OGI

Obstetric & Gynecological Imaging

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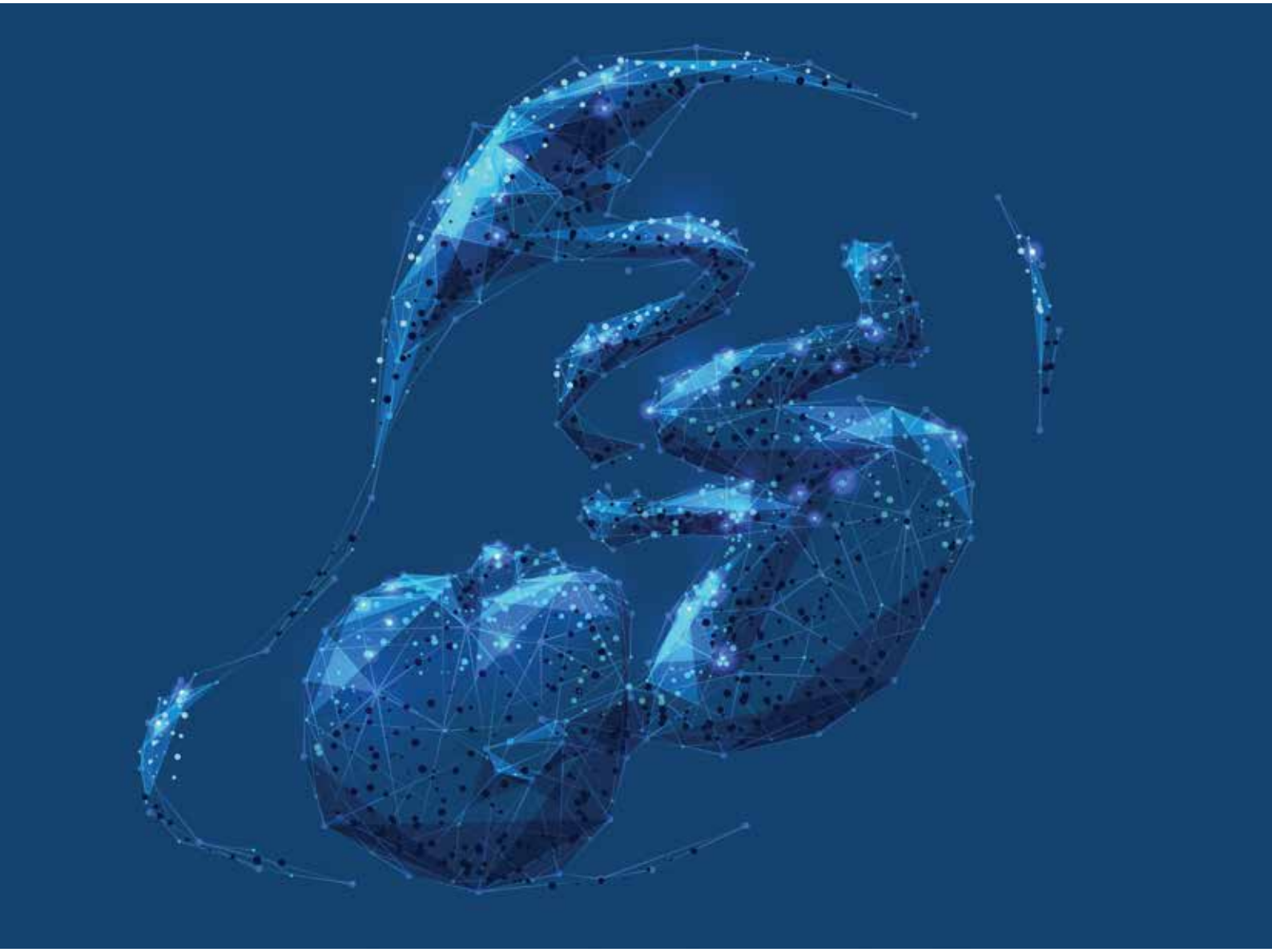


Ελληνική Εταιρεία Υπερήχων στη Μαιευτική & Γυναικολογία
Hellenic Society For Ultrasound In Obstetrics & Gynecology

Hellenic Society For Ultrasound
In Obstetrics & Gynecology

ARTIFICIAL INTELLIGENCE

Voluson SWIFT

Voluson™ SWIFT is changing everything with powerful AI tools for obstetric imaging. Enhance efficiency and improve consistency with SonoLyst, a suite of AI tools that automatically identify fetal anatomy seen on standard views. Using SonoCNS on Edison AI deep learning technology simplifies assessment of the fetal brain.

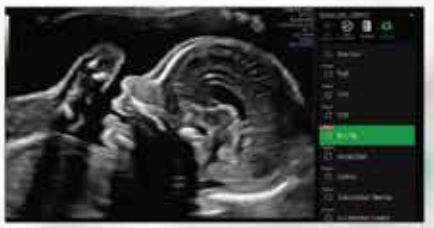
gehealthcare.com

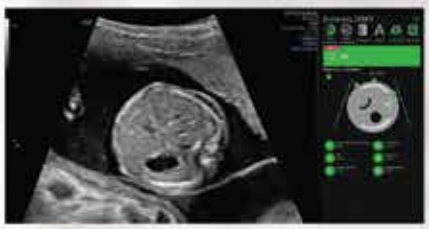
This Changes Everything

Introducing SonoLyst

SonoLystIR

Simply scan then freeze and SonoLystIR (Image Recognition) does the rest. SonoLystIR identifies the anatomy visualized, checks it off the list and can initiate annotations or measurements. Confirm, and data is entered into the Scan Assistant checklist and report.





SonoLystX

Build and refine your skills with SonoLystX your virtual, on-board ultrasound expert. Using AI the system compares the image or view acquired to standard criteria accepted by experts to ensure it meets the accepted clinical standards. Ideal for teaching and training, progress can be monitored for quality assurance to ensure the highest quality imaging standards and consistency.

Includes the 20 views recommended by ISUOG mid-term practice guidelines

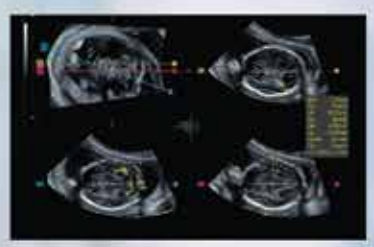
*Optimize workflow by more than 70% with AI***

Edison

SonoCNS an Edison AI Application

"Central nervous system (CNS) malformations are one of the most common congenital abnormalities"

SonoCNS helps properly align and display recommended views and measurements of the fetal brain.



GE Healthcare AE – Σωρού 8-10, 15125 Μαρούσι Ελλάδα
Δέσποινα Χριστοδούλου, 6979 988828, email: Despina.Christodoulou@ge.com

*SonoLyst incorporates the AI technology of Intelligent Ultrasound
**Comparison performed using GE's Voluson SWIFT vs. Voluson P8

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25 ΧΡΟΝΙΑ

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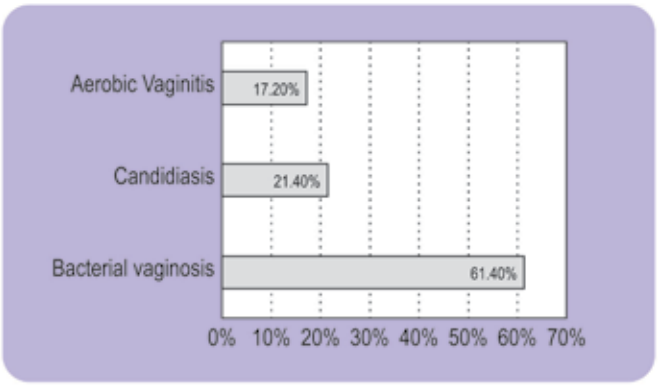
ΚΛΙΝΙΚΗ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ EVA INTIMA BIOLACT

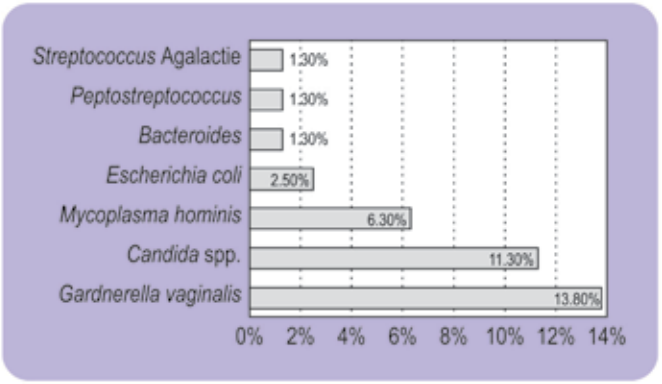
Σημαντική βελτίωση των κυριότερων συμπτωμάτων αιδοιοκολπίτιδας σε 4 ημέρες χωρίς αντιμικροβιακή αγωγή

Πρόσφατη μελέτη που πραγματοποιήθηκε από τη **Μαιευτική & Γυναικολογική κλινική του Αρεταίειου Νοσοκομείου** και δημοσιεύτηκε στο ***Beneficial Microbes*** με τίτλο ***"Alleviation of vulvovaginitis symptoms: can probiotics lead the treatment plan?"***, απέδειξε ότι η **ενδοκολπική χορήγηση των γαλακτικών βακτηρίων *Bacillus coagulans* που προσφέρει το Eva Intima Biolact πριν τη χορήγηση αντιμικροβιακής αγωγής, μειώνει σημαντικά τα τέσσερα βασικά συμπτώματα** που εμφανίζουν οι γυναίκες με αιδοιοκολπίτιδα όπως ο κνησμός, το αίσθημα καύσου, ο ερεθισμός και οι κολπικές υπερεκκρίσεις με ταυτόχρονα σημαντική βελτίωση και στην τιμή κολπικού pH **μέσα σε 4 μόλις ημέρες**.

Σημαντικό το όφελος που προκύπτει για την ασθενή, για το διάστημα που μεσολαβεί μεταξύ της πρώτης συνάντησης μέχρι και την ολοκλήρωση των διαδικασιών διαγνωστικού ελέγχου, βάση του οποίου θα χορηγηθεί η κατάλληλη αντιμικροβιακή αγωγή.

Πιο συγκεκριμένα η κλινική μελέτη περιλαμβάνει 70 γυναίκες αναπαραγωγικής ηλικίας με συμπτώματα κολπικής ενόχλησης τα οποία καταγράφονται κατά την πρώτη επίσκεψη σε ειδικά ερωτηματολόγια.
Παράλληλα πραγματοποιείται μέτρηση κολπικού pH και λαμβάνονται δείγματα μέσω κολπικών στυλεών για μικροσκοπικό έλεγχο και καλλιέργεια. Για τις επόμενες 4 ημέρες οι ασθενείς λαμβάνουν κολπικές πλύσεις και κολπικά υπόθετα με B. coagulans (Eva Biolact), με την κατάλληλη αντιμικροβιακή αγωγή (βασισμένη στα αποτελέσματα του διαγνωστικού ελέγχου) να προστίθεται μετά την τέταρτη ημέρα της αγωγής.
Οι ασθενείς επανέρχονται στην κλινική μετά από 16 ημέρες για να συμπληρώσουν εκ νέου το ερωτηματολόγιο. Η αξιολόγηση των διαφορών της έντασης των κλινικών σημείων της κολπίτιδας καθώς και της μέτρησης του κολπικού pH μεταξύ των συναντήσεων επανελέγχου έγινε με βάση τη Wilcoxon signed-ranked test.





Κλινικά & εργαστηριακά ευρήματα: φυσική εξέταση & κριτήρια Amstel (επάνω) vs καλλιέργεια (κάτω).

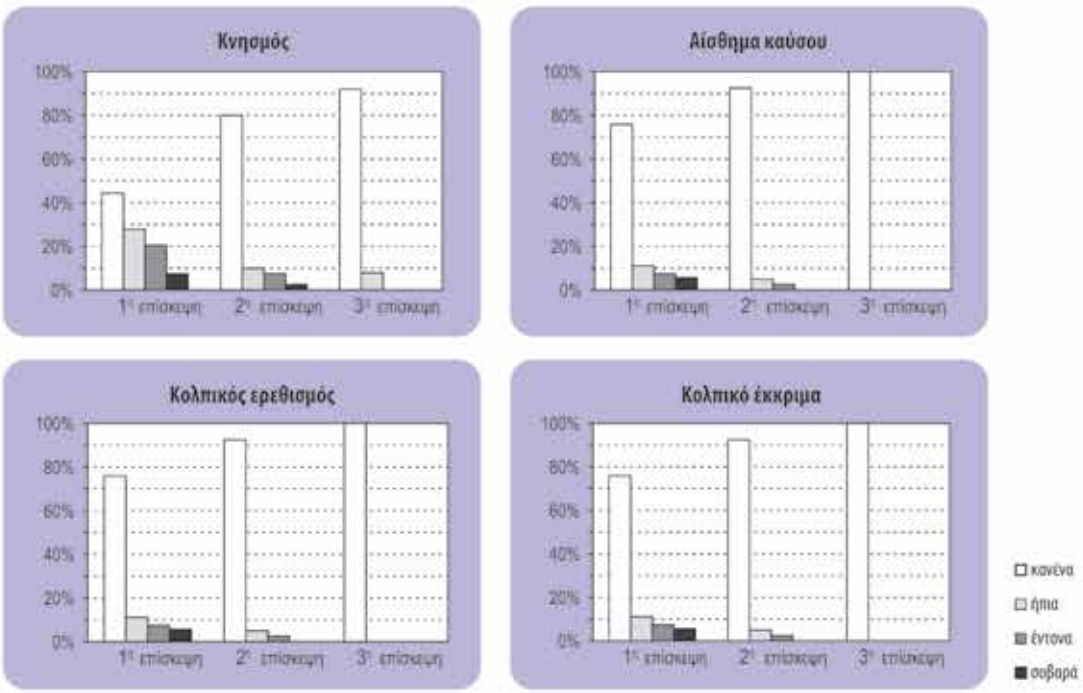
Τα αποτελέσματα που καταγράφηκαν είναι τα εξής:

Μετά από 4 ημέρες αποκλειστικής χορήγησης Eva Biolact douche & Eva Biolact ovules* (μεταξύ της πρώτης και δεύτερης επίσκεψης):

- **Το 91% των ασθενών παρουσίασε σημαντική μείωση της εμφάνισης αισθήματος καύσου (P<0.001)**
- **Το 85% των ασθενών παρουσίασε σημαντική μείωση της εμφάνισης κνησμού (P<0.001)**
- **Το 76% των ασθενών παρουσίασε σημαντική μείωση της εμφάνισης ερεθισμού (P<0.001)**
- **Το 75% των ασθενών παρουσίασε σημαντική μείωση του κολπικού pH (P<0.001)**
- **Το 71% των ασθενών παρουσίασε σημαντική μείωση της εμφάνισης κολπικού εκκρίματος (P<0.001)**

** κολπική εφαρμογή μιας πλύσης Eva Biolact douche & από 20-30' λεπτά κολπική εφαρμογή ενός Eva Biolact ovules.*

Με τη χορήγηση του κατάλληλου αντιμικροβιακού παράγοντα η εφαρμογή του Eva Biolact ovule συνεχίστηκε για 10 ακόμα ημέρες με τα παραπάνω κλινικά σημεία να βελτιώνονται επιπλέον βάση της αξιολόγησης που πραγματοποιήθηκε στην τρίτη και τελευταία επίσκεψη της ασθενούς στην κλινική (σχηματογράφημα).
Ωστόσο, η κλινική βελτίωση των συμπτωμάτων είναι σημαντικότερη κατά το διάστημα αγωγής μόνο με προβιοτικά συγκριτικά με το διάστημα χορήγησης του συνδυασμού αντιμικροβιακής αγωγής/προβιοτικού.



Tsimaris et al, Beneficial Microbes, 2019;10(8):867-877, Alleviation of vulvovaginitis symptoms: can probiotics lead the treatment plan?

Συμπερασματικά:

Είναι γνωστό πως η μείωση του αριθμού των γαλακτοβακίλων στην περιοχή του κόλπου πιθανότατα οδηγεί στην εμφάνιση μικρότερων ή μεγαλύτερων διαταραχών με την πρόκληση απλών κολπίτιδων έως επιπλοκών στην εγκυμοσύνη και πρόωρη γέννηση.

Η υιοθέτηση της χορήγησης γαλακτικών βακτηρίων τις πρώτες μέρες της αγωγής προσφέρει:

- Άμεση ανακούφιση των συμπτωμάτων με φυσικό τρόπο - Άμεση ικανοποίηση των ασθενών
- Απόδοση χρονικού περιθωρίου για ορθή άσκηση διαγνωστικού ελέγχου και χορήγηση κατάλληλης θεραπευτικής αγωγής
- Άμεση έναρξη αποκατάστασης της φυσιολογίας της περιοχής και ενίσχυση των αμυντικών μηχανισμών
- Συμβολή στο θεραπευτικό αποτέλεσμα
- Θεραπευτική επιτυχία

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✓ Τα μοναδικά σκευάσματα με προβιοτικά στελέχη στη μορφή του σπόρου.
✓ Άριστη εμφύτευση ζωντανών στελεχών σε υψηλούς πληθυσμούς μέχρι την τελευταία δόση.
✓ Με την υψηλότερη αξιοπιστία & το χαμηλότερο κόστος ημερήσιας αγωγής.

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Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα Συμπληρώνοντας την «ΚΙΤΡΙΝΗ ΚΑΡΤΑ»

Στο έντυπο περιλαμβάνεται η ΠΧΠ του προϊόντος.

ADV01/04-2021/FYS

Iofolen®

στην εγκυμοσύνη

Το Iofolen® είναι ένα **πολυβιταμινούχο συμπλήρωμα διατροφής για την εγκυμοσύνη,** που περιέχει **ακριβώς τα θρεπτικά συστατικά** που χρειάζονται η μητέρα και το μωρό της, στις **σωστές αναλογίες.**

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Αριθμός Γνωστοποίησης ΕΟΦ: IOFOLEN: 48265/13-07-2007, IOFOLEN TWIN: 69802/30-05-2019, IOFOLEN PRECONCEPTION: 54454/17-05-2018.
Ο αριθμός γνωστοποίησης στον ΕΟΦ δεν επέχει θέση άδειας κυκλοφορίας από τον ΕΟΦ.

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ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ. 1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: FYSIOFOL 800 (40 Fe^{3+}) mg + 0,185 mg/DOSE κόνις και διαλύτης για πόσιμο διάλυμα. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ.** Σίδηρος πρωτεϊνοηλεκτρικός (Iron proteinsuccinylate) + Ασβέστιο φυλλινικό πενταϋδρικό (Calcium folinate pentahydrate): Διάλυμα (στο φιαλίδιο): σίδηρος πρωτεϊνοηλεκτρικός 800 mg (ισοδυναμεί με 40 mg Fe^{3+}). Κόνις (στο αποθηκευτικό πώμα): ασβέστιο φυλλινικό πενταϋδρικό 0,235 mg (αντιστοιχεί σε 0,185 mg φυλλινικού οξέος). Έκδοχα: με γνωστές δράσεις: παραϋδροξυβενζοϊκού νατρίου μεθυλεστέρας, παραϋδροξυβενζοϊκού νατρίου προπυλεστέρας, σορβιτόλη. Για τον πλήρη κατάλογο των εκδόχων, βλ. παράγραφο 6.1. **3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ.** Κόνις και διαλύτης για πόσιμο διάλυμα. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ. 4.1 Θεραπευτικές ενδείξεις.** Πρόληψη της αναιμίας της κύησης. **4.2 Δοσολογία και τρόπος χορήγησης.** Ένα έως δύο φιαλίδια ημερησίως χορηγούμενα κατά προτίμηση πριν από τα γεύματα. **4.3 Αντενδείξεις.** • Υπερευαισθησία στις δραστικές ουσίες ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1. • Μεγαλοβλαστική αναιμία που οφείλεται σε έλλειψη βιταμίνης B12 ή μεγαλοβλαστική αναιμία αδιευκρίνιστης αιτιολογίας. • Αιμοσιδήρωση, αιμοχρωμάτωση. • Απλαστική, αιμολυτική και σιδηροαχρηστική αναιμία. • Αναιμίες από χρόνια νοσήματα ή όψιμη δερματική πορφυρία. • Χρόνια παγκρεατίτιδα. • Κίρρωση του ήπατος. • Γαστροδωδεκαδακτυλικό έλκος εν ενεργεία, γαστρορραγία, φλεγμονώδεις παθήσεις του εντέρου (ελκώδης κολίτιδα, νόσος του Crohn) που είναι σε έξαρση. **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση.** Είναι πολύ σημαντικό πριν τη θεραπεία με οποιοδήποτε σκεύασμα σιδήρου να καθορίζεται το αίτιο της σιδηροπενικής αναιμίας και να αποκλείονται σοβαρά υποκείμενα αίτια (π.χ. γαστρικές διαβρώσεις, καρκίνος παχέος εντέρου). Η χορήγηση σιδήρου από το στόμα μπορεί να επιδεινώσει τη διάρροια σε ασθενείς με φλεγμονώδη νοσήματα του εντέρου (ελκώδης κολίτιδα, νόσος του Crohn), σύνδρομο δυσαπορρόφησης. Προσοχή ακόμη χρειάζεται σε ασθενείς με στένωση του εντέρου και εκκολπώματα. Το FYSIOFOL περιέχει παραϋδροξυβενζοϊκού νατρίου μεθυλεστέρα και παραϋδροξυβενζοϊκού νατρίου προπυλεστέρα (parabens). Μπορεί να προκαλέσουν αλλεργικές αντιδράσεις (πιθανόν με καθυστέρηση) και σε εξαιρετική περίπτωση, βρογχόσπασμο. Το FYSIOFOL περιέχει σορβιτόλη. Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη φρουκτόζη δεν πρέπει να πάρουν αυτό το φάρμακο. Το FYSIOFOL περιέχει πρωτεΐνες γάλακτος και πρέπει να χρησιμοποιείται με προσοχή από άτομα με δυσανεξία στις πρωτεΐνες γάλακτος, καθώς μπορεί να προκαλέσει αλλεργικές αντιδράσεις. Το FYSIOFOL δεν περιέχει σουκρόζη και είναι κατάλληλο για ασθενείς με διαβήτη. Η θεραπεία με σιδηρούχα σκευάσματα γενικώς μπορεί να χρωματίσει τα κόπρανα μαύρα. Συνιστάται η διακοπή της χορήγησης του φαρμάκου σε περίπτωση εμφάνισης σοβαρών συμπτωμάτων δυσανεξίας. **4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης.** Να μη συγχορηγείται με διμερκαπρόλη. Η απορρόφηση του από του στόματος σιδήρου μειώνεται από τα άλατα του μαγνησίου και ασβεστίου, τα αντιόξινα (να χορηγείται με διαφορά τουλάχιστον 2 ωρών), τα παγκρεατικά ένζυμα και τη χολεστυραμίνη και αυξάνεται από συγχορήγηση ασκορβικού οξέος. Αντιστρόφως, ο από του στόματος σίδηρος μειώνει την απορρόφηση των κινολονών, διφωσφονικών, κυτταροτοξικών, της εντακαπόνης, πενικιλλαμίνης, ρισεδρονάτης, λεβοθυροξίνης (να χορηγείται με διαφορά τουλάχιστον 2 ωρών) και πιθανώς της λεβοντόπα. Η απορρόφηση του από του στόματος σιδήρου μειώνεται από τις τετρακυκλίνες (να χορηγούνται με διαφορά τουλάχιστον 2 ωρών) και τον ψευδάργυρο και αντιστρόφως. Ο από του στόματος σίδηρος ανταγωνίζεται την υποτασική δράση της μεθυλντόπα, ενώ η συγχορήγησή του με ΜΣΑΦ μπορεί να εντείνει τον ερεθισμό του γαστρεντερικού βλεννογόνου. Η αλλοπουρινόλη αυξάνει την εναπόθεσή του στο ήπαρ σε κιρρωτικούς ασθενείς. Η χλωραμφενικόλη μπορεί να επιβραδύνει την ανταπόκριση στη σιδηροθεραπεία. Ουσίες που δημιουργούν σύμπλοκα με σίδηρο (όπως φωσφορικά, οξέα που περιέχονται σε δημητριακά ολικής άλεσης και οξαλικά) που περιέχονται στα φαγώσιμα λαχανικά και είναι συστατικά του γάλακτος, του καφέ και του τσαγιού, αναστέλλουν την απορρόφηση του σιδήρου. Οι αντινεοπλασματικοί παράγοντες, ανταγωνιστές του φυλλικού οξέος (φθοριοουρακίλη, μεθοτρεξάτη, κ.λ.π.) και τα αντιεπιληπτικά, ιδίως η φαινυτοΐνη, μπορεί να προκαλέσουν ένδεια φυλλικού οξέος ή να παρεμποδίσουν το μεταβολισμό του. Το φυλλικό και το φυλλινικό οξύ μπορεί να ελαττώσουν τη δράση των ανταγωνιστών του φυλλικού οξέος, καθώς και τη στάθμη της φαινυτοΐνης στο αίμα. Για ανάλογα φαινόμενα ανταγωνισμού του φυλλικού οξέος το FYSIOFOL δεν πρέπει να χορηγείται με συγκεκριμένα αντιβακτηριακά φάρμακα, όπως σουλφοναμίδες, διαμινοβενζυλοπυριμιδίνη και τριμεθοπρίμη, η αποτελεσματικότητα των οποίων μπορεί να ελαττωθεί. **4.6 Γονιμότητα, κύηση και γαλουχία.** Η χορήγησή του ενδείκνυται κατά την κύηση. **4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανών.** Το FYSIOFOL δεν έχει καμία επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανών. **4.8 Ανεπιθύμητες ενέργειες.** Το FYSIOFOL είναι πολύ καλά ανεκτό. Ενδέχεται όμως, ιδιαίτερα σε πολύ υψηλές δόσεις, να εμφανιστούν διαταραχές του γαστρεντερικού (διάρροια, ναυτία, δυσκοιλιότητα, επιγαστρικό άλγος), οι οποίες υποχωρούν με την ελάττωση της δόσης ή με τη διακοπή της θεραπείας. Πολύ σπάνια μπορεί να συμβούν αλλεργικές αντιδράσεις. Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών. Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες: **Ελλάδα:** Εθνικός Οργανισμός Φαρμάκων. Μεσογείων 284. GR-15562 Χολαργός, Αθήνα. Τηλ: + 30 21 32040380/337, Φαξ: + 30 21 06549585. Ιστότοπος: http://www.eof.gr. **Κύπρος:** Φαρμακευτικές Υπηρεσίες. Υπουργείο Υγείας. CY-1475 Λευκωσία. Φαξ: + 357 22608649. Ιστότοπος: www.moh.gov.cy/phs. **4.9 Υπερδοσολογία.** Κατά τη διάρκεια των πρώτων 6-8 ωρών από τη λήψη υπερβολικής δόσης αλάτων σιδήρου, ο ασθενής μπορεί να παρουσιάσει επιγαστρικό άλγος, ναυτία, έμετο, διάρροια και αιματέμεση, τα οποία συνοδεύονται συχνά από υπνηλία, ωχρότητα, κυάνωση, καταπληξία μέχρι και κώμα. Η αντιμετώπιση πρέπει να αρχίσει όσο το δυνατόν πιο γρήγορα και συνιστάται η χορήγηση ενός εμετικού, μετά τη χορήγηση του οποίου πιθανό να χρειασθεί πλύση στομάχου, καθώς και κατάλληλη υποστηρικτική θεραπεία. **5 ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ. 5.1 Φαρμακοδυναμικές ιδιότητες.** Φαρμακοθεραπευτική κατηγορία: Σίδηρος σε συνδυασμό με άλλα φάρμακα, κωδικός ATC: B03AE10. Το FYSIOFOL είναι ένας συνδυασμός σιδηροπρωτεϊνικού συμπλόκου και φυλλινικού ασβεστίου. Ο σίδηρος είναι συνδεδεμένος με τις ηλεκτρυλιωμένες πρωτεΐνες του γάλακτος, κατά τρόπο ώστε να σχηματίζει ένα σιδηροπρωτεϊνικό σύμπλοκο, το οποίο περιέχει 5% ± 0,2 Fe^{3+}. Ένα από τα πιο ενδιαφέροντα φυσικοχημικά χαρακτηριστικά αυτής της πολύ διαλυτής στο νερό οργανικής ένωσης είναι ότι ενώ καθιζάνει σε pH < 4, επαναδιαλύεται σε μεγαλύτερο pH. Επίσης η ένωση αυτή δεν διασπάται από την πεψίνη, υδρολύεται όμως από την παγκρεατίνη σε ουδέτερο pH. Λόγω αυτών των ιδιοτήτων του, ο σίδηρος που περιέχεται στο FYSIOFOL παρουσιάζει το πλεονέκτημα να παραμένει προστατευμένος, χάρη στο πρωτεϊνικό του περίβλημα, από την υδροχλωροπεπτική δράση του γαστρικού υγρού και, κατά συνέπεια, δεν προκαλεί γενικά τις καταστροφικές επιδράσεις που έχουν στο βλεννογόνο του στομάχου η πλειονότητα των αλάτων του σιδήρου (ιδιαίτερα με τη μορφή Fe^{3+}). Το φυλλινικό οξύ είναι το 5-formyl παράγωγο του τετραϋδροφυλλικού οξέος, ενδιάμεσο προϊόν μεταβολισμού του φυλλικού οξέος και αποτελεί την ενεργό βιολογική του μορφή. Μέσα στον οργανισμό, το φυλλικό οξύ μεταβολίζεται σε τετραϋδροφυλλικό, το οποίο είναι συνένζυμο υπεύθυνο αρκετών μεταβολικών διεργασιών, περιλαμβανόντων τη σύνθεση των νουκλεοτιδίων πουρίνης και πυριμιδίνης και τη σύνθεση του DNA στο αιμοποιητικό σύστημα. Η απευθείας χορήγηση φυλλινικού οξέος συντελεί στην αντιμετώπιση έλλειψης της βιταμίνης, ακόμη και απουσία ηπατικών ενζύμων, τα οποία ενεργοποιούν τη μετατροπή του φυλλικού οξέος σε φυλλινικό. Το φυλλινικό οξύ έχει άριστη αντιαναιμική δράση και είναι αποτελεσματικό στην αναιμία που οφείλεται σε έλλειψη του φυλλικού οξέος. **5.2 Φαρμακοκινητικές ιδιότητες.** Ο πρωτεϊνοηλεκτρικός σίδηρος απορροφάται ικανοποιητικά χορηγούμενος από το στόμα. Η απελευθέρωση του σιδήρου από το FYSIOFOL και, επομένως, η απορρόφησή του, γίνεται προς το τέλος του δωδεκαδακτύλου και κυρίως στη νήστιδα, όπου η φυσιολογική αύξηση του pH κάνει την ένωση και πάλι ευδιάλυτη, ενώ επιτρέπει τη διάσπαση του πρωτεϊνικού περιβλήματος από τα παγκρεατικά ένζυμα. Κατά αυτό τον τρόπο, ο σίδηρος καθίσταται διαθέσιμος για φυσιολογική απορρόφηση χωρίς να δημιουργούνται πολύ υψηλές συγκεντρώσεις (ακόμη και σε μεγάλες δόσεις), οπότε δεν επηρεάζεται η φυσιολογική ομοιόσταση. Με ένα σταθερό βαθμό απορρόφησης, επιτυγχάνεται βαθμιαία και ανάλογα με τις ανάγκες του οργανισμού η απορρόφηση και η αποθήκευση του σιδήρου στα διάφορα μέρη του σώματος. Γι' αυτό το λόγο με τη χορήγηση του FYSIOFOL δεν παρατηρείται γαστρεντερική δυσανεξία. Κάτω από φυσιολογικές συνθήκες η απώλεια του σιδήρου είναι πολύ περιορισμένη. Η αποβολή του γίνεται κυρίως μέσω της εμμήνου ρύσεως και σε ελάχιστη ποσότητα μέσω της χολής, του ιδρώτα και της απολέπισης του δέρματος. Το φυλλινικό ασβέστιο απορροφάται γρήγορα από τον γαστρεντερικό σωλήνα, όταν χορηγείται από το στόμα και μετατρέπεται σε βιολογικά ενεργό φυλλινικό οξύ. Το φυλλινικό οξύ κατανέμεται σε όλους τους ιστούς του σώματος, συγκεντρώνεται στο εγκεφαλονωτιαίο υγρό. Η αποβολή του γίνεται μέσω των ούρων. **5.3 Προκλινικά δεδομένα για την ασφάλεια.** Η LD50 του πρωτεϊνοηλεκτρικού σιδήρου μετά από χορήγησή του από το στόμα βρέθηκε να είναι σε επίμυες> 4000 mg/kg, ενώ μετά από ενδοπεριτοναϊκή χορήγηση βρέθηκε να είναι 700 mg/kg και 710 mg/kg σε επίμυες και μύες αντίστοιχα. Πειράματα χρόνιας τοξικότητας πρωτεϊνοηλεκτρικού σιδήρου σε πειραματόζωα (δωδεκάμηνη χορήγηση, από το στόμα, σε δόσεις έως 200 mg/kg ημερησίως), δεν έδειξαν αξιόλογες τοξικολογικές επιδράσεις. Κατά τη διάρκεια της εγκυμοσύνης, ο πρωτεϊνοηλεκτρικός σίδηρος δεν επεμβαίνει στην ομαλή ανάπτυξη του εμβρύου. Το φυλλινικό ασβέστιο δεν παρουσιάζει ιδιαίτερη τοξικότητα, αφού η LD50 του φυλλινικού οξέος κατά τη χορήγησή του από το στόμα σε επίμυες βρέθηκε να είναι > 7000 mg/kg. **6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ. 6.1 Κατάλογος εκδόχων.** Διάλυμα στο φιαλίδιο: Σορβιτόλη, προπυλενογλυκόλη, παραϋδροξυβενζοϊκού νατρίου μεθυλεστέρας, παραϋδροξυβενζοϊκού νατρίου προπυλεστέρας, βελτιωτικό γεύσης morella, σακχαρίνη νατριούχος, ύδωρ κεκαθαρμένο. Κόνις στο αποθηκευτικό πώμα: Μαννιτόλη. **6.2 Ασυμβατότητες.** Καμία. **6.3 Διάρκεια ζωής.** 24 μήνες. **6.4 Ιδιαίτερες προφυλάξεις κατά την φύλαξη του προϊόντος.** Μη φυλάσσετε σε θερμοκρασία μεγαλύτερη των 30°C. **6.5 Φύση και συστατικά του περιέκτη.** Χάρτινο κουτί με 10 ή 20 πλαστικά φιαλίδια των 15 ml, εφοδιασμένα με αποθηκευτικό πώμα που περιέχει 100 mg διαλυτής κόνεως. **6.6 Ιδιαίτερες προφυλάξεις απόρριψης και άλλος χειρισμός.** Για το άνοιγμα του φιαλιδίου, πρέπει να αποκοπεί το επάνω μέρος του πώματος, να πιεστεί με δύναμη το επάνω μέρος του αποθηκευτικού πώματος, μέχρις ότου η κόνις πέσει στο διάλυμα, και να ανακινηθεί μέχρι πλήρους διάλυσης. Στη συνέχεια, πρέπει να απομακρυνθεί το αποθηκευτικό πώμα και να χορηγηθεί το διάλυμα απευθείας από το φιαλίδιο ή προστιθέμενο σε νερό ή γάλα. Κάθε αχρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατά τόπους ισχύουσες σχετικές διατάξεις. **7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ.** ITF Hellas A.E. Άρεως 103 & Αγίας Τριάδος 36, 175 62 Παλαιό Φάληρο, Ελλάδα. **8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** 61975/17/19-09-2019 (Ελλάδα), S00864 (Κύπρος). **9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ.** 22-5-2001/16-3-2007 (Ελλάδα), 21-12-2012/11-1-2021 (Κύπρος). **10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ.** 31-08-2018. **Τρόπος διάθεσης:** Με ιατρική συνταγή. Λ.Τ. FYSIOFOL PS.OR.SOL (800mg+0,185mg)/DOSE BT x 10 DC (Πλαστικά φιαλίδια με διάλυμα 15,0 ml + πώμα με κόνις 100,0 mg): 8,58 €.

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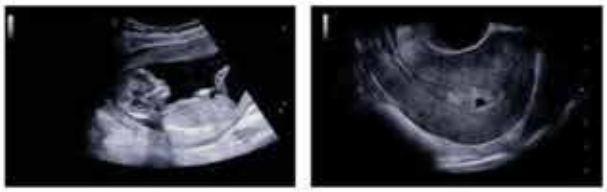

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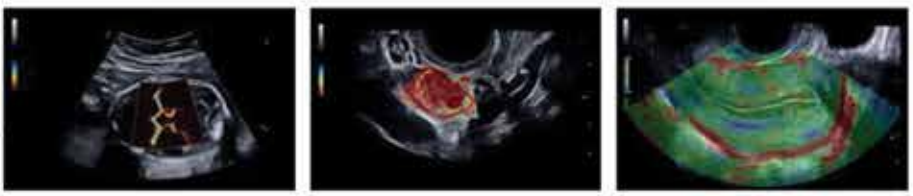

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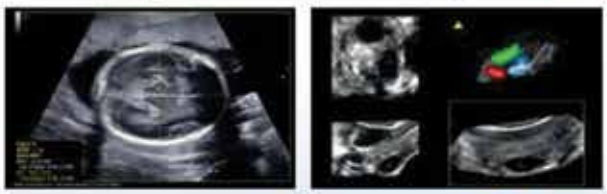

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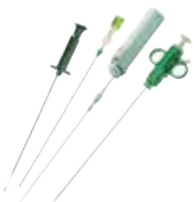

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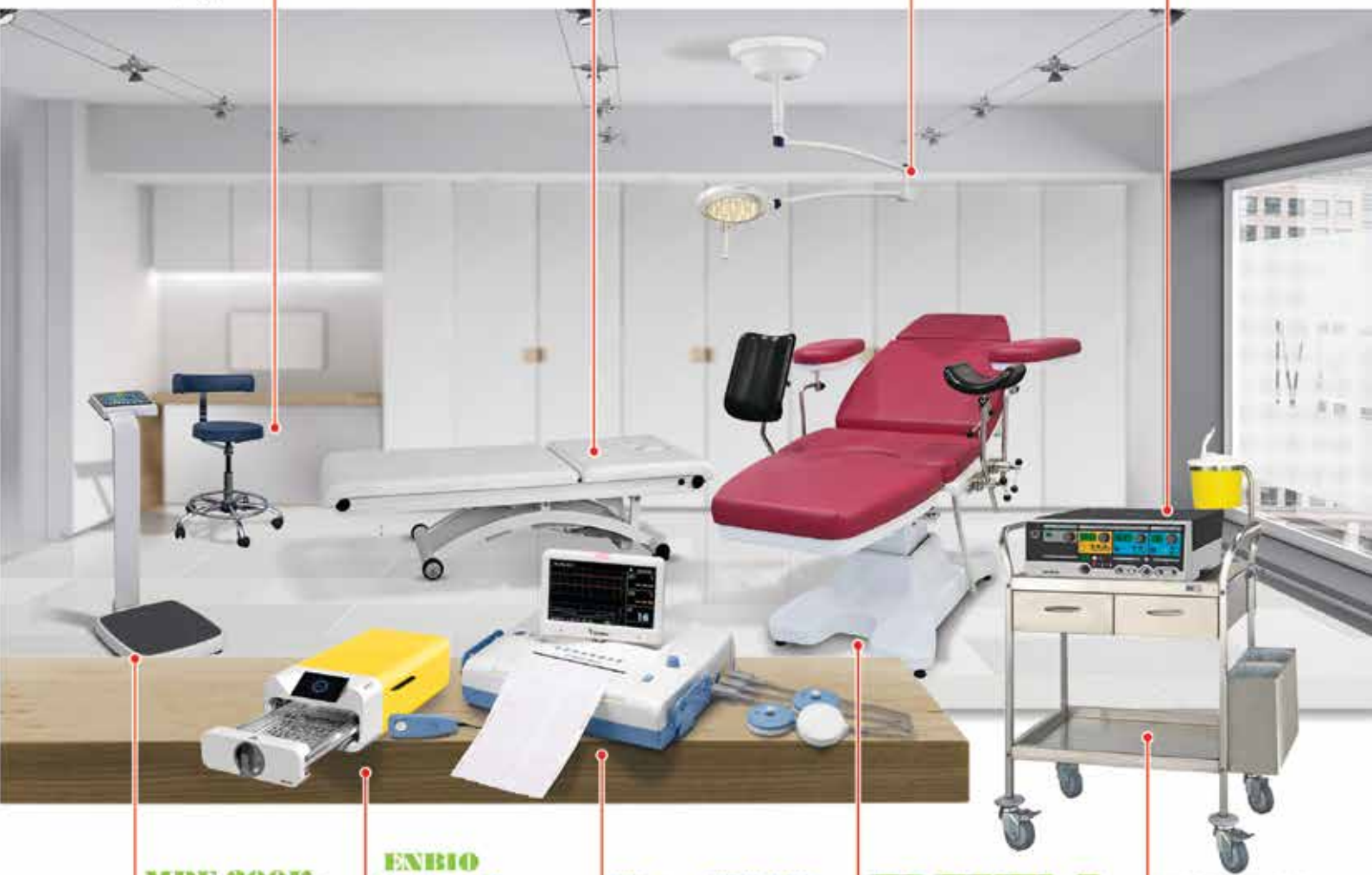

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LETTER FROM THE EDITOR

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

Athena P. Souka, Despoina Kitmiridi, Athanasios Pilalis
Emvryo-Mitriki Fetal Medicine Unit, Athens, Greece

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

Corresponding author and guarantor:
Dr Athena Souka
Adress: Emvryo-MitrikiFetal Medicine Unit, 11, Hatzikostastr, Pl. Mavili, Athens 11521, Greece, Tel: 0030-210 6451132, Fax: 0030-210 6471161, e-mail: athena.souka@gmail.com

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.

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

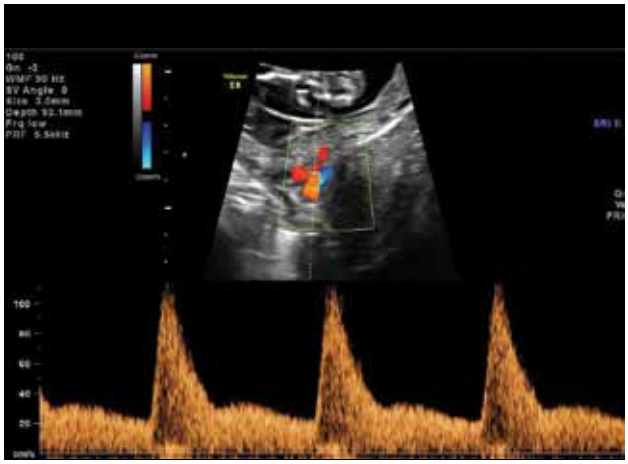

Figure 1a. *Transabdominal view of the uterine artery at 12 weeks of gestation.*

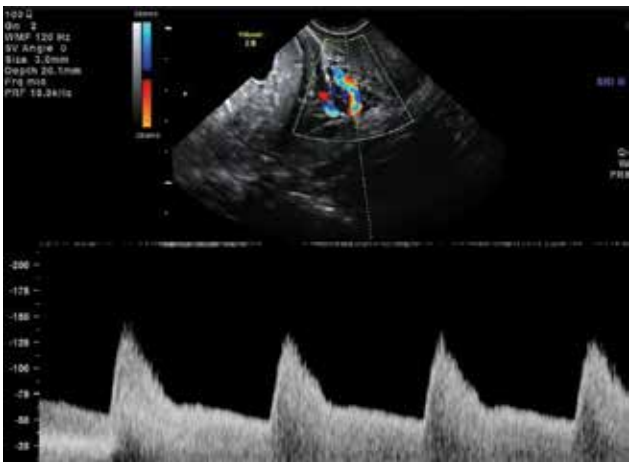

Figure 1b. *Transvaginal view of the uterine artery at 12 weeks of gestation.*

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

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. ■

REFERENCES

1. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, Khan KS, Aquilina J, Thangaratinam S. Uterine artery Doppler in the first trimester as a risk factor for adverse pregnancy outcomes: A meta-analysis involving 55,974 women. Ultrasound Obstet Gynecol 2014; 43: 500-507.
2. Pilalis A, Souka AP, Antsaklis P, Kavalakis I, Papantoniou N, Mesogitis S, Antsaklis A. Screening for pre-eclampsia and fetal growth restriction by uterine dopplers and PAPP-A at the 11-14 weeks ultrasound scan. Ultrasound Obstet Gynecol 2007; 29(2):135-40.
3. Audibert F, Boucoiran I, An N, Aleksandrov N, Delvin E, Bujold E, et al. Screening for preeclampsia using firsttrimester serum markers and uterine artery Doppler in nulliparous women. Am J Obstet Gynecol. 2010;203:383.e1–8.
4. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation Neil O'Gorman, MD; David Wright, PhD; Argyro Syngelaki, RM; Ranjit Akolekar, MD; Alan Wright, PhD; Leona C. Poon, MD; Kypros H. Nicolaides, MD. Am J Obstet Gynecol 2016 214:103.e1-12.
5. Scazzocchio E, Crovetto F, Triunfo S, Gratacos E, Figueras F. Validation of a first-trimester screening model for pre-eclampsia in an unselected population. Ultrasound Obstet Gynecol 2017; 49: 188–193.
6. Cheng YKY, Leung TY, Law LW, Ting YH, Law KM, Sahota DS. First trimester screening for pre-eclampsia in Chinese pregnancies: case-control study. BJOG 2018;125:442–449.
7. Sepúlveda-Martínez A, Rencoret G, Silva MC, Ahumada P, Pedraza D, Muñoz H, Valdés E, Parra-Cordero M. First trimester screening for preterm and term pre-eclampsia by maternal characteristics and biophysical markers in a low-risk population. J Obstet Gynaecol Res. 2019;45(1):104-112
8. Townsend R, Khalil A, Prekumar A, Allotey J, Snell KIE, Chan C, Chappell LC, Hooper R, Green M, Mol BW, Thilaganathan B, Thangratinam S, on behalf of the IPPIC Network. Prediction of pre-eclampsia: review of reviews. Ultrasound Obstet Gynecol 2019; 54: 16–27.
9. Bujold E, Morency AM, Roberge S, Lacasse Y, Forest JC, Gigue`re Y. Acetylsalicylic acid for the prevention of preeclampsia and intra-uterine growth restriction in women with abnormal uterine artery Doppler: a systematic review and meta-analysis. J Obstet Gynaecol Can. 2009;31:818–26.
10. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017 Jun 28. doi: 10.1056/NEJMoa1704559.
11. Park F, Russo K, Wiliams P, Pelosi M, Puddephatt R, Walter M, Leung C, Saaid R, Rawashdeh H, Ogle R, Hyett J. Prediction and prevention of early-onset pre-eclampsia: impact of aspirin after first-trimester screening. Ultrasound Obstet Gynecol 2015; 46: 419–423.
12. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Preeclampsia (PE): A Pragmatic Guide for First Trimester Screening and Prevention. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar , Divakar H, McAuliffe F, da Silva Costa F, von Dadelszen P, McIntyre HD, Kihara AB, Di Renzo GC, Romero R, D'Alton M, Berghella V, Nicolaides KH, Hod M. Int J Gynaecol Obstet. 2019 May ; 145 (Suppl 1): 1–33.
13. Khalil A, Nicolaides KH. How to record uterine artery Doppler in the first trimester. Ultrasound Obstet Gynecol 2013; 42: 478–479.
14. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, Martins WP, Odibo AO, Papageorghiou AT, Salomon LJ, Thilaganathan B. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol 2018. DOI: 10.1002/uog.20105.
15. Ridding G, Schluter PJ, Hyett JA, McLennan AC. Uterine artery pulsatility index assessment at 11-13 weeks' gestation. Fetal Diagn Ther. 2014;36(4):299-304.
16. Ferreira AE, Mauad Filho F, Abreu PS, Mauad FM, Araujo Junior E, Martins WP. Reproducibility of first- and second-trimester uterine artery pulsatility index measured by transvaginal and transabdominal ultrasound. Ultrasound Obstet Gynecol 2015; 46: 546–552.
17. Marchi L, Zwertbroek E, Snelder J, Kloosterman M, Bilardo CM. Intra- and inter-observer reproducibility and generalizability of first trimester uterine artery

pulsatility index by transabdominal and transvaginal ultrasound. Prenat Diagn. 2016; 36(13):1261-1269.
18. McGraw K, Wong S. Forming Inferences about some intraclass correlation coefficients. Psychological Methods 1996; 1(1):30-46.)
19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159 –74.
20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307 -310
21. Kottner J, Audigé L, Brorson S, Donner A, Gajewski BJ, Hróbjartsson A, Roberts C, Shoukri M, Streiner DL. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. J Clin Epidemiol. 2011;64(1):96-106.
22. Coelho Neto A, Roncato P, Nastri CO, Martins WP. True Reproducibility of UltraSound Techniques (TRUST): systematic review of reliability studies in obstetrics and gynecology Ultrasound Obstet Gynecol 2015; 46: 14–20.
23. Welsh A, Henry A. Reproducibility of Doppler evaluation: need to include physiological variation in determination of achievable ICCs, Correspondence to UOG. Ultrasound Obstet Gynecol 2015;46:128–29.
24. Martins WP, Nastri CO. Reply: examining the reproducibility of ultrasound techniques. Ultrasound Obstet Gynecol 2015;46:128–29.
25. Comparative study of transabdominal and transvaginal uterine artery Doppler pulsatility indices at 11-13 + 6 weeks. Hypertens Pregnancy. 2011;30:414-20.

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ORIGINAL ARTICLE

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

Makarios Eleftheriades[1], Christos Chatzakis[2], Konstatinos Dinas[2], Nikolaos Vlahos[1], Alexandros Sotiriadis[2]

[1]*Second Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece*

[2]*Second Department of Obstetrics and Gynecology, Faculty of Medicine, Aristotle University of Thessaloniki, Greece*

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

Corresponding author

Dr Alexandros Sotiriadis

92 Tsimiski Street, 54622 Thessaloniki, Greece

Telephone: +30 2310230283, E-mail: asotir@gmail.com

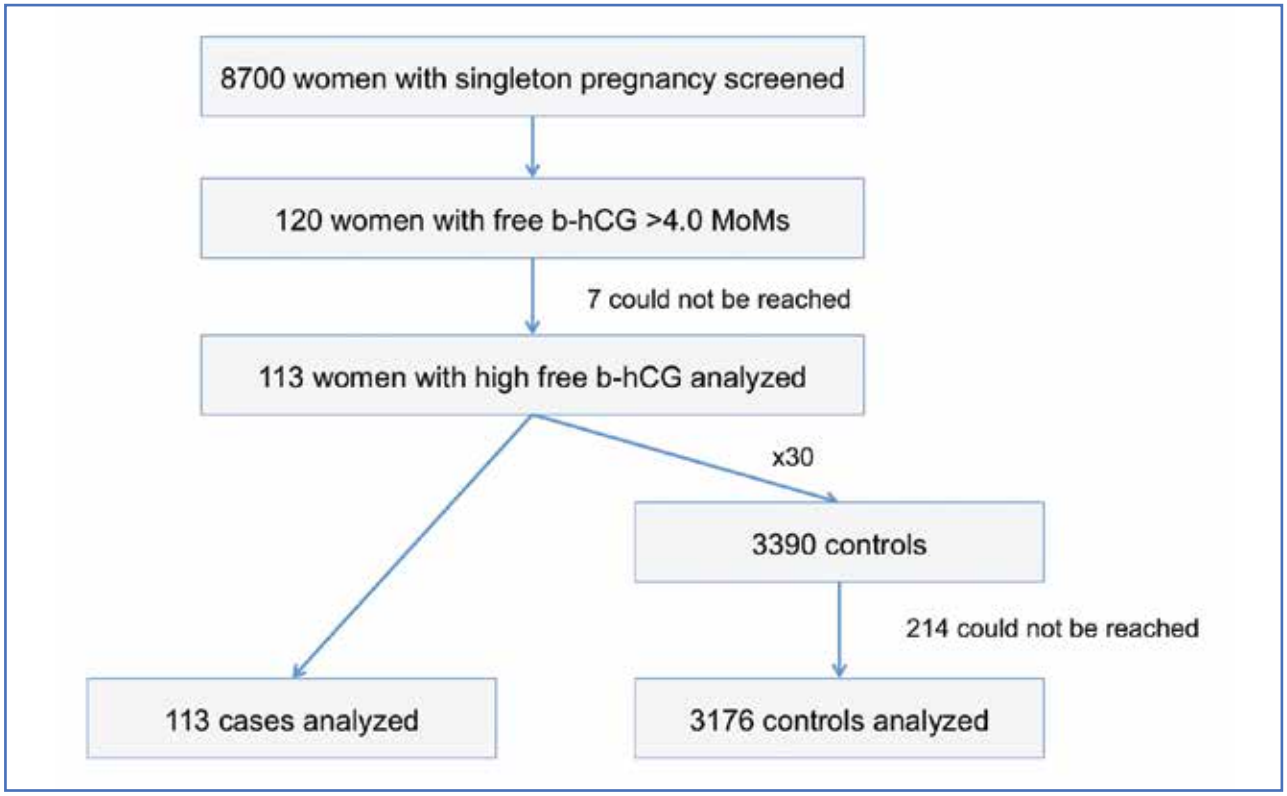

Figure 1. *Flow chart of participant selection*

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

REFERENCES

1. Spencer K, Souter V, Tul N, Snijders R, et al. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 1999;13:231-7.
2. Kagan KO, Wright D, Valencia C, Maiz N, et al. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free beta-hCG and pregnancy-associated plasma protein-A. Hum Reprod 2008;23:1968-75.
3. Spencer K, Liao AW, Skentou H, Cicero S, et al. Screening for triploidy by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn 2000;20:495-9.
4. Spencer K, Yu CK, Cowans NJ, Otigbah C, et al. Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with sec-

ond-trimester uterine artery Doppler. Prenat Diagn 2005;25:949-53.
5. Tul N, Pusenjak S, Osredkar J, et al. Predicting complications of pregnancy with first-trimester maternal serum free-betahCG, PAPP-A and inhibin-A. Prenat Diagn 2003;23:990-6.
6. Spencer K, Cowans NJ, Avgidou K, et al. First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of impending fetal death. Ultrasound Obstet Gynecol 2006;28:637-43.
7. Lepage N, Chitayat D, Kingdom J, et al. Association between second-trimester isolated high maternal serum maternal serum human chorionic gonadotropin levels and obstetric complications in singleton and twin pregnancies. Am J Obstet Gynecol 2003;188:1354-9.
8. Sharony R, Itzhaky D, Amiel A, et al. Adverse outcome of pregnancies with extremely high levels of maternal serum human chorionic gonadotropin. Fetal Diagn Ther 2008;23:233-6.
9. Kagan KO, Wright D, Spencer K, et al. First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics. Ultrasound Obstet Gynecol 2008;31:493-502.
10. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound Obstet Gynecol 1998;11:30-8.
11. Karahasanovic A, Sorensen S, Nilas L. First trimester pregnancy-associated plasma protein A and human chorionic gonadotropin-beta in early and late pre-eclampsia. Clin Chem Lab Med 2014;52:521-5.
12. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. Prenat Diagn 2008;28:7-10.
13. Mikat B, Zeller A, Scherag A, et al. betahCG and PAPP-A in first trimester: predictive factors for preeclampsia? Hypertens Pregnancy 2012;31:261-7.
14. Kuc S, Koster MP, Franx A, et al. Maternal characteristics, mean arterial pressure and serum markers in early prediction of preeclampsia. PLoS One 2013;8:e63546.
15. Poon LC, Nicolaides KH. First-trimester maternal factors and biomarker screening for preeclampsia. Prenat Diagn 2014;34:618-27.
16. Jelliffe-Pawlowski LL, Baer RJ, Currier RJ, et al. Early-Onset Severe Preeclampsia by First Trimester Pregnancy-Associated Plasma Protein A and Total Human Chorionic Gonadotropin. Am J Perinatol 2014.
17. Tavor O, Shohat M, Lipitz S. The relationship between perinatal outcome of singleton pregnancies and isolated highly elevated levels of maternal serum human chorionic gonadotropin at mid-gestation. Isr Med Assoc J 2007;9:509-12.
18. Kharfi A, Giguere Y, De Grandpre P, et al. Human chorionic gonadotropin (hCG) may be a marker of systemic oxidative stress in normotensive and preeclamptic term pregnancies. Clin Biochem 2005;38:717-21.
19. Kharfi Aris A, Leblanc S, Ouellet A, et al. Dual action of H2O2 on placental hCG secretion: implications for oxidative stress in preeclampsia. Clin Biochem 2007;40:94-7.
20. Chambers AE, Griffin C, Naif SA, et al. Quantitative ELISAs for serum soluble LHCGR and hCG-LHCGR complex: potential diagnostics in first trimester pregnancy screening for stillbirth, Down's syndrome, preterm delivery and preeclampsia. Reprod Biol Endocrinol 2012;10:113.
21. Brameld KJ, Dickinson JE, O'Leary P, et al. First trimester predictors of adverse pregnancy outcomes. Aust N Z J Obstet Gynaecol 2008;48:529-35.

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REVIEW ARTICLE

Neurofibromatosis type-1 and pregnancy: a review

Kalmantis Konstantinos[1], Karagiannopoulos Asimakis[1], Sifakis Stavros[2]
[1]Alexandra Hospital, Athens, Greece; [2]Mitera Maternity Hospital, Heraklion, Greece

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

Corresponding author and guarantor:
Sifakis Stavros, MD, PhD
Mitera Maternity Hospital, 71202
Heraklion, Crete, Greece, tel: +306932701813, email: stavros.sifakis@yahoo.com

[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.

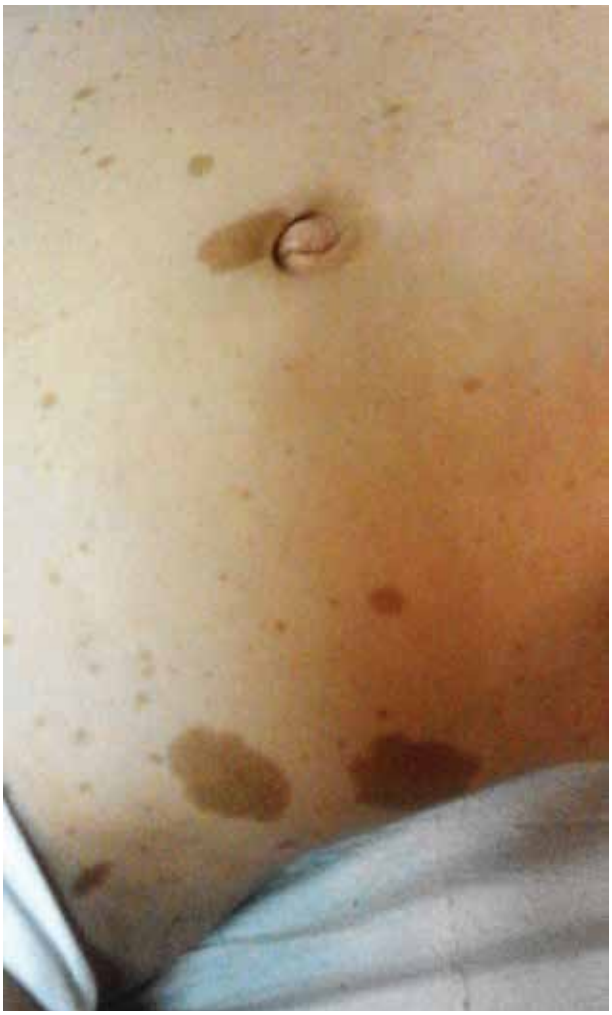

Fig 1. *Freckling and cafe au lait spots*

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. ■

REFERENCES

1. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. Am J Pathol 2011;178:1932–1939
2. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet 2007;44:81-88.
3. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Primers 2017;3:17004.
4. Anderson JL, Gutmann DH. Neurofibromatosis type 1. Handb Clin Neurol 2015;132:75-86.
5. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999;89:1–6.
6. Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 19899;26: 704–711.
7. McKeever K, Shepherd CW, Crawford H, Morrison PJ. An epidemiological, clinical and genetic survey of neurofibromatosis type 1 in children under sixteen years of age. Ulster Med J 1989;77:160–163.
8. Roth TM, Ramamurthy P, Muir D, et al. Influence of hormones and hormone metabolites on the growth of Schwann cells derived from embryonic stem cells and on tumor cell lines expressing variable levels of neurofibromin. Dev Dyn 2008; 237:513-524.
9. Kitano Y, Okamoto E, Saito K, Okano Y. Effects of several growth factors on cultured neurofibroma cells. J Dermatol Sci 1992;3:137-144.
10. Gashi AM, Gjocaj C, Ismajli J, Gojnovci X. JKIMSU 2018;7(1):82-85.
11. Dugoff L, Sujansky E. Neurofibromatosis Type 1 and Pregnancy. Am J Med Genet 1996;66:7-10.
12. Weissman A, Jakobi P, Zaidise I, Drugan A. Neurofibromatosis and pregnancy. An update. J Reprod Med 1993;38:890-896.
13. Terry AR, Barker FG, Leffert L, Bateman BT, Souter I, Plotkin SR. Neurofibromatosis type 1 and pregnancy complications, a population-based study. Am J Obstet Gynecol 2013;209:46.e1-8.
14. Sangwan N, Duhan N. Normal obstetric outcome in neurofibromatosis-1 complicating pregnancy. J Science 2008;20:197-198.
15. Yap YS, McPherson JR, Ong CK, et al. The NF1 gene revisited - from bench to bedside. Oncotarget 2014;5:5873-5892.
16. Theos A, Korf BR. Pathophysiology of neurofibromatosis type 1. Ann Intern Med 2006;144:842–849.
17. Mavani G, Kesar V, Devita M, Rosenstock J, Michelis M, Schwimmer J. Neurofibromatosis type 1-associated hypertension secondary to coarctation of the thoracic aorta. Clin Kidney J 2014;7:394-395.
18. Isakson SH, Rizzardi AE, Coutts AW, et al. Genetically engineered minipigs model the major clinical features of human neurofibromatosis type 1. Commun Biol 2018;1:158.
19. Ruggieri M, Huson SM. The neurofibromatoses. An overview. Ital J Neurol Sci 1999;20:89–108.
20. Zimmer A. Neurofibromatosis. Radiologe 2013;53:1077–1083.
21. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. J Am Acad Dermatol 2009;61:1–14.
22. Brems H, Beert E, de Ravel T, Legius E. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol 2009;10:508–515.
23. Evans DGR, Kallionpää RA, Clementi M, et al. Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study. Genet Med 2020;22:398–406.
24. Ansari AH, Nagamani M. Pregnancy and neurofibromatosis (von Recklinghausen's disease). Obstet Gynecol. 1976;47:25S-29S
25. Swapp GH, Main RA. Neurofibromatosis in pregnancy. Br J Dermatol 1973;80,431-435.
26. Jarvis GJ, Crompton AC. Neurofibromatosis in pregnancy. Br J Obstet Gynecol 1978;85:844-847.
27. Hadi HA. Clinical significance of neurofibromatosis in pregnancy. Am J Perinatol 1995;12:459-461.
28. Segal D, Holcberg G, Sapir O, Sheiner E, Mazor M, Katz M. Neurofibromatosis in pregnancy Maternal and perinatal outcome. Eur J Obstet Gynecol RB 1999;84:59–61.
29. Isikoglu M, Has R, Korkmaz D, Bebek N. Plexiform neurofibroma during and after pregnancy. Arch Gynecol Obstet 2002;267:41–42.
30. Posma E, Aalbers R, Kurniawan YS, van Essen AJ, Peeters PMJG, van Loon AJ. Neurofibromato-

sis type I and pregnancy: a fatal attraction? BJOG 2003;110:530-532.
31. Kosec V, Márton I. Neurofibromatosis Type 1 in Pregnancy. Coll Anthropol 2006;30:247–249.
32. Nelson D, Greer L, Wendel G. Neurofibromatosis and Pregnancy: A Report of Maternal Cardiopulmonary Compromise Obstet Gynecol 2010;116:507–509.
33. Islam S. Neurofibromatosis type 1 and pregnancy Arch Dis Child Fetal Neonatal Ed 2012;97:A70.
34. Cecchi R, Frati P, Capri O, Cipolloni L. A Rare Case of Sudden Death Due to Hypotension during Cesarean Section in a Woman Suffering from Pheochromocytoma and Neurofibromatosis. J Forensic Sci 2013;58:1636-1639.
35. Harshini V, Vidyashree JB, Renuka R. A pregnant woman with NF-1. EJBPS 2015:2:170-173.
36. Ramos-Zúñiga R, Saldaña-Koppel DA. Neurofibromatosis type 1 and pregnancy: The transformation of a nodular to cystic neurofibroma in the cervical region. Surg Neurol Int 2015;6:S487-489.
37. Jain K, Sharma M, Mangal H. Neurofibromatosis in pregnancy: study of 2 cases. Jain K et al. Int J Reprod Contracept Obstet Gynecol 2015;4:483-485.
38. Xiong M, Gilchrest BA, Obayan OK. Eruptive neurofibromas in pregnancy. JAAD 2015;1:23–24.
39. Dahiya S, Mukherjee S, Premi HK. Neurofibromatosis in Pregnancy. Int J Adv Integr Med Sci 2016;1:91-92.
40. Remon-Ruiz P, Aliaga-Verdugo A, Guerrero-Vazquez R. Pheochromocytoma in neurofibromatosis type 1 during pregnancy Gynecol Endocrinol 2017;33:93-95.
41. Leppävirta J, Kallionpää RA, Uusitalo E, et al. The pregnancy in neurofibromatosis 1: A retrospective register-based total population study. Am J Med Genet A. 2017;173:2641-2648.
42. Kalmantis K, Petsa A, Daskalakis G, et al. Neurofibromatosis-1 and pregnancy: Case report. HJOG 2018;17:35-40.
43. Well L, Jaeger A, Kehrer-Sawatzki H, et al. The effect of pregnancy on growth-dynamics of neurofibromas in Neurofibromatosis type 1. PLoS ONE 2020;15: e0232031.
44. Shapre JC, Yoting RH. von Recklinghausen's neorofibromatosis. Clinical manifestations in 31 cases. Arch Intern Med 1937;59:299.
45. Moritz HC, Snider E. von Recklinghausen's disease exacerbated during pregnancy: case report. Harper Hospital Bulletin 1962;20:79.
46. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using US death certificates. Am J Hum Genet 2001;68:1110-1118.
47. Zoller M, Rembeck B, Akesson HO, Angervall L. Life expectancy, mortality and prognostic factors in neurofibromatosis type 1. A twelve-year follow-up of an epidemiological study in Goteborg, Sweden. Acta Derm Venereol 1995;75:136-140.
48. Friedman JM, Arbiser J, Epstein JA, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. Genet Med 2002;4:105-11.
49. Rosser TL, Vezina G, Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 2005;64:553-555.
50. Ullrich NJ, Zimmerman M, Smith E, Irons M, Marcus K, Kieran MW. Association of rapidly progressive moyamoya syndrome with bevacizumab treatment for glioblastoma in a child with neurofibromatosis type 1. J Child Neurol 2011;26:228-230.
51. Oderich GS, Sullivan TM, Bower TC, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. J Vasc Surg 2007;46:475-484.
52. Lasater EA, Li F, Bessler WK, et al. Genetic and cellular evidence of vascular inflammation in neurofibromin-deficient mice and humans. J Clin Invest 2010;120:859-870.
53. Bajaj A, Li QF, Zheng Q, et al. Loss of NF1 expression in human endothelial cells promotes autonomous proliferation and altered vascular morphogenesis. PLoS One 2012;7:e49222.
54. Cesaretti C, Melloni G, Quagliarini D. Neurofibromatosis type 1 and pregnancy: maternal complications and attitudes about prenatal diagnosis. Am J Med Genet A 2013;161A:386–388.
55. Brickner SM. Fibroma molluscum gravidarum. A new clinical entity. Am J Obstet Gynaecol 1906;53:191.

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CASE REPORT

Prenatal Diagnosis of Atretic Parietal Cephalocele

Psarris Alexandros[1], Syndos Michael[1], Dimopoulou Stefania[1], Chlapoutaki Chrysanthi[2], Asimakopoulos George[1], Theodora Marianna[1], Antsaklis Panagiotis[1], Rodolakis Alexandros[1], Daskalakis George[1]

[1]1st Department of Obstetrics and Gynecology, "Alexandra" General Hospital, National and Kapodistrian University of Athens

[2]Iaso Maternity Hospital, Athens

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

Corresponding author

Psarris Alexandros MD MSc Phd

1st Department of Obstetrics and Gynecology, "Alexandra" General Hospital National and Kapodistrian University of Athens, Vasilissis Sofia 80 and Lourou Street, 11528 Athens, Greece, Tel: 0030 6979232977

E-mail: Psarris.alexandros@gmail.com

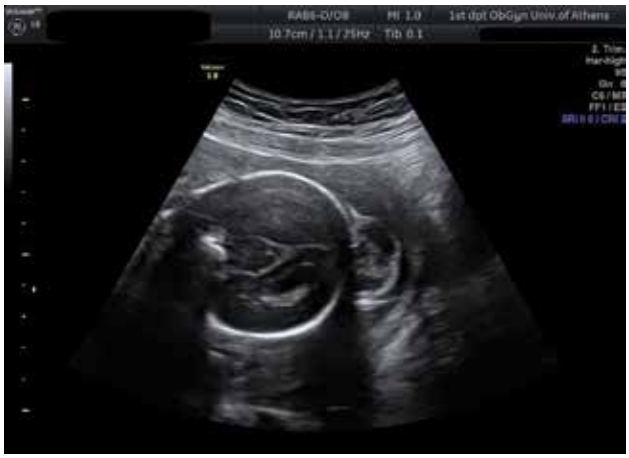

Figure 1

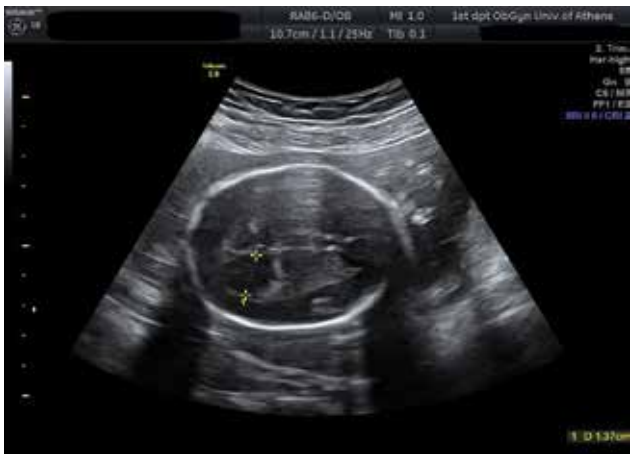

Figure 2

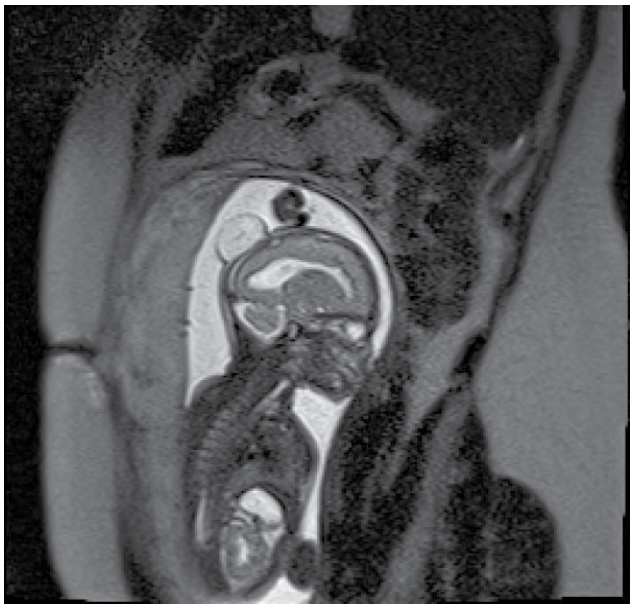

Figure 3

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.

REFERENCES

1. F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, et al. Williams Obstetrics [Internet]. 25e ed. McGraw-Hill Medical; [cited 2020 Oct 26]. Available from: https://accessmedicine.mhmedical.com/book.aspx?bookID=1918
2. Yokota A, Kajiwara H, Kohchi M, Fuwa I, Wada H. Parietal cephalocele: Clinical importance of its atretic form and associated malformations. J Neurosurg [Internet]. 1988 [cited 2020 Oct 26];69(4):545–51. Available from: https://pubmed.ncbi.nlm.nih.gov/3418387/
3. Lo BWY, Kulkarni A V., Rutka JT, Jea A, Drake JM, Lamberti-Pasculli M, et al. Clinical predictors of developmental outcome in patients with cephaloceles: Clinical article. J Neurosurg Pediatr [Internet]. 2008 Oct [cited 2020 Oct 26];2(4):254–7. Available from: https://pubmed.ncbi.nlm.nih.gov/18831658/
4. Baradaran N, Nejat F, Baradaran N, El Khashab M. Cephalocele: Report of 55 cases over 8 years. Pediatr Neurosurg [Internet]. 2010 Mar [cited 2020 Oct 26];45(6):461–6. Available from: https://pubmed.ncbi.nlm.nih.gov/20110760/
5. Martinez-Lage JF, Sola J, Casas C, Poza M, Almagro MJ, Girona DG. Atretic cephalocele: The tip of the iceberg. J Neurosurg [Internet]. 1992 [cited 2020 Sep 6];77(2):230–5. Available from: https://pubmed.ncbi.nlm.nih.gov/1625010/
6. Morioka T, Hashiguchi K, Samura K, Yoshida F, Miyagi Y, Yoshiura T, et al. Detailed anatomy of intracranial venous anomalies associated with atretic parietal cephaloceles revealed by high-resolution 3D-CISS and high-field T2-weighted reversed MR images. Child's Nerv Syst [Internet]. 2009 Mar [cited 2020 Oct 26];25(3):309–15. Available from: https://pubmed.ncbi.nlm.nih.gov/18839185/
7. Patterson RJ, Egelhoff JC, Crone KR, Ball WS. Atretic parietal cephaloceles revisited: an enlarging clinical and imaging spectrum? Am J Neuroradiol. 1998;19(4).
8. Azusawa H, Ozaki Y, Shindoh N, Sumi Y. Usefulness of MR venography in diagnosing sinus pericranii: case report. Radiat Med. 2000;18(4):249–52.
9. Budorick NE, Pretorius DH, McGahan JP, Grafe MR, James HE, Slivka J. Cephalocele detection in utero: sonographic and clinical features. Ultrasound Obstet Gynecol [Internet]. 1995 [cited 2020 Oct 26];5(2):77–85. Available from: https://pubmed.ncbi.nlm.nih.gov/7719871/
10. Heidi Lewis, Gerald F. Tuite, Ignacio Gonzalez-Gomez, Felice Baron, Richard B Towbin, Alexander J Towbin, et al. Atretic cephalocele: Prenatal and postnatal imaging features. Appl Radiol 2017;46(8)36-39 [Internet]. [cited 2020 Oct 26]; Available from: https://appliedradiology.com/articles/atretic-cephalocele-prenatal-and-postnatal-imaging-features.

CITATION

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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

Panagiotis Antsaklis, Thomas Economou, Alexandros Psarris, Marianna Theodora, Michael Syndos, George Daskalakis

1st Department of Obstetrics and Gynecology, "Alexandra" General Hospital, National and Kapodistrian University of Athens

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

Corresponding author

Psarris Alexandros MD MSc Phd, 1st Department of Obstetrics and Gynecology, "Alexandra" General Hospital National and Kapodistrian University of Athens, Vasilissis Sofia 80 and Lourou Street, 11528 Athens, Greece

Tel: 0030 6979232977, E-mail: Psarris.alexandros@gmail.com

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 investiga-

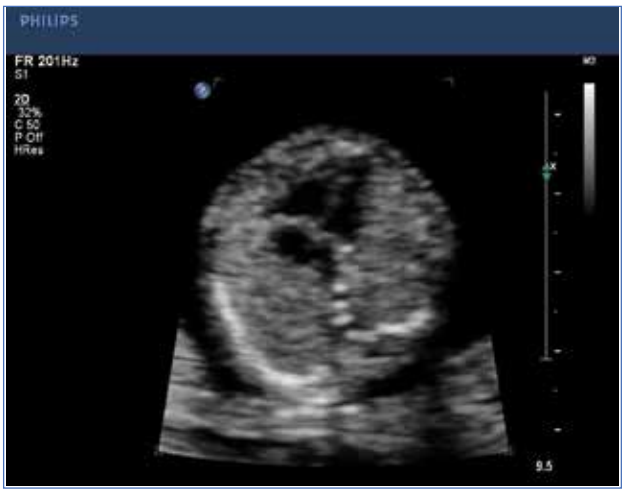

Figure 1. *Normal 4 chamber view of the fetal heart*

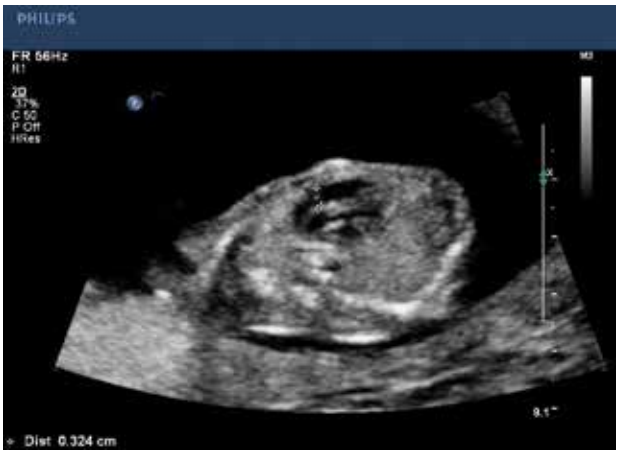

Figure 2. *The parallel course of the great arteries*

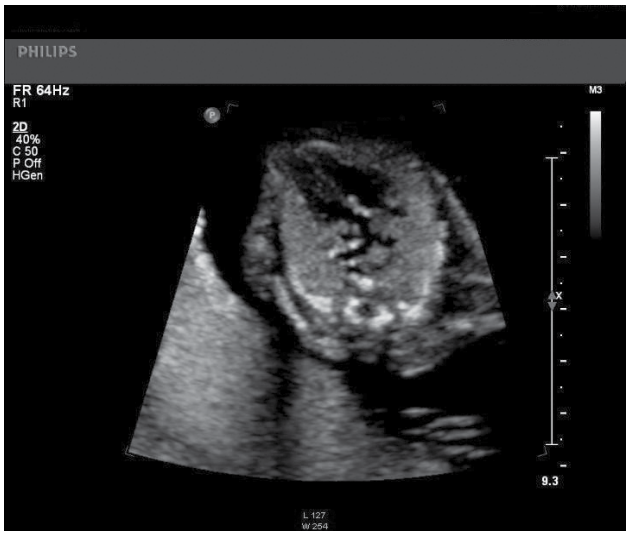

Figure 3. *The pulmonary artery coming out from the left ventricle*

tion 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.

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.

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.

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. ■

REFERENCES

1. Abuhamad A, Chaoui R. A practical guide to fetal echocardiography. Normal and abnormal hearts. 2nd edition. Chapter 20 pp 282-297
2. Martins P, Castela E. Transposition of the great arteries. Orphanet J Rare Dis. 2008 Oct 13;3:27
3. Bianca S, Ettore G. Sex ratio imbalance in transposition of the great arteries and possible agricultural environmental risk factors. Images Paediatr Cardiol. 2001;8:10–14.
4. Sampayo F, Pinto FF. The sex distribution of congenital cardiopathies. Acta Med Port. 1994;7:413.
5. Samánek M. Boy girl ratio in children born with different forms of cardiac malformation: a population-based study. Pediatr Cardiol. 1994;15:53–7.
6. Vorisek CN, Enzensberger C, Willomeit S, Kurkevych A, Stessig R, Ritgen J et al. Prenatal Diagnosis and Outcome of Congenital Corrected Transposition of the Great Arteries - A Multicenter Report of 69 Cases. Ultraschall Med. 2020 Jan 29. English. doi: 10.1055/a-1069-7698. Epub ahead of print. PMID: 31995816.
7. Bull C. Current and potential impact of fetal diagnosis on prevalence and spectrum of serious congenital heart disease at term in UK. Lancet 199; 354: 1242-7
8. Jaeggi ET, Sholler GF, Jones OD et al. Comparative analysis of pattern, management and outcome of pre- versus postnatally diagnosed major congenital heart disease: a population based study. Ultrasound Obstet Gynecol 2001; 17: 380-5
9. Garne E, Stoll C, Clementi M and the European Group. Evaluation of prenatal diagnosis of congenital heart diseases by ultrasound: experience from 20 European registries. Ultrasound Obstet Gynecol 2001; 17: 386-391
10. Garne E, Loane M, Dolk Het al. Prenatal diagnosis of severe structural congenital malformations in Europe. Ultrasound Obstet Gynecol 2005; 25: 6-11
11. Vinals F, Ascenzo R, Poblete P et al. Simple approach to prenatal diagnosis of transposition of great arteries. Ultrasound Obstet Gynecol 2006: 28: 22-5
12. Blyth M, Howe D, Gnanapragasam J et al. The hidden mortality of transposition of the great arteries and survival advantage provided by prenatal diagnosis. BJOG. 2008 Aug;115(9):1096-100
13. Khoshnood B, De Vigan C, Vodovar V et al. Trends in prenatal diagnosis, pregnancy termination, and perinatal mortality of newborns with congenital heart disease in France, 1983-2000: a population-based evaluation. Pediatrics. 2005 Jan;115(1):95-101
14. Becker R, Wegner RD. Detailed screening for fetal anomalies and cardiac defects at the 11-13-week scan. Ultrasound Obstet Gynecol. 2006 Jun;27(6):613-8
15. Atzei A, Gajewska K et al. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. Ultrasound Obstet Gynecol. 2005 Aug;26(2):154-7
16. Sairam S, Carvalho JS. Early fetal echocardiography and anomaly scan in fetuses with increased nuchal translucency. Early Hum Dev. 2012 May;88(5):269-72
17. Volpe P, De Robertis V, Campobasso G et al. Diagnosis of congenital heart disease by early and second-trimester fetal echocardiography. J Ultrasound Med. 2012 Apr;31(4):563-8.
18. Yagel S, Cohen SM, Messing B. First and early second trimester fetal heart screening. Curr Opin Obstet Gynecol. 2007 Apr;19(2):183-90.
19. Rustico MA, Benettoni A, D'Ottavio G et al. Early screening for fetal cardiac anomalies by transvaginal echocardiography in an unselected population: the role of op-

erator experience. Ultrasound Obstet Gynecol. 2000 Dec;16(7):614-9
20. Gonçalves LF, Espinoza J, Romero R et al. A systematic approach to prenatal diagnosis of transposition of the great arteries using 4-dimensional ultrasonography with spatiotemporal image correlation. J Ultrasound Med. 2004 Sep;23(9):1225-31
21. Fuchs IB, Muller H, Abdul-Khaliq H, Harder T, Dudenhausen JW, Henrich W. Immediate and long-term outcomes in children with prenatal diagnosis of selected isolated congenital heart defects. Ultrasound Obstet Gynecol 2007;29:38–43.
22. Mair DD, Ritter DG. Factors influencing intercirculatory mixing in patients with complete transposition of the great arteries. Am J Cardiol. 1972 Nov 8; 30(6):653-8.
23. Thanopoulos BD, Georgakopoulos D, Tsaousis GS, Simeunovic S. Percutaneous balloon dilatation of the atrial septum: immediate and midterm results. Heart. 1996 Dec; 76(6):502-6.
24. Losay J, Touchot A, Serraf A, Litvinova A, Lambert V, Piot JD et al. Late outcome after arterial switch operation for transposition of the great arteries. Circulation. 2001 Sep 18; 104(12 Suppl 1):I121-6.
25. Michailidis DW. OC15.05: impact of training in the prenatal recognition of major cardiac anomalies. Ultrasound Obstet Gynecol 2005;26:333–4.
26. Marino B. Patterns of congenital heart disease and associated cardiac anomalies in children with Down syndrome. In: Marino B, Pueschel SM. editors. Heart Disease in Persons with Down Syndrome. Baltimore, MD: Paul H Brookes Publishing; (1996). p. 133–40
27. Ferencz C, Brenner JI, Loffredo C, Kappetein AP, Wilson PD. Transposition of great arteries: etiologic distinctions of outflow tract defects in a case-control study of risk factors. In: Clark EB, Markwald RR, Takao A. editors. Developmental Mechanism of Heart Disease. Armonk, NY: Futura Publishing; (1995). p. 639–53
28. Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD. Genetic and environmental risk factors of major cardiovascular malformations: the Baltimore-Washington Infant Study 1981–89. In: Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD. editors. Perspectives in Pediatric Cardiology. Vol. 5 1st Edn. Armonk, NY: Futura Publishing Co. Inc. (1997). p. 867–8
29. Jiang ZY, Pircova A, Sekarski N, Hack I, Laurini R, Janzer R et al. Transposition of the great arteries, pulmonary atresia, and multiple ventricular septal defects associated with multiple cardiac rhabdomyomas in a case of tuberous sclerosis. Pediatr Cardiol. 2000 Mar-Apr; 21(2):165-9.
30. Jacobsen P, Hauge M, Henningsen K, Hobolth N, Mikkelsen M, Philip J. An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. A clinical, cytogenetical, and gene marker study. Hum Hered. 1973; 23(6):568-85.
31. Digilio MC, Marino B, Giannotti A, Di Donato R, Dallapiccola B. Heterotaxy with left atrial isomerism in a patient with deletion 18p. Am J Med Genet. 2000 Sep 18; 94(3):198-200.
32. Unolt M, Putotto C, Silvestri LM, et al. Transposition of great arteries: new insights into the pathogenesis. Front Pediatr. 2013;1:11. Published 2013 Jun 6. doi:10.3389/fped.2013.00011
33. Germanakis I, Sifakis S. The impact of fetal echocardiography on the prevalence of liveborn congenital heart disease. Pediatr Cardiol. 2006 Jul-Aug;27(4):465-72. doi: 10.1007/s00246-006-1291-6. Epub 2006 Jul 6. PMID: 16830077.

CITATION

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CASE REPORT

Evaluating Ductus Venosus absence by three-dimensional ultrasonography

Aikaterini Karavida[1], Apostolos Zavlanos[2], Ioannis Dimitrakopoulos[3], Vera Kelesidou[4], Apostolos Athanasiadis[4]

[1]*Prenatal Diagnostic Center, Thessaloniki, Greece*
[2]*Prenatal Diagnostic Center, Thessaloniki, Greece*
[3]*GE Healthcare , Thessaloniki, Greece*
[4]*3rd Department of Obstetrics & Gynecology, Aristotle University of Thessaloniki, Thessaloniki, Greece*

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

Corresponding author
Aikaterini Karavida
Obstetrician, Gynecologist, Prenatal Diagnostic Center, Ag. Sofias 15, 54623, Thessaloniki, Mob: +30 6974426318,
Email: aa.karavida@gmail.com

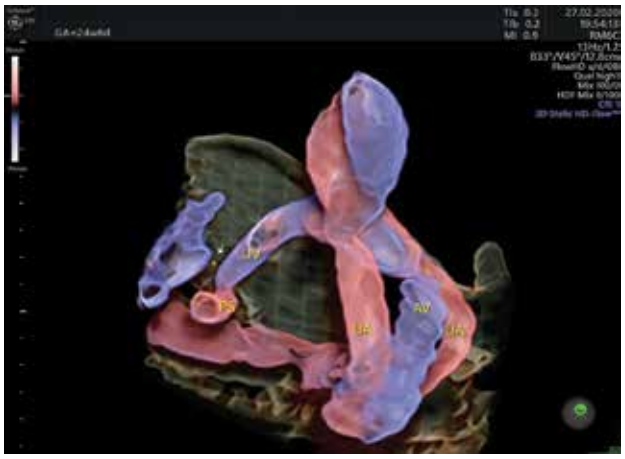

Figure 1: *Three-dimensional (3D) Doppler ultrasound image of ductus venosus (DV) absence at 24+6 weeks. The DV is absent (arrow *) and umbilical blood flow is diverted to the inferior vena cava by an aberrant vessel (AV). UV: umbilical vein, UA: umbilical artery, PS: portal system.*

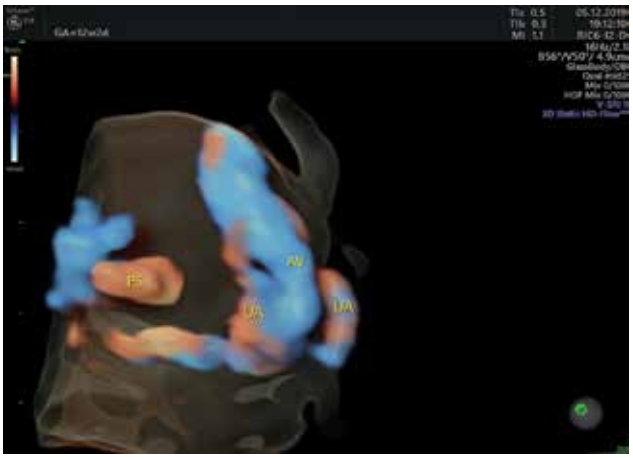

Figure 2: *Three-dimensional (3D) Doppler ultrasound image of ductus venosus (DV) absence at 12+2 weeks. Umbilical blood flow is diverted to the inferior vena cava by an aberrant vessel (AV). UA: umbilical artery, PS: portal system.*

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].

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. ■

REFERENCES

1. Pacheco D, Brandao O, Montenegro N, Matias A. Ductus venosus agenesis and fetal malformations: what can we expect? – a systematic review of the literature. J Perinat Med 2019; 47(1): 1-11
2. Athanasiadis A, Karavida A, Chondromatidou S, Tsitouridis J, Tarlatzis B. Prenatal diagnosis of Abernethy malformation by three-dimensional ultrasonography. Ultrasound Obstet Gynecol 2015; 46: 638–639
3. Morgan G, Superina R. Congenital absence of the portal vein: two cases and a proposed classification system for portosystemic vascular anomalies. J Pediatr Surg 1994; 29: 1239–1241.

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ORIGINAL ARTICLE

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

Ioannis Tsakiridis[1], Aikaterini Apostolopoulou[2], Efstathios Papaefstathiou[3], Menelaos Kyriakakis[1], Ioannis Kalogiannidis[1], Apostolos Mamopoulos[1], Themistoklis Dagklis[1*], Apostolos Athanasiadis[1]

[1]*3rd Department of Obstetrics and Gynaecology, School of Medicine, Aristotle University of Thessaloniki, Greece*

[2]*Laboratory of Hygiene, Social & Preventive Medicine and Medical Statistics, School of Medicine, Aristotle University of Thessaloniki, Greece*

[3]*2nd Department of Urology, School of Medicine, Aristotle University of Thessaloniki, Greece*

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

Corresponding author

Themistoklis Dagklis MD, PhD

Assistant Professor in Obstetrics and Gynecology

3rd Department of Obstetrics and Gynaecology, School of Medicine, Aristotle University of Thessaloniki

Tel and Fax: +30 2310 992150, e-mail: dagklis@auth.gr

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,

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**	

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).

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. ■

Conflict of interest
The authors declare no conflict of interest.

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no.

REFERENCES

1. Maxwell GL. Preterm premature rupture of membranes. Obstet Gynecol Surv. 1993;48(8):576-83.
2. Merenstein GB, Weisman LE. Premature rupture of the membranes: neonatal consequences. Semin Perinatol. 1996;20(5):375-80.
3. Douvas SG, Brewer MJ, McKay ML, et al. Treatment of premature rupture of the membranes. J Reprod Med. 1984;29(10):741-4.
4. Dagklis T, Tsakiridis I, Mamopoulos A, et al. Modifiable risk factors for spontaneous preterm birth in nulliparous women: a prospective study. J Perinat Med. 2020;48(2):96-101.
5. Tsakiridis I, Mamopoulos A, Chalkia-Prapa EM, et al. Preterm Premature Rupture of Membranes: A Review of 3 National Guidelines. Obstet Gynecol Surv. 2018;73(6):368-75.
6. Tsakiridis I, Mamopoulos A, Athanasiadis A, et al. Antenatal Corticosteroids and Magnesium Sulfate for Improved Preterm Neonatal Outcomes: A Review of Guidelines. Obstet Gynecol Surv. 2020;75(5):298-307.
7. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of the membranes: a systematic review. Obstet Gynecol. 2004;104(5 Pt 1):1051-7.
8. Weiner E, Barrett J, Zaltz A, et al. Amniotic fluid volume at presentation with early preterm prelabor rupture of membranes and association with severe neonatal respiratory morbidity. Ultrasound Obstet Gynecol. 2019;54(6):767-73.
9. Melamed N, Hadar E, Ben-Haroush A, et al. Factors affecting the duration of the latency period in preterm premature rupture of membranes. J Matern Fetal Neonatal Med. 2009;22(11):1051-6.
10. Kagan KO, Sonek J. How to measure cervical length. Ultrasound Obstet Gynecol. 2015;45(3):358-62.
11. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med. 1996;334(9):567-72.
12. Lee YJ, Kim SC, Joo JK, et al. Amniotic fluid index, single deepest pocket and transvaginal cervical length: Parameter of predictive delivery latency in preterm premature rupture of membranes. Taiwan J Obstet Gynecol. 2018;57(3):374-8.
13. Gire C, Faggianelli P, Nicaise C, et al. Ultrasonographic evaluation of cervical length in pregnancies complicated by preterm premature rupture of membranes. Ultrasound Obstet Gynecol. 2002;19(6):565-9.
14. Pergialiotis V, Bellos I, Fanaki M, et al. The impact of residual oligohydramnios following preterm premature rupture of membranes on adverse pregnancy outcomes: a meta-analysis. Am J Obstet Gynecol. 2020;222(6):628-30.
15. Lee J, Romero R, Kim SM, et al. A new anti-microbial combination prolongs the latency period, reduces acute histologic chorioamnionitis as well as funisitis, and improves neonatal outcomes in preterm PROM. J Matern Fetal Neonatal Med. 2016;29(5):707-20.
16. Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013(12):CD001058.

CITATION

Tsakiridis I, Apostolopoulou A, Papaefstathiou E, Kyriakakis M, Kalogiannidis I, Mamopoulos A, Dagklis T, Athanasiadis A. Sonographic predicting factors of latency interval in pregnancies complicated by preterm premature rupture of membranes. OGI 2021; 1(1): 60-65.

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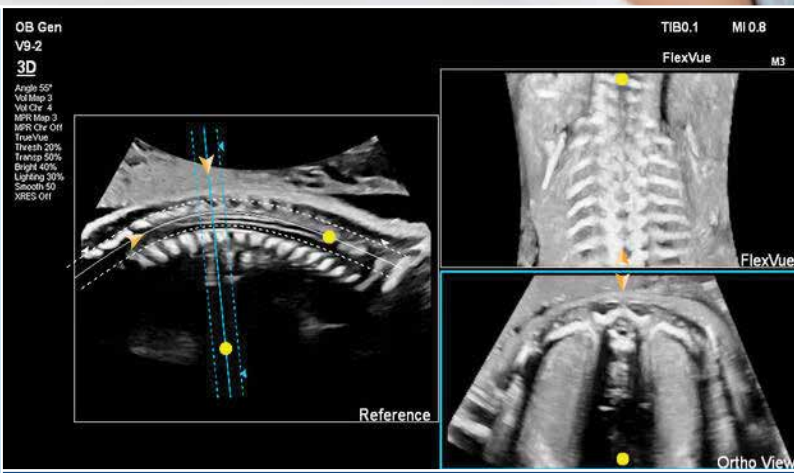

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