Preeclampsia is a major contributer to the maternal and neonatal mortality and morbidity.\textsuperscript{1,2} It is the 2nd largest cause of maternal mortality worldwide and affects 5% to 7% of pregnant women worldwide.\textsuperscript{3,4} The precise etiopathogenesis of preeclampsia remains to be a subject of extensive research, but it is believed that it is likely to be multifactorial. Nevertheless, it is accepted that it is the presence of the placenta rather than the fetus, which is responsible for development of preeclampsia. Although the placenta plays a crucial role in the development of preeclampsia, the onset, severity, and progression is significantly affected by the maternal response to placentally derived factors and proteins. Therefore, mother and fetus should be taken into account when calculating the risk for preeclampsia.

Preeclampsia is generally defined as the development of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman,\textsuperscript{3,4} although different variations of this have been proposed by different groups and organizations. (ACOG, ISSHP, Australian college). It has also been further subdivided into mild, moderate, and severe preeclampsia as well as early and late onset preeclampsia, of which the latter is a more contemporary concept.\textsuperscript{5} It has been suggested that early (before 34+0 weeks) and late (after 34+0 weeks) onset preeclampsia have different etiologies and therefore a different clinical expression, but it is still a subject of considerable research. There are, however, some basic differences between the 2 groups:

A. The late onset type of preeclampsia comprises more than 80% of all preeclampsia cases worldwide. Most of these late onset cases are associated with:

- A normally grown baby with no signs of any growth restriction;
- A normal or only slightly altered behavior of the uterine spiral arteries (no changes in the Doppler waveforms or slight increase of the pulsatility index [PI]);
- No changes in the blood flow of the umbilical arteries;
- An increased risk for pregnant women displaying an enlarged placental mass or surface (diabetes, multiple pregnancies, anemia, high altitude).

B. The early onset type of preeclampsia comprises a small subset of all preeclampsia cases (5% to 20%, depending on the statistics), but comprises the most severe cases of respective clinical relevance. The typical features of this type of preeclampsia can be summarized as follows:

- An inadequate and incomplete trophoblast invasion of maternal spiral arteries;
- Changes of the blood flow within the placental bed spiral arteries and thus in the uterine arteries (notches and other changes [increased PI] of the Doppler waveforms);
- An increased peripheral resistance of the placental vessels may be one cause of an abnormal blood flow of the umbilical arteries (increased systolisis/diastolisis (S/D) ratio in still preserved flow or absent and even reversed end diastolic blood flow velocity in these arteries);
- Clear signs of a fetal growth restriction.

It needs to be clarified that all the above features of the early onset type of preeclampsia are not specific for this type of pregnancy pathology. Most of the cases with early onset preeclampsia are associated with another major pregnancy pathology, intrauterine growth restriction (IUGR). The typical features of early onset IUGR cases are an inadequate trophoblast invasion, an inadequate transformation of spiral arteries, followed by respective changes in the blood flow of the uterine arteries, alterations of the umbilical blood flow, and restrictions of fetal growth.

Because the subgroup with early onset of preeclampsia is associated with relatively severe complications, it has been the focus of basic and clinical research. The combination of the 2 syndromes (preeclampsia and IUGR) in these cases may have lead to the presumption that the early onset type of preeclampsia is caused by alterations described to be causative for IUGR, such as changes in the blood flow of the uterine as well as the umbilical arteries and growth restriction of the baby. But “pure” early onset IUGR cases show exactly the features listed above. Thus it is doubtful whether such alterations are indeed related to preeclampsia at all.

This is supported by studies trying to use uterine artery Doppler as a predictor of preeclampsia. In a study with 10 early onset preeclampsia cases and 423 controls Nicolaides et al used uterine artery Doppler at 11+0 to 13+6 weeks as a...
cells have reached the maternal side of the syncytiotrophoblast mass. This is the time of the first contact of mononucleated trophoblast cells with the maternal decidua. Thus only in week 5 postmenstruation (p.m.) the subtype of extravillous trophoblast cells is established.

At this stage of human development the 2 major subtypes of trophoblast, villous and extravillous, are established and their further subpopulations (villous cytotrophoblast and syncytiotrophoblast versus interstitial [mono- and multinuclear], endomural, and endovascular extravillous trophoblast) are developing.

The development of the trophoblast lineage takes place in week 1 p.c., whereas the definition of the 2 pathways (villous and extravillous) gets in place in week 3 p.c. This temporal difference may become important in terms of the placental origins of pregnancy pathologies such as preeclampsia and IUGR.

Serum Markers to Predict Preeclampsia

There is a general trend in clinical sciences to focus on early predictive markers. This is probably because of the fact that early prediction/detection allows for planning appropriate management, early detection of complications, and in some cases instituting preventative measures thus eventually improving overall outcome. Pregnancy is limited to 40 weeks, and because preeclampsia is defined as new onset of hypertension and proteinuria in the second half of pregnancy, i.e, after 20 weeks of gestation, there are at least 20 weeks (from implantation to week 20 of pregnancy) left for prediction.

Today women who develop preeclampsia can only be detected by the appearance of clinical symptoms such as hypertension and proteinuria. No predictive test is available to identify pregnant women who will subsequently develop preeclampsia and moreover, which of those may develop the early or late type of the syndrome, the mild or severe type, even turning into eclampsia. This is opposed by the high prevalence of preeclampsia (5%), which is associated with a high risk for life threatening events of the mother (18% of all maternal deaths during pregnancy). Furthermore, it has become clear that there are short- and long-term complications for those babies who have been born early, with low birth weight, or after exposure to a stressful environment such as during preeclampsia. Also the women who experienced preeclampsia are known to have a higher risk for health problems later in life such as a higher prevalence of cardiovascular diseases. As preeclampsia has such a high impact on maternal and neonatal morbidity and mortality, it has been and still continues to be a subject of intensive clinical and basic research aimed at identifying new and effective serum markers for risk assessment and reducing complications attributable to it.

In 2004 the new era of serum markers for the prediction of preeclampsia began. Soluble VEGF receptor-1 (soluble fms-like tyrosine kinase 1, sFlt-1) and soluble placental growth factor (PIGF) were identified as potential serum markers for preeclampsia. In the following years it became clear that these markers have some disadvantages such as:

- They can be used to predict preeclampsia only a few weeks before the onset of clinical symptoms.
- They are not specific for preeclampsia but show similar changes in pure IUGR as well. Even worse a recent study...

Figure 1. The diagram presents an overview of early trophoblast development. The first development of the trophoblast lineage at the blastocyst stage is followed by the separation of cytotrophoblast and syncytiotrophoblast, which subsequently is followed by the differentiation of the 2 pathways of trophoblast differentiation, villous and extravillous. On the right, the time course of development after fertilization (p.c., post coitum) is shown.

What Then Is the Origin of Preeclampsia?

Trophoblast Development

Taking a look at early human development (Figure 1) the trophoblast is the first cell lineage to differentiate at the stage of the blastocyst at about day 6 postconception (p.c.). Further differentiation steps result in the formation of the 2 different pathways of trophoblast differentiation, villous and extravillous. On day 15 p.c. the cytotrophoblast...
has shown that higher levels of sFlt-1 at 11 to 14 weeks of gestation were not associated with the risk of preeclampsia but were associated with a reduced risk of delivery of a small for gestational age infant.\(^{15}\)

- A large number of women developing preeclampsia will not be detected by elevated sFlt-1 or decreased VEGF. In a study of Savvidou et al only 3 of 16 preeclampsia cases were detected by measuring sFlt-1 and VEGF at 23 to 25 weeks.\(^{16}\)

More recently, soluble endoglin, an antiangiogenic protein, was raised as a new marker with increasing levels in women who subsequently will develop preeclampsia.\(^{17}\) Soluble endoglin concentrations were significantly different already 2 to 3 months before onset of clinical symptoms. Thus early onset cases could be detected at about week 20, whereas late onset cases could be detected at about week 28 of gestation.\(^{17}\)

The above markers may be able to predict the development of preeclampsia, but only later in gestation. The time window that will be given by such markers may not be wide enough for a successful treatment, especially if an early administration of putative medications is needed and effective only if started in the first trimester. As a consequence there are enormous efforts on the way that are directed toward identifying new and noninvasive serum markers for the early and accurate prediction of preeclampsia in the first trimester of pregnancy. This would enable the use of effective prophylactic or preventive therapies starting as early as possible during pregnancy.\(^{18,19}\)

Such new serum markers showing significant differences already in the first trimester of pregnancy include placental protein 13 (PP13),\(^{6,20,21,22}\) placenta associated plasma protein A (PAPP-A),\(^{21,23}\) long pentraxin 3 (PTX3),\(^{24,25}\) as well as a revival of sFlt-1.\(^{26}\) Taking PP13 as an example of one of the new and early serum markers, it has been shown very recently that this marker may be able to detect even late onset preeclampsia cases as early as 7 to 8 weeks of gestation.\(^{22}\)

The discovery of serum markers capable of predicting preeclampsia with good detection rates and low false-positive rates will pave the way for improved antenatal and perinatal care. This will also allow introducing these markers into routine testing in the first or second trimester similar to the markers currently used in screening for trisomy 21. If such markers enable prediction around the end of the first trimester, this will open a long time window to tailor medications and respective prevention strategies.\(^{3,4,10,11,18,27}\) Hence, such markers and implementations for the early detection and prediction of preeclampsia are urgently required.

### Current Hypothesis: Placental Origins of Preeclampsia

During the last decades a variety of hypotheses has been generated aiming to explain the placental origins of preeclampsia.\(^{28–31}\) Most of them disappeared soon, although a few are still discussed and need approval.\(^{32}\) The last few years there was a shift in defining the placental origin of preeclampsia from midgestation, just before onset of clinical symptoms more toward very early stages of pregnancy.\(^{33}\) This shift was further substantiated by the detection of new and early biomarkers as described above.

The current hypothesis to describe the origin and stages toward the clinical symptoms of preeclampsia can be summarized as follows:

1. Any deleterious effect on the extravillous trophoblast;
2. Failure of the extravillous trophoblast to adequately transform the uterine spiral arteries;
3. Reduced flow of maternal blood into the intervillous space;
4. Hypoxia or intervals of hypoxia followed by reoxygenation of the placenta;
5. Hypoxic damage of the villous trophoblast;
6. Release of STBM (syncytiotrophoblast membrane fragments);\(^{34}\) into the maternal blood stream;
7. Maternal inflammatory response to the STBM resulting in the development of the clinical symptoms of preeclampsia.

### Challenging the Current Hypothesis

The current concept on the placental origin of preeclampsia starts with a failure to transform the maternal spiral arteries, subsequently followed by alterations of the villous trophoblast and its release of material. Figure 2 brings these 2 events into a time frame during pregnancy and clearly shows that the temporal sequence of events does not fit with the current hypothesis.

A few years ago it has been very clearly demonstrated that during the first trimester of pregnancy there is no flow of maternal blood cells into the intervillous space of the placenta.\(^{35}\) Only at around 11 to 12 weeks of gestation the plugs of extravillous trophoblast cells blocking the lumen of the spiral arteries are dislocated and open the flow of maternal blood toward the placenta. This can be traced by the increase of oxygen from the first to the second trimester.

In parallel, the last few years have witnessed an enormous increase in the knowledge of serum markers for preeclampsia, especially those showing significant alterations in their concentrations as early as 7 weeks.\(^{22}\) Thus, these alterations can be measured weeks before the onset of flow of maternal blood cells through the intervillous space.

A failure of transforming the spiral arteries may lead to a reduced diameter and thus will affect the blood volume flowing toward the intervillous space. Because blood flow is only established at the beginning of the second trimester, such
An insult occurring very early during trophoblast development, before or at the blastocyst stage, may affect the villous as well as the extravillous pathways of trophoblast differentiation thus leading to a combination of preeclampsia and IUGR. Such very early insults are often the most severe ones, thus the resulting combination of early onset preeclampsia and IUGR is the most frightening situation for both mother and child. If the insult is too strong it may even result in a spontaneous abortion of the baby.

It may even be true that an insult leading to alterations of the villous trophoblast and thus causing preeclampsia may in a second stage also affect the growth of the fetus—if the villous trophoblast is no longer able to maintain its transport capacities to adequately feed the fetus.

Thus the new hypothesis brought forward here reads as follows:

Preeclampsia is the result of a failure of villous trophoblast differentiation, which—on the placental side—ultimately leads to an abnormal release of trophoblast material into the maternal circulation.

The different scenarios are (Figure 4):

1. Normal Pregnancy

During normal pregnancy aged and late apoptotic syncytiotrophoblast nuclei are packed into apical protrusions of the syncytiotrophoblast,36,37 called syncytial knots9 (Figure 4, light gray). These membrane-sealed corpuscular structures are apoptotically generated and released from the apical syncytiotrophoblast membrane into the maternal circulation. They are transported through the maternal venous system behind the placenta and reach the first capillary bed behind the placenta, the lungs.38 Here these huge apoptotic structures, containing multiple nuclei, are engulfed by lung macrophages (Figure 4, light gray) and thus cannot be detected in peripheral maternal blood behind the lungs.39 In peripheral blood of healthy pregnant woman these structures are virtually absent.40 It has recently been described that the engulfment of apoptotic material by macrophages leads to a silencing of such macrophages, thus reducing the secretion of proinflammatory cytokines.41,42

2. Preeclampsia, Induced by Intrinsic Placental Factors

During preeclampsia the release of the syncytiotrophoblast material does no longer follow the normal rules. Because of an alteration in villous trophoblast differentiation early in pregnancy, the release of syncytial knots is no longer the main mechanism of disposal. Now other mechanisms take over such as necrosis and aponecrosis43 (Figure 4, dark gray). The latter term has been introduced by Formigli et al44 and describes the start of the apoptosis cascade followed by a failure of the program to end normally. This then results in a necrotic release of already apoptotically cleaved material.

The 2 mechanisms, necrosis and aponecrosis, give rise to the necrotic and cell-free release of trophoblast material. Such necrotic trophoblast fragments can be detected in high numbers only in preeclampsia whereas in pure IUGR they are not elevated above normal levels.45 The trophoblastic fragments, termed STBM,44 are nonapoptotic and thus no longer

**New Hypothesis: Placental Origins of Preeclampsia**

The very early alterations in the concentrations of serum markers point out that preeclampsia seems to develop already at the onset of placentation, somewhere around implantation or even earlier. As shown in Figure 3, at these early stages of human development there may be several differentiation steps and developmental stages, where any insult on trophoblast differentiation could result in preeclampsia or IUGR or any other pregnancy pathology up to spontaneous abortion:

1. If the very first differentiation of the trophoblast cell lineage is affected during development from morula to blastocyst (Figure 3), this may result in a severe defect of the trophoblast cell lineage in general. This may result in a combination of IUGR and preeclampsia or even more severe outcomes such as spontaneous abortions.

2. If the insult takes place slightly afterward, when the blastocyst trophoblast differentiates into the first cytotrophoblast and syncytiotrophoblast (Figure 3), the same dramatic outcome as described above may result.

3. Afterward, if only the differentiation of the extravillous trophoblast pathway is affected, this may result in pure IUGR (Figure 3) with all the typical characteristics such as failed invasion and abnormal uterine artery Doppler.

4. If only the villous pathway is affected, then a preeclampsia may result (Figure 3) with its typical characteristics such as release of STBM and a maternal inflammatory response.

**Figure 3.** The diagram represents the early development of the trophoblast lineage. The decisive differentiation steps are highlighted with gray boxes. The dark gray boxes indicate the very early differentiation steps. If there is a failure during this time development the pregnancy may result in a combination of preeclampsia (PE) and IUGR. If only the villous pathway is affected, it may result in a preeclampsia (lower left). And if only the extravillous pathway is affected it may result in an IUGR (lower right).

A failure in transformation can only be effective after onset of blood flow, ie, after week 12 of gestation (Figure 2). How can a failure that is effective only at the beginning of the second trimester lead to alterations of the release of proteins from the villous trophoblast already in mid first trimester?
membrane-sealed structures. They are small (200 to 600 nm;\(^{44}\)) and can pass the lungs; therefore they can easily be detected in peripheral blood and may cause systemic alterations of the maternal endothelium and inflammatory system.

Although early serum markers may predict preeclampsia already in the first trimester of pregnancy, the respective clinical manifestation of preeclampsia only occurs after midgestation. This discrepancy can be explained as follows: During the first trimester of pregnancy trophoblast turnover is different to the turnover later in gestation. In the first trimester most of the fusion events of cytotrophoblast cells with the syncytiotrophoblast are needed for growth of the syncytiotrophoblast rather than for the maintenance of this layer.\(^{37}\) Only later in gestation a steady-state between input of new material by cytotrophoblast fusion and release of syncytial knots is established. During the first trimester the release of trophoblast material is much lower than later in gestation. This is not only true because of the lower total placental mass and surface early in gestation but also because of the differences in trophoblast turnover at the two different stages of trophoblast development.

3. Preeclampsia, Induced by Extrinsic and Maternal Factors
The origin of preeclampsia may not be restricted to an intrinsic alteration of the villous trophoblast alone. Looking at the conditions with an increased risk to develop preeclampsia, they may be divided into those that increase placental mass or surface and those that alter the response of the mother to what is released by the placenta.

Specific conditions increase placental mass (diabetes or multiple pregnancies) or placental surface (hypoxic conditions of the mother: anemia, high altitude; Figure 4, gray pathway on the left, extrinsic factors). This increase will be paralleled by an increase in the release of syncytiotrophoblast. If the maternal clearance system cannot cope with this increased number of apoptotic fragments, they may undergo secondary necrosis within the blood and thus may lead to the clinical symptoms of preeclampsia as well.

The same may be true if the maternal disposal or inflammatory systems are not working properly and react inappropriately to the release of apoptotic trophoblast fragments (Figure 4, gray pathway on the left, maternal factors). Again, this may lead to an overload of the disposal machinery, thus inducing a systemic activation and damage of endothelial cells, resulting in preeclampsia.

Conclusion
Ultimately, preeclampsia is a syndrome of early placentation. An insult resulting in an aberrant development and differentiation of the villous syncytiotrophoblast causes an impaired maintenance of the placental barrier. This will subsequently lead to the release of necrotic and aponecrotic trophoblast fragments culminating in a systemic inflammatory response of the mother. By contrast, a failure of extravillous trophoblast invasion is correlated with the pathophysiology of IUGR. The new concept brought forward here clearly separates the origins of preeclampsia and IUGR and proposes alterations in different trophoblast differentiation pathways as origins for both syndromes.
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Berthold Huppertz

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