ITALIAN ADVISORY BOARD: SFLT-1/PLGF RATIO AND PREECLAMPSIA, STATE OF ART AND DEVELOPMENTS IN DIAGNOSTIC, THERAPEUTIC AND CLINICAL MANAGEMENT.

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BACKGROUND

To date, preeclampsia (PE) is still a leading cause of fetal and maternal morbidity and mortality[1]. Even if many progress have been made in these last decades, its aetiology is still largely unknown[2].

It is debated if preeclampsia should be considered as a unique disease, presenting a continuum of clinical expression and severity, which appear to be worse as soon as PE symptoms arise during pregnancy or as a syndrome, characterized by different clinical phenotypes[3]. An increasing number of scientific evidences have already established two possible distinct pathogenic mechanisms of PE: on one side we have a placental dysfunction that originates at the very beginning of placentation and is consequently associated with fetal growth restriction (Burton et al, 2010) and on the other side, late changes in placental function associated with the size of the term placenta restricting intervillous perfusion, this type of placental lesion is associate with appropriate for gestational age newborn (AGA) or even large for gestational age newborns (LGA). Both lesions yield a syncytio trophoblast stress (STB) disorder with by-products that impact the maternal endothelial function (Redman et al, 2014). In addition to this both conditions might add to a pre-existing maternal systemic inflammatory pattern (Borzychowski et al, 2006; Steegers et al, 2010) usually associated with a maternal metabolic syndrome. Among the co-factors of this syndrome dyslipidaemia is made more severe by the typical energy metabolism of pregnancy possibly facilitating an abnormal increase in spiral arteries atherosis (Staff et al, 2014). Maternal cardiovascular adaptation in these different clinical phenotypes seems to be characterized by different cardiac output and total peripheral resistances,

although controversial findings need further research (Valensise et al, 2008; Melchiorre et al 2014, Circulation).

PREECLAMPSIA TODAY

In spite of these two predominant models of placental dysfunction and the insight into the contributory predisposition of maternal conditions, clinical diagnosis of PE is still based on non-specific symptoms and signs (hypertension and proteinuria) as they were determined prior to any biophysical and biochemical diagnostic tool that can be routinely applied in clinical obstetrics such as fetal biometry, Doppler interrogation of uterine and umbilical arteries (Ferrazzi et al, 2015) and placental markers of integrated STB oxidative stress. (NICE, 2010; WHO Guidelines, 2011; ACOG, 2013). These basic old criteria are now integrated with sign and symptoms of all possible complications arising from a generalized endothelial dysfunction associated with any symptoms and/or sign of organ failure, other than proteinuria (Royal College of Obstetrics and Gynaecology, 2006; Society of Obstetric Medicine of Australia and New Zealand, 2008; Society of Obstetricians and Gynaecologists of Canada, 2008; American Society of Hypertension, 2008). Some (Magee et al, 2014), but not all guidelines, consider fetal growth restriction as marker of damage that associated with maternal hypertension fall into the realm of PE in addition to maternal symptoms and maternal end-organ dysfunction. Recently even the prognostic factor of proteinuria has been "downgraded". Once proteinuria is no longer the sole co-factor that added to hypertension qualify a clinical condition for preeclampsia, then a larger definition could be welcomed for this syndrome and Hypertensive Disorders of Pregnancy (HDP) might serve for this role.

EPIDEMIOLOGY

In Europe Hypertensive Disorders of Pregnancies (HDP) affect the 4-8 % of pregnancies, representing one of the main complication of pregnancy (Steegers et al, 2010). Among these preeclampsia constitutes a sub group the prevalence of which is largely dependent on how strict are the prenatal controls and subsequent clinical interventions such as antihypertensive drugs, work leave, induction of labor for hypertension, delivery for fetal growth restriction, and above all how severe is the burden of maternal obesity and truncal obesity at a country level. In Europe where a reasonably strict control of pregnancy is offered to the universe of pregnant women the severe evolution of hypertension not associated with IUGR is rare, and the most severe form is represented by HDP associated with IUGR. Worldwide, the killer among HDPs is preeclampsia not associated with early placental dysfunction and IUGR (Conde-Agudelo et al, 2000; Lozano et al, Lancet 2010), the early symptoms of HDP are not screened and pregnant women consult medical personnel late or are admitted to hospitals when in severe conditions with organ damage far beyond the endothelial dysfunction that leads to hypertension.

CONTRIBUTION OF PlGF AND OF sFlt-1.

At the beginning of this last decade, different studies discovered that women affected by preeclampsia show an unbalanced proportion of anti-angiogenic and pro-angiogenic soluble plasmatic factors[13] (Cetin 2010). Excessive placental production of soluble fmf-like tyrosine kinase receptor-1 (sFlt-1), an antagonist of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), contributes to the pathogenesis of PE.

An increased sFlt-1/PlGF ratio is more pronounced in early-onset rather than late onset disease and is associated with severity of clinical disorder; furthermore, the unbalanced of PlGF and sFlt-1 causes vasoconstriction and endothelial damage that may lead to fetal growth restriction and preeclampsia[14,15,16].

Steps forward were also made thanks to the implementation of a elettrochemo luminescence method for the dosage of the anti- and pro- angiogenic factors ratio in an automated, rapid, precise, reproducible test[17,18].

Moreover, the sFlt-1/PlGF ratio has been approved as a diagnostic aid for preeclampsia in conjunction with other clinical findings[18] and was recently incorporated into German guidelines[19]. Also the NICE, recently established that the triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio, used with standard clinical assessment, are recommended as diagnostic aid for preeclampsia in women between 20 and 34 weeks of gestation plus 6 days (16 December 2015, article in press).

Extensive research has been published demonstrating the usefulness of angiogenic markers in both diagnosis and subsequent prediction and management of PE and placenta-related disorders[20]. A recent article published by the New England Journal of Medicine provide evidences for an helpful cut off for the ratio sFlt-1 and PlGF, that identifies women at risk of preeclampsia weeks before its clinical onset[21]. It is a prospective, multicenter, observational study that identifies a sFlt-1/PlGF ratio cut-off of 38 as having an important predictive value: a ratio of 38 or lower has a negative predictive value, for the diagnosis of PE in the subsequent week, of 99,3%, with 80% sensitivity and 78,3% of specificity. The positive predictive value of a sFlt-1/PlGF ratio above 38 for a diagnosis of PE within 4 weeks is 36,7%, with 66,2% sensitivity and 83,1% specificity.

That is why, the measurement of the sFlt-1/PlGF ratio has the potential to become an additional tool in the early diagnosis and management of PE,

Therefore, it is now essential to evaluate the clinical implication of this test, together with its social, legal, economical and ethical implications.

CONSENSUS STATEMENT

This panel of experts suggested the preconception identification of the main risk factors of HDP, such as obesity, hyperglycaemia, dyslipidemia, chronic hypertension, congenital and acquired thrombophilic conditions, autoimmune disease, and chronic renal disease is fundamental. These conditions, when possible, should be removed or minimized prior to conception by an adequate information about life style and healthy nutritional regimen. Accurate family and personal history and laboratory

diagnosis should be pursued in case of clinical conditions that could require ad hoc prophylactic or therapeutic regimens prior to conception.
In early gestation, predictive examinations should be added to clinical history in order to identify the subset of pregnant women who deserves closer monitoring and prophylactic intervention.
Prenatal and postnatal attempt should be pursued for adequate assessment of placental and fetal involvement in cases of HDP, so that to add fetal medicine contributes to maternal medicine standard diagnosis and therapy.
Severe and severe early cases should be referred to tertiary centres for maternal and fetal intensive monitoring and therapy.
Special attention should be aimed to disentangle the role of sFlt-1 and PlGF within the different clinical phenotypes of this syndrome. sFlt-1 and PlGF and sFlt-1/PlGF ratio, varies consistently in normal gestations from 30-32 weeks to term showing how in normal pregnancies the pro-angiogenic factors progressively decline and blocking factors progressively increase (Levine et al, 2004). This is expected given the growth trajectory of human placenta. These angiogenic factors are altered both in early gestation in cases that later will develop HDP with IUGR and become altered in women that develop HDP and PE with AGA and LGA fetuses.
Taking into account this possible different etiopathogenesis, this test could be also used to differentiate between intrauterine growth restricted foetuses and small for gestational age (SGA) neonates. Nowadays, even if the unbalanced proportion of these two plasmatic factors in women affected by preeclampsia is known, their exact role in the development of hypertensive disorders of pregnancy is not completely understood.

PURPOSE OF FOCUS GROUP:
The purpose of this focus group is to promote the evaluation of the clinical utility of sFlt-1/PlGF ratio at the italian country level as regards:

1. Patients with risk factors for preeclampsia (previous PE, chronic hypertension, chronic kidney disease, type 1-2 diabetes, thrombophilia, autoimmune disease, altered uterine arteries Doppler ultrasound after 24 gestation weeks).
2. Patients with non-specific signs and symptoms of PE: "***suspected***" PE[22].
3. Patients with blown PE.

POSSIBLE SFLT-1/PLGF RATIO APPLICATIONS:

1. Prediction of different phenotypes of HDP, especially as regards PE according to its definition by the Canadian Guidelines. Prediction in the first trimester is of major importance for the development of future studies on preventing therapies.
2. Prediction of recurrence among patients with previous HDP
3. Triage of patients suffering from gestational hypertension

4. Evaluation of HDP degree/severity in patients with clinical disease
5. Prediction of possible adverse maternal and fetal outcomes.

1- Prediction during the first trimester

The additional measurement of the sFlt-1/PlGF ratio has been shown to improve the sensitivity and specificity of Doppler measurement in predicting PE[23,24,25,26,27], supporting its implementation in screening algorithms. Furthermore, considering that no preventive or therapeutic strategy is yet available, with the exception of low dose acetylsalicylic acid, which has moderate preventive effect in high-risk pregnancies after the first trimester[28], clinical experience suggests that early detection and monitoring are beneficial[7]. An Italian multicenter trial about PE predictivity would be useful, considering the different clinical phenotypes (HDP-IUGR, HDP-AGA), in order to evaluate if the test would be useful only among high risk population or also among low risk population and to evaluate its utility also for the prediction of intrauterine growth restriction.

2- Prediction or exclusion of new onset or recurrence among patients with risk factors for PE.

sFlt-1/PlGF ratio dosage may be useful for pregnant outpatients presenting with risk factors for PE (previous PE, chronic hypertension, chronic kidney disease, type 1 diabetes, lupus, thrombophilia, autoimmune disease, altered uterine arteries Doppler velocimetry after 24 gestation weeks), especially for its elevated negative predictive value, which excludes the onset of PE in the subsequent week.

3- Triage of patients suffering from gestational hypertension.

In tertiary care centres, for outpatients or at the obstetrical emergency room, the ratio dosage may be applied in the triage of pregnant patient presenting with gestational hypertension, also to evaluate their need for hospitalization and the subsequent clinical management, especially if:

- non-specific signs or symptoms of PE are described (epigastric pain, severe swelling, face edema, sudden weight gain, headache, visual disturbances, low platelets, transaminases augmentation);
- differential diagnosis with other clinical forms characterized by proteinuria is needed (e.g., chronic kidney disease with first manifestation during pregnancy);
- differential diagnosis between previous chronic pathology and PE overlap is needed;
- intrauterine growth restriction is diagnosed.

4- **Evaluation of disease severity**.
In hospitalized preeclamptic women, the ratio dosage can be repeated after 48 hours to evaluate its trend: a sudden increase may point out a rapid worsening of the patient's condition, while the finding of a stable value can reassure the physician the patient will not deteriorate rapidly and allows test repetition at two weeks[29].

5- **Prediction of adverse maternal and foetal outcomes**.
In hospitalized preeclamptic women, a repeat measurement of the sFlt-1/PlGF ratio may help to distinguish whether a patient is at moderate, high or very high risk of developing a complication[7,24,30,31,32,33].

CONCLUSIONS

Despite our knowledge about sFlt-1/PlGF ratio, more data are needed in order to improve the clinical applicability of the test. In order to obtain this result, further research should be use a different classification of hypertensive disorders of pregnancy considering the possible different pathogenic mechanisms which lay under different clinical forms of PE.
Moreover, new trials will be helpful to evaluate if the routinely use of this test could improve the clinical management of preeclamptic women, avoiding unnecessary hospital admissions.
Finally, the diffusion of scientific data and their implementation in defined guidelines would be of great interest, in order to obtain a better homogeneous clinical management.

LITERATURE

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