Antenatal Care of Preeclampsia: From the Inverted Pyramid to the Arrow Model?

Tullio Ghi^a Andrea Dall'Asta^a Herbert Valensise^b

^aDepartment of Medicine and Surgery, Obstetrics and Gynaecology Unit, University of Parma, Parma, Italy;

^bObstetrics and Gynaecology Unit, University of Rome Tor Vergata, Rome, Italy

Keywords

Hypertensive disorder of the pregnancy · Pyramid model · Antenatal screening · Pregnancy care

Abstract

The recent demonstration of the effectiveness of low-dose aspirin administered from the first trimester in the prevention of preeclampsia will probably lead to establishing and radicating the “inverted pyramid” screening model for preeclampsia. Such a multiparametric approach for the screening of preeclampsia in the first trimester, albeit highly sensitive in identifying early-onset disease, is poor at screening the forms of preeclampsia occurring close to term. Late-onset preeclampsia is 3 to 6 times more common than early-onset preeclampsia and currently represents the major determinant of maternal morbidity related to hypertensive disorders of the pregnancy. On this ground, we discuss our idea to construct a second “screening checkpoint” in the third trimester with the aim of reassessing the risk of preeclampsia of those women who screened negative in the first trimester. If implemented, the sequential screening model we propose would convert the “inverted pyramid model” into an “arrow model” for the antenatal care of preeclampsia.

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Much clinical interest has been raised in the last few months by the publication of the ASPRE trial [1]. In this large multicentric randomised controlled trial, the first-trimester screening of preterm preeclampsia based on maternal factors (history and mean arterial pressure), uterine Doppler findings, and biochemistry has proven to be valuable. In the screen-positive group, the administration of 150 mg aspirin compared with the placebo has yielded a 62% reduction in the rate of preterm preeclampsia, although no differences in terms of maternal and perinatal events have been demonstrated due to insufficient power of the study. This extraordinary large trial (almost 26,000 women enrolled) has confirmed that a multiparametric assessment at 11–13 weeks is able to detect, at the screen-positive rate of 10%, the vast majority of women who will develop preeclampsia before 37 weeks, and virtually all those who will be affected before 34 weeks. The excellent performance of the screening combining maternal factors, uterine Doppler, and placental biochemistry in identifying those pregnancies destined to preterm preeclampsia had been previously reported by the same and other groups [2–6]. With the ASPRE study, for the first time, it was demonstrated that the early screening does make sense because the onset of the dis-

Fig. 1. Shifting from the inverted pyramid to the double arrow model for the antenatal care of preeclampsia.

ease can be prevented in positive cases through the administration of aspirin. In principle, albeit not yet proven, this is expected to have a dramatically favourable impact on maternal and perinatal health as the occurrence of preterm preeclampsia is notoriously associated with high risk of perinatal and maternal morbidity and mortality [7–10]. On this ground, the scientific community has welcomed this study as a major advance in pregnancy care and the wide implementation of the first-trimester screening of preeclampsia in clinical practice is endorsed by many experts [11].

Very recently, the performance of first-trimester screening for preeclampsia combining maternal factors with biomarkers was shown to be far superior to that of the model currently recommended by NICE guidelines and based on maternal characteristics and medical history [12].

This will probably lead to establishing and radicating for preeclampsia the “inverted pyramid” screening model as originally envisaged in this journal by one of the authors of the ASPRE trial [13]. This model is based on the background concept that a massive and efficient screening of the population early in gestation is able to select the exceedingly small number of high-risk women who will be worthy to be followed up later in gestation. In other words, regarding the antenatal care of preeclampsia, it seems better to allocate more resources in the early stage of pregnancy rather than close to term and this becomes particularly true if an early intervention on the screen-positive cases as demonstrated by the ASPRE [1] can decrease in fact the occurrence of preterm preeclampsia and the number of pregnancies who will need special care and surveillance.

However, we would like to work out further the fascinating idea of the inverted pyramid model for the antenatal care of preeclampsia. As consistently reported across the various studies cited above, the multiparametric screening of preeclampsia in the first trimester is poor

at identifying the forms of disease occurring close to term. At the same screen-positive rate, the detection rate of late preeclampsia is in fact below 50%, and this modest performance of the screening has been also confirmed by the ASPRE trial, which has identified only 40% of pregnancies who have developed preeclampsia beyond 37 weeks. This is biologically plausible since the pathophysiology of the late forms of preeclampsia seems completely different from the early forms as recently highlighted by some authors [14, 15]. While in the preterm preeclampsia, the abnormal placentation seems the trigger factor of the disease and its effects are amenable to be detected at 11–13 weeks, in the late-onset form, the placental dysfunction seems to depend upon the villous overcrowding which takes place in the third trimester and does not give any clue at the time of the first-trimester screening [14]. Moreover, a different cardiovascular profile has been shown at maternal echocardiography among normotensive asymptomatic patients who will develop preeclampsia at late gestation rather than prior to 34 weeks [15]. These findings further support the hypothesis of a different pathophysiology for early and late preeclampsia.

Therefore, we should bear in mind that the “inverted pyramid model” cannot pick up the vast majority of women who will develop term preeclampsia. This is not a small problem as late-onset preeclampsia is 3 to 6 times more common compared with the early-onset type and available data have shown that, although outcomes for the mother and baby are more severe with preterm preeclampsia, the contribution of term preeclampsia to maternal morbidity is substantial [10]. Furthermore, in a recent series, the risk of emerging major complications such as peripartum cardiomyopathy has been reported to be significantly more likely in women with late preeclampsia compared with early forms [16].

Because of that, if we want to optimise the antenatal care of preeclampsia, the inverted pyramid model based

on first-trimester screening does not seem to meet all the requirements. Using this approach and giving aspirin to the screen-positive cases may certainly reduce the incidence of preterm preeclampsia and its related complications, but this has little effect on late preeclampsia and its associated maternal risks. Indeed, according to the inverted pyramid model, most of the pregnancies who will develop term preeclampsia would be assigned to the apparently low-risk group, which falls outside of the pyramid.

On this ground, some leading authors in this field have felt the need to remodulate the antenatal care of preeclampsia in order to pick up and possibly to prevent also the cases occurring late in gestation who might be overlooked by the first-trimester screening. The emerging idea is to construct a second checkpoint in the third trimester with the aim of reassessing the risk of preeclampsia of those women who were labelled as screen negative at first trimester. Some preliminary data have shown that at 35 to 37 weeks, a multiparametric screening based on maternal factors, uterine Doppler, and angiogenic markers may identify the vast majority (85%) of women who will develop late preeclampsia [17]. Recent data from a longitudinal proteomics study have demonstrated that elevated MMP-7 early in gestation (8–22 weeks) and low PlGF later in gestation (after 22 weeks) are good predictors for the subsequent development of late-onset preeclampsia, suggesting that the optimal identification of patients at risk may involve a two-step diagnostic process [18]. On this basis, a new large RCT which will evaluate the role of pravastatin in preventing preeclampsia among women found to be at high risk of preeclampsia during the third trimester is on its way and will contribute to clarify if and how this new approach may affect the epidemiology of the late forms of the disease [19].

The work in progress concept is to transform the antenatal care of preeclampsia from an inverted pyramid model to a double arrow model (Fig. 1); in other words, a sequential screening of preeclampsia where the primary assessment is repeated close to term in all women who were screen negative in the first trimester with the aim of identifying the vast majority of cases who will develop term preeclampsia. This approach would add back to the antenatal care a significant number of women who are at high risk of term preeclampsia and would be left out of the vertex in a pyramid model. The clinical usefulness and the cost-effectiveness of this new type of screening will hopefully be clarified by the ongoing study [19].

We are aware that this “arrow model” to date cannot be recommended in clinical practice because the accuracy of the third-trimester screening test of preeclampsia should be validated on a large population and we still do not know if pravastatin or any other intervention can be offered to the screen-positive cases to prevent the onset of late preeclampsia or its complications. Meanwhile, before this ideal double arrow is built, it is better to keep our eyes open also outside of the pyramid.

Finally, in the attempt of optimizing the antenatal care of preeclampsia, beside the issue of screening and prevention, the continuing need for appropriate recognition and management of preeclampsia should be emphasized. The fullPIERS model has been shown to improve the prediction of adverse maternal outcomes once preeclampsia is diagnosed and can favourably impact on patient care [20].

Disclosure Statement

All the authors state no financial disclosures nor conflict of interest related to this work.

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