Preeclampsia –
from basic science to clinical management

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Abstract

Preeclampsia is a pregnancy specific disease, defined by a new onset of hypertension and proteinuria. It affects up to 4% of all pregnancies, and untreated it can develop to eclampsia. It may also be the cause of intrauterine growth restriction. The objective of this assignment is to examine the mechanisms behind the disease and the future risks regarding subsequent pregnancies and cardiovascular disease. Management of affected patients will also be reviewed.

The pathogenesis behind the disease is still not fully known. A central aspect in the development of preeclampsia is a failure of trophoblast invasion of the spiral arteries during placentation. The result is low perfusion of the uteroplacental unit, and increased release of placental factors affecting the maternal circulation. High levels of sFlt-1 binding and inactivating VEGF and PlGF, endothelin-1 and angiotensin II autoantibodies all affect the maternal circulation and are believed to contribute to the endothelial dysfunction. Hypertension, overweight, age and other maternal factors also increase the risk of preeclampsia. The risks of recurrence in subsequent pregnancies and cardiovascular disease are increased compared to women without a history of preeclampsia. Women who have had preeclampsia in a prior pregnancy should receive counselling by experienced obstetricians before their next pregnancy and a close follow-up. The goal in the management is to reduce maternal risk factors and optimize maternal health before conception and detect complications as early as possible during pregnancy. More research is necessary to achieve full knowledge of the disease.

Introduction

During the six years of education at the Faculty of Medicine of the University of Oslo, students are to write a thesis on a medical topic of their choice. I developed a particular interest in preeclampsia during my obstetrics and gynaecology term.

I learnt an interesting fact at a lecture given by my supervisor, Tore Henriksen, Obstetrics Professor, that the cause of preeclampsia is still unknown. The uncertainty of the cause of a disease of such common occurrence worldwide, as well as the fact that it literally translates to "pregnant poisoning" in Norwegian, made me more excited to learn about it.

I have read numerous articles on the pathogenesis of preeclampsia, as suggested by my supervisor, and its complexity soon became very clear. I believe this topic to be highly relevant and important in gaining further knowledge in women's health. This experience has proven to be extremely stimulating and rewarding. I was fortunate enough to gain a deeper understanding of a disease of such complexity and acquire knowledge on how to manage these patients in the future.

Part I: Pathogenesis

Preeclampsia

Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity, complicating 3-4% of pregnancies. It is a pregnancy-specific disease defined by a de-novo development of hypertension (140/90 mmHg) recorded on at least two separate occasions and significant proteinuria (<0,3g/24h) arising at or after 20 weeks' gestation[1]. The disease can progress to cause maternal liver dysfunction, renal impairment and ultimately seizures and death[2]. In Latin America and the Caribbean, hypertensive disorders are responsible for 26 % of maternal deaths. In high-income countries maternal mortality is low, however, 16 % of maternal deaths can be assigned to hypertensive disorders [1]. This shows that preeclampsia is a major contributor to maternal mortality, with a total estimate of 100 000 maternal deaths a year worldwide[3].

The mechanisms behind preeclampsia are not fully understood. However, hypertension associated with preeclampsia develops during pregnancy and remits after delivery that leads to the logical implication that the placenta is a central keystone in the process[4]. Removal of the placenta is the only effective treatment to stop disease progression.

Hypertension and proteinuria is essential for the diagnosis. Hypertensive disorders during pregnancy are *chronic hypertension* (known hypertension prior to pregnancy), *gestational hypertension* (blood pressure > 140/90 mmHg in a normotensive pregnant women who is >20 weeks of gestation and has no proteinuria or any signs of preeclampsia) and *superimposed preeclampsia on chronic hypertension* (development of preeclampsia in a patient with chronic hypertension or renal disease).

Other aspects of the preeclampsia syndrome include thrombocytopenia, elevated transaminases and microangiopathic haemolytic anaemia (HELLP syndrome). Placental abruption, hepatic rupture, pulmonary oedema and acute renal failure are some complications to preeclampsia that may lead to maternal death. Preeclampsia may lead to the development of eclampsia when the vascular dysfunction affects the vasculature of the brain. These complications may be avoided with appropriate treatment[5].

Generally, preeclampsia is divided into early onset (before week 34) and late onset preeclampsia (after week 34). Both the maternal and perinatal risk is higher the earlier pre-eclampsia occurs.

Pathogenesis

One of the reasons for the not fully understood pathology is the vast heterogeneity of the disease and mechanisms. Some patients may have a perfectly normal placenta and severe maternal symptoms, while others may have the exact opposite. Also, everything in between these poles may be possible. Knowing this, it is therefore important to look on different hypotheses to get a hold of the complexity of the disease.

The placenta

Preeclampsia is a complex disorder involving multiple organ systems and much progress has been made towards understanding the pathophysiology. Strong evidence supports that the placenta plays a central role in the pathogenesis.

The uterine spiral arteries are vital in supplying nutrients to the placenta and fetus, and the remodelling that occurs when pregnant, is essential for the supply. During normal pregnancy, cytotrophoblast derived from the foetus will invade the maternal uterine spiral arteries replacing the endothelium as showed in figure 1. This is a complex process that results in a conversion of the high-resistance, small-diameter vessels into high-capacitance, low-resistance vessels to accommodate the increasing demand of blood from the developing uteroplacental unit[4].

Preeclampsia occurs only in the presence of the placenta, even when there is no fetus, as in hydatidiform mole[6]. Beginning during the first trimester, an initiating event in pre-eclampsia is believed to be reduced placental perfusion which leads to widespread dysfunction of the maternal vascular endothelium and hypertension by mechanism that remain to be defined[4]. Pathology specimens have shown placental infarcts, likely due to ischemia and occlusion of the spiral arteries. It is therefore believed that the invasion of spiral arteries is incomplete.

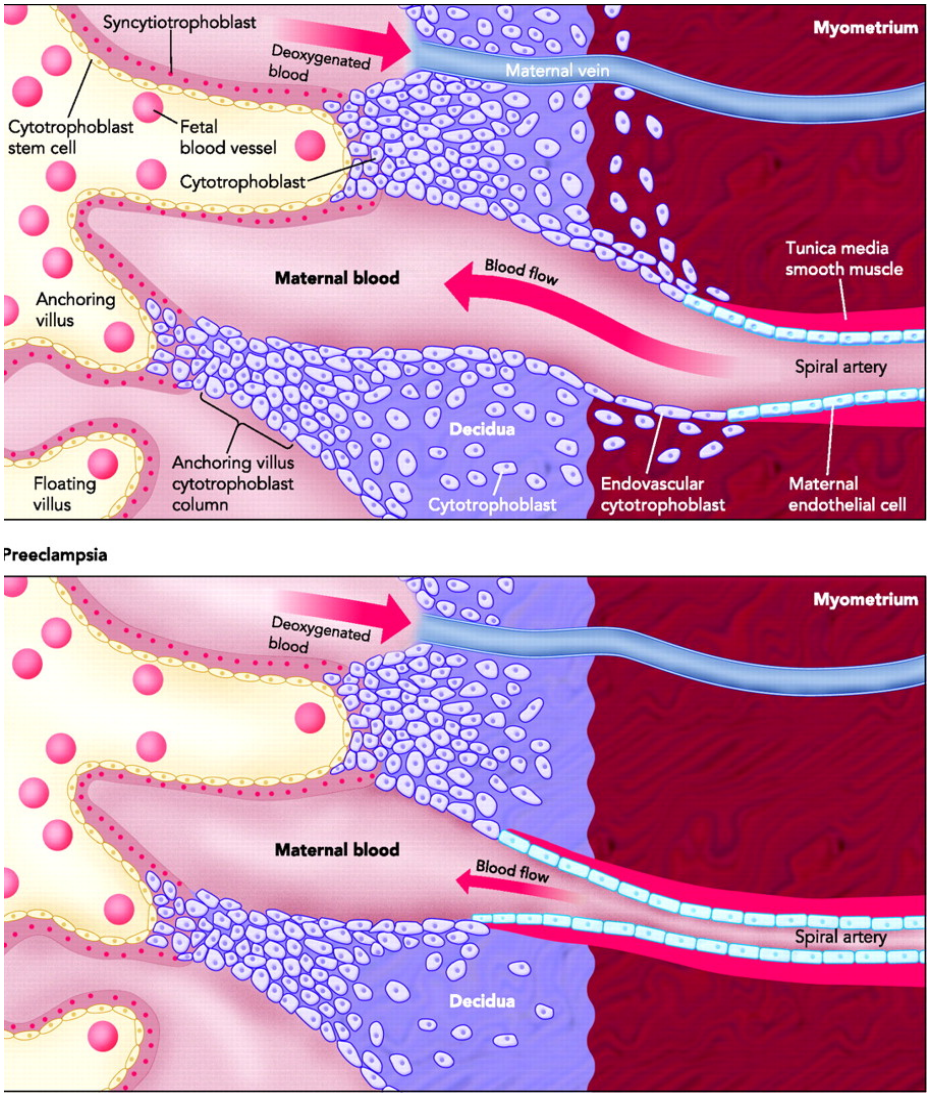

Fig 1. Invasion of cytotrophoblasts in normal pregnancy and preeclampsia (Illustration from physiologyonline.physiology.org)

Several factors have been implicated in placentation; Notch signalling pathway, STOX1, components of the renin-angiotensin system and the intracellular serpin proteinase inhibitor. The Notch signalling is believed to be fundamental in the invasion and remodelling of the maternal blood vessels by the trophoblast. It is shown that absence of Notch 2 in mice is associated with a reduced spiral artery diameter.

The normal maternal responses to presence of trophoblastic tissue may, somehow simplified, be divided in an immunological response and an endocrine/metabolic/vascular response. Studies have led to a hypothesis that the clinical manifestations of preeclampsia result from an imbalance between circulating proangiogenetic and angiogenetic factors in the maternal circulation[6].

Dysfunction of the endothelium

The cause of preeclampsia can roughly be divided in two components; placental factors and maternal risk factors. The placental factors are believed to be released from the placenta and in to the maternal circulation where they cause a dysfunction of the endothelium. The vascular endothelium has many important properties such as controlling the smooth muscle tone through release of vasoconstrictor and vasodilatory substances, regulation of anticoagulation, antiplatelet and fibrinolysis functions via different soluble factors.

Alterations in circulating levels of markers of endothelial dysfunction have been reported in women that develop preeclampsia, and the fact that the dysfunction can be shown in women prior to the disease supports the theory that an endothelial dysfunction is a cause to the development of preeclampsia[4].

The production of pathogenic factors, which enter the maternal blood flow, is believed to be due to the placental hypoxia[4]. Once in the blood flow, the pathogenic factors will cause the endothelial dysfunction and other clinical manifestations such as hypertension and leakage of proteins in the urine. A variety of factors are released, but the anti-angiogenic and inflammatory factors have received the greatest attention. Vascular growth factor (VEGF) signalling pathway is one of the best-understood pathways in the manifestation of pre-eclampsia.

VEGF and placental growth factor (PlGF) play a crucial role in maintenance of endothelial cell function as well as angiogenesis. High levels of the VEGF receptor fms-related tyrosine kinases (sFlt-1) have been detected in the placenta and in the maternal blood. sFlt-1 binds to VEGF and PlGF in the blood and neutralises these factors leading to a decrease of VEGF and PlGF in the maternal circulation (Figure 2) . It is postulated that sFlt-1 inactivates these factors and leads to low levels of VEGF and PlGF, successively a failure to stimulate angiogenesis and preservation of the endothelial integrity[4]. Rapid developing oedema can be a symptom of the disease and failing endothelial integrity is thought to be cause.

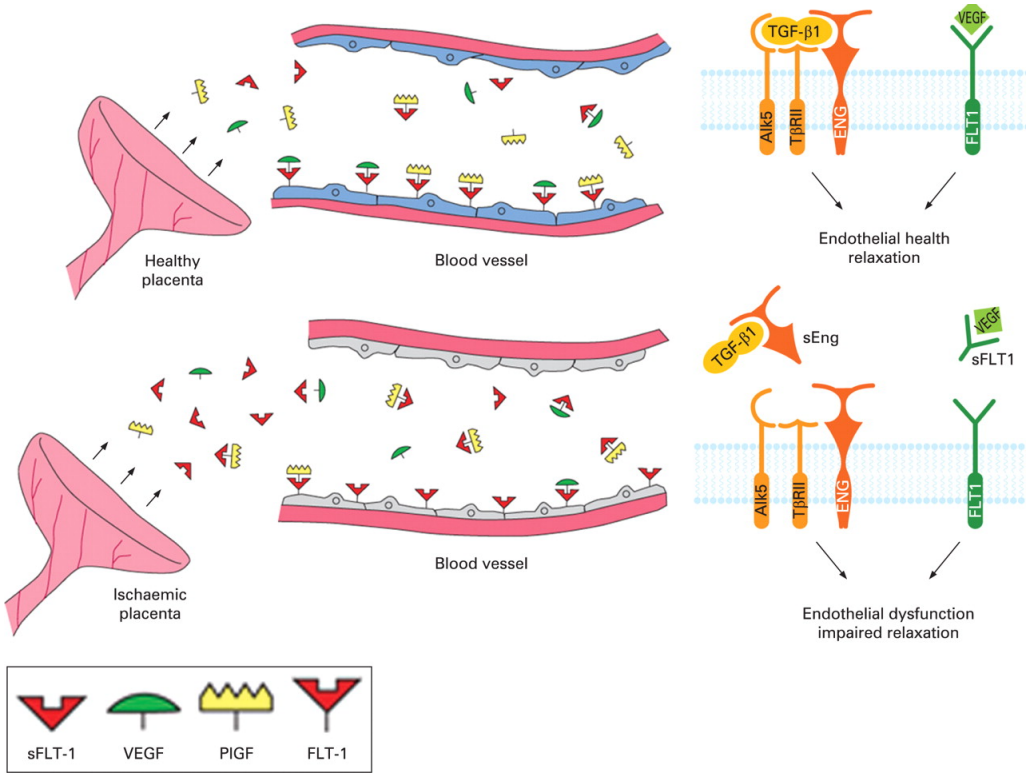

Fig 2. High level of sFlt-1 inactivating VEGF and PGlF (Illustration from the journal of clinical pathology: http://jcp.bmj.com/content/61/12/1254/F1.expansion)

VEGF and PlGF are in particular required for the maintaining the integrity of the fenestrated endothelium, found in the kidneys liver and brain. These organs are typically affected in pre-eclampsia[5]. Soluble Flt-1 is an important contributor the maternal syndrome. It is nonetheless important to remember that not all with preeclampsia have raised levels of sFlt-1.

Angiotensin II Autoantibodies

High levels of autoantibodies to the angiotensin type I receptors have been detected in preeclamptic women. The action of these autoantibodies is that it causes hypertension. The angiotensin II autoantibodies are shown to stimulate sFlt-1 expression from trophoblast cells and IL-6 production from mesangial cells[7]. They increase intracellular Ca2+ signalling in platetelets, ET-1 and oxidative stress in the placenta.

Endothelin

Endothelin-1 is the most potent vasoconstrictor known, produced mainly by the endothelium, and binds to the endothelin type A (ET-A) receptor in the vascular smooth muscles[4]. Studies have shown a connection between elevated levels of ET-1 and preeclampsia, some even

suggesting that the severity of the disease correlates with the serum level of ET-1. ET-1 is produced locally and plasma levels do not reflect the levels in different tissues. It also appears that ET-1 is a final common pathway linking factors produced during ischemia of the placenta and the maternal hypertension and is widely accepted as an important factor in the development of preeclampsia[4]. The ET-1 system may become a therapeutic target for the treatment of preeclampsia in the future.

Nitric Oxide

Nitric Oxide is an important regulator of the vascular tone. The production of NO increases during normal pregnancy and it contributes to the decrease in vascular resistance. Knowing this, it has not been unlikely to believe that a NO deficiency during pregnancy may play a role in the development of preeclampsia. It has been difficult to conclude that there is a drop in the production of NO. Studies on pregnant rats have nonetheless shown an increase of hypertension, proteinuria and intrauterine growth restriction when the NO system has been suppressed[4].

The immune system

Natural Killer cells (NK cells) perform an important role in the innate immune response providing protection against viruses and tumor cells. Studies suggest that they also play a role in the reproduction[7]. The NK cells make up a large part of the lymphocytes of the uterus, secreting VEGF and PlGF among other proteins and cytokines. They interact closely with trophoblast and play an important role in the differentiation, growth, and spiral artery invasion of the trophoblast. They can also induce lysis of the trophoblast cell that will cause a poor invasion of the trophoblasts and inhibit the remodelling of the spiral arteries. Incomplete invasion of the spiral arteries, poor perfusion of blood and nutrients to the placenta may in turn lead to preeclampsia[7].

For a fetus to grow, the maternal immune system must accept the new cells, unequal to the host cells. This maternal immune tolerance involves CD4+ T-cells in an interaction with NK cells that leads to maternal acceptance of the foreign antigens displayed on the fetal cells. Complete failure in this will lead to spontaneous miscarriage whereas an incomplete failure, i.e. a partly inhibition of the local immune system, will lead to poor placentation, perfusion and placenta insufficiency and damage[7].

Pro-inflammatory mediators

There is an up regulation of pro-inflammatory systems in preeclampsia. Harmful factors that are released from the placenta can be considered to be damage-associated molecular pattern molecules (DAMPs or alarmins). These are strongly pro-inflammatory, and are normally released from cells after stress or injury.

Syncytiotrophoblast express several alarmins, and the levels of them are increased in PE. Trials on rats, where alarmin-like molecules have been injected, have shown to induce intravascular coagulation and organ dysfunction. This occurs in severe preeclampsia[5].

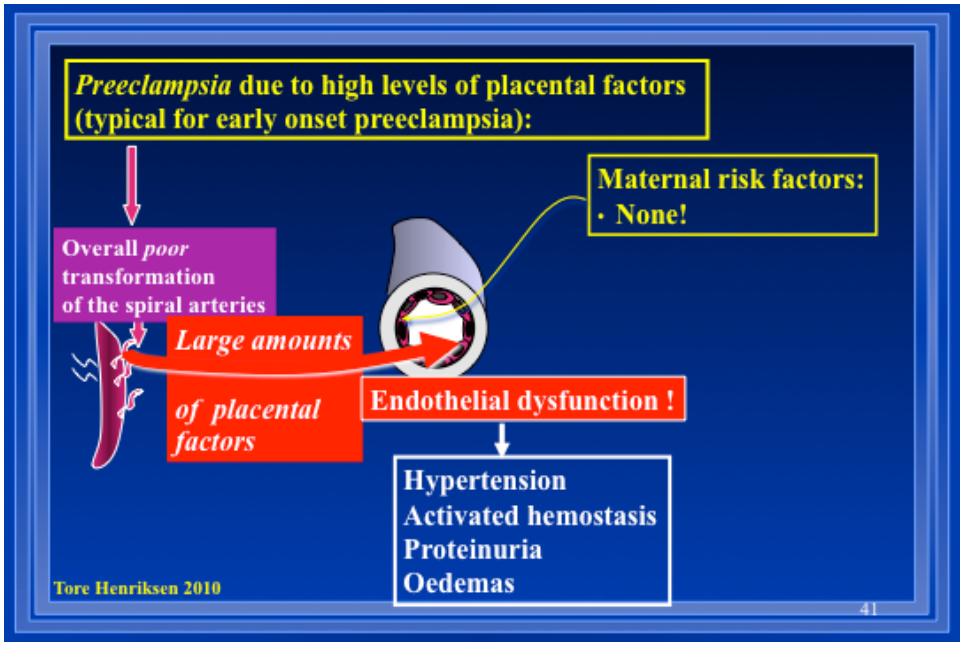

Fig 3. An overview of preeclampsia due to placental factors
(Illustration used with permission from Professor Dr Tore Henriksen)

Maternal risk factors

Known maternal risk factors for developing preeclampsia are:

-Preeclampsia in any previous pregnancy

-Nulliparity

-Age >40

-BMI >35

-Family history of preeclampsia

-Multiple pregnancies

-Chronic hypertension

-Kidney disease

-Diabetes

-SLE and antiphospholipid syndrome

-Race

Nulliparous women and women who change sex partners have less exposure to paternal antigens and a greater risk of developing preeclampsia. This observation underscores the immunological aspects of the disease. Mortality increases with maternal age, and black women are 3,1 times more likely to die from preeclampsia or eclampsia than white women[8].

Both maternal and paternal genotypes contribute to the development of preeclampsia, because men and women who themselves where a product of preeclampsia has a greater risk of having a child complicated by the disease[9]. Exposure to paternal antigens via immune tolerance is believed to offer protection against preeclampsia. The risk is greater in a new-paternity multigravidae compared to a same-paternity gravidae[10].

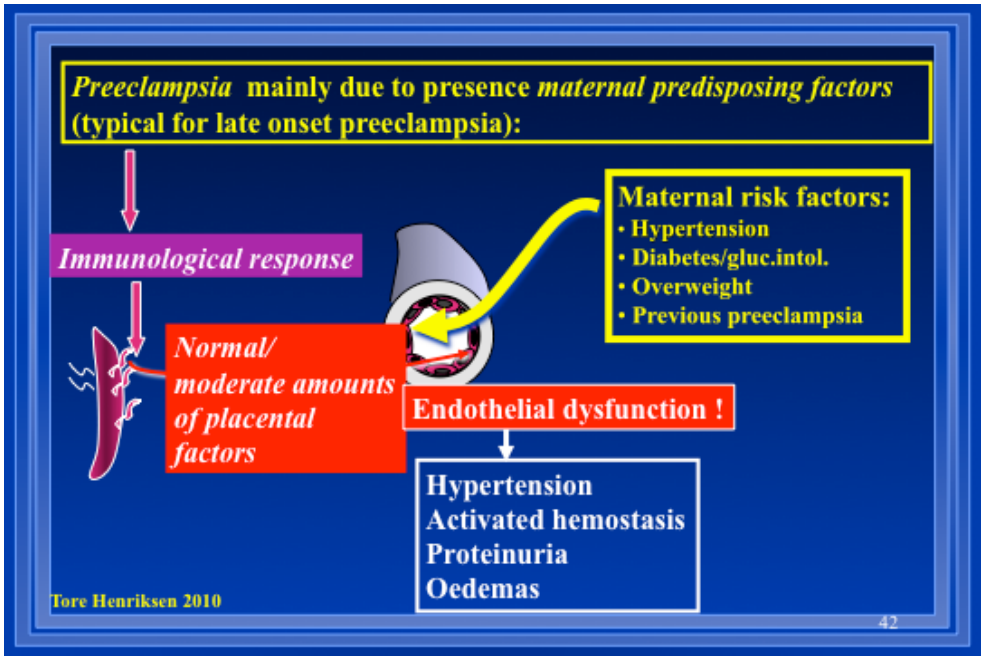

Fig 4. An overview of preeclampsia mainly due to maternal factors
(Illustration used with permission from Professor Dr Tore Henriksen)

Smoking

A surprising fact is that smoking appears to decrease the risk of preeclampsia. Evidence shows that the incidence of preeclampsia is lower in the population that smokes during pregnancy. Studies have shown that cigarette smoke affects the angiogenic markers and endothelial function[9].

Fetal effects

It has been suggested that maternal hypertensive disorders during pregnancy affect fetal growth. Decreased placental blood flow would also affect the flow of nutrients to the fetus and may lead to intrauterine growth restriction. There is an association between higher maternal blood pressure and smaller fetal growth characteristics in the third trimester and at birth[11]. Women with preeclampsia had increased risks of having children who were preterm, had a low birth weight, or were small for their gestational age.

PART II: Future risks

Recurrence

It is well known that women with a previous pregnancy complicated by preeclampsia have an increased risk for recurrence in subsequent pregnancies. The risk of recurrence will depend on the presence of the maternal risks listed in the pathogenesis section. The recurrence is also linked to the severity of preeclampsia in the first pregnancy and presence of other medical disorders. In the review by Dildy[12] and co workers it was found that the highest risk for recurrence are when the initial case was preterm, severe, or complicated by eclampsia, HELLP syndrome or intrauterine growth restriction.

The reported rate of recurrent preeclampsia ranges from 11,5 % to 65%, varying from different studies[13]. In a study by Sibai[14] and colleagues the risk rate was as high as 65%. These were women with severe second trimester preeclampsia. Out of 125 women, 108 had 169 subsequent pregnancies. Out of the women with preeclampsia, one third developed recurrence <28 weeks, one third between 28 and 36 weeks, and the last third after 36 weeks.

Trogstad[15] and colleagues obtained data registered inn the Medical Birth Registry in Norway. The data included the first and second pregnancies of 550 218 women, spanning from year 1967-1998. 20 285 of the first pregnancies where complicated by preeclampsia, giving an overall prevalence at 3,7 % in first pregnancy. The recurrence risk in the second pregnancy for women with a first time singleton pregnancy with preeclampsia was 14,1%. They also estimated the risk for women with a first time twin pregnancy, which was lower at 6,8 %. Mostello[16] estimated a recurrence rate of 14,7% and concluded that the risk of recurrence increases with earlier gestational age at the first delivery complicated by preeclampsia and with increasing maternal BMI.

Sibai[17] and co workers also described women with HELLP syndrome and complications in the subsequent pregnancy. The retrospective analysis consisted of 341 patients from 1977-1992, of which 152 patients had subsequent pregnancies. Complications included preeclampsia (19%), preterm delivery (19%), HELLP (3%), intrauterine growth restriction (21%), abruptio placentae (2%), and perinatal death (4%). 13 of the patients had pre-existing chronic hypertension, and had 20 subsequent pregnancies. They had higher rates of pre-eclampsia (75%), preterm delivery (80%) and perinatal death (40%). The rate for HELLP syndrome was however low: only 5% of the patients had a recurrence in a subsequent

pregnancy. The results showed that women with a previous HELLP syndrome have an increased risk of pregnancy complications in future pregnancies but a low risk of repeated HELLP syndrome.

Eclampsia is a complication that one strives to avoid. A prospective study by Adelusi and Ojengbede[18] included 64 eclamptic patients from Ibadan, Nigeria. 16% experienced recurrent eclampsia despite the benefit of antenatal care. Sibai[19] and colleagues followed 223 women with eclampsia between 1977 and 1989. Of the 336 subsequent pregnancies, 22% were complicated by preeclampsia and 1,9% by eclampsia. The rate of recurrence is also dependent on gestational age at the onset of the eclampsia.

Prediction of preeclampsia

Routine antenatal blood pressure measurement has been the mainstay of preeclampsia diagnosis. Prediction has been difficult due to the different and not fully understood mechanisms responsible for the disease and clinical heterogeneity of the condition. In later years it has become accepted that early-onset and late-onset preeclampsia are associated with different biochemical, histological and clinical features[20]. Early-onset preeclampsia is associated with placental insufficiency and growth restriction of the fetus whereas in late-onset form the placental involvement is believed to be small.

There are markers and risk factors of preeclampsia. Some of them, maternal factors are known ahead of pregnancy. Others are secondary to pathological changes that occur prior to onset of clinical symptoms. The fact that there is no single test available that is clinically useful in prediction has lead to the combining of several tests as the best available alternative.

Maternal history is done in booking. Family, medical and obstetric history should give an indication of risk. Preeclampsia in previous pregnancy, family history of preeclampsia and cardiovascular diseases, antiphosopholipid syndrome, obesity and chronic hypertension are some of the factors that may increase the risk. Obesity is an unquestionable risk factor and has a strong link with insulin resistance, another known risk factor for the condition[13].

There are *several pregnancy related* risk factors that may affect the risk of developing preeclampsia; hydrops, multifetal gestation, unexplained fetal growth restriction, gestational

hypertension and urinary tract infection. The magnitude of risk depends on the number of factors[13].

As mentioned earlier, high levels of sFlt-1 and Endothelin-1 can be detected in pre-eclamptic women, also prior to onset of preeclampsia. Simultaneously, serum placental growth factor (PlGF) is reduced. A systematic review of published literature by Widmer et al[21] dealt with the potential role of serum PlGF and sFlt-1 in prediction of preeclampsia. The review included 10 studies analyzing sFlt-1 and 14 studies analyzing PlGF. They concluded that increase of sFlt-1 and decrease of PlGF in the third semester is associated with preeclampsia, specifically severe preeclampsia.

Levine et al[22] compared preeclamptic women to normotensive controls. 120 pairs of women were randomly chosen, and serum concentration of total sFlt-1, free PlGF and free VEGF were measured throughout pregnancy. During the last two months of pregnancy sFlt-1 increased and PlGF decreased in the normotensive controls. In the women whom later developed preeclampsia, these changes occurred earlier and were more pronounced. The conclusion was that increased levels of sFlt-1, and reduced levels of PlGF predict the subsequent development of preeclampsia.

Myatt[23] and colleagues tried to identify clinical characteristics and biochemical markers in the first trimester of pregnancy. 2434 nulliparous women at low risk were selected for the study. A multivariable analysis of clinical data and biochemical markers in the first trimester did not prove to be reliable for predicting preeclampsia for women at low risk.

Uterine artery Doppler may be used to assess the flow of blood in the uterine arteries. As mentioned, reduced perfusion is believed to be one of the mechanisms behind preeclampsia. It has been proposed as a screening method in the first and second trimester[13]. According to Scazzocchio[20], Doppler is better for early-onset preeclampsia considering that it is associated with placental insufficiency. However, the use of Doppler evaluation is acceptable for overall preeclampsia. Preformed the first trimester it allows an earlier identification of risk, whereas in the second trimester there are higher detection rates (48-66 %).

Long-term effects of the cardiovascular system

We know preeclampsia is characterised by hypertension and endothelial damage. After delivery, it slowly regresses. The long-term cardiovascular effects after preeclampsia are still debated. McDonald[24] published a systematic review on this topic in 2008 to determine if women with a history of preeclampsia are at an increased risk of cardiovascular sequelae. Five case-control and ten cohort studies met the criteria with a total of 116 175 women with and 2 259 576 women without preeclampsia/eclampsia. The review concluded that the risk of early cardiac, cerebrovascular, and peripheral arterial disease was approximately two times higher in women with a history of preeclampsia or eclampsia. The relative risk (RR) for cardiac disease was 2.33 (95% CI 1,95-2,78), RR 2,03 (95% CI 1,54-2,67) for cerebrovascular disease, and RR 1,87 (95% CI 0,94-3,73) regarding peripheral arterial disease. The cardiovascular mortality was also increased with a RR 2,29 (95% CI 1,73-3,04) [24]. One of the studies[25] included in the review concluded with an even greater risk in the presence of fetal compromise and their recommendation was to asses the women's blood pressure and weight 6 months postpartum and encourages a healthy lifestyle.

The results from Bellamy et al[26] regarding risk of future diseases after preeclampsia were similar to McDonald. The review included 25 studies, with a total of 3 488 160 women of whom 198 252 had pre-eclamspia. The relative risks for hypertension were 3,7 after 14.1 years, for ischaemic heart disease 2,16 after 11,7 years, for stroke 1,81 after 10,4 years, and 1,79 for thromboembolism after 4,7 years. Overall mortality after preeclampsia was increased: 1,49 after 14,5 years. Early onset preeclampsia is associated with an even greater risk of future cardiovascular disease. They also looked on the risk for future cancer. No increase in risk of any cancer was found, including breast cancer, 17 years after pre-eclampsia.

A study[27] was preformed in Holland, where they compared differences in cerebral images (MRI) between women with a history of preeclampsia (n=73) and a control group (n=75). This study was based on the indication that preeclamptic women have an increased risk of stroke later in life[26] and because the research group in Holland had demonstrated cerebral white matter lesions (WMLs) in women with a history of pre-eclampsia. The average age in the control group was 36,9 and 36,6 in the pre-eclamptic group. Mean elapsed time since pregnancy were similar in both groups, 5,0 years and 5,3 (preeclamptic). Birth weight of child and estimated gestational age at delivery were significantly different. The mean weight and

estimated gestational age at delivery in the control group were 3464 g and week 39,9. In the pre-eclamptic group, the equivalent figures were 1842 g and week 33.

Significantly more women in the formerly preeclamptic group had WMLs relative to women in the control group (37% vs 21 %). WMLs were also more severe in the formerly preeclamptic women, and they had larger WML volume[27].

PART III: Dealing with preeclampsia

Prevention of preeclampsia

As previously discussed, there are several factors that can increase the risk of preeclampsia that can be addressed before pregnancy, such as overweight and hypertension. Women that are overweight or obese should be encouraged to achieve an ideal body weight before conception and hypertensive women should achieve control of their blood pressure before conception.

An article by Henriksen[28] addressed the issue of overweight. The increasing proportion of obesity in the population is also leading to an increase of complications, preeclampsia included, during pregnancy and delivery. Physical activity during pregnancy does not harm the fetus and may reduce the risk during pregnancy and delivery. Regular physical activity, or even increased in those who do not exercise regularly, is ought to be encouraged by the physicians.

Hypertension is an accepted risk factor for developing preeclampsia. *Antihypertensive drug therapy* for mild to moderate hypertension during pregnancy is shown to halve the risk of developing severe hypertension[13]. However, there is no difference in the risk of developing preeclampsia compared to placebo treatment leading to the conclusion that antihypertensive therapy hardly has a preventive effect regarding the development of preeclampsia.

Clausen[29] and colleagues did a cohort study of pregnant women where they investigated dietary intake in the second trimester. The results showed that high intakes of energy, sucrose and polyunsaturated fatty acids independently increase the risk for preeclampsia. High intake of sugar increases the risk independently of the maternal weight. Dietary advice should be given, and a balanced diet is ought to be achieved.

It has been postulated that antioxidants vitamin C and vitamin E may have an effect in the prevention of preeclampsia because oxidative stress may contribute to the development of preeclampsia. It is now clear that vitamin C and E are not effective interventions to prevent preeclampsia[30]. Calcium may be useful to reduce the severity of preeclampsia in populations with low calcium intake. If one suspects calcium deficiency, 500-1000 mg calcium pr day should be administrated[28].

It appears that administration of *low-dose aspirin* (60-80mg) may reduce preeclampsia. This is mainly relevant for women with a medical history of preeclampsia and preterm delivery at less than 34 weeks of gestation or women with more than one pregnancy complicated by preeclampsia[30]. Women with antiphospholipid syndrome should also be treated with aspirin during pregnancy, usually in combination with low molecular heparin.

Management of preeclampsia

Pregnant women should be evaluated for signs and symptoms of preeclampsia at each prenatal visit after 20 weeks of gestation. This is a key aspect of routine prenatal care. If the diagnosis is made, the women should be referred to a nearby obstetrical department. The definitive treatment is delivery. When to initiate delivery is based upon gestational age, the severity of the disease and the maternal and fetal condition[31].

Recommended treatment for late-onset preeclampsia, >34 weeks, is delivery even in the absence of features of severe disease. Management of preeclamptic women without features of severe disease at 34+0 to 36+0 weeks is still controversial due to lack of data from randomized trials. These pregnancies are generally managed expectantly to enable further fetal growth and maturation. However, delivery is indicated as soon as they develop signs or symptoms of severe preeclampsia[32].

Early onset preeclampsia without features of severe disease should be managed expectantly given the high risk of complications of prematurity. There ought to be a close maternal and fetal monitoring. Antenatal corticosteroids should be administered to women <34 weeks of gestation to promote fetal lung maturity.

There is no evidence that supports the use of one antihypertensive drug over others[33]. According to the review, there are insufficient data for reliable conclusions. Labetalol is one drug that is recommended, and is known to have fewer maternal and perinatal events. The choice of antihypertensive should depend on the clinician's familiarity with the drug, and the known side effects. Nimodipine, diazoxide and ketanserin are best avoided.

For women with severe preeclampsia and/or eclampsia, the administration of parenteral magnesium sulfate is strongly recommended[30]. Once the mother is stabilized, delivery is the recommended treatment.

Management of women with preeclampsia in prior pregnancies

Women who have had preeclampsia in a prior pregnancy should receive counselling by experienced obstetricians before their next pregnancy[1]. This preconceptual consultation should include information of the risks for both the mother and her fetus in a new pregnancy. The goal in the management is to reduce the maternal risk factors and optimize the maternal health before conception and detect complications as early as possible during pregnancy[13].

The previous pregnancy history should be discussed and reviewed, identification of other risks should also be considered. Information concerning gestational age at onset of preeclampsia, maternal complications, perinatal complications and laboratory tests from the previous pregnancy ought to be obtained[13]. Any chronic disease should be stabilised and well controlled before pregnancy (diabetes, systemic lupus, hypertension, kidney disease, inflammatory bowel disease, haematological diseases etc). Encouraging the patients to lose weight, modify lifestyle and address hypertension is important and easily done during counselling. Folic acid supplementation should be recommended.

Early and individually adjusted prenatal visits should be planned. Firs-trimester ultrasound may be indicated to determine gestational age and assess fetal number. Laboratory blood tests should be obtained according to individual evaluation of each patient to establish a baseline for future assessment[13].

It is also important to inform the women of the risks of a new pregnancy. This is often a question asked and they should be notified if not.

Conclusion

Preeclampsia is a complex, pregnancy specific disease. The mechanisms behind are still not fully understood, but much research has been made in order to solve the mystery. Both maternal and placental factors are believed to play a part in the development of the disease. Insufficient blood supply to the placenta leading to a release of placental factors and causing maternal endothelial dysfunction is one of the most accepted theories. Women with a previous history of preeclampsia have a higher risk of developing cardiovascular disease later in life. Knowing that some of the risk factors of both preeclampsia and cardiovascular disease are identical, it is still not clear if preeclampsia in itself is causing the elevated risk. There is also a risk of recurrence in subsequent pregnancies, and it is essential to reduce maternal risk factors and optimize maternal health prior to conception. A close follow up in subsequent pregnancies may be necessary. It is important to treat these patients to prevent further complications such as eclampsia. Even though the mortality is low in high-income countries, preeclampsia is a leading cause to maternal deaths in the developing parts of the world. Much has been done to understand the pathology of the disease, but there are still many unanswered questions and further research is necessary to achieve full knowledge.

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