs at 11-13 wks
- Left CP is larger than the right
- Size difference in CPs is a possible early sign of 'developmental' laterality

Special Acknowledgement: Professor Michael Corballis at the University of Auckland, New Zealand









Thank you from Lebanon…

Acceptability of Non-Invasive Prenatal Testing in Lebanon

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Objective

Non-invasive prenatal testing (NIPT) using cell-free fetal DNA became available in Lebanon at the beginning of 2013. In general, and due to several cultural and religious beliefs, as well as fear of pregnancy loss, very few of our patients are wiling to undergo invasive testing. At our center, we tend to offer invasive testing as an option to all women over the age of 35 while discussing the various screening modalities that are available to them. As such, we sought to compare the number of patients in the advanced maternal age group who accepted invasive testing versus those who accepted invasive testing and NIPT during two time periods, a year apart, prior to and after the availability of NIPT.

Methods

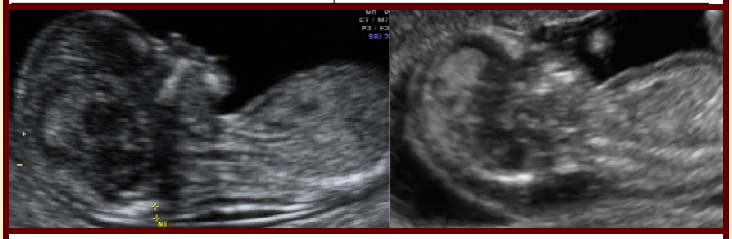
This was a retrospective study of patients in our database presenting for either first or second trimester ultrasound during 2 similar time frames, one year apart, prior to and after the availability of NIPT. Invasive testing was offered to all patients over the age of 35 in the first time frame. NIPT and invasive testing were offered to all patients over the age of 35 in the second time frame. All scans and counseling were carried out by a single sonologist certified by the Fetal Medicine Foundation. Data was analyzed utilizing chi-square test. $P < 0.05$ was considered statistically significant.

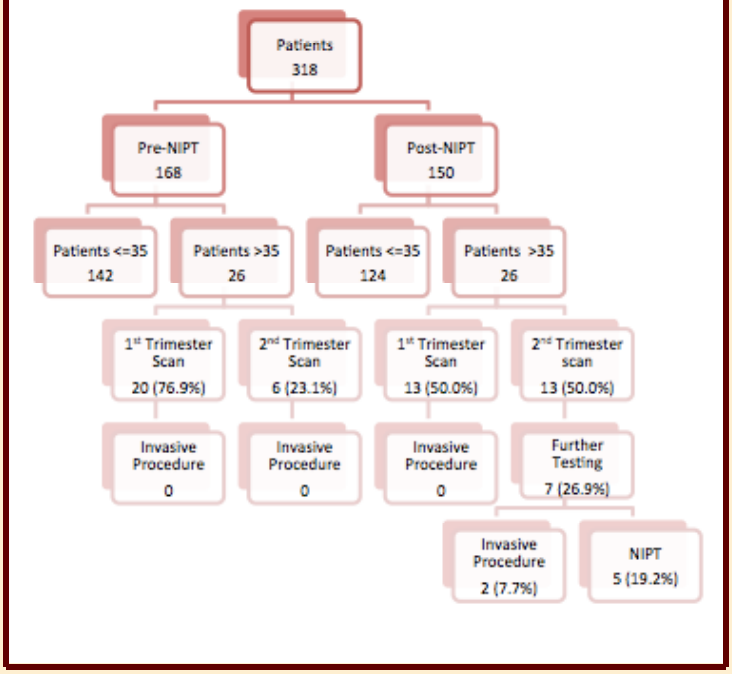
Results

Out study included 318 patients. Of those, 168 were in the first time frame, and 26/168 (15.5%) were over the age of 35. None of them opted to undergo invasive testing. During the second time frame a year later, there were a total of 150 patients and 26/150 (17%) were over the age of 35. Even though a significantly higher number of patients over the age of 35 presented later on in gestation in the second time frame after the availability of NIPT (p 0.044), a statistically significant proportion of them, 7/26 (26.9%), opted for further fetal assessment (p 0.004). Of those 7 patients, 2/26 (7.7%) opted for invasive testing, and 5/26 (19%) opted for NIPT.

Patient Characteristics

	Pre-NIPT	Post-NIPT	P-value
Total Number of Patients	168 (100%)	150 (100%)	
First Trimester Scan	83 (49.4%)	76 (50.7%)	0.822
Second Trimester Scan	85 (50.6%)	74 (49.3%)	
Patients With Age > 35 (years)	26 (100%)	26 (100%)	
First Trimester Scan	20 (76.9 %)	13 (50.0%)	0.044
Second Trimester Scan	6 (23.1%)	13 (50.0%)	
Patients >35 Accepting Further Testing	0	7 (26.9%)	0.004
Invasive Procedure	0	2 (7.7%)	
NIPT	Not Available	5 (19.2%)	





Conclusion

Even in this small cohort of patients, our study attests to the acceptability of NIPT in our cultural set-up, in comparison to invasive testing. During two similar time periods, there was a significant increase in the number of patients willing to have their fetuses evaluated for trisomies, the majority of whom opted for NIPT, despite the lack of public awareness about NIPT, and the nearly doubling in cost of NIPT when compared to invasive testing. This attests to the acceptability of NIPT in our cultural setup. In addition, it highlights the potential impact that NIPT has on increasing the number of patients who opt for further evaluation of their fetuses whether via NIPT or invasive testing. The evidence provided by this study, in support of the acceptability of NIPT in our unique cultural set-up, may serve as the basis to encourage the incorporation of NIPT as a safe and acceptable option to our patients in Lebanon.

Normogram for the Fetal Nasal Bone at 18-24 Weeks in an Unselected Lebanese population

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Objective

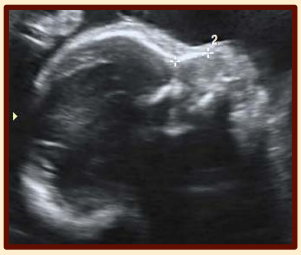
The fetal nasal bone (NB) is a second trimester (ST) marker for aneuploidy. However, it has been shown to vary with ethnicity. As such, the objective of this study was to establish the normogram for the NB in an unselected low risk Lebanese population, and to compare the nasal bone of male to female fetuses. In addition, we sought to assess for any ethnic variations precluding its application as a second trimester marker of aneuploidy, and to investigate how to potentially correct for this ethnic variation.

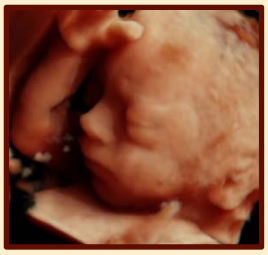
Methods

This was a prospective study on 1001 fetuses with confirmed dating undergoing a ST scan at 18 to 24 weeks at two centers in Lebanon. The NB was measured on all fetuses in a mid sagittal plane according to the guidelines of the Fetal Medicine Foundation. The ratio of the fetal biparietal diameter (BPD) to the fetal NB was calculated on all fetuses. Twin gestations and cases with aneuploidy or structural abnormalities were excluded from the analysis. All fetuses were term live births with a normal neonatal examination at birth. Regression analysis was used to establish the relationship between the fetal NB and gestational age (GA). ANOVA test of means was employed to establish the mean NB, and to evaluate the changes in the BPD/NB ratio according to the gestational age. T-test or chi square test, as appropriate, were used to compare the different demographic characteristics, as well as the NB and BPD/NB between male and female fetuses. The normogram and the centiles of the Lebanese NB, together with the ratio of the BPD/NB according to fetal gestational age, were established. P < 0.05 was considered statistically significant.

Results

A total of 1001 fetuses were included in the analysis. Mean GA was 22.18 weeks. Mean NB was 8.17 mm. Mean maternal BMI was 25.51. There were 48.5% female and 51.5% male fetuses. Our data revealed that the nasal bone increases with advancing gestation according to the relationship: $NB=0.0376GA^2 + 2.034GA-18.399$ (P<0.001). In the Lebanese fetus, the fetal nasal bone tends to be larger than what has previously been established by both Sonek and Persico. However, the BPD/NB ratio remained stable with advancing gestation, with a mean of 6.6, and this ratio remained stable with advancing gestation, irrespective of fetal gender (P=0.055).



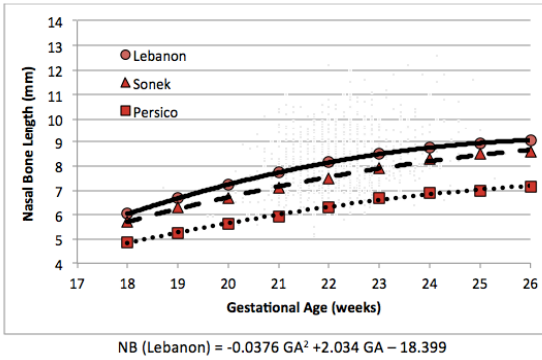


Population Demographics

	Total	Male	Female	P-value
Subjects (n)	1001	516 (51.5%)	485 (48.5%)	
Gestational age (weeks)	22.18 (0.88)	22.16 (0.83)	22.21 (0.94)	0.422
BMI	25.51 (4.06)	25.53 (4.03)	25.48 (4.09)	0.862
Nasal Bone length (mm)	8.17 (1.17)	8.16 (1.17)	8.17 (1.16)	0.930
BPD	53.59 (3.73)	53.98 (3.58)	53.16 (3.85)	<0.001
Ratio (BPD/NB)	6.68 (0.98)	6.74 (0.99)	6.62 (0.96)	0.061

Data presented as mean (SD) or n (%) as appropriate

Gestational age (weeks)	Subjects (n)	Percentiles for NB			Percentiles for Ratio (BPD/NB)		
		5%	50%	95%	5%	50%	95%
Total	1001	6.5	8.0	10.3	5.2	6.6	8.3
20 and less	50	5.8	7.2	9.1	5.2	6.5	8.5
[21 to 22[	327	6.3	7.9	9.9	5.2	6.5	8.2
[22 to 23[	457	6.6	8.1	10.3	5.2	6.7	8.3
[23 to 24[	125	7.0	8.2	10.5	5.4	6.8	8.2
24 and greater	42	6.8	8.7	11.8	4.9	7.2	9.0
P-value		<0.001			0.055		



NB (Lebanon) = -0.0376 GA^2 +2.034 GA – 18.399

Conclusion

Our study demonstrates that in an unselected low risk Lebanese population, the normogram for the fetal nasal bone is different than what has previously been established with the Lebanese nasal bone being larger. This ethnic variation may be corrected for by utilizing the BPD/NB ratio, which remains stable irrespective of gestational age and fetal gender. As such, prospective studies are necessary in order to determine the optimal BPD/NB cut-off which may be utilized in our population as a potential marker for aneuploidy.

Limitations of 3D Ultrasound in the Prenatal Evaluation of a Skin Denudation Syndrome

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Case Report

We present the case of a 33 year old female, gravida 4 para 3003, in a consanguineous marriage, referred at 33w2d for evaluation of new onset polyhydramnios. She had a negative past medical history and a normal prenatal course until this point in gestation.

Upon evaluation, polyhydramnios was present, with particulate, echogenic amniotic fluid consistent with a 'snowflake' pattern (Figure 1). On fetal assessment, there was shortening of all fetal long bones and a dilated stomach filled with a mass of echogenic debris (Figure 2). The fetus had one clenched hand. The biggest challenge encountered, despite the abundant pockets of amniotic fluid, was in attempting to obtain surface-rendered images of the fetal face. The amniotic fluid was extremely echo-dense, prohibiting an image generation. As such, the volume settings had to be adjusted significantly in order to generate surface-rendered images of the fetal face, which were seemingly normal, utilizing HD*live* (Figure 3).

Later on that same day, the patient went into preterm labor and delivered a live born female with well-limited skin erosions on the nose, the left side of the neck and the dorsal surface of the left hand (Figure 4). The left ear was also abnormal with no visible ear canal. After birth, new blisters and erosions appeared with the handling of the newborn. Plain abdominal film and abdominal ultrasound were highly suggestive of duodenal versus pyloric atresia with evidence of proximal gastrointestinal obstruction. There was high clinical evidence for the diagnosis of epidermolysis bullosa. The baby passed away on day of life 6 secondary to dehydration and sepsis.

Skin denudation syndromes may manifest in the 'snowflake pattern', a sonographic sign that is a result of echogenic particles floating in the amniotic fluid, well before the gestational point at which vernix appears. The role of three-dimensional sonography has been evaluated in cases of epidermolysis bullosa with varying conclusions. Though three-dimensional sonography may aid in the identification of constrictive lesions, with reported narrowing and constriction of a limb, and it may demonstrate suggestive skin findings, such as abrupt defects of the soft tissue, it oftentimes is of limited value. And though thus far, there is no clinical evidence as to the diagnostic contribution of ultrasound in the diagnosis of skin ulcers, there have been reports that three-dimensional sonography might aid in the detection and visualization of raised bullous lesions.

Our case attests to the fact that there are still considerable limitations in the in-utero assessment of desquamating skin disorders. The in-utero and post-natal images provide further evidence that three-dimensional ultrasound is of limited value in the prenatal evaluation of skin denudation syndromes and that caution must be employed when utilizing three-dimensional sonography for the evaluation of the fetal skin. The key to the correct diagnosis remains a high clinical index of suspicion for an underlying skin denudation syndrome, irrespective of family history, whenever there is consanguinity, polyhydramnios, echogenic amniotic fluid and signs of gastrointestinal obstruction on two-dimensional sonographic evaluation.

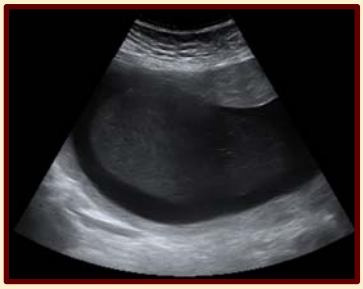

Figure 1: 2D image demonstrating the echogenicity of the amniotic fluid, depicting the "snowflake" pattern.

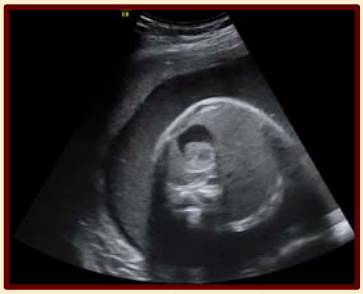

Figure 2: 2D demonstrating the fetal stomach filled by a mass of echogenic debris. The density and texture of the surrounding amniotic fluid can be appreciated in the background.

Figure 3: 3D surface-rendered image of the fetal face, utilizing HD*live*, after adjusting the image settings to a threshold in excess of 120. Note the absence of any signs of denudation affecting the fetal nose. The fetal ears were concealed by the fetal hands.

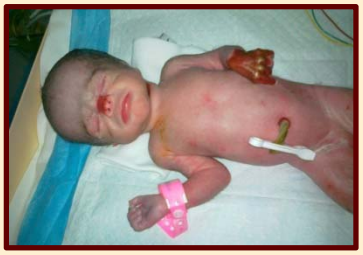

Figure 4: Postnatal image of the newborn

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False Positive Cell-Free Fetal DNA Testing for Trisomy 13: Our First False Positive Result in Lebanon

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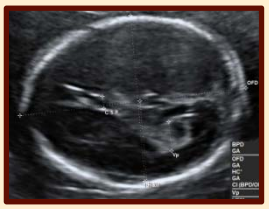
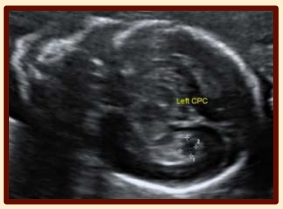
Case Report

We present the case of a 39 year old female, gravida 3 para 1001, with a normal first trimester nuchal translucency, who opted for non-invasive prenatal testing (NIPT) using cell-free fetal DNA for further reassurance given her advanced maternal age. Sonographic evaluation prior to the NIPT at 18w1d revealed an appropriately grown fetus with an estimated fetal weight of 268 grams, normal amniotic fluid index, no ventriculomegaly, normal fetal echocardiography, no echogenic intracardiac focus, normal nasal bone and facial profile, no short long bones, no pyelectasis, and no echogenic bowel. However, there was an isolated unilateral choroid plexus cyst of 4.6 mm on the fetal left side.

NIPT testing was carried out and the results were available within 10 days, surprisingly indicating a high fetal risk for trisomy 13. A repeat scan at 20 weeks was again within normal limits except for the isolated left CPC. As such, an amniocentesis was performed and sent for Quantitative Fluorescent-PCR for Trisomy 21, 18 and 13 as well as for full fetal karyotype. The results were consistent with a normal male fetus.

This represents the first false positive result of NIPT performed in Lebanon. Our case attests to the importance of a properly performed ultrasound in the evaluation of trisomy 13, and to having a high clinical index of suspicion in cases when the NIPT indicates a fetus with a high risk of trisomy 13, in contrast to having no significant findings on a properly performed sonographic evaluation. Caution should always be utilized in such cases even if the NIPT indicates a fetus at high risk. Invasive testing remains a must in order to confirm the diagnosis, properly counsel the family and manage the pregnancy accordingly.





Test Results

CHROMOSOME	RESULT	PROBABILITY	RECOMMENDATION
Trisomy 21 (T21)	Low Risk	Less than 1/10,000 (0.01%)	Review results with patient
Trisomy 18 (T18)	Low Risk	Less than 1/10,000 (0.01%)	Review results with patient
Trisomy 13 (T13)	HIGH RISK	Greater than 99/100 (99%)	Genetic counseling and additional testing
Y Analysis	Male Fetus	Greater than 99/100 (99%)	Review results with patient

- ***DNA analysis***

Fetal DNA was analyzed using Elucigene QST*R*PlusV2* Kit on chromosomes 13, 18, 21, X and Y based on the QF-PCR method (Quantitative Fluorescent-PCR)

Marker	*Allele size 1 (bp)*	*Allele size 2 (bp)*	*Peak Area 1 A1*	*Peak Area 2 A2*	*Allele dosage ratios (A1/A2)*
D13S252	294	302	9456	7355	1.29
D13S305	449	453	14916	13854	1.08
D13S628	454	458	14017	13011	1.08
D13S634	400	410	22833	19268	1.19
D13S800	303	-	46723	-	-
D18S386	384	-	46269	-	-
D18S390	367	371	28796	25064	1.15
D18S535	488	-	27301	-	-
D18S819	409	413	11460	9960	1.15
D18S978	214	224	25267	25814	0.98
D21S11	252	262	15904	15040	1.06
D21S1409	224	238	12752	9611	1.33
D21S1435	185	189	21650	18709	1.16
D21S1437	335	343	30496	27025	1.13
D21S1442	359	-	20336	-	-
D21S1446	217	233	26730	29529	0.91
DXS1187	141	-	29687	-	-
DXS6803	141	-	30426	-	-
HPRT	283	-	38478	-	-
SRY	252	-	14016	-	-
TAF9L	117	121	38547	19333	1.99
AMEL	106	112	14755	19878	0.74

** Results interpretation*

Normal	:	0.8<A1/A2<1.4
Uninformative	:	0.65<A1/A2<0.8 or 1.4<A1/A2<1.8
Trisomic	:	A1/A2>1.8 or A1/A2 <0.65 Presence of three alleles

- ***Conclusion***

- Markers on chromosomes 13, 18 and 21 showed no numerical abnormalities
- Markers on chromosomes X and Y correlate most likely with a male fetus
- These results are to be used in conjunction with fetal karyotype analysis

Department of Laboratory Medicine

Result and Interpretation:

46,XY
Male chromosome complement observed
No abnormality detected