First Trimester Prediction and Prevention of Pre-term Pre-eclampsia

A transcript of Professor Kypros Nicolaides’s webcast, broadcast on April 24th 2018
In early 2018 Professor Kypros Nicolaides presented a webinar in which he discussed the latest developments in the prediction and prevention of pre-term pre-eclampsia. In particular, he reviewed the detailed analysis of the secondary findings from the ASPRE study, including the impact of compliance, the impact of Aspirin on Chronic Hypertension and how first trimester pre-eclampsia screening in combination with aspirin treatment can improve the cost-effectiveness of prenatal care. This booklet is based on an abridged transcript of his talk.

We thank Professor Nicolaides for allowing us to reproduce his material here.

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Hello. Today I will be discussing some of the latest developments in the prediction and prevention of pre-eclampsia. Of course, you all know that pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity. It is estimated that more than 50,000 women die every year throughout the world as a result of pre-eclampsia — and pre-eclampsia of course has long term consequences for the mother with a doubling in her risk of major cardiovascular disease. Similarly, for the baby, there’s a very high risk of perinatal death and cerebral palsy, primarily as a result of the associated fetal growth restriction, and premature birth. It is also believed that for babies that do survive, in adulthood there is an increased risk of cardiovascular disease.

**PREDICTION OF PRE-ECLAMPSIA**

First, let’s discuss developments in the prediction of pre-eclampsia.

Let us look at the established method of screening for pre-eclampsia. Here is a summary of the major international bodies that have made recommendations on how to screen for pre-eclampsia. In all of the existing methods, the basis of screening, is obtaining a series of factors from the maternal history. In England for example, with the NICE guidelines, we have five major risk factors, and if you have any one of these, previous pregnancy affected by pre-eclampsia, chronic hypertension, chronic renal disease, maternal diabetes, autoimmune disease with SLE (systemic lupus erythematosus) and anti-phospholipid syndrome, then you are classified as being screened positive. You are also classified as being screened positive, if you have any two of five moderate risk factors that relate to maternal age and size, whether you are in your first pregnancy, the interval from a previous pregnancy and family history of pre-eclampsia.

In the United States, the American College of Obstetricians and Gynecologists recommends that women at high risk of developing pre-eclampsia should receive aspirin, but they classify somebody as being at high risk, if they have had two previous pregnancies affected by pre-eclampsia or one affected by pre-eclampsia leading to delivery before 34 weeks. Until now, we have not been certain about the performance of these methods of screening. We have not really known what the detection and the screen positive rates are.

A new approach to screening

The Fetal Medicine Foundation, over the last decade, has developed a different approach to screening. We use Bayes Theorem to estimate the prior risk, which is derived from a multiple regression model of the various maternal risk factors, where each one of the factors is given its own separate importance, and such an approach takes into consideration the interrelationship between the different factors. Then the prior risk is modified by the results of various biophysical and biochemical examinations. We measure various biomarkers, we modify the values to convert them into multiples of the normal median, and then we multiply the prior risk with the likelihood ratios derived from these biomarkers to estimate the posterior risk. And with this method, we can estimate the risk of any individual of developing pre-eclampsia before any desired gestational age. So, if you want to derive the risk of severe early onset pre-eclampsia, before 32 weeks, we can do so, or preterm pre-eclampsia with delivery before 37 weeks, or term pre-eclampsia with delivery at or after 37 weeks.
Over the years, we have examined a very large number of potential biomarkers, but essentially, four have been found to be useful in screening in the first trimester at around 11 to 13 weeks. And these are the measurement of the mean arterial pressure, the Doppler measurement of the uterine artery pulsatility index, and the biochemical markers of PAPP-A (Pregnancy Associated Plasma Protein A), and PlGF (Placental Growth Factor). And in a major publication involving more than 35,000 pregnancies that were prospectively examined using these biomarkers, we reported that at the false positive rate of 10%, the detection rate of pre-eclampsia before 34 weeks was 90%, preterm pre-eclampsia before 37 weeks was 75%, and term pre-eclampsia was about 45%. And this of course was the first step. Once you establish a method of screening, you need to validate your results in a new set of patients.

In this slide you can see the results of the first validation study. This involved more than 8000 prospectively examined singleton pregnancies in a study that was part of the ASPRE trial and it involved patients that were examined in Spain, in Italy, in Belgium, in Greece and several centers in the United Kingdom. And this study showed that the prediction was correct. We had very similar results in the validation model, so we can conclude that it is true that with the first trimester combined test we can detect about 90% of cases of pre-eclampsia before 34 weeks, 75% of pre-eclampsia before 37 weeks and about 45% of pre-eclampsia at term.

The second validation study came from a multicenter study that was funded by the British government. We prospectively examined in seven national health system hospitals more than 16,000 women at 11 to 13 weeks, and in these women the clinicians decided whether to recommend aspirin or not based on the NICE guidelines. We performed the combined test, but we did not give the results to the patients or to the managing clinicians. This study, for the first time, demonstrated the performance of screening by the NICE guidelines.

At the screen positive rate of about 10%, NICE guidelines could identify about 40% of women with preterm pre-eclampsia, 26% of women with term pre-eclampsia, and the overall rate of detection of all pre-eclampsia was about 30%. So we now know, that the current method of screening performs quite poorly.

The SPREE Study, as it is known, also demonstrated that with the first trimester combined test using history, mean arterial pressure, placental growth factor and uterine artery pulsatility index, the performance of screening, the detection rate for the same screen positive rate of about 10%, was twice as good with our approach compared to that using the NICE guidelines.
Here you can see the ROC curves for the performance of each individual marker or combinations of different markers. And the best combination was that of the mean arterial pressure, uterine artery pulsatility index and placental growth factor.

Selection of cut-off for predicting preterm pre-eclampsia

In this section, I would like to raise the question of which risk cut-off we should be using in the prediction of preterm pre-eclampsia. Before I address the question of selecting the appropriate risk cut-off in screening for preterm pre-eclampsia, I want us to be reminded of the lessons that we have learned from screening for Down’s syndrome.

We all know that with the first trimester combined test, the detection rate is about 90% for a screen positive or false positive rate about 5%. However, in England the recommended risk cut-off to classify somebody is being at high risk is 1 in 150 at term, which is equivalent to a risk of 1 in 100 at 12 weeks. With this risk cut-off, the performance of screening is not a detection of 90% for 5%, but it is a detection of about 86 to 88% for a screen positive rate of about 2.5 to 3%. And when we are counseling an individual patient, we cannot give this summary statistic for the whole population, because the performance of screening is dependent, very much so, on the prior risk. And in the context of Down’s, the prior risk is defined by the maternal age-related risk.

In this slide I summarize all of our extensive studies on first trimester screening in singleton pregnancies at 11 to 13 weeks involving more than 60,000 pregnancies. And you can see the performance of screening for different combinations of the various biomarkers, and an overall detection rate of more than 75% of preterm pre-eclampsia by the triple test.

We now have a good method of screening. Of course, we need to go further, we need to carry out more research, we need to find new biomarkers. In the case of screening for Down’s, we have started with a detection rate of 30% using maternal age, we advanced to 60 to 70% using second trimester serum biochemistry. We went further to about 90% using the first trimester combined test, and of course now we have gone to more than 99% using cfDNA testing.

So in terms of screening for pre-eclampsia, we have gone from about 40% using NICE guidelines to more than 75% using the first trimester combined test. Still a long way to go, but a great major advancement over what we used to have.
cut-off in population screening, the performance will vary in different populations, because in different populations there will be different prior risks.

These are the results from prospective screening in these more than 60,000 pregnancies. And you can see, that we can either use a risk cut-off of 1 in 70 for our population with our racial mix-up to have a screen positive rate of about 10%. However, you can see that in white women there is a lower all-over risk of developing pre-eclampsia and the screen positive rate of 10% is achieved with a risk cut-off of 1 in 100. But if we were to use a risk cut-off of 1 in 100 in a predominantly black population, the screen positive rate would be much higher than 10%, but of course at the same time we would have a much better detection rate. And in South East Asians, the situation is also similar to that in black women. There is a higher risk of pre-eclampsia and for a risk cut-off of 1 in 100 the screen positive rate is going to be more than about 15%. So if you want to adhere to the screen positive rate of around 10%, we should be selecting a risk cut-off of 1 in 70.

So let me re-emphasize this point: when we are screening in a multi-ethnic society, we cannot possibly use different risk cut-offs for different racial groups in screening for Down’s. We cannot use a particular risk cut-off for screening women that are in their twenties, a different one for women in their thirties, and another different one for women in their forties. In terms of the public health perspective, you select one risk cut-off and then you accept the reality that the screen positive rate and detection rate will vary depending on your prior risk. My personal view is, that we should be using overall a risk cut-off of 1 in 100. If black women are at higher risk of developing pre-eclampsia then there would be a higher screen positive rate, but you should tolerate that because we will be achieving a much better detection rate. And one of the differences in screening for Down’s compared with screening for pre-eclampsia, is that until recently, the consequence of being screened positive for Down’s was to go through an invasive test that carries a risk of miscarriage whereas being screened positive for pre-eclampsia, means treatment with aspirin that does not have any known adverse effects on the mother or the baby.

PREVENTION OF PRE-ECLAMPSIA

I will now present some of the important, recent findings in relation to prevention of pre-eclampsia.

PREVENTION OF preeclampsia

I will start of by summarizing our knowledge acquired over the last fifty years. We know that bed rest and various dietary manipulations do not reduce the risk of pre-eclampsia. The only thing that we know is beneficial is in populations or individual women with low intake of calcium – calcium supplementation can then halve the risk of pre-eclampsia. Bed rest, salt restriction, various vitamins are not useful.

Aspirin treatment

I now come to the long history of aspirin. In 1985 a study from Paris, reported in the Lancet, examined 102 women that were at very high risk of developing pre-eclampsia. In that study, women were given 150 milligrams of aspirin per day starting from 12 weeks. In the subgroup of women that received aspirin, there were no cases of pre-eclampsia, fetal growth restriction, stillbirth. Whereas in the subgroup that did not receive aspirin, quite a few women developed pre-eclampsia or had growth restriction and stillbirth. So that was the beginning. Let us now see what happened in the subsequent decades.

A series of major multicenter studies were conducted in which, surprisingly, the dose of aspirin varied from 40 to 160 milligrams. And in the vast majority of the studies the dose of aspirin was less than 100 milligrams. In most of
We decided that the dose of aspirin should be 150 milligrams per day. After all, this is what the original recommended dose was, and over the years we have also learned that lower doses of aspirin will find high proportions of the population that are non-responders. So if you want to maximize the benefit for the potential value of aspirin, we have to use the dose of 150 milligrams.

I feel very strongly and very critical about the rationale of some meta-analyses where completely heterogeneous types of studies are somehow put together, and conclusions are reached that, if wrong, dominate thought for several decades. That is unfortunately what has happened in the case of these meta-analyses in relation to the various studies that had been conducted until that time. So if you ask any clinician in any part of the world, most probably they will tell you that aspirin is useful at a dose depending on what you can buy from the local chemist in any given country, ranging from 40 to 60 to 80 (usually milligrams) and that given at any time of pregnancy it reduces the risk of pre-eclampsia by 10%. Is this true?

**Major multicenter study (ASPRE)**

To address this question, we decided to conduct, hopefully, the definitive study in relation to the use of aspirin. A series of centers from Europe participated in this multicenter-study which was funded by the European Union.

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We decided that it was important to start treatment before 16 weeks, and preferably at around 12 weeks. What was the reason for that? Well, if aspirin works by improving placentation, placentation is completed by 16 weeks, and therefore if we want to affect placentation, we should be treating at the time when placentation is still ongoing. We wanted to stop at 36 weeks, because we had a concern that perhaps aspirin could produce brain hemorrhage or other haemorrhagic events for the fetus and the neonate. So we wanted to stop at 36 weeks before the vast majority of women would be delivering.

Then we had a decision to make, as to what was the best time of day to give the aspirin. It is sometimes being given in the morning or at lunch time, but there are a series of studies, mainly from Spain, that have addressed the question through randomized studies, and they concluded that the greatest effectiveness in prevention of pre-eclampsia was achieved if the drug was given in the evening.

And then we had to address the question of what is the outcome. Any pre-eclampsia, term pre-eclampsia or preterm pre-eclampsia? Accumulated evidence over the last few decades suggests that we can possibly divide pre-eclampsia into preterm and term. The pathophysiology of these two conditions, although they may be overlapping, is likely to be different, with preterm pre-eclampsia being predominantly a consequence of impaired placentation and term pre-eclampsia being a consequence of metabolic disorders in the mother and pre-existing cardiovascular risk factors. In many respects not truly understanding term pre-eclampsia, we wanted to limit our outcome measure to preterm pre-eclampsia.
And the last point was, how do you go about selecting the high risk group that should be used to determine whether they can benefit from the use of aspirin? Well it was obvious on the basis of all of our studies over the last decade that the best way of selecting the high-risk group where we would maximize the detection rate, was by using the FMF algorithm with a combination of maternal factors with biomarkers.

We assumed that aspirin at 150 milligrams per day would reduce the rate of preterm pre-eclampsia by 50%. We were also assuming that about half of the screen positive women would agree to take part in the study. On the basis of these assumptions and the results of our screening studies, we arrived at the conclusion that we needed to randomize 1600 high-risk women to achieve significance with a power of 90%. We were very proud of the rate of recruitment to the study, which was essentially completed within ten months. So I am very happy about these results; it demonstrates the commitment of the various centers towards at least addressing the question of whether aspirin is useful or not.

Results of the multicenter study

We screened more than 25 000 women, we identified a high-risk group of about 11%. We had the series of exclusion criteria. We then had a good uptake of randomization. Some of the women that enthusiastically accepted randomization to begin with, subsequently decided to withdraw, and we had our final target for further assessment. The study was published in the New England Journal of Medicine.
better the compliance, the more effective the drug would be. We took a cut-off of a compliance of 90%, which was met by the vast majority of the women in the ASPRE trial, and with this the effectiveness of aspirin was greater in terms of reducing the rate of preterm pre-eclampsia.

The next question that we addressed through another secondary analysis of the ASPRE data, was whether it matters which risk group you come from. Does it matter whether you are young or older? Does it matter whether you are thin or overweight? Does it matter whether you are black or white? Does it matter whether you smoke or not? Does it matter whether you have a family history of pre-eclampsia? Whether you are a nulliparous? Or whether you had pre-eclampsia in a previous pregnancy or not?

And you can see that you have a variation in the values from each one of the subgroups, but all of the results suggest that none of these factors has a major effect or a deviation from the overall result. This provides, for example, an answer to a question that I’m often asked, about whether we should be giving the same dose of aspirin to a woman that is thin as to a woman that is overweight; the answer is, yes we can. With the dose of 150 milligrams it doesn’t seem to matter whether you are thin or overweight, it doesn’t matter which group you come from.

There was only one factor in the maternal history that appeared not to be affected by the use of aspirin. And that was where women had chronic hypertension. And this is interesting, because chronic hypertension of course is the most important risk factor for developing pre-eclampsia. And if you start off your pregnancy with chronic hypertension, you have a 20% risk that you will develop pre-eclampsia. But somehow aspirin was not effective in this group. We are currently investigating alternative strategies for this group of women including very strict control of blood pressure starting from the first trimester, and the possible value of pravastatin in the prevention of pre-eclampsia in this group. But it appears that all risk factors other than chronic hypertension do not deviate in their responsiveness to aspirin.

We took the story further and went on to look at the group of women that did not have chronic hypertension and the subgroup that actually had a good compliance of more than 90%. Well, in those women, that still constitute the majority of the population, the reduction in the rate of preterm pre-eclampsia may be up to 95%.

**Why not give aspirin to all women?**

At this point I would also like to address a question that is often asked, as to why not give aspirin to everybody and why go through this laborious process of screening? Well there are two reasons for that. The first one is that I believe, that we will get a much better compliance if we identify somebody as being at a high risk and we explain to them that it would be beneficial for them to take aspirin. And the second reason, of course, is that although, so far, we believe that aspirin is safe, this cannot be always stated if you have mass treatment of the whole population. There is some evidence from the use of aspirin in older people, as part of prevention of cardiovascular disease, that aspirin increases the risk of haemorrhagic events a little bit. But if you are treating a lot of people then that small possible increase in haemorrhagic events would have a major adverse effect. So I think it is rational that we should screen, identify the high-risk group where aspirin would certainly be beneficial, and emphasize to these women the necessity of a high compliance.

A question that is often asked is, if a woman is at high risk of pre-eclampsia, because she has chronic hypertension, or diabetes or she had pre-eclampsia in a previous pregnancy, should you just treat her and screen only the women in the low risk group? In many respects, this sort of question was asked many years ago when we introduced screening in the first trimester for Down syndrome.

People at that time were saying “I think we should continue to offer invasive testing to women over the age of 35 and offer screening to women under the age of 35.” Of course, all of that argument very soon became a non-argument, and the main reason why that happened is because women in the older age groups understood better than doctors and public health doctors that they did not want to have
invasive testing if their combined test risk was reducing their maternal age related risk. So let’s consider a woman who is 40 years old. By the traditional 1970’s approach to screening she should be offered invasive testing; by the 1990’s method of combined screening, the nuchal (nuchal translucency) is good, free beta (free beta hCG) is good, PAPP-A is good, her risk becomes the same as when she was 20 years old. Should we still be giving her an invasive test just because she is 40 years old? Well, of course not.

Dose and timing of aspirin administration

We now summarize the evidence in relation to the dose, the timing of onset of aspirin and the target of aspirin therapy. In this recently published meta-analysis involving 16 trials we have found that aspirin does not have any effect on the rate of term pre-eclampsia, but it has a major effect in reducing the rate of preterm pre-eclampsia.

In the same meta-analysis in relation to prevention of preterm pre-eclampsia, we found that aspirin, at less than 100 milligrams, started after 16 weeks, does not reduce the rate of preterm pre-eclampsia. Whereas aspirin at a minimum dose of 100 milligrams, and starting before 16 weeks, reduces the rate of preterm pre-eclampsia by 67%.
Many doctors are worried that aspirin at 150 milligrams per day may increase the risk of placental abruption and antepartum hemorrhage. And this is a justified concern, because most of the studies of the past had shown that aspirin does not increase the risk of abruption, but in most of those studies the dose of aspirin was less than 100 milligrams.

To address this question, we conducted a major meta-analysis of all of the published studies, that gave information on the dose and the timing of aspirin and the reported on the rate of abruption or antepartum hemorrhage. And we were reassured to find that aspirin at less than 100 milligrams per day, given either before or after 16 weeks, does not increase the rate of abruption, but unfortunately we have already seen that such a low dose does not improve the risk of pre-eclampsia either. Considering a dose of aspirin of more than 100 milligrams gives the interesting finding that if you start before 16 weeks you tend to reduce the risk of abruption whereas if you start after 16 weeks you increase the risk of abruption. There was a significant difference between the effects of more than 100 milligrams given before compared to after 16 weeks. To me this is completely logical. One of the major causes of abruption is impaired placentation, and if aspirin is given at the right dose at the right time, it makes sense that by improving placentation it would reduce the rate of abruption. Whereas if you give a high dose of aspirin to women beyond 16 weeks, in the presence of impaired placentation, which you can no longer improve, you may well be increasing the risk of hemorrhage including placental abruption. So the lesson from this is: aspirin before 16 weeks, at more than 100 milligrams; not only does it not increase but it may well decrease the risk of abruption.

In the primary analysis of the ASPRE trial, we found that the rate of admission to the neonatal intensive care unit was not significantly different between those that had received aspirin compared to those that had received placebo. And this was a bit worrying, because people were saying, “Well, you may well be reducing the risk of preterm pre-eclampsia, but you are not demonstrating any benefit for the babies”.

So we looked at the data again in greater detail in this secondary analysis, and we confirmed that although the overall rate of admission to the neonatal intensive care unit was not different between the two groups, the rate of admission for babies that were born before 32 weeks was significantly lower in the aspirin group. And this is important.
really matters, a marker of morbidity and perhaps long-term morbidity, is how long the child actually stays in the neonatal intensive care unit. And we found this massively significant 68% reduction in the overall length of stay in the neonatal intensive care. So aspirin was associated with a major reduction in the total length of stay in the neonatal intensive care unit, and this has important implications.

What does this 68% reduction in the total length of stay mean in terms of costs? If we screen 10 000 women, and we identify 10% as being at high risk for preterm pre-eclampsia, and then we treat this group with aspirin, we estimated that, by comparison to a group that does not receive aspirin, we are reducing the mean length of stay in the neonatal intensive care unit by 1.4 days. If we then take 1000 pregnancies, each contributing 1.4 days, we have a total saving of 1400 days of neonatal intensive care in the group that would receive treatment with aspirin. And if I take an average cost of 2000 dollars per day in the neonatal intensive care unit, then you have a cost saving of $2.8 million dollars. We can then use this to offer screening to the total population of the 10 000 pregnancies. To be cost neutral, we can allow 280 dollars per screening test, and it is absolutely clear that the cost of each screening test is much much less than 280 dollars. Why?

A major reduction in the total length of stay that is primarily attributed to a reduction in the rate of very premature birth, as a consequence of reduction in the rate of early pre-eclampsia (more than 80% of pre-eclampsia before 34 weeks, 90% before 32 weeks) translates into a major decrease in risk of being born prematurely. And what is the consequence of that?

Well, what are the components of screening? Taking a history: This is part of the routine in prenatal care.

Measuring the mean arterial pressure: If the mean arterial pressure is to be measured properly, it takes about 5 minutes and proper care has to be taken in allowing the women to rest, selecting the right cuff, measuring the blood pressure in both the left and right arm once, and then waiting for a minute and measuring it again. But I think that in most health care systems, an auxiliary nurse can easily be trained to undertake this task, and I don’t believe that this would be very expensive.

Measurement of the uterine artery pulsatility index: In countries where there is routine first trimester screening either by just performing an ultrasound scan at 11 to 13 weeks or by performing the combined test in screening for Down’s, the patient is there, the ultrasound machines are exactly the same, they all now have facilities for color Doppler, so it will add a couple of minutes to the first trimester ultrasound scan to measure the uterine artery pulsatility index.

Measurement of placental growth factor: Again we already have an infrastructure of screening for Down syndrome, the equipment is available, and the blood sample is collected from the women, free beta hCG and PAPP-A are measured; the cost of measuring the placental growth factor would be marginal.

And all together, we come nowhere near the amount of cost saving from the major reduction in the length of stay in the neonatal intensive care unit. But this is not all.
CONCLUSION

So what is new? What have we learned in the last year and what have we added to the knowledge of the last 30 years?

We have learned that aspirin at more than 100 milligrams per day starting at less than 16 weeks can reduce the risk of pre-eclampsia before 32 weeks by 90%, pre-eclampsia before 34 weeks by 80%, pre-eclampsia before 37 weeks by 65% and higher if you have a good compliance. We have an associated reduction in the risk of abruption by 30%, and a reduction in the length of stay in neonatal intensive care by 65%.

We have the results of an extremely good study from France, published this year in the British Medical Journal, that shows the massive difference in terms of death and handicap in survivors within two years of premature birth. You can see a massive difference as to whether you are born before or after 32 weeks. A tenfold difference between the two. But you have more than that.

A few years ago there was a major epidemiological study from Norway, published in the New England Journal of Medicine, that looked at babies according to the gestational age at delivery, and what happened to them in terms of the risk of death in the first five years of life, the risk of cerebral palsy, and also the chances of impairment that would interfere with their ability to integrate into society and take a job in the subsequent 20 years and beyond. And you can see that there is a massive difference in terms of risk of death in five years, cerebral palsy and inability or impairment in working in the long term, if you are born before 30, before 32, before 34 weeks. And although the individual statistics may have changed because of improved neonatal care in the last few decades, still the relative proportion of risks for each one of these components remains substantial.

So, a reduction in the risk of severe early pre-eclampsia translated into a reduction in risk of premature birth translated into a major reduction in length of stay and therefore cost, immediate cost to the healthcare system, is also translated into a reduction in death, handicap and long-term cost from looking after such individuals.

If you wish to see the full webcast, please go to: http://prenataltesting.perkinelmer.com/aspre#webinar