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Sessione 1: PARTO PRETERMINE

002 . PRETERM BIRTH: GENETIC AND NON GENETIC ASPECTS

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INTRODUZIONE
Globally, each year, an estimated 13 million infants are born before 37 completed weeks of gestation. Prematurity is the leading direct cause of early neonatal death, responsible for 27% or approximately 1 million annual neonatal deaths. Preterm birth (PTB) also increases the risk of dying from other causes. The proportion of deaths that are directly related to preterm birth is lower in low and middle-income Countries than in high-income Countries. However, other factors related to neonatal deaths, such as neonatal sepsis and birth asphyxia are often indirectly related to preterm birth. Overall, prematurity and its consequences contribute to an estimated 50% of neonatal deaths. Preterm birth also leads to significant neonatal morbidities. Compared with infants born at term, preterm infants have greater rates of temperature instability, respiratory distress, infections, apnea, hypoglycemia, seizures, jaundice, kernicterus, feeding difficulties, necrotizing enterocolitis, periventricular leukomalacia, and rehospitalizations. Mortality rates increase proportionally with decreasing gestational age (and hence decreasing birth weight) and are greatest among infants born at less than 32 weeks. Infants born from 32 to 36 weeks represent approximately 75% of all preterm births and the group of infants who make up the fastest-growing proportion of the preterm births in high-income Countries, with a 25% increase during 1990-2005. Although improvements in medical care have led to improved survival and long-term outcomes among moderately and extremely preterm babies in high-income Countries, these babies still account for the majority of deaths. The overall incidence of PTB is between 12-13% in the U.S. and between 5% and 10% in Europe; in Italy is around 6.2%. Premature babies are at risk of complications related to incomplete organ development or adaptation problems to extra-uterine life, and generally, they have a higher risk of mortality in the very first year of life than other term babies.
The duration of pregnancy and the moment of birth is mainly determined by the presence of a "placental clock" that is activated from the early stages of pregnancy and which involves the activation of a series of hormonal, inflammatory and apoptotic mechanisms, some already studied and others still to be investigated. These mechanisms can be regulated either by genetic factors such as single nucleotide polymorphisms (SNPs), often responsible for individual susceptibility to diseases, or by non-genetic factors such as ethnicity, maternal age, BMI (Body Mass Index) previous abortions or PTB or caesarean sections as well as lifestyle (type of job, physical activity and eating habits).
The studies conducted to date on the etiopathogenesis of PTB have focused on the molecular mechanisms, genetically determined, involved in the inflammation process, while still little attention has been paid to the involvement of apoptosis in the placental preterm birth.
Since placental apoptosis is one of the mechanisms responsible for the onset of labor and then the birth, the aim of this study was to determine whether certain SNPs of genes involved in placental-induced oxidative stress (TNFa, JNK, Mst3, caspase 3) and some non-genetic factors could trigger early and spontaneously that mechanism bringing to preterm delivery

MATERIALI E METODI
Pregnant women admitted as inpatients to the Department of S.C. of Obstetrics and Gynaecology of the Hospital Santa Maria della Misericordia, Perugia between 22 + 0 and 36 + 6 weeks of gestation for risk of PTB were enrolled as cases while pregnant women between 37 + 0 and 42 + 0 weeks were included as controls.
The risk of spontaneous PTB was defined based on the results of the following tests: fibronectin test, cervicometry and amnisure test.
Fibronectin test is based on identification of fetal fibronectin, a glycoprotein that acts as the glue between the maternal decidua and the amniotic membranes; its discovery in vaginal secretions, taken with a simple vaginal swab, from 22 +0 weeks is a sensitive marker of detachment of the amniotic membranes from the uterine wall, indicating a high risk of PTB. A negative test allows to exclude patients at risk. Cervicometry is used to measure the length of the cervix and is made by transvaginal ultrasound. The measurement of the cervix is important to identify cases that may progress to PTB. Furthermore, the transvaginal ultrasound permits to identify the change in external and the internal uterine orifice (funneling and dilation), the protrusion of the membranes and their detachment. Normally, the cervix measures between 35 and 45 mm and, if the measurement is less than 25 mm (taken as cutoff), there is an increased risk of PTB. Amnisure test is based on the identification of placental alpha 1-microglobulin (PAMG-1) a protein which is abundant in the amniotic fluid but nearly absent in the cervicovaginal fluid in the absence of rupture of the membranes. This protein is identified by the use of monoclonal antibodies and a positive test is indicative of rupture of fetal membranes and thus of increased PTB risk. Then, the group of cases will consist of pregnant women with positive test of fibronectin and / or cervical lenght equal or lower than 25 mm and / or positive Amnisure test.
Enrollment of both cases and the controls was performed according to the following inclusion criteria: single pregnancy and fetus apparently not malformed or genetically abnormal. Multiple pregnancies, fetal abnormalities and birth by cesarean section without labor were instead

considered exclusion criteria. A questionnaire was given to every recruited pregnant woman, their medical history was collected and after informed of the purposes of the study, an informed consent was required. It was subsequently performed a withdrawal of peripheral blood in EDTA tubes. The blood was centrifuged to recover the buffy coat stored at -80°C until the extraction of DNA. It was also performed placental tissue sampling by freezing it in liquid nitrogen within 10 minutes after delivery and then storing at -80°C until the extraction of DNA.
Genomic DNA, extracted by commercial kits either from nucleated blood cells present in the buffy coat or from placental tissue homogenates, was analyzed by Real Time PCR (7300 Sequence Detection System, Applied Biosystems).
SNPs are one of the most common genetic variation and are characterized by a point mutation in a pair of bases in a specific locus, usually consisting of 2 alleles (mutant and wild type), of which the frequency of the rare (mutant) is greater than 1%. An individual is considered to be homozygous when the polymorphism is present on both alleles (homozygous for the mutant allele) or in none of the two alleles (homozygous for the wild type allele); on the other hand, an individual is considered heterozygous when the polymorphism is present only on one allele. The PCR used to identify SNPs is based on the amplification of exact sequences of DNA recognized by specific primers and probes. These small regions of genomic DNA can be directly analyzed by the use of fluorescent molecules excited by a laser during the amplification reaction. The sequences of our interest, situated in the genes TNF alpha, JNK, Mst3 and Caspase 3, and in particular their respective SNPs were amplified with two allele-specific fluorescent probes, containing a different reporter dye at the 5' end (FAM for the mutant and VIC for the wild type) and a non-fluorescent quencher at the 3' end.
After the PCR reaction, the fluorescence signals were analyzed to determine the distribution of gene-specific polymorphisms (TNFa -rs180068318-rs1800629, JNK -rs7560, MST3-rs9517320 and CASP3-rs1049216) in the study population. The differences in the genotype frequencies between cases and controls and deviations of genotype frequencies observed from Hardy-Weinberg equilibrium, were calculated using the X2 test. The test of Mann-Whitney was used to evaluate differences between cases and controls with regard to the continuous variables (eg. maternal age, gestational age, BMI, weight of the newborn, placental weight). The results were expressed as the median of values. Data analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) release 20.0, August 2011 (SPSS Inc., Chicago, IL, USA)

RISULTATI

Among the 357 pregnant women enrolled in the study, 300 delivered at term (controls) and 57 preterm with labour (sPTB) (cases). Maternal age was 32 and 34 years for cases and controls, respectively. The gestational age at delivery for the case group was 33 weeks and for controls was 39 weeks. BMI and deltaBMI (difference between BMI at birth and at the beginning of pregnancy) were significantly lower ($p < 0.05$) in controls than in cases (25.2 kg/m2 vs. 26.7 kg/m2, and 3.5 vs. 4.8, respectively). In addition, the weight of the placenta and the baby were significantly lower ($p < 0.005$) in cases than in controls (475 vs 575 g and 2,430 g vs. 3,340, respectively).
Among non-genetic factors, smoking and eating habits were not related to sPTB. Information on maternal smoking and eating habits were based on self-declaration of pregnant women. Eating habits were then classified according to five criteria that characterize the Mediterranean diet: 1st - consumption ≥ 5 servings of fruits and vegetables a day; 2nd - consumption of ≥ 2 servings of fish per week; 3rd - use of olive oil for cooking and seasoning; 4th - consumption of ≤ 2 servings of red meat per week; 5th - consumption ≤ 2 cups of coffee a day. None of the enrolled pregnant women had a diet that met all five criteria simultaneously. In addition, 71.4% of pregnant women who delivered preterm not practiced any sport or physical activity, compared to 48.3% of controls ($p = 0.01$), confirming the correlation between the lack of sport or physical activity and sPTB .
It was also noted that in pregnant women who delivered at term were more frequent previous caesarean sections compared to the cases (16.4% vs. 3.6%, $p = 0.037$). Any significant difference was found between female fetuses and male fetuses respect to the possibility to deliver preterm and any correlation was found between neonatal pathologies at birth, such as neonatal breathing problems and bradycardia, and sPTB.
As regards the genetic components, all the SNPs analyzed in cases and in controls were in the Hardy –Weinberg equilibrium. The distribution of allele frequencies of each SNP in cases and controls are shown in Table 1. From these data, it was found that between the 5 SNPs studied, there was no association between genotype frequencies and sPTB nor in placental tissue or maternal blood

CONCLUSIONI

Our results confirm that sPTB is influenced by many factors, mainly of non-genetic nature.
Among non-genetic factors, obesity and high increase of maternal weight during pregnancy rise the risk of sPTB. This finding is in contrast with those of previous studies where it was demonstrated that obese pregnant women had lower risk of sPTB than normal weight woman since the first exhibited less uterine activity than the second.
Unlike demonstrated by other studies, smoking and eating habits are not correlated with sPTB. This finding could be explained for the smoke by a bias due to self-declaration of pregnant women often do not match reality, resulting in underestimation of the actual number of women who smoke during pregnancy. Rearding eating habits, since no pregnant woman has fully satisfied the criteria of the Mediterranean diet, probably, a significant protection for the risk of sPTB was not found. The fact that no pregnant woman followed a true Mediterranean diet reflects the current changes in diet oriented to increased consumption of foods rich in fat and sugar and a reduction of intake of fruits and vegetables.

In addition, it was confirmed the beneficial effect on the pregnancy of the sport and / or physical activity, which reduce the risk of sPTB,
Previous cesarean sections seems to reduce the risk of sPTB: the reason of this finding is unclear. On the other hand, obesity and high increase of maternal weight during pregnancy increase the risk of sPTB, probably due to a greater systemic inflammation and thus to oxidative stress, which consequently could induce apoptosis.
Moreover, neither fetal gender nor the studied neonatal pathologies at birth influence the risk of sPTB.
As regards the genetic component, none of the 5 SNPs studied was correlated to sPTB.
Finally, it was not possible to demonstrate the relationship between genetic and non-genetic factors in the etiology of sPTB.
These latest findings may depend on the number of pregnant women enrolled in the study, that despite substantial, may still be scarce for a study on the SNPs, characterized by frequency distribution in the general population very low.
Therefore, further studies should be conducted by increasing the number of samples to be analyzed in order to better evaluate the interference of genetic and non-genetic components in the etiopathogenesis of sPTB

021 . POSSIBILI APPLICAZIONI TRASLAZIONALI DELLA METABOLOMICA NELLA DIAGNOSI NON INVASIVA DI TRAVAGLIO A TERMINE E PRETERMINE

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INTRODUZIONE
La metabolomica appartiene alla classe delle scienze cosiddette scienze "omiche"insieme alla mRNA-trascrittomica, genomica e proteomica. Attraverso essa è possibile studiare la complessità metabolica delle cellule, dei tessuti, come anche di interi organismi , valutando in tal modo il prodotto finale del metabolismo ed ottenendo il fenotipo metabolico del singolo individuo.
Durante la gravidanza l'indagine "omica" può contribuire all'identificazione di molecole chiave in condizioni fisiologiche, quali il travaglio a termine, ma anche di alcune patologie della gravidanza come la rottura prematura delle membrane, pretermine e non, ed il parto pretermine. Diversi studi hanno mostrato le capacità della metabolomica nel definire i profili metabolici di condizioni sia di fisiologia che di patologia, grazie allo studio di diversi fluidi biologici, ottenibili dalla quasi totalità dell'organismo umano,mediante tecniche quali la H-NMR e la GCMS, che spaziano dal sangue, al plasma, alle urine, alle feci e perfino al liquor ed al liquido amniotico. Soprattutto quest'ultimo ha dato, nello studio del parto pretemine, interessanti risultati.
Riteniamo che questa sia la scienza più adatta a delineare un quadro metabolico della gravidanza fisiologica e a rischio e ad individuare, in futuro, strumenti diagnostici di tipo non invasivo in condizioni cliniche quali il travaglio spontaneo a membrane integre e rotte ed il travaglio pretermine.
Nel nostro studio abbiamo scelto di analizzare l'urina giacché ottenibile in maniera non invasiva e in volumi più ampi e più accettata dalle pazienti.
Obiettivo L'applicazione dell'analisi metabolomica sulle urine di donne in gravidanza a basso rischio, per ampliare la conoscenza riguardo alle vie metaboliche che si modificano tra fasi di quiescenza a termine (in fase pre-travaglio) e in travaglio di parto a termine (Fase 1).Successiva inclusione nello studio di pazienti in regime di ricovero per PROM, (FASE 2) e PPROM, (FASE 3)

MATERIALI E METODI
Sono state reclutate per il nostro studio gestanti afferenti alla clinica Ostetrica-Ginecologica dell'AOU di Cagliari. Ciascun reclutamento è stato preceduto da una fase di colloquio informativo della donna e dalla sottoscrizione da parte della stessa di un consenso scritto, previa approvazione dal Comitato Etico locale.
FASE 1: Abbiamo reclutato un campione di 59 donne fuori travaglio in gravidanza a basso rischio, (donne con gravidanza a termine EG >37, assenza di patologia materna o fetale al reclutamento, feto singolo in presentazione cefalica), e le abbiamo seguite sino a termine gravidanza in modo da poter raccogliere dei campioni seriati di urine in cui analizzare i diversi metaboliti.
Per ciascuna donna è stata compilata una scheda di raccolta dati di tipo anagrafico ed anamnestico, nonché di una serie di informazioni cliniche rilevate sia durante le visite fuori travaglio della paziente (visita ostetrica o monitoraggio a termine) che durante il periodo di degenza per l'espletamento del parto.
A questo momento ha fatto seguito la raccolta del campione biologico (campione di urina) in urobox conservato immediatamente a -20° e successivamente, nell'arco di tempo delle 24H, aliquotato in provette da 3ml e riposto in freezer a – 80°. Un codice alfanumerico (AOU + num progressivo) è stato assegnato a ciascun campione, identificandone così le caratteristiche (dati paziente, data e orario).
35 campioni sono stati raccolti durante visite di routine a termine di gravidanza mentre i restanti 24 durante il travaglio di parto in fase attiva (dilatazione della bocca uterina di 3-4 cm e attività contrattile uterina regolare e dolorosa) la cui diagnosi è stata confermata in maniera retrospettiva.
I campioni sono stati inizialmente scongelati portandoli a temperatura ambiente, centrifugati a 12000 rpm per 10 minuti a 4° C. Successivamente sono stati analizzati con due tecniche: la 1H-NMR e la GC/MS.
FASE 2: Abbiamo reclutato un campione di 11 donne in regime di ricovero per PROM, abbiamo raccolto e analizzato n°52 campioni di urine di cui il primo raccolto prima della rottura delle membrane ed i seguenti al momento o successivamente alla diagnosi di PROM. Per ciascuna donna è stata compilata apposita scheda di raccolta dati, i campioni raccolti in urobox sono stati conservati immediatamente a -20° e successivamente, nell'arco di tempo delle 24H,aliquotati in provette da 3ml e conservati in freezer a – 80°. Un codice alfanumerico (AOU + num progressivo) è stato assegnato a ciascun campione, identificandone così le caratteristiche (dati paziente, data e orario). I campioni sono stati scongelati, portati a temperatura ambiente, centrifugati per rendere il campione omogeneo ed analizzati con tecnica GC/MS.
FASE 3: Attualmente stiamo reclutando e raccogliendo campioni seriati di pazienti in regime di ricovero per PPROM

RISULTATI

FASE 1:L'indagine NMR ha mostrato, quali metaboliti maggiormente rappresentativi del travaglio attivo, in ordine decrescente per importanza, la glicina, l'acido lattico, l'acido 3 idrossibuttirrico, l'acido acetoacetico, l'acetone ed il glucosio.
Alla GC/MS i metaboliti discriminanti il travaglio attivo sono risultati: la glicina, gli acidi 2,3,4 triidrossibutirrici, l'acido succinico, l'acido aconitico, l'acido D-gluconico, il D-galattosio, la N acetilglucosamina ed il mio inositolo.
Considerati nell'insieme questi metaboliti definiscono, sui campioni esaminati, l'impronta metabolica del travaglio di parto differenziandolo in maniera significativa dalla gravidanza quiescente a termine.
FASE 2: Attraverso l'analisi GC/MS dei campioni è stato possibile definire un'impronta metabolica preliminare dei casi di PROM. La PLS-DA ha mostrato infatti due classi di metaboliti che differiscono nelle donne con MAC integre rispetto a quelle con rottura prematura delle membrane, in travaglio e fuori travaglio. Utilizzando la piattaforma web METABO ANALYST abbiamo potuto identificare 5 vie metaboliche significative della PROM: 1) la biosintesi di Aminoacil-tRNA, 2) il ciclo del Citrato, 3) il metabolismo del Nitrogeno, 4) il metabolismo dell'Alanina, dell'Aspartato e del Glutammato e 5) il metabolismo di D-Glutammina e D-Glutammato

CONCLUSIONI

Avvalendosi delle tecniche 1H-NMR e GC/MS l'analisi dei campioni fuori travaglio vs travaglio ha mostrato due differenti cluster di metaboliti a riprova del diverso metabolismo nelle due fasi e della possibilità, in futuro, di ottenere un test diagnostico di travaglio di parto da affiancare alla clinica a cui, ad oggi, è ancora affidata in toto tale diagnosi . Questo porterebbe ad una diagnosi di travaglio di tipo prospettico e non più retrospettiva quale quella odierna, riducendo, se non eliminando del tutto, i ricoveri per falso travaglio. Questi sono ancora oggi causa di costi in termini economici per il SSN e di sfiducia per la paziente verso se stessa ed il personale medico/ostetrico che si vede spesso perciò "costretto"ad intervenire al fine di accelerare un processo che, forse, fisiologicamente non sarebbe dovuto verificarsi in quel dato momento.
Confortati dai dati positivi da noi ottenuti sui campioni delle donne in gravidanza a basso rischio e supportati da dati della letteratura, [3], abbiamo ritenuto importante estendere il nostro studio ai casi di rottura prematura delle membrane e compararli a quelli già raccolti in precedenza.
La scelta è stata dettata sia dalla frequenza con cui tale evento patologico si verifica (10% di tutte le gravidanze, nel 20-40% si verifica pretermine ovvero prima delle 37 settimane) ma soprattutto per l'importanza rivestita da tale condizione nel parto pretermine (40% dei casi), sindrome che rappresenta la più importante causa di mortalità e morbilità perinatale.
Ancora oggi l'eziopatogenesi del parto pretermine non è ben definita, dipende difatti dall'intersecarsi di differenti modificazioni biologiche, cellulari, ormonali, molecolari che portano alla prematura attivazione dei processi che preludono al travaglio di parto (maturazione cervicale, attivazione miometriale e rottura prematura delle membrane.) e anche la diagnosi clinica non è certo scevra da difficoltà. Poter disporre di uno spettro metabolico sui campioni provenienti da gravidanze con PPROM, quale analogamente a quello da noi ottenuto sui campioni di urine di donne con PROM , a cui rifarsi potrebbe consentire, in futuro, di ottenere, in caso di PPROM, un test prognostico per il parto pretermine e le complicanze ad esso associate

034 . FATTORI NUTRIZIONALI ED EPIGENETICI ASSOCIATI AD UNA RIDOTTA CRESCITA POST-NATALE DELLA CIRCONFERENZA CRANICA IN NEONATI VLBW

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INTRODUZIONE
Una restrizione di crescita della circonferenza cranica (HC) alla dimissione rappresenta un evento frequente nel neonato pretermine VLBW e correla con un peggior outcome neurocognitivo a distanza (1). Adeguati apporti nutrizionali sembrano necessari oltre che per un normale accrescimento somatico anche per un normale sviluppo neurocognitivo. Inoltre, i meccanismi che sottendono la relazione tra condizioni critiche embrio-fetali, basso peso alla nascita, crescita post-natale e patologie cronico-degenerative dell'adulto sembrano legati a fenomeni epigenetici

MATERIALI E METODI
Nell'ambito di uno studio retrospettivo su 75 neonati VLBW con EG ≤ 32 settimane, abbiamo analizzato alcuni fattori di rischio pre- e post-natali per lo sviluppo di una restrizione di crescita della HC alla dimissione. In particolare, per quanto riguarda gli aspetti epigenetici abbiamo analizzato (alla nascita ed alla dimissione), su un piccolo campione della nostra popolazione (n=10) il grado di metilazione del DNA nella regione 15 del braccio corto del cromosoma 11 (11p15), la quale contiene un cluster di geni soggetti ad imprinting con un importante ruolo nella regolazione della crescita. Questo cluster è regolato da un centro di imprinting che presenta una struttura bipartita, caratterizzata da due indipendenti imprinting control region (ICR) (IC1 e IC2) che coordinano l'espressione di due diversi "pacchetti" di geni: IC1 regola l'espressione di H19 e IGF2 (in particolare quest'ultimo ha una funzione di stimolo sulla crescita), mentre IC2 coordina i geni KCNQ10T1, KCNQ1, CDKN1C e PHLDA2 (questi ultimi tre geni sono considerati "growth inhibitors").
La restrizione di crescita è stata definita come il riscontro di valori di HC <10° percentile rispetto alla crescita intra-uterina attesa, valutata al momento della dimissione, ad un'età post-mestruale (EPM) tra le 36 e le 42 settimane, utilizzando come riferimento le carte antropometriche di Bertino (2)

RISULTATI
Tra i fattori prenatali la nascita SGA rappresenta un fattore di rischio per tale complicanza (OR 4,86 - p=0,014). La valutazione del peso tramite lo z score a 36 settimane EPM evidenzia una forte associazione con lo sviluppo di restrizione di crescita post-natale per HC: in particolare maggiore è il valore di z score minore è il rischio di essere EUGRhc (OR 0,15 - p=0,001). L'analisi dei singoli apporti nutrizionali medi nella prima settimana di vita evidenzia come l'apporto proteico giochi un ruolo chiave nello sviluppo di restrizione della crescita, in particolare i neonati EUGRhc (n=19) avevano ricevuto apporti proteici significativamente inferiori rispetto ai neonati che non presentavano tale restrizione di crescita (n=56) (p=0,009). Un'alimentazione esclusiva con latte umano è associata ad un peggior accrescimento della HC rispetto ai neonati che abbiano assunto una formula specifica per pretermine o comunque un allattamento di tipo misto (OR 3,61 - p=0,023). Inoltre, valori di TSH più elevati alla dimissione rappresentano un fattore di rischio per lo sviluppo di EUGRhc, (OR 1,33 - p=0,031).
Per quanto riguarda gli aspetti epigenetici, in accordo con la letteratura, il nostro studio ha riscontrato una correlazione inversa tra la metilazione delle ICR e la crescita della circonferenza cranica, che quindi si conferma essere marker più sensibile, rispetto al peso, del fetal programming. I neonati che presentavano alla dimissione l'ipermetilazione in IC1 risultavano essere gli stessi che presentavano una restrizione di crescita della circonferenza cranica ed un ridotto apporto proteico

CONCLUSIONI
Un costante monitoraggio della gravidanza per ridurre l'incidenza della nascita SGA ed una corretta gestione del neonato pretermine durante la degenza in TIN con l'attenta valutazione di possibili fattori di rischio sono necessari per ridurre il fenomeno della restrizione di crescita postnatale. I meccanismi che sottendono lo sviluppo e la crescita neonatale sono ancora in larga parte sconosciuti, ma le recenti acquisizioni nel campo dell'epigenetica sembrano conferire loro un fondamento molecolare, correlando modificazioni ambientali occorse in periodi critici, embrio-fetale e neonatale, a cambiamenti nel fenotipo dell'individuo

062 . IS A WOOLEN CAP EFFECTIVE IN MAINTAINING NORMOTHERMIA IN PRETERM INFANTS DURING KANGAROO CARE IN LOW-INCOME COUNTRIES?

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INTRODUZIONE
The days and weeks following childbirth – the postnatal period – is a critical phase in the lives of mothers and newborn babies. Most maternal and infant deaths occur during this time.1
In this period, neonatal hypothermia is an important challenge associated with morbidity and mortality.2 Hypothermia increases the newborn's metabolic requirements and is associated with hypoglycemia, hypoxia, and ultimately severe infections and newborn mortality.3 Preventing neonatal hypothermia is important in high resource countries, but is of fundamental importance in low resource settings where supportive care is limited. For the postnatal care of the newborn, the World Health Organization (WHO) guidelines state: "Appropriate clothing of the baby for ambient temperature is recommended. This means one to two layers of clothes more than adults, and use of hats/caps." Whenever possible, KC is also strongly recommended for temperature maintenance.4
Previous studies show that neonatal heat loss following delivery may be reduced or prevented by the application of simple woolen hats. 5-7 On the other hand, also hyperthermia should be avoided.8
Although WHO guidelines recommend the use of cap/hat during KC, the effect of the cap on neonatal temperature during the days and weeks following childbirth has not been previously studied. It's unknown whether covering the head of the neonate with a wool cap during KC may help temperature maintenance. The results of the present study will allow to understand whether the use of a cap during KC will be effective and safe.
The aim of the present study will be to assess the effectiveness and the safety of a woolen cap in maintaining normothermia in low birth weight infants (LBWI) during KC

MATERIALI E METODI
This is a multi-center, prospective, unblinded, randomized clinical trial of KC treatment with and without a woolen cap in LBWI that will be run through a collaboration of the Department of Women and Children Health, University of Padua and Doctors with Africa CUAMM, a non-governmental-organization that works to strengthen healthcare services in Africa.
The study will be conducted in three hospitals that have different levels of healthcare in three African countries and three different attitude to Kangaroo Care (well established, medially established and not established yet) where Doctors with Africa CUAMM has ongoing projects on maternal-neonatal health. They are:
- the Central Hospital of Beira in Mozambique, which is a governmental hospital (III level) ;
- the St. Luke Wolisso Hospital in Ethiopia, which is a not-for-profit zonal hospital (II level);
- the Aber Hospital in Uganda, which is a not-for-profit rural hospital (I level).

Inclusion criteria for the study are:
1. birth weight <2500 g (and)
2. candidate to KC treatment (and)
3. parental consent; a written informed consent will be obtained by a member of the neonatal team involved in the study from a parent or guardian before KC treatment.

While twins, patients with major congenital malformations, or babies with parental refusal to participate to the study, will be excluded.
The study will enroll a total number of 400 patients who will be randomly assigned to KC + cap or KC group without cap in a 1:1 ratio according to a computer-generated, randomized sequence. The primary outcome measure will be the time spent by the neonate in the normal temperature range (36.5-37.5°C) in course of KC during the first week of life. In all participants, axillary temperature will be measured with a

digital thermometer 4 times per day. For each patients will also be estimated the number of hours spent in KC. Secondary variables will be: number of episodes of apnea, sepsis, mortality before hospital discharge, in-hospital growth and age at discharge

RISULTATI
In this trial, we expect to assess the efficacy and the safety of using a woolen cap during KC treatment.
We also expect to detect differential effect of using woolen caps stratified for the number of hours spent in KC by patients

CONCLUSIONI
There are unique features of this trial compared to prior studies on KC. World Health Organization guidelines recommend the use of a cap during KC treatment, but evidence for this practice is still lacking

Sessione 2: ASFISSIA PERINATALE

003 . CONTINGENT VERSUS ROUTINE THIRD-TRIMESTER SCREENING FOR LATE FETAL GROWTH RESTRICTION

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INTRODUZIONE
Annually ~400,000 pregnancies in the Europe alone can be complicated by fetal growth restriction (FGR). However, antenatal detection falls short in clinical practice, failing to recognize up to 75% of babies at risk of FGR before delivery1. Such poor performance takes a toll in terms of perinatal health, given that small babies who are overlooked have higher risks of adverse perinatal outcomes and stillbirth.2,3
There are several baseline risk factors that should raise suspicion of FGR.4 Nevertheless, the performance of these factors is poor, with detection rates (DRs) of 50% and 20% for early- and late-onset FGR, respectively.5 Uterine Doppler (to assess trophoblastic invasion) has been proposed as a screening tool, yielding DRs of about 25% and 75% at first and second trimesters, respectively.6,7 By combining uterine Doppler findings and baseline maternal characteristics, DRs for early-onset FGR reach clinically acceptable levels.5,8 Unfortunately, FGR developing late in pregnancy is still largely undetected9-12, although representing the largest fraction of adverse perinatal outcomes and stillbirths.10
Current growth screening strategies involve measuring the symphysis fundal height, but less than 25% of small-for-gestational-age infants will be detected using this methodology in a low-risk population.13 Routine third trimester scan for fetal growth assessment, in place in many countries, has DRs ranging from 50% to 80%,2,11 but the beneficial impact on perinatal outcome is also unclear. Eight trials have been included in a recently updated meta-analysis12 concluding that routine late pregnancy ultrasound (US) in low-risk or unselected populations does not confer benefit on mother or baby, cost issues aside. Furthermore, serial third trimester US have not been demonstrated to improve this performance.14,15
Because there is no evidence to support a routine third trimester US, it seems reasonable to select subgroups of women who are at the highest risk, for whom third-trimester growth assessment may be both effective and efficient.
The aim of this study was to evaluate the performance of third-trimester US done on a contingency basis (according to risk accrued at second trimester) in an unselected population, as a means of predicting late FGR

MATERIALI E METODI
Study population
Between January, 2010 and December, 2012, a prospective cohort of consecutive singleton pregnancies was recruited, each referred to the Department of Maternal-Fetal Medicine in the Hospital Clinic of Barcelona for routine first-trimester screening of aneuploidies (8+0 to 13+6 weeks of gestation). Calculated gestational age was based on crown-rump length at first-trimester scan.16 Any pregnancies with aneuploidies or major fetal abnormalities, and those involving termination, miscarriage or fetal death, suspected FGR (estimated fetal weight1715% were considered relevant. For type I error rate of 5% and target power of 90%, required instances of FGR was 65 (for 0.2 correlation rank coefficient). Assuming a 5% prevalence of FGR, a maximum total sample size of 1300 was estimated.19 Because a validation cohort was designed of the same size than the construction cohort, the final sample size was set at 2600.
Outcome measures and clinical management
FGR was defined as birth weight <3rd percentile by local standards18; or birth weight between 3rd and 10th percentiles with prenatal abnormalities of cerebroplacental ratio (95th percentile).21 In pregnancies complicated by FGR a specific clinic protocol was applied.22
To define preeclampsia, guidelines of the International Society for the Study of Hypertension in Pregnancy23 were applied.
All women underwent continuous fetal monitoring during labour, using a three-tiered classification for heart tracings.24 Non-reassuring fetal status during labour was defined as a pathological fetal heart rate23 or a suspicious tracing with a fetal blood scalp sampling below 7.15 or below 7.20 in two sample 30-minute apart.
Neonatal metabolic acidosis at birth was defined as umbilical arterial pH 90th percentile (12 mEq/L).25
Predictive variables
1. Maternal characteristics
Data on maternal characteristics, including age, ethnicity, low socioeconomic status (routine occupation, long-term unemployment, or never worked), body mass index (BMI), nulliparity (no prior deliveries after 22 weeks of gestation), smoking status, method of conception (spontaneous or assisted reproductive technique [ART] including ovulation induction, in vitro fertilization and oocyte donation), medical

history (known chronic disease, such as hypertension, diabetes mellitus, renal disease, autoimmune disorder, and congenital or acquired thrombophilic conditions), and obstetric history (including prior pregnancy complicated by stillbirth, FGR and preeclampsia) were recorded in the hospital database at study inclusion. In addition, all data pertaining to follow-up, developing complications, US evaluations, and perinatal conditions were prospectively collected.

2. Biophysical parameters

At first-trimester screening, blood pressure was recorded by a nurse in our outpatient clinic, in accordance with standard procedure. An automated calibrated device (M6 Comfort; Omron Corp, Kyoto, Japan) was used, selecting one arm (right or left) at random, with subjects seated after a 5-min rest. Mean arterial pressure (MAP) was calculated as: diastolic BP (systolic – diastolic)/3.

3. Ultrasound evaluation

First trimester screening for chromosomal abnormalities by a combination of fetal nuchal translucency and biochemical measurements (previously obtained at 8+0 to 9+6 weeks) was offered at 11+0 to 13+6 weeks of gestation.

Second- and third-trimester US examinations (regularly performed at 19+0 to 21+6 and at 32+0 to 33+6 weeks, respectively) included the following biometric parameters: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). All measurements were obtained by one of seven trained sonograhers, adhering to recommended technique.26 At third trimester, estimated fetal weight (EFW) was calculated using the Hadlock formula.17

4. Doppler measurements

Prenatal Doppler studies were conducted using either a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or a General Electric Voluson E8 (GE Medical Systems, Zipf, Austria), each equipped with a 6-2 MHz linear curved-array transducer. Uterine artery Doppler evaluations were performed transabdominally in second trimester, according to recommended methodology.21 Mean pulsatility index (PI) represented an average of right and left arterial values.

Statistical analysis

The cohort was randomly subdivided (1:1 ratio) into construction and validation sub-cohorts. Student-t test, Pearson chi-squared or Fisher's exact test were performed to make univariate comparisons of quantitative and qualitative variables, respectively, between two groups. A binomial distribution model was used to determine the 95% confidence interval (CI) of proportions.

The following steps (detailed in Supplementary data) were taken to develop (in the construction cohort) the full model for predicting late FGR:

1. Logarithmic transformations to normalize mean MAP, UtA-PI and all fetal biometric parameters.
2. Multiple linear regression (forward stepwise selection, with p-value cut points of 0.05 for inclusion and exclusion) formulas were calculated to derive first-trimester expected log MAP; second-trimester expected log UtA-PI, BPD, HC, AC, and FL; and third-trimester expected log BPD, HC, AC, FL, and EFW.
3. Individual expected log values were then predicted for both affected and unaffected pregnancies.
4. From expected log values calculated in the steps 2 & 3, multiples of the median (MoM) were calculated for each subject as follows: observed log values – expected log values.
5. Receiver-Operator-Characteristic (ROC) curves to predict FGR were constructed for each predictor (log MoM values).

Multiple logistic regression analysis (forward stepwise selection with p values cut-offs for inclusion and exclusion of 0.05) was performed for individual estimates of the following FGR risks:

6. A priori risk (covariables: maternal age, BMI, ethnicity, low socioeconomic status, nulliparity, smoking, ART, previous obstetric complications, medical diseases).
7. A posteriori first-trimester risk (covariables: nuchal translucency, MAP, mean UtA-PI, and a priori risk).
8. A posteriori second- trimester risk (covariables: biometric measures, mean UtA-PI, a posteriori first- trimester risk).
9. A posteriori third- trimester risk, full model (covariables: biometric measures, EFW, a posteriori second- trimester risk).

In the validation cohort, predictive performances of the various strategies stipulated for contingent third-trimester scanning (based on second-trimester a posteriori risk and conducted in 10%, 25%, or 50% of the study population) were delineated in ROC curves, and each ROC curve was tested27 against the full model (i.e., routine third-trimester scan).

With highly correlated measurements (R>0.75), such as US biometric measures, only a variable with the largest individual area under the ROC curve was entered in a model for regression.

Assumptions for regression were checked in each model, and goodness-of-fit was assessed by calculating R2 or Nagelkerke R2 for linear and logistic models, respectively

The statistical software R version 2.15.1 (The R Foundation for Statistical Computing) with the package pROC version 1.7.2 was used for all statistical analysis and graph construction

RISULTATI

Of the 2,775 women recruited in first trimester of pregnancy, 79 (2.8%) were excluded for the following reasons: 1) lost to follow-up (n=20), 2) miscarriage (n=13), 3) congenital malformation/chromosomopathy (n=20), 4) termination of pregnancy without medical indication (n=5),

5) stillbirth (<32 weeks) (n=6) and 6) early-onset (<32 weeks) FGR/preeclampsia (n=15). A total of 155 (5.7%) of the 2,696 women analyzed exhibited FGR, that were randomly divided into construction (73 FGR and 1320 controls) and validation (82 FGR and 1221 controls) sub-cohorts. Table 1 in the supplementary material details the epidemiologic and perinatal characteristics of both sub-cohorts. Of note, significant differences between the construction and validation sub-cohorts were only found in white ethnicity (63.1% vs. 59.3%), chronic hypertension (0.9% vs. 2.1%) and gestational diabetes (6.8% vs. 4.9%).
Epidemiologic, clinical characteristics and perinatal outcomes of the validation cohort are summarized in Table 1. Maternal demographics (ethnicity, smoking status, and medical and obstetric maternal histories) differed significantly in pregnancies with and without FGR. As expected, perinatal outcomes in terms of preeclampsia, emergency caesarean section for non-reassuring fetal status, and neonatal metabolic acidosis were poorer in FGR pregnancies.
Biophysical and ultrasound variables of the validation cohort in first, second and third trimesters are reported in Table 2, where AUCs are detailed individually for each parameter.
The following models best fit specific risks for late FGR:
A priori risk
Logit= -1.613 - 0.064*BMI + 0.133 if Latin-American ethnicity - 0.746 if nulliparity + 1.506 if smoker + 1.036 if previous adverse obstetric outcomes; R2 10 %
A posteriori 1st trimester risk
Calculation of Log MAP (mmHg): Expected Log MAP (mmHg) =1.84 + 0.00153*BMI + 0.000602*maternal age;
Logit=0.421 + 2.491*Log a priori risk + 11.884*Log MoM MAP; R2 12.4%
A posteriori 2nd trimester risk
Calculation of AC MoM: Expected Log AC= 2.006 -0.0058*GA (weeks) + 0.00074*GA2 + 0.0061 if male
Calculation of UtA-PI MoM: Expected Log UtA-PI= 1.946 - 0.176*GA + 0.0039*GA2 + 0.0125 if male
Logit= 0.199 + 2.796*Log 1st trimester a posteriori risk – 31.614* Log MoM AC + 3.456*Log MoM UtA-PI:R2=22.4%
A posteriori 3rd trimester risk
Calculation of EFW MoM: Exp_Log_EFW=-1.891+ 0.28*GA – 0.00368*GA2 + 0.00604 if male
Logit=-1.591 + 1.841*Log(a posteriori 2nd trimester risk) – 29.1* Log MoM EFW;R2 47.5%
Table 3 and figure 1 provide the predictive performance of each model derived. At first trimester, a combination of a priori risk and MAP (i.e., a posteriori first-trimester risk) yielded an AUC of 0.71 (95% CI 0.65-0.77) (DR of 36.6% at 10%FPR). At second trimester, a posteriori first-trimester risk combined with second-trimester AC and UtA Doppler (i.e., a posteriori second-trimester risk) yielded an AUC of 0.81 (95% CI 0.74-0.87) (DR of 43.1% at 10%FPR). Finally, the combination of a posteriori second-trimester risk plus third-trimester EFW (full model) yielded an AUC of 0.92 (95% CI 0.88-0.96) (DR of 74% at 10%FPR). All formulas for calculating these risks are appended as Supplementary material.
Cut-offs for second-trimester risk, as the basis for contingent third-trimester scanning of 10%, 25%, and 50% of subjects, were 12.3%, 5%, and 1.7%, respectively. In other words, third-trimester scanning was warranted at a posteriori second-trimester risk above these cut points. Respective AUC values (95% CI) for models at 10%, 25%, and 50% of subjects were 0.81 (0.75-0.88), 0.84 (0.78-0.91) and 0.89 (0.84-0.94), respectively. Only the 50% contingency model proved statistically equivalent to the full model (p=0.11). Table 4 and Figure 2 show ROC curves of each contingent model and the full model

CONCLUSIONI

In predicting late FGR, our study shows that a strategy of scanning at third trimester in 50% of the population based on the combined first and second trimester risks is equivalent to routinely scanning the whole population of pregnant women.
Although evidence from randomized trials fails to demonstrate any real benefit from routine third-trimester scanning7,12, it may be argued that the results of this meta-analysis have limited contemporary validity as it included studies using outdated surrogates of fetal growth, such as BPD28, or protocols where diagnosis of FGR elicited no change in management. Subsequently, a trial to investigate the impact of third-trimester US should find willing participants29, but a large sample size would be mandatory to assess the effects on hard outcomes, such as perinatal mortality related to birthweight percentile outside the normal ranges.
The effectiveness of routine third-trimester US biometry in diagnosing FGR is also unclear. DR of AC for a birthweight <10th percentile ranges from 48-87%, with a specificity of 69-85%.30 For EFW, DRs of 25-100% and specificities of 69-97% have been reported.14,30 A recent and large study shows that improvements in the detection SGA can be obtained combing maternal characteristics and fetal biometry at 30-34 week, achieving detection rates of 80% of neonates delivering within 5 weeks after assessment.31 Recently, Lesmes et al32 demonstrated the potential value of uterine artery pulsatility index at 19-24 weeks' gestation, in combination with maternal characteristics, medical history and fetal biometry for prediction of delivery of SGA babies, achieving DR of 66% and 43% for those delivering at 32-36 and ≥37 weeks' gestation, respectively. By refining our definition of FGR to include only those pregnancies with evidence of placental insufficiency before delivery or severe smallness we tried to minimize the contamination of our cohort with constitutional small babies, which represent the end of the spectrum of the normal population and do not represent a predictive target in itself.

Souka et al11 have already evaluated a contingency strategy for SGA, rescanning 50% of an unselected cohort (N=2310) according to first-trimester risk. DRs here were 50-60%, with a 5-10% false-positive rate. Our higher rate of detection is attributable to the incorporation of second-trimester UtA Doppler, which is known to be the single best predictor of FGR.12

In view of the goal of improving health care system, economic evaluations of interventions against the not well justified scans are increasingly recommended. Very few studies have addressed cost-effectiveness of ultrasound scans. Estimated costs from a payer perspective for an US exam in the United States have included 200 $ in 199833 and 43 $ to 74 $ (year unreported) for Medicaid reimbursement.34 In Europe a routine third trimester policy is in place in most countries35,36, resulting in an exceedingly large number of scans. At an estimated cost of 29-39 €37 per ultrasound, this policy can generate annual costs of over 95-125million€.35,36 Additionally, when scans are performed by sonographers, rather than sonographists or technicians, the costs are likely to be much higher, up to 20% more.38 A contingent strategy may result in relevant savings, and, according to our findings. The research of new strategies for improving the economic balance in health coasts could benefit from a reduction of 50% of the number of third trimester, without any reduction in the overall predictive capacity for FGR. Consequently, in this less expensive scenario, US target can be identified and managed according protocols that integrate current evidences to classify stages of deterioration in FGR, and establishes both follow-up intervals and optimal delivery timings.22

We do concede some limitations to our study. First, we have no available information on Doppler at third trimester. Existing evidence does not provide conclusive evidence that the use of routine umbilical artery Doppler ultrasound, or combination of umbilical and uterine artery Doppler39, or combination of mean arterial pressure and uterine artery Doppler benefits either mother or baby in low-risk or unselected populations.40 Recent evidence from observational studies suggests that uterine Doppler at third trimester, as a proxy of trophoblastic invasion, adds to biometrical measurement in the detection of FGR.41,42 It could be argued that uterine Doppler earlier in pregnancy could already identify those cases of defective trophoblastic invasion. However, it is interesting to note that in recently reported longitudinal series43, approximately one-third of abnormal third-trimester uterine Doppler studies occurred in women with normal scans during the second trimester, also suggesting that a segment of placental disease emerges late in pregnancy. Finally, as opposed to routine scan before 34 weeks (as done in this study), it could be argued that because lagging growth is accentuated as term approaches, routine third-trimester US studies near term may improve detection rates of severe growth restriction. Indeed, a recent study44 showed that US at 35-37 weeks predicted 89% of SGA neonates (birthweight < 5th percentile) delivering within 2 weeks following assessment.

Furthermore, the addition of cerebral Doppler in term pregnancies has recently been suggested to improve the detection of placental insufficiency.45 Our findings of a similar performance of based-risk screening and routine third trimester ultrasound could not be translated into other strategies of scanning late in the third trimester.

In conclusion, a policy of scanning at third trimester in 50% of the population based on the combined first and second trimester risks achieves a diagnostic performance for FGR that is equivalent to that resulting from performing a routine third trimester scan to the whole population of pregnant women predicting late FGR

038 . PLACENTAL GROWTH FACTOR (PLGF) AS A PREDICTIVE MARKER OF PREECLAMPSIA (PE)/ INTRAUTERINE GROWTH RESTRICTION (IUGR) IN WOMEN WITH A PRECONCEPTION RISK OF DEVELOPING PE AND/OR IUGR

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INTRODUZIONE
To evaluate the clinical utility of placental growth factor (PlGF) as a predictive marker of preeclampsia (PE)/ intrauterine growth restriction (IUGR) in women with a preconception risk of developing PE and/or IUGR

MATERIALI E METODI
Prospective study was performed in two University Hospitals of Northern Italy and included 72 pregnant women in the following groups: (1) patients with uncomplicated pregnancies (n = 11); (2) patients with a preconception risk of developing PE and/or IUGR (n = 61). Blood samples were collected at prenatal visit or during hospitalization.
Plasma concentrations of PlGF were measured using commercially available ELISA kits.
Serum placenta growth factor levels were analyzed according to pregnancy outcome.
Changes in the maternal plasma concentrations of PLGF were compared among normal patients and those destined to develop PE or IUGR

RISULTATI
Serum PlGF levels were significantly lower after 32 weeks among women who developed PE/IUGR (n=10) compared with women controls and women with preconception risks but normal outcome in the next pregnancy [table 1 and figure 1]

CONCLUSIONI
Our study shows that maternal serum PlGF concentration levels decrease from 32 weeks of gestation in pregnancies with a preconception risk of developing PE and/or IUGR and destined to develop PE/IUGR also in the next pregnancy. Therefore the PlGF dosage after this gestational age can be useful to select women at high risk of adverse outcome and so to manage these pregnancies

076 . METABOLIC DISORDERS IN PREGNANT WOMEN WITH GESTATIONAL DIABETES MELLITUS AND FETAL CARDIOVASCULAR RISK

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INTRODUZIONE
Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, that is not clearly overt diabetes, affects from 5–6% to 15–20% of pregnancies worldwide, depending on population demographics, screening methodology, diagnostic criteria in use and maternal lifestyle. GDM seems to be associated to an increased risk of subsequent development of diabetes mellitus type 2 in adult life or obesity in childhood. An early identification of fetal and maternal risk factors predictive of poor outcomes in GDM patients is critical to providing primary prevention strategies during pregnancy and early in life.
The aim of the study was to compare GDM patients with a control group by evaluating fetal ultrasonographic markers and maternal biochemical profile to evaluate if the maternal metabolic environment might influence the fetal vascular system

MATERIALI E METODI
This was a case-control study. Singleton pregnancies affected by GDM and controls were included. The patients underwent to a sonographic evaluation at 30 weeks and at 35 weeks of gestation to assess fetal biometry and fetal-maternal Doppler. For every patient, we collected race, age, parity, maternal glucidic profile (OGTT, the area under the curve (AUC) executed at 24-25 weeks, HbA1c) and lipidic profile (cholesterol, triglyceride, High Density Lipoprotein, Low Density Lipoprotein). During the ultrasound examinations, fetal aorta intima media thickness (aIMT), a marker of endothelial dysfunction, was also evaluated. Delivery data were collected (birth weight, mode and gestational age at delivery, indication of caesarean section, Apgar score at 5')

RISULTATI
One hundred and thirty cases and 130 controls were included. There were not differences between the groups about maternal age, ethnicity and rate of nulliparous. BMI at 30 weeks was higher in GDM group than control (29.8 vs 27.6, $p<0.001$). Estimated fetal weight and abdominal circumference were statistically different in the two groups (p 0.001), while maternal and fetal Doppler were similar. Fetal aIMT was significantly higher in GDM group than controls, at 30 weeks and 35 weeks (0.86 vs 0.70, $p <0.0001$; 0.74 vs 0.64, p 0.0006). AUC was higher in GDM group (966 vs 709, $p < 0.0001$) and presented a positive correlation with birth weight ($p < 0.0001$). Finally, aIMT showed a a positive correlation with AUC (at 30 wks r2 0.11 and p 0.03; at 35 wks r2 0.10 and p 0.01), maternal cholesterol levels (at 30 wks r2 0.31 and p 0.0002; at 35 wks r2 0.71 and $p<0.0001$) and a negative association with maternal HDL (at 30 wks r2 $p <0.0001$; at 35 wks r2 0.30 and $p <0.0001$)

CONCLUSIONI
Maternal hyperglycemia and dislipidemia in presence of GDM could influence fetal vascular function. Prenatal GDM diagnosis should be aimed primary at the prevention of labour and delivery complications, but not less importantly, should help to recognized risk factors for the development of cardiovascular events and metabolic syndrome later in life

093 . INDOLEAMINE-2,3-DEOXYGENASE (IDO1) OXYGEN-MEDIATED REGULATION IN NORMAL, PREECLAMPTIC AND CHRONIC KIDNEY DISEASE (CKD) PLACENTAE

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INTRODUZIONE
IDO1 is key a heme-enzyme expressed by the human placenta. Through depletion of oxygen and tryptophan and kynuerenine production, it reduces proliferation and activity of T cells avoiding maternal-placental "rejection". Moreover, IDO1 plays a role in reactive oxygen species management and it is inversely correlated to oxidative stress (OxS).
Preeclampsia (PE) is a placenta-related syndrome characterized by abnormal maternal immune-response leading to aberrant placenta development and oxidative stress. According to the maternal/placental immune-maladaptation model, a role for IDO1 in PE pathogenesis has been hypothesized but never accurately demonstrated.
Herein, we characterized IDO1 placental oxygen-mediated regulation and its expression in PE and CKD placentae, clinically indistinguishable from PE despite a different etiology and no placental compromise

MATERIALI E METODI
Human term placental villous explants (n=21) were cultured for 12h at 20%pO2. Next, explants were treated oxygen-filled nanobubbles (OLNs-500ul) and incubated in hypoxic conditions (3%pO2) or standard conditions (20%pO2) for 8h. Untreated explants at 3%/20%pO2 were used as controls. Physiological (n=15), PE (n=15) and CKD (n=21) placentae were collected. Placental biopsies and explants were processed for mRNA isolation. IDO1 mRNA levels were determined by Real Time PCR

RISULTATI
IDO1 mRNA levels were significantly increased in 20%pO2+OLNs ($p<0.05$, 8.3 Fold Increase; OxS condition) and 3%pO2 ($p<0.05$, 4.6 Fold Increase) explants vs 20%pO2 controls. Interestingly, 3%pO2+OLNs explants showed a reduction of IDO1 mRNA levels ($p<0.05$, 2.0 Fold decrease) vs 3%pO2 controls. IDO1 expression was significantly reduced in PE compared to both CKD and control placentae ($p<0.05$)

CONCLUSIONI
In the present study, we demonstrated, for the first time to our knowledge, IDO1 oxygen-mediated expression in the human placenta. IDO1 down-regulation further contributes to the pathological OxS environment typical of PE placentae. CKD placentae showed normal IDO1 expression, underlying a physiological placental environment

Sessione 3: INFETTIVOLOGIA PERINATALE

009 . MATERNAL ONE CARBON METABOLISM AND FIRST TRIMESTER EMBRYONIC GROWTH USING VIRTUAL REALITY: THE ROTTERDAM PERICONCEPTIONAL COHORT (PREDICT STUDY)

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INTRODUZIONE
Derangements in maternal one carbon (I-C) metabolism are related to impaired fetal growth and increased risk of adverse pregnancy outcome. The aim of this study is to assess the association between maternal biomarkers of I-C metabolism (vitamin B12, serum folate, total homocysteine (tHcy)) and first trimester embryonic growth trajectories

MATERIALI E METODI
In a prospective periconceptional cohort study, 236 singleton pregnant women enrolled before 8 weeks of gestation underwent weekly transvaginal three-dimensional ultrasound (3D-US) scans from 6+0 up to 12+6 weeks of gestation. Embryonic crown-rump length (CRL) and volume (EV) were determined using virtual reality (V-Scope software program, BARCO I-Space). First trimester maternal venous blood samples were collected for vitamin B12, tHcy and folate assessment. Associations between biomarker concentrations and longitudinal CRL and EV measurements were investigated using linear mixed models adjusted for potential confounders (parity, alcohol use, smoking habit, folic acid use, maternal age, BMI and comorbidity, fetal gender) in the total population (n=236), spontaneous subgroup (n=139) and assisted reproductive technology (ART) subgroup (n=97)

RISULTATI
A median of five scans per patient was performed. 1029 out of 1207 datasets were of sufficient quality to perform CRL measurements (85.3%) and 941 for EV measurements (78%). Vitamin B12 was positively associated with CRL and EV measurements in the total population and in the spontaneous group (table 1). tHcy concentrations were inversely and strongly related to CRL and EV measurements in all the study groups. In the total population, higher tHcy levels (+2SD, corresponding to10.3 µmol/l) decreased CRL by 1.7 mm (-13.4%) and EV by 0.10 cm3 (-33.3%) at 7 weeks and by 3.6 mm (-7.1%) and 1.65 cm3 (-16.1%) at 11 weeks compared to lower tHcy concentrations (-2SD, corresponding to 3.0 µmol/l)

CONCLUSIONI
This study shows that maternal tHcy and vitamin B12 significantly impact embryonic growth trajectories. These data provide support to the role of micronutrient status in the periconceptional period, not only for prevention of malformations, but also for early embryonic growth, potentially impacting perinatal conceptus growth and health

035 . FAT MASS AND CYTOKINES PLASMA LEVELS IN PREGNANT OVERWEIGHT/OBESE WOMEN INCLUDED IN A LIFESTYLE PROGRAM

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INTRODUZIONE
To determine a possible correlation between maternal fat mass (FM) and the plasma levels of pro and anti-inflammatory cytokines (IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IFN-gamma and TNF-alfa) among overweight/obese pregnant women

MATERIALI E METODI
57 women (40 obese, 17 overweight) with BMI ≥ 25 Kg/m2 included in a lifestyle program (a low glycemic hypocaloric diet and moderate physical activity) were enrolled. Weight, FM (evaluated through a bioimpedence analysis, BIA), and plasma cytokines were measured at 9th-12th week and at 35th-36th week. BIA evaluated the distribution of FM for the whole body and for the different body segments, namely arms, trunk and legs

RISULTATI
Mean BMI at enrollment was 34.7±6.4 (range 25.8-54.6) Kg/m2 and FM percentage was higher in obese (44.9±4.5) than in overweight women (40±2.7). Among the investigated cytokines, only IL-6 at first trimester correlated with BMI ($p<0.001$; $r=0.614$) and FM ($p=0.002$; $r=0.405$).Changes throughout pregnancy are reported in table. Significant decrease of IL-1a e IL-2 and increase of IL-6 were found. The increased levels of IL-6 correlated with both GWG ($p=0.002$; $r=0.454$), increased FM ($p=0.022$; $r=0.340$) and increased trunk FM ($p=0.001$; $r=0.482$), while not with arms and legs FM. At third trimester, a regression analysis proved that IL-6 is an independent predictor for FM ($p<0.001$; $R2=0.864$) and for trunk FM ($p=0.046$; $R2=0.381$), after correcting for pre-pregnancy BMI and age

CONCLUSIONI
IL-6 strongly correlates with BMI and body composition in overweight/obese pregnant women. It increases during pregnancy in relation to GWG and it is a marker of visceral FM increase

077 . GESTATIONAL WEIGHT GAIN (GWG) IS AN INDEPENDENT RISK FACTOR FOR ADVERSE PREGNANCY OUTCOME IN WOMEN WITH GESTATIONAL DIABETES (GDM)

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INTRODUZIONE
Pre-pregnancy body mass index (BMI), obesity and gestational weight gain (GWG) are independent risk factors for an adverse pregnancy outcome. The increasing of maternal BMI is a significant risk factor for Gestational Diabetes Mellitus (GDM). All these conditions are associated with a rising occurrence of Large for gestational age (LGA) babies and foetal macrosomia, a rising occurrence of Caesarean Sections and shoulder dystocia. Furthermore, the increasing prevalence of these conditions is related to a higher risk of developing metabolic complications in the offspring.
The incidence of obesity and GDM is rising worldwide and approximately 40% of pregnant women gain more weight than that recommended. Some studies demonstrated that limiting GWG in overweight and obese women could be beneficial for a better pregnancy outcome.
When obesity, overweight and GDM complicate pregnancy, the only modifiable factors could be the glycaemic control and GWG.
The aim of the present study is to investigate if in women affected by GDM with an optimal glycaemic control the excessive GWG (eGWG) is a risk factor for adverse obstetrical outcome independently from pre-pregnancy BMI

MATERIALI E METODI
Three thousand fifth-hundred eight women with a singleton pregnancy were followed in our tertiary referral centre from January 2009 to January 2014. An Oral Glucose Tolerance Test (OGTT) was performed between 24 and 28 pregnancy week. According to HAPO study thresholds, 393 women resulted affected by GDM. After the diagnosis, all patients were provided with a reflectometer for capillary blood glucose self-monitoring (SMBG) with the indication to intensify glycaemic control with a target value <6.1 mmol/l before meals, < 7.8 mmol/L 1 hour postprandial and <6.7 mmol/l 2 hours post-prandial. Both the gynaecologist and the diabetologist assisted all women, and glycaemic values were serially controlled from the diagnosis of GDM till the delivery. After the diagnosis, all women started a diet therapeutic regimen and the capillary blood glucose self-monitoring. In patients that did not achieve a glycaemic control, the diet therapeutic regimen was converted to an insulin therapy.
Optimal glycaemic control was defined when a woman required no more than two changes in therapy or increasing in insulin dose. Two hundred eighty-three women had an optimal glycaemic control.
According to the WHO indications, pre-pregnancy BMI (kilograms/meters2) was categorized as underweight (BMI<18.5), normal weight (BMI ≥18.5 and < 25. 0), overweight (BMI≥25.0 and < 30.0), obese (BMI ≥30.0) women. Total gestational weight gain (GWG) was calculated as the difference between maximum-recorded weight gain during pregnancy and body weight recorded at the first visit 18.0 Kg for underweight women, >15. 8 Kg for normal weight woman, >11. 3 Kg for overweight women and >9.0 Kg for obese women. Gestational age was defined on the basis of the last maternal menstrual date confirmed by early ultrasound examination. Preterm birth was defined as a delivery occurred ≤ 37 the gestational week. Macrosomia was defined as a newborn infant with a birth weight ≥ 4000g; Large for Gestational Age (LGA) was defined as a birth weight >90°Pc and Small for Gestational Age (SGA) was traditionally defined as an estimated foetal weight <10° percentile, according to the national standard curve for singleton birth.
Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), release 15.0. All data were first analysed for normality of distribution using the Kolmogorov-Smirnov test of normality. Continuous variables (Maternal age, GWG, Birth Weight, GW at delivery and Weight Percentile) were expressed as mean ± SD, categorical variables (LGA, Macrosomia, Preterm Delivery and Caesarean Sections) displayed as frequencies.
Appropriate parametric (one-way ANOVA, Student-Newmann-Reuls's post hoc-test) or non-parametric test ($\chi 2$ test) were used to assess significance of the differences among subgroups.
Multiple linear or logistic regression with backward-stepwise method (Reduced model) was also performed to study the dependence of neonatal weight and neonatal weight percentile by maternal and foetal covariates: BMI classes, GWG, hypertension, macrosomia, gestational week at GDM diagnosis, fasting glucose levels, preterm delivery, birth weight. Covariates introduced in the model were variables significantly correlated at the univariate analysis.
All of the tests for statistical significance were two-sided and a P value < 0.05 indicated a significant difference

RISULTATI

Data from 283 women were analysed. Ninety-three women (32.9%) demonstrated an eGWG. There were no significant differences between the two groups in term of maternal age, ethnicity, parity, gravidity, pre-pregnant BMI and mean glucose value at 60 min and 120 min of OGTT testing. Mean basal glucose levels were significantly higher in women with an eGWG (92,70 ±19,31 vs. 88,66±11,66, P=0.03).

Table 1 shows the pregnancy and neonatal outcome between the two groups. Women with an eGWG had a significantly higher incidence of LGA infants, macrosomia and hypertensive disorders of pregnancy. Furthermore, mean birth weight and mean birth weight percentile, were increased in this group respect to women with a normal GWG according to IOM recommendations.

A multivariate logistic regression was carried out to evaluate the independent association between exposure variables and the following outcomes: macrosomia, LGA, hypertensive disorders and mean birth percentile. Both pre-pregnant BMI and eGWG resulted to be independent risk factors for macrosomia and LGA after adjusting for other risk factors (parity, maternal age, insulin treatment, basal glycaemia). Pre-pregnant BMI was associated with the risk of developing hypertensive disorders of pregnancy (P< 0.001), while eGWG was not an independent risk factor for this outcome. Furthermore, eGWG, pre-pregnant BMI and parity were independent risk factors for a higher birth weight percentile.

Figure 1 shows the percentage of LGA newborns among the different pre-pregnant BMI categories in women with eGWG and normal GWG (nGWG). The proportion of LGA infants was significantly higher in women with an eGWG than in those with a nGWG, both in obese (P= .005) and overweight women (P= .002). Excessive gestational weight gain was associated with an increased risk for LGA newborn that is a 7.8-fold higher in obese women (OR=7.83 CI 1.6 to 38.9; p=0.01) and a 9.3-fold increased risk in overweight women (OR=9.33 CI 1.82 to 47.71; p=0.007). A similar trend was observed in normal and underweight women even if this difference was not significantly different probably due to the small sample size (OR= 1.07 CI 0.11 to 10.76; P = 0.95)

CONCLUSIONI

For the first time, an exclusively cohort of diabetic women with an optimal glycemic control was considered and the evaluation of GWG was undertaken according to the IOM guidelines. Regarding baseline characteristics, mean basal glucose levels were higher in women with eGWG. This may highlight that the eGWG could start during the first gestational weeks and could be related to the impared glucose tolerance at the basal test. Our principal findings about eGWG related to neonatal outcome and, in particular, to indices of a pathological fetal growth (rate of LGA, macrosomia). These data are novel in testing the importance of GWG in a population of women at high risk for the presence of GDM intensively managed during pregnancy also in normal weighting women. By the multivariate analysis adjusted for other potential confounders, we demonstrated that eGWG is associated with fetal growth (expressed by birth percentile) (P=0.002) and with the risk of macrosomia (OR=4.97) and LGA infants (OR=4.43) independently by pre-pregnant BMI. We also observed increasing proportion of LGA among BMI categories but in obese and overweight women eGWG is an independent risk factor for LGA infants.

Although this result cannot be explained by the current analysis due to the small sample, the incidence of hypertensive disorders of pregnancy is higher in women with eGWG. However, multivariate analysis shows that only pre-pregnant BMI is an independent risk factor for this outcome.

When a GDM occur, GWG could be the only modifiable risk factor. Our data suggest that an improved obstetrical outcome can be achieved using an intensive control of GWG for all women with diabetes, irrespective of antenatal BMI. Care providers should give the same attention in dietary, lifestyle intervention and weight gain control both in obese and in normal weight women and use, as a target, IOM recommendations according to the different BMI classes.

In conclusion, understanding the interplay between GDM, obesity, GWG, hypertensive disorders and metabolic syndrome is imperative for both care providers and women and pregnancy is a unique occasion to inform women on their future health

100 . EFFECTS OF MODULATORS OF NITRIC OXIDE SIGNAL ON VALPROIC ACID-INDUCED TERATOGENICITY

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INTRODUZIONE
Valproic acid (VPA) is an antiepileptic drug largely used for the treatment of epilepsy, migraine and bipolar disorder. Although it is well known that the in utero exposition to VPA leads to an increase risk of major congenital malformations, the exact mechanism underlying its teratogenicity remains poorly understood. Increase in oxidative stress, alteration in folate metabolism and more recently inhibition of histone deacetylase (HDAC) have been postulated to account for the teratogenicity of this drugs. Intriguingly, results from recent studies carried out using in vitro systems suggested that VPA may have the ability to inhibit nitric oxide synthase (NOS). Considering the crucial role of nitric oxide (NO) in organogenesis, we became interested on the possible link between NO and VPA-induced teratogenicity. The present study was undertaken to evaluate the effects of agents with the capacity of modulating the NO signal on the teratogenicity mediated by VPA in the mouse

MATERIALI E METODI
In the first experiment, mice were injected on gestation day 8 with a non-teratogenic dose (20 mg/kg) of the nitric oxide synthase (NOS) inhibitor N(G)-nitro-L-arginine methyl esther (L-NAME). Thirty minutes later, animals received a teratogenic dose of VPA (400 or 500 mg/kg). Developmental end-points were evaluated near the end of gestation. Half of the fetuses were prepared for the skeletal examination. The remaining fetuses were fixed in Bouin's solution and subsequently examined for visceral anomalies.
In the second study, ICR (CD-1) mice were treated on gestation day 8 by gastric intubation with sildenafil citrate (SC) at 0 (vehicle), 1.0, 2.5, 5.0 or 10 mg/kg. One hour later, animals received a teratogenic dose of VPA (600mg/kg) or vehicle. Developmental endpoints were evaluated near the end of gestation. In this experiment, all the fetuses were prepared for skeletal examination

RISULTATI
After treatment with VPA at 400 mg/kg, 35.2% of fetuses exhibited skeletal teratogenesis. The rate of skeletally affected fetuses significantly increased to 53.7% after L-NAME co-administration. In the group treated with VPA at 500 mg/kg group, L-NAME pre-treatment increased the incidence of exencephaly from 5.4% to 22.2%.
Twenty-eighth percent of fetuses exposed to VPA had neural tube defects (exencephaly). Pretreatment with SC at 2.5, 5.0 or 10mg/kg significantly reduced the rate of VPA-induced exencephaly to 15.9%, 13.7%, and 10.0%, respectively. Axial skeletal defects were observed in 75.8% of VPA-exposed fetuses. Pre-treatment with SC at 10mg/kg, but not at lower doses, significantly decreased the rate of skeletally affected fetuses to 61.6%

CONCLUSIONI
These results support the concept that NO plays a protective role from VPA-induced teratogenesis. Specifically, the use of a NOS inhibitor (L-NAME), a substance with the propriety to reduce the NO levels, resulted in an enhancement of the VPA-induced teratogenicity leading to an increase of both, exencephaly rate and skeletal malformations. Coherently, the pre-treatment with SC, a substance that act prolonging the NO signal resulted effective in the prevention of VPA-induced exencephaly in a dose-dependent manner. It has been reported that VPA (like others HDCAs inhibitors) may interfere with NOS leading to a reduction of NO levels in cells culture and that these effects can be reversed by the use of a NO donor. It is well known that NO is a molecule which plays fundamental roles in reproduction and development and that its imbalance may alter organogenesis. Focusing on the process of neurogenesis, studies carried out in chick embryos showed that proper levels of NO are required for the correct development of neural tube system. Our results seems to be in line with this recent line of research indicating the possible relationship between VPA-teratogenicity and alteration in NO status. Overall, the findings of the present study, may be relevant not only in terms of the comprehension of mechanisms behind VPA teratogenesis, but also in the development of potential interventions to reduce the occurrence of neural tube defects in babies delivered by mothers requiring VPA treatment during pregnancy

Sessione 4: I NATI DA PARTO VAGINALE O DA TAGLIO CESAREO: COME CAMBIA LA NOSTRA SPECIE?

007 . HOW LATE IS TOO LATE FOR VAGINAL DELIVERY: EFFECT OF ADVANCED MATERNAL AGE ON OBSTETRIC OUTCOMES

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INTRODUZIONE
Cesarean Delivery (CD) rate rises at maternal age increase. Advanced maternal age has been associated with an increased risk of obstetrical complications, but the association between CD and maternal age alone is controversial.
The objective of our study is to compare obstetric outcomes between mothers under and over 40 years using the Robson classification system in Lombardia

MATERIALI E METODI
We included all deliveries occurred in the 82 hospitals of Lombardia between January and December 2013. Patients were divided into two groups according to maternal age: A) less than 40 years (ys); B) 40 ys or older. The certificate of delivery care (CeDAP) has been used as data source. The Robson classification of CD was applied to compare the rate of CD in the different classes between the two groups. Pregnancy outcomes were analyzed as antepartum and intrapartum. T-student test was used to compare recurrence rates in the comparison between the two studied groups

RISULTATI
During the study period 8,416/ 87,681 (9.6%) women aged 40 years or older. Overall CD rate was 28.3% (24,776/87,681). This rate was significantly higher in women aged ≥ 40 ys compare to aged < 40 ys (42.2% vs 27.5%, p<0.001). The differences were highly significantly different in Robson classes I (nulliparous, single cephalic, ≥ 37 weeks, with spontaneous labor) and VIII (all multiple pregnancies, including previous CD), approaching significance in all other classes, excluding previous CD (Robson class V) and classes for which fetal malpresentation was the main indication for surgery (classes VII and IX) (table 1)

CONCLUSIONI
Risk for CD is higher in women older than 40 years compare to younger women in Lombardia. Indeed, a nulliparous women aged 40 years or older with spontaneous term cephalic delivery has a 27% probability of CD, that is twice as a women under 40 years. Moreover, maternal age does not influence the rate of CD in the category of previous CD. The preferences of the individual care provider and the mother on mode of delivery may play a key role and require further investigation

024 . ANHEDONIA, ANXIETY, AND DEPRESSION COMPONENTS OF EDINBURGH POSTNATAL DEPRESSION SCALE IN CESAREAN DELIVERED MOTHERS

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INTRODUZIONE
BACKGROUND.
Previous studies have indicated that cesarean delivery might pose risk factors for post-partum depression (PPD). However, results are conflicting and have failed to clearly distinguish between elective and emergency cesarean section
OBJECTIVE.
The rate of elective cesarean delivery is rapidly increasing all over the world and it is important to identify whether the mode of delivery has an influence of PPD. The Edinburgh Postnatal Depression Scale (EPDS) is a widely used instrument for PPD screening, also capable to detect in subscales anhedonia, anxiety, and depression factors

MATERIALI E METODI
A cohort of 959 Italian mothers delivering a healthy baby at Policlinico Abano Terme, Italy, completed the EPDS 2 days after delivery

RISULTATI
EPDS scores were lower in mothers with a vaginal delivery compared to mothers with a caesarean delivery (6.1 ±4.2 vs. 7.0 ± 4.8, p<0.01) and less frequently (25.2 vs. 6%, p9. But only the women who elected to have a caesarean section had significantly higher scores (7.1 ±3.9 vs. 6.8 ± 4.1, p<0.001) and more frequently (25.2 vs. 39.4%, p9. Additionally, the factor analysis of EPDS indicated that anhedonia, anxiety, and depression were significantly higher in mothers with a caesarean delivery compared to mothers with a vaginal delivery (anhedonia: 0.32±0.59 vs. 0.19±0.48, p<0.003; anxiety: 0.07±0.88 vs. 1.16±0.93, p<0.02; depression: 0.53±0.72 vs. 0.37±0.65, p<0.007), but only the women who elected to have a caesarean section had significantly higher scores: anhedonia (0.19±0.48 vs. 0.31±0.64, p<0.001), anxiety (1.17 ± 0.93 vs. 1.07 ± 0.88, p<0.006), and depression (0.37± 0.65 vs. 0.45 ± 0.68, p<0.004). Of note, anhedonia was quantitatively more important also in EmCD women compared to VD women (0.19±0.48 vs. 0.30±0.68, p<0.002)

CONCLUSIONI
The results of our study indicate that women who had an ElCD have an increased risk of developing early symptoms of post-partum depression, anxiety, and anhedonia. In particular, this study shows that the use of EPDS subscales in the immediate post-partum is a good tool to better understanding the spectrum of maternal post-partum psychological problems related to delivery mode

032 . PLACENTAL WEIGHT-BIRTH WEIGHT RATIO: AN INDEX FOR THE PERINATAL OUTCOMES

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INTRODUZIONE
In clinical practice placental weight is usually recorded in all delivery room. Its value is still under discussion as to have a correct interpretation. Fetus health and newborn is associated to environment during pregnancy. Placental weight reflects placental efficiency and growth as well as it is able to provide an explanation for the underlying mechanism by which birth weight is associated with morbidity and mortality in infants, children and adults. The correlation between fetal weight and placental weight is the fetoplacental weight ratio (FPR). The primary endpoint of the study was to correlate the FPR at birth with neonatal outcome (Apgar score at 5° and 10° minute, pH at birth and BE) in order to detect possible association with neonatal well-being. The secondary endpoint was to find correlation between FPR weight with pathologies of the 3rd stage of labor such as postpartum hemorrhage (intrapartum bleeding> 1000ml), manual removal of placenta (MROP), instrumental revision of the uterine cavity because of placental retention. The tertiary endpoint was to evaluate if placental weight is influenced by maternal history, pregnancy and delivery

MATERIALI E METODI
An observational prospective cohort study on pregnant single women admitted to the delivery room of University of Padua, Woman and Child Health Department, was conducted. We
collected data on maternal characteristics: maternal age, parity, race, weeks of gestation, BMI in early pregnancy and at term of pregnancy. Obstetric characteristics were analyzed: spontaneous or IVF pregnancy, mode of labor (spontaneous or induced), mode of delivery (vaginal or operative delivery, elective caesarean section, emergency caesarean section) and possible difficulties during the 3rd stage of labor. We obtained data on fetal-neonatal characteristics: fetal presentation at birth, sex, weight, Apgar score at 5° and 10° minute, pH at birth, base excess (BE) and the need of intensive care. Placental characteristics were collected: placental insertion site detected with ultrasound, weight placental at birth and its morphology

RISULTATI
A cohort of 702 patients was eligible for our study. The comparison between placental weight and obstetric history showed a statistically significant difference with pre-gestational maternal weight [p<0.001], maternal baseline BMI [p<0.05], maternal weight at term [p<0.05], maternal BMI at the delivery [p<0.05] and gestational age [p<0.001]. We found significant differences between the PFR and perinatal outcomes in terms of Apgar score at 5°/10° minute, neonatal pH and BE. With ratio greater than 0.29 (mean value ratio of our sample 0.195) we observed a 5° minute Apgar score < of 7 with an estimated exponential growth trend compared to the increase ratio. We found the same results analyzing the ratio cut off and 10° minute Apgar score.
The mean ratio cut off obtained (0.125) is statistically connected to pH values at birth considered normal. The correlation between PFR and pathologies of the 3rd stage of labor showed statistically significant differences only in blood loss >1000 ml for cut off ratio between 0.195-0.29 [p than 0.29 [p<0.001]

CONCLUSIONI
High values of FPR are associated with adverse perinatal outcomes (linked to Apgar score <7 at 5° minute and < 8 at 10° minute, altered pH values at birth and non-physiological BE). Postpartum hemorrhage (blood loss > 1000 ml) is associated to heavier placental weight in relation to normal neonatal weight. Placental weight is correlated to maternal BMI pre-pregnancy and at term. Even if placental weight increases with advancing of gestational age, high placental weight were found also between 35 and 38 weeks of gestation

065 . CTG PARAMETERS IN A LARGE POPULATION OF HEALTHY TERM SINGLETON PREGNANCIES IS NOT INFLUENCED BY FETAL GENDER

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INTRODUZIONE
Fetal gender has been identified as an important factor influencing both fetal and maternal outcomes. In pregnant patients with male fetuses an increased risk of delivering preterm, undergoing cesarean section, failing labor induction, suffering a stillbirth and developing gestational diabetes has been demonstrated. Pregnant women with female fetuses instead have an increased risk of developing gestational hypertension, preeclampsia, IUGR although females have better perinatal outcomes.
These differences on the basis of fetal gender have been theorized to be the result of a different hormonal secretion of various substances during pregnancy influenced by fetal sex and/or alterations in the functioning and development of the placenta in males and females.
Given this difference in obstetric and perinatal outcomes between male and female fetuses, various authors have examined fetal hearth rate changes during labor, delivery and antepartum period but only in particular conditions, related to individual fetal behavioral states thus with minimal applicability in the clinical setting.
The objective of this study was to assess Short Term Variability and other additional CTG parameters in relation to fetal gender during daily clinical activities, referring to a large population of uncomplicated singleton term pregnancies between 37 to 40 weeks of gestation

MATERIALI E METODI
We conducted a retrospective analysis of computerized FHR monitoring in pregnant women with uncomplicated singleton gestation between 37 to 40 weeks who were referred to the outpatient clinic of the University of Florence-Careggi Hospital for an uncomplicated term gestation. Consent was obtained from all participants, in accordance with the Helsinki Declaration. FHR monitoring was performed with the Sonicaid FM800. Subject clinical information was obtained from the Sonicaind FM 8000 data registry and matched with the electronic patient record (Argos 3.34 Dedalus SpA Italy)
When evaluating CTG data obtained from the Sonicaid FM800 the following information was evaluated: the length of the registration in minutes, baseline FHR, presence or absence of uterus contractile activity, number of accelerations and/or decelerations, episodes of high variability, short term variability (STV), percentage of signal loss, time to termination and fetal movements.
Categorical variables were compared using the chi-square test, continuous variables were compared using the Mann-Whitney test, given a non-normal distribution of the data. For multivariate analysis we used a linear regression model with a binary outcome (dependent variable) and several predictors (independent variables). Specifically, the multivariate analysis pooled together the maternal demographics characteristics and the CTG results in order to exclude possible confounders during data interpretation. The software used for the statistical analysis was SPSS 23.0 (IBM, USA)

RISULTATI
Considering the weaknesses of the previous studies, we examined a large study group of 689 fetuses where 335 were male and 354 were female . No statistically significant difference regarding the characteristics of the mothers distributed by fetal sex was found except for the ethnic origin of the patients during univariate analysis which was not confirmed by multivariate linear regression.
There was no difference in Apgar score, pH, SBE, gestational age at delivery and mode of delivery between genders. The only difference found was in the birth weight, which was higher in male fetuses than in female ones ($p<0.05$).
Analyzing the CTG results of the newborn gender, there was no significant difference in terms of signal loss, contractions, movements, accelerations, decelerations, HVT and STV in both uni- and multivariate analysis. In the univariate analysis there was a statistically significant difference in FHR (mean value was 135 bpm for males and 136 bpm for female with $p < 0.05$), which was not confirmed by a multivariate analysis (Tab.3)

CONCLUSIONI
CTG parameters in a population of healthy term singleton pregnancies is not influenced by fetal gender. Considering the close connection between pregnancy disease status and CTG changes, it would be worth evaluating a larger population, including preterm and pathological pregnancies