ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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Τίτλος: «Early or late onset preeclampsia and neurodevelopment in the offspring: a systematic review and meta-analysis»

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Περιεχόμενα

Γενικό μέρος-Βιβλιογραφική ανασκόπηση

1. An overview of Preeclampsia

1.1. Hypertensive disorders - Introduction: Hypertensive disorders constitute a very broad subject of pregnancy pathology as it is related to a large share of morbidity and mortality each for the mother and the infant (1,2). It seems that women who underwent hypertensive conditions during pregnancy have correlated with specific population groups, like those with increased body mass index, advanced age, or other health problems at the same time (3,4). Nowadays, four types of hypertensive disorders can be recognized. Chronic high blood pressure is the case when increased blood pressure is present before the onset of pregnancy or before the 20 weeks of gestation or until 12 weeks after delivery and it is not accompanied by organ failure or maybe the effect of pre-existing renal or endocrinological comorbidities. The percentage of women that are affected with this type of hypertension is up to 5% these days, but it is expected to be elevated in the coming years as a result of the overweight women and increased first gestational age (3,4).

A special case is considered preeclampsia which arises from pre-existing chronic hypertension. The overall risk for preeclampsia in this group of women is up to 40% and the complications both for mother and fetus are much more severe in comparison with every situation alone (3–5). According to the American College of Obstetricians and Gynecologists, the diagnostic criteria for this type of preeclampsia are the presence of further increased blood pressure after 20 weeks or weakness of typical antihypertensive agents to regulate blood pressure or further increase in proteinuria in a woman with pre-existing proteinuria early in pregnancy (3–5). Despite this pattern, diagnosis of preeclampsia remains very challenging. So, several early biomarkers are necessary to be found, and in this way patients with increased risk for developing this disorder to be under careful monitoring (1,2). The last two disorders have to do with hypertension arising after 20 weeks of gestation and these are gestational hypertension and preeclampsia. Gestational hypertension is the first appearing pressure rise beyond 20 weeks that is not accompanied by the diagnostic criteria of preeclampsia. However, it can be converted to preeclampsia in up to 50% of these women, but of course in direct correlation with the time of the presence (3–5).

1.2. Epidemiology of preeclampsia: The most severe condition of hypertensive disorders seems to be preeclampsia and any complication that can arise because of this. Preeclampsia is a multisystemic disorder that entangles pregnancy and can affect up to 8% of all women during gestation in developed countries. It is related to the possible presence of preeclampsia in previous pregnancy (2,6). At the

same time, it seems that the risk for the onset of preeclampsia for the first time is greater in the first pregnancy (3-7%) and this possibility is reduced in the next pregnancies (1-3%) (6,7). Generally, the result for mother and fetus is very controversial as preeclampsia has been convicted for remarkable mortality and morbidity perinatally because of the possible complications from high blood pressure and organ dysfunction. This disorder has been correlated with many maternal deaths worldwide, especially in complications like eclampsia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome or pulmonary edema. At the same time, it is very usual for these complicated pregnancies to end up with a small for gestational age baby (SGA) or preterm birth, having, as a result, notable effects on the lung formation of the infant and possible presence of cerebral palsy (1,3,7,8).

1.2.1 Risk factors: It is very important at the onset of pregnancy to recognize women who are at great risk of developing this hypertensive disorder during gestation and put them under frequent monitoring. As particularly important risk factors are identified as chronic hypertension, preeclampsia in previous gestation or presence of first-diagnosed hypertension in pregnancy before 20 weeks, chronic kidney disease, any type of diabetes, and auto-immune disorders like systemic lupus erythematosus or antiphospholipid syndrome (1,4,6,7). At the same time, other factors to be considered are the first pregnancy, the advanced age of mother and mainly beyond 40 years old, increased body mass index > 30, 5-10 years interval between pregnancies, multiple gestations, and previous history with preeclampsia in the family (1,4,7). Also, possible adverse situations in a previous pregnancy may have an association with the onset of preeclampsia, such as a stillborn fetus, a possible abruption of the placenta, and the presence of intrauterine growth restriction previously [7]. Finally, it seems that pregnancies that come from assisted reproductive technology may result in the development of preeclampsia and trisomy 13 and X-linked differentiation in gene expression in the placenta are not so frequent causes (7,9).

1.3. Pathophysiology of preeclampsia: According to the data, the risk for developing preeclampsia later in pregnancy is related to many early changes in the formation of the placenta. In a completely normal pregnancy cytotrophoblasts penetrate the decidua basalis and cause rehabilitation of the spiral arteries as they replace the muscle wall with fibrinoid material. Thus, the muscle tone is lost, and the blood flow is smooth and thus providing oxygen and other useful products for the development of the fetus (4,6,9,10). In preeclamptic women, this configuration does not take place and the wall of the vessels remains unaffected. Particularly, spiral arteries do not lose their muscle tone and the resistance to the blood flow is remarkable and this is the first stage of the preeclampsia's pathogenetic mechanism (4,6,9). At

this stage there are no complications for the mother or fetus, however, hypoxia at a time when oxygen demand is very high can cause the activation of maternal inflammation response. Many weeks before the onset of the first symptoms of preeclampsia, the installed hypoxia leads to the release of hypoxia-induced factors 1a and 2a which have related to many complications in tested animals, and the concomitant oxidative stress causes the loss of normal function of the endothelial wall of the spiral arteries and this is the second stage (4,9,10).

It seems that this inflammatory procedure is installed as a result of the increase of T-helper cells type 1 in comparison with T-helper cells type 2 due to hypoxia and leads to the production of cytokines like TNF-a and IL-6 that work by preventing further penetration of the placenta to the endometrial wall and vascular destruction (10–12). Respectively, IL-10 has a different but equally important role in the placentation process because of the T-helper cells' type 2 response, which is increased in the normal placentation process and helps to prevent immune rejection of the placenta. It seems that in preeclampsia, where T-helper cells type 2 response is limited to benefit of T-helper cells type 1 response, IL-10 is decreased. In this way, Fas-mediated apoptosis can be activated and there is an increased elimination of matrix metalloproteinases and serine proteases locally that can provoke placental rejection and prevent the normal invasion of the vessels (13). These inflammatory changes lead to the development of three different types of pathological microscopic forms of the placenta. Particularly, one form has to do with damage to the endothelial wall and concomitant necrosis of the arteries locally and as a result impossibility of penetration and smooth perspiration. The second form has to do with the lack of oxygen in this environment and the development of necrotic areas in the placenta and the presence of trophoblastic obstacles that cause placental insufficiency. The last form is less related to inflammation and the main cause is the absence of the regular trophoblastic penetration into the endometrial wall because of improperly differentiated trophoblasts (10,12).

The hypoxic environment in the placenta leads to the release of antiangiogenic factors in the circulation of the mother, such as soluble fms-like tyrosine kinase 1(sFlt-1) and soluble endoglin (sEng) much before the presence of symptoms of preeclampsia (4,9,11). sFlt-1 is considered an analog of vascular endothelial growth factor receptor 1(VEGFR1). VEGFR1 is useful in the formation of the vessels when factors like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) bind on this receptor. In preeclamptic women these factors are reduced because of their binding on the sFlt-1, so that formation of the endothelial wall of the vessels to be inhibited. Also, it seems that this factor is increased in the last months of

pregnancy and normally may have a role in shutting down the development of the placenta, but in preeclampsia, its presence is much more increased earlier, even up to 5 weeks before the onset of the disease (4,9–11,14,15). Respectively, sEng is a factor that has been correlated with more severe preeclampsia as it inhibits transforming growth factor β1(TGF-β1) and takes part in the “vascular effect” of preeclampsia (4,9,14,15).

Other pathways have been related to the pathogenesis of preeclampsia. Heme oxygenase pathway has to do with hypoxia-induced increased release of HO enzyme in two forms Hmox1 and Hmox2 that can cause the secretion of CO and dilation of the vessels in the placenta so that better blood perfusion to be achieved. However, in preeclampsia, this enzyme is decreased and there is hypoperfusion (9,14). Some studies also examined the relationship between endothelin-1 (ET-1) with the presence of preeclampsia and complications from the cardiovascular and renal systems. It seems that the levels of ET-1 are increased in preeclamptic mothers, particularly in those who had an elevated sFlt-1. At the same time, some data show that in this hypertensive disorder the levels of matrix metalloproteinases (MMPs) are also elevated and can cause the corresponding elevation in ET-1 levels and as a result vasoconstriction that could cause the blood pressure deregulation in the mother (10–12,14).

Another factor that seems to be related to the pathogenetic mechanism of preeclampsia is hydrogen sulfide (H_2S), which can be produced by the placenta and other tissues. Particularly, H_2S can cause dilation of the vessels, restricts inflammation from any cause locally, induces angiogenic procedure, and prevents cell damage and destruction after reperfusion. H_2S formation can take place with the expression of three enzymes and the pathway to involvement in the pathogenetic mechanism of preeclampsia is related to the reduced expression of one of these enzymes; cystathionine γ-lyase (Cth). Many data have shown that if this enzyme is not expressed in the placenta, thus there is a low quantity of circulating H_2S. At the same time, other data correlate the blockage of this enzyme with the increasing levels of sFlt-1 and sEng and as a result, can lead to anomalies in the formation of the placenta and contribute to the intrauterine growth restriction (IUGR). As far as treatment is concerned, studies with the evaluation of H_2S analog show encouraging results in reducing the severity of preeclampsia and the better angiogenic process by induction of VEGF receptor (14,16).

Some data have also highlighted the abnormal nitric oxide (NO) pathway in pregnancy as a possible way for a woman to develop preeclampsia during gestation. The deregulation of NO synthase type 3, which has its place on the endothelium of the

vessels, can lead to the reduced release of NO in the circulation and limited vascularity. This can cause fetal-placental circulation disorder, as a result of the reduced relaxation of the muscle tunic of the vessels in the placenta. At the same time, some data from research models show that this pathway is related to the presence of changes in uterine and spiral arteries. Also, NO deregulation is associated with some of the features of preeclampsia, such as upregulation of the blood pressure, protein elimination by the tails, and platelet abnormalities (9,14,16).

Beyond all these mechanisms, there is evidence that preeclampsia is related to the presence of circulating autoantibodies against angiotensin receptor 1(AT1). This immune response may cause complications by the activation of oxidative factors or the endothelin pathway. However, the relationship between AT1-autoantibodies and sFlt-1 is still controversial according to some studies (14). All of these end up in increased blood pressure and are considered an early stage before the onset of preeclampsia, but if an angiotensin receptor blocker is administered, it seems that hypertension can be regulated. Also, hypertension via these autoantibodies influences the endothelin pathway by upregulating the expression of ET1 and as a result, increases the potential of ETa receptor on the vascular wall and decreases on the other hand ETb receptor effects by binding on this. Thus, if there is a blockage on these two receptors with different factors, hypertension that can be caused may be treated (9,10).

Among the most frequent factors for the pathogenesis of preeclampsia seems to be oxidative stress, as it is present in every pregnancy already from the first stages of placentation. However, when there is abnormal penetration of the spiral arteries, the oxygen available in the area is very limited for the occasion and, thus, the oxidative stress is increased. The main reason for this situation is the imbalance between pro-oxidant and antioxidant factors locally, as is portrayed by the increased reactive oxygen species (ROS) and mitochondrial activity (9,10,14,16). Data show that the presence of ROS has been related to the interruption of some pathways, like Wnt/β-catenin, that are important in placentation. At the same time, there are some studies to support that ROS production can be the result of significant mitochondrial abnormalities, such as the restriction of the active mitochondrial electron transport chain (ETC) enzyme cytochrome C oxidase in placental cells that causes the increase in sFlt1 effect on vessel formation (9). Oxidative stress may also derive from many other placental factors like maternal leukocytes and endothelium (14).

1.4. Diagnosis of preeclampsia: Evaluation of preeclampsia can be made in many stages starting from the early history of the mother, blood pressure measurements, and laboratory values that can show up the possible organ

dysfunction. The complete history includes screening for potential risk factors that could be related and physical examination of the woman (4,7,12,17). Many studies have demonstrated the fact that the presence of risk factors for a mother must be analyzed in combination with other characteristics during the early stages of pregnancy to predict the possibility of developing preeclampsia later. However, the individual report of any risk factor can be correlated to preeclampsia and must be taken into consideration and be examined with closer monitoring (12,17).

To be diagnosed with preeclampsia, certain criteria must be met. Particularly, it has to do with the presence of increased blood pressure for the first time, after 20 weeks of gestation. This hypertension must be verified in two different measurements with systolic blood pressure >140mmHg or diastolic >90mmHg with a 4- to 6-hour interval time and having as a fact that the woman is in the appropriate position with the right cuff in her arm and measurement that can be assessed with the correct device. Without any other abnormality, this can be characterized as gestational hypertension (3,6,8,18–20). However, when this is accompanied by remarkable proteinuria ≥300 mg/24h or 1+ protein on urine dipstick or protein/creatinine ratio ≥30 mg/mmol or albumin/creatinine ratio ≥8 mg/mmol, then the diagnosis of preeclampsia can be made. Also, if instead of proteinuria, there are indications of organ dysfunction from laboratory tests or physical examination, then respectively the diagnosis advocates for preeclampsia. The new onset of doubling in liver enzymes value, doubling in creatinine value or creatinine value >1,1mg/dl, platelets <100.000 μL, but also possible epigastric pain, pulmonary edema, or neurological symptoms has been correlated with the diagnosis of preeclampsia (4,9,18–21).

Among the women with preeclampsia during gestation, it is very important to distinguish those with severe disease to ensure a more aggressive treatment. In these cases, women show up with quite high systolic blood pressure ≥160mmHg accompanied or not by diastolic blood pressure ≥110mmHg in two consecutive measurements in 15 minutes. These values in blood pressure should be mixed with the organic failure points mentioned above to characterize the condition as severe preeclampsia (3,4,19,22). This condition requires immediate treatment for the best outcome for both mother and fetus. Otherwise, it is possible to end up with eclampsia and HELLP syndrome. Findings from physical examination like severe headache, right upper quadrant or epigastric pain, nausea, or vomiting must also make everyone suspicious of severe preeclampsia and its complications (4,7).

Particularly, for each of the three components for the diagnosis of preeclampsia, there are new data. Regardless of the blood pressure values that are considered scary for pre-eclampsia, it is now better known than this gestational

dysfunction can be present even without elevated blood pressure values and the diagnosis can be made or make us suspect it from other symptoms during pregnancy (7,23). In addition, women with multiple risk factors for developing preeclampsia need more intensive monitoring, which is why the option of measuring blood pressure at home may be acceptable. Data show that in this way pregnant women avoid unnecessary hospital admissions, and, at the same time, it can reject the case of hypertension of “white coat” [23]. As far as proteinuria is concerned, there are data to support the view that 24-hour urine collection is problematic and can no longer be trusted as the “gold standard” (3,4,21).

About laboratory tests for the emergence of possible organic deficiency in the context of preeclampsia, it seems that apart from the standard tests, many biomarkers are now useful for early diagnosis during the last trimester of pregnancy. sFLT1, sEng, and PIGF are factors providing new features in approaching women with possible preeclampsia (21,24). As is known above, sFLT1 is a variant of VEGFR and binds to VEGF and PIGF instead of this receptor when there is a hypoxic environment in the placenta. So, in preeclampsia sFLT1 increases widely in proportion to the severity of the disease, and the higher it is, the earlier the symptoms related to preeclampsia appear. Another fact is that women with early-onset preeclampsia or diagnosed with preeclampsia combined with a small for gestational age (SGA) fetus seem to have even more increased levels of sFlt-1. Also, many data show that sFLT1 is increased a few weeks before the onset of symptoms (9,21,24,25). sEng is another biomarker that seems to act cooperatively with sFlt1 in the development of preeclampsia and many studies have highlighted elevated levels of this factor in women with placental surface disorder. Particularly, as in the case of sFlt-1, this factor is increased earlier before the onset of the disease, when it has its peak level. However, some other studies do not come to the same conclusion and suggest that this biomarker should be considered in conjunction with others (9,24,26).

These two biomarkers are antagonizing placental growth factor (PIGF), which is a key factor in the placenta formation process in combination with other angiogenic properties. Thus, many studies support the fact that in women with preeclampsia the presence of PIGF is very limited even during the first and second trimester of pregnancy, but the most important thing is that it can be very low either weeks before the presence of symptoms or at the time of diagnosis (9,21,24). The measurement of PIGF contributes to the faster confirmation of preeclampsia and in some cases can be very helpful in avoiding the onset of unwanted symptoms in the mother, but unfortunately not in the fetus (21).

Combining these biomarkers results in a ratio, which as has been shown in several studies, is very crucial not only for the early confirmation of preeclampsia but also for the prediction of this condition. It seems that the sFLT1/PIGF ratio takes different “cut-off points” depending on the gestation stage. In case this ratio is ≥85, then preeclampsia is a very possible diagnosis in women who are in the 34th week of pregnancy or lower with acceptable sensitivity up to 89% and specificity up to 97% (9,19,24). This approach, at this gestational age, provides the opportunity to identify these pregnant women who are going to develop symptoms of preeclampsia soon and are likely to give birth within 2 weeks (9,19). At the same time, corresponding values of this ratio are sFLT1/PIGF ≥33 concerning pregnancy after 20 weeks and sFLT1/PIGF ≥110 concerning the gestational age after 34 weeks [16]. However, this ratio is more useful in excluding the possibility of this condition than in formalizing its presence when the values are below the cut-offs (9,21). The very important thing about this diagnostic tool is that it is easily accessible, can be done quickly, and gives results within a day, which is necessary for the confirmation of preeclampsia. These biomarkers individually but also in combination appear to be sensitive in the diagnosis of preeclampsia early and especially in high-risk pregnant women (9,19).

Because of the very known uteroplacental dysfunction, which is responsible for most preeclampsia cases, it is necessary during the examination of women with symptoms related to this condition and several risk factors for developing preeclampsia, to undergo a detailed examination of the placenta. In some cases, the combination of this examination results and the abovementioned sFLT1/PIGF ratio can be correlated with this hypertensive disorder (21). The main anatomical structure that is examined and seems to be useful in determining the likelihood of preeclampsia is the uterine arteries and the mean pulsatility index of both arteries. Many data show that this marker is weaker in diagnosing preeclampsia, the later the gestational age is. Thus, if the measurement of this index is within normal limits, then the diagnosis of preeclampsia is controversial. The usefulness lies in the case of the abnormal or unavailable index and this case is necessary to combine this result with the sFLT1/PIGF ratio. If this ratio is very high above the 95th percentile, then the diagnosis of preeclampsia is very likely and immediate management is necessary, even urgent childbirth within 48 hours. However, if this ratio is nearly above the 95th percentile, then these pregnancies should have close monitoring rather than immediate delivery or delivery before 34 weeks of gestation, always in combination with the absence of clinical signs of immediate need for intervention (21,27).

1.5 Prediction and Prevention of Preeclampsia: Given the fact that preeclampsia is correlated with severe adverse outcomes for mother and infant, it is of

great importance for screening testing to be developed even from the very early gestation. Particularly, early-onset preeclampsia has been convicted for most side effects and in most cases needs urgent processing of pregnancy before 34 weeks, in contrast with the late-onset in which delivery takes place at 34 weeks or later, and it is not related to such severe adverse events. Thus, the main target of screening is to optimize the prediction of the first case even from the 11–13-week ultrasonography scan (17,28). However, before correlating all these laboratory, imaging, and clinical findings, that are nowadays known about the early prediction of preeclampsia, the possible risk factors need to be considered. Many studies support the fact that maternal history and characteristics must always be examined during the first visit of a pregnant woman for the nuchal translucency scan at 11-13 weeks of gestation (2,17,28). The risk factors that have been mentioned above are the first step in a sequence of appropriate forecasting tools and can only contribute a percentage of about 30-40% to the final detection rate, and particularly according to some studies this percentage has to do with the early onset type of preeclampsia, whereas the detection rate for late-onset type is about 20% with a false positive rate of 5-10% depending on each study (2,8,28,29).

Having these risk factors known is a very useful part of the prediction, but it can only help in a very limited separation among women as high and low risk for developing preeclampsia later in gestation. Thus, the novel approach to the detection of possible development of this hypertensive disorder later in pregnancy is the calculation of the risk for every pregnant woman individually, assuming that if the pregnancy continues normally without any intervention, these women will develop preeclampsia (28,29). By this method, every risk factor depending on its severity affects the final time that preeclampsia would probably occur so that women with fearful risk factors are in a high probability of developing this disorder earlier and therefore manifesting before childbirth, whereas pregnant women with low-risk factors prolong the time of the onset. The data from the studies examined converge on the fact that the risk factors that lead to a high risk for the development of early-onset preeclampsia are the Afro-Caribbean and South Asian origin, presence of preeclampsia, or hypertension in the past, and the gestation by IVF techniques. On the other hand, the late-onset type is also related to these factors, less to IVF, but it can be affected by the age and weight of the mother and family history. However, as mentioned earlier these risk factors contribute to a very small percentage of disease prognosis but by using this new approach in risk detection, it is easy to combine the result with ultrasound and biochemical markers (8,28,29).

Having as a fact that preeclampsia can be caused by the affected placental function and that the uterine artery flow is a very important part of the adequate perspiration and proper gas exchange in the placental microcirculation, many data have highlighted its critical position as a predictor that can be correlated with others in the preeclampsia screening. During gestation, the uterine artery flow is increased as is expected because throughout the uterus the placenta takes the appropriate oxygenated blood for the right development of the fetus, but this normal flow is disturbed when there is no adequate trophoblastic penetration to the placenta and the spiral arteries have the unexpected shape of non-muscular tubes (4,5,9,17,28). Using the Doppler ultrasound has become possible to assess the completeness of the circulation in the placenta by measuring uterine artery pulsatility index (PI), as many studies show that measurements at 11–13-week scan and second-trimester scan in combination with pathological images from placentas certify that women with preeclampsia have an increased value in uterine artery PI even from the first scan. Thus, the main target of the first-trimester scan is to determine the value of uterine artery PI as accurately as possible and this procedure requires the contribution of an experienced and certified physician in the performance of the ultrasound (5,17,28).

The measurement of uterine artery PI preferably requires transabdominal access to the ultrasound, as much data show that the transvaginal approach is related to overestimated values of uterine artery PI. Then the cervix and the internal cervical os must be in a sagittal view so that it is feasible to make both uterine arteries visible at this anatomical level in the first trimester, whereas at a later gestational age the assessment of the value of uterine artery PI presupposes the search of these arteries in the external iliac artery anatomical position. If these criteria are met, then the measurement can be made with the average of the values of the two arteries (5,16,25,27). Having as fact that uterine artery PI is also affected by several factors, such as the age of pregnancy at the time of measurement, age of the mother, origin, maternal weight, and preeclampsia in the past, this value needed to be expressed by considering all this factor and that becomes possible by the expression in multiple of the median (MoM). Particularly, uterine artery PI seems to be increased in the first-trimester scan in women that later will develop preeclampsia and that value seems to be inversely proportional with the gestational age at delivery (17,28).

By using this measurement as a single factor for the preeclampsia prediction, there are conflicting data, mainly due to the design of the studies. A meta-analysis showed that when there is disturbing uterine artery PI, this was an important predicting factor for preeclampsia with increased specificity up to 92%, but decreased sensitivity. However, this can be a trigger for the use of precautionary measures from the early

first trimester (2). A corresponding meta-analysis examined the usefulness of uterine artery PI above the 90th percentile, but in this case, the detection rate of early-onset preeclampsia was very low. The result was that although the increased PI is correlated with preeclampsia, the use of this value only, without any other risk factors to be considered, is not a reliable method (30). Thus, the improvement in the detection of this hypertensive disorder can be evaluated by combining the measurement of uterine artery PI and other factors of the mother, like different characteristics as mentioned above and other biomarkers. It seems that the pulsatility index is a very serious predicting factor for early-onset preeclampsia and many times only its existence can be compared with one high-risk factor and requires the vigilance of the physicians (2,17,28).

In line with the biophysical method mentioned above, a very useful tool for early prediction of the risk of preeclampsia is to measure the mother's blood pressure from the first prenatal visits. However, the process of measuring the blood pressure in every woman is not the same and many factors can affect the result. The use of the well-known method with the sphygmomanometer has many disadvantages starting from the contribution of the person who takes the measurement and then the size of the cuff, the right position of the pregnant woman, and the difference in the measurement between the two arms. A better way of approaching the right calculation of blood pressure is by measuring the mean arterial pressure with a digital device, which allows repeated measurements without so many conflicting factors (17,28,31,32). Several studies support the fact that measuring mean arterial pressure excels as an early predicting method for preeclampsia in comparison with either systolic or diastolic blood pressure alone. Also, as in the case of uterine artery pulsatility index, mean arterial pressure is affected by several somatometric factors of the mother and the history of preeclampsia, and it is also expressed in MoM after considering these characteristics. The measurement at the first-trimester visit has proven that mean arterial pressure is significantly affected at this time in women having the prospect to develop preeclampsia later in pregnancy. Particularly, predicting this hypertensive disorder by considering maternal characteristics in combination with mean arterial pressure achieves better detection rates, up to 58% (FPR 5%) or 73% (FPR 10%) for the case of preeclampsia in need of delivery before 34 weeks. This detection rate is even better if there is a combination of the two biophysical methods above and maternal factors (17,28,32).

Apart from the data above, there is nowadays a wide variety of serum biomarkers examined to be used as new preeclampsia predictors, as this hypertensive disorder is too difficult to be evaluated by a factor only. Most of these markers are

related to the etiopathogenetic mechanisms in preeclampsia development, and in particular placental insufficiency as a result of the disrupted placentation process. PP-13 and PAPP-A are two of the markers that are significantly related to the possible development of trisomies and are measured during the 11–13-week scan, but new data show their usefulness in the prediction of preeclampsia. PP-13 as part of the galectin family plays a significant role in the formation of placenta and vessels and the results of many studies demonstrate that lower levels of this biomarker are proven to be an early sign of preeclampsia later in pregnancy, especially for the early-onset form that can be detected up to a percentage of 79%(FPR 20%), but some others support that this marker could not be correlated with others in the prediction of this disease (2,32). On the other hand, PAPP-A, which is a metalloproteinase participating in the development of the placenta, has also been correlated with a predicting value for preeclampsia if it is low, but is not a reliable factor if it is used alone. Thus, PAPP-A is preferred to be part of a multi-marker predicting procedure to confirm or not a high probability of the presence of the hypertensive disorder (2,17,28,30,32).

Several other biomarkers have also been used alone or in combination with those above for the early evaluation of preeclampsia. The levels of angiogenic factors, such as sFlt-1, PlGF, and sEng, may be affected well earlier, even 5-8 weeks, before the final onset of the disease (2,19). However, PlGF seems to be a marker that can be used even from the first trimester. The placenta under formation needs the presence of PlGF for the better penetration of the vessels after the binding of this marker with the VEGF receptor 1. Thus, when this glycoprotein is decreased, there is a subsequent placental hypofunction which is correlated to the development of preeclampsia. As in the case of the previous markers, PlGF must be measured in the light of various factors and in this way to generate a value in MoM. Findings from many studies support the fact that PlGF is reduced in the 11–13-week scan, in fact much more reduced in relation to other biomarkers, in pregnant women suspected of developing preeclampsia (17,28,30). Neutrophil gelatinase-associated lipocalin (NGAL) is a decomposition product of endothelial cells present in the circulation of mother even from the first trimester of pregnancy. The important fact about this factor is that typically increases during pregnancy, but in pregnancies complicated with preeclampsia the NGAL levels are significantly increased in the first trimester (33,34). Also, NGAL can be set as part of the inclusion of several biomarkers providing a quite reliable detection rate for the development of preeclampsia, as in case of a combination with maternal age and BMI and measurement of uterine artery PI during the second trimester there is a specificity for detection reaching 94% (34).

Over the years there were many different combinations of biophysical methods and markers aiming to find the one that succeeded with the highest detection rate. At first, the consideration of maternal factors with these markers offered a significant improvement in the detection rate. However, it seems that the simultaneous measurement of mean arterial pressure, uterine artery pulsatility index, PAPP-A, and PlGF succeeds very high detection rate up to 94% for an FPR 5% and 100% for an FPR 10% for the prediction of early-onset preeclampsia before 32 weeks of gestation. Generally, a combination of these maternal characteristics, biomarkers, and biophysical profiles are used for the more effective prediction of preeclampsia and data show that the detection rates approach 90% for the early-onset form, 80% for intermediate form, and 60% for the late form of the disease with an FPR of 5% (2,19,28,30,35–37).

Besides the very promising biomarkers which can be used during the first-trimester scan, there is another possible marker for the early prediction of preeclampsia. Cell-free DNA is a non-invasive test that can take place after the 10th week of gestation and has the most accurate result if the blood sample is taken during the 12th week. It is a fact from studies that cell-free DNA is significantly increased in preeclamptic pregnant women at the time of the diagnosis of this entity in comparison with the levels in normal pregnancies, in which there is a gradual increase due to changes in the formation of the chorionic villus. Also, it is known that cell-free DNA derives only from the placenta. Thus, the high value early in pregnancy can be enough to stand out a possible placental malformation that can be correlated to later development of preeclampsia and can help for precautionary measures to be taken. However, there is a significant weakness in all studies that examined the usefulness of measurement of cell-free DNA and that has to do with the fact that maternal characteristics and other factors have not been considered to lead to a value expressed in MoM as in biomarkers above. Thus, if these factors are included, there is evidence that total cell-free DNA is not that much higher to justify its usefulness. But for sure, new studies are needed (2,28,38).

Having as a fact that all the biomarkers mentioned previously are related to the prediction of early-onset preeclampsia, it is also necessary to examine other biomarkers or biophysical methods for the prediction of late-onset preeclampsia as well. The period that is more effective for the late-onset form to be predicted is between 30-33 weeks of gestation, as at this time is very important to find out possible impending development of preeclampsia for early interventions with medication or even immediate childbirth. Respectively to the methodology of the first trimester, the prediction of preeclampsia in the third trimester can be achieved by the measurement

of uterine artery PI and mean arterial pressure with the inclusion of several characteristics of these pregnant women expressed in MoM. By considering these parameters, there is a quite acceptable percentage in the detection rate of late-onset preeclampsia, which is about 55% in 32-34 weeks for FPR 10%. It is also important to correlate epidemiological factors known even from the first trimester with measurements of mean arterial pressure and uterine artery PI in the third trimester, as it seems that this approach can help in the prediction and it is cost-effective [13,26,30]. Specific epidemiological features are more relevant to the late-onset form of preeclampsia than in the early-onset form. Particularly, the age of the mother at the time of gestation and the body mass index seem to be risk factors for threatened late-onset preeclampsia, as there is an increased prevalence of up to 4% per year above 32 years old and 10% per 1 kg/m^2 above 24 kg/m^2. Also, the racial origin can play a significant role in the prediction models for late-onset preeclampsia (39,40).

However, there is some data to give us even more accurate predictions for a shorter period. Particularly, through sFlt-1:PlGF ratio can be obtained an early rejection of the possibility of developing preeclampsia in the short term. This PROGNOSIS study was very important as it allows to rule out the onset of the symptoms of preeclampsia within 1 week from the time of the measurement if the sFlt-1: PlGF ratio is 38 or lower and at the same time this was reassuring for fetal morbidity. The data from this study showed that the negative predictive value for this occasion comes up to 99,3%, which is impressive but also it is important the fact that this percentage is independent of the week of gestation. Also, the negative predictive value for predicting the onset at 4 weeks if the measurement of this ratio is <38% is up to 95% too. There is a lack in the prediction of the possibility for preeclampsia to come up within 4 weeks with this ratio if it is >38, having as a fact that the positive predictive value was about 37-40% depending on the study. But the data from this study were generally crucial for the opportunity that gives for clinical decisions between hospital admission and home monitoring (12,17,41). Generally, prediction of preeclampsia in all trimesters cannot be evaluated by only one factor and there is a need for multi-marker analysis for the approach of a high detection rate for both forms of this hypertensive disorder (17,28,30,40).

Considering that this hypertensive disorder of pregnancy can cause many adverse events to mother and infant in the context of preterm birth, special initiatives must be taken during gestation. Preterm birth has been related to crucial fetal morbidity with cerebral palsy, neurodevelopmental disorders, and several organ dysfunctions, such as pulmonary and renal immaturity, diabetes, and weight disorder. At the same time, mothers are also affected as they have multiple probabilities up to 5 times for

increased blood pressure in the rest of their lives and all the possible complications from this (14,42). These women not only have the perspective of developing hypertension during their lives, but they also have the probability of earlier onset of the disease and as a result a high risk of cardiac events. Other data show that preeclampsia has been correlated with incidents of both types of strokes, either ischemic or hemorrhagic and venous thromboembolism events. A very special case of preeclampsia complication is the end-stage kidney disease that may occur when the severity of preeclampsia during gestation is marked and in case of recurring episodes of this hypertensive disorder (21,42,43).

The main role of the predictive models referred above is the intersection of women that are going to develop preeclampsia in pregnancy and mainly these women who are going to face the most severe complications after delivery in the early-onset group. After the identification of high-risk women, there are several measures to be taken to prevent the possible development of preeclampsia. In the past, several data in the literature supported that antioxidants intake could solve the problem of oxidative stress that has been correlated to the pathophysiology of preeclampsia. However, many studies proved that the consumption of vitamins C and E during pregnancy did not seem to protect women from manifesting symptoms of preeclampsia later in gestation (2,44). Another factor that has been studied in the past is calcium quantity in the circulation of pregnant women and the correlation with the development of preeclampsia, especially since there seems to be an inversely proportional relationship. In the past, there was an analysis from the World Health Organization that showed an important contribution of the addition of calcium in the diet of pregnant women who had a low intake of food consumption in the prevention of eclampsia and severe complications for infant and mother, but no significant decrease in the risk for preeclampsia. However, there was recent data to show a significant reduction of the risk for preeclampsia with additional consumption of calcium and that was the reason for the suggestion of calcium supplementation of 1,5-2 gr per day in women with calcium deficiency in diet. Also, another study compared the addition of Vitamin D, calcium, or both in the prevention of preeclampsia proving the superiority of Vitamin D, but the number of the participants was a limitation to this result. So, calcium seems to be the most acceptable supplementation in pregnancy to prevent the onset of preeclampsia and the use must be started well before 20 weeks of pregnancy (2,8,45,46).

Based on data derived from the pathophysiology of preeclampsia, it is known that this hypertensive disorder is characterized by the abnormal release of prostacyclin into the circulation and significantly increased thromboxane activity, which is related to

the microcirculatory thrombosis of the placenta. Administration of low dose aspirin <300mg seems to inhibit the action of COX-1 enzyme and in this way limits down the production of prostacyclin, but mainly thromboxane from the conversion of arachidonic acid. Also, the protective potential of aspirin is confirmed by the prevention of the increased release of sFlt-1 because of the oxidative stress of preeclampsia [33,38]. From the very old times, the aspirin administration for the prevention of the onset of preeclampsia was examined in several studies by administering different doses of this antiplatelet agent to find the perfect one for better protection. Already since 2007, a Cochrane analysis showed that the use of aspirin reduced the risk for the development of preeclampsia and this reduction was even more important when the analysis restricted high-risk pregnant women in comparison with women of moderate risk (2,42).

In the meantime, several other studies also examined the same hypothesis with conflicting results and that was the reason why the ASPRE trial in 2016 took place. This trial was based on some assumptions from previous studies as far as dosage and method of administration are concerned. Particularly, it was obvious that doses equal to or higher than 150 mg seem to be more effective in preeclampsia prevention, as many data show that in daily usage of 162 mg aspirin the percentage of women that aspirin had no effect was lower than 5%. Also, other data proved that the best time for administration of aspirin was before rest at night after checking all possible times to achieve the best efficiency. ASPRE trial included women that had had a high risk for the development of preeclampsia according to an extended model that includes maternal characteristics, measurement of different biophysical and biochemical markers mentioned above, and history of several medical problems resulting in a value of risk index. Thus, this study included women that had a risk of 1 in 100 or higher mainly for the early-onset form of this hypertensive disorder. The results were very encouraging given the fact that there was a significant reduction of preeclampsia cases up to 62% as far as the early and most dangerous form of the disease is concerned. Apart from these main results, some additional data from the analysis showed that this beneficial effect of aspirin is not achieved when there is a pre-existing chronic hypertensive condition. Also, the response rate to the supplementation of aspirin is increased when there is a proper use of this medication, ranging from 76% to 90% in some cases of ideal use of the therapeutic regimen (2,42,47).

The results of this trial stood the occasion for several other studies which examined the time of administration start and the proper dose of aspirin were examined and from the analysis of the data came up with significant outcomes which could be made immediately applicable. Particularly, this review of the studies ended up that the

best time for administration of aspirin in high-risk women was before or at most 16 weeks of gestation, while at the same time the value that seemed to have an increased impact on the prevention of preeclampsia was 100 mg of daily aspirin use or more (2,14,48). A very important study also reinforces the results of all the previous ones after including women who started the addition of aspirin during 11-14th weeks of gestation and until 36 weeks and proved that in comparison with women who took a placebo medication, those in the aspirin group had a significantly reduced prevalence of the development of preeclampsia before 37 weeks. The administration of a dose of 150 mg of aspirin at night daily was a prerequisite for this analysis especially since smaller doses have shown insufficient antiplatelet effect (49).

As in every medication administered during pregnancy, the safety of both mother and infant is a crucial fact. Among the studies that examined aspirin use, a special report was made on the possible effects and all the data concluded that there is no burden of risk for developmental abnormalities in the infant. At the same time, there was no evidence of complications like intracranial hemorrhage for the infants or bleeding after birth for mothers, even if the aspirin is stopped shortly before delivery. The only correlation with aspirin use is the increased possibility for placental abruption mainly when the administration of this antiplatelet agent after 16 weeks when the formation of the placenta is integrated. Similarly, in multiple pregnancies, the possibility for the early-onset form of preeclampsia is increased mainly due to the proportionately large placental mass. Thus, these pregnancies must be under the influence of aspirin treatment and in fact under an increased daily dosage of 150 mg, especially in case of other coexisting risk factors. However, the evidence is not so strong and the need for further studies on this subject is necessary (14,42,47).

Apart from any kind of medication or dietary supplements, several actions must be made during pregnancy for the prevention of preeclampsia as far as a healthier lifestyle and a more balanced diet are concerned. Many studies have concluded that a diet full of vegetables and fruits is the most appropriate as women seem to have a quite reduced probability of preeclampsia development during gestation. However, these interventions are more effective when applied to women that have a normal body mass index, even women with diabetes mellitus in pregnancy, but the results were not so encouraging when pregnant women with high body mass index were examined. All the measures above can be used to help women at high risk for the early-onset form of preeclampsia to avoid the onset of the disease, at the same time with a very close antenatal care (2,8,42).

1.6. Management & Treatment of Preeclampsia: Management of preeclampsia aims to prevent possible adverse events for mother and fetus by

maintaining systolic blood pressure during pregnancy below 150mmHg and diastolic must range between 80 and 100mmHg or lower (1). This disorder requires immediate treatment in case of urgent deregulation. If the initial treatment interventions are successful, then close monitoring is necessary for the rest of the pregnancy. However, in case of exacerbation or fetal distress, then delivery is the appropriate treatment [3,19]. If blood pressure deviates from the normal levels for more than 15 minutes and systolic blood pressure exceeds 160mmHg and/or diastolic is increased above 110mmHg, then this hypertensive crisis requires immediate treatment with intravenous administration of labetalol or hydralazine and oral nifedipine (1,4,8). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) cannot be used during pregnancy because of severe adverse events that they have been blamed for, such as fetal growth restriction, pulmonary hypoplasia, and stillbirth (8,22). It is very important to avoid acute reduction of blood pressure aiming only to protect the mother, as there is a great possibility to cause placental hypoperfusion and fetal distress (22).

Apart from the regulation of blood pressure, the management of preeclampsia must be based on the best outcome for the infant. Given the fact that this hypertensive disorder ends up in preterm birth in a large percentage, physicians must take care to the prevention of prematurity complications. Administration of magnesium sulfate is preferred in comparison with other anticonvulsants for the prevention of the complications of severe preeclampsia or eclampsia. However, it is appropriate for these women and fetuses to be under close monitoring due to the immediate consequences of high doses of $MgSO_4$, such as depression or respiratory failure. Many data confirm the significance of administration of $MgSO_4$ in the severe form of the disease, whereas in the mild form the use is controversial (8,20,22). The use of $MgSO_4$ is effective between 24 and 32 weeks of gestation and if delivery is imminent within the next 24 hours. There are studies to conclude that this administration in preterm births in the context of preeclampsia or other complications, reduces the risk for cerebral palsy or white-matter injury or even death in offspring, but not significantly (50,51). However, a meta-analysis succeeded in highlighting statistical significance in the beneficial impact of $MgSO_4$ use in the prevention of cerebral palsy in the newborn, without suspicion of increased risk for perinatal or postpartum death of the infant (52).

At the same time, the use of corticosteroids is imperative in case of threatened childbirth between 24-34 weeks of pregnancy and if delivery is going to take place within the next seven days, as it has been proven that the administration at this time of gestation reduces significantly the risk for respiratory distress syndrome (RDS), necrotizing enterocolitis, even death of the infant (53,54). Administration of

corticosteroids between 34 and 37 weeks of gestation has also been examined and the results were that if delivery is going to be processed within the next seven days, then the use of betamethasone improves the development of the respiratory system and reduces the possibility of respiratory support at the first 3 days of life (55). Intramuscular administration of two 12mg betamethasone doses with 24-hour interval or four 6mg dexamethasone doses with 12-hour interval seems to be the most beneficial use of antenatal corticosteroids. However, in case of threatened delivery, even a single dose of corticosteroids may be effective for the prevention of neonatal morbidity and mortality, according to data (54).

Severe preeclampsia or eclampsia needs immediate delivery because of the possible maternal and fetal adverse outcomes. However, for the mild form of the disease, there is no clear data for the appropriate management. Depending on the onset time of preeclampsia, delivery or expectant management can be discussed (20). In the case of severe early-onset preeclampsia before 34 weeks of gestation, the decision of delivery or expectant management is controversial. Immediate delivery prevents maternal morbidity due to eclampsia or renal failure but can lead to a lack of pulmonary function with the need for continuous respiratory support, fetal growth restriction, intraventricular hemorrhage, and even fetal demise. The most recent meta-analysis on this issue concluded that expectant management seemed to be beneficial in reducing intraventricular hemorrhage cases, possible mechanical respiratory assistance, and in general morbidity of the infant. Because of the limitation of the small number of participants in this study, there were no results regarding the impact on the maternal outcome depending on the decision of delivery or not (21,56).

At the same time, two other studies tried to find out what is the best management for pregnancies that developed preeclampsia between 34-37 weeks. HYPITAT-II examined women with onset of mild preeclampsia during this time of pregnancy and the result was that delivery within the upcoming 24 hours from the diagnosis may have a little benefit for mothers but can significantly affect an infant's respiratory system. Thus, it is acceptable to extend pregnancy, but set it under close monitoring to prevent any adverse outcome (49,57). On the other hand, the corresponding trial which included women diagnosed with preeclampsia at the same period of pregnancy compared delivery among 48hrs from diagnosis with the extension of gestation. The authors concluded that the earlier a pregnancy can be processed, the less the impact on the maternal outcome, whereas at the same time there were more hospitalizations for the infants of such mothers. However, the duration of stay and the severity of these cases did not cause any hesitation regarding this management (58).

As far as the cases of preeclampsia beyond 37 weeks are concerned, a randomized controlled trial that took place in 2009 examined singleton pregnancies complicated by preeclampsia in this period of gestation and showed that there is decreased possibility for maternal complications and adverse outcomes, if delivery takes place immediately, in comparison with the continuation of pregnancy and monitoring. As it turned out, expectant management was correlated with worse maternal adverse events, whereas infants did not appear to be affected in one case or another (20,59). All these options are indicative and applicable if there are no signs of possible maternal or fetal deterioration, which can lead to immediate delivery. For this reason, close monitoring is extremely necessary to rule out the possibility of maternal complications, such as severe hypertension, eclampsia, HELLP syndrome, placental abruption, and complications of the infant. Evaluation of these pregnancies includes an examination of the well-being of the fetus via ultrasonography, weekly laboratory tests, and measurement of blood pressure, but any crucial symptom during the meantime needs to be reported (21,60).

Considering that preeclampsia can affect the fetal outcome, several studies have tried to find out any medication that can weaken this effect on newborns. Data from a randomized controlled trial showed that a seven-day administration of antithrombin in cases of early-onset severe preeclampsia could improve the fetal biophysical profile, prolong pregnancy duration contributing to the development of the respiratory system and prevent cases of fetal growth restriction (61). However, a most recent analysis came to refute these results as included pregnancies with early-onset preeclampsia before 30 weeks and failed to detect a significant impact of the administration of antithrombin on the extension of pregnancy or the prevention of any unfavorable adverse events for mother and infant (62).

Another option that has been widely examined as beneficial in preeclamptic pregnancies is sildenafil, which at first seemed to have some positive impact as data from use in rats suggested that the outcome was much better with its supplementation (63). On the contrary, these results did not come in agreement with a randomized controlled trial that examined the use of sildenafil or placebo in pregnancies with gestational age ranging from 20 to 30 weeks and infants with restrictions on weight gain and development and found out that this option was not useful in preventing morbidity and mortality of the fetus (64). A meta-analysis which included data from many randomized controlled trials ended up that sildenafil could help by increasing fetal weight despite some limitations, but from all the available studies there are no reassuring characteristics for this medication so that to be used in everyday practice (65). Similar conflicting data are present for the role of statins in the management of

preeclampsia even though a systematic review showed that in some cases of severe preeclampsia this medication may be beneficial and at the same time there were no indications for possible anomalies in the newborns (66,67). Metformin and plasma apheresis have also been proposed as medications for the prevention of preeclampsia and better outcome of pregnancies complicated with this hypertensive disorder but still lack to be considered appropriate for clinical practice (21).

Preeclampsia is a hypertensive disorder of pregnancy that can affect the maternal and fetal well-being in immediate and distant time after gestation. There are component studies to support that this disorder is associated with cardiac, cerebrovascular, or peripheral arterial disease and in some cases can lead to death due to these reasons. A recent meta-analysis comes in line with these assumptions as proved that women that underwent preeclampsia during their pregnancies had a significantly increased possibility of cardiovascular complications and adverse events that can cause even death. At the same time, these women are candidates for the development of chronic hypertension even in the first 1-2 years after the controversial pregnancy and metabolic syndrome, and this risk is increased in case of early-onset preeclampsia (21,68,69).

Preeclampsia has also been associated with a correspondingly increased risk for cardiovascular disease in newborns later in their lives, as there are signs of increased blood pressure and body mass index in these children from an early age. Particularly, a study that examined data from the Norwegian population and compared adults that have been exposed to the negative effect of high blood pressure during gestation with adults coming from uncomplicated pregnancies concluded that preeclampsia may lead to the development of some characteristics at an early age that can be related to later increased cardiovascular disease risk. This assumption was not so obvious when maternal factors were adjusted (21,70). The risk for cardiovascular disease was also confirmed by a recent analysis that showed up that preeclampsia can affect cardiac formation leading to a concentric type of remodeling and as a result causing cardiovascular adverse events, even stroke (21,71) Also, other studies provide evidence that this effect could be associated with microvascular changes in newborns or changes in microRNAs' expression during the preeclamptic pregnancy that could be responsible for the long-term presence of hypertensive disorders related to endothelial lesions (72,73). However, this is a field in need of further research.

2. An overview of Cerebral Palsy

2.1. Introduction - Neurodevelopment in the fetus: Cerebral palsy is characterized by substantial heterogeneity in all aspects of its study as a disease of early childhood. There are a different kinds of possible risk factors, different clinical manifestations depending on the severity and the extent of brain damage, and possible correlation with a wide range of other developmental diagnoses and genetic factors (74). The central nervous system undergoes a complex development process with the contribution of genetic factors and the effect of different kinds of factors inside and outside the uterus that can disturb the formation of the uteroplacental circulation and interaction leading to neurodevelopmental impairment (75). Particularly, cerebral palsy (CP) is not another disease that makes its onset during childhood, but a complex of irreversible motor and posture disorders affecting the well-being and functionality of the newborns as a result of abnormalities of the developing fetal or infantile brain (76–78). The main fact about this disorder is the absence of progression in the anomalies. However, although the survival rates over the past years were not very encouraging, significant progress has been made according to data that showed up improvement in the quality of life of these children (77).

2.2. Epidemiology of Cerebral Palsy: Cerebral palsy has been considered the most common motor disorder that can be diagnosed in young childhood. However, the calculation of the frequency of this disease could not be reliable due to incomplete data from birth certificates and hospitals. Several studies examined many different populations around the world regarding cerebral palsy have ended up that the prevalence of this entity ranges from 1.5 to 3 cases per 1000 live infants, depending on the different regions that have been studied (76–80). The increased number of newborns that undergo cerebral palsy in their lives is associated with the improvement in survival rates. This reflects better health services provided in developed countries even though unfavorable perinatal outcome continues to be present in some cases (76,77).

2.2.1 Risk factors: From the very first time of the overview of cerebral palsy, many different possible risk factors have been blamed for causing this disease. In the past, there were many references in the literature for the possible association between cerebral palsy and asphyxia-induced brain destruction. However, subsequent studies proved that was not hypoxia during delivery alone that caused this disease, but mainly

other factors during pregnancy (76,81). Many data have shown that the possible presence of structural anomalies of the developing brain during gestation, such as cortical malformations, have been correlated to the later presence of cerebral palsy. Particularly, these anomalies are nowadays even easier to be diagnosed early in pregnancy based on the improvement of the available imaging techniques. In the context of antenatal risk factors, TORCH (toxoplasma, rubella, cytomegalovirus, and herpes simplex virus) infections during pregnancy have been already known for their adverse effect on neurodevelopment, especially in low-income countries where the prevalence of such infections is increased. Other infectious factors can complicate pregnancy, such as other viruses or bacteria. This inflammatory background can often be complicated by thrombophilias in the mother or fetus and a serious risk of thrombosis may occur leading to a hypoxic environment. As far as intrauterine growth restriction (IUGR) is concerned, the correlation with cerebral palsy arises from the overall development retardation and the presence of some birth defects, which may affect the brain tissue as well (76,77,80–83).

Preterm birth has been convicted for most cases of cerebral palsy as there are references to support that this factor is responsible for approximately 30-50% of the cases in developed countries and a more limited percentage in developing countries. The possibility of developing cerebral palsy is increased when pregnancy is forced to terminate before 28 weeks for any reason and the striking point is the 50-fold higher risk for this disease in this group of pregnancies in comparison with the group of pregnancies that are processed at term (77,79,82–84). This association can be explained by specific characteristics of preterm births, such as organic hypoplasia, absence of useful hormones and growth factors, the possible effect of metabolic factors and toxins, and other complications during delivery that may lead to this neurodevelopmental disorder in early childhood. Particularly, at this time of pregnancy, it is much more common for ultrasound findings, such as periventricular leukomalacia and intraventricular hemorrhage, to be identified. Also, because of the underdevelopment of the respiratory system, these children may undergo hypoxia during delivery or postnatally and require mechanical ventilation. Hypertensive disorders and in vitro fertilization (IVF) should be considered as well because in most of these cases pregnancies must be processed prematurely (77,79,80,82,84–86).

The cases of perinatal hypoxic-ischemic injury are significantly reduced nowadays because of the improvement of health systems around the world. However, this is still an existing complication during delivery, and it is necessary to be considered a risk factor for neurodevelopmental impairment. Several events, such as prolapsed cord, delay of labor due to shoulder dystocia, delay in the second stage of labor, abnormal

position of the fetus inside the uterus, placental insufficiency caused by any factor, have been associated with cerebral palsy in the early childhood. A cesarean section is an option in pregnancy for which there is ambiguous data regarding its association with cerebral palsy. It seems that in case of emergency cesarean section and mainly at term the risk for this neurodevelopmental disorder is higher. The so-called hypoxic-ischemic encephalopathy (HIE) is the impact of reduced perspiration and oxygen supply for the fetus because of all these events. This can manifest as a low Apgar score, signs of metabolic acidosis in blood gas measurements, seizures, and even MRI findings. Seizures are not the only result of hypoxia, but they can also be a manifestation of perinatal stroke, which is another risk factor for cerebral palsy that can be a complication perinatally or even at the first days of a newborn's life (74,76,77,79,80,87–89).

Many references in the literature have demonstrated that cerebral palsy is also quite common in cases of twin pregnancies, and it is something that can be explained by the high frequency of preterm births and small for gestational age infants in this type of pregnancy. However, the risk for this disorder is increased even in term twin pregnancies in comparison with term singleton ones (76,80,82,90). Also, after delivery, some factors have been associated. Any kind of accident with consequent head trauma could cause neurodevelopmental failure at this age, as well as infection, such as meningitis, should be treated immediately for fear of this possible complication (76,80,91).

2.3. Pathophysiology of Cerebral Palsy: The numerous factors that have been studied as possible causes for cerebral palsy highlight the lack of complete knowledge of the pathophysiology of this neurodevelopmental disorder and the fact that still, an additional research project is underway. In the past, cerebral palsy had been attributed to any case of brain trauma or hemorrhage, but this of course had to do with low-quality imaging techniques and as a result limited diagnostic accuracy of the lesions. During the intervening years, the extended MRI use led to some findings of periventricular leukomalacia (PVL) along with white matter damage (81,92). Among the factors that can cause these lesions in a developing infant's brain, it seems that prenatal factors are related to the half of cases of cerebral palsy, while factors that complicate delivery represent one-third of the cases (84).

Based on data from the maturation of the fetal brain, it seems that the crucial pregnancy period is between 24-34 weeks, as during this time takes place a complex process of configuration of the brain neurons and axons. In preterm labor, this process of fetal brain shaping can be disrupted with abnormal migration of cells and damage to brain tissue and can lead to the development of cerebral palsy later. However,

according to recent references, this cause is related to only 10% of the cases of this neurodevelopmental disorder (77,92,93). On the contrary, it seems that there are other factors like inflammation, infection, or hypoxic events during pregnancy that affect the immature brain and can cause brain lesions and be responsible for the majority of cases of this disorder (77). According to some other findings, the immature vessels and oligodendrocytes of the infant during this period are much more prone to the effect of free radicals and inflammatory factors which are responsible for the permanent damage to the developing brain (92,93).

Fetal hypoxia is a second mechanism that has been studied and it is related to either preterm or term infants. Low oxygen supply can be present during the last stages of pregnancy because of placental insufficiency or can be associated with chronic placental lesions, such as chronic villitis or thrombotic infarcts. When the exposure to hypoxia is chronic and takes place before 34 weeks of gestation, it can lead to a reduced size of the fetal head and mental development. On the other hand, if an infant is exposed to a hypoxic environment after 34 weeks, the possible brain lesions could not be ruled out, even though there is a normal Apgar score and good general condition of the newborn (74,80,84). Also, any kind of perinatal trauma has been correlated with the later presence of cerebral palsy, but recent studies suggest that only a very limited percentage of these events are leading to an impaired oxygen supply, as a result of the primary care and protective mechanisms of the newborn (80,94).

Another pathway that has been associated with the development of cerebral palsy is the effect of an inflammatory procedure during gestation. Any maternal infection can lead to the release of proinflammatory cytokines in maternal and fetal blood circulation, even in the amniotic fluid. The presence of IL-6 and Il-8 is related to the possible damage to the immature fetal brain in preterm births and especially IL-6 and TNF-a are considered primarily responsible for cases of periventricular leukomalacia (PVL) (79,80). However, it is a fact that even in term pregnancies a hypoxic environment can cause an inflammatory process in the context of the present oxidative stress and can affect formed neurons with a possible impact later (77,95).

2.4. Diagnosis of Cerebral Palsy: A diagnosis of cerebral palsy can be made clinically based on perinatal history, neurological examination, imaging testing, and laboratory assessment. With this approach, the timely detection of cerebral palsy or “high-risk” for cerebral palsy is nowadays more effective and can lead to a diagnosis even in the first six months of a newborn’s life. This comes in comparison with the fact that in most cases the diagnosis can be established between 12 and 24 months of life, according to references in the literature (78,80,96). Early diagnosis of this disorder is appropriate given the fact that early interventions can prevent an aggravating

progression for the newborn and, at the same time, can help parents psychologically by avoiding intense stress because of this disorder. Some studies have proven that parents prefer to be aware of the full clinical situation of their children to take immediate decisions for treatment and multifaceted care (80,96).

The first step for the evaluation and detection of cerebral palsy is to obtain a detailed history of the newborns to examine the possible risk factors that are associated with this entity. This is appropriate because there are different factors responsible for this disorder in those infants that were forced to be born preterm and, as it is perceived, there are different interventions depending on the gestational age (79,96). In the case of preterm birth, many studies have concluded that the use of some therapies during the prenatal period can reduce the possibility of the development of cerebral palsy later and, at the same time, there is increased vigilance and close monitoring from the first day of newborn's life. In term births, the development of cerebral palsy is much more associated with hypoxia due to placental hypoperfusion in pregnancy and some cases of perinatal trauma, but other factors, such as fetal size disorder in relation to gestational age, hemorrhage, increased length of labor, must be also considered. If there is such suspicion from the references during pregnancy, then frequent visits and neurological examinations in the early stages of life are required (96–98).

There are imaging methods that have a significant contribution to the diagnosis of this neurodevelopmental disorder, mainly as far as the detection of the etiology is concerned, regarding the fact that cerebral palsy can be evaluated based on neurological signs and motor disabilities. Brain magnetic resonance imaging (MRI) and cranial ultrasound are the most specific methods for the investigation of any brain abnormality and prediction of the development of cerebral palsy (79,80,96). Cranial ultrasound was a widely used method in the past because of the easy access and fairly high rates in the detection of lesions. Depending on the grade of intraventricular hemorrhage calculated via the ultrasound, the risk of developing cerebral palsy is increased respectively, with the highest possibility to be considered when there is significant hemorrhage with simultaneous dilatation of the ventricle. Also, the location and the extent of possible cysts that can include a large part of ventricles as well has been correlated with increased risk for cerebral palsy (92,96). Ultrasound seems to be a pretty good method in the detection of grade 4 intraventricular hemorrhage and even more reliable in the case of cystic periventricular leukomalacia with a positive predictive value amounting to 77% according to the findings of a study (92,96,99).

On the other hand, MRI is a more accurate method of diagnosing different patterns that may be associated with neurodevelopmental disorders and the results can be

combined with neurological signs to provide a better diagnostic tool. It is not always an easily performed diagnostic examination as sedation or general anesthesia is needed in newborns. Findings in MRI that are correlated with this disorder include white matter damage which may be the result of lesions, such as periventricular leukomalacia or hemorrhagic infarction or stroke, or gray matter lesions in the context of cranial hemorrhage or developmental abnormalities. MRI seems to have better diagnostic accuracy in the detection of diffuse white matter lesions in comparison with ultrasonography and a severe form of this malformation is correlated with an increased positive predictive value for cerebral palsy. However, there is a percentage of 9-16% of newborns that may develop cerebral palsy without any presence of a lesion in this examination (80,96,98,99). A systematic review that examined both MRI and cranial ultrasonography as predictive methods concluded that the cranial US displays a sensitivity of 74% and specificity of 92% in the prediction of cerebral palsy, but it must be considered that the study concerned a high-risk population. In this study the corresponding percentages for MRI were 86-100% for sensitivity and 89-97% for specificity, depending on the study that was considered in each case (78,100).

Apart from all the available imaging techniques, motor and neurological examinations are necessary to be done during the diagnostic procedure and there are data to support that in a wide majority of cases these neuromotor assessments are enough to identify cerebral palsy. Various techniques have been proposed, but regarding data from studies that have examined the reliability of these tools, the Prechtl General Movement Assessment (GMA) and Hammersmith Infant Neurological Examination (HINE) seem to be the most acceptable methods for the evaluation of newborns' neurodevelopment. The crucial fact about these methods is that the identification of possible diagnosis presupposes the repetition of the neurological examination and not a single check (78,80,96).

Prechtl General Movement Assessment (GMA) is a method of early evaluation of a newborn's neurodevelopmental status that examines spontaneous movements which deviate from the normal pattern for the specific age via a recorded video for 3-5 minutes. Many studies suggest that this tool is used in very preterm infants regarding the fact that at this age it is best to avoid invasive techniques for the detection of any neurodevelopmental disorder. Based on many data from the monitoring of newborns' movements, it seems that the presence of cramped synchronized general movements or restriction of rotational movements, or lack of fidgety movements are often indicative and related to the later detection of cerebral palsy, but in some cases of premature infants the repetition of this procedure can lead to more specific findings (80,96,98,101). Different studies converge on the fact that this diagnostic tool is

considered of great reliability, as it can be used from the early neonatal period, but it has the maximum efficacy between 12 and 20 weeks after birth and the results from studies in high-risk populations for cerebral palsy demonstrate sensitivity and specificity of 95-98% and 89-96% respectively. The absence of fidgety movements has been associated with higher percentages of diagnostic reliability based on data that have distinguished this motor disability as a predicting point for cerebral palsy later (96,98,100–102). It is a fact that there is a very limited period after birth that this examination has its diagnostic usefulness and for this reason high-risk or preterm newborns must be under close monitoring and repetition of this method is necessary for the detection of cerebral palsy. However, this technique lacks accuracy and detection rate when volitional movements are present and disorient the examination (96,98).

On the other hand, Hammersmith Infant Neurological Examination (HINE) is another crucial diagnostic tool and can be used even after 5 months of age, having the best predictive value for cerebral palsy when it is taking place between 2 and 24 months of newborn's life. This method is distinguished for its standardization in the way that the different motor functions are examined. Particularly, there is a calibration for nerve function, sensitivity of movements, reflexes, tone, and posture rating from 0 to 3, and the overall result, ranging from 0 to 78, is taken into consideration for the detection of many disorders including cerebral palsy (80,96,98,103). The important thing about this assessment is that it can be easily performed and the practitioners that undertake to carry it out require limited training to perform it. Most studies support that HINE can be very useful when there are signs of birth asphyxia and preterm birth, but it can also be an important tool in term pregnancies (96,103). According to a review, there are specific cut-off points for the best prediction and detection of possible cerebral palsy, as an overall score of ≤56 at 3 months and ≤65 at 12 months have been associated with up to 90% possibility for this diagnosis. Also, a score ≤of 40 was associated with an increased possibility of development of a severe form of cerebral palsy (80,104). Finally, there is one study to support that the neurologic evaluation of the right and left side of a newborn's body and the corresponding difference in the final overall HINE score is a more accurate method in the diagnosis of hemiplegia (80,103).

By combining all these diagnostic tools, it is possible to set the diagnosis of cerebral palsy with significant accuracy. However, in some cases, there is a strong suspicion of cerebral palsy, but there is not much data to lead to the diagnosis. In these cases, it is important to consider the newborns as "high-risk" to be set under close monitoring and interventions (78,80,105). Novak *et al.* described a completed protocol

for the detection of this neurodevelopmental disorder. Particularly, this study suggested that abnormal movements of the newborn visible via the GMA examination or impaired neurological function in the context of the HINE test are the first appropriate requisite. Then, the presence of MRI findings or signs from clinical history and risk factors during pregnancy or both is the second necessary condition for the final diagnosis of cerebral palsy. Also, this study made a separation to newborns having a significant risk factor for developing cerebral palsy and could have a diagnosis of cerebral palsy before 5 months of life, in contrast with the category of newborns that do not have an obvious risk factor and the possible diagnosis could be set after 5 months mainly because of motor disorders present at this stage of life (78,80).

All these diagnostic tools are very useful in diagnosis, but many cerebral palsy cases are detectable later in life. However, there are early signs and symptoms which may not be considered during GMA and HINE tests. Particularly, behavioral changes, such as hyperactivity or sleep disorders, or diminished perception, can set the first suspicion, and at the same time, some persistent presence or absence of a reflex, observation findings on tone and posture difficulties could also cause significant concern. Another crucial examination is the assessment of motor milestones during different periods in a newborn's life (97,106). In many cases, the neurological profile and signs of motor dysfunction may be capable of disorienting the final diagnosis and the practitioners must consider that other neurological and metabolic disorders can be associated with these signs. This can be even more typical when there are no findings in MRI or risk factors correlated to cerebral palsy. Finally, in the differential diagnosis of these disorders could also be considered some genetic syndromes and a very often detected condition of motor abnormalities in preterm and very low birth weight infants without neurological deficit, known as the developmental coordination disorder (DCD) (80,97).

2.5. Prediction and Prevention of Cerebral Palsy: Besides the crucial diagnosis of cerebral palsy as an entity, the final assessment of the clinical phenotype and the corresponding motor deficit is of great importance for the practitioners to decide on the appropriate management. Over the years, several classification systems have been proposed for the evaluation of this disorder, depending on the brain lesion topography, the pattern of movements, the muscle tone, as some indicative such cases (80,107). The most frequently and traditionally used of these systems describes four categories of motor deficit: (1) cerebral palsy characterized by spasticity, which represents the highest percentage of cases (85-91%) and it can be distinguished in spastic diplegia mainly as a result of periventricular leukomalacia or infarction, spastic quadriplegia that may be associated with cases of multi-cystic encephalomalacia or spastic hemiplegia

which affects unilateral leg and arm and may be correlated with visual effects as well, (2) cerebral palsy characterized by dyskinetic findings in the examination, which relates to a percentage of 4-7% of the cases and includes the subcategories of choreo-athetoid movements with abnormal and unspecified mobilization and contractions of different muscle groups and dystonic form, (3) ataxic cerebral palsy that represents a percentage of 4-6% among the overall cases of this disorder and, finally, (4) hypotonic cerebral palsy, which is a form that is not categorized in all countries and has to do with about the 2% of the overall cases (78,106,107).

Another classification scale is the Gross Motor Function Classification System (GMFCS) and nowadays is considered the most useful one given the fact that this system examines motor development in combination with the age of the child. Particularly, the limitation of movements may range from the level I negligible observation of speed and balance disorder or non-simultaneous action of muscle groups up to the level V complete weakness of controlling the legs, arms, and even head, and these children are forced to move in a wheelchair with the assistance of another person. This system seems to be easily applicable with significant accuracy in the evaluation of movement disorders, mainly after the age of 2, and, according to data, by this scale, physicians can predict the progression of the disease to a large extent. Thus, this can lead to the decision for precautionary measures as soon as possible to improve the clinical outcome (77,80,107).

Prediction of cerebral palsy could not be based on these systems as they only provide a temporary clinical model of the disease, and their benefit may be useful later in life. Thus, the evaluation of possible risk factors is starting even from the prenatal period, as cases of preterm birth, congenital anomalies, twin pregnancy, and fetal hypoxia due to any reason can be considered predictive occasions for the development of cerebral palsy. Especially for the latter factor, data support that the diagnostic methods that are used for the identification of possible high-risk pregnancies, such as umbilical artery or middle cerebral artery Doppler measurements, lack reliability for the prediction of cerebral palsy (77,107). However, hypoxia during delivery seems to be a more crucial factor that can be highlighted via fetal heart rate measurement in labor and cord blood gas analysis and could help in the prediction of the neurological outcome. At the same time, all the physicians should be suspicious of the cases of intraamniotic infection and the release of pro-inflammatory cytokines that have been correlated with brain lesions and the possible presence of cerebral palsy later in life. Generally, the prediction of cerebral palsy is based on the combination of clinical history, neuroimaging, and some standardized tools that examine movements and posture (107,108).

Over the years, many studies have tried to relate cerebral palsy to several biomarkers in the context of the constant effort for early prediction and as earlier intervention as feasible. Many from the well-known genetic syndromes, such as Rett (MECP2), Angelman (UBE3A), or protein C deficiency (PROC) have been associated with this neurodevelopmental disorder, while at the same time some genetic-induced brain anomalies, such as pontocerebellar hypoplasia type 1 (VRK1) and classic lissencephaly (PAFAH1B1), have also been considered as suspicious for development of cerebral palsy. Neurometabolic anomalies, such as glutaric acidemia type 1 (GCDH) and Lesch-Nyhan syndrome (HPRT), is another category that should be considered (107,109). Also, the development of cerebral palsy later in life has been correlated with some epigenetic changes that cause DNA alteration and can lead to several neurodevelopmental disorders. At the same time, some data support that DNA methylation may be responsible for the increased possibility of cerebral palsy in one of the two monozygotic twins in a pregnancy. The greatest predictive potential among these biomarkers seems to have the evaluation of the microRNA profile among neonates (107,110–112). Finally, several inflammatory factors have been examined as possible biomarkers for cerebral palsy and there are several studies to converge that increased levels of IL-6 in the context of intraamniotic infection have been associated with a higher risk for this neurodevelopmental disorder. As far as factors, such as IL-1β, IL-8, and TNF-α are concerned, the data are a bit ambiguous, although recent analyses support that the increased levels during the first weeks of a newborn's life are more likely to be indicative of an undesirable neurodevelopmental development (107,113).

The importance of early diagnosis or, even better, early prediction of cerebral palsy cases can be reflected in the significant improvement in the clinical outcome that can be achieved with preventing measures. Even though two of the main risk factors for this disorder are the installed hypoxia during delivery and possible infection, there are limited data to support that obstetric care could benefit pregnancies at term. However, many studies have verified that preterm birth is one of the most frequent conditions to lead to cerebral palsy and many interventions have been proposed. Particularly, special care is needed for the number of fertilized eggs that be set during in vitro fertilization, limitation of smoking to the minimum, aspirin use in high-risk pregnancies for preeclampsia, cervical cerclage in women with a history of preterm birth in a previous pregnancy or short cervix (77,114). There are conflicting data regarding the use of corticosteroids for the prevention of cerebral palsy, although it seems that the administration of glucocorticoids in pregnancies before 34 weeks may improve the neurodevelopmental process. Also, a study has highlighted the superiority

of betamethasone versus dexamethasone on this issue, as it seems that the administration of such medication is correlated with limitation of the risk for periventricular leukomalacia in preterm births (77,114–116). On the other hand, administration of corticosteroids after pregnancy and, particularly, during the first days after delivery seems to be beneficial for pulmonary development, while in some studies has been associated with increased risk for cerebral palsy, mainly if high doses have administered at first. The most important thing in this medication is that individualized administration is required, depending on the risk for bronchopulmonary damage (80,116,117).

Magnesium sulfate administration is one of the most crucial prenatal interventions over the years, mainly in the context of improving the outcome of preterm birth. Based on a wide variety of studies that tried to evaluate the usefulness of magnesium sulfate, there is no longer any objection to its use to prevent eclamptic seizures or even help in their treatment. More limited use of this medication has also been examined as far as the tocolysis is concerned, but in this case, it seems that there are conflicting data and some doubts as to the possible adverse events (118,119). Especially for cerebral palsy, many data coming from well-organized randomized control trials and meta-analyses have proved that the use of magnesium sulfate in pregnancies that are going to end up in preterm birth acts protectively in the neurodevelopmental process. Particularly, if magnesium sulfate is administered in case of a preterm birth going to take place among the next 24 hours between 24-32 weeks of pregnancy, it seems that the risk for development of cerebral palsy during the first 2 years of a newborn's life is quite reduced (80,118–122). Many data support the fact that magnesium is leading to this result by preventing the inflammatory procedure that is caused by oxidative stress which is present in such pregnancies. Also, it is believed that this medication contributes to the better perspiration of an infant's brain leading to a reduced risk for hypoxia and the possibility of brain lesions that may be associated with neurodevelopmental disorders (80,119,121,122).

As far as infants born at or near term are concerned, the main cause of the development of cerebral palsy later is related to the possible limited oxygenation or ischemia of the fetal brain during delivery, which is reflected in the entity of neonatal encephalopathy. In such cases hypothermia localized only in head or extending to the whole body has been proposed as an early intervention that must be implemented within 6 hours from delivery and having an overall duration of 72 hours (77,80,123). Many data have proven that cooling is a method that prevents the harmful effect of excitatory amino acids and the nitric-oxide-induced destruction of membrane cells in the brain. Many studies have also verified that the appropriate duration of this

intervention is the 72 hours, given the fact that the extension of cooling has not been associated with a better outcome in neurodevelopmental process (80,123). Finally, in some cases of very low-birth-weight infants, there are data to support that use of caffeine has been associated with decreased possibility for cerebral palsy, when it is administered at the first 10 days after delivery for improvement of extubation process (80,116).

2.6. Management and Treatment of Cerebral Palsy: During the years, many different interventions have been examined and proposed for the possible improvement of the outcome in children born with cerebral palsy, even though there are not many data to highlight great results so that the corresponding medication or instruments to be used as “gold-standard” for the best management of this neurodevelopmental disorder. It is essentially a multifaceted process that requires the assistance of many different physicians of different specialties both for the improvement of motor and posture functions and the psychological support. In some severe cases, it is necessary for the management of this disorder that conditions, such as epileptic seizures, nutritional and feeding difficulties, hearing and vision deficits, to be under special care (80,124,125).

Disabilities in movement are, by definition, present in any case of cerebral palsy and the subject of ongoing research with very promising results. Data show that in developed countries newborns that are placed to close monitoring from the first days of their lives and interventions for motor improvement are made, have impressively increased possibility to develop a walking ability close to normal in a percentage up to 75% (124,125). Particularly, based on the Gross Motor Function Classification System (GMFCS), and less in other classification systems, it is much easier to evaluate the possible deficit and by this way to individualize the process of motor improvement. The main target of all the available interventions is the reclamation of impaired movements due to upper motor neuron syndrome and, at the same time, the limitation of posture and muscle tone disorders, so that motor plasticity to be achieved. This process requires the assistance of physiotherapists and orthopedists with specific programmes based on the goal-directed training methods that taking place even at home and with the use of special rehabilitation instruments, treadmill training even with weight support of the child, and empowerment programs. Especially, after botulinum toxin injection many studies have shown that are necessary many supportive therapies aiming to increase muscle power, regulate posture and improve gait condition and, by this way, this intervention could have much better result on the final outcome of the newborn (80,97,97,124–126).

Contractures remain a very crucial subject in the management of cerebral palsy and requires, even from the first years of life, continuous movement and strengthening of the short muscles aiming to prevent their inadequacy and, therefore, to avoid the expected spasticity. According to data, spasticity is established and constantly worsens until the age of 14, when the contractures are stable causing significant difficulties in movements. Considering that the muscles involved in one joint have a reduced risk for ending up in a contracture in comparison with muscles involved in two joints, there are some surgical interventions that have as a target to make the two-joint muscles to function like one-joint muscles. Surgical interventions are also available in case of fixed contractures by extension of the muscle-tenon unit leading to a more harmonized movement and gait with measurable results via the follow-up process. On the contrary, in case of spastic contractures the condition may be reversed by the use of braces in the joints and relaxation (77,106,124).

Surgical management is the appropriate method of care in case of the characteristic long bone deformities of cerebral palsy. Femoral and tibial anomalies are the most frequent and can be treated via rotational osteotomy with simultaneous surgical correction of contractures and postoperative rehabilitation between 6-12 years of age leading to significant improvement mainly at gait quality (127,128). Another intervention that has been analyzed as a possible solution to cerebral palsy's motor difficulties is surgical dorsal rhizotomy. It is a surgical procedure on the dorsal lumbosacral roots of the spinal cord that separates the afferent from the abductor sections of the reflex arc, and, by this way, significant progress seems to be made if this intervention combines with rehabilitation program. Data have proven that children with spastic form of cerebral palsy seem to have the greatest benefit from this procedure. Particularly, children that are recognized with a GMFCS level of II or III, and less level I, are considered as candidates for dorsal rhizotomy aiming to end up to a life close to normal (106,129).

After any intervention it is necessary that rehabilitation process could take place to strengthen the outcome of motor improvement, based on devices and physiotherapy programs. Many types of ankle foot orthoses have been studied for the gait anomalies treatment, given the fact that depending on the anatomical position of the joint with the problem and the impact on swing or stance part of the gait, the use of corresponding devices helps to the greatest outcome. In fact, recent studies have tried to evaluate the effectiveness of personalized treatment of such conditions with very promising results (77,130). At the same time, there are several technological innovations that have associated with better progress on newborn's gait and communication abilities. In this category can be included not only devices that help in the better oral expression,

such as speech technologies, but also wheelchairs that can be driven through finger movements and virtual reality games that encourage children in constant movements (77,124).

In the context of cerebral palsy, many associated adverse events usually arise and can cause significant difficulties in the overall physical activity of the young guy. Pressure ulcers are very frequent condition mainly in severe forms of cerebral palsy with reduced motility and require close care for position changes, use of appropriate clothing and air mattresses and in case of present ulcer, surgical assessment and treatment is needed (97,124). Osteoporosis is another disorder that can be caused because of the specific features of cerebral palsy, such as poor growth, feeding difficulties, reduced exposure to sunlight or anticonvulsants administration. The main risk about this condition is the increased possibility of fractures that may aggravate the motor function and, for this reason, in such cases there is need for administration of medication, such as calcium and vitamin D supplements and bisphosphonates. These interventions have been considered as protective for the fragile bones of the young guy and are widely used nowadays (97,131). Epileptic seizures are, also, frequent found complication of cerebral palsy up to 40% of the cases with severe form of movement disorder. There should be high suspicion and correspondingly close monitoring especially in those cases of newborns that manifest a seizure shortly after delivery and have quadriplegic cerebral palsy and based on the type, duration and other characteristics of the seizure, the appropriate anti-epileptic medication should be administered (77,132,133). Another important part of cerebral palsy's consequences has to do with the inability of the children to have a proper nutrition because of difficulties in feeding. For this reason, newborns must be under a frequent check of their nutrition status and care for improvement of their feeding skills. However, in case of severe malnutrition there is need for alternative interventions, such as gastrostomy, even though there are references for some complications regarding these techniques (77,106).

Several medications have been reported as effective in the management of symptoms and manifestations of cerebral palsy. Dystonia causes many problems in quality of life of these children and anticholinergic agents, such as trihexyphenidyl, carbidopa-levodopa, have been considered as very frequently used and it seems that improve widely the motor function. Other agents that have been used are baclofen, benzodiazepines, muscle relaxants, dopaminergics. However, their administration is based on retrospective studies and case reports and thus their efficacy is debatable (125,134). Also, among the children that are recognized to suffer from cerebral palsy there are up to 50% that are going to develop a psychiatric disorder and the part of

management of such condition is just as useful as medication. Cognitive behavior therapy seems to be a very useful tool for the improvement of mental health and requires systematic cooperation of physicians and psychiatrists (135).

Generally, all these interventions are aiming in a better quality of life (QOL) for the children that undergo this unwanted neurodevelopmental disease. Quality of life is not only related to the management of pain and gait disabilities of cerebral palsy, but also to psychological condition, family and social acceptance and support, school adaptation to the children's needs and financial resources (80,136). Trying to evaluate the impact of all these situations, physicians are in need for extraction of information from the close family environment, but it is a fact that parents of these children can provide a poor quality-of-life report because of present parental stress and depression (80). Thus, children affected by cerebral palsy and their environment should be under multifaceted care which should focus, on the one hand, on the pain management and, on the other hand, on family support. It is a fact that parents undergo a crucial psychological impact with anxiety and depression that may affect their mental health and, as a result, child's general outcome because of the disease (124,137). Early diagnosis of the disease and the immediate information of the parents with every detail about the characteristics and complications of cerebral palsy seems to be a more effective way to avoid later the higher levels of parental stress. During the announcement of the problem, it is necessary the presence of psychologist to help parents understand their critical role in the treatment either with the psychological support that are going to provide to their children or their support to the everyday activities of the child. Parents should be encouraged to ask any questions and caregivers of different related specialties should be available for any information aiming to fulfill parents with hope and leading to a better overall outcome for the children (96,106,124,138).

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1. Introduction

Preeclampsia (PE) is a multisystemic pregnancy disorder and can affect up to 8% of all women during gestation in developed countries. It is characterized by hypertension and proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria. It can range from mild to severe form. Additionally, it can be developed early or late in pregnancy, but sometimes even after delivery during puerperium (2,6). However, it has been proposed that early and late PE are not two different clinical entities, but rather a spectrum of the same disorder, the degree of which is reflected in both the gestational age at the time of delivery and the severity of the disease based on clinical and laboratory findings (36).

The diagnosis of preeclampsia is based on increased blood pressure (systolic blood pressure > 140 mmHg or diastolic > 90 mmHg) that can be verified in two different measurements with a 4 to 6 h interval accompanied with proteinuria ≥ 300 mg/24 h or 1+ on urine dipstick or protein/creatinine ratio ≥ 30 mg/mmol (1,4,7). However, the diagnosis of preeclampsia can still be made in the absence of proteinuria if hypertension is accompanied by specific signs or symptoms indicating significant end-organ dysfunction, such as central nervous involvement (severe headache, photopsia, and scotomata), impaired hepatic function, renal insufficiency, thrombocytopenia, and pulmonary edema (8,9,21).

Risk factors for preeclampsia include a previous history of preeclampsia, chronic hypertension, autoimmune diseases (systematic lupus erythematosus and antiphospholipid syndrome), chronic kidney disease, gestational diabetes, nulliparity, twin pregnancy, a family history of preeclampsia, maternal overweight or obesity, and previous history of placental insufficiency, such as fetal growth restriction (FGR), stillbirth, and placental abruption (3,4,9). The pathophysiology of preeclampsia is associated with environmental, maternal, and placental factors. Defects in the development of placental vasculature early in pregnancy, such as abnormal remodeling of spiral arteries and defective trophoblast differentiation, may result in placental hypoperfusion, hypoxia, and ischemia. The consequence of the abnormal placentation is reduced production and expression of angiogenic parameters, such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and increased placental expression and secretion of antiangiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1), into the maternal circulation, causing maternal systematic endothelial dysfunction. The outcome of the altered endothelial function is maternal hypertension and further clinical signs of the disease, such as proteinuria and renal insufficiency, platelet activation and hemolysis, ischemia,

necrosis and dysfunction, central nervous system manifestations, and visual disturbances, and cardiac and pulmonary dysfunction. However, the trigger for abnormal placental development and the subsequent cascade of events remains unknown (4,9,14,16,25,26).

Nowadays, screening tests are used early in gestation to identify high-risk pregnancies for developing preeclampsia. Based on historical risk factors (maternal and pregnancy characteristics), only approximately 30 % of women who will develop preeclampsia can be predicted (32,34,35). Particularly, in the context of personalized prediction, emphasis is given to maternal characteristics, medical and obstetric history, and biochemical and biophysical measurements. In terms of prevention, there is strong evidence that in pregnancies at high risk of PE, the administration of aspirin (150 mg/day) reduces the rate of early PE (<32 weeks) by about 90% and preterm PE by 60% (8,48,49,139). Furthermore, lifestyle changes such as weight loss in obese women, avoiding excessive gestational weight gain, and multifetal pregnancies following assisted reproductive technology (ART) for infertility treatment have been associated with a significant reduction in the risk of developing preeclampsia. PE has been associated with increased perinatal mortality and morbidity, as it is a major risk factor for developing serious complications of eclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, prematurity, and long-term maternal diseases, such as cardiovascular disease, kidney disease and type 2 diabetes (8,140). Management of this disease aims to maintain blood pressure at acceptable levels below 150 mmHg for the systolic blood pressure and 80–100 mmHg for the diastolic blood pressure. In case blood pressure deviates from the normal levels for more than 15 min and systolic blood pressure exceeds 160 mmHg and/or diastolic blood pressure is increased above 110 mmHg, immediate treatment with intravenous administration of labetalol or hydralazine or oral nifedipine is the appropriate solution. However, if there are signs of seizures or fetal distress, then delivery is required (1,4,8).

Cerebral palsy (CP) is the result of abnormalities of the developing fetal or infantile brain (78). This is the most common motor disorder in children, and its prevalence is estimated to vary from 1.5% to 3% (77). As far as its risk factors are concerned, preterm birth is a major one, and if delivery takes place before 28 weeks, the risk of cerebral palsy is significantly higher; other complications such as inflammation during pregnancy, perinatal hypoxic-ischemic injury, and hypertensive disorders leading to preterm birth have also been correlated with cerebral palsy (77,79).

A diagnosis of cerebral palsy can be made clinically based on perinatal history, neurological examination, imaging testing, and laboratory assessment. Early detection of cerebral palsy before 5 months of age can be evaluated with magnetic resonance

imaging (MRI) of the infant, the Prechtl Qualitative Assessment of General Movements (GMA), and the Hammersmith Infant Neurological Examination (HINE). Infants with an identified risk factor related to cerebral palsy must be considered “high risk” and must be closely monitored for the administration of every useful early treatment. In most cases, the diagnosis can be established between 12 and 24 months of life. Different subtypes depending on the affected brain area, motor disability type, and the level of functionality have been described (78,80). In terms of prevention, measures include the prediction and prevention of preterm labor, the administration of magnesium sulfate for neuroprotection in preterm pregnancies, delayed umbilical cord clamping, the maintenance of sufficient ventilation, cerebral perfusion, metabolic status, and therapeutic hypothermia (79,80). As far as management is concerned, the earlier the diagnosis of cerebral palsy, the better the outcome for newborns’ motor and spasticity recovery, aiming to maximize daily functional activities’ independence and decrease the extent of disability (80,96).

Hypertensive disorders of pregnancy and particular preeclampsia have been associated with an increased risk of neurodevelopmental disorders and cerebral palsy in childhood. Pregnancy comorbidities such as preterm birth, gestational diabetes, and fetal growth restriction seem to further increase the abovementioned risk. Furthermore, the severity of the hypertensive disorder and gestational age at the onset of the disease may contribute to developmental impairment and neurological sequelae. However, even preeclampsia at term has a lasting effect on the neurodevelopment of the offspring. Data regarding the association between preeclampsia and infantile cerebral palsy are conflicting, though there are studies supporting that the overall likelihood of cerebral palsy is reduced in the offspring of preeclamptic mothers irrespective of magnesium administration, and this risk is mainly limited in cases complicated by preterm birth (79,82,141–143). The mechanisms of this controversial association remain to be elucidated; nevertheless, placental insufficiency and the associated oxygen and nutrients deprived in the utero environment have been proposed as a possible etiology (144). The present study aims to conduct a systematic review and meta-analysis of all the available data that have assessed the association between preeclampsia and the risk of cerebral palsy in offspring.

2. Materials and Methods

2.1. Search Strategy and Eligibility of Studies

The present systematic review and meta-analysis were performed according to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines (145), and the completed PRISMA statement. Additionally, the Systematic Review registration statement is available on PROSPERO (ID:306467). The study protocol was discussed, and there was a broad consensus among all authors. A careful search was performed in PubMed/Medline and EMBASE (end-of-search: 22 November 2021) based on the following algorithm: (preeclampsia OR pre-eclampsia OR eclampsia OR pre-eclamptic OR preeclamptic) AND ("cerebral palsy"). No restriction was set regarding the publication language. At the same time, we performed a search in all the studies used for analysis for some data within the subject of this review in a "snowball" procedure. Additionally, we performed a search in Google Scholar using the keywords "pre-eclampsia" and "cerebral palsy", and we examined the first 300 hits, aiming to find additional relevant studies.

The eligible studies for our analysis were randomized controlled trials, case-control, and cohort studies, but no case reports or case series. Search and selection of the studies were made by two reviewers who worked independently, and any disagreement was resolved with the broad consent of all authors. A very crucial fact in our selection criteria was that the follow-up should be started immediately after birth, as the diagnosis of cerebral palsy most likely occurs between 12 and 24 months of life (78,80). Additionally, among the studies that we identified for analysis, we excluded some because of population overlapping, and we included the larger ones.

2.2. Data Collection and Effect Estimates

Data extraction was carried out based on the general background of every study (first author's name and year of publication), characteristics (study design and period of interest, geographical region), and a follow-up period of the newborns. At the same time, data extraction was carried out for cohort size and cases of cerebral palsy (for cohort studies), number of cases and controls (for case-control studies), features of mothers with preeclampsia and infants with cerebral palsy, and the main results of every study, including the factors adjusted for in the multivariate analyses. As in the selection of the studies, the two reviewers extracted data autonomously, and then the writing team, after consultation, concluded on what was appropriate and useful for the analysis. Odds ratios, along with their 95% confidence intervals (95% CI), as well as relevant data for calculation, were abstracted from each study; whenever possible, adjusted effect estimates were preferred over unadjusted ones.

2.3. Synthesis of Results

Random effects (DerSimonian–Laird) models were implemented for the estimation of pooled odds ratios and 95% CIs. As far as heterogeneity between studies is concerned, this was evaluated by Q-test and I^2 [35]. Subgroup analyses were performed by the degree of adjustment (unadjusted; adjusted for variables except for gestational age; adjustment for variables including gestational age), geographical region (Europe, USA), or study design (case-control or cohort) in focus to find out possible reflect to the results. We used STATA/SE version 13 (Stata Corp, College Station, TX, USA) for all our analyses.

2.4. Assessment of Quality and Publication Bias

Authors examined the quality of the studies included in the analysis via the Newcastle–Ottawa Quality scale, and study quality was considered “low” when the Newcastle–Ottawa score measured between 1 and 3, “intermediate” when the score was between 4 and 6, and “high” when the score ranged between 7 and 9. The two researchers again worked independently and evaluated the studies regarding the quality based on this scale and recorded their results. Additionally, it was very important for the follow-up period in every study to be checked, and in advance, the authors set the restriction of immediate start after birth, based on what was already known for cerebral palsy. Then, consensus followed.

We evaluated the possible existence of publication bias using Egger’s formal statistical test [36] and visual inspection of the funnel plot. The level of statistical significance for this test was set at $p < 0.1$. For this test, we again used the STATA/SE version 13 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Features of Eligible Studies

During the search of the literature, we identified 559 studies that met our eligibility criteria (152 from PubMed/Medline, 300 from Google Scholar, and 107 from EMBASE), and all the steps of our selection process are available in Figure 1.

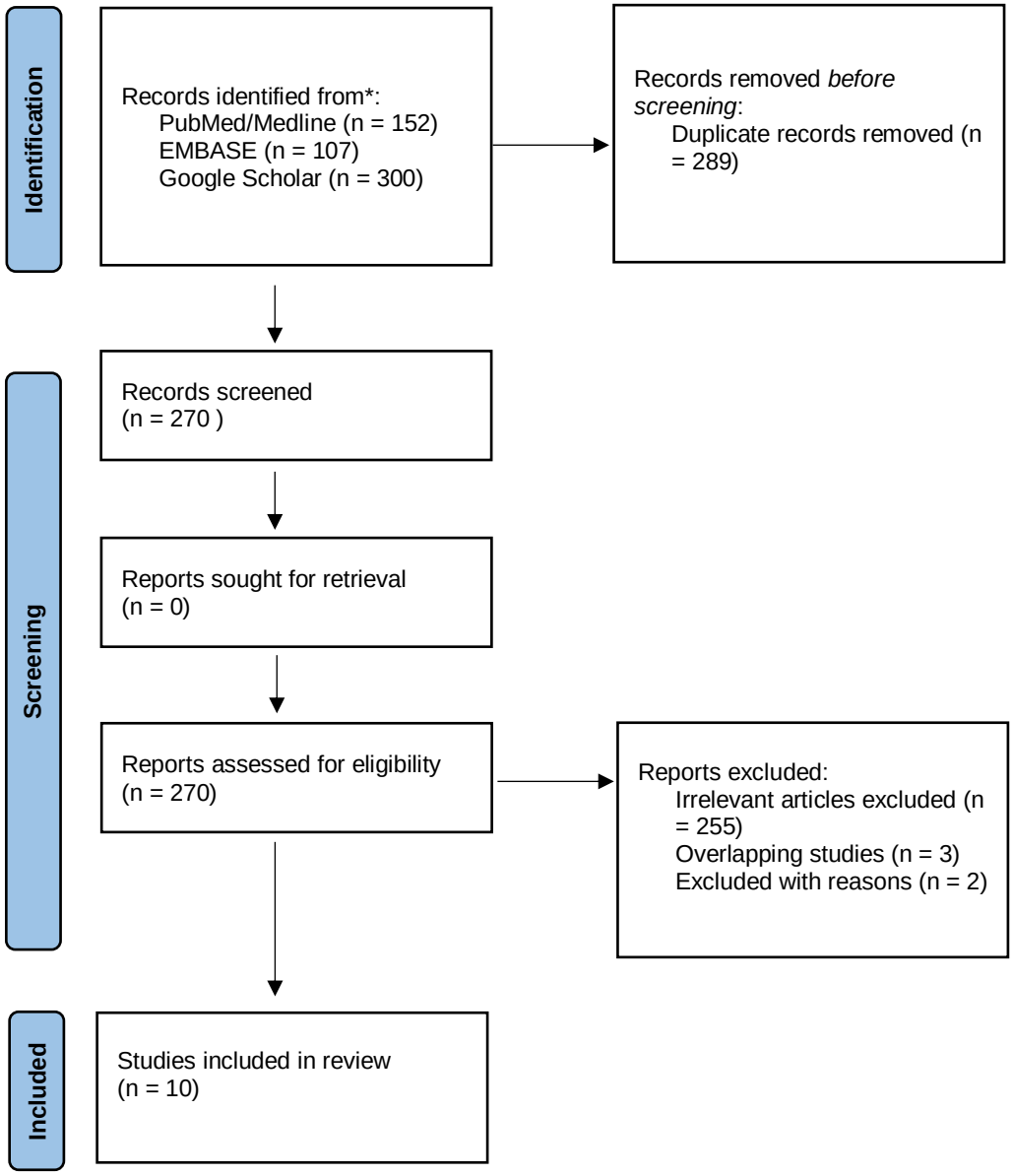

Figure 1. Flow chart presenting the steps in the selection of eligible studies.

When all the studies were gathered, we excluded 289 studies based on the title or the abstract as irrelevant or as duplicate. Then, the 270 studies remained for further full-text evaluation. Out of this number of studies, three were excluded due to overlapping in the populations that were examined, one because it also included cases of pregnancy-induced hypertension without separation of the cases of preeclampsia,

and one because of a lack of provided odds ratio for the association that this analysis examines (Table 1).

Study	Title	Reason for exclusion
Studies excluded due to overlap		
Spinillo (1994)	Two-year infant neurodevelopmental outcome after expectant management and indicated preterm delivery in hypertensive pregnancies	The study period 1986-1990 is overlapped from the study of Spinillo that took place on 2006 and its study period is 1983-2002. Also, the population was drawn from the same computer database In Pavia, Italy and was extracted by taking into account the same characteristics
Spinillo (1998)	Preeclampsia, preterm delivery and infant cerebral palsy	The study period 1987-1993 is overlapped from the study of Spinillo that took place on 2006 and its study period is 1983-2002. Also, the population was drawn from the same computer database In Pavia, Italy and was extracted considering similar characteristics
Mor (2016)	Early onset preeclampsia and cerebral palsy: a double hit model?	The study period 1990-2013 is overlapped from the study of Nahum Sacks that took place on 2019 and its study period is 1991-2014. Also, the population was drawn from the same computer database In Soroka University Medical Center, Israel and was extracted considering similar characteristics
Studies excluded due to other reasons		
Blair (2016)	Cerebral palsy and perinatal mortality after pregnancy-induced hypertension across the gestational age spectrum: observations of a reconstructed total population cohort	The study included all cases of pregnancy-induced hypertension and preeclampsia and excluded due to authors' criteria

Sacks (2016)	Long-term neuropsychiatric morbidity in children exposed prenatally to preeclampsia	The study does not provide odds ratio for the association between preeclampsia and cerebral palsy

Table 1. Studies excluded with their reason for exclusion.

Finally, 10 studies were considered eligible for this systematic review. Two studies followed the case-control design (146,147), and eight followed the cohort style (148–155) All the characteristics of the studies included are presented in Tables 2 and 3.

First author (Year)	Number of cases	Number of controls	Study design	Study period	Region	Definition/features of women with preeclampsia	Definition of infants with cerebral palsy	Main results
Stelmach (2005)	158	316	Case-Control	-	Tartu City, Estonia	153 cases and 268 controls (available for analysis)/ CP group: mean BW 2927.2gr, mean GA 36.1w/ Control group: mean BW 3494.3gr, GA varied from 30-43w	Several antenatal, intrapartum and neonatal factors associated with cerebral palsy examined	Out of 11 cases with preeclampsia 9 correlated with CP (81.8%) and out of 410 cases without preeclampsia 144 correlated with CP (35.1%%), by statistical software pack- age R 1.6.2 - A Language and Environment/adjustment factors: sex, time of birth, place of residence
Ozturk (2005)	98	530	Case-Control	1990-2004	Duzce, Turkey	CP group: mean GA 38,1w, mean BW 2887gr, preeclampsia 7 cases / Control group: mean GA 39,2w, mean BW 3230, preeclampsia 10 cases	The diagnosis of CP was confirmed by at least two physicians (a pediatrician and a neurologist) /	Out of 17 cases with preeclampsia, 7 correlated with CP (41.2%), whereas among 611 cases without preeclampsia 91 correlated with CP/ statistics made with x2 test and Student's f-test / univariate analysis

Table 2. Characteristics of all the eligible case-control studies.

First author (Year)	Cohort size	Incident cases	Follow-up period	Study design	Study period	Region	Definition/features of women with preeclampsia	Definition of infants with cerebral palsy	Main results
Withagen (2005)	574	21	Median 7 years	Cohort	-	Rotterdam, The Netherlands	Study group(192): mean GA 32w, mean BW 1215gr, Ventilation 101/ group I(192): mean GA 30w, mean BW 1337gr ,Ventilation 160/ group II: mean GA 32w, mean BW 1785gr,Ventilation 103	Child morbidity and development were assessed by means of the Child Behaviour Checklist (CBCL) / The information obtained by means of the questionnaires was supplemented by review of medical records when available.	5/159 of mothers with preeclampsia developed CP (3.1%) and 16/232 of mothers without preeclampsia developed CP (6.8%), p>0.05 by McNemar test / univariate analysis
Spinillo (2006)	534	50	2 years	Cohort	1983-2002	Pavia, Italy	Intact Survival: mean GA 30,2w, mean BW 1148gr, preeclampsia 120 cases/ Minor Abnormalities: mean GA 29,6w, mean BW 1131gr, preeclampsia 26 cases/ CP: mean GA 29w, mean BW 1049gr, preeclampsia 5 cases	Neurodevelopmental evaluation of the infants at discharge,3,6, 9,12 and 24 months of corrected age	Out of 178 cases with preeclampsia 5 correlated with CP (2.8%) and out of 525 women without preeclampsia 45 correlated with CP(8.5%) (not referring to a test used) / univariate analysis

McElrath (2009)	1455	120	2 years	Cohort	2002-2004	Boston, USA	GA ranges from 23w to 27w of gestation with the majority at 27w(357 infants), BW ranges from <750gr(385 inf) to >1250gr(20 inf), Preeclampsia came up to 7 cases in the CP group	The neurologic evaluation was performed by examiners using a structured data collection form. /The topographic diagnosis of cerebral palsy (quadriparesis , diparesis, or hemiparesis) was based on an algorithm that used these data	Among 139 infants correlated with preeclampsia in mothers , 7 diagnosed with CP (5%), whereas among 917 infants without preeclampsia in mothers, 113 correlated with preeclampsia to mothers (12.3%), with Pearson's x2 or Fisher's exact test / univariate analysis
Mann (2010)	122.476	337	3 years	Cohort	1996-2002	South Carolina, USA	Singleton pregnancies and exclusion of pregnancies that performed before 21 weeks and have no opportunity for the presence for preeclampsia / Infants from singleton pregnancies and exclusion of infants with chromosome or genetic abnormality	Confirmed cases of children with CP according to ICD-9 / Diagnosis set by two different health care providers	Among 337 infants with CP, 22 correlated with preeclampsia to mothers (6.5%) and among 122.139 infants with CP, 4204 correlated with preeclampsia (3.4%), p=0.002 with X2 test or Fischer's test for categorical variables and Student's t-test for continuous variables / Models are adjusted for maternal age and race, genito-urinary infection in the first two trimesters and child's sex.

Love (2012)	28.967	-	-	Cohort	1995-2008	Aberdeen, UK	Women were divided in three categories depending on the hypertensive status / Out of 1774 women with preeclampsia 149 was very premature and 317 premature	Children recorded on the SNS were categorised according to their registered diagnoses. On investigation, there were over 95 different diagnoses documented so these were grouped into seven categories according to clinical judgement. These categories were 'congenital abnormality', 'cerebral palsy', 'autism', 'attention deficit hyperactivity disorder', 'developmental delay', 'communi-cation difficulties/learning difficulties' and 'other'	Preeclampsia as a maternal abnormality responsible for CP: Unadjusted OR 2,72 /Adjusted OR 1,26 (95% CI 0.43, 3.68)}, p=0,668 using the Statistical Package for the Social Sciences 17.0 (SPSS Inc. Chicago, Illinois) / All OR adjusted for maternal sociodemographic characteristics and simultaneously for other variables included in the model
Strand (2013)	617.506	849	-	Cohort	1996-2006	Trondheim, Norway	Women dichotomised as nulliparous and parous and depending on the time of birth as term, moderate preterm and very preterm / Children separated to SGA(=FGR) and defined SGA(<10th percentile)	Diagnosis of CP confirmed in all children when they were at least four years old, according to the recommendations of the Surveillance of Cerebral Palsy in Europe network	Among 22.956 mothers underwent preeclampsia in pregnancy , 75 correlated with CP (0.3%), whereas among 594.551 mothers without preeclampsia, 774 correlated with CP(0.13%), analyzing with x2 statistics and SPSS programme / adjusting factors: maternal age, parity, smoking in pregnancy, assisted fertilisation, and sex of the child and at the same time were checked for gestational age and small for gestational age

Tronnes (2014)	1.764.509	3151	>4 years	Cohort	1967-2001	Bergen, Norway	Exclusion criteria for the children was the week of gestation and the birthweight in the corresponding gestational week (Children born <23w or >43w or with BW more than 3SDs excluded)	CP cases were identified by the International Classification of Diseases codes 342.0 to 344.9 (9th revision) and G80–G83.9 (10th revision) in the insurance database	Out of the 50.209 cases with preeclampsia, 174 cases came up with CP [0.34%, crude OR 2.0 (1.7-2.3), adjusted OR 1.7(1.5-2.0), whereas out of 1.714.300 cases without preeclampsia, 2977 cases came up with CP/ statistical analysis made by using PASW software, version 18.0; IBM SSPS Statistics, IBM Corp. NY, USA / adjusted ORs for several factors, but not for gestational age

Sun (2020)	980.560	995	14 years	Cohort	1991-2009	Washington, Seattle	Preeclampsia Group: mean GA 39.3w, mean BW 3463gr / Non-exposed to preeclampsia: mean GA 39.8w, mean BW 3628gr / Year of birth was included as a continuous variable - Maternal age was categorized as 19 years or younger, 20 to 24 years, 25 to 29 years, 30 to 34 years, 35 to 39 years, or 40 years or older - Parity was dichotomized as primiparous or multiparous	A range of adverse neurodevelopmental outcomes—cerebral palsy, ADHD, ASD, epilepsy, intellectual disability, and vision and hearing loss—were examined and the association between exposure to preeclampsia and each outcome by logistic regression was investigated	Among 28.068 mothers developed preeclampsia during pregnancy, 40 correlated with cerebral palsy in the infants (0.14%), while among 952.492 mothers without preeclampsia, 965 correlated with CP in the infants (0.1%), in term singleton births/ Among all children term and preterm the corresponding percentages was 0.3% for the preeclampsia group and 0.1% for non-preeclamptic mothers / adjusted for sex, year of birth, mother's age, parity, marital status, maternal and paternal educational levels, and parental immigrant status, but not for gestational age

Table 3. Characteristics of all the eligible cohort studies.

Additionally, all the studies were evaluated based on Newcastle–Ottawa Scale, and the results of this rating are presented in Tables 4 and 5. Quality scores ranged between 6 and 9.

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability on age and other factors**	**Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
Stelmach (2005)	1	1	1	1	1	1	1	0	7
	Population-based prevalence study in the city and county of Tartu and were entered into a computer data- base.	One hundred fifty-eight cases of cerebral palsy of all severity stages (mild to severe) were initially ascertained / It is the biggest and most representative part of that region and belongs to the catchment area of the Children's Clinic of Tartu University Clinics	Two controls for each case were selected from the whole population reg- ister of Tartu city and county in Estonia	The family physicians of control children were contacted by telephone to exclude possible unattended developmental problems in children with a minimum age of 4 years.	The controls were matched by sex, year and month of birth, and place of residence at the time of birth (urban or rural area), the latter being well descriptive of the socioeconomic status of families in the Estonian context.	Multiple sources of ascertainment were used to compile the database / o check the developmental status of control subjects, we searched through the hospital admission database and the register of out-patient visits to pediatric neurologists at Tartu University Clinics	Hospital admission database and the register of out-patient visits to pediatric neurologists at Tartu University Clinics.	Neither obstetric nor neonatal records could be found for 47 selected controls and 1 child with cerebral palsy. We excluded one child with cerebral palsy owing to missing data pertaining to the perinatal period	
Ozturk (2007)	1	1	1	0	2	1	0	0	6
	Cross-sectional study within the rural and urban area of Duzce province was performed between January 2006 and March 2006	All children with CP were sought from multiple sources, including the health services, population registry service, education authorities, the office of the village headman (Mukhtar) and associations for CP, and a rehabilitation center for disabled children.	CP and to compare them with normal population, a cross-sectional study within the rural and urban area of Duzce	No description	Specific complications of pregnancy encompassing abortion, hemorrhage in late pregnancy, premature rupture of membranes (PROM), gestational diabetes, preeclampsia, and preterm labor were examined.	All children with CP were sought from multiple sources, including the health services, population registry service, education authorities, the office of the village headman (Mukhtar) and associations for CP, and a rehabilitation center for disabled children / A structured questionnaire was filled it out face to face and mothers' past medical and obstetrics history were obtained	No	No description	

Table 4. Evaluation of the eligible case-control studies with the Newcastle-Ottawa scale.

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed	**Selection of non-exposed**	**Ascertainment of exposure**	**Outcome not present at start**	**Comparability on age and other factors**	**Assessment of outcome**	**Long enough follow-up (median ≥2 years)**	**Adequacy (completeness) of follow-up (≥85% response rate)**	
Withagen (2005)	1	1	1	0	2	1	1	0	7
	The study obtained approval of the Institutional Medical Ethics Committee. The study group consisted of all live-born and one year surviving infants of 222 consecutive patients, admitted with severe pre-eclampsia between 24 and 32 weeks of gestation, who underwent haemodynamic treatment aimed at prolongation of pregnancy	Each infant of a pre-eclamptic mother was matched for gestational age, gender and year of birth in a blinded fash-ion, without knowledge of neonatal characteristics and clinical outcome, with two liveborn infants of non-pre- eclamptic mothers	The information obtained by means of the questionnaires was supplemented by review of medical records when available	No description	Gestational age, birthweight, umbilical arterial pH, ventilation, BPD, ICH, PVL	Questionnaires was supplemented by review of medical records	Yes	Follow-up rate <85% in all the three groups	
Spinillo (2006)	1	1	0	0	2	1	1	1	7
	The study used a database containing obstetric and infant information of an historical cohort of all VLBW infants delivered at the Department of Obstetrics and Gynecology of the University of Pavia during the period 1983–2002.	All the VLBW infants born over a 20-year period (1983–2002) at a single institution.	No description	No description	Odds ratio and 95% CI as obtained by logistic regression equations containing neonatal death or cerebral palsy as a combined outcome variable, and gestational age, antenatal corticosteroid and postnatal surfactant use as explanatory variables.	Neurodevelopmental evaluation of the infants was carried out by a child neuropsychiatrist who was not involved in the intensive care of the infants. Examinations were carried out at discharge and after 3, 6, 12 and 24 months of corrected age. Neurological evaluation of the newborns was based on the methods of Amiel-Tison and Grenier.[12] The Bayley scales of infant development were used to assess cognitive develop- ment (mental developmental index [MDI] at 12 and 24 months).	Yes	534 (88.4%) completed the neurodevelopmental follow-up programme.	

McElrath (2009)	1	1	1	0	2	1	1	0	7
	During 2002–2004, women delivering before 28 weeks of gestation at one of 14 participating institutions in 11 cities in 5 US states were asked to enroll in the study. At each site, the enrollment and consent processes were approved by the local institutional review board.	During 2002–2004, women delivering before 28 weeks of gestation at one of 14 participating institutions in 11 cities in 5 US states were asked to enroll in the study. At each site, the enrollment and consent processes were approved by the local institutional review board.	The neurologic evaluation was performed by examiners using a structured data collection form.	No description	Compared each of the pregnancy complications with pre- eclampsia and adjusted for gestational age and receipt of an antenatal steroid.	The neurologic evaluation was performed by examiners using a structured data collection form	Yes	No statement	
Mann (2010)	1	1	1	1	1	1	1	1	8
	De-identified South Carolina Medicaid billing records for pregnancies and deliveries that occurred between 1996 and 2002 inclusive. We also obtained linked files to birth certificates and Medicaid billing records for children.	De-identified South Carolina Medicaid billing records for pregnancies and deliveries that occurred between 1996 and 2002 inclusive. We also obtained linked files to birth certificates and Medicaid billing records for children.	The outcome of CP was determined by identifying children diagnosed with CP in the Medicaid data	Therefore, we limited our analyses to 'confirmed cases' of CP, defined as children who were diagnosed with CP by at least two different health care providers	The regression models were adjusted for maternal age and race ('white', 'black' or 'other'), genito-urinary infection occurring in the first two trimesters and child's sex / the primary models were estimated without controlling for gestational age	The outcome of CP was determined by identifying children diagnosed with CP in the Medicaid data	Yes	10 669 for whom the absence of CP could not be confirmed because they did not remain enrolled in Medicaid until at least age 3 and never enrolled in public schools;	
Love (2012)	1	1	1	1	2	1	0	0	7
	This was a retrospective cohort study and the population consisted of all children born to mothers in Aberdeen city and district between 1995 and 2008	This was a retrospective cohort study and the population consisted of all children born to mothers in Aberdeen city and district between 1995 and 2008	The database from which the study population is derived - the Aberdeen Maternity and Neonatal Databank (AMND) has been in existence since 1950. The Support Needs System (SNS) is part of a Scottish-wide database recording information about children who have additional	The primary outcome of interest was whether a child had developed a record in the Support Needs System	All OR adjusted for maternal sociodemographic characteristics and simultaneously for other variables included in the model	The data stored in both the AMND and SNS databases are of high quality and consistency, with stringent coding criteria used by trained staff. They also claim a high degree of completeness. The data have been collected prospectively, eliminating recall bias	No reference	No statement	

			support needs for more than six months and has been utilised in Grampian since 1998						
Strand (2013)	1	1	1	1	2	1	1	1	9
	All singleton babies surviving the early neonatal period in Norway between 1 January 1996 and 31 December 2006 were eligible for this study	All singleton babies surviving the early neonatal period in Norway between 1 January 1996 and 31 December 2006 were eligible for this study	From the Medical Birth Registry of Norway we extracted data on pre-eclampsia in pregnancy, maternal health and delivery, and the early neonatal period.	1494 children born between 1996 and 2006 had a diagnosis of cerebral palsy. By 27 March 2012, detailed data for 381 of these children (25.5%) had not been recorded in the cerebral palsy registry. Since no information was available on these children, including birth dates, we were not able to exclude these children from the reference population	The regression models were adjusted for maternal age and race ('white', 'black' or 'other'), genito-urinary infection occurring in the first two trimesters and child's sex / the primary models were estimated without controlling for gestational age	The recording of data in the cerebral palsy registry of Norway and linkage with the medical birth registry requires informed consent from the parents. In addition to this detailed consent based information, the habilitation centres report the total number of children with cerebral palsy for whom they care (summative information).	Yes	Small number lost	
Tronnes (2014)	1	1	1	1	1	1	1	1	9
	We identified all live births from 1967 to 2001 regis- tered in the MBRN	We identified all live births from 1967 to 2001 regis-tered in the MBRN	By using the personal identification number in an encrypted form, we linked information from the MBRN, Statistics Norway, and the National Insurance Scheme. MBRN pro- vided information on maternal health, pregnancy disorders, delivery, and birth	We also excluded children who died within the first year of life, since these children were not likely to have been diagnosed with CP	We calculated the odds ratios of CP according to gestational age and examined whether odds ratios changed after adjustment for sociodemographic fac- tors and year of birth, and after additional adjustment for pregnancy disorders / Not adjusted for gestational age	CP cases were identified by the International Classi- fication of Diseases codes 342.0 to 344.9 (9th revision) and G80–G83.9 (10th revision) in the insurance database	Yes	Small number lost	

Sun (2020)	1	1	1	1	1	1	1	1	8
	We identified all singleton live births from January 1, 1991, to December 31, 2009, defining term births as children born at a gestational age of at least 37 completed weeks by ultrasonographic measure if available and otherwise by last menstrual period	We identified all singleton live births from January 1, 1991, to December 31, 2009, defining term births as children born at a gestational age of at least 37 completed weeks by ultrasonographic measure if available and otherwise by last menstrual period	Information on all pregnancies delivered in Norway after 16 weeks' gestation is reported to the Medical Birth Registry of Norway at delivery by the mother's clinician	Neurodevelopmental diagnoses of participants were obtained from the *International Classification of Diseases, Ninth Revision*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, codes in the National Insurance Scheme registry	Multivariable logistic analyses for participant sex and year of birth, maternal age, parity, maternal marital status, maternal and paternal educational levels, and parental immigrant status. Year of birth was included as a continuous variable	Neurodevelopmental diagnoses of participants were ob- tained from *International Classification of Diseases, Ninth Re- vision*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, codes in the National Insurance Scheme registry / Data were linked across these population registries by each per- son's unique Norwegian identification number.	Yes	Small number lost	

Table 5. Evaluation of the eligible cohort studies with the Newcastle-Ottawa scale.

3.2. Synthesis of Studies and Meta-Analysis

All 10 studies were included in the overall analysis. All the results of the general analysis and the subgroup analyses are presented in Table 6. In the overall analysis, there was no statistical significance regarding the association between preeclampsia and cerebral palsy (pooled OR = 1.16, 95% CI: 0.77–1.74).

	n§	OR (95%CI)	Heterogeneity I^2, p
Overall analysis	10	1.16 (0.77-1.74)	85.8%, 0.000
Subgroups by degree of adjustment			
Adjusted, but not for gestational age	3	1.62 (1.36-1.93)	23.0%, 0.273
Adjusted, including gestational age	3	1.63 (0.48-5.50)	80.5%, 0.006
Unadjusted	4	0.65 (0.20-2.18)	82.6%, 0,001

Subgroups by study design			
Case-control studies	2	5.00 (2.17-11.50)	0.0%, 0.416
Cohort studies	8	0.93 (0.61-1.41)	86.8%, 0.000
Subgroups by geographic region			
Europe	7	1.22 (0.68-2.20)	88.2%, 0.000
USA	3	1.06 (0.53-2.13)	83.6%, 0.002
Subgroups by overall quality rating			
Low (NOS 1-3)		No studies	
Intermediate (NOS 4-6)	3	0.74 (0.14-3.92)	87.9%, 0.000
High (NOS 7-9)	7	1.30 (0.87-2.15)	85.2%, 0.000

Table S6. Results of the meta-analyses examining the association between pre-eclampsia during pregnancy and cerebral palsy in the offspring; subgroup analyses by the degree of adjustment, study design, geographic region, overall quality rating

Three studies (149,153,154) provided adjusted odds ratios for several variables except for gestational age; three studies (147,148,152)presented a multivariate analysis, adjusting also for gestational age; and four remaining studies (146,150,151,155) provided unadjusted odds ratios. A significant association arose only in the subgroup of studies that performed a multivariate analysis, adjusting for variables other than gestational age (pooled OR = 1.62, 95% CI: 1.36–1.93). In the subgroup of studies that performed a multivariate analysis including gestational age, the pooled was equal to 1.63 (95% CI: 0.48–5.50), and in the subgroup of studies that performed univariate analysis, the pooled OR was 0.65 (95% CI: 0.20–2.18). These results are presented in Figure 2.

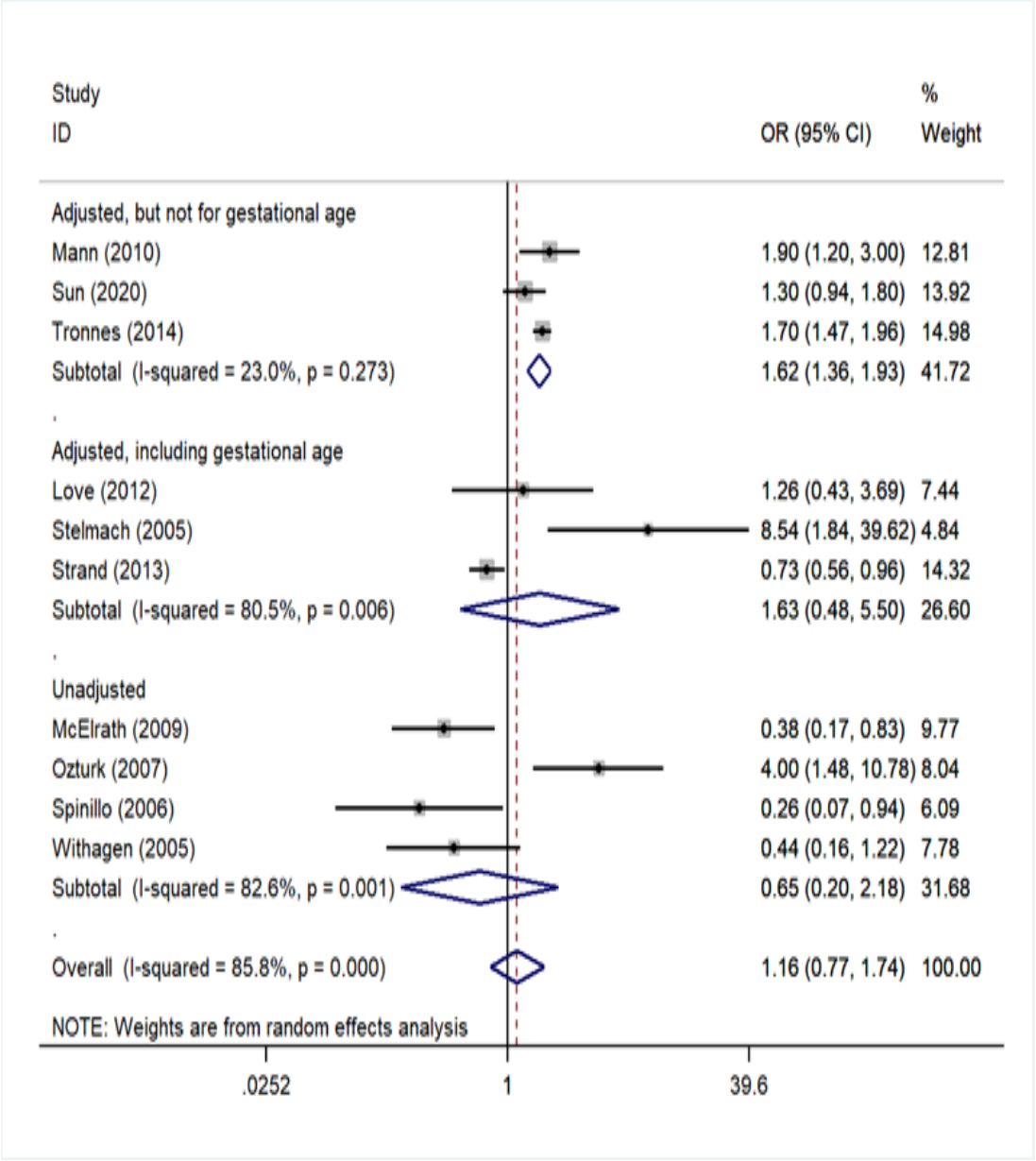

Figure 2. Forest plot describing the association between preeclampsia and cerebral palsy and the subgroup analysis by degree of adjustment.

Regarding geographical region, there was no association either in studies of European populations, including in Turkey and Israel or the USA (Europe OR = 1.22, 95% CI: 0.68–2.20 and USA OR = 1.06, 95% CI: 0.53–2.13). The analysis in the subgroup of cohort studies did not find any association either (Cohort OR = 0.93, 95% CI: 0.61–1.41). However, a significant association was noted in the subgroup of the case-control studies (pooled OR = 5.00, 95% CI: 2.17–11.50), but in this group, the number of studies was only two. All these data are presented in Figure 3 and Figure 4. No statistically significant publication bias (p = 0.456) was identified, according to Egger's statistical test and the funnel plot of the studies is also available in Figure 5.

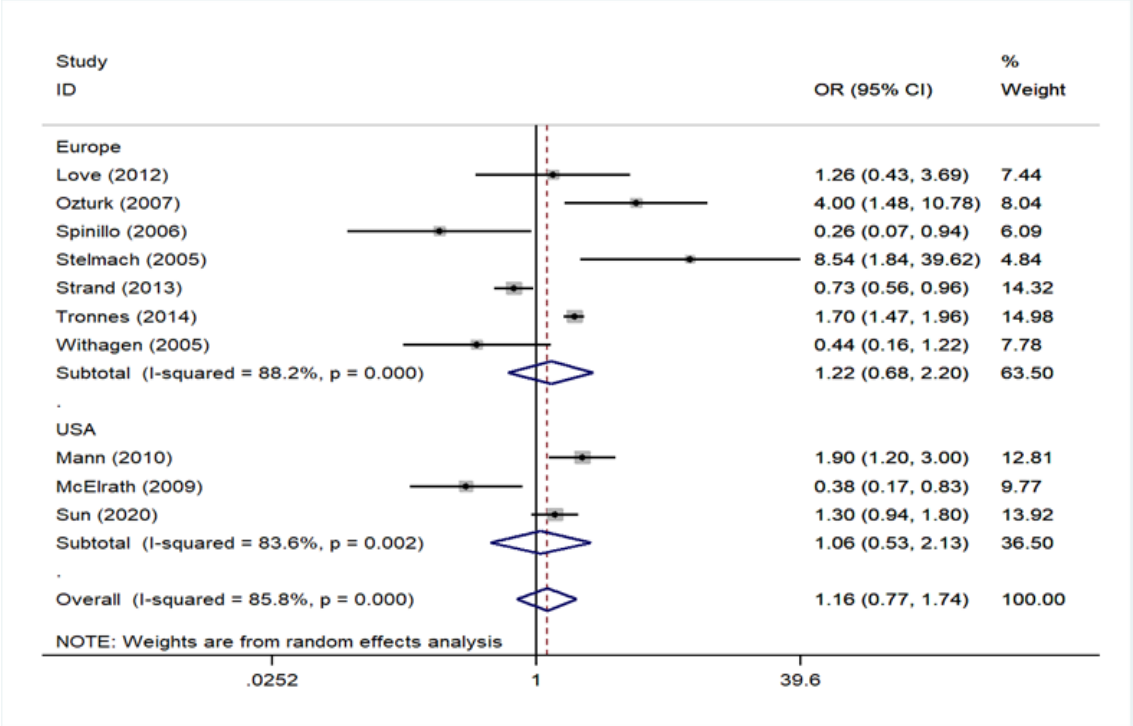

Figure 3. Forrest plot describing the association between preeclampsia and cerebral palsy based on the subgroup analysis of studies depending on geographical region.

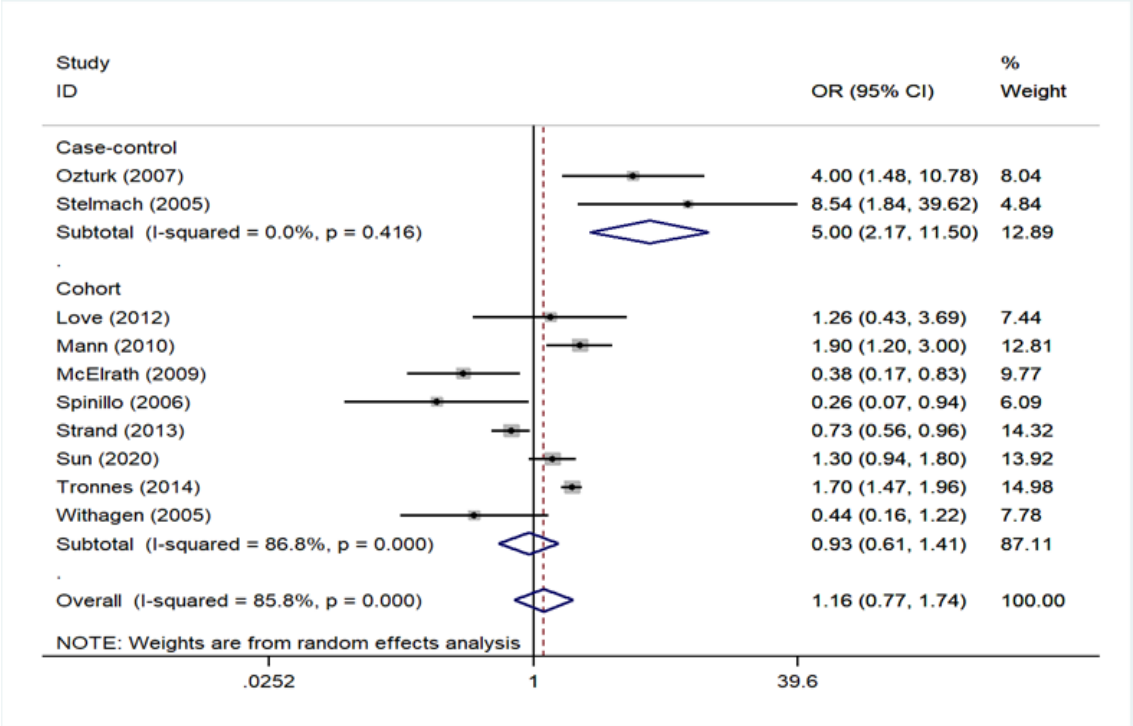

Figure 4. Forest plot describing the association between preeclampsia and cerebral palsy based on the subgroup analysis of studies depending on study design.

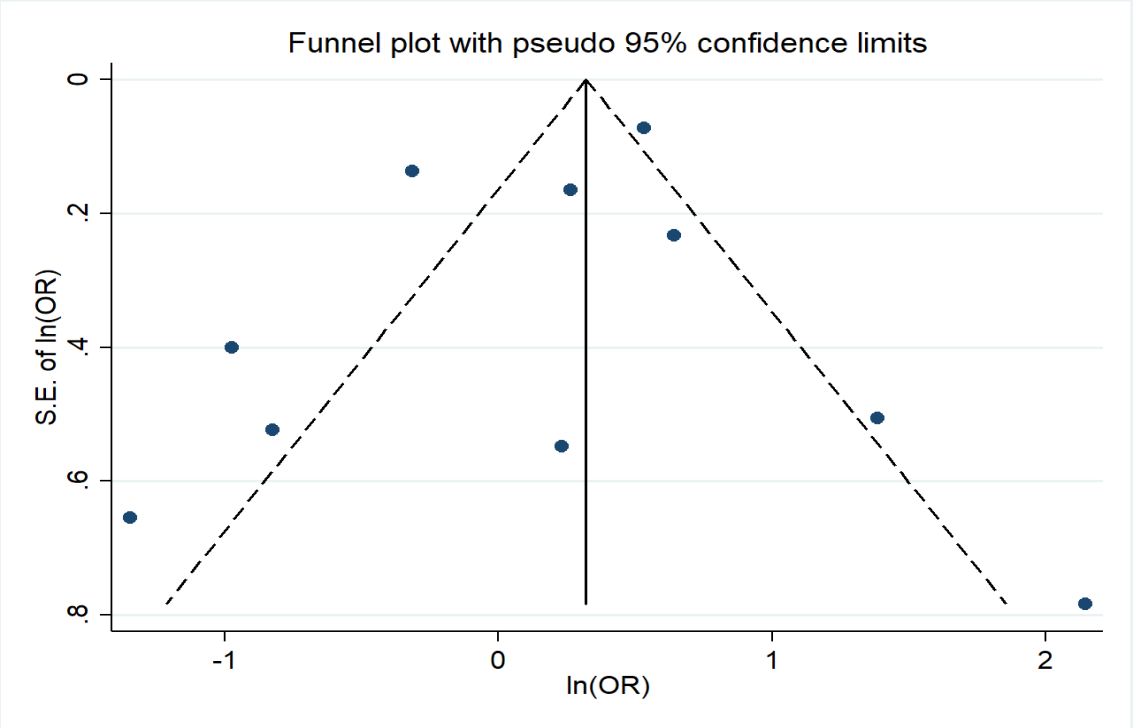

Figure 6. Funnel plot of the meta-analysis on the association of preeclampsia with cerebral palsy shows evidence of publication bias.

4. Discussion

This systematic review and meta-analysis focused on preeclampsia and the possible independent association with cerebral palsy in the offspring of such mothers after comprising the data from 10 studies, which were eligible according to the authors' criteria. The analysis that took place pointed to an overall lack of an independent association between preeclampsia and cerebral palsy, especially after adjusting for gestational age.

The two case-control studies that we included were based on specific population groups in Estonia and Turkey and tried to find out the most related factors to the development of cerebral palsy. Stelmach et al. compared cases diagnosed with mild to severe impairment due to cerebral palsy with two controls for every case from the same population, aiming to include all cases with a mild form of cerebral palsy, and concluded that preeclampsia could be an important parameter for the onset of this disease (OR = 8.54, 95% CI: 1.84–39.62), especially since this result was adjusted for several factors including gestational age (147). On the other hand, Ozturk et al. made a univariate analysis by including all children with cerebral palsy, regardless of its severity, in comparison with healthy controls arising from various guaranteed sources

in a specific region of Turkey. This study also highlighted a greater number of pregnancies complicated with preeclampsia in the group of cases, rather than in the group of controls (OR = 4.00, 95% CI: 1.48–10.78) (146). In both studies, the results were statistically significant, but we must consider that there were some design issues.

Eight cohort studies were considered compatible with our criteria for analysis. Withagen et al. included three groups of infants, one coming from mothers that underwent treatment for a severe form of preeclampsia before 32 weeks of pregnancy and two others related to normal pregnancies with infants born either on admission time of preeclamptic mothers or at the same gestational age as the infants of these mothers. By comparing these groups without adjusting for any factor, the study showed that there is no statistically significant result of a possible association between preeclampsia and cerebral palsy (OR = 0.44, 95% CI: 0.16–1.22) (155). Two other studies that followed the univariate analysis model examined the prevalence of cerebral palsy among infants born very preterm (150) and infants with very low birth weight (151), trying to find a possible association with many perinatal risk factors. Both studies concluded that in these special categories of newborns, preeclampsia may act protectively for the development of cerebral palsy, and the results were enhanced by statistical significance.

Mann et al. and Tronnes et al. tried to find out the independent association and included large population groups in their analyses. The two studies managed to identify that preeclampsia, especially the early-onset form, is strongly related to the development of cerebral palsy later, after adjusting for several factors but not for gestational age. Particularly, the first study was based on secured records from the South Carolina Medicaid program and demonstrated that the earlier the diagnosis of preeclampsia is set, the higher is the risk for cerebral palsy (OR = 1.90, 95% CI: 1.20–3.00) (149), and the second one also showed that many perinatal complications that occur in premature pregnancies (<32 weeks) have been associated with cerebral palsy, but especially for preeclampsia, the adjusted OR was 1.70 with 95% CI: 1.47–1.96 (154). The same pattern was followed by a study based on a Norwegian population that performed a multivariate analysis without adjusting for gestational age. When the authors focused on term pregnancies, the study failed to conclude with statistical significance on the association examined (OR = 1.30, 95% CI: 0.94–1.80). However, in the group of preterm infants, preeclampsia seemed to have a significant effect on the possibility of cerebral palsy, but that result is certainly affected by the complications of prematurity (153).

Two studies in the group of cohort ones included gestational age as a variate in the statistical analysis. Love et al. examined all newborns from women that underwent

preeclampsia in pregnancy in Aberdeen, taking advantage of records about these pregnancies in databases of this region, and showed that there was no association with the later presence of cerebral palsy (OR = 1.26, 95% CI: 0.43–3.69), even though the univariate analysis had estimated increased existing risk of cerebral palsy (148). In the last analysis, Strand et al. led to many conclusions depending on the level of adjustment, namely univariate analysis, small adjustment for gestational age, and small adjustment for gestational age. The study did not find any association in the group without any adjusted factor but showed enhanced association in the group of infants that were small for gestational age and a statistically significant reduced association when the study population was adjusted for gestational age (OR = 0.73, 95% CI: 0.56–0.96) (152).

The results of our analysis are linked to the conclusions of another systematic review that examined factors responsible for the onset of cerebral palsy. Going back to 1998, Collins et al. tried for the very first time to clarify the association between preeclampsia and cerebral palsy based on studies that had taken place at that time. This failed to find an association, but it was understood that preeclampsia caused preterm births and babies that were small for gestational age, which may have cerebral palsy, and this agrees with the findings of our systematic review (156). Van Lieschout et al. in 2016 described possible factors for the development of cerebral palsy. Although this study showed that there are conflicting data for the association between chorioamnionitis and gestational age with cerebral palsy, most of them converge on a positive association. The strongest association was with low birth weight, whereas as far as preeclampsia is concerned, the study concluded that the data are limited to some primary studies, and the results failed to provide a clear answer in this field (OR = 0.91, 95% CI: 0.35–2.41), as in our study (157).

Clark et al. in 2008 described the possible association between preeclampsia and cerebral palsy, and from the studies that were taken into consideration, concluded that preeclampsia may not directly affect the risk for this disorder, and it may be the gestational age at birth that affects the results (82). This agrees with the results of our meta-analysis in general and the results of some primary studies included that found that gestational age may be considered a mediator between preeclampsia and cerebral palsy (152). It seems, therefore, that preeclampsia itself might not cause cerebral palsy, and there are probably mediating factors, as gestational age or babies small for gestational age are important effects in the development of this disorder (152).

Commenting on subgroup analyses, a significant association arose only in studies that adjusted for several covariates, except for gestational age; also, in the synthesis

of the two eligible case-control studies, a statistically significant correlation emerged. Therefore, from a methodological point of view, the present systematic review and meta-analysis point to the need for well-designed cohort studies, adjusting for gestational age among other covariates.

In terms of limitations to the present systematic review and meta-analysis, there were no studies originating from East Asia, Africa, or South America. Another important limitation was the considerable heterogeneity of the studies included, but this was, to some extent, explained by the different approaches to the association, including different sets of covariates in the multivariate models and variable study designs. Additionally, other reasons for heterogeneity might be the different follow-up periods among the studies and geographical regions mentioned above.

However, among the strengths of this analysis, is the fact that we conducted an extensive search on three of the most important online databases. Then, we prepared our analysis and described our results based on the PRISMA guidelines (145). Another important fact in our analysis was that there was no statistically significant publication bias.

5. Conclusions

In conclusion, the analysis of the currently available data suggests that preeclampsia does not seem to be independently associated with the odds of cerebral palsy in offspring. However, because of conflicting results, additional future cohort studies based on well-designed protocols are needed.

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