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EDITORIAL

Low molecular weight heparin: does it represent a clinical opportunity for preventing preeclampisa associated with fetal growth restriction?

Introduction

The Cochrane Collaboration and Blood recently published two meta-analyses showing that low molecular weight heparin (LMWH) improved ''outcomes in women at risk of placental dysfunction'', and ''may be a promising therapy for recurrent, severe, placenta-mediated pregnancy complications''. This editorial attempts to define which of the many phenotypes of hypertensive diseases of pregnancy (HDP) might benefit from such prevention. Shallow trophoblastic invasion, dysfunctional placenta and endothelial damage, associated with fetal growth restriction, do not match all clinical phenotypes. A large majority of women suffering from pre-eclampsia give birth to normal weight babies and placentas. It is very likely that in these latter cases, endothelial dysfunction, hypertension and organ damage are mainly caused by maternal factors that result in the low grade inflammation of normal placentas at term. However, if prevention is targeted just at placental pre-eclampsia, then the powerful immunomodulation of LMWH might play a role. Heparin is not primarily an antithrombotic peptide: it is parsimoniously released by mast-cells in sites of tissue injury, with a substantial impact on inflammation and oxidative stress and displays critical immunomodulation activities on trophoblast. This explains why LMWH worked better in trials focused on early severe HDPs associated with fetal growth restriction. LMWHs should be considered to prevent the recurrence of placental pre-eclampsia.

Definition of the target of prevention

A recent publication by ''the Cochrane Collaboration'' of a systematic review of 10 randomized trials of fair to good quality on pregnant patients without thrombophilic conditions [1] showed that low molecular weight heparin (LMWH) improved ''maternal or infant health outcomes in women considered at risk of placental dysfunction''. Soon after that, ''The Study Group: Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications'' reported similar conclusions in blood [2]: ''LMWH may be a promising therapy for recurrent and especially severe, placenta-mediated pregnancy complications''.

These evidence-based conclusions differ in their clinical impact, the first established grounds for the clinical use of LMWH in women at risk, the second calls for a new series of well-designed trials. Yet, such research will cause quite a few people's heartbeats to race and probably raise many more eyebrows, depending on the country, the medical school attended, and individual opinions and beliefs.

It might help to sit back and focus on the definition of exactly what we are aiming to prevent. A recent paper by Leslie Myatt, Christopher Redman, Anne Staff et al for the Global Pregnancy CoLaboratory [3] might help define a way out of the maze of Hypertensive Diseases of Pregnancy (HDPs) and make the most of the new scope for prevention, as reported by these two systematic reviews: ''It is possible that within the syndrome there may be different phenotypes with pathogenic pathways that differ between the subtypes. The capacity to recognize and to exploit different subtypes is of obvious importance for prediction, prevention, and treatment''.

What are we trying to prevent with LMWH? A single disease, or the whole syndrome? The very sound of the name ''pre-eclampsia'' conjures up the marvels compiled over the last twenty years on the critical relationship between the appendices of the new creature, the trophoblast, and its host environment, the maternal decidua and uterus [4]. This background directs us to those pregnancies with abnormal placental vascular development, fetal growth restriction, maternal endothelial dysfunction, hypertension and in some case proteinuria. Yet this picture explains only a fraction of the causes leading to endothelial dysfunction that have tentatively been put forward as a common final pathway to this syndrome [5]. In spite of its solid scientific background, this sequence of placental, fetal and maternal damage does not apply to the definition of pre-eclampsia according both to some of the current guidelines provided by the major scientific societies [6–9] and by some medical blogs. In fact, some guidelines include fetal growth restriction in the very definition of pre-eclampsia [6,7], while others do not [8,9]. To add to the paradox, in 2014, diagnosis of this pregnancy complication is still based on the identification of proteinuria as described in 1840 by Pierre Rayer, a Frenchman, the first to describe proteinuria in eclamptic pregnant patients, and later complemented by the introduction of the Scipione Riva-Rocci's mercury blood pressure manometer in 1896 that led to the recognition that pre-eclampsia/eclampsia was a hypertensive disorder.

As a matter of fact, the idea that pre-eclampsia diagnosed by nineteenth century criteria could be a single disease had already been challenged [5,10,11] even though this did not gain general credence and had little impact on clinical guidelines. The paper by the Global Pregnancy CoLaboratory group [3] prudently addresses different markers of this complex syndrome. We recently reviewed this problem [12] by trying to identify the subset of cases with hypertension and proteinuria without vascular placental damage and fetal growth restriction. Every day in labor and delivery rooms worldwide, two major clinical phenotypes can be observed: women affected by ''pre-eclampsia'' or HDPs may deliver normal weight babies, with normal placentas, most of them after 34 weeks, but more commonly after 37 weeks of gestation, sometimes even associated with gestational diabetes and big babies. Less frequently, women with a similar diagnosis of ''pre-eclampsia'' or HDP deliver growth restricted fetuses and small placentas regardless of the gestational age, even if the most severe cases of IUGR occur before 34 weeks of gestation. Yet, to the great surprise of external observers, such entirely different conditions still go under the same name of ''pre-eclampsia, or HDP, and the same CDI9 number.

Early and late onset pre-eclampsia, or how time domain criteria ousted physiology from clinical obstetrics

Attempts have been made to adhere to clinical real life scenarios by sub-classifying pre-eclampsia into an early onset form, occurring before 34 weeks of gestation, and a late onset form occurring after 34 weeks of gestation. We are all aware of similar attempts to classify diseases based on the time axis. The distinction between juvenile and adult diabetes as a possible classification of diabetes survived for a few years before being replaced by a physio-pathological classification, yet that vision was based on a large time domain and an accepted overlapping between the two. Probably for the first time in western medicine the passage of one single day, from 33 weeks and 6 days to the next day in pregnancy, changes the name of a disease, with all the consequences in terms of epidemiology, prediction, prevention, diagnosis and therapy. Time does not qualify severity as in premature delivery, in the world of pre-eclampsia, time dictates categories that might even result in different prognoses or even preventive strategies.

In spite of this time dependent classification, placental pathology [13] and the clinical hard facts, fetal and placental weight, fare better under this definition. The obvious fact is that endothelial dysfunction due to low grade maternal inflammation resulting in late pregnancy fetal-placenta TH1 milieu [6] rarely occurs before 34 weeks of gestation and hence the physio-pathological background of these early onset cases is more homogeneous. This sub-classification satisfies some experts in that it provides prevention strategies for early onset PE but not for late onset cases [14], or vice versa [15,16]. In fact, the real area of confusion concerns the ''late onset'' disease where the epidemiology of maternal metabolic syndrome and its low grade inflammatory vascular damage differs from country to country [17], and according to macro-ethnicity, whereby mothers of south American origin, and of Afro-Caribbean ethnicity proved to have the highest prevalence of maternal pre-eclampsia delivering normal weight newborns [18] at term.

The object of prevention: placental pre-eclampsia associated with fetal growth restriction

The following sentences, quoted successively below, pave the way for the definition of the object of prevention/help to define what we are aiming to prevent: ''The diagnosis of pre-eclampsia using blood pressure and proteinuria is of limited use because they are tertiary, downstream features of the disease'' [19]; ''Poor early placentation is especially associated with early onset disease. Predisposing cardiovascular or metabolic risks for endothelial dysfunction, as part of an exaggerated systemic inflammatory response, might dominate in the origins of late onset pre-eclampsia'' [10]; ''... a major cause (*of pre-eclampsia*) is the failure to develop an adequate blood supply to the placenta, leading to placental oxidative stress. This ... triggers an inflammatory response and endothelial dysfunction. Alternatively, pre-eclampsia can develop in the presence of a normal placenta in women who are susceptible to systemic inflammation'' [5]; ''In conclusion ... A growing body of evidence suggests that the development of early and late pre-eclampsia are two distinct pathophysiological processes with distinct maternal phenotypes predisposing to the development of each'' [20]; ''... with profoundly reduced placental perfusion ... almost any woman would get pre-eclampsia. Conversely, the woman with extensive predisposing constitutional sensitivity could develop pre-eclampsia with very little reduced perfusion'' [11].

What we wish to discuss in the following chapters is how to prevent ''placental pre-eclampsia'' as described by Steegers [10], and beautifully distinguished from maternal pre-eclampsia by Borzychowski et al. [5]. The placenta is obviously also part of the picture in maternal pre-eclampsia, but does not share the distinct lesions that are typical consequences of early shallow trophoblastic invasion.

How to diagnose placental pre-eclampsia associated with fetal growth restriction

This clinical phenotype is not just a hypothetical model, it can be easily diagnosed and differentiated when maternal high blood pressure and proteinuria are observed in a pregnant women. Fetal growth restriction can be determined by traditional ultrasound biometry. In our recent experiment that is part of a larger ongoing multicenter observational trial, 23 of 34 consecutive patients delivered with HDP $\leq$ 34 weeks of gestation gave birth to SGA newborns with a prenatal diagnosis of growth restricted fetuses (68%), whereas only 56 of 217 patients delivered with HDP >34 weeks of gestation gave birth to growth restricted fetuses (26%) ($p<0.0001$). Average Body mass index, as a proxy of the risk of metabolic syndrome and maternogenic endothelial dysfunction was 25.9 in mothers of IUGR fetuses and 30.1 in mothers of AGA newborns ($p<0.0001$). Fetal growth restriction is a robust, reproducible, worldwide spread clinical skill that can easily be applied prenatally to all pregnancies with HDP.

Like all biological measurements, including blood pressure, ultrasound fetal biometry has its limitations. Yet this is the most simple, universally available, first-step approach to defining different HDP phenotype during pregnancy, when classification is most needed. This is possibly the first criterion that can be used to differentiate the two main HDP clinical phenotypes amongst those addressed in depth by Myatt and co workers [3]. Uterine Doppler velocimetry could be added to confirm placental vascular insufficiency [3,4,21], and the severity of placental insufficiency can even be predicted by arterial umbilical Doppler since Pulsatility Index [22] proved by and large to be a good proxy for the reduction of blood flow volume from the placenta to the fetal body [23]. We have recently been able to complement these traditional biophysical landmarks with biochemical markers [19] that help to define the severity of the evolution of the maternal condition among women with poor angiogenic placental factors. As would be expected from the above, the reported sensitivity of low PIGF values, a marker strongly associated with poor vascular placental development, in predicting delivery within 14 days in pre-eclamptic patients is as high as 68% in cases delivered before 35+0 weeks, and as low as 22% later on.

Heparin – a potential key player for prevention

In common obstetric medical parlance, heparin is considered to be a systemic antithrombotic molecule. Heparin is in fact an ancestral polypeptide, present in the evolutionary scale in shrimps, mussels, lobsters, whales, turkey, and finally mammals. Heparin bears the highest negative charge among mammalian polypeptides and its remarkable properties are safely stored in mast cells [24], while the coagulation balance is controlled by heparin sulphate proteoglycans produced by endothelial cells [25]. Heparin is released by mast cells into small vessels at sites of tissue injury where its main role is that of a key co-factor in tissue from bacteria and foreign materials [26].

LMWH: a window of opportunity for immunomodulation

It is very likely that our knowledge of trophoblast invasion and its modulation by peripheral T_{reg}, despite the considerable amount of data, is insufficient to provide clues for primary prevention. However, we can probably modulate the pro-coagulatory effect of inflammation using low dose aspirin [14], we can try to modulate established tissue inflammation using LMWHs [1], or reduce inflammation and oxidative stress, and possibly in the future protect local and systemic endothelium dysfunction using statins (parvastatin) [27,28]

There is a growing body of evidence to show that LMWH plays a role in inflammation by decreasing inflammatory cytokines [29], leukocyte adhesion to damaged tissues [30], and by reducing the production of inflammatory cytokines such as IL8-IL6-IL1β and TNFα and of the NkB factor [31] by monocytes, and possibly by reducing complementary activation by similar trophoblastic cells with specific anti-phospholipids activating properties [32].

Among the controversial questions regarding the role of LMWHs in human reproduction, there are observations that consistently prove the role of LMWHs in counteracting the role of anti-phospholipids by inhibiting endometrial neo-angiogenesis [33], in stimulating epidermal growth factors in human throphoblast in the first trimester, and according to Drewlo et al. [34]: ''lower doses of LMWH, equivalent to levels that the placental villi would be exposed to in pregnancy, induce syncytial fusion, hCG secretion and placental apoptotic turnover''.

Controversies regarding the possible negative side effects of LMWHs on syncytial knots through the unwanted release of soluble factors binding the placental growth factor had been elucidated by Yagel [35]: in brief, the findings reported showed that although syncytial knots do indeed release the blocking soluble factor sFlit-1, they do so together with two to four times the amount of VEGF, hence establishing a favorable ratio.

LMWH from bench to trials and bedside

If the research done so far on LMWH is scientifically consistent, and it is consistent, then its possible application from bench to bedside in the prevention of placental pre-eclampsia could be considered.

Criticisms have been levelled against the possible clinical use of LMWH to prevent the recurrence of ''pre-eclampsia''. As a matter of fact, when a variety of abnormal pregnancy outcomes were included in clinical trials such as in the HAPPY study [36], no effects were observed from the early adoption of LMWH prophylaxis. In that study, of 135 patients recruited over four years in eight centers, only 28 patients had had a previous growth restricted fetus, while 48 women had had previous uneventful pregnancies. Furthermore, when such preventive potential was established in women who had had previous repeated miscarriages before 14 weeks of gestation, no therapeutic advantage was observed [37]. An additional complicating factor had long been the ''translation'' of LMWH's prevalent role as an anti-thrombophilic agent in clinical hematology into maternal-fetal medicine [38,39], where immunomodulation is most wanted and expected from LMWH prophylaxis.

The HAPPY negative findings have been recently replicated by the TIPPs' study [40] on a similar background. Eligibility criteria suffered from the scientific background of the late nineties, when the study was designed. Thrombophilic conditions included hetero-zygosity for factor V Leiden and Prothromobin mutation, as well as first degree relative with deep vein thrombosis (31% of the cohort). Similarly ''placenta-mediated pregnancy complications'' included early pregnancy loss (16% of the cohort), as well as all phenotypes of preeclampsia (16%) (early, late, severe, non severe). Overall in a 12 years recruitment, as regards severe placenta mediated pregnancy complications, only five SGA fetuses $<$ the 5th percentile and 11 cases of early or severe preeclampsia were included in this study. Its conclusions are unfortunately embedded in the discussion and not in the abstract: ''In summary, higher quality evidence suggests that LMWH does not prevent recurrent non-severe placenta-mediated pregnancy complications, whereas lower quality evidence suggests

that LMWH might prevent recurrent severe placenta-mediated pregnancy complications''.

As a matter of fact, both de Vries and Rey observed positive results from the adoption of LMWH prophylaxis, even if the first trial [41] excluded non-thrombophilic patients with previous early onset PE and the second trial [42] excluded thrombophilic patients from cases with severe APO in previous pregnancies. These two studies serve to further illustrate that the anti-thrombophilic role of LMWH is not the key feature in placental pre-eclampsia. In our prospective cohort [43] of pregnant women with previous severe APO associated with small babies or unexplained fetal death between 20 and 37 weeks of gestation, LMWH proved to have a positive effect both in 50 thrombophilic women and in 50 non-thrombophylic women.

The last 10 years of pilot studies [43,44], small trials [45–47], and finally large trials [48] have built up different levels of evidence that have, in the final analysis, prompted a systematic revision of the selected randomized trials [1].

In this recent Cochrane systematic revision [1], despite the fact that the HAPPY study [36] data had been included with its burden of non-placental abnormal pregnancy outcomes, and that the paper by de Vries [41], focusing mainly on cases of placental insufficiency had been left out, the odds are in favor, or even strongly in favor, of LMWH proving valuable in preventing pre-eclampsia, preterm birth before 34 weeks of gestation and fetal growth restriction below the 10th percentile and other main outcomes. In the meta-analysis reported by blood [2], the impact on severe or early pre-eclampsia was measured by a relative risk of 0.16 (C.L. 0,07–0,36), more than a fourfold reduction of the risk of recurrence. Overall, these positive findings may result in a change in clinical attitudes even among ''purists'' who had consistently rejected the contribution of LMWH in reducing the risk and severity of recurrence of abnormal pregnancy outcomes due to shallow trophoblastic invasion. The additional advantage of this therapy is its negligible impact in terms of side effects and unwanted complications [49]

On the basis of the above evidence, it could be of interest to go back to an important finding reported by our prospective cohort [43]. Patients had in fact been recruited on the grounds of the severity of their obstetrical history between 12 and 24 weeks of gestation. One might argue that it is too late to convey a positive shift with regard to trophoblastic invasion. As a result of this real life clinical recruitment, the recurrence of the disease was similar to that reported by cohorts of severe placental APO, i.e. 25%. The striking result was the marked reduction in the severity of cases where hypertensive diseases of pregnancies and fetal growth restriction recurred. In the obstetrical history of our cohort, 53% of pregnancies were delivered before 34 weeks of gestation. This was assumed to represent a robust score of severity in the pregnancy index. In the treated pregnancies, the percentage of cases delivered $<$34 weeks of gestation was brought down to 4%.

To explain these findings, we can speculate that the immunomodulation promoted by LMWH and its impact on growth factors and apoptosis and upon the overall turnover of placental cells might and should be deployed throughout gestation, even if the early and primitive trophoblastic dysfunction cannot be entirely modified or reversed.

Perspectives

In conclusion, the secondary prevention of a disease requires that the limits of the disease itself be clearly defined. It is very likely that placental pre-eclampsia associated with fetal growth restriction should be considered separately from maternal pre-eclampsia with normally grown fetuses [50]. LMWH might then play a role in preventing the recurrence of placental pre-eclampsia or more widely in hypertensive diseases of pregnancy associated with fetal growth restriction at any gestational age of onset. This role derives by and large from the core biological immunomodulation activity of LMWH.

There is now evidence, in accordance with the principles of evidence-based medicine, that LMWH helps reduce the recurrence and severity of placental pre-eclampsia, and in our opinion there is no reason to deprive patients who could benefit from this secondary prevention of this opportunity.

In our opinion, the next step is to start to study the possible role of LMWH in first-time patients suffering from HDP with fetal growth restriction, and possibly design strict randomized trials on preventing placental pre-eclampsia in first-time mothers who tested positive in the first and second trimesters when screening for placental insufficiency. Statins or not, it would be a pity if the potential benefits of LMWHs were not properly investigated just on the basis of opinions that sometimes seem to be more rooted in personal credence rather than scientific grounds.

Declaration of interest

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